Peer Review File

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Reviewer A

General comment

The manuscript in reference compiles the reported Anti (angiogenic) food components: can be a major source of bias in the investigation of angiogenesis inhibitors. The manuscript has relevant information and organization that will be interesting for readers. However, some points need to be addressed before further consideration.

Reply 1: We appreciate the reviewer for acknowledging the importance of our work. We agree with the points raised and we have answered all your comments.

Abstract

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Comment 1:

Introduction

Should be added information about:

- Highlights of this research

Reply 1: We added a highlight box to the end of the paper. Editorial office may determine which place is the best to insert this box.

Changes in the text: Highlight box in now prepared and included after conclusion section.

Comment 2:

-The utilization of this research in various aspects

Reply 2: Thank you very much for this constructive comment. We have indicated utilizations and implications of this study in page 1 lines 35-36: “Implications of this expert opinion cover similar angiogenesis-related diseases”. To address this important comment, in new version, we have added a summary of various implications and utilizations within the **Highlight box**.

Changes in the text: In page 15 we added the Highlight box, it now reads as:
“Implications of this expert opinion cover similar angiogenesis-related eye diseases (such as age-related macular degeneration, retinal/macular neovascularization, different types of retinopathy, dry eye diseases), a wide range of cancers, hypertension and cardiovascular outcomes, just to mention a few. There is an urgent need for developing and validating a semi-quantitative food frequency questionnaire to gather data on natural angiogenesis inhibitors/promotors.”

Comment 3:

Content

“Plant lectins and Capsaicin” should be added relevant research.

Reply 3: Done

Changes in the text: Page 4, lines 82-101, we added two paragraphs about “Plant lectins”. It now reads as:

“There are different types of lectins. Concanavalin A is a legume lectin, has gained a great deal

of attention for its remarkable anti-tumor and anti-proliferative activities to a variety of cancer cells (18). Galectins, another type of plant lectins- are involved in a variety of biological functions such as angiogenesis, maternal-fetal immune tolerance, placental development and trophoblast invasion and are currently regarded as important mediators of successful embryo implantation during pregnancy (19).
Galectins are also implicated in the occurrence and development of many autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and type 1 diabetes by regulating apoptosis, cell adhesion and other mechanisms such as translocation to nucleus by carbohydrate-recognition independent manner (20). Two most widely expressed members of the galectin family, are galectin-1 and galectin-3 have showed remarkable therapeutic potential in autoimmune diseases (21) and glioblastoma (22).
Surprisingly, there are some types of lectins (such as Collectin-11 which is a soluble C-type lectin) with completely opposite properties. For instance, it was recently shown that Collectin-11 plays an important role in melanoma cell proliferation and tumor growth in mice model (23). Consequently, it was just reported that in endothelial cells dimerization of the C-type lectin-like receptor CD93 promotes its binding to Multimerin-2 (24). These observations provide insight into the future design of new drugs able to hamper CD93 function in neovascular pathologies.

Also, ins page 6, lines 155-165, specific references are added. It now reads as:

"In most published papers, capsaicin is considered a potential anti-tumor compound and its anti-cancer properties are mainly attributed to induction of apoptosis and autophagy, anti-proliferation, anti-angiogenesis and anti-metastasis. The pivotal point here is that its biological functions are greatly influenced by its concentration and the effective concentration in different malignant tumors differs significantly, highlighting the importance of quantifying and measuring its oral intake in clinical trials in study arms. Moreover, it would be pertinent to note capsaicin can affect the anti-cancer activity of radiation therapy or conventional chemotherapeutic drugs (49). It worth reminding that progression of cancer is an intricate multistep process consisting of angiogenesis of the primary tumor, then its invasion into the surrounding stroma and eventually its migration to distant organs to produce metastases."

Comment 4

Figure 1.

"A schematic of our model." It should be written concisely and easily understood.

Reply 4: Done

Comment 5

Conclusions

-Should be summarized important points of the article, suggestion, and additional study guidelines in the future.

Reply 5: Done

Changes in the text:

Page 14, lines 371-385 we summarized our important points of the article, suggested some simple and practical methodologic considerations, and proposed an important additional study guideline future studies.

It now reads as:

"There are significant intra-individual differences in terms of dietary intake of natural angiogenesis inhibitors/promotors (e.g. some diets such as vegetarian diets contain higher amounts of these compounds), and most importantly, different types of food processing techniques drastically change the level of digestibility and solubility of these compounds and their bioactivity and bioavailability. On the other hand, biological functions of these compounds

are greatly influenced by their concentration and the effective concentration in different malignant tumors differs significantly, which is in turn a function of their oral intake and food processing techniques, which obviously varies among different people and communities. There are no clinical trial on angiogenesis inhibitors designed to assess the magnitude of bias following short term or prolonged natural consumption of these compounds in oncological and ophthalmological research, highlighting the importance of quantifying and measuring the oral intake and their serum concentration in clinical trials and balancing the study arms based on baseline serum concertation of these compounds. The take home message herein is to inform the oncological and ophthalmological researchers of the potential unwanted bias of food based diet-derived natural angiogenesis inhibitors/promotors as discussed."

Comment 6

References

Should be checked the reference format according to the journal's requirements.

Reply 6: Reference are now formatted according to the journals requirement.

Reviewer B

The manuscript "Anti (angiogenic) food components: can be a major source of bias in the investigation of angiogenesis inhibitors" presents an interesting topic and it is sufficiently described. However, some points should be improved:

We appreciate the reviewer for acknowledging the importance of our work. We agree with the points raised and we have answered all your comments.

1. Language editing by a native speaker or a professional translation office is required.

Reply 1: Paper is now edited by a native speaker.
Changes in the text: New version is submitted which is completely edited by a native English speaker.

2. What is the exact significance of this study?

Reply 2: This study highlights the fact that how these seemingly negligible compounds can create uncertainty in clinical trials of oncological and ophthalmological research.

We changed the page 7, lines 198-206 to clarify this further. It now reads better as below:

"To the best of our knowledge, there are no clinical trial on angiogenesis inhibitors designed to assess the magnitude of bias following short term or prolonged natural consumption of these compounds in oncological and ophthalmological research, especially as it relates to cancerous tumors. In fact, this is true for tumor promoting or tumor preventing properties in both oncological and ophthalmological investigations. Moreover, the oncological and ophthalmological field should carefully, consider that there are large inter-individual differences in terms of these compounds. For instance, there are significant inter-individual differences for alcohol and wine consumption between countries (71)."

3. A paragraph about other sources and/or other polyphenols should be included.

Reply 3: Done.
Changes in the text: Page 6-7, lines 178-184, we added a paragraph which now reads as:

“***Polyphenols*** are regarded as naturally occurring micronutrients that are present in plant kingdom as necessary physiological bioactive compounds (56). These compounds comprise a wide family of molecules bearing one or more phenolic rings and are present in several food sources like vegetables, green tea, red fruit, wine, grapes and coffee (57). Most polyphenols exhibit antioxidants (58) and anti-inflammatory properties (59). However, their anti-angiogenic properties have recently been a focus of attention in cancer research (60). ”