

## Format for ANSWERING REVIEWERS

November 4, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14140-review-revision.docx).

**Title:** The role of phytoestrogens in prevention and management of type 2 diabetes

**Author:** Mohammad Talaei, An Pan

**Name of Journal:** *World Journal of Diabetes*

**ESPS Manuscript NO:** 14140

In order to facilitate the review process, we also provided a point-by-point response to each of the comments raised by the reviewers (changes are highlighted in yellow in the revised manuscript). We have added a Table as suggested by the reviewers. Should you have any additional requests or questions, please do not hesitate to contact me. We look forward to hearing from you.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,

A handwritten signature in blue ink, appearing to be 'An Pan'.

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#### **Reviewer 1 comments:**

Current evidence from animal and human studies suggests that diets rich in soy and phytoestrogens have beneficial effects on many aspects of diabetes and obesity. In animals studies it has been found that soy and phytoestrogens are effective at reducing adipose tissue and increasing glucose uptake. However, available data from human studies do not offer clear support. The current review has compared several studies and discussed their limitations which are critical in considering soy products and phytoestrogens as a component of healthy diet and for prevention and management of Type 2 diabetes.

Over-all this review has successfully incorporated the information highlighting the importance of phytoestrogens in prevention and maintenance of T2D. The findings from most of the clinical trials and prospective cohort studies have been compared and commented upon. Clear application possibilities have been defined and reviewed by the author. Here are some minor comments to be considered before publication.

**Response: We appreciate your summary and positive comments for our review.**

1. In the abstract section there are few typographical errors, like thread instead of threat and global instead of globe. This section may be revised for minor corrections.

**Response: Thank you for pointing those typos, and we have corrected them. We also carefully checked the manuscript throughout.**

2. In Introduction- third paragraph- References are required for showing that phytoestrogens belong to isoflavones, structure and other properties of phytoestrogens.

**Response: We apologize for omitting the references for this paragraph. We have added the relevant references for this paragraph.**

**Kurzer MS**, Xu X. Dietary phytoestrogens. *Annu Rev Nutr* 1997; **17**: 353-381 [PMID: 9240932]

**Dixon RA**. Phytoestrogens. *Annu Rev Plant Biol* 2004; **55**: 225-261 [PMID: 15377220]

#### **Reviewer 2 comments:**

In this review, authors examine the current evidence linking phytoestrogens and T2D from epidemiological studies and clinical trials, and explore the potential underlying mechanisms of phytoestrogens' effect on glucose metabolism from animal and experimental studies, and propose research priorities for future investigations in this field. Although plausible arguments to explain possible mechanisms linking phytoestrogens and glucose metabolic disorders has been emphasized, results from epidemiologic studies and clinical trials are controversial.

**Response: We appreciate your summary and positive comments for our review.**

1. On this regard, the most important issue in a review article, is the inclusion of specific comments from authors focused in their interpretation of data and possible phenomena involved to explain the controversial results. As example, the sentence "...lower levels of soy foods, genistein intake

was significantly associated with 2-h postchallenge insulin concentrations, but not fasting or 2-h glucose concentrations." (Page 6, 2nd paragraph) how can be interpreted? It was due to improvement of insulin action?

**Response: we appreciate your suggestion and have added the following sentences to explain the inconsistent results here.**

**"This suggested that isoflavones may have direct effect on  $\beta$ -cell function and insulin secretion, which is supported by experimental studies [40]."**

2. In the same way, the sentence "...among 2811 Chinese adults, soy protein intake was significantly associated with increased odds of hyperglycemia in men, ..." (Page 6, 2nd paragraph) imply that soy protein intake is a risk factor for developing diabetes?

**Response: we appreciate your suggestion and have added the following sentences to explain the inconsistent results here.**

**"The increased odds of hyperglycemia in men could be a chance finding, and residual confounding and reverse causation are possible in the cross-sectional studies. The sex-specific effects may also linked to the estrogen-like activity of isoflavones [4, 5], but the underlying mechanisms are complex and unclear [11]."**

3. Throughout manuscript, several issues and sentences deserve to be discussed in a rationale way in order to clearly establish the authors' point of view.

**Response: many epidemiological and clinical trials have been published on this topic, therefore, it will be difficult to discuss the potential explanations for the inconsistent results for each study, given that the human studies are different in many aspects, e.g., the consumption levels (or dosage in clinical trials), genetic background, gender, study design, potential confounding and bias, study period (intervention time) etc. We have tried to give a summary of the literature at the end of each section, and then give an overall summary under "Implications and recommendations for future studies".**

4. Studies of meta-analysis (references 47 and 49) should be included in review, rather than the meta-analysis.

**Response: There have been more than 20 clinical trials included in the previous meta-analysis, and it will be difficult to include the description of all the published clinical trials in our review. Therefore, we have decided to briefly discuss the findings from the two meta-analyses, and selected some high-quality papers (i.e., studies with long-term intervention period and relatively larger sample size) to be discussed in our review. If the readers are interested in the results of specific clinical trials, they can refer to the meta-analyses.**

5. A table that summarizes results of clinical trials and cross-sectional studies is needed. How can be explained that prevalence of diabetes and pre-diabetes among Chinese population (in whom consumption of soy products is generally high) reach 9.7% and 15.5%?

Response: Again, the clinical trials have been summarized in previous meta-analyses. Therefore, we do not think it is meaningful to have a table to show the results of the clinical trials. However, we think it would be useful to provide a table to summarize the findings from cross-sectional and prospective studies. We have added a new table in the revision.

The increase prevalence of diabetes and pre-diabetes in the Chinese population is due to many reasons: increase in obesity and reduction in physical activity, changes in dietary habits from traditional Chinese diet to western pattern, as well as the mismatch between early life exposures and modern environment. The details have been reviewed by Ma et al. (Ma RC, Lin X, Jia W. Causes of type 2 diabetes in China. *Lancet Diabetes Endocrinol.* 2014 Sep 10. pii: S2213-8587(14)70145-7. doi: 10.1016/S2213-8587(14)70145-7.) Although soy products may have anti-diabetic effect and the consumption level is high in Chinese population, but we would not expect a single food (or food group) could counteract the dramatic impacts from other lifestyle and dietary changes. Taken together, diabetes is a multifactorial disease caused by complex environmental and genetic interactions, and soy products alone are not able to explain or solve the problem.