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COMMENTARY

How does *Eucommia* leaf extract prevent smooth muscle cell proliferation induced by high-fat diets at the aortic tunica media?

Fusako Takayama and Yuri Fujihara

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A cluster of conditions including hypertension and dyslipidemia often occur together. This clustering of conditions, often referred to as metabolic syndrome, is a problem not only in developed countries but also in developing countries. Moreover, these conditions frequently lead to cardiovascular diseases, such as myocardial infarction and stroke. In 2016, the World Health Organization warned that cardiovascular diseases are the number one cause of death globally and recommended that people with cardiovascular disease or who are at high cardiovascular risk need early detection and management (WHO 2016, http://www.who.int/mediacentre/factsheets/fs317/en/). Risk factors common to metabolic syndrome include tobacco and alcohol intake; diets high in sugar, fat and salt; and physical inactivity. Metabolic syndrome can be avoided by making individual lifestyle modifications, which are frequently easier said than done.

Hypertension is the most prevalent trigger for cardiovascular diseases, and it is responsible for ~16.5% of annual deaths worldwide (WHO 2013, http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/). In addition, hypertension plays a major role in the onset of atherosclerosis, stroke, peripheral artery disease, kidney disease, dementia and blindness. The initial lesion involved in the pathogenesis of atherosclerosis is a thickening of the arterial lining by fatty deposits or plaques. Retained oxidatively modified low-density lipoprotein develops into foam cells, triggering a proinflammatory cascade that promotes subsequent proliferation of smooth muscle cells as the plaque progresses.[1] Long lasting vascular inflammation and oxidative stress have been shown to play a role in all stages of the genesis of arterial disease in both animal and clinical studies.[2]

Many drugs including diuretics, sympathoplegic agents, renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and beta-adrenergic blockers are used to treat hypertension.[3] Unfortunately, only 34% of hypertensive patients receive treatment.[4] High costs of hypertensive treatment, undesired side effects and poor patient compliance are the major limiting factors for higher treatment rates. Frequently, hypertensive people living in rural areas who desire fewer side effects seek alternative approaches such as herbal medicine. Even in developed nations, 70% of the population relies on complementary and alternative medicine for treatment purposes, and herbal medicine forms a large proportion of these cases (WHO 2008, http://apps.who.int/medicinedocs/en/d/Js21429en/).

In the present issue of this journal, Hosoo *et al.*[5] report their study of the preventive effects of *Eucommia ulmoides* Oliver (Eucommiaceae) leaf extracts (ELE) on aortic tunica media hypertrophy in Wistar Kyoto rats fed a high-fat diet (HFD). The active ingredients of ELE are geniposidic acid and asperuloside (ASP), iridoid glucosides and chlorogenic acid, a caffeic acid derivative; together, these components have been shown to promote lipid metabolism, to inhibit intestinal lipid absorption and to improve insulin resistance. Hosoo *et al.*[5] show that long-term ELE administration decreased blood sugar levels in rats on a HFD and improved all the observed changes induced by the HFD. More specifically, ELE prevented increases in weight gain, visceral (mesenteric vascular bed) fat accumulation, blood pressure, and carotid artery medial wall thickening and decreased the ratio of blood adiponectin to leptin.

With regard to a mechanism for lowering blood pressure in the HFD-ELE rats, the authors showed higher adiponectin to leptin ratios in the HFD-ELE treated rats. Leptin is known to peripherally promote neovascularization, intimal hyperplasia and atherosclerosis. Centrally, leptin functions to increase appetite suppression, energy metabolism and blood pressure. Leptin also stimulates innate immunity cells to produce inflammatory cytokines, subsequently increasing inflammatory reactions. On the other hand, adiponectin exerts insulin-sensitizing and anti-arteriosclerotic effects.

Independent of the angiotensin system, leptin has been shown to directly upregulate aldosterone synthesis in adrenal glomerulosa cells to increase aldosterone synthase and CYP11B2 expression via calcium-dependent mechanisms.[6] Along these lines, leptin-mediated CYP11B2 induction via aldosterone synthase activation was blunted by calcium chelation. Excess aldosterone secretion contributes to cardiovascular disease by promoting endothelial dysfunction and the expression of profibrotic factors. Chlorogenic acid, the active ingredient of ELE, exerts strong metal and calcium-chelating actions. Chlorogenic acid also has strong fat combustion effects.

ELE and ASP have also been reported to stimulate metabolic function in rats by accelerating β-oxidation of free fatty acids

F Takayama and Y Fujihara are at Department of Clinical Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, Okayama University, Okayama, Japan
E-mail: takayamf@okayama-u.ac.jp

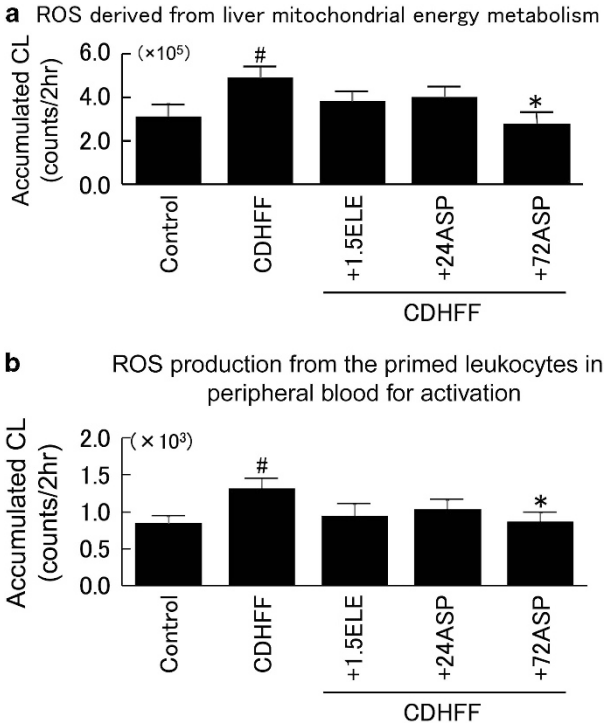

Figure 1 Effects of *Eucommia ulmoides* leaf extract (ELE) and asperuloside (ASP) administration on the formation of reactive oxygen species (ROS) from liver mitochondrial energy metabolism and from leukocytes primed for activation that were induced by feeding rats with a choline-deficient, high-fat and fructose-enriched diet (CDHFF). ELE and ASP were administered during the same time period as the CDHFF feeding. (**a**) ROS derived from the liver mitochondrial energy metabolism of rats. Each value denotes the mean ± s.e.m. of 5-7 rats. $^{\#}P<0.05$ *vs.* the control group fed with standard rodent diets; $^{*}P<0.05$ *vs.* CDHFF group. (**b**) ROS production from the leukocytes primed for activation in peripheral blood of rats. Each value denotes the mean ± s.e.m. of 5–7 rats. $^{\#}P<0.05$ *vs.* the control group fed with standard rodent diets; $^{*}P<0.05$ *vs.* CDHFF group. CL, chemiluminescence.

and inducing uncoupling protein to yield thermogenesis. In other words, ELE and ASP help burn off calories and thus exhibit anti-obesity and anti-metabolic syndrome effects. Moreover, long-term intake of ELE decreased blood pressure in human subjects with high normal blood pressure and mild hypertension.

A growing body of evidence proposes that visceral and ectopic fat accumulations are linked to metabolic disturbances, and are accompanied by a state of chronic, low-grade, systemic oxidative stress and inflammation that increases risk for metabolic syndrome-associated diseases.[7,8] These results are consistent with our study using ELE and ASP in non-alcoholic fatty liver disease rats induced by feeding animals with choline-deficient, high-fat and fructose-enriched diets (CDHFF). Our results showed that in Wistar rats fed a CDHFF diet, both ASP and ELE could reverse the increased reactive oxygen species (ROS) formation from hepatic mitochondrial energy metabolism and the priming and activation of leukocytes in peripheral blood (Figure 1).[9] We found that 4 weeks CDHFF diet in rats induced hepatic steatosis and insulin resistance but not hyperlipemia. At the same time, increased ROS formation from liver mitochondria and the leukocytes primed for activation in peripheral blood were detected in the CDHFF rats. ELE and ASP administered alongside the CDHFF diets reversed the mitochondrial ROS formation and leukocyte priming (Figures 1a and b). On the basis of these observations, ELE and ASP could prevent arterial medial wall thickening by decreasing both oxidative stressors that are systemically circulating and inflammatory signaling, including NF-κB, associated with proinflammatory cytokines and cell proliferation.

Diverse plant-based and herbal extracts and their individual metabolites can modulate signaling cascades implicated in the physiology of the cardiovascular system; their use in an asymptomatic individual is a reasonable strategy that could result in morbidity and/or mortality. A list of herbs that prevent hypertension is now available online (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4717468/).

The above-mentioned results and recent reports indicate that effective agents possess both ancillary and synergistic effects, including oxidative stress reduction, increased nitric oxide bioavailability,[10] suppression of inflammatory adipocytokine secretion, and downstream responses of inflammation and vascular smooth muscle cell proliferation. ELE effectively inhibits smooth muscle cell proliferation at aortic tunica media induced by the HFD.

Readers should take note of one limitation when interpreting the data in the article entitled 'Preventive effect of Eucommia leaf extract on aortic tunica media hypertrophy in Wistar Kyoto rats fed HFD'.[5] The authors measured a portion of the thoracic aorta to assess for changes in medial wall thickness. Compared to atherosclerosis of the abdominal aorta or aortic arch, atherosclerosis of the thoracic aorta is not as robust; moreover, medial wall thickness may be the result of hypertension caused by HFD and not necessarily related to atherosclerosis. Precursors of atherosclerosis always start as fatty streaks in the intima.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Ishimitsu T, Ohno E, Ueno Y, Onoda S, Nagase A, Ohira T, Nakano N, Satonaka H. Effects of atorvastatin and ezetimibe on endothelial function in dyslipidemic patients with chronic kidney disease. *Clin Exp Nephrol* 2014; **18**: 704–710.
2 Nakashima T, Umemoto S, Yoshimura K, Matsuda S, Itoh S, Murata T, Fukai T, Matsuzaki M. TLR4 is a critical regulator of angiotensin II-induced vascular remodeling: the roles of extracellular SOD and NADPH oxidase. *Hypertens Res* 2015; **38**: 649–655.
3 Suzuki J, Shimamura M, Suda H, Wakayama K, Kumagai H, Ikeda Y, Akazawa H, Isobe M, Komuro I, Morishita R. Current therapies and investigational drugs for peripheral arterial disease. *Hypertens Res* 2016; **39**: 183–191.
4 Haller H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. *Int J Clin Pract* 2008; **62**: 781–790.
5 Hosoo S, Koyama M, Watanabe A, Ishida R, Hirata T, Yamaguchi Y, Yamasaki H, Wada K, Higashi Y, Nakamura K. Preventive effect of *Eucommia* leaf extract on aortic media hypertrophy in Wistar- Kyoto rats fed a high-fat diet. *Hypertens Res* 2017; **40**: 546–551.
6 Huby AC, Antonova G, Groenendyk J, Gomez-Sanchez CE, Bollag WB, Filosa JA, Belin de Chantemèle EJ. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation* 2015; **132**: 2134–2145.
7 Alvey JN, Pedley A, Rosenquist JK, Massaro MJ, O'Donnell CJ, Hoffmann U, Fox SC. Association of fat density with subclinical atherosclerosis. *J Am Heart Assoc* 2014; **3**: 1–7.

8 Al-Magableh MR, Kemp-Harper BK, Hart JL. Hydrogen sulfide treatment reduces blood pressure and oxidative stress in angiotensin II-induced hypertensive mice. *Hypertens Res* 2015; **38**: 13–20.

9 Pak W, Takayama F, Mine M, Nakamoto K, Kodo Y, Mankura M, Egashira T, Kawasaki H, Mori A. Anti-oxidative and anti-inflammatory effects of spirulina on rat model of non-alcoholic steatohepatitis. *J Clin Biochem Nutr* 2012; **51**: 227–234.

10 Ye BH, Lee SJ, Choi YW, Park SY, Kim CD. Preventive effect of gomisin J from Schisandra chinensis on angiotensin II-induced hypertension via an increased nitric oxide bioavailability. *Hypertens Res* 2015; **38**: 169–177.