

**Journal title:** World Journal of Diabetes

**Manuscript NO:** 80553

**Title:** Future Applications of Exosomes Delivering Resolvins and Cytokines in Facilitating Diabetic Foot Ulcer Healing

**Response to the Comments of Reviewer #1**

**Comment:** On manuscript entitled "Future Applications of Exosomes Delivering Resolvins and Cytokines in Facilitating Diabetic Foot Ulcer Healing": In my opinion, the authors have considered all the details of their main topics and have done all the necessary discussions around it well. Moreover, I think that the manuscript is well organized and useful to many interested readers.

**Response:** Thank you for your encouraging comments.

**Response to the Comments of Reviewer #2**

**Comments:** *The authors summarized the therapeutic effects of the intake of resolvins and cytokines via exosomes in the diabetic foot. The article introduces the pathogenesis of the subtypes of diabetes mellitus in a modern and comprehensible manner, as well as the steps in the development of diabetic foot. Then, the molecular and immunological connections between diabetes and inflammation are properly discussed.*

**Response:** Thank you for your encouraging comments.

**Concern 1:** *In the next chapter, the resolvins involved in reducing inflammation and their immunobiological effects are illustrated. In this section, they also cover a number of diseases that are not the subject of the article. Table 1 is also like this.*

**Response:** Thank you for your comments and suggestions. We have modified the text in the revised manuscript and removed Table 1 and the text related to other diseases, as suggested by the reviewer.

**Concern 2:** *The presentation of the structure of exosomes and their therapeutic application in DFU is correct. However, Chapters 4.2 and 4.3 repeatedly deviate from the original objective of the article: in the summary of drug delivery and loading possibilities of exosomes, no mention is made of DM and DFU. In chapter 4.4, the pros and cons of the use of exosomes are also presented through aspects not related to the topic of the article. Chapters 4.5 and 4.6 are correct. The conclusion is also appropriate. I recommend a DFU-focused rewrite of the chapters indicated above. If there is no literature data on DFU, then the indicated chapters should be combined and shortened. It is also necessary to check the grammar of the English language and correct syntactical errors. A major revision is required.*

**Response:** Thank you for your comments and suggestions. We have modified the manuscript as suggested. Sections 4.2 and 4.3 have been merged and the Table has been deleted. Section 4.4 has been modified to discuss the advantages and limitations, though few citations are from different diseases, but we think that they are important to include to highlight the pros and cons to get an insight for designing loaded exosomes for DFUs.

### **Response to the Comments of Reviewer #3**

**Comments:** *It is a valuable review on one important aspect of wound healing in DM patients viz. control of inflammation. As authors rightly pointed out, the healing process is related also to angiogenesis and granulation formation, they could discuss more about these aspects apart from concentrating on exosomes alone.*

**Response:** Thank you for your comments and suggestions. We have included the text related to the role of angiogenesis and granulation tissue in DFU healing in the revised manuscript.

### **Response to the Comments of Reviewer #4:**

**Concern 1:** *Section :Inflammation-resolving mediators should be reduced. Just mention the beneficial effects of resolvins in attenuating inflammation in various inflammatory conditions but the table is not needed.*

**Response:** Thank you for your comment and suggestion. We have modified the text in the section “Inflammation-resolving mediators” and have removed the Table in the revised manuscript.

**Concern 2:** *Section : Future perspectives needs to be more clearly written. The review is related to diabetic foot ulcer healing while the authors report the promising role in the treatment of other inflammatory diseases. Also in this paragraph the table is not necessary.*

**Response:** Thank you for your comments and suggestion. We have revised the section “Future perspectives” and have removed the Table in the revised manuscript.

#### **Response to the Comments of Revision reviewer #**

**Comments:** *I sincerely thank the authors that have responded to all comments and suggestions.*

**Response:** Thank you for your comments and suggestions.

The authors sincerely thank the reviewers for their constructive criticisms. We have responded to all comments and suggestions. We hope that the revised manuscript is now acceptable for publication in the *World Journal of Diabetes*.