

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

**Manuscript NO:** 68694

**Manuscript Type:** REVIEW

**Editor in Chief,**

Thank you for considering this manuscript for publication in the *World Journal of Diabetes*. The authors would like to thank the reviewers for their valuable comments that helped us to present current manuscript in a better way. All points addressed by the reviewers were answered and every addition/modification is highlighted in the manuscript whenever possible. I hope that our replies will be satisfactory. We look forward to your positive feedback.

**Sincerely,**

Mona F. El-Azab

### **Response to reviewer's comments**

#### **Reviewer # 1:**

##### **Comments to the authors**

The article with the title “The Role of Cannabinoids and the Endocannabinoid System in Modulation of Diabetic Cardiomyopathy” is in generally well done, but I would offer these comments to the investigators:

1. Several words throughout the manuscript appear to be merged. Please correct it.

**Response:** The manuscript was revised, and any merged words were rectified.

2. Some minor grammatical errors occur. The manuscript contains significant language-related issues. Please correct these types of grammatical errors throughout the paper.

**Response:** The manuscript was revised, and all grammatical errors were corrected.

2. The references are quite old. Please add or replace some of the current references with more recent articles.

**Response:** References were updated; new recent references and self-cited references were added while some of the old references were replaced.

4. I strongly suggest to add some figures and tables which summarize the main topic of the manuscript.

**Response:** Four figures and 2 tables summarizing the main topics of the article were added and properly cited.

5. In the section “3.5. Autophagy” authors should explain the main step of autophagosome formation.

**Response:** As recommended by the reviewer, the main steps of autophagosome formation were explained briefly in page 20, the before last paragraph. References were inserted accordingly.

6. In the section “3.5. Autophagy” authors should add details about the role of ATGs and some autophagy markers such as Beclin-1, LC3 and p62.

**Response:** As suggested by the reviewer, details about the role of autophagy-related (ATG) genes, ubiquitin-like yeast protein LC3, Beclin-1, p62 and other proteins involved in the regulation of autophagy were added on page 20 (last paragraph) and on page 21 (1<sup>st</sup> and 2<sup>nd</sup> paragraphs). References were updated accordingly.

7. The titles of section and sub-section of the manuscript must be revised in order to reflect more accurate information.

**Response:** Authors would like to thank the reviewer for this remark. The titles were revised, and the numbers were removed to comply with the journal format.

## **Reviewer # 2:**

### **Comments to the authors**

This article aims to elucidate the possible mechanisms through which cannabinoids and the endocannabinoid system could interact with the pathogenesis and the development of diabetic cardiomyopathy. Better understanding of the role of

cannabinoids and the endocannabinoid system in diabetic cardiomyopathy may provide novel strategies to manipulate such a serious diabetic complication. This article has a clear logic and a comprehensive summary, but there are still some small problems.

1. In the introduction section, the description of diabetic cardiomyopathy and cannabinoids and the endocannabinoid system can be simplified.

**Response:** The authors would like to confirm with the reviewer if the “introduction section” is meant in this comment as this section is already simplified.

2. It is hoped that the author can provide a map of the mechanism so that readers can better understand the role of cannabinoids and the endocannabinoid system in diabetic cardiomyopathy.

**Response:** Table 2 was added to summarize possible mechanisms through which cannabinoids and the endocannabinoid system could modulate diabetic cardiomyopathy.

### **Reviewer # 3:**

#### **Comments to the authors**

This is an interesting review to introduce the role of cannabinoids and the endocannabinoid system in modulation of diabetic cardiomyopathy. This review aims to elucidate the possible mechanisms through which cannabinoids and the endocannabinoid system could interact with the pathogenesis and the development of diabetic cardiomyopathy. These mechanisms include oxidative/nitrative stress, inflammation, accumulation of AGEs, cardiac remodeling, and autophagy. Better understanding of the role of cannabinoids and the endocannabinoid system in diabetic cardiomyopathy may provide novel strategies to manipulate such a serious diabetic complication. However, I still have some minor suggestions.

1. It would be much better that the author can use some Table or Figure to summarize these useful information, so that the reader can easier to learn the updating knowledge in this review article.

**Response:** As suggested by the reviewer, four figures and 2 tables summarizing the main topics of the article were added and properly cited.

- (1) 68694-Answering Reviewers **DONE**
- (2) 68694-Audio Core Tip **DONE**
- (3) 68694-Conflict-of-Interest Disclosure Form **DONE**
- (4) 68694-Copyright License Agreement **DONE**
- (5) 68694-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s) **N/A**
- (6) 68694-Non-Native Speakers of English Editing Certificate **DONE**
- (7) 68694-Video **N/A**
- (8) 68694-Image File **DONE**
- (9) 68694-Table File **DONE**
- (10) 68694-Supplementary Material **N/A**