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April 27, 2021

Dear Editor,

We are very grateful for the helpful comments provided by the reviewers to our manuscript titled **"Exosomal MicroRNAs from Mesenchymal Stem/stromal Cells: Biology and Applications in Neuroprotection"**. Attached please see the revised manuscript with all the reviewers' comments addressed. We have also included a point-to-point response to the reviewers' concerns. The updated and added materials are in blue. We wish the revised manuscript would meet the requisites for publication in ***World Journal of Stem Cells***.

Please do not hesitate to let me know if you or the reviewers have any other questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Aijun Wang".

**Aijun Wang, PhD**  
Associate Professor  
Co-Director, Surgical Bioengineering Laboratory  
University of California, Davis

## REVIEWER REPORT(S):

### Comments to the Author

The review is well written using fluid language, and the title chosen is regarded as one of the important titles that have begun to attract attention in recent years due to its importance and applications.

On the other hand, there are issues that need to be clarified and added:

1) When we talk about MSC as a topic of interest to research, we start with one of the known definitions and its types.

**Response:** We really appreciate the reviewer for the suggestion. We replaced the starting sentence with the following, "Mesenchymal stem/stromal cells (MSCs) are multipotent stem cells with self-renewing capacities that can be isolated from a variety of human tissues including adipose, peripheral blood, muscle, amniotic fluid, placenta, skin, and dental pulp (1–3)."

2) The second point, as selecting a specific Exosomal miRNA group, we are expecting at least one rationale for this selection , especially as there are many other Exosomal miRNAs.

**Response:** We thank the reviewer very much for the comments. We end the "MSC-DERIVED EXOSOMAL miRNAs" section with the following sentence, "In this study the clinically relevant miRNAs were selected based on their involvement in neurological pathologies and their potential translational applications in neurodegenerative pathways."

3) The authors referred to EVs, it could also be appropriate to mention other types other than Exosomal miRNA.

**Response:** We thank the reviewer very much for this important comment. We added the following section to the introduction, "EVs are membrane-bound vesicles secreted by cells and can be categorized into three subtypes, exosomes (50–150 nm), microvesicles (100–1000 nm), and apoptotic bodies (500–5000 nm) Apoptotic bodies are formed during the late stages of apoptosis and contain intact organelles and chromatin along with small amounts of glycosylated proteins [1]. Exosomes and microvesicles are involved in the transfer of biological information and have shown to have potentials in the treatment of neurological disorders [2,3]."

-The method used in that review was not explained in detail, or whether it was included or excluded criteria.

**Response:** We really appreciate the reviewer's comment. We added the following section to the introduction, "English language peer reviewed studies on neuroprotective MSC-derived exosomal miRNAs were located through PubMed online search using keywords: mesenchymal stem cells, extracellular vesicles, and miRNA. This review includes papers in the past decade that studied neuroprotective potential of MSC-derived exosomal miRNAs and did not exclude studies on basis of methodologies. Letters and conference abstracts were excluded."

5) The relationship of MSC types and its source with Exosomal miRNA was not addressed in some details.

**Response:** We thank the reviewer very much for this important suggestion. Based on our online research there is a gap in knowledge regarding the relationship of MSC types and its source with exosomal miRNA. We added the following section to the discussion section, “The content and yield of exosomes vary depending on the cell that they are derived from. For instance, exosomes from amniotic fluid stem cells had 1.3 times more particles/mL compared to BM-MSCs <sup>[4]</sup>. The variation in the neuroprotective effect of exosomes derived from different sources also shows that the composition of exosomes depends on the origin of MSCs. For example, a study compared the effect of MSC-derived exosomes harvested from bone marrow, umbilical cord, chorionic, and menstrual fluid on neurite outgrowth. It was shown that exosomes derived from menstrual-MSCs and BM-MSCs increased the rate of neurite growth while umbilical cord and chorionic stem cell-derived exosomes did not show any changes in neurite growth <sup>[5]</sup>. Although it is clear that the exosomal content varies depending on the origin of the MSCs, the relationship between the sources of MSCs and their exosomal miRNA content needs to be investigated in the future studies.”

Editorial Office Comments:

1) The “Author Contributions” section is missing. Please provide the author contributions;

**Response:** We appreciate this comment. Author contribution has been added as “Author Contributions: Conceptualization— A.W and A.N.; writing—original draft preparation, A.N.; writing—drafting, editing and revising, A.N., P.K.; L.R.; K.C.; D.H.; S.V.L and A.W.; visualization, A.N.”

2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

**Response:** We appreciate the reviewer’s comment. The grant application has been uploaded.

3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Response:** We appreciate the reviewer very much for this suggestion. The images are provided in PowerPoint format.

4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

**Response:** We thank the reviewer very much for this suggestion. The authors’ names, PMID and DOI were added to the reference list.

5) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published.

**Response:** We thank the reviewer very much for this suggestion. All the images are made by the authors and none of the images are reused from outside sources.