Scientific research process

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Title: A new botanical drug, HL tablet, reduces hepatic fat as measured by magnetic resonance spectroscopy in patients with nonalcoholic fatty liver disease: A placebo-controlled, randomized, phase II trial

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1. What did this study explore?

We evaluated a validity for a change of liver fat volume which was measured by magnetic resonance spectroscopy (MRS) on 12 weeks against after administering HL tablet extracted from *magnolia officinalis* (MO) to patients with nonalcoholic fatty liver disease (NAFLD). Also, we investigated the safety of HL tablet for treating patients with NAFLD.

2. How did the authors perform all experiments?

This study is multi-center, randomized allocation, double blind, placebo controlled, 3rd group parallel, Phase 2.

After receiving the written agreement, the administration with corresponded drug for clinical test was implemented for eligible subjects to screening during 12 weeks by randomly allocating a high-dose group (400 mg HL Tablet), a low-dose group (133.4 mg HL Tablet), and a placebo group in the ratio of 1:1:1. By executing total 4 times of regular visitings including Baseline Visit 2 and three visits (Visit 3, Visit 4,

and Visit 5) in every 4 weeks, the validity evaluation of MRS and laboratory tests were performed in a designated time of each visit and a series of tests for safety were followed in an identification of an adverse event, laboratory tests, vital signs, and physical tests. A tracking observation for adverse events was completed by calling and visiting at the time of 16 more weeks (Visit 6).

3. How did the authors process all experimental data?

The 18 subjects in each group provided a power of 90% for identifying a difference of 4.6% in liver fat decrease between placebo and the low dose HL group. In previous studies, pioglitazone was shown to produce a 10% reduction in liver fat compared to baseline and 0% in the placebo. Also, the 8 % weight loss group in a weight loss program was shown to have a 4.6% reduction in liver fat compared to baseline. Therefore, we considered that the high dose HL group would have a 10% reduction in liver fat compared to baseline and the low dose HL group a 4.6% reduction. To detect these levels of change, a sample size of 23 subjects in each group was needed, assuming a 20% drop-out rate.

Analyses were conducted principally by full analysis set and were supplemented by per protocol set. Continuous variables are given as mean values with standard deviations (SD) or median values with inter-quartile ranges (IQR). Categorical variables are given as frequencies or percentages. Baseline characteristics of the placebo group and each HL group (high dose vs placebo, low dose vs placebo) were evaluated using a two sample t-test or Wilcoxon's rank sum test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Differences between variables were evaluated using two-sample t-tests or Wilcoxon's rank sum tests. Changes of HFC from baseline after 12 weeks of treatment within each group were evaluated using paired t tests or Wilcoxon signed rank tests. P-values < 0.05 in 2-sided tests were considered statistically significant. SPSS 19.0 for Windows (SPSS Inc, Chicago, Ill) was used for all statistical analyses.

4. How did the authors deal with the pre-study hypothesis?

MO is a traditional medicinal plant that has been used to treat liver diseases and other diseases. Some constituents extracted from MO are reported to have anti-inflammatory and antioxidant effects, and MO can be effective against NAFLD. In vitro honokiol, extracted from MO, induces apoptosis of the activated hepatic stellate cells responsible for hepatic fibrosis Honokiol and magnolol extracted from MO significantly inhibited hepatic toxicity induced by galactosamine, generation of intracellular reactive oxygen species and glutathione depletion. Also, MO inhibited lipid accumulation in FFA-exposed hepatocytes. In another study, MO ameliorated body fat accumulation, insulin resistance, and adipose inflammation in high fat-fed mice. So, we hypothesized that MO would improve steatosis and inflammation in patients with NAFLD.

5. What are the novel findings of this study?

HL tablet, a new botanic drug extracted from MO, is effective in reducing hepatic fat content without any negative lipid profiles, body mass index changes and adverse effects.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*

Sincerely yours,

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