Author’s response to reviews

Title: Effects of Brazilian Green Propolis on Proteinuria and Renal Function in Patients with Chronic Kidney Disease: A Randomized, Double-Blind, Placebo-Controlled Trial

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Answers to the reviewers

Regarding review of manuscript entitled “Title: Effects of Brazilian Green Propolis on Proteinuria and Renal Function in Patients with Chronic Kidney Disease: A Randomized, Double-Blind, Placebo-Controlled Trial” with manuscript numbered BNEP-D-18-00662, this points need revision or answers by dear authors.

1-In line 24-25 needs exact revision regarding aim of study.

We revised and added: The aim of this study was to evaluate the impact of Brazilian green propolis extract on proteinuria reduction and the changes in the estimated glomerular filtration rate (eGFR). (lines 23-25).

2-In line 29-30 the definition of albuminuria is not clear .more than 30mg/g or 300 mg/g?

We admitted patients with micro- or macro-albuminuria (urinary albumin-to-creatinine ratio >30 mg/g or >300 mg/g, respectively). The microalbuminuria was defined by UACR >30 and < 300mg/g and macroalbuminuria was defined by > 300mg/g.

3- What was your formula for sample size and what was the method of your randomization?
To calculate the sample size we use the t-test derivation for comparing two independent sample means (Chow et al., 2008), expected standard deviation was considered to be similar using a similar trial as a reference [26]. (Lines 186-188).

We used stratified randomization based on age, ACE inhibitor or ARB use, the presence of type 2 diabetes, proteinuria and creatinine levels (lines 94-96). Randomization was performed by an external investigator who was not involved in the care or follow-up of the patients (lines 97-98).

Reference:

4-although the authors also point it as a limitation but the sample size in each group is low and Increase the chance of error.

We added: that needs further investigation in other and larger populations (lines 354-355).

5-The duration of intervention and also placebo is so long .is there any reference or reason?

This is the first clinical study using propolis for so long time in patients with chronic kidney disease; in a double-blind manner we conducted for 12 months and at the end of this period we opened the data.

The decision to performed for so long was defined from the beginning, as described on the clinicaltrials.org platform; also helped us to have experience with the medication, as well as we could evaluate its safety.

Previous studies have shown changes in proteinuria or albuminuria in periods of less than 12 months, but not sufficient to demonstrate changes in glomerular filtration rate.

References

We added as a limitation: “A relatively short follow-up period was adequate to evaluate changes in proteinuria, but too short to analyze changes in glomerular filtration rate.” (Lines 354-356).

6- topographic errors such as have on in the line 24 and 50 and 76 …. need revision .it’s better that we say effect of instead of the effect that have on.
We revised and changed “effect on” to “impact of”. (line 24; line 76)

7- In line 24 of table 1 in spite of clear difference between two groups 5 versus 10 but p value is not significant. is it correct?

It is a discrete categorical variable and we did not find, in fact, a significant difference between the groups. “The unpaired Student’s t-test was used to evaluate the differences between two groups.” (lines 194-195).

8- The number of tables and figures are more and some of them unnecessary.

We used tables and figures in accordance with the number permitted by the journal. We can check with the Editor if some changes are desired.

Reviewer 2

ADDITIONAL REQUESTS/SUGGESTIONS:
In the introduction add in detail what Brazilian propolis is and what the known physiological effects in animal studies have revealed. There is no mention at all of any reported side effects that any of the two groups had. The authors have also not specified how dosage of 500 mg/day was arrived at and on they need to specify that.

“To assess safety, we measured markers of hepatic, muscle, and pancreatic injury, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatine kinase, and amylase. Throughout the study, we also monitored patients to identify any adverse events or reactions.” (lines 127-130).

“None of the participants reported any adverse effects or allergic reactions during the treatment. (lines 281-282).

“Patients in the propolis group received EPP-AF propolis at a dose of 500 mg/day (4 tablets of 125 mg each, divided into 2 daily doses). The chosen dose of propolis was based on studies that had used similar doses without observing adverse effects [24,25].” (lines 146-148).

References