OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00462
Title: Quercetin protects against diabetic retinopathy in rats by inducing heme oxygenase-1 expression
Reviewer's Name: Jiaxing Wang
Reviewer's country: USA

COMMENTS TO AUTHORS

This study investigated the role of Quercetin in DR rats. The author showed that Quercetin protect the retina by inducing BDNF in a HO-1 dependent way and reducing the pro-inflammatory cytokine levels in the retina of diabetic rats. The experiment is well designed and the manuscript is well written. The only major concern I have is that there are so many inflammatory factors involved in this study and it makes the readers easily lose focus. I strongly recommend the author to add a pathway figure which shows where all those factors play a role and how do they regulate the DR together, especially the key ones, like HO-1, Quercetin, Znpp, HMGB1, BDNF, Tlr4 and NF-kappaB… I believe such a figure will significantly increase the quality of this paper.

Minor concerns:

1.   There are different types of charts for data presentation, bar charts, bar charts with data points, points of mean with error bar and box plots… I recommend the author to unify with bar charts with data points, like Figure 2. Figure 1F is fine with line charts.

2.   Figure 4A, the bar chart is missing labels for x-axis.

OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-20-00462
Title: Quercetin protects against diabetic retinopathy in rats by inducing heme oxygenase-1 expression
Reviewer's Name: Giacinto Bagetta
Reviewer's country: Italy

COMMENTS TO AUTHORS
The Ms on the protection afforded by repeated administration of quercitine on the retinal inflammatory and degenerative effects of a single dose of streptozotocine in rat. The sequence of experiments and the discussion of the results are logic though the whole set of experiments and methodology used need tightening.

The title and the abstract reflect the content of the Ms; the introductory paragraph sets well the need for retinal protection in diabetes and propose an acute experimental model using streptozotocine as a tool.

Whilst a large number of similar studies are present in the literature, the experimental setting proposed here appers not sufficiently explained for the reader as well as the methodologies used for morphological assessment of the retinal damage and protection.

In particular, it is not clear to this referee how the Authors have decided to use 10 rats per experimental group. There is no reference to sample power calculation and this is mandatory for the 3R approach to the use of experimental animals. The Authors refer to random assignment of the rats to the experimental and control groups; however, there is no explanation how the random sequence has been generated. Quite importantly, there is no reference to an authorization number released by an animal welfare control authority and this should be available worldwidely.

The protocol of treatment with quercitin should be reported in detail. It is not clear when it was administered during the day; was it given before or after stretozotocin administration and how much before or after; same considerations are for the antagonist.

The methodology used to measure the thickness of the the retinal layers and the number of GC should be better described. There is no reference to a validated method for these calculations except for a generic reference to blindness of the two operators. There is a large variability in such countings in relation to the point in the tissue where the measurement was made.

The biochemical data (wb, mRNA, gene products etc) seem all to go in the direction of confirming the antiinflammatory action of quercitin and the key role for HO-1 in mediating its effect. However, the statistical assessment of the data requires a two way analysis of variance followed by a multiple comparisons test (Bonferroni's for instance) and, in the legends, the F value and the degree of fredom should be reported together with the p value.