**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Diabetes

**Manuscript NO:** 85269

**Title:** Potential role of microRNA-503 in Icariin-mediated prevention of high glucose-induced endoplasmic reticulum stress

**Provenance and peer review:** Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer’s code:** 02817134

**Position:** Editor-in-Chief

**Academic degree:** MD, PhD

**Professional title:** Professor

**Reviewer’s Country/Territory:** United States

**Author’s Country/Territory:** China

**Manuscript submission date:** 2023-04-20

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-05-07 18:50

**Reviewer performed review:** 2023-05-19 09:02

**Review time:** 11 Days and 14 Hours

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<th>Scientific quality</th>
<th>Grade A: Excellent</th>
<th>Grade B: Very good</th>
<th>Grade C: Good</th>
<th>Grade D: Fair</th>
<th>Grade E: Do not publish</th>
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<th>Novelty of this manuscript</th>
<th>Grade A: Excellent</th>
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<th>Grade D: No novelty</th>
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<th>Creativity or innovation of this manuscript</th>
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<th>Grade B: Good</th>
<th>Grade C: Fair</th>
<th>Grade D: No creativity or innovation</th>
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In this study, the authors have investigated the potential molecular mechanism by which Icarin (ICA) prevents high glucose (HG)-induced endoplasmic reticulum (ER) stress-dependent apoptosis by regulating miR-503/SIRT4 axis in primary rat kidney (PRK) cells. This study is potentially interesting and innovative, but the reviewer has several concerns that the authors should address before considering its publication in this journal. 1. The title should be changed since currently it is a conclusive; however, this study was only based on cultured cells, therefore, there was no evidence to support these findings in the cultured cells exposed to only high levels of glucose for 24 or 48 hr with and without ICA can be recaptured in diabetic rats, no evidence whether ICA treatment also regulate the miR-503 and ER stress as seen in the vitro study. Therefore, the authors should not conclude “miR-503 promotes the progression of diabetic nephropathy ……” 2. Abstract: (1) Lacking miR-503 and SIRT4 information in AIM, which two are very important component in this vitro study; (2) Lacking animal model and HG experimental information; (3) Conclusions need to be revised based on what the authors have done and seen. 3. Keywords should include one “Kidney damage” or
“Diabetic kidney injury” 4. Several comments regarding the Introduction, Methods, Results are directly provided in the manuscript. Generally these include (1) need clearly presenting how innovative of this study; (2) clearly presenting the model information for both in vitro and in vivo; lacking information for how many times of the vitro experiments were repeated and whether the cells for each experiments were come from different isolations from the rats (3) Since you do not have DN evidence (renal dysfunction and remodeled kidney pathology), DN should be removed from figures of results; 4) Discussion needs focusing on what you found, do not imply its directly to DN.
PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

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Title: Potential role of microRNA-503 in Icariin-mediated prevention of high glucose-induced endoplasmic reticulum stress

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 05754965

Position: Peer Reviewer

Academic degree: PhD

Professional title: Postdoc

Reviewer’s Country/Territory: United States

Author’s Country/Territory: China

Manuscript submission date: 2023-04-20

Reviewer chosen by: Geng-Long Liu

Reviewer accepted review: 2023-05-27 00:45

Reviewer performed review: 2023-06-01 00:54

Review time: 5 Days

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In this study, Su et al investigated the mechanism of Icariin to regulate apoptosis in high glucose (HG)-induced primary rat kidney cells (PRKs). Firstly, the authors identified miR-503 to be upregulated in diabetic nephropathy. Then they showed that Icariin treatment could repress miR-503. Next, they provided data to show that SIRT4 is a target of miR-503. In summary, they identified a Icariin/miR-503/SIRT4 in diabetic nephropathy. Here I have the following concerns about this study. 1. A major issue is that there were little data to demonstrate the role of miR-503 in the pathology of diabetic nephropathy. This should be a necessary part for this research. Authors only revealed the correlation between miR-503 level and diabetic nephropathy. The causative data between them is required. They need to prove that miR-503 contribute to diabetic nephropathy. 2. ERS could not be only determined by the expression of CHOP. Other markers are needed. 3. The role of miR-503 on the expression of SIRT4 should be demonstrated in different cell lines. 4. If the authors can validate their results in vivo, that will be better. 5. In fig 3E, the SIRT4 band seemed over-exposed. Please replace it with a less-exposed band. 6. In fig 4C, authors need to mark “SIRT4 WT” and “SIRT4
“Mut”. In the manuscript and figure legend, this luciferase assay should be depicted in detail. 7. The expression “HG induction” is confusing and not appropriate. Authors need to revise it.
Name of journal: World Journal of Diabetes

Manuscript NO: 85269

Title: Potential role of microRNA-503 in Icariin-mediated prevention of high glucose-induced endoplasmic reticulum stress

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 05452652
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer’s Country/Territory: India
Author’s Country/Territory: China
Manuscript submission date: 2023-04-20
Reviewer chosen by: Geng-Long Liu
Reviewer accepted review: 2023-05-31 08:59
Reviewer performed review: 2023-06-01 01:42
Review time: 16 Hours

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### Specific Comments to Authors

This study can be accepted in the present format. It will be of interest to the clinicians and researchers and also help in developing newer drugs for prevention and treatment of diabetic nephropathy. Congratulations to these authors for an excellent study demonstrating the molecular mechanisms for development of nephropathy in diabetes and potential role of ICAn in the management of diabetic nephropathy.
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Reviewer’s code: 05754965
Position: Peer Reviewer
Academic degree: PhD
Professional title: Postdoc
Reviewer’s Country/Territory: United States
Author’s Country/Territory: China
Manuscript submission date: 2023-04-20
Reviewer chosen by: Jia-Ru Fan
Reviewer accepted review: 2023-06-13 13:54
Reviewer performed review: 2023-06-13 13:58
Review time: 1 Hour

| Scientific quality          | [ ] Grade A: Excellent | [ ] Grade B: Very good | [ ] Grade C: Good |
|                            | [ ] Grade D: Fair      | [ ] Grade E: Do not publish |
| Language quality           | [ ] Grade A: Priority publishing | [ ] Grade B: Minor language polishing |
|                            | [ ] Grade C: A great deal of language polishing | [ ] Grade D: Rejection |
| Conclusion                 | [ ] Accept (High priority) | [ ] Accept (General priority) |
|                            | [ ] Minor revision     | [ ] Major revision      | [ ] Rejection |
| Peer-reviewer              | Peer-Review: [ ] Anonymous | [ ] Onymous |
SPECIFIC COMMENTS TO AUTHORS

This version can be accepted now.