INTRODUCTION

Ginseng has been used in traditional Korean and Asian herbal medicine for the restoration and enhancement of normal well-being; it is often referred to as an adaptogenic. Red ginseng, of three types of ginseng cultivated in Korea, is harvested when the ginseng is six years old; it is steamed or heated and subsequently dried, resulting in an increase in saponin content. Korean red ginseng (KRG) is believed to contain ingredients that possess a variety of health enhancing effects including anti-diabetic effect, enhanced erectile function, and cognitive-enhancing effect. Several human studies have reported that administration of KRG had positive effects on maintenance of sugar control and improving insulin resistance in type 2 diabetes mellitus (T2DM) patients. In addition, a previous animal study suggested the potential beneficial effects of KRG on amelioration of insulin resistance and prevention of T2DM through activation of AMPK in fat rats, however, no human study on these effects of KRG has been reported. Korean red ginseng is also expected to have beneficial effects on prevention of T2DM or impaired glucose tolerance in apparently healthy people. However, the benefits of long-term KRG on insulin sensitivity in healthy individuals have not been established. Overweight or obese adults are at risk of cardio-metabolic consequences. Previous studies have also hypothesized that obese subjects tend to be insulin resistant and as a result, the subjects of these studies were selected from obese people. Therefore, this study attempted to determine whether KRG has an effect on the insulin sensitivity in healthy overweight or obese Korean subjects who do not have overt diabetes or hypertension.

METHODS

Participants

The study was approved by the Institutional Review Board at Pusan National University Yangsan Hospital, and informed written consent was obtained from all sub-

Corresponding Authors: Drs Soon Cheol Ahn and Sang Yeoup Lee, 1Department of Microbiology and Immunology, and 2Medical Education Unit, Pusan National University School of Medicine and Family Medicine Clinic, Pusan National University Yangsan Hospital, Beomeo-ri, Mulgeum-eup, Yangsan, Gyeongsangnam-do, 626-770, South Korea. Tel: +82-10-9134-5959; Fax: +82-51-510-8125. Email: ahnsc@pnu.edu; saylee@pnu.edu. Manuscript received 13 November 2012. Initial review completed 30 November 2012. Revision accepted 13 April 2013. doi: 10.6133/apjcn.2013.22.3.04
jects prior to participation. Overweight was defined as having a BMI of 23.0 to 24.9 kg/m² and obesity was defined as a BMI ≥ 25 kg/m² based on the Asia-Pacific criteria. A total of 80 adults between the ages of 20 and 60 years with a BMI ≥ 23 kg/m² were initially enrolled through a tertiary hospital in Busan and a secondary hospital in Yangsan. The subjects had not taken any supplements or medications, including anti-diabetic drugs, anti-hypertensive drugs, steroids, or hormonal products, during the previous four weeks. The subject was also excluded if their systolic BP was above 140 mmHg or diastolic BP above 90 mmHg or their fasting blood glucose was above 100 mg/dL prior to enrollment in the study. Eight subjects met the exclusion criteria and four subjects declined to participate. Finally 68 participants were enrolled. After baseline measurements, the participants were randomly assigned to one of two groups: the intervention group (n = 34) and the control group (n = 34). One participant in the intervention group and two in the control group dropped out during the study without completing the study procedure. The characteristics of those who withdrew were similar to those who participate.

Treatments
This study had a randomized, placebo-controlled, double-blind controlled design. Each subject was randomized to either the intervention group or the control group. Four capsules (500 mg per capsule) each of powdered red ginseng were administered to the subjects in the intervention group 40 minutes before breakfast, lunch and dinner, totaling 12 capsules (6 g) per day, for a period of 12 weeks, according to the previous trial. Korean red ginseng powder was manufactured by Korea Ginseng Corporation, Seoul, Korea from rootlets of a six-year-old red ginseng, Panax ginseng Meyer, harvested in the Republic of Korea. Korean red ginseng was made by steaming fresh ginseng at 90-100 °C for 3 h and then drying at 50-80 °C. Korean red ginseng powder is prepared from ground red ginseng. Standard techniques were used in measurement of the ginsenoside profile. The ginsenosides composed primarily of a family of steroids known as dammarane-type triterpene glycosides with either (20S)-protopanaxadiol (PPD) or (20S)-protopanaxatriol (PPT) as the aglycone. High-performance liquid chromatography-UV techniques were used in analysis of KRG. Ginsenosides, the active constituent of KRG, composed of Rb1 (5.16%), Rb2 (1.82%), Rc (2.22%), Rd (0.47%), and Rg3 (0.22%) for PPD and Rg1 (2.89%), Re (2.16%), and Rf (0.93%) for PPT. Subjects in the control group were given the same quantity of placebos three times per day for 12 weeks. Each subject was instructed to visit the clinic after 1, 4 and 12 weeks from the start of treatment.

Baseline and follow-up measurements
BMI was calculated as weight (kg) divided by height squared (m²). Sagittal abdominal diameter (SAD) was measured using a portable sliding-beam caliper (Holtain-Kahn Abdominal Caliper; Holtain Ltd., Dyfed, Wales, UK) to the nearest millimeter of the caliper. Sagittal abdominal diameter was recorded at the umbilical level as the height of the abdomen, measured from the examination couch when lying down with the legs straight. A mercury sphygmomanometer was used to measure each subject’s BP, in the sitting position after a 10-min resting period. Two readings each for the systolic and diastolic BPs were recorded at 3-min intervals, and the average of each measurement was included in our analysis.

At baseline and at 12 weeks, blood samples were taken after at least 8 hours of fasting for general blood testing, biochemical testing and lipid testing to evaluate metabolic risk factors and monitor for potential adverse effects of KGR. Metabolic risk factors included blood pressure, serum lipid, blood sugar, insulin, homoeostasis model assessment index-insulin resistance (HOMA-IR) and quantitative insulin-sensitivity check index (QUICKI).

Liver enzyme level, total cholesterol, triglyceride, and high density lipoprotein (HDL) cholesterol were determined by colorimetric methods (Roche Diagnostics, Mannheim, Germany) using autoanalyzer Toshiba TBA-200FR (Toshiba Co Ltd, Tokyo, Japan). Measurement of low density lipoprotein (LDL) cholesterol was performed using direct measurement method. Measurement of serum creatinine was performed using an automated technique based on measurement of Jaffe chromogen. Plasma glucose was determined immediately by an enzymatic colorimetric assay using a glucose oxidase method (LX-20, Beckman Coulter, Fullerton, CA), with an intra-assay coefficient of variation (CV) of 2.2% and inter-assay CV of 3.8%. Fasting plasma insulin was measured in duplicate by radioimmunoassay using a solid phase, single antibody assay (Coat-a-Count Insulin, TKN2, Diagnostic Products Corporation, Los Angeles, CA) with an intra-assay CV of 4.2% and inter-assay CV of 6.3%.

Due to possible influences on insulin sensitivity, both diet and physical activity were evaluated. Each subject’s diet was monitored by a semi-quantitative FFQ at baseline and after 12 weeks. Excessive drinking was defined according to the guidelines of the National Institute on Alcohol Abuse and Alcoholism when more than 14 glasses (alcohol 196 g) were consumed for male and 7 glasses (alcohol 98 g) for female. Physical activity was assessed at baseline and after 12 weeks using the International Physical Activity Questionnaire. We expressed physical activity levels as MET-minute. HOMA-IR, which is a known insulin resistance index, was calculated using the following formula: [fasting plasma insulin (µU/mL)×fasting plasma glucose (mg/dL)]/22.5×18.182. QUICKI, a quantitative criteria for insulin sensitivity, was calculated using the following formula: 1/[log fasting insulin (µU/mL) + log fasting blood sugar (mg/dL)].

Statistical analysis
The mean and standard deviation of HOMA-IR from previous studies were used in development of the statistical power for this study. To test the hypothesis that HOMA-IR would be at least 15% lower in the intervention group than in the control group (2-sided test), a sample size of 26 subjects per group provided 90% power for detection of this difference with an α of 5%. Efficacy analyses were based on the intent-to-treat population of subjects who received at least one dose of prescribed KRG or placebo and had at least one assessment post-baseline. Normally distributed data, determined using Shapiro-Wilk test, were expressed as means and standard deviation, whereas
variables with a skewed distribution were reported as median and interquartile range. Between-group comparisons were performed using the two-sample t-test or Mann-Whitney U test for continuous variables as appropriate or chi-square test for categorical variables. Within-group comparisons were analyzed by a paired t-test or Wilcoxon signed-rank test when appropriate. A repeated measure ANOVA was used to analyze within-group changes. In addition, subgroup analysis was performed for the following predefined subgroups according to baseline measurements: HOMA-IR (<1.6 versus ≥1.6); 15 and BMI (overweight vs obesity). 10 A p value less than 0.05 was considered statistically significant. The SPSS version 14.0 statistical package was used for all statistical analyses.

RESULTS

General characteristics of study subjects

Compliance was satisfactory and participants in both groups took more than 90% of the medications. According to the Asia-Pacific criteria, 26.5% of the study subjects were overweight, while a higher proportion (73.5%) were obese but not overweight. Randomization was successful, as the two groups generated were comparable for most variables, with no significant differences in the baseline demographic, anthropometric, and nutritional data between the intervention and control groups (Tables 1 and 2). Caloric intake and physical activity as MET-minute remained unchanged throughout the 12-weeks period, both within the group and between the groups. Also, no statistically significant differences in BMI, percent body fat, or SAD were observed between the groups at baseline.

Safety

Most of the subjects completed the protocol without adverse symptoms. Four subjects in the Intervention group and three subjects in the control group complained of increased appetite. No changes in liver function (alanine aminotransferase) or renal function (creatinine) were observed in the intervention group. An increase in creatinine was observed in the control group; however, it was within the normal reference range. (Table 3)

Within-group analyses

No difference in fasting blood sugar level was observed after 12 weeks of administration in the intervention group and in the control group. No statistically significant differences in insulin, HOMA-IR, or QUICKI were observed between the groups at baseline. No change in total cholesterol, LDL cholesterol, or HDL cholesterol and triglyceride levels was observed in either group (Table 2).

Between-group analyses

Table 3 shows the differences in the change of metabolic and biochemical characteristics between the intervention and control groups during the experimental period. Repeated measures ANOVA showed no significant main effects of intervention and time. We found that KRG had no significant effect on insulin resistance over time. In addition, no significant effect of KRG supplementation over time in any other metabolic characteristics was detected between the groups at week 12. For the subgroup with intermediate or insulin resistance KRG did not have any significant effect on improving insulin sensitivity. Subjects who were obese at baseline also did not show a significant change in HOMA-IR after KRG supplementation.

DISCUSSION

To the best of our knowledge, the present study is the first well-controlled, randomized clinical study to examine the long-term metabolic efficacy of KRG in healthy overweight or obese subjects without overt diabetes and hypertension. This study was conducted according to a previous study that reported an acute postprandial glycemia effect on healthy euglycemic adults; all participants took 2 g of KRG rootlet 40 min before each meal (total 6 g). KRG had no observable effects on our subjects. In addition, it had no positive effects when sub-grouped according to the HOMA-IR and BMI. Many studies in both animal model and human support have reported a positive effect of red ginseng on glucose metabolism. Ginseng has been shown to increase insulin production and reduce cell death in pancreatic beta-cells in an animal model. 16, 17 Two studies examining the long-term anti-diabetic effect on T2DM patients reported that taking KRG supplement for 12 weeks resulted in improved insulin sensitivity. 2, 3 Unfortunately, the high rate of follow-up loss and the changes in caloric intake and physical activity were limitations that caused difficulty in interpretation of the results. A recent study on overweight and obese subjects with impaired glucose tolerance or diabetes concluded that taking ginseng supplements did not result in improved insulin sensitivity; however that study was designed for only 30 days, which is a relative short period of time, and each group included only five people. 18 In addition, a systematic review concluded an

Table 1. Sociodemographic characteristics of the study subjects at the start of treatment

<table>
<thead>
<tr>
<th></th>
<th>Korea Red Ginseng (n=34)</th>
<th>Placebo (n=34)</th>
<th>p valuechr</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.6 ± 9.1</td>
<td>43.1 ± 8.9</td>
<td>0.493</td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>35.3</td>
<td>38.2</td>
<td>0.801</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123 ± 10.3</td>
<td>120 ± 10.9</td>
<td>0.302</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80.0 ± 7.1</td>
<td>79.2 ± 8.9</td>
<td>0.687</td>
<td></td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>14.7</td>
<td>5.9</td>
<td>0.231</td>
<td></td>
</tr>
<tr>
<td>Heavy drinking (%)</td>
<td>29.4</td>
<td>23.5</td>
<td>0.582</td>
<td></td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; DBP: diastolic blood pressure
Data are expressed as means ± SD or frequency (percent)
The p value was estimated using two sample t-test or chi-square test
Statistical differences are based on two-sample t-test or chi-square test
### Table 2. Anthropometric and nutritional characteristics at the start of the study and after 12 weeks of treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Korea Red Ginseng (n=34)</th>
<th>Placebo (n=34)</th>
<th>p value†</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 12</td>
<td>p value</td>
<td>Week 0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (23.0-33.4)</td>
<td>26.3 (23.0-33.0)</td>
<td>0.053</td>
<td>0.283</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>30.7 ± 6.6</td>
<td>30.7 ± 10.0</td>
<td>0.116</td>
<td>0.753</td>
</tr>
<tr>
<td>SAD (cm)</td>
<td>19.2 (16.0-23.0)</td>
<td>19.0 (16.3-24.0)</td>
<td>0.092</td>
<td>0.046</td>
</tr>
<tr>
<td>Caloric intake (Kcal/day)</td>
<td>1871 ± 530</td>
<td>1865 ± 553</td>
<td>0.951</td>
<td>0.225</td>
</tr>
<tr>
<td>Activity (METs/week)</td>
<td>1503 ± 1417</td>
<td>1304 ± 1518</td>
<td>0.177</td>
<td>0.086</td>
</tr>
</tbody>
</table>

SAD: Sagittal abdominal diameter. One MET is roughly equivalent to 1 kcal/min for a 60-kg person
Data expressed as means ± SD or median and inter-quartile ranges
†Paired t-test (means ± SD) or Wilcoxon signed-rank test (median and inter-quartile ranges) for within group (p value in Korea Red Ginseng group, p value in placebo group), ‡Two-way repeated-measures ANOVA over time for between groups, §P>0.05 by two-sample t-test or Mann–Whitney U test

### Table 3. Metabolic and biochemical characteristics at the start of the study and after 12 weeks of treatment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Korea Red Ginseng (n=34)</th>
<th>Placebo (n=34)</th>
<th>p value†</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 12</td>
<td>p value</td>
<td>Week 0</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>89.9 ± 15.1</td>
<td>90.5 ± 19.0</td>
<td>0.818</td>
<td>0.451</td>
</tr>
<tr>
<td>Fasting insulin (IU/mL)</td>
<td>5.3 (1.2-15.2)</td>
<td>5.6 (0.2-15.2)</td>
<td>0.300</td>
<td>0.321</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.11 (0.2-3.94)</td>
<td>1.12 (0.2-3.02)</td>
<td>0.351</td>
<td>0.278</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.38 (0.31-0.52)</td>
<td>0.37 (0.24-0.88)</td>
<td>0.285</td>
<td>0.228</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>172 ± 31.8</td>
<td>172 ± 31.2</td>
<td>0.995</td>
<td>0.872</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>110 ± 28.9</td>
<td>109 ± 29.8</td>
<td>0.711</td>
<td>0.368</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.6 ± 12.8</td>
<td>47.8 ± 13.7</td>
<td>0.583</td>
<td>0.820</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>107 ± 55.6</td>
<td>119 ± 63.8</td>
<td>0.131</td>
<td>0.737</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.73 ± 0.16</td>
<td>0.75 ± 0.17</td>
<td>0.070</td>
<td>0.018</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>25.8 ± 17.2</td>
<td>24.8 ± 16.1</td>
<td>0.591</td>
<td>0.651</td>
</tr>
</tbody>
</table>

HOMA-IR: homeostasis model assessment insulin resistance index; QUICKI: quantitative insulin sensitivity check index; LDL: low density lipoprotein; HDL: high density lipoprotein; ALT: alanine transaminase
Data expressed as means ± SD or median and inter-quartile ranges
†Paired t-test (means ± SD) or Wilcoxon signed-rank test (median and inter-quartile ranges) for within group (p value in Korea Red Ginseng group, p value in placebo group), ‡Two-way repeated-measures ANOVA over time for between groups, §P>0.05 by two-sample t-test or Mann–Whitney U test
unclear effect of red ginseng for treatment of T2DM.\(^{19}\)
We aimed to evaluated the benefits of long-term KRG in healthy individuals with overweight and obesity who are at risk of insulin resistance. Most participants were obese, and 33.8% of them had insulin resistance.

There is uncertainty with regard to whether intact ginsenosides can be absorbed from the human gastrointestinal tract and which hydrosolysis products of PPD and PPT reach the systemic circulation. Few studies have examined the degradation pathway of ginsenosides in humans. One study examining the total amount of PPT and PPD in human urine reported recovery of approximately 1.2% of the orally ingested dose of PPT and very low amounts of the PPD (<0.2%) of the administered dose.\(^{20}\) In another study using human plasma, less absorbance of ginseng was observed after oral administration.\(^{21}\) Therefore, the negative result of the present study may be explained by the low amount of ginsenosides and their degradation products reaching the systemic circulation from the gastrointestinal tract and liver enzyme pathway through the oral administration of red ginseng.

Korean red ginseng, which is considered a food supplement, not a drug, is available in many countries including Korea. Unfortunately, this study demonstrated that KRG has no effect on insulin sensitivity in healthy nondiabetic overweight and obese adults. Our study has some limitations, including the relatively short duration of the study (12 weeks) and the fact that no attempt was made to measure HOMA-IR prior to the start of the study, including in insulin resistant subjects. Other limitations are the lack of direct physiological measure of glucose and insulin homeostasis. However, HOMA-IR is an inexpensive and simple method for determination of insulin sensitivity, and previous studies have reported high correlation of HOMA-IR with the gold standard euglycemic-hyperinsulinemic clamp in Asian peoples with or without type 2 diabetes.\(^{22}\) Thus, further research is needed on order to reconfirm these findings. Nevertheless, this double-blinded study enrolled 68 subjects, which, to the best of the author’s knowledge, is the largest number of participants, and examined the long term efficacy after administration of KRG for a period of 12 weeks. In addition, in the KRG group administration of KRG was confirmed by detecting the existence of ginsenosides in blood samples from the participants by high performance liquid chromatography. In conclusion, KRG does not improve insulin sensitivity in overweight and obese adults who do not have diabetes or hypertension. However, replication will be needed in order to confirm the results of this first-stage study for current practice in the field.

ACKNOWLEDGMENT
This study was supported by the 2010 grant from the Korean Society of Ginseng funded by Korea Ginseng Corporation.

AUTHOR DISCLOSURES
All authors have no conflicts of interest.

REFERENCES
Effect of Korean red ginseng on insulin sensitivity in non-diabetic healthy overweight and obese adults

Young Hye Cho MD¹, Soon Cheol Ahn PhD², Sang Yeoup Lee MD¹,³, Dong Wook Jeong MD¹, Eun Jung Choi MD¹, Yun Jin Kim MD⁴, Jeong Gyu Lee MD⁴, Yu-Hyun Lee MD⁴, Byung-Cheul Shin OMD⁵

¹Family Medicine Clinic and Research Institute of Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, South Korea
²Department of Microbiology and Immunology, Pusan National University School of Medicine, Yangsan, South Korea
³Medical Education Unit, Pusan National University School of Medicine, Yangsan, South Korea
⁴Department of Family Medicine, Pusan National University Hospital, Busan, South Korea
⁵Division of Clinical Medicine, School of Korean Medicine, Pusan National University, Yangsan, South Korea

無糖尿病之過重及肥胖成人攝取韓國紅蔘對其胰島素敏感性之影響

韓國紅蔘是全球知名的中草藥之一，被認為具有多種促進健康的效益，其中包括糖尿病的預防及改善。本研究目的，為評估韓國紅蔘補充劑，是否影響無糖尿病及高血壓病史之過重及肥胖成人的胰島素敏感性。研究設計為隨機雙盲對照試驗，共 68 位 (BMI ≥23 kg/m²) 參與者。介入組 34 位，每日給予含有 500 毫克紅蔘粉的膠囊 12 顆；控制組則給予安慰劑，共為期 12 週。介入前，兩組的胰島素濃度及胰島素敏感性指標，無顯著差異。研究結果顯示，韓國紅蔘並無助於提昇無糖尿病及高血壓病史之過重及肥胖成人的胰島素敏感性。

關鍵字：人蔘、過重、肥胖、胰島素敏感性