Author’s response to reviews

Title: Effects of Cinnamon Supplementation on Expression of Systemic Inflammation Factors, NF-κB and Sirtuin-1 (SIRT1) in Type 2 Diabetes: A Randomized, Double Blind, and Controlled Clinical Trial.

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Author’s response to reviews:

Dear Editor,

We sincerely thank you for all constructive comments which helped us to improve the manuscript. And, we are very appreciative to have been given the opportunity to revise our manuscript. We carefully considered the comments which have been offered. Herein, we address all comments point-by-point, discussing the subsequent modifications based on those comments and recommendations. We would like to extend our appreciation for taking the time and effort.

On behalf of all co-authors,

Dr. Behrouz Talaei,
Corresponding author
Reviewer comments

First reviewer:

Interesting article since it aimed to investigate the use of a herb in the control of blood glucose in diabetic using antihyperglycemic drug.

Results were not as expected (improved glycemic control). In this sense, some doubts/questions arose throughout the reading and were not answered by the authors:

1) Where are the blood glucose values of the groups?
RESPONSE: With regard to your valuable comment, the result of blood glucose indexes, as well as, demographic characteristics and anthropometric measurements have been represented in previous study (https://www.ncbi.nlm.nih.gov/pubmed/28885566). For this reason, a short brief of these features has been summarized in result section, but, to more clarifying, we also added two tables to this section include Table 1 (demographic characteristics and anthropometric measurements) and Table 2 (blood glucose indexes) (Page 19 and 20 in Figure legends).

2) What dose of metformin were they using?
RESPONSE: 500 - 1000 mg, 2-3 times each day (Page 6, paragraph one, lines: 105 and 106).

3) Has food intake been investigated (prior and during the experimental period)?
RESPONSE: Your valuable comments are absolutely right and rational. So, to neutralizing the potential effect of diet on mentioned factors, it was asked from all participants kept their previous routine diet. For this purpose, food intake of all patients was assessed in terms of intake of energy, carbohydrate, protein, fiber, total fat, saturated fatty acid, poly and mono unsaturated fatty acid, vitamins C and E, and selenium by Food Frequency Questionnaire in before and after supplementation. As well as, our patients before entering to our study, their diet was controlled by diabetes clinicians and all of them had a diabetic diet, too (Page 6, paragraph 3, line 122).

4) Most importantly, what was the species of Cinnamon used? Was there standardization of the extract used?
RESPONSE: In our study, we applied Ceylon species. The supplements had produced under supervision and cooperation of School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Iran. At first, the supplements were verified in terms of microbial. Then, we gathered cinnamon powder in capsules in Traditional Pharmacy sector (Page 6, paragraph 3, line 120).

5) I missed a discussion about the pharmacodynamic interactions between metformin and the treatment used in the study, which may explain why there were no positive results.
RESPONSE: We added a paragraph about your valuable comment and highlighted it (Page 11 line 233-236, Page 12 line 237-241)

Second reviewer:

1- Line 172 states: "Also, we observed no significant reduction (P=0.055) in placebo group at the same time.", referring to the effects on NFKB in the placebo group. However, this P value seems to be 0.2 in the table.
RESPONSE: Based on your valuable comment, Table 3 was reformed (Page 21 in table legends).

2- The table should be clearer. Unnecessary P values should be excluded. Symbols in front of P values (i.e. < 0.22 are not needed).
RESPONSE: With regard to this comment, Table 3 was revised (Page 21 in table legends).

3- The manuscript should be edited and proofread for English
RESPONSE: With respect to this comment, the manuscript was revised.
4- figures should be added
RESPONSE: With regard to this comment, we added two graphs (Figures 2 & 3) to manuscript (Page 23,24 in figure legends).

MINOR COMMENTS
Response: All of below comments reformed and considered and highlighted in manuscript.
Line 101-Forty four adult subjects were recruited, and all patients were obtained informed consent- Please rephrase to "Forty four adult subjects were recruited, and informed consent was obtained for all patients" (Page 5, paragraph 2, line 94-96)
Line 109-This sentence is very long. Please consider dividing into multiple sentences. Probably the word "while" in line 109 should be replaced by "during" Page 6, paragraph 1, line 104
Line 116-Should read: " 22 patients for each group (44 patients in total). After an interview, 44 subjects were eligible for participating in the study by convenience sampling method" Page 6, paragraph 2, line 110-112
Line 124- "have" should be replaced by "maintain" Page 6, paragraph 3, line 120
Line 128- "Subjects removed their shoes wore light clothing" should be replaced by "Subjects removed their shoes, and wore light clothing" Page 7, paragraph 1, line 125
Line 132- "and" should be removed from this sentence Page 7, paragraph 1, line 129
133- "We expressed clinical and biological measurements methods including fasting blood sugar and fasting insulin in our former study" should read "We expressed clinical and biological measurements methods, including fasting blood sugar and fasting insulin, in our former study". Page 8, paragraph 1, line 152
Lines 133-140- If the authors want to mention the sensitivity of the ELISA kits, they should do so for all kits. However, this information can be omitted Line. Page 7, paragraph 2, line 129-135
139- Typo
Line 143- "The p-value less than 0.05 was considered significant" should be replaced with "P-values less than 0.05 were considered significant". Page 7, paragraph 3, line 137
Lines 145-146 Student's t-test was used for between groups comparison. Page 7, paragraph 3-4, line 140-144
Line 150- Withdraw from the trial. Page 8, paragraph 1, line 147
Line 152- The mean (± SD) age. Page 8, paragraph 1, line 149
Line 171- In the treatment group. Page 8, paragraph 2, line 162-163
Line 173- at baseline. Page 8, paragraph 2, line 164
Line 193- Findings. Page 9, paragraph 5, line 190
Line 198- prevents. Page 10, paragraph 1, line 202
Line 198- In addition, the anti-inflammatory effects of cinnamon are mediated by nitric oxide synthase inhibition in inflamed areas. Page 10, paragraph 1, line 202-203
Line 200- Reduces. Page 10, paragraph 1, line 204
Line 201- Human studies showed that cinnamon consumption for 6 weeks had no impact on IL-6 level in female athletes. Page 10, paragraph 1, line 205-206
Line 203- non-alcoholic fatty liver disease. Page 10, paragraph 1, line 207
Line 203- 15 grams/day? please specify correct posology. Page 10, paragraph 1, line 207
Line 204- could decline should be replaced with "decreased". Page 10, paragraph 1, line 208
Line 204- "Even though the findings were not similar to the present study, its results could not be generalized to the diabetic patients. Because our target population was patients with type 2 of diabetes." this sentence should be replaced with "These results were not replicated in our study, potentially because of the different disease tested, or because our dosage was different". Page 10, paragraph 1, line 208-209
Line 206- eliminate "other views" as it is not necessary. Page 10, paragraph 1, line 209
Line 207- regulates. Page 10, paragraph 1, line 210
Line 210- promoting. Page 10, paragraph 1, line 213
Line 210- In the cytoplasm. Page 11, paragraph 1, line 214
Line 211- (I-kB) protein, which suppresses it. Page 11, paragraph 1, line 215
Line 212- "Then, I-kB apart from NF-kB so, NF-kB activated and transferred to the nucleus" please rephrase this sentence in correct English. Page 11, paragraph 1, line 216-217
Line 217- This function could be impressive in cellular glucose metabolism pathways- Please double check wording and rephrase. Page 11, paragraph 2, line 221-222
Line 218- of SIRT1 protein. Page 11, paragraph 2, line 223
Line 227- supplementation NF-kB" should read "supplementation on NF-KB". Page 11, paragraph 2, line 231
Line 228- The section "Limitations" should be checked for English and rephrased. Page 12, paragraph 2, line 242-254
Line 223- 225. This statement seems contradictory. Maybe the authors meant that the placebo group had a significant decrease in NF-KB. Page 11, paragraph one, line 231.