Author's response to reviews

Title: Effect of fenugreek (Trigonella foenum-graecum L.) intake on glycemia: a meta-analysis of clinical trials

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Author's response to reviews: see over
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Dear Dr. Gabriel,

Re: Manuscript reference No. 1439913409103808

It is with excitement that we resubmit to you a revised version of our manuscript “Effect of fenugreek seed intake on glycemia: a meta-analysis of clinical trials”. Thank you for giving us the opportunity to revise and resubmit this manuscript.

We would like to extend our sincere thanks to the reviewers for their constructive and insightful comments which enabled us to improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the comments of the reviewers.

Revisions in the text are shown using yellow highlight for additions, and strikethrough font [example] for deletions. Changes are made in accordance with reviewers’ suggestions. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in *Nutrition Journal*.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

*Nithya Neelakantan*

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Response to reviewer 1 (Prof. Shah Ebrahim)

This is systematic review and meta-analysis demonstrates a potentially important effect of fenugreek seeds in 10 small trials. The paper is generally well written and the analyses are conducted and reported well.

We thank the reviewer for his kind remarks about our manuscript and are grateful for the highly insightful comments.

Major compulsory revisions

1. The search used yielded a very small number of hits (175) which reflects their inclusion of outcome terms in the search strategy. The Cochrane Handbook (http://handbook.cochrane.org/) states: “a search strategy to identify studies for a Cochrane review will typically have three sets of terms: (1) terms to search for the health condition of interest, i.e. the population; (2) terms to search for the intervention(s) evaluated; and 3) terms to search for the types of study design to be included (typically a ‘filter’ for randomized trials).” Searching on outcomes is not recommended as these are not systematically indexed in bibliographic databases.

A rather simplistic RCT filter has been used which will also reduce the sensitivity of the search (#2 Search (clinical trial OR trial* OR trial OR intervention OR therapy -

As suggested, we have repeated the search process (using a search strategy that includes, (1) terms to search for health condition of interest; (2) terms to search for the intervention evaluated; and (3) terms to search for the types of study design to be included) and have updated the figure 1 - Flow of trial selection. Please refer to the attachments, i). Supplemental material and ii). Figure 1

The search yielded 199 potentially relevant articles after excluding the outcome terms in the search strategy which is slightly larger than the earlier search results, 178. This relatively small number of hits could be due to the reason that the herb ‘fenugreek’ has not been as widely evaluated in scientific studies as many other dietary and pharmacological exposures.
2. EMBASE was not searched. This database indexes a range of journals that are not included in MEDLINE, has deeper indexing of interventions, contains conference abstracts and is recommended in Cochrane search methodology. The search must be repeated to ensure that all relevant trials have been found.

The EMBASE database is not subscribed to by our educational institution (National University of Singapore Libraries). Instead, another database, ‘Scopus’, from the same publisher (Elsevier) which includes all the content of EMBASE, including index terms, was searched. Scopus is the largest abstract and citation database of peer-reviewed literature, with more than half of Scopus content originates from outside North America representing various countries Europe, Latin America and the Asia Pacific region.

(http://cdn.elsevier.com/assets/pdf_file/0019/148402/contentcoverageguide-jan-2013.pdf)

In addition to MEDLINE (PubMed) and Scopus, we also searched Web of Science (a multidisciplinary database indexing journal articles and conference proceedings in diverse fields including medicine), BIOSIS, Cochrane Trials Registry, CINAHL, SCIRUS, ProQuest and Google Scholar to identify additional studies. The bibliographies of all included trials were hand-searched for additional relevant studies. We believe that the combination of these literature sources provided a high likelihood that all relevant published studies were identified.

**Minor essential revisions**

1. The rationale for using a random effects model a priori needs to be explained.

Given the nature of the herbal fenugreek product, we anticipated large differences in the preparation format, active components/chemical composition, administration of fenugreek supplements, and dosages. In addition, variation in the study population and study design could be expected to add to between-study variation in results. Hence, we believed a priori that there would be substantial between-study variation in results in addition to chance variation. Please refer to page 7, line 125-129.

2. In these small trials it is common that not all those randomized complete the full outcome assessments. How did the trial investigators deal with missing data (e.g. imputing the last follow up blood glucose; dropping the patient from the analysis; using an average outcome value)? How were these problems dealt with in the meta-analysis?

Four studies have reported drop-outs. Of which, three studies have reported low % drop-out ranging between 0 to 5% and one study has reported 25% drop-out as reported in Table 1 of our manuscript. These subjects were not included in the statistical analyses that were conducted for the primary studies. Please refer to page 10, line 183-184.

We also conducted a sensitivity analysis after excluding the Alamdari et al. trial (17) that reported the highest drop-out rate (25%). The pooled effect on fasting blood glucose (-1.00 mmol/l, 95% CI: -1.62, -0.38), 2h glucose (-2.50 mmol/l, 95% CI: -3.68, -1.33) and HbA1c (-
0.90%, 95% CI: -1.59%, -0.22%) remained similar. We have not added this specific result to the manuscript as we already report that the impact of removing any individual study on the pooled results is not substantial as part of the sensitivity analyses.

3. The opening paragraph does not need to repeat the findings of the meta-analysis and could be shortened markedly.

We have shortened the opening paragraph of the Discussion section.

4. The differences observed seem quite large and while they are statistically significant, the authors should focus on answering the question of how clinically important were the observed effect sizes. How do they compare with effects of diet, drugs and physical activity on these outcomes? A related question that would be useful to answer is what size (and design) of trial would be optimal for informing clinical practice.

The magnitude of effects of fenugreek on glycemia is indeed substantial and similar to the effects of other lifestyle and pharmaceutical therapies that complement standard treatment of diabetes (Goldhaber-Fiebert, J.D., et al., Diabetes Care 2003; 26: p. 24-29 and Wing, R.R. Arch Intern Med, 2010. 170:1566-75). For example, in the multicenter U.S. Look AHEAD trial intensive lifestyle intervention reduced HbA1c 0.36% (95% CI -0.40, -0.33) as compared with standard diabetes therapy (Wing, R.R. Arch Intern Med, 2010. 170:1566-75). DPP-4 inhibitors reduced HbA1c by 0.7% and fasting glucose by 1.0 mmol/L (Deacon C, Diabetes, Obesity and Metabolism, 2012. 14(8): p.762-767). Our meta-analysis suggested that the fenugreek supplement changed the HbA1c by -0.85% (95% CI -1.49%, -0.22%) and fasting glucose by -0.96 mmol/l (95% CI: -1.52, -0.40) as compared with control interventions. Thus, fenugreek may be a promising complementary therapy for the clinical management of diabetes if confirmed in higher quality trials. We have added a statement in p.17, l. 341-343.

In order to test the effect of fenugreek on blood glucose and HbA1c, a randomized double-blinded trial in at least 180 (90 subjects in each of study arms) persons with diabetes is warranted. The duration should preferably be at least three months to be able to evaluate effects on HbA1c levels and given the longer duration a parallel trial appears most appropriate. The trial should be conducted according to rigorous standards (CONSORT guidelines for herbal interventions) with an appropriate randomization procedure, an adequate method of allocation concealment and transparent reporting of these methods. The herbal product must be standardized and tested for the composition and may be administered in the form of capsules with a recommended fenugreek dose of at least 5g per day. We have added these statements in p.17, l. 348-357.

5. Minor points. Some of the sentence structure needs attention for sense – for example:

p.7, l. 117-8: For none of the outcomes this sensitivity analysis had a substantial effect on the pooled results.

p. 15, l. 295-6: For none of the studies major harmful side effects of fenugreek were reported.

p.16, l. 320-1: ...and only part of the trials provided information on blinding status and drop-out rates
We have rephrased the above mentioned sentences.

p.7, I. 119: … the pooled estimates did not change substantially

p. 15, I. 297: No major harmful side effects of fenugreek were reported in all included studies

p.16, I. 326: and only a few trials provided information on blinding status and drop-out rates

Response to reviewer 2 (Prof. Matam Vija-Kumar)

1. In the title remove 'seed' and include fenugreek botanical (scientific) name

We have deleted the word ‘seed’ and we have included botanical name of fenugreek in the title as suggested. “Effect of fenugreek (Trigonella foenum-graecum L.) intake on glycemia: a meta-analysis of clinical trials”

2. In the introduction, please include few sentences with references on active component(s) responsible for observed hypoglycemic activities of fenugreek.

Lines (29-31): We have now included information on active components that may be responsible for observed hypoglycemic activities of fenugreek