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Research article

Antihypertensive effect of Korean Red Ginseng by enrichment of ginsenoside Rg3 and arginine–fructose

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ABSTRACT

Background: Ginsenoside Rg3 and arginine–fructose (Arg-Fru) are known as the hypotensive compounds of *Panax ginseng*; however, their efficacy on antihypertension has not been reported yet to our best knowledge. Thus, hypotensive components-enriched fraction of red ginseng (HCEF-RG) was prepared from fine root concentrate (FR) and their antihypertensive effects were investigated in spontaneously hypertensive rats (SHR).

Methods: Male SHRs were divided into six groups: control (Wistar Kyoto, SHR); FR 500; FR 1,000; HCEF-RG 500; and HCEF-RG 1,000; samples (mg/kg body weight) were orally administered every day for 8 wk. Blood pressure was monitored at 1 wk, 2 wk, 3 wk, 4 wk, 6 wk, and 8 wk by tail cuff method. At 8 wk after samples administration, mice were killed for the measurement of renin activity (RA), angiotensin-I converting enzyme inhibition, angiotensin II, and nitric oxide (NO) levels in plasma.

Results: HCEF-RG with four-fold more Rg3 and 24-fold more Arg-Fru contents was successfully prepared from reacted mixtures of FR and persimmon vinegar (12 times against FR, v/v) at 80°C for 18 h. Both FR 1,000 and HCEF-RG 1,000 showed lowered systolic blood pressure than SHR control group and HCEF-RG 1,000 group exhibited a significant decrease in diastolic blood pressure. RA was significantly lowered in all treated groups, while angiotensin II did not affect by FR and HCEF-RG treatment. However, angiotensin-I converting enzyme inhibition and NO in FR 1,000 and HCEF-RG 1,000 were significantly increased compared with SHR control group.

Conclusion: HCEF-RG is more effective and useful for alleviating hypertension than FR, implying the health benefit of Rg3 and Arg-Fru.

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1. Introduction

The incidence of various age-related degenerative neurological and cardiovascular diseases continues to increase significantly as lifestyles change and the population ages. Hypertension is characterized by an increase in arterial blood pressure due to increased cardiac output or peripheral vasoconstriction. The incidence of hypertension as a disease is low; however, this disorder has been strongly associated with stroke, myocardial infarction, diabetes, and heart failure. Hypertension also leads to cardiac and vascular muscle hypertrophy, as well as arteriosclerosis [1]. The vascular complications of hypertension are exacerbated by concomitant vascular injuries such as hyperlipidemia or hyperglycemia, which are attributable to cell characteristics, expression of autocrine or paracrine growth hormones, and changes in growth hormone receptors [2].

Clinically, hypertension is defined as a condition in which the systolic blood pressure exceeds 120 mmHg and the diastolic pressure exceeds 80 mmHg. Blood pressure is mainly modulated by the renin–angiotensin systems (RAS) and the vasopressin system. Angiotensin-converting enzyme (ACE), which plays a key role in the RAS, converts angiotensin I to angiotensin II and the dipeptide histidine–leucine. To treat hypertension, ACE inhibitors such as enalapril, captopril, ramipril, and lisinopril have been developed

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and commercialized; however, these drugs are associated with side effects such as changes in taste, leukopenia, vascular edema, liver function abnormalities, and dry cough [3]. New antihypertensive drugs with established efficacy and safety are necessary to improve treatment regimens for patients that suffer from hypertension. Various *in vitro* and *in vivo* studies have examined the antihypertensive activities of different plants such as *Gastrodia elata* [4], *Alisma canaliculatum* [5], and *Monascus* [6].

The persimmon tree (*Diospyros kaki*) produces fruits in the fall season; as described in Oriental medicine, the fruits are characterized by a sweet and refreshing taste, with no poisonous substances. In particular, a colloidal fluid from unripe persimmon fruits has been used for treating hypertension [7]. In Japan, persimmon juice has been traditionally used to treat hypertension and prevent heart attacks [8]. The hypotensive effect of *Panax ginseng* is attributable to the saponin, ginsenoside Rg3, which could be converted by acidic hydrolysis from protopanaxadiol-type saponins and exhibits protective effects against hypertension [9–14]. Furthermore, arginine–fructose (Arg-Fru) produced from arginine–fructose–glucose (Arg-Fru-Glc) by the Maillard reaction under acidic condition is known to be a specific active compound in Korean Red Ginseng [15]. Arg-Fru is absorbed into the small intestine after release from Arg-Fru-Glc by maltase and then participates in the nitric oxide (NO)-mediated vasodilation [16]. Therefore, if ginsenoside Rg3-Arg-Fru-enrichment materials can be produced, they will be useful in alleviating hypertension and consequently allowing the food industry to develop new hypotensive compounds-fortified products. Thus, in this study, we prepared a hypotensive components-enriched fraction from red ginseng (HCEF-RG) under various conditions with persimmon vinegar and evaluated the ability of HCEF-RG to improve the hypertension in spontaneously hypertensive rats (SHR).

2. Materials and methods

2.1. Materials

The red ginseng tail root (4-year-old, 2010) was provided by Cheon Ji Yang (Seoul, Korea) and Korean persimmon vinegar (pH 3.6) was purchased from Nong Hyup (Wanju, Korea). Other reagents were purchased from Sigma–Aldrich (St. Louis, MO, USA).

2.2. Preparation of HCEF-RG

The antihypertensive fractions with enriched ginsenoside Rg3 were made by modifying a method described by Ko et al [13]. To obtain the fine root concentrates (FR), red ginseng tail root (10 kg) was added to 70% ethanol (100 L, v/w) and extracted at 60 ± 2°C for 8 h. The extracts were centrifuged at 2,250*g* for 30 min and the supernatant was collected and then concentrated in a rotary evaporator at 60°C. FR was subjected to the preparation for antihypertensive fractions by mixing with persimmon vinegar (12 times, v/v) and then reacting in a water bath (WEB Multi-purpose Extraction Water Bath, Daihan, Korea) with a reflux condenser at 70°C, 80°C, and 90°C for 3 h, 6 h, 12 h, 18 h, 24 h, and 48 h.

2.3. Ginsenoside analysis by HPLC

Sep-Pak C18 cartridge (Waters, Milford, MA, USA) was used to pretreat the sample and then a C18 cartridge with 5 mL of 100% methanol and 15 mL of distilled water was gradually activated. The resulting samples (5 mL) were loaded onto the C18 cartridge, and gradually washed thoroughly with 15 mL of distilled water and 20 mL of 30% methanol. Next, crude saponin was used to rinse with 5 mL of 100% methanol. The fractions were filtered by a 0.22-μm membrane filter and the filtering fractions from methanol and distilled water were used for ginsenoside and Arg-Fru, respectively.

The Waters 486 Tunable Absorbance Detector HPLC system (Waters) equipped with an YMC-Pack Pro C18 column (4.6 mm × 250 mm, 5 μm; Waters) was used for ginsenoside separation. The detection wavelength was set at 203 nm and the solvent flow rate was held constant at 1.6 mL/min and the temperature of the column was set at 45°C. The mobile phase used for the separation consisted of solvent A (acetonitrile) and solvent B (water). A gradient elution procedure was used at 0 min, 15%; 0–14 min, 15–20%; 14–17 min, 20–39%; 17–57 min, 39–48%; 57–70 min, 48–70%; 70–80 min, 70–100%; 80–120 min, 100–60%; and 120–130 min, 60–15%. The injection volume was 20 μL. Standard ginsenoside materials (Embo Laboratory, Daejeon, Korea) were prepared in HPLC-grade methanol.

For the analysis of Arg-Fru, the Amperometric Detector HPLC system (Waters) equipped with an CarboPac PA-1 column (4 mm × 250 mm, 5 μm; Waters) was used. The solvent flow rate with the isocratic mobile phase (water: 250mM NaOH = 50:50, v/v) was held constant at 1.0 mL/min and the temperature of the column was set at 30°C. The injection volume was 5 μL and the working and reference electrode were Au and Ag/AgCl, respectively.

2.4. Animals and diets

The experiment was performed using 8-wk-old male Wistar Kyoto rats (WKY; normal group, male, 130–175 g body weight; Charles River Co., Kanawa, Japan) and SHR (hypertension group, male, 180–215 g body weight, Orient Bio Co. Ltd., Seoul, Korea). The animals were allowed to acclimate for a wk and then randomly divided into six groups (n = 8 each): WKY-control; SHR-control; SHR- FR 500; SHR- FR 1,000; SHR- HCEF-RG 500; and SHR- HCEF-RG 1,000. The animals were housed individually in stainless steel cages arranged in a randomized complete block design at a temperature of 23 ± 1°C and humidity of 53 ± 2% in a light-controlled room under a 12 h light–dark cycle. The animals had access to food (18% protein, 2018S; Harlan Laboratories Inc., Indianapolis, IN, USA) and water *ad libitum*. The control groups (WKY, SHR) were provided with sterile distilled water, and the other groups (FR, HCEF-RG) were given forced oral administration (500 mg/kg, 1,000 mg/kg bodyweight) using a disposable syringe for 8 wk. The weight and dietary intake were measured once per wk. At the end of the experimental period, the animals were anesthetized with isoflurane, nitrogen, and oxygen withholding food for 12 h, and blood samples were taken from the inferior vena cava to determine the levels of plasma biomarkers. The blood sample was centrifuged in a tube with EDTA coating at 1,006*g* for 10 min to remove plasma, and the resulting sample was stored at −80°C before analysis. The care and treatment of rats were approved by the Woojung Life Science Research Center Animal Care Committee (Suwon-si, Gyeonggi-do, Korea) (WJIACUC110818-03-04), and the procedures were in accordance with the Korean Guide for the Care and Use of Laboratory Animals.

2.5. Heart rate and blood pressure

Heart rate, systolic blood pressure, and diastolic blood pressure were measured at 1 wk, 2 wk, 3 wk, 4 wk, 6 wk, and 8 wk by electrosphygmomanometer (Letica LE 5002; Panlab, Barcelona, Spain). After stabilization for 15 min at 37°C in a mold, blood pressure was measured by the tail cuff method.

2.6. Renin activity

The plasma (200 μL) was added to 200 μL of precooled enzymatic inhibitor and was divided into two equal volumes of 200 μL

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