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Research article

Anti-inflammatory and antifatigue effect of Korean Red Ginseng in patients with nonalcoholic fatty liver disease☆

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ABSTRACT

Background: Korean Red Ginseng (KRG) is a well-known natural product with anticarcinogenic and antioxidant effects. We evaluated the antifatigue effect of KRG in patients with nonalcoholic fatty liver disease (NAFLD).

Methods: Eighty patients with NAFLD were prospectively randomized to receive 3 wk of KRG or placebo in addition to counseling on healthy eating and regular exercise. Liver function test, proinflammatory cytokines, adiponectin, antioxidant activity, and fatigue score were measured and compared according to the body mass index between the KRG and placebo groups.

Results: The liver function tests were significantly improved after 3 wk of treatment in both groups. The mean levels (at baseline and after treatment) of tumor necrosis factor-α were 108.0 pg/mL ± 54.8 pg/mL and 92.7 pg/mL ± 39.0 pg/mL ($p = 0.018$) in the KRG group and 123.1 pg/mL ± 42.1 pg/mL and 127.5 pg/mL ± 62.2 pg/mL ($p = 0.694$) in the placebo group, respectively. There was a significant difference in change of adiponectin levels between the KRG (7,751.2 pg/mL ± 3,108.1 pg/mL and 8,197.3 pg/mL ± 2,714.5 pg/mL) and placebo groups (7,711.6 pg/mL ± 3,041.3 pg/mL and 7,286.1 pg/mL ± 5,188.7 pg/mL, $p = 0.027$). In patients with overweight, the fatigue score was significantly decreased in the KRG group (35.0 ± 13.2 and 24.5 ± 8.9, $p = 0.019$).

Conclusion: Our results show that KRG might be effective in reducing proinflammatory cytokine and fatigue in overweight patients with NAFLD, in addition to improvements in adiponectin levels.

1. Introduction

Fatty liver is defined as a condition in which triglycerides accumulate in hepatocytes to the extent that they comprise over 5% of the mass of the liver. It is divided into alcoholic fatty liver disease and nonalcoholic fatty liver disease (NAFLD) [1,2]. NAFLD and nonalcoholic steatohepatitis are major global public health problems, because they are related to insulin resistance, obesity, and metabolic syndrome [3]. Most NAFLD patients show chronic fatigue with peripheral inflammation and immune activation, which causes serious social, economic, or medical problems and impairs physical function [4,5].

The World Health Organization defines being overweight as having a body mass index (BMI) of 25 kg/m^2 or more, whereas a

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BMI of 30 kg/m^2 or more is considered to indicate obesity. Being overweight or obese significantly increases the risk of developing metabolic syndrome and liver disease [6]. In Western countries, 20–30% of NAFLD patients develop hepatocellular carcinoma [7]. Many overweight patients have been found to suffer from excessive daytime sleepiness [8]. Ginseng (*Panax ginseng* Meyer) root has been widely used as an herbal treatment in East Asia for more than 2,000 yr. Several studies have demonstrated that ginseng has anticarcinogenic, anti-inflammatory, and antioxidant activities, which were associated with fatigue syndrome [9,10].

Ginsenoside Rb1, the most abundant ginsenoside in the herb, activates 5′-adenosine monophosphate-activated protein kinase, which suppresses the expression of genes that encode lipogenesis-inducing enzymes in rats with fatty liver disease [11]. Moreover, ginseng has been used to treat cancer-related fatigue without significant side effects [12]. Based on these findings, it is conceivable that ginseng might contribute to reduce fatigue by modulating inflammation and signal pathway in NAFLD patients. Some studies have demonstrated the antifatigue effect of ginseng [13,14]. However, few studies have evaluated whether ginseng has a direct effect on fatigue resulting from liver disease or on the biomarker of liver disease. Therefore, in this study, we evaluated the anti-inflammatory antioxidant, and antifatigue activities of Korean Red Ginseng (KRG) in patients with NAFLD.

2. Materials and methods

2.1. Patients

Between April 2011 and August 2012, we conducted a single-blind, randomized, controlled clinical trial evaluating the efficacy of KRG (trial registration number: NCT02331589; http://clinicaltrials.gov/ct2/show/NCT02331589). Patients aged over 20 yr and with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of 50 IU/L or more were enrolled. Patients who had viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, pancreatitis, hemochromatosis, Wilson's disease, drug-induced liver injury, or cancers were excluded. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration as reflected by *a priori* approval of the Institutional Review Board for Human Research in all participating hospitals. Informed consent for study participation was obtained from each patient.

Randomization was performed using a computerized procedure.A total of 80 patients were enrolled. Among them, 14 patients (5 patients in the KRG group and 9 patients in the placebo group) were excluded (8 patients refused to participate, 4 patients had inadequate records, and 2 patients were consuming alcohol; Fig. 1). The levels of liver enzymes, proinflammatory cytokines [tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)], adiponectin, antioxidant activity, and fatigue severity score were measured at the beginning of the study (baseline) and after 3 wk of medication (Fig. 2). We performed subgroup analysis by dividing the overweight and normal groups by BMI, because a previous report suggested that obesity was closely associated with fatigue [15].

We conducted a baseline evaluation, which included obtaining data for the following: family history, BMI, abdominal ultrasound results, a complete blood count, a liver function test, and viral markers. Serum biochemical parameters included total bilirubin (TB), ALT, AST, gamma-glutamyl transpeptidase (γ-GT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin, blood urea nitrogen, α1-antitrypsin, creatinine, α-fetoprotein, prothrombin time, blood glucose, triglycerides, total protein (TP), and total cholesterol. All patients were tested for several hepatitis viruses and human immunodeficiency virus. Hepatitis A virus was detected using antihepatitis A IgG and IgM antibodies, and hepatitis B virus was detected using the IgM antibody against the hepatitis B core antigen, the hepatitis B surface antigen, and the hepatitis B surface antibody. Hepatitis E virus was detected using antihepatitis E IgG and IgM antibodies, and hepatitis C virus was detected using antihepatitis C antibodies with or without the presence of hepatitis C RNA.

2.2. Medical treatment

All patients were treated with *Silybum marianum* (Legalon, Bukwang Pharmaceutical, Co., Ltd., Seoul, South Korea) capsule (450 mg/d) and all patients were advised by the same clinician (K.T.S.) to perform regular aerobic exercise for more than 30 min/d. In addition, all patients also received counseling on healthy eating. Patients who met the inclusion criteria were randomly assigned to receive a KRG capsule (ginsenosides Rg1 + Rb1 6.0 mg/g; 3,000 mg/d) or a placebo three times a day for 3 wk (Fig. 2). No other medication was prescribed. The placebos were manufactured at the Korea Ginseng Corporation (Seoul, South Korea), and resembled the KRG capsule powder in both shape and size.

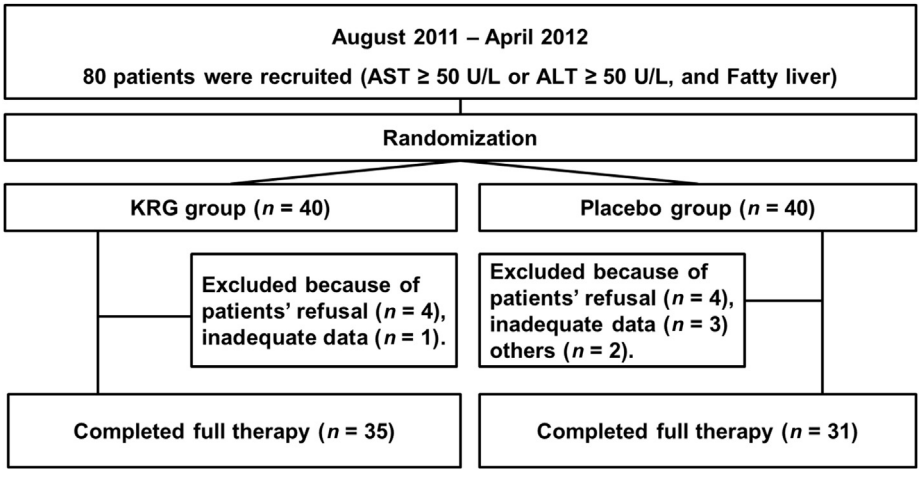

Fig. 1. Flow chart for enrollment. ALT, alanine aminotransferase; AST, aspartate aminotransferase; KRG, Korean Red Ginseng.