REVIEWER 1.
Comments and Suggestions for Authors
Dear Authors of "Hydroxytyrosol Interference with Inflammaging via Modulation of Inflammation and Autophagy":

The proposed topic is quite interesting and innovative. English language is good and only minor style and spell errors have been detected. However, I find some points that need probable revision interventions:

Major issues:
1. To include some clinical studies although Hydroxytyrosol is administered with other antioxidant compounds, e.g.: Mosca A, Crudele A, Smeriglio A, Braghini MR, Panera N, Comparcola D, Alterio A, Sartorelli MR, Tozzi G, Raponi M, Trombetta D, Alisi A. Antioxidant activity of Hydroxytyrosol and Vitamin E reduces systemic inflammation in children with paediatric NAFLD. Dig Liver Dis. 2021 Sep;53(9):1154-1158. doi: 10.1016/j.dld.2020.09.021. Epub 2020 Oct 13. PMID: 33060043.
Response to point 1. Done, look at ref. 180.

2. To include a graphical abstract to sum up all the biological processes and main molecular mechanisms regulated by Hydroxytyrosol to prevent and/or treat different pathologies included in the manuscript.
Response to point 2. Done, look at "Graphical Abstract".

3. To explain in more detail the tissue expression of NLRP3 and how it is activated under different stressor stimuli
Response to point 3. NLRP3 is a cytoplasmic pattern-recognition receptor (PRR) and, as the receptors of innate immunity, is mainly expressed by innate immune cells such as monocytes, macrophages, dendritic cells and neutrophils. However, it can also be expressed by T lymphocytes and plasma cells, as well as by non-immune cells, including endothelial cells, fibroblasts, muscle cells, adipose progenitor cells, adipocytes. Therefore, NLRP3 is expressed by several tissues, such as adipose tissue, muscles, heart, kidney, liver, lung, pancreas and skin.
NLRP3 inflammasome formation is triggered by pathogen-associated molecular patterns/PAMPs or damage-associated molecular patterns/DAMPs, which are generated by endogenous stress, tissue damage, or metabolic imbalances, and trigger downstream inflammatory pathways to eliminate microbial infection and repair damaged tissues (*Blevins HM, Xu Y, Biby S, Zhang S The NLRP3 Inflammasome Pathway: A Review of Mechanisms and Inhibitors for the Treatment of Inflammatory Diseases. Front Aging Neurosci. 2022 Jun 10;14:879021.*) However, how NLRP3 responds to those signaling events and initiates the assembly of the NLRP3 inflammasome is not fully understood (*Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. Int J Mol Sci. 2019 Jul 6;20(13):3328*).
Therefore, in chapter 3.1., page 6, we have changed and added as follows:
"Inflammasomes are a family of intracellular multi-protein complexes, belonging to the family of cytoplasmic innate immune receptors, which activate inflammatory caspases [88]. The NLRP3 inflammasome is mainly expressed by inflammatory innate immune cells such as monocytes/macrophages, dendritic cells and neutrophils. However, it can be also expressed by T lymphocytes and plasma cells, as well as by non-immune cells, including endothelial cells, fibroblasts, muscle cells, adipose progenitor cells and adipocytes. NLRP3 inflammasome formation, whose signaling events and way of assembly are not fully understood, is triggered by pathogen- or damage- associated molecular patterns, which are generated by endogenous stress, tissue damage, or metabolic imbalances. Thus, once the NLRP3 protein complex has formed, it activates caspase-1,

which initiates the processing and the release of active IL-1β and IL-18 pro-inflammatory cytokines."

Minor issues:

1. To write "in vitro" and "in vivo" in italics in all the manuscript

Response to point 1. Done.

2. The sentence "Moreover, Per-HTyr suppressed the activation of the non-canonical NLRP3 inflammasome (which inhibits caspase-11), decreasing thus the IL-18 pro-inflammatory cytokine level" is not well expressed. Please, reformulate it.

Response to point 2. Activation of the NLRP3 inflammasome through canonical and non-canonical pathways has the same effects, but through different mechanisms. The non-canonical pathway results in inflammasome formation mediated by human caspase-4, caspase-5, and mouse caspase-11 (also called caspase-4/11).

Therefore, in chapter 3.2.1., page 8, we have reformulated the sentence as follows:

"Moreover, Per-HTyr suppressed the activation of the non-canonical NLRP3 inflammasome (which has the same effect as the canonical NLRP3, but it is mediated by caspase-11 instead of caspase-1), decreasing thus the IL-18 pro-inflammatory cytokine level"

3. Line 361: The word "p65NF-B" is not well-written.

Response to point 3. We have corrected.

4. Line 507: "4.2. HTyr as **a** Modulatory Agent of Autophagy"

Response to point 4. We have corrected.

5. Table 3: Chemical Carcinogenesis in Human Primary Colonic Epithelial Cells: HCoEpC + B[a]P: autophagy via????

Response to point 5. In the experimental model of Human Primary Colonic Epithelial Cells: HCoEpC + B[a]P, HTyr inhibits autophagy via inhibition of "mTOR, which can directly activate a variety of cellular effectors, including the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), to inhibit autophagy [81, 144]", as we reported in chapter 4.1, page 13.

6. The title of reference 72 is duplicated

Response to point 6. We have deleted the duplicated title.

7. To change mTORC1 instead of mTOR in both lines 447 and 453

Response to point 7. Done.