

# Evaluation of the Efficacy of Daily Consumption of *Eucommia ulmoides* Leaves in A Sample of Healthy Volunteers

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## Abstract

**Context:** More than 80% of the population around the world believes with traditional medicine to overcome the side effects, resistance, and cost of synthetic medications. Herbal medicines take the upper hand in this manner as they safe, effective with low cost. *Eucommia ulmoides* (EU) belongs to Eucommiaceae family widely cultivated in China. It contains many active compounds and used traditionally and pharmacologically as cardioprotective, neuroprotective, and hepatoprotective effects due to antioxidant activities. **Aims:** The aim of this study is to evaluate the efficacy of EU leaves if consumed daily. **Settings and Design:** This study was done in Faculty of Pharmacy-Clinical Pharmacy and Pharmacy Practice unit-Pharmacology Unit at University of Science and Technology after taking Permission from the University Ethics Committee - Sana'a, Yemen. **Methods and Material:** A total of 26 healthy volunteers (15 male and 11 female) participated in this study. They allowed to drink 2 g of EU leaves twice daily (tea) for 4 weeks. The parameters were taken before and after the study that including body mass index, systolic blood pressure (SBP), diastolic blood pressure, and mean arterial pressure (MAP). In addition, biochemical studies were done, including the measurement of fasting blood sugar, complete blood count, and lipid profile; liver function tests, kidney function tests, electrolytes, and sex hormones. **Statistical Analysis Used:** Results of representative values were expressed as a mean  $\pm$  standard error of the mean. Comparisons between two groups were made using a paired *t*-test (SPSS Version 21).  $P < 0.05$  were considered statistically significant. **Results:** The outcomes of this study showed that EU reduced blood pressure (SBP, DBP, and MAP), lipid profile (cholesterol, triglyceride, and low-density lipoprotein cholesterol), and kidney function tests (urea and creatinine), besides that it improved hematopoiesis and reduced inflammatory cell. **Conclusions:** It is suggested that the EU can be used as an adjuvant therapy due to its beneficial antihypertensive, dyslipidemic, nephroprotective, hematopoietic, and anti-inflammatory effects as well as estrogenic-like effect

**Key words:** *Eucommia ulmoides*, healthy volunteers, the efficacy

## INTRODUCTION

*Eucommia ulmoides* (EU) belong to the family of Eucommiaceae, a genus tree cultivated in China.<sup>[1]</sup> This plant is widely used as a traditional herb due to its medicinal importance. It contains many active constituents, which include phenolics, lignans, iridoids, steroids, and many other compounds. It used as a famous tea that formed from leaves rather than fruits or flower.<sup>[2,3]</sup> The leaves of this plant can build up the bone, muscle as well as the human fertility.<sup>[4,5]</sup>

Lignans (sesquilignans, neolignans, and monoepoxylicignans) are the most important components isolated from a different part of the EU, including seeds, bark, and leaves.<sup>[6]</sup> In

addition, as a secondary metabolite that found in this plant is iridoid glycoside and generally known as glycosides. Asperuloside, aucubin, and geniposidic acid are examples of these isolated compounds that characterized by potent pharmacological action.<sup>[7-9]</sup> Besides all these natural components there are also two new conjugated iridoid and amino acids known as Eucommides-A and-C.<sup>[10]</sup>

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However, the EU is rich in many natural active compounds including phenols and flavonoids that have antioxidant and health benefits.<sup>[11-13]</sup> Seasonal climate plays an important role in the contents of this compound, for example, higher contents of this compound are found in August and May, especially aucubin, quercetin, geniposidic acid, and Rutin.<sup>[14]</sup> Many other compounds were isolated from different parts of this plant; especially bark these including terpenoids and steroids.<sup>[15,16]</sup> Some studies showed that the presence of Polysaccharides in The EU showed the nephroprotective effect and antioxidant activity.<sup>[17,18]</sup> Moreover, this plant contains minerals, vitamins, amino acids, fatty acids, and tetracosanoic-2,3-dihydroxpropylester, and n-octacosanoic acid which they are new compounds recently discovered.<sup>[19-21]</sup>

This plant is characterized by general health benefits including cardioprotective,<sup>[22-24]</sup> neuroprotective, hepatoprotective,<sup>[25]</sup> and antioxidant effects,<sup>[26,27]</sup> antibacterial, antiviral, and anti-inflammatory activity.<sup>[25,28]</sup> In addition, it has antiobesity, and antimetabolic syndrome activity<sup>[27]</sup> referred to the presence of many active compounds particularly geniposidic acid, asperuloside, and chlorogenic acid.

Glycosides in the EU were found to protect and increase the integrity of the bone and can be used to control osteoporosis as it activates osteoblast and suppresses the action of osteoclast.<sup>[29,30]</sup> However, it was found that the bark of this plant contains isoflavonoids with phytoestrogenic-like effect. These compounds may show phytoandrogenic-like effect that plays a role in sex drive, bone density, and skeletal muscle development.<sup>[26-33]</sup>

The aim of this study is to evaluate the efficacy of EU leaves in a sample of healthy volunteers.

## SUBJECTS AND METHODS

### Plants

EU leaves were purchased from a special herbal store in Sana'a City and identified by Botanist in the Faculty of Agriculture-Sana'a University.

### Participants

A total of 26 healthy volunteers (15 male and 11 female) participated in this study. Their ages range from 22 to 24 years old and body mass index (BMI) (20.4–23.3 kg/m<sup>2</sup>).

The participated volunteers were allowed to take 2 g of EU leaves twice daily as a form of tea.<sup>[34]</sup> The leaves should steep within the hot water for 10 min and then strained. Food and drinks were kept in a fixed situation throughout the study. The measurable parameters were taken before, and after the 4 weeks, which are the duration of this study, these included BMI, systolic blood pressure, diastolic blood pressure, and

mean arterial pressure (MAP). In addition, biochemical studies were measured, including complete blood count (CBC), fasting blood sugar (FBS), and lipid profile; liver function tests, kidney function tests, electrolytes, and sex hormones.

### Data analysis

Results of representative values were expressed as a mean  $\pm$  standard error of the mean. Comparisons between two groups were made using a paired *t*-test (SPSS Version 21).  $P < 0.05$  were considered statistically significant.

## RESULTS

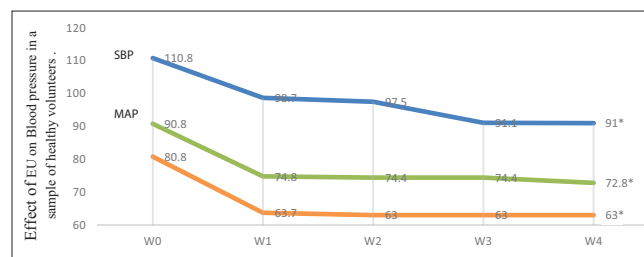
The outcomes of this study showed that daily consumption of the EU had a significant reduction ( $P < 0.05$ ) in all components of blood pressure, including systolic, diastolic, and mean arterial blood pressure in both sexes compared with control (before) values [Figures 1 and 2].

With regard to the effect of EU on BMI, there was no significant change ( $P > 0.05$ ) in both sexes, neither before intake EU nor after [Figures 3 and 4].

According to the biochemical studies, including lipid profile and liver function tests, there was a reduction in all lipid profile parameters and liver function tests compared with control (before) in both sexes but insignificantly ( $P > 0.05$ ) [Tables 1 and 2].

EU consumption showed a reduction in the kidney biomarkers compared with control (before) but still insignificant ( $P > 0.05$ ) except its effect on electrolytes, especially calcium and sodium. It showed significant ( $P < 0.05$ ) reduction in calcium level in both sexes compared with control (before) as well as significant ( $P < 0.05$ ) increase in sodium levels in both sexes compared with control (before) [Table 3].

In addition, EU consumption for 4 weeks showed insignificant changes ( $P > 0.05$ ) change in CBC, except its effect on hemoglobin (Hb) and monocyte. The EU showed



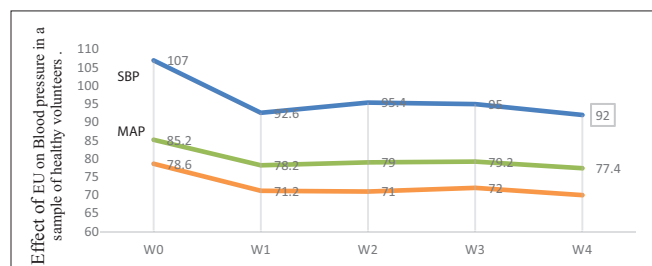
**Figure 1:** Effect of *Eucommia ulmoides* on the average (mean $\pm$ standard error) blood pressure (SBP, DBP, and MAP) for 4 weeks in a sample of healthy volunteers ( $n=11$  females). \*Significant as compared with control (before) at  $P < 0.05$ . SBP: Systolic blood pressure, DBP: Diastolic blood pressure, and MAP: Mean arterial pressure

significant ( $P < 0.05$ ) increase in Hb level and a significant ( $P < 0.05$ ) reduction in monocyte [Table 4].

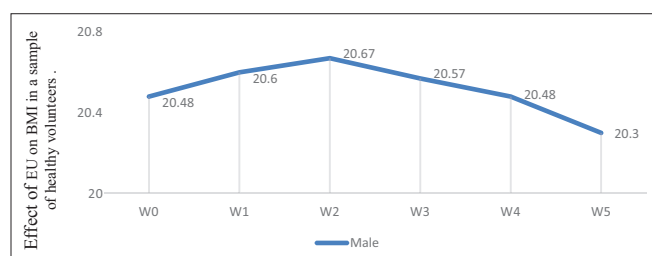
## DISCUSSION

EU leaves as tea is considered as traditional drinks in China and Japan. Recently, this habit is distributed in the most countries. It has beneficial effects in many ailments including, hypertension, diabetes, inflammation, and gastric ulcer.<sup>[24-30]</sup>

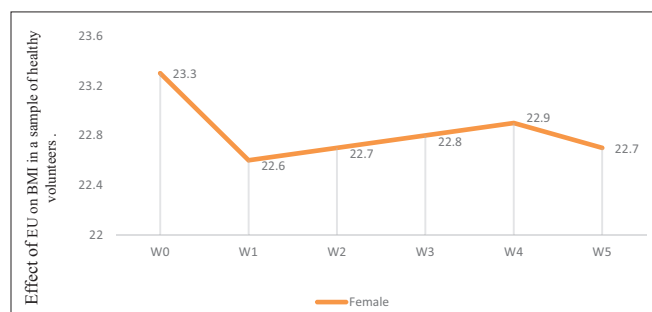
In the present study, EU consumption daily for 4 weeks showed significant reduction in the blood pressure, including systolic, diastolic, and MAP. This effect may refer to endothelium-dependent relaxing factors that stimulate nitric oxide-relaxing of blood vessels. This effect evoked K<sup>+</sup> channel rather than muscarinic receptor.<sup>[35]</sup> Antihypertensive outcomes of this study are in agreement with Lang, 2005, Greenway *et al.*, 2011, and Shingo 2015 who found that the EU has a hypotensive effect in both animals and human.<sup>[22,36,37]</sup> In addition, EU contains caffeic acid, epicatechin, catechin, and n-octacosanoic acid, which possess a diuretic effect as they act in the second segment of the proximal convoluted tubules of nephron. This effect explained the reduction in the level of calcium, potassium, and uric acid as they facilitated their excretion, contradictory elevated the level of sodium. Meanwhile, this plant showed a nephroprotective effect as it reduced kidney function tests including urea and creatinine. This effect is in agreement with the findings of Cai *et al.*, 2013.<sup>[38]</sup> However, the intake of EU showed reduction in lipid profile and FBS, especially in female participants, but insignificantly, this may be due to the duration of this study. Lee *et al.*, 2005 supported our findings as they found that using of EU reduced significantly blood sugar in diabetic rats.<sup>[39]</sup> In addition, Park *et al.*, 2006 studied the effect of EU water extract in diabetic mice for 6 weeks, they found that the EU has hypoglycemic and dyslipidemic effects.<sup>[26,40]</sup> From the outcomes of this study, the using of the EU showed insignificant changes in body weight or BMI, which is compatible with the findings of Shingo 2015.<sup>[37]</sup> On the other hand, the EU obviously showed an increase in Hb and mean corpuscular Hb concentration significantly, high concentration of flavonoids in the EU exert their antioxidant effect through scavenge free radicals in different part of body including hematopoietic system. Lidia and Ewa, 2009 showed that flavonoids may reduce the oxy Hb, which is responsible



**Figure 2:** Effect of *Eucommia ulmoides* on the average (mean±standard error) blood pressure (SBP, DBP, and MAP) for 4 weeks in a sample of healthy volunteers ( $n=15$  males). \*Significant as compared with control (before) at  $P<0.05$ . SBP: Systolic blood pressure, DBP: Diastolic blood pressure, and MAP: Mean arterial pressure



**Figure 3:** Effect of *Eucommia ulmoides* on the average (mean±standard error) body mass index for 4 weeks in a sample of healthy volunteers ( $n=15$  males)



**Figure 4:** Effect of *Eucommia ulmoides* on the average (mean±standard error) body mass index for 4 weeks in a sample of healthy volunteers ( $n=11$  females)

**Table 1:** Effect of EU on the average (mean±SE) lipid profile for 4 weeks in a sample of healthy volunteers ( $n=26$ )

Parameters	Male (Mean±SE)			Female (Mean±SE)		
	Before	After	P	Before	After	P
Chol. (mg/dl)	168.3±5.53	162.9±6.84	0.095	162.6±8.16	158.1±7.00	0.64
LDL-c (mg/dl)	121.0±6.33	112.8±7.67	0.079	112.4±7.71	107.2±7.03	0.59
TG (mg/dl)	135.6±15.08	114.4±12.3	0.70	82.5±7.97	81.6±5.99	0.76
HDL (mg/dl)	46.5±2.04	45.7±3.80	0.29	52.5±2.92	48.8±2.79	0.36
FBS (mg/dl)	80.0±2.81	84.4±2.01	0.23	91.5±13.8	87.0±2.48	0.77

EU: *Eucommia ulmoides*, SE: Standard error, LDL-c: Low-density lipoprotein cholesterol, TG: Triglyceride, HDL: High-density lipoprotein cholesterol, FBS: Fasting blood sugar

**Table 2:** Effect of EU on the average (mean±SE) liver function tests for 4 weeks in a sample of healthy volunteers (*n*=26)

Parameters	Male (Mean±SE)			Female (Mean±SE)		
	Before	After	P	Before	After	P
T. Bilirubin (mg/dl)	0.858±0.106	0.852±0.066	0.96	0.618±0.053	0.513±0.028	0.49
D. Bilirubin (mg/dl)	0.250±0.029	0.303±0.029	0.22	0.175±0.017	0.155±0.008	0.46
SGOT (U/L)	19.57±0.70	19.14±0.89	0.66	15.1±0.978	16.5±1.35	0.37
SGPT (U/L)	27.0±2.76	25.2±3.02	0.61	16.83±1.21	14.66±0.88	0.78

EU: *Eucommia ulmoides*, SE: Standard error**Table 3:** Effect of EU on the average (mean±SE) kidney function tests and hormones for 4 weeks in a sample of healthy volunteers (*n*=26)

Parameters	Male (Mean±SE)			Female (Mean±SE)		
	Before	After	P	Before	After	P
Urea (mg/dl)	21.8±1.18	21.6±1.47	0.96	25.2±0.75	18.1±1.03	0.001*
Creatinine (mg/dl)	0.78±0.027	0.700±0.056	0.22	0.535±0.036	0.460±0.045	0.20
Uric acid (mg/dl)	4.17±0.31	3.99±0.25	0.61	2.92±0.20	3.17±0.17	0.32
Sodium (mmol/l)	134.8±0.34	137.5±0.59	0.001*	136.5±0.421	138.2±0.304	0.002*
Calcium (mmol/l)	10.32±0.157	9.16±0.104	0.001*	9.25±0.122	8.69±0.079	0.002*
Potassium (mmol/l)	4.16±0.073	3.95±0.089	0.081	4.15±0.104	4.03±0.079	0.36
Testosterone (ng/ml)	7.27±0.607	7.25±0.479	0.94	-	-	-
Estradiol (pg/ml)	-	-	-	86.8±24.5	100.48±25.5	0.69

\*Significant as compared with control (before) at *P*<0.05. EU: *Eucommia ulmoides*, SE: Standard error**Table 4:** Effect of EU on the average (mean±SE) CBC for 4 weeks in a sample of healthy volunteers (*n*=26)

Parameters	Male (Mean±SE)			Female (Mean±SE)		
	Before	After	P-value	Before	After	P-value
Hb (g/dl)	16.0±0.21	16.8±0.25	0.032*	13.6±0.022	14.8±0.27	0.001*
PCV %	48.5±0.50	48.1±0.55	0.55	42.0±0.60	42.2±0.79	0.70
MCV femtoliters	83.6±1.30	83.5±1.24	0.97	85.2±2.33	85.9±105	0.80
MCH (pg)	27.5±0.55	28.9±0.56	0.087	27.6±0.84	29.9±0.43*	0.024
MCHC (g/dl)	33.0±0.24	34.4±0.33	0.004*	32.3±0.22	34.9±0.14	0.001*
RBC 10 <sup>12/l</sup>	5.76±0.12	5.81±0.110	0.78	4.87±0.18	4.94±0.12	0.72
T.WBC×10 <sup>9/l</sup>	5.42±0.33	5.78±0.37	0.50	6.37±0.47	6.11±0.68	0.71
Neutrophil %	41.2±2.44	42.98±2.70	0.55	48.7±2.75	49.1±2.88	0.91
Lymphocyte %	48.5±2.27	49.7±2.90	0.66	42.0±2.65	44.3±2.32	0.52
Monocyte %	4.89±0.47	3.06±0.33	0.002*	6.36±0.41	4.18±0.40	0.005*
Eosinophil %	3.06±0.28	2.40±0.41	0.19	2.54±0.34	2.27±0.38	0.63
Platelets×10 <sup>9/l</sup>	252.9±13.3	281.7±15.1	0.122	296.7±23.7	294.4±23.1	0.93

\*Significant as compared with control (before) at *P*<0.05. EU: *Eucommia ulmoides*, SE: Standard error, CBC: Complete blood count, PCV: Packed cell volume, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, WBC: White blood cells

for Hb damage and reduced its production. This process protected Hb from hydroperoxides that when react with ferryl Hb produced oxy Hb.<sup>[41]</sup> Monocytes, which is a type of white blood cell that elevated in response of chronic inflammation or infections, showed significant reduction in this study after intake of EU drinks for 4 weeks, this may indicate that this

plant possesses a potent anti-inflammatory through inhibition the inflammatory mediators, especially prostaglandin E synthase 2, cyclooxygenase-2, tumor necrosis factor- $\alpha$ , and interleukin-1 $\beta$ .<sup>[42]</sup> This plant has a unique estrogenic-like effect due to the presence of isoflavonoids that possess phytoestrogenic-like effect that can bind with estrogen



receptors and enhancing the effect of this hormone.<sup>[26-32]</sup> All these in agreement and supported our findings.

## CONCLUSION

From the outcomes of this study, it is suggesting that the EU can be used as an adjuvant therapy due to the beneficial antihypertensive, dyslipidemic, nephroprotective and anti-inflammatory effects, as well as hematopoietic, and estrogenic-like effect.

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