



**SDI Review Form 1.6**

Journal Name:	<b><u>British Journal of Medicine and Medical Research</u></b>
Manuscript Number:	<b>2014_BJMMR_13820</b>
Title of the Manuscript:	<b>Dose-dependent Modulation of Lipid Parameters and Inflammatory Biomarkers by <math>\delta</math>-Tocotrienol in Hypercholesterolemic Subjects</b>
Type of the Article	<b>Original Research Article</b>

**General guideline for Peer Review process:**

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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**PART 1: Review Comments**

	<b>Reviewer's comment</b>	<b>Author's comment</b> (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<b><u>Compulsory</u></b> REVISION comments	<b>The study design is that of a modified Forced Titration with very brief washout periods. The time to development and washout of on target as well as off target drug effects is probably not clearly known. Therefore, this type of study design cannot distinguish response to increased dose from response to increased time on drug or cumulative drug dose effect. This type of study can give a reasonable first approximation of both population average dose response and the distribution of individual dose response relationships. Without a concurrent placebo group, it cannot provide clear evidence of effectiveness. These limitations should be discussed by the authors in their "Discussion" Section.</b>	
<b><u>Minor</u></b> REVISION comments	<p>p 6, lines 156-158: sentence is awkward. Rephrase as "There was a 2 week washout period after each 4 week active drug intervention period, with, however, continuation of the AHA Step-1 diet.</p> <p>P7. lines 176-179: The authors relate determination of LDL-C by both direct assay as well as Friedewald Equation calculation. It is unclear which of these results, however, are utilized in their data reporting !</p> <p>In all Figures presented, I would suggest removing the arabic numerals preceding the various phases of the study. The Roman numerals are already given below and</p>	<p>The manuscript is rewritten and modified according to reviewer's all very valuable suggestions.</p> <p>All the tables and figures were also modified according to reviewer's comments and suggestions.</p>



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	<p>even though the arabic numbers are separated from the dose of tocotrienols by a period, this still results in unnecessary confusion by the reader.</p> <p>There is only one Figure 3,4,5 and 6 that I can see. Therefore, "3A" should be changed to "3", "4B" to "4", "5C" to "5" and "6D" to "6".</p> <p>Legend to Figures 4 and 5: Clarification of which special character ¶ or § corresponds to <math>P &lt; 0.03</math> and <math>P &lt; 0.05</math> would be helpful.</p> <p>p.9, line 218 and Fig "5C". The Figure revealing an approximate 3% reduction in triglycerides from baseline with AHA Step 1 Diet is inconsistent with the "Results" on line 218 (6% reduction).</p> <p>p.10, line 231 and Figure "5C": The Figure appears to reveal an approximate 2 % reduction in triglycerides from baseline with 125 mg dose of tocotrienol while line 231 of "Results" section states 9 % reduction.</p> <p>p.10, line 234: "...significant (<math>P &lt; 0.05</math>) increases of ... Increased relative to what ? The math would suggest relative to the 250 mg tocotrienol dose except the 8% increase in LDL-C is incorrect and should be 18%.</p> <p>p.11, Table 2. Is the change in LDL-C/HDL-C ratio of the 250 mg dose tocotrienol intervention compared to baseline not significant ?</p> <p>p.11, lines 241-242: The reference to proteosome inhibitors etc. belongs in the "Discussion" section of the manuscript.</p>	
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	<p>p.13, Table 3: What dose of <math>\delta</math> tocotrienol is represented by the column titled "AHA-Step-1+<math>\delta</math> -T3, RLU*" ?</p> <p>p.13, lines 264-269: Some of this material might be more appropriate in the "Discussion" Section of the manuscript.</p> <p>p.14, Table 4: What dose of <math>\delta</math> tocotrienol is represented by the column titled "AHA-Step-1+<math>\delta</math> -T3, RLU*" ?</p> <p>p.14, lines 276-281: Some of this material might be more appropriate in the "Discussion" Section of the manuscript.</p> <p>p.15, Table 5: What dose of <math>\delta</math> tocotrienol is represented by the column titled "AHA-Step-1+<math>\delta</math> -T3, RLU*" ?</p> <p>p.15, Table 5: P values corresponding to the % change in RLU with <math>\delta</math> tocotrienol intervention would be helpful</p> <p>p.16, line 317: would change "...were indicated" to "...may be indicated"</p> <p>p.17, lines 348-349: Levels of miRNAs in non-hypercholesterolemic patients, presumably from the literature are not given. Would rephrase, therefore, to read "...Since levels of miRNAs in the present study appear to have been down-regulated in the hypercholesterolemic population, up-regulation by <math>\delta</math> tocotrienol may be associated with beneficial effects."</p> <p>p.17, line 363: Would end sentence after reference # 30 and start new sentence at that point with "...<math>\delta</math>-tocotrienol's up-regulation..."</p>	
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	<p>p.18, lines 369-370: No data is presented to show an upregulation of any biomarkers ! The only data related to the effects of tocotrienol dosing greater than 250 mg is for lipid parameters.</p> <p>The "Abstract" should be rewritten to be consistent with the alterations suggested above.</p>	
<b><u>Optional/General</u></b> comments	<p>The authors are clearly experts in the area upon which they are reporting. Nevertheless, the manuscript while employing high level analytical techniques in its Methodology, does suffer from conceptual methodological limitations as discussed in my "Compulsory Comments" above.</p> <p>As such, I would recommend acceptance for publication only if ALL the specific issues presented in my "Minor Revision Comments" are appropriately addressed.</p>	