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Beneficial effects of Yerba Mate tea (*Ilex paraguariensis*) on hyperlipidemia in high-fat-fed hamsters

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ABSTRACT

Yerba Mate tea (Mate), an infusion made from the leaves of the tree *Ilex paraguariensis*, is a widely consumed beverage in South America. Mate has previously been shown to have hypolipidemic effects. However, its mechanism of action is not well understood. This study was conducted to determine the effect of Mate on hyperlipidemia induced in hamsters by a high-fat diet, as well as its mechanism of action. Fifty male hamsters were randomly assigned to normal control, high-fat control, and high-fat with Mate tea aqueous extract (1%, 2% or 4% w/v) groups. We evaluated the effects of Mate aqueous extract on body weight, serum lipids, antioxidant enzyme activity, lipoprotein metabolism enzyme activity, and gene expression involved in lipid metabolism in hyperlipidemic hamsters. Mate aqueous extract significantly decreased body-weight gain and lowered serum lipid levels in the hyperlipidemic hamster model. Meanwhile, Mate treatment increased antioxidant enzyme activity, improved lipoprotein lipase (LPL) and hepatic lipase (HL) activities in serum and liver, upregulated mRNA expression of peroxisome proliferator-activated receptor α and low density lipoprotein receptor, and downregulated mRNA expression of sterol regulatory element-binding protein 1c and acetyl CoA carboxylase in the liver. The results indicate that Mate tea ameliorates hyperlipidemia partly by reducing lipid peroxidation, improving endothelial function and LPL and HL activities, and modulating the expression levels of genes involved in lipid oxidation and lipogenesis.

1. Introduction

Hyperlipidemia is considered to be one of the major risk factors for cardiovascular diseases, including atherosclerosis, myocardial infarction, stroke and cerebrovascular diseases (Watts and Karpe, 2011). It has become the primary threat to human health due to the increased daily intake of high-fat diet (Sharma et al., 2008). Therefore, lowering blood lipids is an important strategy in preventing the occurrence and progression of these diseases.

Recently, there has been a resurgence of interest in natural plants that can regulate blood lipid levels. A considerable part of ethnopharmacological research in recent years has been directed toward a better understanding of the hypolipidemic and antiatherogenic effects of medicinal plants (El-Beshbishy et al., 2006; Garjania et al., 2009). Phytochemicals are attracting increasing attention not only for their health benefits, but also for their relatively low toxicity, and might be suitable for long-term supplementation (Lee et al., 2011). Medicinal plants contain a wide array of active components such as flavonoids, polyphenols and alkaloids, which can explain their hypolipidemic activities (Anila and Vijayalakshmi, 2002; El-Beshbishy et al., 2006).

Yerba Mate tea (Mate tea, Mate) is widely consumed in South America, including Argentina, Brazil, Uruguay and Paraguay, and is rapidly penetrating all world markets. It is a herbal tea beverage that is made from the leaves of the tree *Ilex paraguariensis* St. Hilaire (Aquifoliaceae). The indigenous people have used it for centuries as a social and medicinal beverage. Mate beverages contain different bioactive compounds such as polyphenols, alkaloids, triterpenoid saponins and flavonoids (Bracesco et al., 2011; Heck and de Mejia, 2007). The phenolic compounds are rich in Mate and have long been known to possess biological functions.

Mate tea has many important pharmacological properties; it is antioxidant (Bixby et al., 2005; Boaventura et al., 2012; Gugliucci, 1996; Gugliucci and Stahl, 1995), anti-inflammatory (Burris et al., 2011), antimutagenic (Miranda et al., 2008), antiobesity (Arçari et al., 2009;

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Kang et al., 2012), and hypoglycemic (Kang et al., 2012; Rodriguez de Sotillo and Hadley, 2002). It has been reported that Mate tea can regulate blood lipids in humans and animals such as rats and mice (Menini et al., 2007; Morais et al., 2009; Stein et al., 2005). However, the exact mechanism underlying its hypolipidemic effect is not well understood. Selection of an ideal hyperlipidemic animal model is the key to studying lipid metabolism. Compared to rats and mice, hamsters are considered to be the best animal model for studying lipid metabolism, because cholesterol metabolism in hamsters is similar to that in humans. However, hamsters have not been used previously to study the lipid-lowering mechanism of Mate tea. To investigate further the hypolipidemic effect of Mate tea and its possible mechanism of action, especially at the molecular level, we studied the effect of Mate tea on lipid metabolism using an animal model of hyperlipidemia in hamsters fed a high-fat diet. To identify the mechanism of the hypolipidemic effect more specifically, we determined the activities of enzymes involved in lipoprotein metabolism and mRNA expression of genes involved in lipogenesis and lipid oxidation in the liver.

2. Materials and methods

2.1. Materials

Commercial Yerba Mate (leaves without stems) was purchased from Las Marias Ltd. (Gdor Virasoro, Argentina). It was authenticated as *I. paraguariensis* St. Hilaire (Aquifoliaceae) based on its microscopic and macroscopic characteristics by Dr. Liyan Sun (College of Pharmacy, Taishan Medical University) who specializes in medical plants. Commercial kits for measuring total cholesterol (TC), triglyceride (TG), high-density lipoprotein–cholesterol (HDL-C) and low-density lipoprotein–cholesterol (LDL-C) were obtained from Beijing Zhongsheng Technology Ltd. (Beijing, China). Commercial kits for measuring superoxide dismutase (SOD), glutathione peroxidase (GSH-PX), malondialdehyde (MDA), nitric oxide (NO), lipoprotein lipase (LPL) and hepatic lipase (HL) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Commercial kits for measuring endothelin (ET-1) were purchased from Purevalley Bio-Technology Ltd. (Beijing, China). Theobromine, chlorogenic acid, caffeine and caffeic acid (purity > 98%) were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Other chemicals used were of the purest analytical grade available.

2.2. Preparation of Mate tea aqueous extract

Herbal commercial samples were weighed and placed in distilled, previously boiled water brought down to 80 °C for 20 min, according to its usual method of preparation for drinking. This extract was filtered using filter paper and then cooled to room temperature. The solid contents of the aqueous extract were 40, 20 and 10 mg/ml (4%, 2% and 1% w/v, respectively). The Mate extract was prepared daily and offered to the animals in place of drinking water, ad libitum.

2.3. Total phenolic content and chromatographic analysis by HPLC of Mate extract

All of the instant Mate tea was from the same batch and contained 340 mg/g total phenolics, determined by the Folin–Ciocalteu methodology. Chlorogenic acid was used as the standard for the calibration curve because it is the main polyphenol in Yerba Mate leaves (Singleton et al., 1999).

In order to characterize the plant material, an HPLC profile was obtained as described previously (Gao et al., 2013). Mate extract was analyzed by HPLC using a Shimadzu LC-20AD (Japan) gradient liquid chromatograph, equipped with an SIL-20A autosampler, LC-20AD gradient pump, and SPD-20A UV/Visible detector. An Eclipse XDB-C18 column (250 mm × 4.6 mm × 5 μm) was used. Column temperature was kept at 30 °C, and a 20 μl sample was injected into the column and eluted with a constant flow rate of 1.0 ml/min. Data were obtained at 273 nm for caffeine and theobromine. The mobile phase consisted of water and methanol (85:15, v/v). The UV detection wavelength was set at 327 nm for chlorogenic acid and caffeic acid. The mobile phase consisted of acetonitrile and 0.3% phosphate (10:90, v/v). Fig. 1 shows that the contents of caffeine, theobromine, chlorogenic acid and caffeic acid in Yerba Mate dried leaves were 1.23%, 0.18%, 2.11%, and 0.03%, respectively.

2.4. Animals and experimental design

Fifty 7-week-old male Syrian golden hamsters were purchased from the Vital River Laboratory Animal Technology (Beijing, China). All experiments were approved by the Laboratory Animals' Ethical Committee of Taishan Medical University, and followed national guidelines for the care and use of animals.

The animals were individually housed in cages in a room at 22 ± 2 °C on a 12-h light–dark cycle with free access to regular rodent chow and water. After 1 week of acclimatization, animals were randomly divided into five groups of 10: normal control (NC); high-fat control (HF); low-dose Mate tea (high-fat diet + 1% Mate); medium-dose Mate tea group (high-fat diet + 2% Mate); and high-dose Mate tea group (high-fat diet + 4% Mate). Hamsters from the NC group were fed a normal diet, while the other groups were fed a high-fat diet (15% lard and 0.2% cholesterol) (Yang et al., 2005) for a total of 8 weeks. After feeding a different diet for the first 4 weeks, Mate tea was administered to the treatment groups for the final 4 weeks by giving the hamsters free access to bottles containing the prepared infusion as the only available liquid source. Hamsters in the NC and HF groups were given water only. Food and Mate/water were changed every day. The daily food and drink per cage were determined for obtaining food (g) and Mate/water intakes (ml) per hamster per day. Food, Mate/water consumption and body weights were measured daily and weekly, respectively.

After 4 weeks of Mate treatment and chloral hydrate anesthesia, blood was collected from the abdominal aorta of the hamsters without dietary exposure for 16 h. The liver was removed and weighed, frozen in liquid nitrogen, and stored at −70 °C for further analysis.

2.5. Measurement of serum lipids

Blood samples were immediately centrifuged at 3000 rpm for 10 min at 4 °C and serum was stored at −70 °C until analysis. Serum levels of TC, TG, HDL-C and LDL-C were determined using enzymatic kits. All serum samples were measured with an automatic analyzer (Hitachi 7600, Tokyo, Japan).

2.6. Measurement of SOD, GSH-PX, MDA, NO and ET-1

Serum was obtained by centrifuging the blood at 3000 rpm for 10 min to detect SOD, GSH-PX, NO and MDA. One milliliter of blood was mixed with 30 μl EDTA and 40 μl aprotinin and centrifuged for 10 min at 3000 rpm and 4 °C to obtain plasma, which was detected as ET-1. Serum SOD activity was measured by xanthine oxidase method, GSH-PX activity was determined based on an NADPH-coupled reaction, and MDA content was determined by using the thiobarbituric acid method. Serum NO was measured by nitrate reductase method and radioimmunoassay was used to detect the levels of plasma ET-1.

2.7. Measurement of LPL and HL activities in serum and liver tissue

Liver samples were homogenized (10%, w/v) in cold saline, and then centrifuged at 1000 ×*g* for 15 min. Supernatant was used for the assay of LPL and HL. Serum was obtained by centrifuging the