NUTRITION RESEARCH 35 (2015) 655–663

Available online at www.sciencedirect.com

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Original Research

Schisandra chinensis fruit modulates the gut microbiota composition in association with metabolic markers in obese women: a randomized, double-blind placebo-controlled study

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ARTICLE INFO

Article history:
Received 19 January 2015
Revised 28 April 2015
Accepted 8 May 2015

Keywords:
Bacteroides
Bacteroidetes
gut microbiota
obesity
Schisandra chinensis fruit

ABSTRACT

Schisandra chinensis fruit (SCF) is known to have beneficial effects on metabolic diseases, including obesity, and to affect gut microbiota in in vivo studies. However, in human research, there have been a few studies in terms of its clinical roles in lipid metabolism and modulation of gut microbiota. A double-blind, placebo-controlled study with 28 obese women with SCF or placebo was conducted for 12 weeks. Anthropometry and blood and fecal sampling were performed before and after treatment. Analysis of the gut microbiota in feces was performed using denaturing gradient gel electrophoresis and quantitative polymerase chain reaction. Although the values did not differ significantly between the 2 groups, the SCF group tended to show a greater decrease in waist circumference, fat mass, fasting blood glucose, triglycerides, aspartate aminotransferase, and alanine aminotransferase than the placebo group. Clustering of the denaturing gradient gel electrophoresis fingerprints for total bacteria before and after treatment indicated more separate clustering in SCF group than placebo. In correlation analysis, *Bacteroides* and *Bacteroidetes* (both increased by SCF) showed significant negative correlation with fat mass, aspartate aminotransferase, and/or alanine aminotransferase, respectively. *Ruminococcus* (decreased by SCF) showed negative correlation with high-density lipoprotein cholesterol and fasting blood glucose. In conclusion, administration of SCF for 12 weeks resulted in modulation of the gut microbiota composition in Korean obese women, and significant correlations with some bacterial genera and metabolic parameters were noted. However, in general, SCF was not sufficient to induce significant changes in obesity-related parameters compared with placebo.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DGGE, denaturing gradient gel electrophoresis; HDL, high-density lipoprotein; PCoA, principal coordinates analysis; qPCR, quantitative polymerase chain reaction; SCF, *Schisandra chinensis* fruit.

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http://dx.doi.org/10.1016/j.nutres.2015.05.001
0271-5317/

1. Introduction

Obesity is a major risk factor for metabolic disease, with involvement in type 2 diabetes, fatty liver disease, and cardiovascular disease [1]. The causes of increased obesity appear to be complex, and obesity is influenced by a mixture of environmental, genetic, neural, and endocrine factors [2]. In recent studies, microbial change in the human gut was proposed as an important cause of obesity, resulting in an increased capacity of the distal gut microbiota to promote host adiposity [3,4]. An increasing number of studies have found relation between imbalances in the composition of gut microbiota and obesity and its associated disease [5].

Nutritional or medicinal approaches are considered potential tools in modulation of gut microbiota, obesity, and metabolic disease. Probiotics or prebiotics have been studied extensively for significant modification of bacterial structure and control of obesity and related metabolic disorders [6-9]. However, investigation of the effects of medicinal herbs on human metabolism and gut microbiota has been inadequate. We reported on *Ephedra sinica*[10] and *Panax ginseng*[11], the main herbs used in Korean medicine for treatment of obesity, which had effects on gut microbiota modulation in obese women, respectively.

Schisandra chinensis fruit (SCF) has a long history in East Asian traditional medicine as a medicinal herb for treatment of chronic cough, night sweating, thirst, diabetes, and obesity [12]. Recent studies have shown the anti-obesity effect of SCF and its main components. *Schisandra chinensis* fruit inhibited preadipocyte differentiation and adipogenesis in 3T3-L1 cells, leading to decreased body weight and fat mass in high-fat diet–induced obese rats [13]. In addition, dibenzocyclooctadiene lignans from SCF have fatty acid synthase inhibitory activity, [14] and schisandrin B isolated from SCF reduces hepatic lipid contents in hypercholesterolemic mice [15]. The influence of gut microbiota in high-fat diet rats has also been reported and an increase in *Bifidobacterium* and a decrease in *Clostridium* species [16]. Although the effects of SCF on obesity and gut microbiota have been demonstrated in in vitro or/and in vivo models, no human trial on gut microbiota modulation in obesity has been reported.

Therefore, the objective of this clinical study was to test our hypothesis that SCF can improve obesity and related metabolic markers through modulation of gut microbiota in a human trial. To investigate the relation of obesity-related metabolic markers and gut microbiota after SCF administration, a randomized, double-blind clinical trial was conducted for analysis of the gut microbiota in feces, body composition, and blood chemistry.

2. Methods and materials

2.1. Subjects

This study was approved by the Institutional Review Board of Dongguk University Ilsan Hospital (approval no. 2012-03) and was registered with the Clinical Research Information Service (https://cris.nih.go.kr/cris/index.jsp no. KCT0000649). Subjects were recruited by advertisements in the local newspaper or posters in the hospital. For qualification, subjects should be obese (body mass index ≥25 kg/m^2). They must have been weight stable within ±10% during the last 6 months and free from antibiotics, probiotics, or any drugs that could impact their weight for the last 3 months. Subjects with weight-influencing diseases, including hyperthyroidism/hypothyroidism, heart diseases, psychogenic diseases, or other chronic systemic diseases, were excluded. Smokers or pregnant women confirmed by a positive human chorionic gonadotropin screening test were also excluded. During the study, subjects who failed to take more than 80% of the required dose of medication withdrew their consent due to inconvenience (personal choices) or refused to communication with members of the research staff were dropped from the study. All participants provided signed informed consent. A total of 40 subjects fulfilled the criteria and were enrolled and then randomly assigned to either the SCF group (n = 20) or the placebo group (n = 20). Twelve subjects failed to complete the study for the following reasons: loss of phone contact and personal choice. Finally, 13 subjects in the SCF group and 15 subjects in the placebo group were included in the analysis.

2.2. Diet control

After enrollment, subjects were instructed to observe the dietary guidelines of the current study, which suggested that they maintain their usual daily diet, limiting energy intake to 83.7–104.6 KJ/kg, according to their energy requirements. It was recommended that they keep a diet diary for every meal. Analysis of the diet data was performed using CAN Pro 3.0 software (The Korean Nutrition Society, Seoul, Korea), and there were no significant differences in energy intake or macronutrient proportion between the SCF and placebo groups.

2.3. *Schisandra chinensis* fruit preparation

After washing, dried SCF (Mungyeong, Korea) was soaked in purified water at 40°C for 6 hours in a ratio of 1:30 (wt/vol). Because the traditional dose of SCF in Oriental medicine ranges from 4 to 12 g, the subjects were required to consume 2 pouches in a day, equivalent to 6.7 g of dried SCF. The extract was added with refined sugar (30% wt/vol) in a stirred tank (Samjin plant, Gwangju, Korea) and then sterilized at 90°C for 5 minutes. The extract had a sweet and sour taste with a light red color. The sugar content of the final product was 12 brix. The placebo was blended with water (87.2%), sugar (12.7% wt/vol), citric acid (0.05%), and red food coloring (0.003%) to make a similar color and taste. Both SCF and placebo were packed in 100 mL pouches. Detailed ingredients of SCF extract are shown in Supplementary Table 1.

2.4. Determination of total polyphenol and flavonoids content

For determination of total polyphenol content to a 50-μL sample, 1 mL 2% Na_2CO_3 was added, followed by 50 μL 50% Folin-Ciocalteu reagent, and the mixture was incubated for 10 minutes at room temperature. Absorbance was measured at 720 nm. Gallic acid was used as a standard of polyphenol. For analysis of total flavonoid contents, 1-mL samples were diluted with 4-mL distilled water and placed in separate test tubes. Then, 0.3 mL 5% sodium nitrite was added to each test tube, and the mixture was