

Response to the reviewer's comments

14 October 2024

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Title : Mangiferin represses inflammation in macrophages under a hyperglycemic environment through Nrf2 signaling
Authors : Jayasuriya R, Ganesan K, and Ramkumar KM*

Response to comments from reviewer #1

Comments: In this manuscript, Jayasuriya et al. report that Mangiferin suppresses hyperglycemia-induced macrophage activation through the induction of the Nrf2 signaling pathway. Overall, the authors address an interesting and relevant topic. The experiments are well designed, and the result is clearly written. The conclusions drawn are consistent with the observations presented. However, the manuscript's impact is somewhat limited by the fact that the activation of the Nrf2 signaling pathway by Mangiferin is already well documented, and the study offers little in terms of novel mechanistic insights into Mangiferin's mode of action. Additionally, a similar pathway has been previously reported by the same group in the context of preventing hyperglycemia-induced endothelial cell injury.

Response: Thank you for spending your valuable time in reviewing the manuscript. While we previously studied the effect of mangiferin on angiogenesis using hyperglycemia-induced endothelial cells as a model, the current study focuses on elucidating the anti-inflammatory action of mangiferin, where hyperglycemia-induced macrophages are chosen as the primary cell model. Further, we have done our best to address all your concerns and revised the manuscript as much as possible.

Comment 1: Moreover, it remains unclear whether the in vitro findings can be translated to in vivo situations, which is a significant limitation.

Response: We understand that in vivo findings are necessary to validate mangiferin's efficacy over diabetic wounds, especially over the inflammation. The current study mainly focusses on the mechanistic action of macrophages over hyperglycemia

microenvironment, and the effect of mangiferin in it. We agree with the reviewer and we condider this in our future prosects.

Comment 2: Given the close relevance to diabetic pathology, the manuscript may still hold value for acceptance with minor revisions.

Minor comments:

Typographical errors should be corrected, such as:

- Line 309: "bar graph" instead of "bar gram."
- Line 187: " 2×10^5 " should be formatted correctly.

Response: As per the reviewer's suggestion, we have made necessary corrections and uploaded the revised version of our manuscript.

Comment 3: The authors should also clarify why control Mangiferin significantly increases macrophage migration and invasion (Fig. 7).

Response: Mangiferin regulates various pathways including PI3K/AKT which is involved in regulation of cell migration and invasion. Additionally mangiferin activates basal Nrf2 level that has a key role in cell migration, which would support macrophage movement.

