Reviewer 3

<table>
<thead>
<tr>
<th>Comment</th>
<th>Reply</th>
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<tbody>
<tr>
<td>Whereas the effects of tocotrienols is well reviewed, a paragraph reviewing and comparing the features and effects of tocotrienols with tocopherols should be added: what is similar and what makes them different? Do the tocotrienols affect the same pathways of signal transduction and gene expression as the tocopherols? This is important in view of the fact the only one of the eight vitamin E analogues can reach high concentrations in plasma and tissue (alpha-tocopherol), and thus may have an advantage over all the other analogues. Why are all the other analogues metabolized and eliminated so that they do not reach high levels and are such low levels enough to have any physiological effects?</td>
<td>Thank you for your suggestion. We have compared the effects of tocotrienol and alpha-tocopherol under the subheading “Difference in the metabolic effect between T3 and alpha-tocopherol”</td>
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<td>It would be nice to show a summary table of the few studies of tocotrienols done with human subjects.</td>
<td>Thank you for the suggestion. We have included the summary table after the section 4.9.</td>
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<td>Figure 1: usually, the chemical structure is depicted with the chromanols facing to the right, e.g. compare to (1)</td>
<td>Thank you for the comment. We had reconstructed the chemical structure accordingly.</td>
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<td>• Line 22: receptors</td>
<td>Thank you for pointing out the grammatical errors patiently. We have corrected them as per your suggestions.</td>
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<td>• Line 26: anti-obesity effects</td>
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<td>• Line 38: triglycerides levels</td>
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<td>• Line 73: was shown... is shown</td>
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<td>• Line 168: might be</td>
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<td>• Line 173: adipocytes</td>
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<td>• Line 174: to confirm the potency</td>
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<td>• Line 175: apoptosis was also</td>
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<td>• Line 181: with increase of</td>
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- Line 185: inhibition of the AMPK pathway
- Line 187: suggested that autophagy
- Line 259: droplets
- Line 291: L-NAME, an inhibitor of...
- Line 296: and to reduce diet-induced
- Line 306: summarizes
- Line 308: from cell culture, preclinical and clinical studies...
- Line 337: mice by increasing
- Line 353: demonstrated a greater
- Line 436: This is contradictory
- Line 443: this sentence is not clear and should be modified
- Line 447: this warrants
- Line 608: therapeutic role of high doses of T3
- Line 614: prevents cross-comparison.... complicates cross-comparison
- Line 619: daily dose .... mg/daily... daily is repeated

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<tr>
<th>Line 75: Composition: annatto oil is in w/w, whereas the others are in mg/ml</th>
<th>Thank you for the comment. Direct conversion from w/w into mg/ml for liquid extract is not provided by the author. We assumed that the density of liquid extract is the density of extraction solvent (n-hexane: 0.659 g/ml) and we calculated that 5.2-5.5% w/w is equivalent to 34.27 – 36.25 mg/ml.</th>
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<tbody>
<tr>
<td>Line 194: RBEE ...explain</td>
<td>Thank you for the comment. RBEE stands for rice bran enzymatic extract which we have defined earlier in text (line 110).</td>
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<td>Line 254: owing to its antioxidant properties.... Given that alpha-tocopherol has similar antioxidant properties as the tocotrienols (2, 3) but reaches much higher concentration in</td>
<td>Thank you for the comment. We did not mean to compare the antioxidant and anti-inflammatory activities of tocotrienol and alpha-tocopherol in this sentence. We agree with the</td>
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</table>
plasma liver and tissue, shouldn’t it be much better in improving liver profile in obesity models if antioxidant properties are at the basis of this mechanism? Thus, alternative mechanisms should be more discussed for T3 action that are non-antioxidant.

reviewer that the liver profile could be improved due to many mechanisms, including antioxidant, anti-inflammatory and mevalonate-suppressing effects. These were discussed in the text. Hence, we have deleted the phrase “owing to its antioxidant properties” to avoid confusion.

| Line 423: RBO ... explain | Thank you for the reminder. RBO stands for rice bran oil. We had corrected this and defined RBO in earlier text (line 76). |
| Line 450: it is unlikely that the small amounts of glycerol in T3 supplements would affect the systemic triglyceride levels | Thank you for the comment. We had removed that statement. |
| Line 555: lens NF-kB activation.... not clear, do lenses express genes? | Thank you for the comment. We had replaced the word “lens” with “lenticular” to avoid confusing. From our understanding, there is a layer of lens epithelium on the surface of lens for lenticular homeostasis. |