



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 78464

Title: The RAGE axis and gallbladder cancer: A forgotten connection that we should reconsider.

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03372482

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Academic Research, Assistant Professor, Associate Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: Chile

Manuscript submission date: 2022-06-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-06-28 07:13

Reviewer performed review: 2022-06-28 07:20

Review time: 1 Hour

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|---------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
| Language quality | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| Conclusion | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection |
| Re-review | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

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| Peer-reviewer statements | Peer-Review: [<input type="checkbox"/>] Anonymous [<input checked="" type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No |
|-------------------------------------|---|

SPECIFIC COMMENTS TO AUTHORS

Compelling pieces of evidence derived from both clinical and experimental research have shown the crucial contribution of chronic inflammation in the development of neoplasms, including gallbladder cancer. Data derived from both clinical and experimental studies have shown that the RAGE/AGEs axis plays an important role in the onset of a crucial and long-lasting inflammatory milieu, thus supporting tumor growth and development. AGEs are formed either in biological systems or in foods, and food-derived AGEs, also known as dietary AGEs (dAGEs) contribute to the systemic pool of AGEs. Once they bind to RAGE, the activation of multiple and crucial signaling pathways is triggered, thus favoring the secretion of several pro-inflammatory cytokines also involved in the promotion of gallbladder cancer invasion and migration. In the present review, they aimed to highlight the relevance of the association between high dietary AGEs intakes and high risk for gallbladder cancer, and emerging data supporting that dietary interventions to reduce gallbladder cancer risk is a very attractive approach that deserves much more research efforts. In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. Results: the results are presented clearly, the authors provide accurate research results, and there is sufficient evidence for each result. Conclusion: in general: Good and the research provides sample data for the authors to



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7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA

Telephone: +1-925-399-1568

E-mail: bpgoffice@wjgnet.com

https://www.wjgnet.com

make their conclusion. Grammar: Need Some revision. (Check The Paper Comments).
Please provide the following information in the Paper 1. Conflict of Interest 2. Source of
Funding Finally, this was an appealing article, in its current state it adds much new
insightful information to the field.



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Reviewer's code: 05846802

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Chile

Manuscript submission date: 2022-06-27

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-04 01:55

Reviewer performed review: 2022-07-04 06:23

Review time: 4 Hours

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|---------------------------|---|
| Scientific quality | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish |
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| Peer-reviewer statements | Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No |
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SPECIFIC COMMENTS TO AUTHORS

Comments to the Author This manuscript summarized the recently topics of receptor of advanced glycation end-products (RAGEs), which might be the risk factor of several cancer. In particular, it may be useful as a new treatment strategy for gallbladder cancer, for which there are few effective treatment other than surgical resection. I have little to point out, but there are a couple of expressions that are of concerns. First, with regard to the manuscript presented by the authors, Mayen et al [32], the credibility of their data analysis is not that high because they did not include various confounding factors in their analysis (they discussed in the limitation). There is no report that actually proves that RAGE itself maligns gallbladder epithelial cells and causes gallbladder carcinogenesis. However, it is very interesting in terms of therapeutic intervention, since many studies have demonstrated malignant transformation (proliferation, or migration) of cancer cells by suppressing RAGE itself. Therefore, it should be emphasized that RAGE in terms of cancer prevention is still controversial. Second, please suggest what exactly you mean by patients at risk for gallbladder cancer. If RAGE itself has a carcinogenic risk, then all humans, not just those at risk for gallbladder cancer, should avoid RAGE. Please let me know the author's opinion on the above two points. Minor concerns: Page6, in the CONCLUSION, there is an excessive space between "the advanced" in the second line.