



October 30th, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5803-review.doc).

Title: Role of Pomegranate and Citrus Fruit Juices in Colon Cancer Prevention

Author: Saravana Kumar Jaganathan, Muthu Vignesh Vellayappan, Gayathri Narasimhan, Eko Supriyanto

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5803

The manuscript has been improved according to the suggestions of reviewers and format has been updated according to the revision policies of BPG.

1. Reviewer No: 00001114

Query 1) I was wondering why the author focused on the fruit juice, not fruit itself. I get the feeling that it is easy to take lots of fruit as juice. If the author consider intake as juice important, comment in Introduction, please.

As suggested by reviewer following lines were added to the manuscript highlighting the juice consumption:

Consumption of fruit juices by various ethnics is prevalent and there is a good market-share between real fruits and the fruit juices. Intake of fruits as juices has gained wider-acceptance among the young population because it is easier to consume and also intake amount of juices can be increased significantly compared to fruits itself. Further, the availability of 100% fruit juices in the retail market and also the functional claims of such juices further motivate people to consume fruit juices.

Query 2) I feel that this review was lack of epidemiological data. Most of this kind of topics was considered based on epidemiological data, for example, dietary fiber, or coffee, etc. And there are some areas where people have lot of intake of those fruit, in particular, citrus fruit. Please provide epidemiological data about the relationship between colorectal cancer and pomegranate and citrus juice. If difficult to show, please discuss the reason in Discussion.

As suggested by reviewer, author had notified the scarcity of epidemiological studies both in abstract and the final conclusion as follows:

In abstract: Moreover, there was a scarcity of studies involving human trials to estimate the preventive nature of these juices against colon cancer.

In Conclusion: However a phase II and phase III clinical trials involving larger groups of participants who are at high risk for colon cancer may validate the effect of these fruit juices and provide information whether these agents has protective effect against biomarkers. However, these research

demands large research grants which makes the study a costly and impracticable thing.

Query 3: I was confusing if pomegranate and citrus juice might be good for the chemoprevention or the treatment of colorectal cancer because of lack of epidemiological data. I feel that the former is suitable for this review even though I understand the mechanism of effect of those fruit juice on colon cancer from *in vivo* or *in vitro* study. In addition, title includes cancer prevention, not treatment of colon cancer. But the author state that the clinical trials should be done especially in patients with colon cancer and the effect produced by the oral consumption of the fruit juices must be noted in the last paragraph. So I feel a bit different about that.

Author would like to thank the reviewer earnestly for effectively pointing out the importance of the use of fruit juices for chemoprevention rather than treatment. Author had revised the paragraph according to the reviewer comments.

To assess whether these juices have preventive effects against colon cancer, a study can be initiated with 25 healthy participants or 25 participants with increased risk for colon cancer to assess its predictive efficiency. However a phase II and phase III clinical trials involving larger groups of participants who are at high risk for colon cancer may validate the effect of these fruit juices and provide information whether these agents has protective effect against the colon cancer biomarkers. However, these research demands large research grants which makes the study a costly and impracticable thing. Moreover, cancer prevention using dietary agents is still a promising field of oncology where scientists in both basic and clinical sciences face great challenges.

2. Reviewer No: 00057837

Query1: Fig. 1 is not necessary as pomegranate and citrus fruits are well-known. A table summarizing the most important studies *in vivo* and *in vitro* on each substance would improve the overview

As reviewer suggested the pomegranate and citrus fruits are well-known Figure 1 was removed. Further Table 1 and Table 2 was added summarizing the *in vitro* and *in vivo* studies of the fruit juices.

Query 2: A reference should be included: Adhami VM, Khan N, Mukhtar H. Cancer chemoprevention by pomegranate: laboratory and clinical evidence. *Nutr Cancer*. 2009;61(6):811-5.

As suggested by the reviewers, this reference was added at no 11.

Query 3: The authors should give an outlook on how to plan and conduct clinical studies (e.g. which population, what numbers needed etc.)

Following text were added to give the outlook on how to plan and conduct clinical studies:

In addition to that, in most of the work done on animal studies, normal rats and mice were utilized as a subject instead of transgenic animals. Hence, the transgenic animals has to be utilized for animal studies involving the efficacy determination of citrus and pomegranate juices against colon cancer to improve the reliability of the results. It would be appropriate for testing the efficacy of the above juices using ApcMin/+ mouse (colon cancer model with a dominant germ-line mutation at codon 850 of the homolog of the human adenomatous polyposis coli (Apc) gene) to confirm its colon cancer prevention potential.

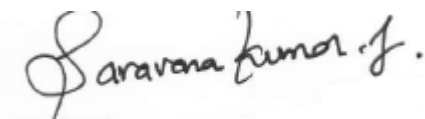
Besides that, our work is also aimed to throw light on importance of carrying out more clinical trials in human beings with the pomegranate and citrus juices. To assess whether these juices have preventive effects against colon cancer, a study can be initiated with 25 healthy participants or 25 participants with

increased risk for colon cancer to assess its predictive efficiency. However a phase II and phase III clinical trials involving larger groups of participants who are at high risk for colon cancer may validate the effect of these fruit juices and provide information whether these agents has protective effect against the colon cancer biomarkers. However, these research demands large research grants which makes the study a costly and impracticable thing. Moreover, cancer prevention using dietary agents is still a promising field of oncology where scientists in both basic and clinical sciences face great challenges.

3. References and typesetting were corrected according to the science editor. Moreover, language polishing was done by native speaker to meet the language requirement by the journal. Certificate copy is attached. Corrections made were highlighted.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, reading "Saravana Kumar J." with a stylized flourish at the end.

Dr Saravana Kumar Jaganathan
Visiting Research Fellow
Cardiovascular Engineering Center
Faculty of Bio-science and Medical Engineering
University Technology Malaysia, Malaysia
Email: jaganathaniitkgp@gmail.com;
Tel : 00607-5558548; Fax: 07-5558553