Author's response to reviews

Title: Effect of a herbal extract powder (YY-312) from Imperata cylindrica Beauvois, Citrus unshiu Markovich, and Evodia officinalis Dode on body fat mass in overweight adults: A 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial

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University of Duisburg-Essen, Germany

Dear Dr. Holger Cramer:

Thank you for the thoughtful reviews. We have taken the recommendations into consideration and have modified our manuscript accordingly.

<Details of revision>

Reviewer 1 (Fang-Rong Chang)

1. P7, L152

According to the ref [16], the dose of YY-312 administrated to C57BL/6 mice was 300 mg/kg. Please make a brief description for the design of dose (2.4g/day) taken by the participants. Or, how to convert the dose between these mice and human?
YY-312 tablet 400mg contains 300 mg of active herbal extract and cyclodextrin 100 mg for enhancement of solubility. So, the daily dose of active herbal extract excluding cyclodextrin in the study is 1,800 mg. The human equivalent dose of 300 mg/kg in mouse is 24 mg/kg (= 300 mg/kg * 0.08), when calculated based on body surface area. The pharmacologically active dose is 1,800 mg/day (= 24 mg/kg * 75 kg) assuming body weight of the overweight to be 75 kg.

We also conducted a pilot study with 600 mg/day, 1,200 mg/day, and 1,800 mg/day of YY-312 (excluding cyclodextrin) to choose safe and effective dose of YY-312 despite unpublished. We make sure that 1,800 mg/day of YY-312 is the most effective and is taken safely.

We described a brief description for the design of YY-312 dose.

(Materials and Methods section, line 152, page 7)

A YY-312 tablet includes 300 mg of active herbal extract and 100 mg of cyclodextrin for enhancement of solubility. A placebo tablet is indistinguishable with a YY-312 tablet. The participants were asked to take 3 tablets twice a day (after breakfast and supper). Thus, the daily dose of YY-312 was 2,400 mg (containing 1,800 mg of active herbal extract and 600 mg of cyclodextrin). The daily dose of YY-312 was calculated from an animal study with C57BL/6 mice [16] assuming body weight of the overweight to be 75 kg (1,800 mg/kg = 300 mg/kg × 0.08 × 75 kg).

2. P7, L157-158:

Was the reduction of 500 kcal/day from participants' usual diet a usual physical situation? The instruction might be led to possible interference happened to the result between YY-312 administration and placebo groups.

Please make a brief explanation of the necessity for the reduction of calorie intake in the trial. Or, what's the strategy for?

The subjects in our clinical trial are overweight patients. We know that the control group should receive the usual care for a corresponding disease during a clinical trial. So, most trials to evaluate the efficacy of anti-obesity agents in overweight patients include diet counseling such as hypocaloric diet (500 kcal/d deficit), which is the same dietary advice in both treatment and control groups (e.g. Gadde KM, et al. JAMA 2003;289:1820-5.). We instructed the same dietary advice to reduce their energy intake by 500 kcal/day from their usual diet in both groups. Because YY-312 was additionally provided only in YY-312 group, we consider it reasonable to attribute the difference in effects between YY-312 and placebo groups to taking YY-312.

3. P8, L182:

Please elaborately and clearly indicate that how to evaluate the BFM and BF%.

BFM and BF% were evaluated using DXA. We amended the explanation on DXA measurement in more detail.
Body composition including BFM, lean body mass (LBM), and BF% were assessed at baseline and after 12 weeks using dual-energy X-ray absorptiometry (Prodigy® DXA Lunar, GE Healthcare, Madison, WI, USA). All DXA measurements were performed by trained technicians after urinating and removing all metallic accessories. The participants were asked to fast for at least 8 hours prior to DXA measurement.

4. P9, L218:

The placebo group showed a decrease of 1.0 kg in body weight as well. Comparing to the reduction of energy intake, please describe the advantage or necessity for the recommendation of YY-312 intake. Additionally, the possible influence of taking YY-312 on the "un-overweight or normal BMI" people should be briefly discussed as well, due to some incorrect concept of losing weight nowadays.

Because we included lifestyle modification including diet counseling in both groups, body weight loss can be happened in placebo group. However, all obesity indicators of BFM, BF%, WC, BMI and body weight reduced greater in YY-312 group than in placebo group. So, we interpret that YY-312 intake has body fat reducing effect in overweight patients above the placebo.

We should give attention to a result that placebo group showed a decrease of 1.0 kg in body weight but a decrease of only 0.1 kg in BFM. This result means that LBM reduction is relatively greater in placebo group than BFM reduction. This is also explained by an increase of BF% in placebo group. Obesity is not excessive body weight but an abnormal accumulation of body fat. So, we cannot interpret that placebo group showed obvious improvement of obesity status.

Additionally, we agree with a reviewer’s concern on possible influence of taking YY-312 on the normal weight adults. So we added the following sentence as a study limitation.

(Discussion section, line 319, page 14)

Because this study was performed only in overweight adults, we could not determine the possible influence of YY-312 in non-overweight adults.

Reviewer 2 (Michal Bijak)

1. The chemical characterization of used extract must be given in this type of study.

Study is correct designed, however in my opinion should be also additional study group treated with commercial available thermogenic. That will provide more reliable results.

We agree with a reviewer’s suggestion. Various products were marketed as anti-obesity agents. But, there are still a few products that have been evaluated on the efficacy and safety in
overweight patients. An animal experiment showed that YY-312 had body fat reducing and adipocyte differentiation suppressing effects. So, we believe that it is valuable to evaluate the effects of YY-312 through human clinical trials. A reviewer suggested additional studies comparing with commercial anti-obesity agents. We have a plan to design a further study to ascertain the long-term efficacy and safety of YY-312. The suggestion will be considered in the design process of a further study.

Thank you for the valuable comments. We look forward to hearing a positive reply from you soon.

Sincerely yours,

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