A Clinical Trial Testing the Safety and Efficacy of a Standardized *Eucommia ulmoides* Oliver Bark Extract to Treat Hypertension

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Abstract

BACKGROUND: A tea made from *Eucommia ulmoides* leaves and bark is part of the Japanese diet. Eucommia is an herbal medicine that, by increasing nitric oxide, reduced blood pressure (BP) in rats and humans in an uncontrolled clinical trial. OBJECTIVE: A controlled clinical trial was conducted to evaluate an aqueous bark extract of Eucommia standardized to eight percent pinoresinol di-beta-D-glucoside (PG) for BP reduction in humans. METHODS: Study 1: Twenty-four healthy adult subjects with a BP between 120-160/80-100 mmHg were randomized to Eucommia extract 500 mg three times daily for eight weeks. Automatic 24-hour ambulatory blood pressure monitoring (24-h ABPM) was utilized at baseline and after eight weeks. Study 2: The effect of the Eucommia extract on isoproterenol-stimulated lipolysis was evaluated in a human fat cell assay to determine whether Eucommia was a beta-adrenergic blocker. Study 3: Thirty healthy adult subjects with a BP between 120-160/80-100 mmHg were randomized to 1 g Eucommia extract three times daily for two weeks with 24-h ABPM at baseline and after two weeks. RESULTS: Study 1: There was no toxicity or any difference in BP between the two groups. Study 2: Eucommia at 0.5% w/v reduced isoproterenol-stimulated lipolysis from 2.67 to 1.4 times the buffer control (p<0.001). Study 3: The Eucommia extract was well-tolerated and reduced BP by an average of 7.5/3.9 mmHg (p<0.008). CONCLUSION: The standardized Eucommia extract reduced BP and has beta-adrenergic blocking activity. Eucommia may be an appropriate nutraceutical intervention for prehypertension. (Altern Med Rev 2011;16(4)338-347)

Background

Eucommia bark and leaves are used as a tea in Japan, and this herb is part of the diet in that area of the world. Eucommia tea has no known toxicity associated with its use. Trials in rats given a water extract of Eucommia orally at 200 mg/kg demonstrated up to 20 mmHg drop in blood pressure two hours after dosing, without untoward effects. The equivalent dose in humans is 2-6.5 g. Although this tea is used in traditional Chinese medicine to treat high blood pressure, and an uncontrolled Russian trial with *Eucommia ulmoides* demonstrated a 25/14 mmHg drop in blood pressure in human subjects with hypertension, no placebo-controlled, human clinical trials have been conducted to test its safety and efficacy.

This trial was preceded by creation of a *Eucommia ulmoides* Oliver bark extract standardized to eight percent pinoresinol di-beta-D-glucoside (PG). Details of this procedure are described in a prior publication. The safety of acute dosing was confirmed in rats up to a dose of 1,200 mg/kg. In addition, repeated dosing of 200 mg/kg, 600 mg/kg, and 1,200 mg/kg over 28 days demonstrated no toxicity in rats as determined by clinical appearance, histopathology, and serum chemistry. Spontaneously hypertensive rats were given Eucommia extract daily for 22 days, resulting in a systolic blood pressure reduction in the male rats, but not the female rats, of 31 mmHg and 28 mmHg over three hours in the 600 mg/kg and 1,200 mg/kg groups, respectively (p<0.001). This gender-specific response has been reported previously in...
spontaneously hypertensive rats and was discussed in greater detail by Lang et al. Since the standardized Eucommia extract was safe and effective in rats, the authors obtained permission from their Institutional Review Board for testing the same extract in hypertensive humans. This publication will describe their controlled clinical trials of the standardized Eucommia bark extract.

**Objectives**

The objectives of these studies were to conduct controlled clinical trials to evaluate an aqueous bark extract of Eucommia standardized to eight-percent PG for BP reduction in humans and to explore the mechanisms by which it may act.

**Methods**

**Study 1**

The trial included 24 healthy male and female volunteers, ages 18-60 years, with a body mass index (BMI) ≤35 and an average blood pressure between 120-160/80-100 (determined from three resting weekly Pennington clinic determinations). This level of hypertension can be safely treated with lifestyle modification alone for six months. Patients with diabetes mellitus, nephropathy, peripheral arterial disease, retinopathy, history of stroke, or heart disease (including left ventricular hypertrophy, prior myocardial infarction, angina pectoris, a prior revascularization procedure, or heart failure) were excluded from the study. Subjects using medications that could produce weight loss, or who were on unstable doses (stable dose=same dose for previous three months) of medicines that influence blood pressure, were also excluded.

At screening, subjects signed an informed consent approved by the Pennington Center Institutional Review Board, provided a medical history, and underwent a physical examination. Testing included a fasting (10-12 hours) chemistry panel (glucose, creatinine, potassium, uric acid, albumin, calcium, magnesium, creatine phosphokinase, alanine-leucine transaminase, alkaline phosphatase, iron, total cholesterol, triglycerides, high density lipoprotein [HDL] cholesterol, and low density lipoprotein [LDL] cholesterol) and complete blood count (CBC; hemoglobin, hematocrit, mean cell volume, platelet count, white blood cell count and differential), an electrocardiogram, and a urinalysis (glucose, protein, specific gravity). Blood pressure was taken using the validated OMRON automated blood pressure monitor after five minutes of rest in a sitting position with the arm at heart level, according to the Pennington Procedure Manual. Patients were required to refrain from smoking and caffeine consumption for four hours before blood pressure measurements. They were also provided with an ambulatory 24-hour blood pressure monitor (24-h ABPM) that automatically recorded blood pressure and heart rate every 30 minutes during the 24-hour period following their screening visit.

After screening, subjects were randomized to placebo or the standardized 500-mg Eucommia extract, each taken three times daily for eight weeks. A pregnancy test was conducted in women with childbearing potential at week 0, prior to study treatment initiation. Previous rat toxicity studies showed safety at the equivalent daily human dose of 21 g. This study utilized less than one tenth of this dose. After the screening visits on weeks -3, -2, and -1, subjects were seen in the clinic on week 0 when the medication was started, and at weeks 1, 3, 5, and 8. Subjects were questioned about adverse events at each clinic visit.

Subjects did not change their baseline diet or physical activity during the study. During clinic visits, medication was dispensed and compliance was monitored by pill count. Weight, pulse rate, and blood pressure were taken. Although a subject with a blood pressure greater than 180/110 on a clinic visit would have been withdrawn from the trial and referred to their treating physician, this did not occur. A repeat 24-h ABPM was performed during the last week of the study. At the study end, repeat physical examinations, chemistry panels, electrocardiograms, and CBCs were administered. At the completion of the study, subjects were instructed in the appropriate dietary and lifestyle recommendations for hypertension, and were advised to follow-up with their treating physicians.

The primary outcome variable was the difference in blood pressure between the Eucommia and placebo groups from baseline to eight weeks by 24-h ABPM. Secondary outcome variables included the differences in pulse rate, clinic OMRON blood pressures, and safety measures (electrocardiograms, physical examination, and laboratory testing).

**Study 2**

To determine whether blocking of beta-adrenergic receptors contributes to the blood pressure-lowering effect of Eucommia, the effect of 0.5 percent w/v Eucommia standardized extract and 10⁻⁷ M propranolol was tested on 10⁻⁷ M isoproteineol-stimulated lipolysis in a human fat-cell assay,
using glycerol generation as a measure of lipolysis. Briefly, differentiated human adipocytes in 96-well plates were obtained from the cell biology core facility of the Clinical Nutrition Research Unit Center, Grant # 1P30 DK072476 awarded to the Pennington Biomedical Research Center. On the day of the assay, 150 µL of medium was removed from each well of the 96-well plate, and 200 µL of wash buffer was then added to each well. Next, 200 µL of medium and wash buffer were removed, and another 200 µL of wash buffer was added to each well; then the medium and wash buffer were removed from each well. The cells were then treated with 150 µL of the test compounds and controls, eight wells at a time. The diluted isoproterenol was treated as a positive control, and the assay buffer was treated as the vehicle control. The plate was incubated for five hours at 37° C (5% CO₂). After incubation, 100 µL of the test compounds were removed and added to a sterile 96-well plate. Glycerol reagent (100 µL) was then added to create a colorimetric assay, dependent on the amount of glycerol released during incubation with the test compounds. A series of glycerol standards were also run with each assay to create a standard curve upon which the results were based. The plates were then read in a spectrophotometer plate reader at 540 nm, and the results were plotted based on the standard curve. The results were analyzed by t-test and expressed as the mean ± the standard deviation, with the number of wells (observations) noted.

Study 3
A second clinical trial was performed using a Eucommia dose of 1 g three times daily for two weeks. The design modifications in this second clinical trial were prompted by lack of a statistically significant drop in blood pressure in the first clinical trial, the safety of Eucommia at much higher doses in animals, the safety of the first clinical trial, and evidence in animals that the effect on blood pressure is apparent in eight days.

The trial included 30 healthy male and female volunteers (n=30; ages 18-70 years) with a BMI <40 kg/m² and an average blood pressure between ± the standard deviation, with the number of wells 120-160/80-100 mmHg, tested on three occasions. The plates were then read in a spectrophotometer (observations) noted.

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Non-normally distributed variables like demographics were analyzed using the Tukey test.

**Results**

**Study 1**

Of the 24 subjects randomized into the study, 20 subjects completed the trial. Three of five subjects on antihypertensive medication were in the Eucommia group. Two subjects withdrew from the study – one in the placebo group, who developed a rash, and one in the Eucommia group, who developed headaches. Two subjects, one in the Eucommia group and one in the placebo group, stopped participation by not following through. There were five adverse events in the Eucommia group (two colds, one headache, one dizziness, and one edema) and, with the exception of the moderately severe headache that resulted in discontinuation, all adverse events were mild and resolved during the study. There were eight adverse events in the placebo group (one diarrhea, one nausea, one anorexia, one headache, one anxiety, one fatigue, and two rashes). The reactions in this group were classified as mild (3), moderate (2), and severe (3).

Serum glucose increased by 3.00±1.67 mg/dL from a baseline of 94.82±2.56 mg/dL in the Eucommia group and fell by 1.72±1.65 mg/dL from a baseline of 97.33±3.20 mg/dL in the placebo group (p=0.043). Serum creatinine increased by 0.02±0.01 mg/dL from a baseline of 0.87±0.03 mg/dL in the Eucommia group and fell by 0.03±0.02 mg/dL from a baseline of 0.97±0.05 mg/dL in the placebo group (p=0.018). There were no other significant differences between groups on blood tests or adverse events observed on physical exams or electrocardiograms.

At the request of the sponsor, an interim analysis was performed for efficacy when 11 subjects (approximately half of the subjects randomized to the study) had completed the trial. Mean 24-h ABPM decreased by 3.2/1.2 mmHg in the Eucommia group and increased by 2.0/3.3 mmHg in the placebo group. The decreases in systolic and diastolic blood pressures in the Eucommia group compared to the placebo group were marginally significant, (p=0.048) and (p=0.028), respectively; by the end of the trial, however, the statistical significance was lost.

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**Figure 1. The Difference in Pulse Rate from Baseline to Week 8 at the Interim Analysis**
suggested to the researchers that the dose of Eucommia extract was just at the threshold of efficacy. Although the heart rate was not significantly different in the Eucommia and placebo groups in the interim analysis, there appeared to be a trend in the Eucommia group to have a lower pulse rate during waking hours, suggesting the possibility that Eucommia might be acting as a beta-adrenergic blocking drug (Figure 1).

Study 2
Isoproterenol at $10^{-7}$ M stimulated lipolysis as measured by glycerol generation $2.67 \pm 0.0066$ (SD) times the buffer control in our human fat cell assay. The addition of propranolol at $10^{-4}$ M to the isoproterenol reduced lipolysis to $1.06 \pm 0.00273$ times the buffer control. The addition of Eucommia (0.5% w/v) to the isoproterenol reduced lipolysis to $1.4 \pm 0.2081$ times the buffer control. The difference between the isoproterenol and isoproterenol plus propranolol or isoproterenol plus Eucommia was significantly different ($p<0.001$, Figure 2). This suggests that Eucommia, like propranolol, may act as a beta-adrenergic blocker.

Study 3
Of the 30 subjects randomized to the study, 29 completed the study. The subjects were well matched at baseline for weight, age, BMI, gender, and race (Table 1). Starting blood pressure was 137/87 mmHg in the Eucommia group and 136/89 mmHg in the placebo group, which was not significantly different. One subject in the placebo group dropped out of the trial due to a pruritic rash and joint pain. There were six subjects who experienced adverse events and all resolved by the end of the trial. All were mild to moderate with the exception of the subject who dropped from the trial due to a rash. There was one subject in the Eucommia group who experienced two adverse events and five subjects in the placebo group who experienced a total of eleven adverse events (Table 2). There were no adverse events observed on blood tests, physical exams, or electrocardiograms.
Systolic blood pressure on 24-h ABPM decreased an average of 3.6 mmHg in the Eucommia group and increased by an average of 3.7 mmHg in the placebo group (p<0.0001, Figure 3). Diastolic blood pressure decreased by an average of 0.9 mmHg in the Eucommia group and increased by an average of 2.0 mmHg in the placebo group (p<0.008, Figure 4). Although the difference between the Eucommia and placebo groups in diastolic pressure was a significant 3 mmHg, the actual reduction in diastolic blood pressure from baseline in the Eucommia group was not statistically significant. There was no significant difference in heart rate between the two groups. Heart rate decreased by an average of 0.4 beats per minute (bpm) in the Eucommia group and increased by an average of 1.1 bpm in the placebo group. There were no significant differences in the OMRON blood pressures taken at the clinic visits. The compliance by pill count was >90 percent, with no significant difference between the Eucommia and placebo groups.

Note: In both Figures 3 and 4, the time points from the 24-hour blood pressure monitoring at the end of the study were subtracted from the same time points as the 24-hour blood pressure monitoring at baseline. This difference was plotted on the vertical axis and the time points of the 24-hour monitoring were plotted on the horizontal axis.
Figure 3. Difference in 24-Hour Ambulatory Systolic Blood Pressure between Eucommia and Placebo Groups

Figure 4. Difference in 24-Hour Ambulatory Diastolic Blood Pressure between Eucommia and Placebo Groups
Discussion

The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) created a new category called “prehypertension,” defined as systolic blood pressure of 120-139 mmHg and diastolic blood pressure of 80-89 mmHg. The report suggests that individuals in this category should be treated with dietary and lifestyle modification. Since Eucommia is consumed as a tea in some Asian cultures, it could be considered a food or a dietary herbal supplement. Thus, *Eucommia ulmoides* might be employed as a “dietary measure” to maintain a healthy blood pressure in individuals with prehypertension and for whom blood pressure medications may not yet be indicated. Given that the prevalence of prehypertension in U.S. adults is 36.3 percent and these adults demonstrate an adverse cardiometabolic profile that places them at higher cardiovascular disease risk compared to those with lower blood pressure (<120/80 mmHg), Eucommia may represent a non-pharmaceutical method to reduce that risk.

In uncontrolled studies, Eucommia has been reported to decrease blood pressure in humans and animals. Prior studies have attempted to define the mechanism by which Eucommia reduces blood pressure. Kwan et al, using rat aortic rings and dog carotid rings contracted with phenylephrine, showed that Eucommia bark extract relaxed the rings in an endothelium-dependent manner, which involved nitric oxide and potassium channels. They then extended these observations by showing that, in large elastic arteries like the aorta, vasorelaxation was entirely endothelium-dependent and nitric oxide-mediated, but in smaller muscular arteries like the mesenteric artery, vasorelaxation was mediated by both nitric oxide and endothelium-derived hyperpolarizing factor. Jin et al, using an aqueous extract of Eucommia leaves in an intact rodent model, confirmed the involvement of endothelium-derived hyperpolarizing factor as a mediator of vasorelaxation in mesenteric resistance arteries. They confirmed endothelium dependency and involvement of potassium channels and gap junctions, but found that the vasorelaxation was nitric oxide-independent. In spontaneously hypertensive rats, Luo et al demonstrated that *Eucommia ulmoides* Oliver extract lowered blood pressure while increasing nitric oxide and reducing rennin and angiotensin II. They also demonstrated that the vascular relaxation was endothelium-independent, suggesting that Eucommia extract had a direct effect on the vessels.

Thus, prior studies into the mechanism of action of Eucommia to reduce blood pressure are conflicting. Most studies, however, appear to agree that nitric oxide plays a role in the vasodilatation seen with Eucommia. We noticed the apparent reduction of heart rate during 24-h ABPM in the first Eucommia trial, which was consistent with the effect of a beta-adrenergic blocker. Testing the effect of Eucommia on isoproterenol-stimulated lipolysis in the human fat cell assay confirmed that Eucommia does indeed have beta-adrenergic blocking properties. Thus, it appears that there may be at least two separate mechanisms by which Eucommia reduces blood pressure. Nipradilol, a beta-adrenergic blocking drug with the ability to stimulate nitric oxide, is thought to have a similar ability to reduce blood pressure to propranolol, which does not increase nitric oxide, but has a renal protective effect that propranolol does not have. Thus, Eucommia might act as a beta-adrenergic blocker, but due to its seeming potential to stimulate nitric oxide, could have renal protective advantages in the treatment of prehypertension over a pure beta-blocking drug.

The adverse effects seen in both trials, including colds, diarrhea, dizziness, edema, and headache, resolved prior to the end of the trial and were consistent with the safety of Eucommia as a food. Although the subjects taking Eucommia in the first trial had a statistically significant increase in blood sugar and creatinine, the changes were not clinically significant and were not seen in the second trial that used twice the dose. In fact, Eucommia has been reported to reduce blood sugar in C57BL/KsJ-db-db mice and improve insulin sensitivity in fructose-drinking rats. Eucommia has also been demonstrated, along with light training, to enhance the ability of muscle to resist fatigue. Since creatinine is a breakdown product of muscle metabolism, one would expect Eucommia to reduce rather than increase creatinine.

To demonstrate the potential importance of the blood pressure reduction of 7.5/3.9 mmHg in this study using an oral standardized aqueous extract of *Eucommia ulmoides*, one can look to the dietary intervention used in the DASH study, which is the recommended dietary intervention for the treatment of prehypertension or high blood pressure. The DASH study participants had hypertension while the Eucommia trial participants had a
mixture of hypertension and prehypertension. Recognizing those differences and the much larger number of subjects in the DASH trial, the DASH diet reduced blood pressure by an average of 5.5/3.0 mmHg.\textsuperscript{18} That reduction in blood pressure was estimated to reduce coronary heart disease by 15 percent and stroke by 27 percent. The second Eucommia study gave a larger reduction in blood pressure and suggests that it also might be effective in reducing cardiovascular risk. Eucommia deserves consideration as a potential nutraceutical intervention to maintain a healthy blood pressure in those with prehypertension who do not achieve the desirable blood pressure of 120/80 or less with the use of the DASH diet alone.

Conclusion

A standardized aqueous bark extract of \textit{Eucommia ulmoides} Oliver appears to be a safe and effective botanical intervention to reduce blood pressure in the prehypertensive and mildly hypertensive range. The current study demonstrates that Eucommia acts as a beta-adrenergic blocker, while other studies have shown it stimulates nitric oxide. Since the Eucommia extract effectively reduces blood pressure, it deserves consideration as a nutraceutical intervention in people with prehypertension, as defined by the JNC7, who do not respond to the DASH diet alone.

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