Reviewer #1: The authors have given a detailed description of the role of Calycosin pretreatment in enhances the therapeutic efficacy of mesenchymal stem cells to alleviate Adriamycin-induced focal segmental glomerulosclerosis by inhibiting podocyte apoptosis. However, there are many flaws and concerns on it. Study can be greatly improved if following suggestions were incorporated.

1. The title of the paper is not accurately expressed, and I think it needs to be rewritten.

Thank you very much for your good advice. I will change the title of the article to "Calycosin synergists bone-marrow-derived mesenchymal stem cells to combat podocyte apoptosis to alleviate Adriamycin-induced focal segmental glomerulosclerosis.", which may be more complete and accurately expressed.

2. Some references missing. For example, “As podocyte injury plays a critical role in FSGS progress, protecting podocytes is promising to prevent ESRD in patients with FSGS.” and etc.

Thank you very much for your good advice. This is of great help to improve the quality of this article. I added references where necessary. For example: “As podocyte injury plays a critical role in FSGS progress, protecting podocytes is promising to prevent ESRD in patients with FSGS.” References is as follows:

Campbell KN, JA Tumlin, Protecting Podocytes: A Key Target for Therapy of Focal Segmental Glomerulosclerosis. Am J Nephrol 2018;47, 14-29[PMID 29852493 doi:10.1159/000481634]

3. In the introduction section, Authors should, in addition to reviewing the results related to MSCs Studies on Focal Segmental Glomerulos Clerosis, presented reviewing to the results of bone marrow-derived MSCs on Focal Segmental Glomerulosclerosis.

Thank you very much for your good advice. I have added the introduction of this aspect: “Bone-marrow-derived mesenchymal stem cells (BMSC) transplantation can attenuate FSGS progression in a rat model of FSGS”. References are as follows:

1. ***Yang RC, XL Zhu, J Wang, F Wan, HQ Zhang, Y Lin, XL Tang, B Zhu, Bone marrow mesenchymal stem cells attenuate the progression of focal segmental glomerulosclerosis in rat models. BMC Nephrol 2018;19, 335[PMID 30466397 doi:10.1186/s12882-018-1137-5]***
2. ***Li Y, Q Liu, ST Ou, WH Wu, LW Gan, Research on mechanism of MAPK signal pathway induced by BMSCs for the proteinuria of rat's kidney, glomerulosclerosis and activity of RAS. Eur Rev Med Pharmacol Sci 2021;25, 795-803[PMID 33577034 doi:10.26355/eurrev_202101_24643]***

4. In order to make the paper more interesting to read, I suggested that the authors could add one graphical abstract to the manuscript.

Thank you very much for your good advice, which greatly improves the readability of the article. I put the graphical abstract in Figure 6M now. In Figure 1A, I described the design, modeling, and grouping methods of the experiment. So, in Figure 6M I focus on describing the discovered phenomena and possible mechanisms. This also achieves the echo from beginning to end.

5. I suggest including clear limitations of the study in the discussion.

Thank you very much for your good advice. I redescribed the limitations of the study in the discussion. I hope that makes it more clearly.As follows:

"There were some limitations to this study. Although we have revealed that MSCs^{CA} improves podocytes apoptosis by inhibiting Smad3 signaling, this study still has certain limitations and the underlying mechanism deserves further exploration. Firstly, how does MSCs^{CA} intervene in the Smad3 signal, directly or indirectly? We speculate that CA may activate the anti-apoptotic activity of MSCs or affect the differentiation, mobilization, and homing of BMSCs as well as the abundance of beneficial exosomes, but the main mechanism and responsible factors are still unknown. Secondly, it is still unclear which molecules in podocytes respond to the activity of MSCs and what their potential relationship with Smad3. Therefore, understanding these mechanisms is conducive in expanding the application of MSCs^{CA}, and we will answer each question

one by one in the future researches."

Reviewer #2: This is a well-designed study showing the positive effect of calycosin on the therapeutic efficacy of mesenchymal stem cells to alleviate Adriamycin-induced focal segmental glomerulosclerosis by inhibiting podocyte apoptosis. The findings in mice model and cultured cells have been validated with desired molecular techniques.

Thank you for your recognition.