Dear editor and reviewers,

We would like to thank *World Journal of Stem Cells* for giving us the opportunity to revise our manuscript entitled **"The multifunctional role of microRNA in mesenchymal stem cell derived-exosomes in the treatment of diseases"**. We appreciate all of the reviewers' comments and thoughtful suggestions. Additionally, we thank the editor for giving us the chance to revise it. We have learnt from these suggestions and comments, which have proved valuable for our future research. We have carefully considered and addressed the concerns raised by the reviewers and the editor; the amendments are highlighted in red font in the revised manuscript. Additionally, the English language has been further edited by Editage (www.editage.cn). A summary of revisions and responses follows below.

Editor and Reviewer comments:

Reviewer #1's comments:

In this review, the authors described mainly the association of microRNA in Mesenchymal stem cell (MSC) derived exosomes with diseases. Firstly, the authors provided general information about exosomes and miRNA, then focused on the function of miRNA in MSC derived exosome. Subsequently, the authors touched upon the prospects for its therapeutic potential for some diseases. Overall, this review is well-written and I believe this paper would be suitable for publication after several improvements.

Authors' response: We are grateful for the **Reviewer #1**'s praise and encouragement about our draft, and we appreciate your professional comment. Your advice is critical for us and could facilitate the use of mesenchymal stem cell-based therapies in translational medicine, helping researchers understand the important mechanisms by which stem cell-derived exosomes treat diseases.

Major comments The authors explained that miRNAs in MSC derived exosomes can affect several biophysical functions, such as regulation of

inflammation, injury repair, and tumor. However, the description of its potential target diseases is insufficient. MSC transplantation has already been put into practical use in some diseases such as graft-versus-host disease after bone marrow transplantation.

Authors' response:

Thank you very much for the scrupulous investigation and helpful suggestion.To your recommendation of "Description of its potential Target Diseases is insufficient", we have added another paragraph named "Other Diseases" to the body, which also introduced several other diseases.These diseases, including Alzheimer's disease[1], Graft-versus-host disease[2], and fibrotic diseases[3-5], have been found to be treated by exosomes from MSC sources in addition to stem cells. This discovery gives us a broad understanding of the role of exosomes from MSC sources.This change is shown in red in the text.

In addition, several MSC transplantation therapies for liver cirrhosis are recently under clinical trials (Tsuchiya et al. Inflamm Regen. 2019, 39: 18 doi: 10.1186/s41232-019-0107-z). MSC derived exosomes recently attracted much attention on their roles in a novel therapeutic strategy for a lot of diseases because it is expected to exhibit potentially a similar effect to MSC transplantation. In fact, in animal disease models, several researches using animal disease models reportedly showed the effect of the miRNAs in MSC derived exosomes (Donald et al. Stem Cells. 2017, 35: 851-858). Therefore, authors should mention a possibility of clinical applications for miRNAs in MSC derived exosomes and their targeted diseases more specifically, and summarize the combinations of the miRNAs and the candidate diseases, then create a schema or a summary table. Minor comments.

Authors' response: Thank you for your valuable advice. Your suggestion will make the whole article more colorful and greatly improve the overall quality of the article. The two recommended references have been added at the revised manuscript (Ref. 82 and Ref. 137). Indeed, microRNA in exosomes derived from MSCS

mentioned in the manuscript is mostly derived from animal models for the treatment of diseases, and the reference value is insufficient. Therefore, a Table was added to introduce the clinical trials of exosomes derived from stem cells for the treatment of diseases (Table 2). The additions are highlighted in red in the text.

You would like us to summarize the targeted potential clinical applications of miRNAs in exosomes from MSCs in some diseases. At present, there are limited reports in this regard. I have identified and tabulated some miRNAs associated with stem cell therapy for certain diseases, but some have not yet been reported. If they are to be added, they may need to be combined with bioinformatics analysis. We are sorry that the final revision may not meet your expectations.

1. **In this review, the term "mesenchymal stem cell derived exosomes" were not unified. The authors use only one abbreviation.**

Authors' response: Thank you for pointing out the problem. The term "mesenchymal stem Cell derived Exosomes" is unified into "MSC-exosomes" in the whole text, marked in red.

2. **Several abbreviations were noted without the long forms.**

Authors' response: Thank you very much for the scrupulous investigation and helpful suggestion. The professional terms, including Mammalian Target of rapamycin (mTOR), heat shock protein 70 (HSP70), heat shock protein 90 (HSP90), interleukin-1 (IL-1) and so on, are expressed with their corresponding full names and written in red.

3. **In "Biogenesis of exosomes" section, RAF-1 must be a typo. It should be RAL-1.**

Authors' response: Thank you for your valuable advice. The typo is corrected in "Biogenesis of exosomes" section and marked in red font.

4. **In "Identification of exosomes" section, the long form of AF4 would be**

also a typo.

Authors' response: Thank you for your valuable advice. The typo is corrected in "indentification of exosomes" section and marked in red font.

5. **Several reference numbers were missing.**

Authors' response: Thank you for pointing out the problem. We used the citation editing processing software to re-edit the citation section to ensure the repair of the citation.

Reviewer #2's comments:

This is an interesting review that focused on the role of miRNA in MSC derived exosomes and the methods commonly used to study miRNA in exosomes. The clinical applications of miRNAs from MSC derived exosomes are also discussed. In general, the manuscript is well written.

Authors' response: We are grateful for the **Reviewer #2**'s praise and encouragement about our draft, and we appreciate your professional suggestions.

please revise the English language and check throughout the text for spelling errors.

Authors' response: Thank you for pointing out the problem. We checked the English editing of the full text, and further modified and polished the language, modified the spelling error, and marked the revised part in red. In order to better meet your language requirements, we asked Editage Company (www.editage.cn) to do the polishing for us, and check and modify again after the polishing. All the changes are shown in red in the text.

I would suggest to include a brief discussion on the importance of regulatory mechanisms that could represent a promising target to develop RNA-based therapeutics against tumors (i.e. Barbagallo C et al, Mol Ther Nucleic Acids 2018).

Authors' response: Thank you very much for the scrupulous investigation and helpful suggestion, and you are so enthusiastic to point out the deficiencies of our draft. We added a description of the importance of MSC sources of exosomes treatment mechanisms in "conclusion and prospection" section, which is conducive to more targeted treatment of diseases. By overexpression of specific microRNA, targeted tumors or other refractory diseases have been reported[6-9]. The reviewer's suggestion was very good, highlighting the significance of this manuscript.

Editorial Office's comments:

(1) I found 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);

Authors' response: Thank you for pointing out the problem. We will upload the approved grant application forms in time.

(2) I found the authors did not provide the original figures. 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;

Authors' response: Thank you very much for the scrupulous investigation and helpful suggestions. The original figures for this article were completed in Adobe Illustrator (AI), and we have added them to Powerpoint and reedited the text on Powerpoint. If needed, we will upload the original AI files.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

(4) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

Authors' response: Thank you for pointing out the problem. We have used professional literature processing software, according to the requirements of your journal, re-edited the citation format, and generated PMID code and DOI code. We are very sorry for the non-standard citation when I submitted my first manuscript.

References:

1 Nakano M, Kubota K, Kobayashi E, Chikenji TS, Saito Y, Konari N, Fujimiya M. Bone marrow-derived mesenchymal stem cells improve cognitive impairment in an Alzheimer's disease model by increasing the expression of microRNA-146a in hippocampus. Sci Rep 2020 2020-07-01; 10(1): 10772. PMID: 32612165DOI: 10.1038/s41598-020-67460-1.

2 Fujii S, Miura Y, Fujishiro A, Shindo T, Shimazu Y, Hirai H, Tahara H, Takaori-Kondo A, Ichinohe T, Maekawa T. Graft-Versus-Host Disease Amelioration by Human Bone Marrow Mesenchymal Stromal/Stem Cell-Derived Extracellular Vesicles Is Associated with Peripheral Preservation of Naive T Cell Populations. STEM CELLS 2018 2018-03-01; 36(3): 434-445. PMID: 29239062DOI: 10.1002/stem.2759.

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4 Mazhari S, Gitiara A, Baghaei K, Hatami B, Rad RE, Asadirad A, Joharchi K, Tokhanbigli S, Hashemi SM, Łos MJ, Aghdaei HA, Zali MR, Ghavami S. Therapeutic potential of bone marrow-derived mesenchymal stem cells and imatinib in a rat model of liver fibrosis. EUR J PHARMACOL 2020

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8 Wei Z, Qiao S, Zhao J, Liu Y, Li Q, Wei Z, Dai Q, Kang L, Xu B. miRNA-181a over-expression in mesenchymal stem cell-derived exosomes influenced inflammatory response after myocardial ischemia-reperfusion injury. LIFE SCI 2019 2019-09-01; 232: 116632. PMID: 31278944DOI: 10.1016/j.lfs.2019.116632.

9 Mao G, Zhang Z, Hu S, Zhang Z, Chang Z, Huang Z, Liao W, Kang Y. Exosomes derived from miR-92a-3p-overexpressing human mesenchymal stem cells enhance chondrogenesis and suppress cartilage degradation via targeting WNT5A. STEM CELL RES THER 2018 2018-09-26; 9(1): 247. PMID: 30257711DOI: 10.1186/s13287-018-1004-0.

We hope that the revised manuscript is acceptable. We look forward to your decision.

Sincerely yours,

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