Point by point explanations to reviewer´s comments.

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First of all, the authors wish to express their gratitude for all the observations and comments made by the reviewers to improve the quality of the manuscript.

Reviewer #1:

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).

We agree with your comment. In this regard, we have modified the text,

See page: 4 paragraph(s): 2 line(s): 9-10

…and thus suggesting that higher intakes of dietary AGEs may increase the risk of gallbladder cancer.

See page: 4 paragraph(s): 3 line(s): 11-12 and 14-15

Although the study of Mayen et al [32] has some limitations, particularly in estimating dietary AGEs exposure, …

… due to the increased endogenous formation of AGEs reported in these entities.

- There is no report that actually proves that RAGE itself maligns gallbladder epithelial cells and causes gallbladder carcinogenesis.

RAGE itself does produce neither gallbladder carcinogenesis nor malignant transformation in any cell type. In this regard, we added a new paragraphs, with new references, to clarify the role of RAGE in malignat transformation.

See, from page: 5 paragraph(s): 2-4 line(s): 7-16

RAGE is recognized as a pattern recognition receptor, and its activation plays a pivotal role in the propagation of immune responses and inflammatory reactions [62].

It is expressed at low levels in most differentiated adult cells in a regulated manner. However, the up-regulation of RAGE expression has been associated with many inflammation-related pathological entities, including cancer [63].

Noteworthy, RAGE engagement subsequently converts transient cellular stimulation into sustained cellular dysfunctional states driven by long-term activation of the nuclear factor-kappaB [64]. The contribution of RAGE activation promote many crucial steps during tumorigenesis, from DNA damage and genetic instability to supporting many phenotypic changes in tumor cells favoring their growth and dissemination[65].

- 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.

We agree with your concern and we added a new paragraph

See page: 7 paragraph(s): 3 line(s): 8-11

However, it must be emphasized that therapeutic interventions, including dietary interventional actions, on RAGE axis have been focused on getting clinical improvements of disease course, and therefore the potential of modulating RAGE activation 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.

At this point, we were referring to individuals at risk as those with metabolic diseases, where the endogenous pool of AGEs in these individuals increases considerably, as well as those subjects who have a genetic ancestry that confers an increased risk, and consequently we added new text as follows.

See page: 8 paragraph(s): 3 line(s):8-11

In this regard, it is important to highlight that some pre-existing clinical conditions such as Diabetes mellitus and metabolic syndrome are risk factors for the development of gallbladder cancer [34,35-38]. Additionally, the demonstrated links between genetic ancestry and GBC development may represent another risk factor for some populations[126,127].

Minor concerns:

- Page 6, in the CONCLUSION, there is an excessive space between "the advanced" in the second line.

  We corrected the excessive space between “the advanced” in the Conclusion section

Reviewer #2:

- 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 make their conclusion.

- Grammar: Need some revision. (Check The Paper Comments).

We checked out the manuscript attached by the reviewer and no comments/changes were found. In any case, the manuscript was revised for any grammar.

- Please provide the following information in the Paper:

1. Conflict of Interest

   Conflict of Interest is now declared

2. Source of Funding

   Declaring the source of funding is optional

   Finally, this was an appealing article; in its current state, it adds much new insightful information to the field.

We greatly appreciate your comments.