Author's response to reviews

Title: Perilla Extract improves GI health in a randomized placebo controlled double blind human study

Authors:

Sybille Buchwald-Werner (sybille.buchwald-werner@vitalsolutions.biz)
Hajime Fujii (hfujii@aminoup.co.jp)
Claudia Reule (c.reule@biotesys.de)
Christiane Schön (c.schoen@biotesys.de)

Version: 4 Date: 30 October 2013

Author's response to reviews: see over
Dear Executive Editor Mr. Tom Rowles,

We hereby re-submit the manuscript entitled “Perilla Extract improves GI health in a randomized placebo controlled double blind pilot human study” by S. Buchwald-Werner, H. Fujii, C. Reule, C. Schön to be considered for publication as research article in BMC Complementary and Alternative Medicine.

There are 6 files in all, the main manuscript file, the consort 2010 checklist and 5 figure files.

The manuscript presents a pilot human study carried out with a standardized Perilla frutescens extract which has shown potential for its application in gut health. In vitro and ex vivo studies showed that the proprietary extract combines prokinetic, antispasmodic and anti-inflammatory effects. The overall aim of our research is to investigate Perilla frutescens extract as potential gut health ingredient for food supplements, which could be used to prevent gastrointestinal discomfort or as alternative, co-medication for irritable bowel syndrome.

The study was performed double blind, randomized, placebo-controlled and with parallel design. 50 healthy subjects, aged 30-70, documented their GI symptoms, stool frequency and consistency daily, during a two week run in phase and a 4 week intervention phase with Perilla frutescens extract or placebo. All GI symptoms were significantly improved by Perilla frutescens extract during the intervention phase. A subscore, calculated for the female subgroup, including bloating and abdominal discomfort was significantly improved against placebo.
We would like to confirm that we have revised the manuscript to answer the questions and comments of the editor.

In addition, please find additional information referring to the comments of the editor

1. **Sample Size, primary objective, responder definition and statistics**
   
   A pilot human study was carried out with *Perilla frutescens* extract to investigate the effects on gastrointestinal discomfort. No human study with this extract was carried out before and no comparative studies were available from literature. Therefore it was not possible to do a sample size calculation. Our aim was to investigate several parameters and to get an indication about the most beneficial effects for gut health to be tested in a further main study. Therefore no primary objective was defined and data were evaluated explorative. We added more information about the statistics to the manuscript and a responder definition.

2. **The study flow**
   
   The study flow was added to the manuscript

3. **Consort Statement 2010:**
   
   The checklist of Consort statement 2010 was ticked and submitted together with the revised manuscript. It was a nutritional human study, which was carried out in orientation to ICH-GCP guidelines, but the study did not fall under German drug law. Therefore and due to pilot study character not all agenda topics of the consort statement were applicable.

4. **Study registration:**
   
   In Germany there is no legal requirement to register nutritional human studies. The feedback of the first editor was that the journal would only publish studies, which are registered and that a post-registration is also accepted. Therefore, we registered the study after completion of the trial.

5. **Independence of study center:**
   
   The whole study was performed by BioTeSys GmbH in Esslingen, an independent study site which focus on nutritional studies. The staff at BioTeSys created the study design in collaboration with the sponsor and Vital Solutions. The study realization (submission to ethics, recruitment, visits of subjects, data collection, data entering, data analysis etc) was independently performed by BioTeSys. The Study was performed double blind. Subjects and study staff was completely blinded. Deblinding was conducted after database lock.
6. **Authors contribution:**

The study was sponsored financially by Amino Up Chemicals. Vital Solutions is the scientific sponsor of the study, the leader of the overall research and development of the Perilla frutescens extract. Vital Solutions initiated the idea and outline for the study and was the discussion partner for BioTeSys GmbH for study design and selection of outcome measures prior to study start. The overall study concept was than discussed and agreed with Amino Up Chemical Co. Due to our understanding the authors contribution is well reflected as we understood that the first and last author is the main contributor. If you have a different option and you define contribution of the authors chronologically, we agree to put H. Fujii from Amino Up Chemical at the end.

Our findings could be applied right away, particularly as gastroenterologists are also looking for alternative therapies to be used in prevention or as concomitant therapy to reduce symptoms of inflammatory bowel syndrome and/or diseases. We believe our results will be of interest to the readers of your journal.

This manuscript describes original work and is not under consideration by any other journal. All authors approved the manuscript and this submission.

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

We suggest the following reviewer:

**Prof. Dr. med. Dr. phil. Gerhard Rogler**  
Klinik für Gastroenterologie und Hepatologie  
Universitätsspital Zürich  
Rämistrasse 100  
CH-8091 Zürich  
Tel. +41-(0)44-255-9477  
Sekretariat +41-(0)44-255-9519  
gerhard.rogler@usz.ch

**Dr. med. Luc Biedermann**  
FMH Gastroenterologie und Innere Medizin  
Klinik für Gastroenterologie und Hepatologie  
Universitätsspital Zürich  
Rämistrasse 100  
CH- 8091 Zürich  
+41 (0)44 255 11 11  
Luc.Biedermann@usz.ch

**Prof. Dr. med Jürgen Drewe**  
Gastroenterologie & Hepatologie  
Universität Basel  
Petersgraben 4  
CH-4031 Basel
Authors’ email-contact details are:
S. Buchwald-Werner: Sybille.buchwald-werner@vitalsolutions.biz
H. Fujii: hfujii@aminoup.co.jp
C. Reule: c.reule@biotesys.de
C. Schön: c.schoen@biotesys.de

Thank you for your consideration.
Sincerely,

Dr. Sybille Buchwald-Werner
Managing Director

Vital Solutions GmbH
Hausinger Strasse 6
D-40764 Langenfeld
Phone: +49 (0) 2173 10 98 202
Fax: +49 (0) 2173 10 98 210
Mobile: +49 (0) 174 1666 856
Email: sybille.buchwald-werner@vitalsolutions.biz