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Research article

An 8-wk, randomized, double-blind, placebo-controlled clinical trial for the antidiabetic effects of hydrolyzed ginseng extract

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ABSTRACT

Background: To investigate the antidiabetic effects of hydrolyzed ginseng extract (HGE) for Korean participants in an 8-wk, randomized, double-blinded, placebo-controlled clinical trial.
Methods: Impaired fasting glucose participants [fasting plasma glucose (FPG) $\geq$ 5.6mM or $<$ 6.9mM] who had not been diagnosed with any disease and met the inclusion criteria were recruited for this study. The 23 participants were randomly divided into either the HGE (n = 12, 960 mg/d) or placebo (n = 11) group. Outcomes included measurements of efficacy (FPG, postprandial glucose, fasting plasma insulin, postprandial insulin, homeostatic model assessment-insulin resistance, and homeostatic model assessment-β) and safety (adverse events, laboratory tests, electrocardiogram, and vital signs).
Results: After 8 wk of HGE supplementation, FPG and postprandial glucose were significantly decreased in the HGE group compared to the placebo group. No clinically significant changes in any safety parameter were observed. Our study revealed that HGE is a potent antidiabetic agent that does not produce noticeable adverse effects.
Conclusion: HGE supplementation may be effective for treating impaired fasting glucose individuals.

1. Introduction

There is much concern about the dramatic increase in the population of type 2 diabetes patients. Both the recent prevalence rate and the estimated increase in incidence have become public health problems and create a serious burden on society. In order to identify an individual at increased risk of developing type 2 diabetes, the concept of impaired fasting glucose (IFG) has been introduced by the American Diabetes Association [1]. Individuals with IFG have fasting plasma glucose levels between 5.6 mmol/L and 6.9 mmol/L [2]. In addition to being more likely to develop diabetes in the near future, these people are at greater risk for cardiovascular disease [3,4]. Therefore, effective approaches to control blood glucose levels are urgently needed. Previous large-scale studies have demonstrated that lifestyle intervention is the best way to achieve this goal [5–7]. Pharmacotherapy is also used to manage individuals with IFG. Paradoxically, medications used to control blood glucose often cause metabolic side effects such as weight gain [8,9]. Thus, the development of alternative therapies is of paramount importance, and in this context, herbal extracts are among the most promising source of new treatments for the prevention of diabetes.

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Ginseng (*Panax ginseng* Meyer) has been used as traditional medicine in the treatment of metabolic diseases, cancer, cardiovascular diseases, and other diseases in a number of Asian countries [10–12]. The bioactive constituents of ginseng include various saponins (ginsenosides) and nonsaponins, and the pharmacological activities of ginseng are mainly attributed to ginsenosides [13,14]. To date, 80 ginsenosides have been identified in ginseng. These ginsenosides are further biotransformed by intestinal bacteria, which increase intestinal absorption and bioactivity and diminish the toxicity of the metabolite compared to its parent compound [15,16]. In this regard, fermentation using microorganisms or treatment with an appropriate enzyme for the production of more effective compounds has been extensively studied.

In previous studies, pectinase was used for the biotransformation of ginsenosides in ginseng extract, and this process increased the level of bioactive compounds, including compound K (also known as IH-901), resulting in improved pharmacological functions [17,18]. Although the antidiabetic activities of ginseng have been well documented in animal [19] and human [20] studies, the improved effects of hydrolyzed ginseng on diabetic patients are not clear. Therefore, in this study, we investigated whether hydrolyzed ginseng extract (HGE) could be effective in reducing the risk of type 2 diabetes in individuals with IFG.

2. Materials and methods

2.1. Study design

This study was an 8-wk, randomized, double-blinded, placebo-controlled clinical trial. The randomization scheme was generated by a computerized procedure. Neither the investigators nor the participants knew the randomization code until the trial was completed and database locked. Participants who responded and met the entry criteria during a telephone screening interview were scheduled for a baseline visit. Participants were scheduled for a screening visit, during which the informed consent was reviewed and signed. At 0 wk and 8 wk, a 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast. A catheter was inserted into a vein and blood samples were obtained prior to (0 min) and after (15 min, 30 min, 60 min, 90 min, and 120 min) consuming a 75-g glucose drink. During the 8-wk intervention period, participants were asked to continue their usual diets and to not take any other functional foods or dietary supplements. Participants were also asked to report for the assessment of any adverse events or any changes in lifestyle and eating patterns and to assess pill compliance.

2.2. Participants

The study participants were recruited from the Clinical Trial Center for Functional Foods at Chonbuk National University Hospital, Jeonbuk, Republic of Korea during 2009. IFG participants [fasting plasma glucose (FPG) $\geq$ 5.6mM and $<$ 6.9mM] who had not been diagnosed with any disease and met the inclusion criteria were recruited for this study. Exclusion criteria for the study were: (1) abnormal lipid profile values; (2) acute/chronic inflammation; (3) treatment with corticosteroids within the past 4 wk; (4) cardiovascular disease, such as arrhythmia, heart failure, myocardial infarction, or a pacemaker; (5) allergic or hypersensitivity to any of the ingredients in the test products; (6) history of a disease that could interfere with the test products or impede their absorption, such as gastrointestinal disease (Crohn's Disease) or gastrointestinal surgery; (7) participation in any other clinical trials within the past 2 mo; (8) renal disease, such as acute/chronic renal failure or nephrotic syndrome; (9) abnormal hepatic function; (10) treatment by hypolipidemic drug therapy within the past 3 mo; (11) treatment by antipsychotic drug therapy within the past 2 mo; (12) a laboratory test, medical, or psychological conditions deemed by the investigators to interfere with successful participation in the study; (13) history of alcohol or substance abuse; or (14) pregnancy or breast feeding. All participants gave written informed consent prior to beginning the study. The protocol was approved by the Functional Foods Institutional Review Board (FFIRB) of Chonbuk National University Hospital (FFIRB number: 2009-02-001). The protocol was registered in www.clinicaltrials.gov (NCT01854164).

Table 1
Composition of test products provided/d

Placebo supplement		Hydrolyzed ginseng extract supplement	
Component	Content (%)	Component	Content (%)
Powdered rice	10	Fermented ginseng extract	30
Pumpkin seeds oil	65.84	Pumpkin seeds oil	55.4
Refined palm oil	15.44	Refined palm oil	9.0
Yellow wax	7.72	Yellow wax	4.6
Sorbic acid	1	Sorbic acid	1
Total	100	Total	100

2.3. Test supplement

HGE was obtained from ILHWA Co. Ltd, (Guri, Republic of Korea), as described previously, with slight modifications [17]. The HGE contained 7.54 mg/g of Rg1, 1.87 mg/g of Re, 5.42 mg/g of Rb1, 0.29 mg/g of Rc, 0.36 mg/g of Rb2, and 0.70 mg/g of Rd. The compound K content in the HGE was 6.3 mg/g. It was administered as a capsule (480 mg/cap and 960 mg/d) composed of 30% HGE and 70% diluting agent (pumpkin seed oil, refined palm oil, yellow wax, and sorbic acid). The placebo capsules were composed primarily of powdered rice and pumpkin seed oil and were matched with regard to energy content, flavor, appearance, and dosage (Table 1).

All participants were instructed to take two capsules/d (one capsule each after breakfast and dinner). HGE and placebo capsules were packaged indistinguishably and labeled with the participant's number. Participants were instructed to bring all remaining supplements at each visit and were withdrawn from the study if the supplement consumption was $>$ 70% of the prescribed dose.

2.4. Outcome measures

Efficacy assessments included the following: glucose [FPG, plasma glucose during OGTT (postprandial plasma glucose: PPG), glucose incremental area under the curve (iAUC), and glucose maximum concentration (C_{max})], insulin [fasting plasma insulin (FPI), plasma insulin during OGTT (postprandial plasma insulin: PPI), insulin iAUC, and insulin C_{max}], homeostatic model assessment (HOMA)—insulin resistance (IR), and HOMA-β, glycated albumin, fructosamine, and HbA1c. The glucose and insulin iAUCs during the OGTT were determined by the trapezoidal method.

Safety assessments included the following: electrocardiogram, hematology, and laboratory tests (white blood cells, red blood cells, hemoglobin, hematocrit, platelet count, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, etc.), pulse rate, and blood pressure, along with a personal report and were recorded at every visits.

Blood samples were analyzed on a Hitachi 7600-110 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan).

2.5. Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS Institute, Chicago, IL. USA). Data are shown as the mean values and