

RESPONSE TO REVIEWER #1

Comment 1: Line 20.....a simulated inflammatory microenvironment induced by proinflammatory cytokines (IL- 1 β , IL-6, TNF- α)... author must provide the full name before using this abbreviation.

Response 1:

Thank you for this observation. In the revised manuscript, we have provided the full names of the cytokines before their abbreviations (line 20): “...*interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumour necrosis factor- α (TNF)*...”.

In addition, the abstract has been briefly modified to comply with the journal’s 200-word limit.

Comments 2: Author must include the chemical structures of the ellagic acid and punicalagin.

Response 2:

We appreciate this suggestion. The chemical structures of ellagic acid and punicalagin have been added as Figure 5 in the *Materials and Methods* section (‘4.1. Preparation and Dilution of Treatment Solutions’) to enhance clarity of the compounds used in this study.

Comment 3: Author showed the cell proliferation of fibroblasts under SIM conditions. Any explanation for why the cell proliferation was less at 10⁻⁷M as compared to 10⁻⁶ M dose treatments for PUN.

Response 3:

We agree that proliferation was slightly lower than 10⁻⁷ M compared to 10⁻⁶ M. Although the study showed that both compounds significantly increased the viability and migration of fibroblasts under inflammatory conditions, it is true that some natural compounds may exhibit a nonlinear or biphasic concentration-dependent response that is frequently observed in polyphenolic compounds, potentially acting through hormetic mechanisms, in which lower concentrations can sometimes cause attenuated effects

compared to higher concentrations. We have added a paragraph in the *Discussion* section to clarify this point and have referenced the relevant literature on the biphasic dose-response effects of these polyphenols (line 171).

Comment 4: Similarly, the measured IL-1 β and IL-6 levels in the supernatants of human fibroblast cultures treated with ellagic acid (EA) or punicalagin (PUN) at concentrations of 10⁻⁶ M and 10⁻⁷ M in the presence of LPS showed the more suppression of IL-1 β and IL-6 in case of EA 10⁻⁷M and PUN 10⁻⁷M, respectively as compared to higher dose of EA and PUN (i.e 10⁻⁶ M). Same was observed for migration studies of fibroblasts where PUN was much more effective at lower concentration than the higher concentration.

Response 4:

Thank you for this comment. We agree this apparent paradox deserves clarification. Studies have reported results consistent with the phenomenon of hormesis or biphasic responses, in which at low/moderate doses, some phenols act as signaling molecules/inducers of protective and repair pathways, while at higher doses they can behave as pro-oxidants or activate apoptosis in sensitive cells, which supports the nonlinear effects observed in our work. We have expanded the *Discussion* section to highlight this aspect and provide references supporting this phenomenon (line 171).

Comment 5: The ellagic acid and punicalagin compounds did not showed any antimicrobial activities at the tested concentration. Did author have tested these compounds at any higher concentrations for antimicrobial activities in Staphylococcus aureus if not please check the result at higher concentrations? Or any other microbes had been tested?

Response 5:

We sincerely appreciate your valuable suggestion and the opportunity to clarify this point. In preliminary work, we tested both compounds at different concentrations up to 10⁻² M against *Candida albicans*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. No zones of inhibition were observed in any case. These results confirmed that ellagic acid and punicalagin lacked direct antimicrobial activity even at much higher

concentrations, so we chose to use only the lowest non-cytotoxic concentrations (10^{-6} and 10^{-7} M) in the assays presented in the manuscript.