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Letter to the Editor

Response to "Quercetin and Nano Quercetin: Cytotoxicity, Antileishmanial and Antimicrobial Activities against Resistance Strains: Insights and Future Directions"

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Dear Editor-in-Chief

We would like to sincerely thank the author of the Letter to the Editor for the careful interpretation of our published article (1) and for his thoughtful and constructive comments. Regarding the proposed investigations into the mechanisms of action of nano-quercetin, we agree that studies focusing on apoptosis induction, reactive oxygen species (ROS) generation, and relevant molecular pathways could offer valuable insights into its biological activity. However, the primary objective of the present study was to evaluate the *in vitro* efficacy and cytotoxicity of nano-quercetin. Mechanistic investigations were beyond the scope of the present study and will be further explored in our future research.

Furthermore, investigation of alterations in membrane permeability, efflux pump inhibition, and ultrastructural changes using advanced techniques such as electron microscopy would undoubtedly contribute to a more

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comprehensive understanding of the antibacterial activity of nano-quercetin. These aspects will be addressed in our future investigations.

We sincerely thank the author for highlighting the importance of reporting the Selectivity Index (SI). Although SI is an important parameter for assessing the therapeutic selectivity of an anti-leishmanial compound, its reliable determination requires a CC_{50} value derived from an appropriate cytotoxicity dose–response curve. In the present preliminary study, cytotoxicity was assessed at the tested concentrations; however, sufficient cytotoxicity was not observed even at the highest concentration evaluated to reliably determine a CC_{50} value. Therefore, a definitive SI could not be calculated from the available cytotoxicity data. We agree that determination and comprehensive reporting of SI would provide valuable information regarding the therapeutic window of nano-quercetin, and this will be specifically addressed in our ongoing and future studies.

We fully agree that *in vivo* studies are essential before clinical translation. The present study was designed as an introductory *in vitro* examination of the anti-leishmanial activity and cytotoxicity of nano-quercetin. Future studies using appropriate animal models will comprehensively evaluate its therapeutic efficacy and systemic and tissue toxicity, particularly in sensitive and vital organs, through histopathological and relevant biochemical assessments. Different treatment and control groups will also be included to evaluate dose-dependent efficacy and safety. In addition, comprehensive physicochemical characterization, including particle size, morphology, zeta potential, polydispersity index (PDI), encapsulation efficiency, and *in vitro* release profile, as well as stability studies under different storage conditions, will be performed to further establish the safety, stability, and potential of nano-quercetin for preclinical development and eventual clinical application.

Regarding nanoparticle characterization, we appreciate and agree with the author's comment that additional physicochemical parameters, including zeta potential, PDI, encapsulation efficiency, *in vitro* release profile, and storage stability, would provide a more comprehensive characterization of the nanoformulation. However, the primary objective of the present study was to evaluate the *in vitro* anti-leishmanial activity and cytotoxicity of nano-quercetin, rather than to develop or optimize a pharmaceutical formulation. Therefore, the characterization parameters reported, particularly particle size and morphology, were considered appropriate for the scope of this preliminary study. Nevertheless, these additional parameters are currently being investigated in a separate research project specifically focused on the formulation and optimization of nano-quercetin, the results of which have not yet been published.

A follow-up study is currently underway within our research group. This ongoing project has been designed to further investigate several aspects highlighted in the present Letter, including the underlying mechanisms of action, comprehensive physicochemical characterization of the nanoformulation, and validation of the findings in experimental models. We believe that the results of this second study will provide a more comprehensive understanding of the therapeutic potential of nano-quercetin and address some of the inherent limitations of the current *in vitro* investigation.

Conflict of Interest

The author declares no conflict of interest.

Reference

1. Hanif H, Javani Jouni F, Zafari J, Rahimi Esboei B, Mousavi P, Vazini H. Quercetin and nano quercetin: Cytotoxicity, antileishmanial and antimicrobial activities against resistance strains. Iran J Parasitol. 2025;20(1):8-16.