Reviewer's report

Title: The Ocular Hypotensive Effect of Saffron Extract in Primary Open Angle Glaucoma: a Pilot Study

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Reviewer: Pradeep Ramulu

Reviewer's report:

The current study by Bonyadi describes the results of a small randomized clinical trial looking at the IOP-lowering effects of oral Saffron on POAG patients already on IOP-lowering therapy. The study describes some promising results, and the study design is generally strong. There are several clarifications and changes that I feel should be made before the article is ready to be further considered for acceptance.

1) The level of English in the paper is poor. The authors should consider getting a medical editor to help improve the grammar throughout the paper, as it is below the standard for acceptance as it is.

2) The authors need to do a better job of listing and discussing the side effects of oral saffron. I find many listed through a quick search, but this are not discussed at all. There may be particular problems with long-term use as well. A well-balanced paper must discuss these in detail. In particular, the possible side effects which might result from short and long-term usage of the dosage employed should be discussed. It would be good to know which of these were discussed on the consent form.

3) How were side effects of treatment gathered and analyzed? It is not enough to say that no side effects were noted.

4) The restriction of patients based on CCT seems extreme. I would guess that at least 50% of patients would be ineligible to participate in the study based on their CCT. Why was this criterion employed?

5) The loss to follow-up is large, and I am not clear when it happened or precisely why. It would be good to present these data in a table.

6) It seems that the chemical content of saffron might vary considerably from plant to plant, strain to strain, year to year, and region of growth to region of growth. Were all patients treated with saffron from the same batch of plants? Also, were any chemical analyses done to calculate how much of the putative active ingredients were present?

7) Why was a group of POAG patients already on 2-drug IOP-lowering studied? It seems like a bizarre group to study, though of course it would be great to show that a 3rd medicine could be so effective.

8) While the results of the study are promising, it would be good to know why the study was conducted? What made the authors think they would find an effect of
saffron?

9) It is not clear in the abstract that saffron is given orally until the conclusions. Nor is it clear from either the abstract or methods whether dorzolamide and timolol doses were continue throughout the randomization process.

10) The background statement that the TM is the most sensitive AC structure to oxidative damage seems silly. Really, the TM is the only AC structure, unless one includes the lens, which is probably as/more susceptible to oxidative damage than the TM.

11) I am not confident that antioxidant treatment for such a short time would lower IOP. Why would this occur, especially as there are already anti-oxidant chemicals in aqueous humor? Presumably, oxidative damage to the TM, if it really plays a role in IOP rise, happens over years, and a few weeks of antioxidant therapy is not likely to do much. One at least needs to consider the possibility that other mechanisms are at play.

12) The authors state on page 5 that eyes were “judged to have stable glaucoma control for at least 6 months based on a series of VF and ONH examinations”. However, this amount of time is insufficient for judging progression/stability. Furthermore, I am not certain this would even be a meaningful criteria.

13) A table describing the features of patients in each group would be of help. I would also include descriptions of CCT, VF MD, and other variables not already described in the text.