Author’s response to reviews

Title: The Antiplaque/Anticariogenic Efficacy of Salvadora persica (Miswak) Mouthrinse in Comparison to that of Chlorhexidine: A Systematic Review and Meta-analysis

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Author’s response to reviews:

Dear reviewers,

We would like to thank you for all the feedback and comments, we appreciate it all. We would also like to thank you for your patience. We have taken all the comments into consideration. Therefore, you will notice drastic changes have occurred in the latest manuscript uploaded (changes were highlighted in yellow).

Listed below are our response to each comment (sequenced according to the original decision letter):

(Reviewer 1):

Introduction:

1) We agree with your opinion. Thus, you will notice that a lot of changes have been made to the introduction section (the changes have been highlighted). We added findings from the published data, more information about the plant itself and introduced chlorhexidine.

As for the aim of the study, it now reflects the PICO. We now added the population (P) group to the aim (introduction section, line 58, page 6) and (materials and methods section, under eligibility criteria, line 2, page 7).

Materials and Methods:
2) The registration has been added to a designated section in materials and method section, under the title of “registration” (materials and methods section, under registration, line 1, page 6).

3) Many thanks for this comment. In regards to the number of assessor, we have added a sentence stating that two authors (EJ & LB) reviewed the results independently (materials and methods section, line 12, page 6). As for the keywords, we decided on it according to the PICO assigned using MESH terms in PubMed and medical terms (keywords) used in previously published papers. “OR” was inserted between each PICO synonym terms. “AND” was inserted between the PICO groups. We then searched the engines using those keywords in all fields.

The search details using the MESH were as follows:


4) Although we planned in our search strategy to solve any disagreement by discussing with the third author (HS), there was no disagreement. The discussion with the third author was only to exclude articles that were reported by both searchers to be not following the inclusion criteria. Therefore, the kappa score was “1” with 100% perfect agreement (results section, line 22, page 11).

5) Since the search strategy was repeated. It is now up to date (December 2018) and is stated in materials and methods section, line 13, page 7.

6) We have taken this suggestion into consideration. We repeated the search strategy to include the suggested search engines. In addition to MEDLINE-Pubmed and google scholar, the new search strategy was conducted using Cochrane Central Controlled Register of Trials, Wiley Online Library and ScienceDirect. This was then reported accordingly in the PRISMA flowchart. This was changed accordingly in the materials and method section, under search strategy, line 6, page 6.

Eligibility criteria:

7) We appreciate your comment. We did not search journals manually. We, however, manually search the references of the studies that were included in this review and meta-analysis.
8) The eligibility criteria is now written according to PICO (materials and methods section, under eligibility criteria, line 2, page 7).

9) We agree with your comment and have taken it into consideration. Hence, the only non-randomized study (Al-Bayaty et al.) was excluded from the quantitative analysis, and was clearly stated (in systematic review results section, line 19, page 11).

10) Thanks for the comment. The data extraction was revised again, and the results were modified accordingly.

11) Thank you for this comment. Accordingly, we evaluated the risk of bias of the included studies based on the Cochrane Handbook for Systematic Reviews of Interventions as you recommended and have indicated that in search strategy section, under the risk of bias assessment, line 8, page 8.

Statistical analysis:

12) We agree and would like to apologize for this editing error. We have removed this part from the statistical analysis section.

Result

Tables:

13) According to the new search strategy followed, 77 results were yield from PubMed

14) There are a number of reasons you will not find 17 studies in one forest plot:

1- The forest plots were divided according to either the antiplaque or anticariogenic efficacy of the interventions assigned, because not all articles studied both the antiplaque and anticariogenic effects. Some studies discussed the antiplaque effects only (15 articles), others discussed only the antibacterial effects (three articles). Whereas, only one article discussed both effects. It was impossible for us to have all the included study in one forest plot.

2- The meta-analysis was conducted depending on the comparison group. Some studies compared Salvadora persica to both chlorhexidine and placebo. Whereas, other studies only compared Salvadora persica rinses to either chlorhexidine (e.g. figure 2a) or placebo (e.g. figure 2b) and not both.

3- Another reason, is pre-treatment values. For example, in figure 3c, some studies were not included because they lacked pre-treatment scores (Deshmukh et al. 2017, Abdulbaqi et al. 2016, Narayan et al. 2016, Singh et al. 2012, and Ghasemi et al. 2014). However, you will find these studies included in other forest plots.
More details of the values given in each included study is presented in table 1.

15) Thank you for the comment. The mean SDs of the plaque score and bacterial counts are listed in table 1. It is also present in all the figures and were discussed in the results section, under meta-analysis results, in pages 11 and 12. However, caries and periodontal inflammatory parameter was not part of this study objectives. Nevertheless, we are planning to include these parameters in a future study.

16) Thank you for your comment. We corrected the statistical model accordingly. However, in figure (3e), despite (3.1) having P=0.06 and (3.2) having P=0.05. The I2 in both analysis was above 70%. This suggest that approximately 70% of variability in treatment effect estimates is due to real study differences (heterogeneity) and only 30% due to chance. This is visually evident from the wide scatter of effect estimates with little overlap in their confidence interval. Therefore, a random effect model was carried out for this figure (figure 3e).

17) We wanted to explore all the data present. Therefore, quantitative analysis was done for all the studies regardless of its quality, which was then subdivided either to high or moderate quality.

18) We added two additional columns to “Table 1: Characteristics of the included studies”. The 15th was named “placebo used” in which we have indicated the type and amount of placebo used in each study. Whereas, the type of chlorhexidine was added in the 16th under the name “% of CHX”.

Discussion:

We made many changes in this section that were later highlighted. Some of the few changes that were made, were as follows; we discussed the antiplaque effects and discussed the effects on the different concentrations of chlorhexidine. We also discussed the effects of duration and refraining of mechanical measures (discussion section, pages 14 and 15).

(Reviewer 2):

1- This has been taken into consideration. Hence, the review is now under the following title “The Antiplaque/Anticariogenic Efficacy of Salvadora persica (Miswak) Mouthrinse in Comparison to Chlorhexidine: A Systematic Review and Meta-analysis.”

2- The search strategy was repeated according to the suggested search engines and suggested keywords. We used 5 search engines this time. We searched in MEDLINE-Pubmed, Cochrane Central Controlled Register of Trials, Wiley Online Library, ScienceDirect and Google Scholar (materials and method section, under search strategy, line 7, page 6).
3- We did not exclude any study based on the medical status, age group or gender. However, the inclusion and exclusion criteria of each of the included study was clearly stated in table 2. It included the medications used along with many other factors that could be recognized as having a confounding effect.

4- We were thankfully able to contact native speakers with a medical background to guide us with the translation.

5- This has been taken into account. We chose to re-select the keywords as suggested and repeat the search strategy all over again. We added the following words: Siwak, Arak, Peelu, mouthwash, mouthrinse and herbal. The new keywords were listed separately and in combination with other words as follows: ((Miswak) OR (herbal) OR (Siwak) OR (Arak) OR (peelu) OR (Salvadora persica)) AND ((chlorhexidine)) AND ((mouthwash) OR (mouthrinse)) AND ((antimicrobial) OR (antibacterial) OR (antiplaque)).

This was modified in the materials & methods section, under search strategy, line 4, page 6.

6- The introduction section has been modified with your comments in mind. We started it with an introduction about plaque and its effect on oral health (introduction section, line 1, page 4). We then added the origin and background of Salvadora persica (introduction section, line 5, page 4). Additional chemical constituents of SP were also added along its pharmaceutical properties (introduction section, line 15, page 4). As for chlorhexidine, a paragraph was added to introduce this mouthwash and its properties (introduction section, line 31, page 5).