Author's response to reviews

Title: High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome

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Author's response to reviews: see over
To  

The Editor  

Nutrition Journal  

Re: High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome.  

Dear Editor,  

Many thanks for asking us to revise this article and enclosing the constructive suggestions by the reviewers. We have now incorporated those suggestions that have markedly improved the manuscript. We hope that the revised manuscript is now suitable for publication in the Nutrition Journal. We enclose the detailed response to the reviewers comments.  

Yours sincerely  

T Sathyapalan
Reviewer: Kelly Pritchett

Reviewer's Comments

Major Compulsory Revisions

• Background: The background information is very brief. The authors propose that “polyphenols and regulation of neurotransmitters might reduce the burden of CFS”. The authors need to elaborate on the mechanisms behind why the chocolate (cocoa) may be beneficial for CFS. What leads the authors to believe this?

We have now added as follows to background

*The effect of chocolate on fatigue appears to have been first described by the Aztec Emperor Montezuma II (born c.1480 reigned 1502-1520) who noted, “The divine drink, which builds up resistance and fights fatigue. A cup of this precious drink [cocoa] permits man to walk for a whole day without food”. The Badianus Codex (1552) noted the use of cocoa flowers to treat fatigue (7). Chocolate is known to increase neurotransmitters like phenyl ethylamine, serotonin, and anandamide in the brain (8). An imbalance in various neurotransmitters including serotonin has also been reported in subjects with CFS(9). The effect of cocoa in subjects with chronic fatigue syndrome has not been studied to date. We hypothesise that chocolate, by modulating neurotransmitters might reduce the symptom burden of CFS.*

• Background, 2nd paragraph: The purpose of the study should be stated and clearly defined.

We have now expressed the purpose of the study in introduction as follows.

We conducted a double blinded, randomised, clinical pilot study comparing high cocoa liquor / polyphenol rich chocolate to simulated iso-calorific chocolate (cocoa liquor free/ low polyphenols) on fatigue and residual function in subjects with chronic fatigue syndrome.
• Methods, 1st paragraph: What is the basis for the requirement for subjects to have a score of 10 on the Chalder Fatigue Scale? How was this scale administered to the subjects?

We have included only CFS subjects with severe fatigue symptoms. We have now expressed this as Subjects having severe fatigue of at least 10 out of 11 on the Chalder Fatigue Scale (binary scored) were enrolled.

The questionnaires were self administered. We have now made it clear as follows - Severity of fatigue and handicap was analysed using using validated self-report questionnaires (Chalder Fatigue Scale (Likert Scored), the London Handicap Scale (LHS) and the Hospital Anxiety and Depression Scale before and after each phase of the trial) (11-13).

• Methods, 2nd paragraph: States that patients taking more than 10gm of chocolate were excluded. How was this measured?

This was assessed by a registered Dietician. We have now expressed this as Subjects were reviewed by the dietician during screening, before and after each intervention to assess whether they were taking more than 10g of chocolate per day prior to recruitment as well as to advise not to consume extra chocolate during the study period. Apart from this, subjects were advised not to change their diet.

• Methods: How was diet controlled in this study? Furthermore, subjects were instructed not to consume any additional chocolate during the study. How was this ensured?

As mentioned to the previous comments this was assessed by this dietician.
Subjects were reviewed by the dietician during screening, before and after each intervention to assess whether they were taking more than 10g of chocolate per day prior to recruitment as well as to advise not to consume extra chocolate during the study period. Apart from this, subjects were advised not to change their diet.

• Results: The authors mention Table 4, but it is missing from the document. Please modify accordingly.

Yes, there was no Table 4 and this has been modified.

• Discussion: The discussion is vague and does not incorporate the findings of other related literature. The authors discuss the issue of weight, and how physical activity may have increased. This would be interesting for the reader to know, Was this measured?

Since this is a proof of concept study, we have not measured physical activity. We have now mentioned this in discussion as follows and incorporated findings of other related literature.

This was a proof of concept study; physical activity was not formally assessed. Biochemical markers including plasma polyphenol levels and inflammatory markers were not measured as part of the study as all of the baseline parameters prior to the study were normal, in accord with the criteria for the diagnosis of chronic fatigue syndrome.

A number of biological systems have been implicated in chronic fatigue syndrome and there is mounting evidence that oxidative stress contribute to the disease process and to some of the symptoms in the illness. Flavanoids have shown to have a protective effect on cells including neuronal cells from oxidative stress however; this mechanism should be explored in further studies.

-Minor Essential Revisions
Chocolate is rich in flavonoids that have shown to be of benefit in disparate conditions including cardiovascular disease and cancers.

We hypothesise that chocolate by modulating neurotransmitters might reduce the symptom burden of CFS.
Thank you. We have now changed that.

- Methods, 3rd para, 1st sentence: reword- prior to participating in the study
  Thank you. We have now changed that.
- Methods, 3rd paragraph, 3rd sentence: the last portion of the sentence needs
  Rewording
  We have now changed this as follows -
  Subjects had 8 weeks of the initial intervention and then 8 weeks of the crossover intervention separated by a 2 week wash out between the 2 arms.
- Methods, 4th paragraph: The 1st sentence is lengthy and could be split up for clarity.
  We have now split up the sentence as suggested as follows –
  *The active product was polyphenol rich chocolate containing 85% cocoa solids (derived from a high cocoa liquor content) compared with chocolate containing cocoa butter alone that contained no non-fat cocoa solids (cocoa liquor) (simulated iso-calorific chocolate).*
  *Chocolate containing cocoa butter alone was dyed to the same colour as the high cocoa liquor/polyphenol rich chocolate (with a recipe specially prepared by Nestlé PTC York. UK).*
- Methods, 4th paragraph, last sentence: The sentence needs rewording, perhaps stating “A taste trial was performed prior to the study to confirm that subjects could not distinguish between the two treatments.”
  Thank you. We have now changed that as suggested.
- Methods, 5th para, 1st sentence: “calculations were done using the” should be Removed
  Thank you. We have now changed that as suggested.
- Methods, 5th para, 2nd sentence: Why is there a range for the glycemic index
for the iso-caloric chocolate?

We have now corrected the glycemic index as follows –

*The glycaemic index of dark chocolate was 41 where as for simulated iso-calorific chocolate was 40.*

- Results, 1st paragraph, 1st sentence: Perhaps, should be reworded to state
  “descriptive characteristics for the subjects are displayed in Table 4.” The authors also state in the abstract that only 5 subjects completed both study arms. The authors do not discuss “why”? The next sentence may be redundant if it is listed in Table 4.

Thank you. Instead of adding additional table we have now included this in results as follows

*Ten subjects (6 females and 4 males) were enrolled in the study. The mean age of subjects was (mean ± SD) 52 ± 8 years and mean body mass index was 28.3 ± 2 kg/m².*

- Results, 1st paragraph, 4th sentence. Should state “A similar trend…”

Thank you. We have now changed that.

- Results, 2nd paragraph: The authors refer to the 2 treatments as “legs” and need to be consistent throughout the paper for clarity.

Thank you. We have now changed that.

- Discussion, 1st paragraph, 2nd sentence: The sentence needs rewording.

Thank you. We have now reworded this as follows.

*As both types of chocolate were iso-calorific and had similar glycemic indices and loads, it could be proposed that the improvement was due to the high polyphenol content from the cocoa liquor content of the active chocolate, rather than a difference in of the micro or macronutrient the composition of the two chocolates.*

- Discussion, 2nd paragraph, 2nd sentence: The authors mention the “active phase” for the first time. What is the active phase?
We have now clarified this as below –

The potential weight gain may have been offset by improvement in functional status and physical activity when they had high cocoa polyphenol rich chocolate.

- Discussion, 3rd paragraph, 3rd sentence: The sentence needs rewording for Clarity

Thank you. We have now reworded this as below.

*It may be the synergy of these compounds in chocolate which might account for the effects of chocolate, which might at least partly explain the results seen in this study.*

- Discretionary Revisions

- Abstract, conclusion: change wording to “this study suggests that…” remove the “increase in Weight”

Thank you. We have now changed that as suggested

- Background, 2nd paragraph: The authors suggest that “chocolate” contains a mixture of polyphenols. Would “Cocoa” be a more appropriate term than chocolate, because not all chocolate has the equivalent flavanoid content?

Thank you. We have now changed that as suggested.

**Reviewer:** Kanwaljit Chopra

Authors must have done few biochemical estimations like inflammatory cytokine levels like TNF-alpha or antioxidant enzyme so as to confirm their results.

We have not done these biochemical estimations since this was a proof of concept study. We have now clarified this in the discussion as follows –

*This was a proof of concept study; physical activity was not formally assessed. Biochemical markers including plasma polyphenol levels and inflammatory markers were not measured as part of the study as all of the baseline parameters prior to the study were normal, in accord with the criteria for the diagnosis of chronic fatigue syndrome.*
Authors should provide various questionnaires used for evaluation in the material and method section.

Since these are widely available, validated questionnaires, we have referenced them in view of limited journal space.

Many thanks

Yours Sincerely

T Sathyapalan