Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "**Role of defensins in diabetic wound healing**" (Manuscript NO: 80041). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers' comments areas flowing:

Reviewer #1:

1. The literature regarding anti-microbial peptide is missing and authors have not discussed in detail what are defensins and their properties. Authors did not add literature regarding the expression level of alpha and beta defensins in case of diabetic wound.

Response: Thanks a lot for the reviewer's comments. In fact, since the article type was classified as "MINIREVIEW", we did our best to use a concise language style in the description. There are so many types of antimicrobial peptides with complex properties, which have been discussed in detail previously in much of the literature[Biomolecules 2021; 11:952; Trends in Immunology, 2002,23(6):291-296]. The latest findings on their biological functions are summarized in Table 1. So, we do not

describe them in detail, but only consider them as the primer to the description of defensins so as not to deviate from the main idea of the manuscript. Regarding the expression levels of alpha and beta defensins for diabetic wounds, we have added a sentence in the "CONCLUSIONS" section: " It was obtained through a biopsy that HBD2-4 were overexpressed in the border area of DFUs [25]. Studies generally agree that inadequate HBD expression is associated with poor wound healing, and many methods that promote diabetic wound healing are seemingly carried out by promoting defensins expression [66, 67]. In diabetic wounds, higher HNP1, HNP3, and HNP4 expressions are more common in the central part than in the marginal areas, thus causing a significant increase in IL-8 expression under the influence of advanced glycation end products (AGEs) [29]."

2. Role of defensins with regards to MMP-2 and MMP-9 is very unclear. More studies related to role of defensins and MMP-2 and 9 need to be added.

Response: Thanks for your suggestion. We have tried to Describe this part in more detail: "Studies have suggested that the use of an inhibitor for MMP-2 and MMP-9 accelerates wound healing in diabetic mice by maintaining the balance between systematic inflammation and cytokine biosynthesis [49]. HBD3 may potentially reverse the pathological condition as they have shown an inhibitory effect on MMP-9, which may result from cytotoxicity for dendritic cells in high concentrations [50]. Instead, HBD3 reportedly increases

the expression of MMP-2, which is essential for angiogenesis and prolonged matrix remodeling [20]. To explain these contradictory findings, further clarification and a comprehensive analysis on the mechanism of wound healing is necessary, as well as verification through specific experiments."

3. Authors should address the findings of in vivo diabetic wound models with regards to healing effect of defensins.

Response: Although there are some experimental conclusions about the effect of defensins on cells in high glucose environment, direct application of defensins in animal models of diabetic wounds has not been explored so far. For the findings of in vivo wound models with regards to healing effect of defensins, as shown in Table 1, defensins including HNP1, HBD2 and HBD3 show a positive therapy to accelerate wound healing. Additionally, in order to solve the puzzle raised by the reviewer, we have added the following sentence in the text: "Studies generally agree that inadequate HBD expression is associated with poor wound healing, and many methods that promote diabetic wound healing are seemingly carried out by promoting defensins expression [66, 67]."

4. Mechanistic pathways are also not discussed in a way that they should be. Authors should add a figure that link the role of defensins with the mechanistic pathway which authors discussed to make it more clear.

Response: We have followed reviewer comments to add a figure presenting the

mechanism of action of defensins as follow:

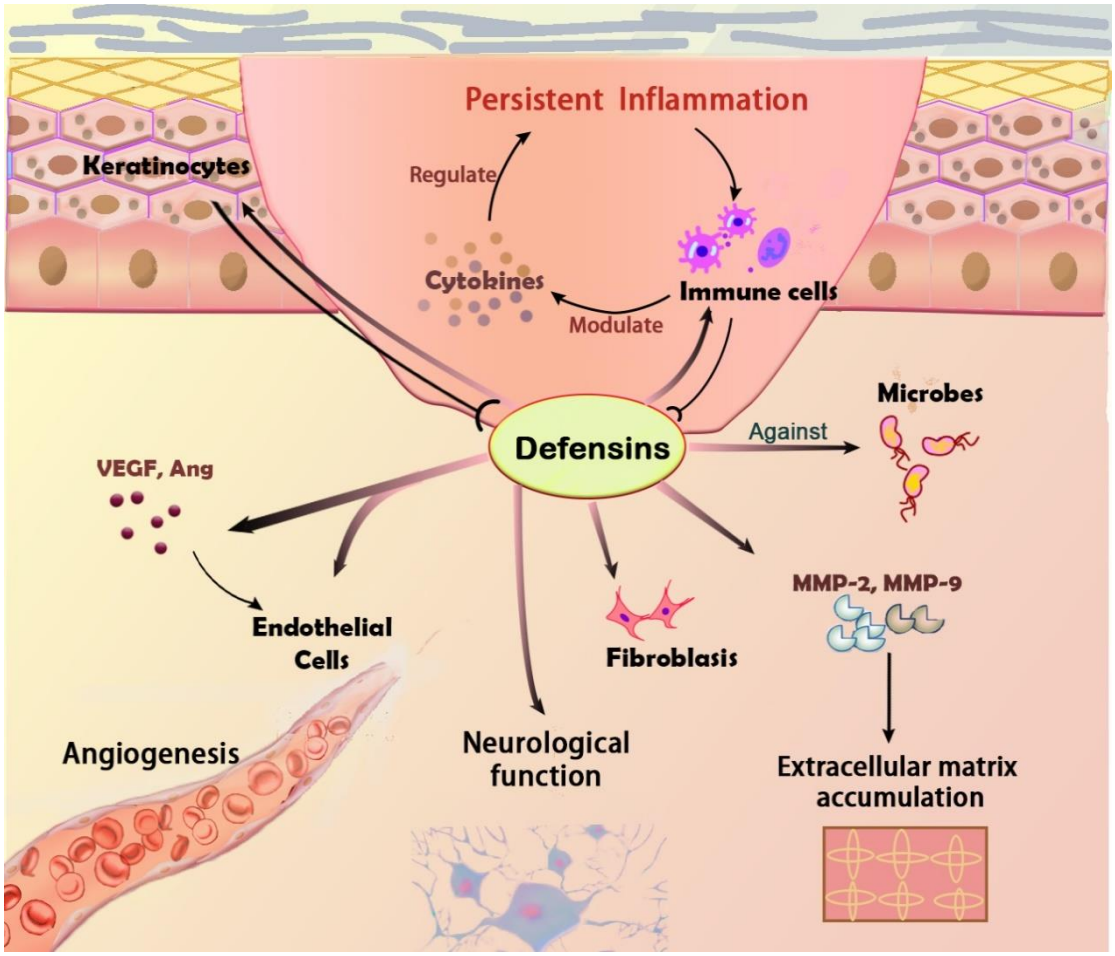

Figure 2 Role of defensins in diabetic wound healing.

Reviewer #2:

The manuscript titled "Role of defensins in diabetic wound healing" is narrative review. The title, abstract and key worlds cover main aspects of the manuscript.

As this is narrative review there is no special methods to be included, however I would ask for the researches search strategies. Yet, as researcher Shen BZ were responsible for navigating the literature and sharing the relevant studies that were included in this review please state the methods.

Response: We have carefully referred to your suggestion, and we are considering including the following sentences at the end: "Research articles on the role of defensins in diabetic wounds, published between inception and September 10, 2022, were collected from various search engines, such as PubMed, Google Scholar, Web of Science, and Science Direct using the following keywords: antimicrobial peptides, defensins, host defense peptides, diabetic, refractory, and chronic wounds, wound healing, etc. Identified studies and relevant citations within these studies were reviewed."

Moreover as in the references (66 numbers) only 27 are from last 5 years it would add more complex informations about the relevant studies were included. Thus discussion about results described by the authors is quite hard to estimate with not known methods strategy. In my opinion the discussion of the found results should be updated - as I wrote only 27 refferences are from last 5 years. The tables and figures are informative and well prapared.

Response: In view of the literature update problem raised by reviewers, we reviewed the content of the article again and focused on the citations before 2017 in the references. We have updated some articles in the article and marked them in red, and the number of citations after 2017 increased to 37 after the adjustment. Occupying a non-negligible part of the cited literature list is the experimentally proven nature of defensins, and we listed the earliest literature although there may be new literature later demonstrating similar conclusions. The remaining citations and contents that

have not been updated are because so far, the relevant research content is too little or the related fields have not been updated too much in the past five years.

Last: I have some doubts to the authors contribution - the "formatting the citations and compilation of the references, verifying spelling, punctuation and grammatical errors" are technical point of article so is it right to be an author of the whole study?

Response: In the writing of this review, our team assigned tasks to each member of the project team. When a member was responsible for "formatting the citations and compilation of the references, verifying spelling, punctuation and grammatical errors", it wasn't mean he only need to complete this task, as a member of the team, he made a lot of auxiliary contributions to the work of other members such as manuscript writing, literature collection and sorting, graphing. Therefore, we consider it eligible for signature. We sincerely apologize for the confusion caused due to the ambiguity in the "Author Contribution". We have revised this section of the description to make the description more detailed.

Author contributions: Tan ZX and Tao Rui wrote the manuscript and proposed research subtopics; Shen BZ was responsible for navigating the literature, sharing the relevant studies, and drawing the tables included in this review; Meng LX and Li SC drew the figures in the manuscript, formatted citations and compiled references, verified spelling, punctuation, and grammatical errors; Zhu ZY revised and formatted the body of the manuscript, and coordinated the whole work.