

Point by Point Response:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This review has well organized the research progress related to MSCs and MNP, and put forward some of its own insights. But it is suggested that some diagrams and tables can be added to increase the readability of the paper. Overall, this article has demonstrated the progress of the application of MNPs in the field of MSCs, and has a good guiding significance for the follow-up research. It is recommended to be accepted for publication after revision.

Response: We would like to thank the reviewer for the he spent in evaluating our manuscript. Your thorough and constructive feedback is really appreciated. We added a table and a schematic diagram to give more readability and to summarize the content of the manuscript.

(1) Reviewer #2 and Science editor comments:

The authors submitted a review providing a summary the role of MNPs in promoting the therapeutic profile of MSCs from several aspects (tracking, migration and homing, differentiation and regenerative abilities). The topic is not within the scope of the WJCC. There are 0 table and 1 figure. A total of 74 references are cited, including 21 references published in the last 3 years. There is no self-cited reference. No academic misconduct was found by the Bing search. This is an invited manuscript. The title reflects the main subject/hypothesis of the manuscript. The abstract summarizes and reflects the work described in the manuscript. Key words reflect the focus of the manuscript.

Response: We would like to thank you for your critical evaluation of our manuscript, your constructive feedback is highly appreciated.

1-: It is very important to note that the review should not be simply a description of what others have published in the form of a set of summaries, but should take the form of a critical discussion, showing insight and an awareness of differing arguments, theories and approaches. It should be a synthesis and analysis of the relevant published work, linked at all times to your own purpose and rationale. However, in this manuscript, the authors

simply present and list the results that have been published in the past without offering any insights of their own at all. Some specific comments are listed below.

We thank you for this valuable comment. We included a critical discussion covering our anticipated thoughts and insights of prospective work that should be done and the existing uncovered and unanswered topics regarding the use of MNPs with MSCs. This has been highlighted in the revised manuscript.

2- Background, the limitations of MSC therapy are far more than described in this manuscript. Please refer to PMID:35107300, batch heterogeneity, dosage and intervals, implantation time windows, disease status, MSC sources, etc. These should be included to lay out all challenges of MSC therapies for readers to judge.

We thank the reviewer for suggesting this. In the current review we highlighted the challenges that have been found to be solved and improved by using magnetic Nanoparticles. We agreed that there are more challenges facing mesenchymal stem cell therapy, but not all challenges have been investigated with magnetic nanoparticles such as undesirable pre-transplantation differentiation. This is why we focused on these challenge that are extensively studied with magnetic Nanoparticles.

3. As authors described, the sources of MSCs include bone marrow, adipose tissues and umbilical cord. However, in the following few sections describing MSC as a contrast agent to track MSCs, an enhancer to the homing of transplanted MSCs, a helper to the migration abilities of transplanted MSCs, a promoter to the differentiation and survival of transplanted MSCs, authors did not mention the source of MSCs. Are there any differences in effects of magnetic nanoparticles to different sources of MSCs?

We thank you for this valuable suggestion. The source of MSCs has been included in the new summary table and will be uploaded with the revised manuscript. There is sometimes a difference in the response of MSCs to the attached MNPs depending on their source of isolation. A study by Labusca et al showed that the use of Fe₃O₄ magnetite MNPs were effective in inducing Chondrogenesis and reducing senescence in adipose derived mesenchymal stem cells with no similar effects reported in Wharton- jelly mesenchymal stem cells. Fan et al studied the differences in intracellular iron content, labeling efficiency, cell viability, and Adipogenic and osteogenic differentiation potentials between adipose-derived mesenchymal stem cells (AD-MSCs) and bone marrow derived mesenchymal stem cells (BM-MSCs) after labelling them with superparamagnetic iron oxide nanoparticles (SPIOs). They found no significant differences between SPIO-labeled AD-MSCs and SPIO-labelled BM-MSCs in terms of labeling efficiency, intracellular iron content, survival, proliferation, differentiation, and MRI imaging. This indicated that the type of MNPs and source of MSCs can affect the final therapeutic outcomes that can result from combining both. More comparative studies are needed to address the differences in MSCs response to MNPs based on their source of extraction. This has been highlighted in the manuscript.

4. Schematic illustration is good for understanding but it is too simple. The authors should describe the structure of magnetic nanoparticles and how they link to MSCs. It is suggested that some diagrams and tables can be added to increase the readability of the paper.

We totally agree with you. A table that summarizes the studies which used MNPs to improve the characteristics of MSCs have been added. Furthermore, two more schematic illustrations have been included to make the manuscript easy to follow. MNPs enter inside MSCs by Endocytosis. MNPs usually are engulfed by MSCs to form endosomes, which are then transformed into Mature multivesicular endosomes (MVEs). The MVEs then combined with lysosomes and got digested and decomposed into Fe³⁺. The free iron released into the cytoplasm of MSCs promoted many cellular pathways to induce their survival, migration, homing, anti-apoptosis and anti-inflammatory, differentiation. The presence of Iron derived from MNPs in the cytoplasm of MSCs can induce de novo endogenous magnetization by overexpressing ferritin which can increase the long-term magnetic effects. These magnetized MSCs can be modulated and guided to enhance their therapeutic outcomes by external magnetic fields. This has been added to the revised manuscript. The internalization of MNPs inside MSCs can be also achieved by passive diffusion if their particle size is small and by using MNPs that bind specific cell surface immune marker found on MSCs.

5. In many cases, authors did not address how magnetic nanoparticles exert their beneficial functions on MSC function. More mechanisms should be included. These data should be summarized into the schematic illustration to educate readers easily.

We thank you for this insightful comment. The mechanisms that are induced by MNPs have been summarized in a schematic illustration which reflects what have been mentioned in the manuscript.

6. The English of the manuscript needs to be improved to a certain extent. There are some errors in grammar and format in the whole manuscript, especially in the case of letters, subscripts, inconsistencies, etc.

We thank the reviewer for careful evaluation of our manuscript. The English quality has been checked by an expert.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's

comments and the Criteria for Manuscript Revision by Authors. Please be sure to use Reference Citation Analysis (RCA) when revising the manuscript. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. For details on the RCA, please visit the following web site: <https://www.referencecitationanalysis.com/>. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. 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; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list.

We thank the editor –in –Chief for giving us this great chance to revise our manuscript. We believe that our manuscript has been improved significantly based on these comments. We will include a single PowerPoint file in which we added our decomposable schemes. Our schemes have been generated by us and we didn't use any schemes from any published articles. A copyright information will be added to our schemes.

Point by Point response:

We would like to thank the reviewers, Science Editor, and the Editor-in- Chief for constructive and critical evaluation of our manuscript. Your valuable comments are highly appreciated.

Reviewer 1: Authors have revised the manuscript substantially by adding a table and revising the figure. Authors should have uploaded a revised manuscript with highlighted changes. I am impressed by the subject of this mini review. I do not mean to give hard time to authors. To increase the attraction of this manuscript after publication, I do think there are two minor revisions that should be addressed. First, to cite relevant literature on MSC challenges are essential for readers to follow on. But authors refused to do so. Second, for the figure, it is better to show the structure of MNPs as shown in original manuscript. Authors could draw one amplified MNP with outer coat and metallic core beside the existing figure.

Response: We thank the reviewer for his valuable suggestions that help us improving our manuscript. We added the challenges of MSCs therapy in the revised manuscript and we cite the references that addressed these challenges.

Regarding the scheme, we modified it based on your suggestion and we added an amplified MNP in the revised scheme.

Science Editor: 1-With respect to the reference to the Figure, determine if it is the original Figure, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed.

Response: Our scheme that has been added to the revised manuscript is original and not been copied from any published study.

2-The format of the Authors column in the table is incorrect. Please modify it to the correct format. It has been marked in the attached table. All references in the table must be included in the REFERENCES section.

Response: We corrected the format of the Authors' column and cited the related references. The modified table will be uploaded with the revised files.