

Comments to the Authors:

Editors

1. Table 1: Please separate in vitro and in vivo studies in Table 1a and 1b. Please add further in vivo studies, there is only one presently.

Response: As suggested, we have separated Table 1 into Table s1a and 1b. We have also added one more in vivo study in Table 1b. There are only few reports about the potential in vivo effects of bergamottin against malignancies.

2. Please add additional columns for concentration range and time points (in vitro) and treatment schedules (in vivo) and observation time.

Response: As suggested, we have added more experimental details in Table 1 and 1b.

3. According to Fig. 3 bergamottin does 'all and everything'. Please be more precise and add signaling paths in more detail.

Response: As suggested, we have changed Fig. 3.

4. Please add considerations of PK interactions with anti-cancer agents that are relevant for anti-cancer agents' metabolism and efficacy.

Response: As suggested, we have now briefly mentioned PK interactions with anti-cancer agents in "Introduction".

Reviewer: 1

Jeong-Hyeon Ko et al. summarized the anti-cancer effects of bergamottin against many types of cancer. The authors could add more experimental details for each study cited in Table 1, such as dosage and length of treatment. Also the authors could discuss more in vivo studies if there are any. The author could discuss the studies using whole grapefruits in comparison with bergamottin if there are any. Overall, this manuscript reviewed adequate studies and is well-written.

Response: We appreciate that the reviewer's comments. As suggested, we added more information about dose and duration of treatment and added one more in vivo study in Table 1. There is no study using whole grapefruit in comparison with bergamottin.

Reviewer: 2

This is an interesting review manuscript about the anticancer potential of the natural coumarin bergamottin. Easily available natural products can feature suitable supplements for common cancer therapies. I recommend acceptance after minor revision:

1. Keywords: please correct ‘‘photochemicals’’.

Response: We appreciate that the reviewer’s comments. We have corrected it now.

2. The authors mentioned the cancerogenic effects of furanocoumarins. Please discuss or mention briefly if bergamottin itself has documented mutagenic or cancerogenic potential.

Response: As suggested, we have discussed it in section “Bergamottin and cancer”.

3. Section ‘‘Bergamottin and cancer’’, Table 1: please reorder this section and table 1. For example, put the hematological malignancies first/on the top and then solid tumor diseases below.

Response: As suggested, we have rearranged it under section ‘‘Bergamottin and cancer’’.

Reviewer: 3

This review manuscript is well organized and can be published in its current form. The paper summarizes the preventive activity of bergamottin in the distinct cancer types and covers most of the published papers in this area. Only 3 review papers can be found in PubMed that discuss bergamottin and cancer and in fact only one is dedicated for this topic directly. This review is unique as it discusses the mechanism of action of the anti-neoplastic activity of bergamottin.

Response: We appreciate that the reviewer’s comments.

Reviewer: 4

The publication is an important collection of information on the risks of cancer. The authors describe the possibilities of clinical use of bergamottin in cancer therapy. This publication is an important for scientific reasons and has a clinical aspect.

Response: We appreciate that the reviewer’s comments.