PART 1:

<table>
<thead>
<tr>
<th>Journal Name:</th>
<th>British Journal of Medicine and Medical Research</th>
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</thead>
<tbody>
<tr>
<td>Manuscript Number:</td>
<td>MS: 2012/BJMMR/2174</td>
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<tr>
<td>Title of the Manuscript:</td>
<td>Differential Vascular Responses of Aorta to Potassium Ion Channel Opener, Citrus Flavonoid Naringenin in Type 1 and Type 2 Diabetes Mellitus in Rats</td>
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</table>

General guideline for Peer Review process: (Note: Title of different sections as proposed below may differ in case of review paper / case reports)

- Is the problem/objective of this study original and important? SCIENCEDOMAIN international strongly opposes the practice of duplicate publication or any type of plagiarism. However, studies which are carried out to reconfirm / replicate the results of any previously published paper with new dataset, may be considered for publication. But these types of studies should have a 'clear declaration' of this matter. If you suspect any unethical practice in this manuscript, kindly write it in the report with some proof/links.

- Materials & methods (Kindly comment on the suitability and technical standards of the methods. Sufficient details of the methods/process should be provided so that another researcher is able to reproduce the experiments described)

- Results & discussion (Kindly comment on: 1. Are the data well controlled and robust? 2. Authors should provide relevant and current references during discussion. 3. Discussion and conclusions should be based on actual facts and figures. Biased claims should be pointed out. 4. Are statistical analyses must for this paper? If yes, have sufficient and appropriate statistical analyses been carried out?)

- Conclusion (Is the conclusion supported by the data, discussed inside the manuscript? Conclusions should not be biased and should be based on the data, presented inside the manuscript only. Authors should provide adequate proof for their claims without overselling them)

- Are all the references cited relevant, adequate? Are there any other suitable current references authors need to cite?

- SDI believes in constructive criticism. Reviewers are encouraged to be honest but not offensive in their language. It is expected that the reviewer should suggest the authors on how they can strengthen their paper to make it acceptable. Comments of the reviewers should be sufficiently informative and helpful to reach a Editorial Decision. We strongly advise that a negative review should also explain the weaknesses of any manuscript, so that the concerned authors can understand the basis of rejection and he/she can improve the manuscript based on those comments. Authors also should not confuse straightforward and true comments with unfair criticism.

- We are very much reluctant to go against suggestions (particularly on technical areas) of the reviewers. Therefore, authors are requested to treat the suggestions of reviewers with utmost importance.

- This form has total 9 parts. Kindly note that you should use all the parts of this review form.
### Review Comments

<table>
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<tr>
<th>Compulsory REVISION comments</th>
<th>Reviewer’s comment</th>
<th>Author’s comment (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)</th>
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</table>
| This study investigates how Diabetes Mellitus (DM) modulates the effect of phenylephrine, acetylcholine, levocromakalim, and (±)-naringenin on the contractility of *in vitro* rat aorta rings. The data presented demonstrate that, at early stage of DM, there is exaggerated vascular response to an α-adrenoceptor agonist and reduced responses to an endothelial-dependent vasodilator as well as to K⁺ channel openers in Type 1 but not Type 2 diabetes model rats. While the finding here presented adds valuable novel information on this topic and the experiments appear to be carefully conducted, the analysis, presentation and discussion of the data devalue the impact of the work. In particular, these data are only descriptive and none has been done to investigate the mechanism(s) responsible for the effects observed. I am confident that if the Authors address the issues raised, a paper of greater impact will result. Furthermore, the Discussion section is sometimes repetitive and should be reduced as well as focused on the data obtained. There are many typesetting errors, particularly in the Reference section. The English style is very poor and has to be improved. In addition, several
important points need to be clarified.

**Major Comments:**

**Title**
The title is not satisfactorily explicative of the data presented in the manuscript, since it deals only with (±)-naringenin.

**Abstract**
- The conclusion is not supported by the data presented and as such is only speculative: the latter should be clearly stated.

**Materials and methods**
- Details on the anesthesia procedure should be given.
- “... cut into segments...”. It should be stated whether rings or strips have been used. Sometimes in the text it is written “rings” and sometimes “strips”. Please clarify and rectify.
- How was an “intact endothelium” defined?

**Results**
- The numerical data presented in this section are already shown in Table 1 and 2, so this is a repetition.
- The pIC$_{50}$ values for (±)-naringenin obtained in the two controls are extremely and, more importantly, significantly different: this should
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<td><strong>Discussion</strong></td>
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<td>The manuscript is only descriptive and this should be clearly stated, especially in the conclusion.</td>
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<td>The first paragraph discusses data that are completely different from those presented in the manuscript.</td>
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<td>The fifth paragraph is not clear at all.</td>
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<td>(±)-Naringenin has been described as a BK$_{Ca}$ channel opener, but this important information does not emerge from the manuscript. Furthermore, it does not improve vasorelaxation, as stated in the Discussion. Finally, a thoroughly comparison of the data presented with those of Fallahi et al. (2012), obtained <em>in vivo</em>, should be presented and discussed.</td>
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<td>It seems like Wistar rats behave as STZ-DM rats: can you comment on this.</td>
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<td>The last paragraph of the discussion is very confusing. A reference should be given to support the first statement.</td>
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<tr>
<td></td>
<td>The conclusion is not supported by the data presented and as such is only speculative: this should be clearly stated. Moreover, what is a “relaxant dysfunction”? Finally, future implications arising from this study should be discussed.</td>
</tr>
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</table>
Figures and Tables

- Table 2 is very confusing. Much statistical significance is different from what stated in the text or even wrong.
### Minor REVISION comments

#### Throughout the text
- Replace “potassium ion channel” with “potassium channel” and “calcium ion channel” with “calcium channel”.
- Replace “sensitivity” with “potency”.
- Replace “dose” with “concentration”.
- Sometimes the “(±)” of naringenin is missing.
- The Authors often used the word “preserved” for a response that is “increased”, and this is confusing.

#### Abstract
- **Background**: “... and impairment of potassium ion channel dys...”.

#### Discussion
- The fourth paragraph can be greatly reduced.

#### References
- This section contains many errors.

#### Figures and Tables
- The legends are not self-explanatory and titles are very confusing. This does not help the reader. Furthermore, they are repetitive “Each data point represents the mean ± SEM of 6 experiments; * = P< 0.05 STZ-diabetic vs. STZ-control, n = 6.” and not homogeneous in their style. Finally, the statistical analysis used
should be clearly stated.

- The X axis range is too wide. I suggest adjusting it to the range of concentrations used for better clarity.

**Optional/General comments**

None

**Reviewer Details:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Fabio Fusi</th>
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<tbody>
<tr>
<td>Department, University &amp; Country</td>
<td>Department of Neurosciences, University of Siena, Italy</td>
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