Reviewer's report

Title: Red wine flavonoids inhibit UGT2B17 and potentially increase circulating testosterone levels

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Reviewer: Lena Ekström

Reviewer's report:

The manuscript is very well written and the finding that red wine inhibits UGT2B17 is an interesting finding. The aims are well defined and the methods are clearly described. However there are some major concerns that the author’s needs to address before it can be acceptable for publication.

Major complementary revisions:

1) The title is too speculative, considering this is an in vitro study. I strongly suggest the authors to remove the last part of the title “and potentially increase circulating testosterone levels”. They should instead clarify in the title that red wine flavonoids inhibit UGT2B17 in vitro.


3) Methods (page + relevant figures and table): Please use Mean ± Standard Deviation (SD) instead of Standard Error of Mean (SEM), since SEM only describes the standard deviation of the sample distribution, not the variability in your sample.

4) For figure 1 and 2 the results presented are from a duplicate sample. If I understand correct the experiment was only performed at one time point? If so, the experiment should be repeated to include results from at least two independent experiments. It would be more scientifically correct if the results are accompanied with statistical analyses which now are missing. Moreover, why was 100 uM testosterone used?

Minor revisions:

5) Figure 3 – the inhibition of different phenolic compounds were studied for 60 min. In respect of their finding that a more pronounce inhibition was found after 2 hours it is surprising that they choose 60 min for the inhibition study – what was the reason for choosing 60 here?

6) Discussion: In addition to the animal studies referred to here, ethanol has been linked to increased testosterone excretion in humans (i.e. it could elevate your T/E ratio) (Falk, Palonek et al Clin Chem. 1988 Jul;34(7):1462-4. and Grosse, Anielski et al., Drug Test Anal. 2009 Nov;1(11-12):526-30). Ethanol of >1 g/kg body weight significantly increases the T/E ratio and it was speculated that
this was due to phase I enzymes, which is consistent with your finding that ethanol did not affect UGT2B17 in amounts # 1%. It is worth thinking about if you are going to perform an in vivo study using red wine.

7) Discussion (paragraph 4) “Whilst it has been found… “: Reference 29 should be replaced with reference Ekström et al (Pharmacogenetic and genomics 2011Jun 21(6):325-32 (as serum concentrations were not measured in reference 29). In addition a very large study has measured serum testosterone concentrations in 1000 young and 1000 elderly men and not found any significant differences between ins/ins+ ins/del and del/del (Swanson et. al., J Clin Endocrinol Metab. 2007 Dec;92(12):4878-82.) and this large study should be added.

8) Introduction: Is reference no 14 relevant?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have no competing interests