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Anti-hypertensive Nutraceuticals and Functional Foods

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Epidemiological studies have demonstrated that elevated blood pressure is one of the major risk factors for stroke and coronary heart disease (CHD). A close association between blood pressure and the incidence of cardiovascular diseases is well established if systolic/diastolic blood pressure is above 140/90 mmHg. In recent years, nutraceuticals and functional foods have attracted considerable interest as potential alternative therapies for treatment of hypertension, especially for prehypertensive patients, whose blood pressure is marginally or mildly high but not high enough to warrant the prescription of blood pressure-lowering medications. This review summarizes the findings of recent studies on the chemistry, production, application, efficacy, and mechanisms of popular blood pressure-lowering nutraceuticals and functional foods including the Dietary Approaches to Stop Hypertension (DASH) diet plan, L-arginine, chlorogenic acid, fermented milk, garlic, onion, tea, soybean, ginger, hawthorn, and fish oil.

KEYWORDS: ACE; chlorogenic acid; eNOS; fermented milk; fish oil; garlic; ginger; hawthorn; hypertension; L-arginine; onion; tea

INTRODUCTION

Hypertension is a major chronic disease. It is defined as a systolic blood pressure (SBP) above 140 mmHg and/or a diastolic blood pressure (DBP) above 90 mmHg (**Table 1**). Hypertension affects up to 30% of the adult population in most countries. However, more than 50% of hypertensive individuals are unaware of their condition (*1*). It is estimated that 7.6 million premature deaths (about 13.5% of the global total) and 92 million deaths and disability-adjusted life years (DALYS) (6.0% of the global total) are attributable to high blood pressure (*2*). Untreated hypertension can lead to stroke, coronary heart disease (CHD), kidney dysfunction, disability, and death. High blood pressure can be classified as either essential or secondary. The former refers to a type of hypertension of unknown causes, whereas the latter is that the high blood pressure happens to be a symptom of other medical conditions such as renal diseases, narrowing of certain arteries, and adrenal cortical disorders.

Essential hypertension is not caused by a single identifiable cause but by a cluster of factors, including heredity, age, body weight, environment, and diet. Treatment of moderate to severe hypertension is a life-long commitment and requires drug therapy in combination with changes in lifestyle, including weight reduction if overweight, limitation of alcohol, and reduction in salt and fat intake. Essential hypertension can be treated with one of several types of medications, including diuretics, β-adrenoreceptor blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, α-adrenoreceptor blockers, vasodilators, and centrally acting agents (*3*). Diuretics work in the kidney and remove excess water and sodium from the body. β-Adrenoreceptor blockers attenuate nerve impulses to the heart and blood vessels and reduce the heart's working load by slowing heartbeats, with a resultant drop in blood pressure (*3*). ACE inhibitors block the formation of angiotensin II, which normally causes blood vessels to narrow, thereby increasing blood pressure. Calcium channel blockers prevent calcium from entering the muscle cells of the heart and blood vessels, relaxing these cells and lowering blood pressure. α-Adrenoreceptor blockers reduce the effect of sympathetic nerve impulses to blood vessels and thus resistance to blood flow (*3*). Vasodilators relax blood vessels and lower blood pressure. For severely and moderately hypertensive patients, it is necessary to use these drugs to bring the blood pressure down to a healthy range.

Some foods and herbs contain natural compounds that have some functions of the medications described above and possess some vasorelaxing activity. Many medicines originate actually from foods. In recent years, there has been considerable interest in the potential for using natural food components as functional foods to treat hypertension, especially for patients with borderline to mild high blood pressure that does not warrant the prescription of anti-hypertensive drugs. This paper is to review the findings of a number of studies conducted in the past few decades on the chemistry, production, application, efficacy, and mechanisms of popular blood pressure-lowering nutraceuticals and functional foods.

CLASSIFICATION OF ANTI-HYPERTENSIVE NUTRACEUTICALS AND FOODS

Low-Salt Foods. The market for low- and reduced-salt foods and beverages is growing worldwide. Sodium helps to regulate fluid balance and maintains blood volume and blood pressure. Human diets contain a very high level of sodium, but they are

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Table 1. Classification of Hypertension for Adults

blood pressure	systolic blood pressure (mmHg)	diastolic blood pressure (mmHg)
normal	<120	<80
prehypertension	120−139	80−90
stage 1 hypertension	140−159	90−99
stage 2 hypertension	≥160	≥100
stage 3 hypertension	≥180	≥110

relatively low in potassium, calcium, and magnesium (*4*). Daily sodium intake is generally recommended to be less than 2.4 g, whereas daily potassium intake is 3.4 g per person. It is estimated that an average of 3.3 g of sodium and 4.1 g of potassium are consumed per person per day in Western countries, compared with 7.2 g of sodium and 1.8 g of potassium per person per day in China (*5*). This striking imbalance is perhaps one of the reasons why China has a greater prevalence of hypertension and stroke mortality than Western countries.

Growing evidence suggests that a higher intake of sodium than potassium is a contributory factor to hypertension (*5*). A meta-analysis conducted by He et al. (*6*) strongly suggests that a modest and long-term reduction in population salt intake can reduce stroke deaths and coronary deaths in both hypertensive and normotensive individuals. Most of us take in more sodium through processed foods than by using table salt. Foods that are usually high in sodium include canned soups and dry soup mixes, canned meats and fish, instant cooked cereals, salted butter and margarine, processed meats such as deli items and hot dogs, prepared mixes such as pancake and muffin, snack foods, salad dressings, and fast foods. Many products have been deliberately developed to cut down on sodium and are marketed with labels such as "sodium-free", "light in sodium", "low sodium", and "very low sodium".

ACE and Rennin Inhibitors. The renin−angiotensin system is a powerful mechanism for controlling blood pressure (**Figure 1**). When blood pressure falls, the kidneys undergo several intrinsic reactions converting prorenin to rennin. When rennin enters the bloodstream, it hydrolyzes plasma angiotensinogen to release a peptide called angiotensin I. When aginotensin I circulates to the small vessels of the lungs, it is immediately hydrolyzed to release an 8-amino acid shorter peptide, angiotensin II, by ACE. Angiotensin II circulates in the blood before it is inactivated by angiotensinase. Angiotensin II is a very potent vasoconstrictor and raises blood pressure by severely constricting the arteries, causing an increase in the peripheral resistance. It is also able to act on the kidneys to retain both salts and water, leading to an increase in the extracellular fluid volume and thus blood pressure. Finally, angiotensin II causes the adrenal glands to release aldosterone, which in turns increases reabsorption of water and salt in kidney.

ACE is not specific for converting angiotensin I to angiotensin II, because it cleaves a number of other peptides including bradykinin, a nonapeptide (**Figure 1**). Bradykinin is a potent endothelium-dependent vasodilator, which causes natriuresis, with a consequent drop in blood pressure. ACE inhibitors not only decrease the formation of angiotensin II but also increase bradykinin, further lowering blood pressure. The mechanism by which some functional foods and nutraceuticals of phenolic type lower blood pressure is mediated by inhibition and down-regulation of expression of ACE and rennin (*7*).

Endothelial Nitric Oxide Synthase (eNOS) Activators. Nitric oxide synthase (NOS) contributes to the blood pressure-lowering activity of many commonly used medicines, nutraceuticals, and

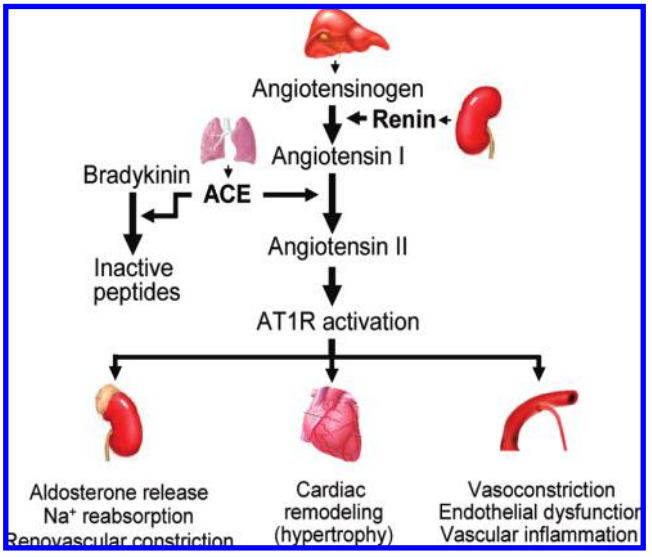

Figure 1. Role of angiotensin I-converting enzyme (ACE) in regulation of blood pressure. On the one hand, the kidney converts prorenin to rennin, which hydrolyzes plasma angiotensinogen to produce angiotensin I. In the lung, angiotensin I is immediately hydrolyzed to release an 8-amino acid shorter peptide, angiotensin II, by ACE. By activating AT1 receptor (AT1R), angiotensin II can cause vasoconstriction and raise blood pressure. Angiotensin II is able to act on the kidneys to retain both salts and water, leading to an increase in the extracellular fluid volume and thus blood pressure. Angiotensin II can cause the adrenal glands to release aldosterone, which in turn increases reabsorption of water and salt in the kidney. On the other hand, ACE can contribute to the elevation of blood pressure by inactivating the vasodilator bradykinin.

functional foods. There are three major types of NOS, namely, eNOS, neuronal nitric oxide synthase (nNOS), and inducible nitric oxide synthase (iNOS). The major function of nitric oxide (NO) is to mediate endothelium-dependent vasodilation (*8*). NOS catalyzes the oxidation of L-arginine to L-citrulline and forms NO, a freely diffusible gas. NO exerts many physiological functions by acting as an intracellular and intercellular messenger. Endothelium-derived NO diffuses into vascular smooth muscle cells (VMSC), where it activates guanylate cyclase (GC) (**Figure 2**). GC in turn catalyzes the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP then activates cGMP-dependent protein kinase (PKG); the latter opens the K-channel, and the resulting membrane hyperpolarization inhibits Ca^{2+} influx through the voltage-sensitive Ca^{2+} channel, leading to vasodilation and attenuation of hypertension (*8*). NO deficiency can lead to clinical hypertension (*9*). It is evident that eNOS knockout mice develop mild to moderate hypertension (*10*).

On the other hand, some vasodilators can activate cyclooxygenase (COX), which is responsible for the biosynthesis of prostacyclin (PGI_2) from its precursor, arachidonic acid (AA). After it is liberated from endothelial cells, PGI_2 binds to prostacyclin receptor, a G-protein-coupled receptor (Gs) in VSMC, leading to stimulation of adenylate cyclase (AC), an enzyme catalyzing the production of cyclic adenosine monophosphate (cAMP) from ATP. Similar to cGMP, cAMP increases the activity of cAMP-dependent protein kinase (PKA). Phosphorylation of the K^+ channel by PKA indirectly leads to a reduced $[Ca^{2+}]_i$ in VSMC and thus to reduced vascular tone.

Theoretically, up-regulation of eNOS and COX in endothelium will result in a drop in blood pressure. A typical example of an eNOS activator is a group of peptides derived from the fermentation of milk. Bioactive ingredients of many functional

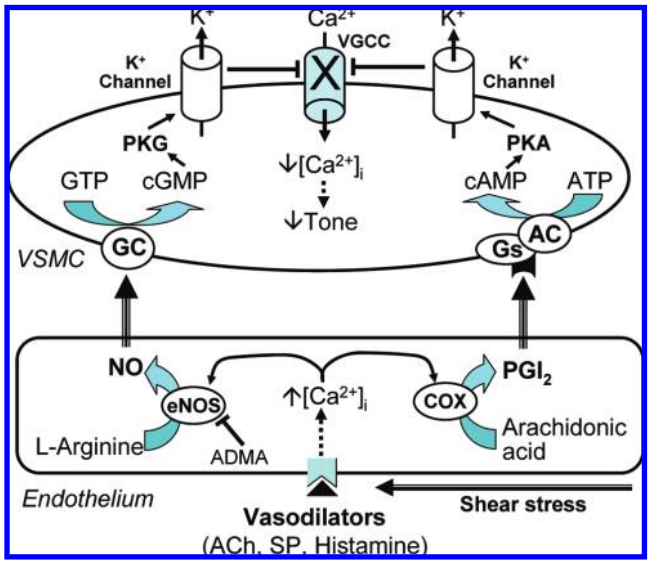

Figure 2. Role of endothelial nitric oxide synthase (eNOS) and cyclooxygenase (COX) in regulation of vasodilation and blood pressure. Endothelial cells are capable of producing and releasing several vasoactive dilating or constricting molecules in response to either shear stress or circulating substances which interact with respective membrane-bound receptors. For example, endothelium-dependent vasodilators such as acetylcholine (ACh), substance P (SP), or histamine can stimulate a rise in the intracellular calcium ion concentration ($[Ca^{2+}]_i$) of endothelial cells, which in turn activates eNOS or COX. eNOS catalyzes chemical conversion of L-arginine to form a gaseous signaling molecule, nitric oxide (NO). NO readily diffuses toward adjacent vascular smooth muscle cells (VSMC) where it activates guanylate cyclase (GC), an enzyme mediating the intracellular production of cyclic GMP (cGMP) from GTP. The activity of eNOS can be attenuated by asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase (NOS) inhibitor. On the other hand, COX is responsible for the biosynthesis of prostacyclin (PGI_2) from its precursor, arachidonic acid (AA). PGI_2 after liberation from endothelial cells binds to prostacyclin receptor, a G-protein-coupled receptor (Gs) in VSMC, leading to stimulation of adenylate cyclase (AC), the enzyme catalyzing the production of cyclic AMP (cAMP) from ATP. cGMP and cAMP increase the activity of cGMP-dependent protein kianse (PKG) and cAMP-dependent protein kinase (PKA), respectively. Phosphorylation of the potassium channel (K^+ channel) by PKG or PKA causes membrane hyperpolarization in VSMC, culminating in the inhibition of calcium ion (Ca^{2+}) influx through voltage-gated calcium channels (VGCC). The reduced $[Ca^{2+}]_i$ in vascular smooth muscle cells (VSMC) usually prevents the increase in vascular contraction and tone or leads to vasodilatation. Bioactive ingredients of many functional foods such as tea and hawthorn are able to elevate endothelial cell $[Ca^{2+}]_i$ and NO production, thus causing endothelial NO or PGI_2-dependent dilatations and contributing to the lowering of raised blood pressure.

foods such as tea and hawthorn are able to elevate endothelial cell $[Ca^{2+}]_i$ and NO production, thus causing endothelial NO or PGI_2-dependent dilatations and contributing to the attenuation of raised blood pressure.

It is also worth mentioning asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor. ADMA produces effects similar to those for exogenous NOS inhibitors. It is synthesized by methylation of arginine residue in proteins catalyzed by protein arginine methyltransferase I (PRMT I). When the proteins are hydrolyzed, ADMA is released in the cytosol. ADMA has been identified as an important risk factor for cardiovascular diseases because it raises blood pressure, causes vasoconstriction, impairs endothelium-dependent relaxation, and increases endothelial cell adhesiveness (*11*), thus enhancing atherogenesis and producing sustained hypertensive damage to end organs (*11*). ADMA is degraded and eliminated when it is converted to N^G-monomethyl-L-arginine (L-NMMA) by an enzyme called dimethylarginine dimethylaminohydrolase (DDAH). The hypotensive activity and protective effect of some nutraceuticals on endothelium are related to reduction of ADMA concentration.

NO Savers and Scavengers of Peroxynitrite-Derived Radicals. Free radicals may be involved in dysfunctions of the endothelium. Endothelial superoxide production can indirectly impair eNOS activity by reacting with NO to yield the oxidant peroxynitrite, which is a highly potent oxidant for tetrahydrobiopterin (BH_4), a crucial cofactor for NOS (*12*, *13*). PGI_2 and NO are two endothelium-derived vasodilators. Peroxynitrite may also deactivate prostacyclin synthetase, thereby affecting endothelial production of PGI_2 (*14*). A wide range of nutraceuticals possess a peroxynitrite scavenging activity in vitro (*12*). It remains to be proved whether these neutraceuticals are capable of scavenging peroxynitrite-derived radicals in endothelial cells and preserving the endothelial pool of BH_4 and the activity of prostacyclin synthetase in vivo, although some in vitro endothelia cell culture studies have suggested this possibility.

ANTI-HYPERTENSIVE NUTRACEUTICALS AND FUNCTIONAL FOODS

DASH Diet. The DASH diet, which stands for the Dietary Approaches to Stop Hypertension eating plan, was developed in 1996 by a group of researchers from the Brigham and Women's Hospital in Boston, MA, the Center for Health Research in Portland, OR, the Duke University Medical Center in Durham, NC, John's Hopkins University in Baltimore, MD, and the Pennington Biomedical Research Center in Baton Rouge, LA. It is highly recommended by the National High Blood Pressure Education Program and by the National Heart, Lung and Blood Institute, National Institute of Health, U.S. Department of Health and Human Services (*15*).

The DASH diet emphasizes that certain other dietary changes are as important as decreasing salt intake in the control of hypertension. It is known that a diet is hypotensive if it is low in sodium, saturated fat, cholesterol, and total fat but abundant in calcium, magnesium, fruits, vegetables, and fat-free or low-fat dairy products, and includes whole grain products, fish, poultry, and nuts (*15*). The DASH eating plan requires a hypertensive patient to consume daily six to eight servings of grains, four to five servings of vegetables, four to five servings of fruits, two to three servings of fat-free or low-fat dairy products, six or fewer lean meats, poultry, and fish, and two to three servings of fats and oil together with four to five servings of nuts, seeds, and legumes per week (*15*). By following the DASH plan diet, individuals can achieve a daily nutrient goal in the following specification: total fat, $<27\%$ of calories; saturated fat, $<6\%$ of calories; protein, 18% calories; carbohydrate, 55% of calories; cholesterol, 150 mg; sodium, 2300 mg; potassium, 4700 mg; calcium, 1250 mg; magnesium, 500 mg; and fiber, 30 g. The nutrient characteristics of the DASH diet is that it reduces lean meat, sweets, and added sugars, but it is rich in potassium, magnesium, and calcium, and also protein and fiber (*15*, *16*).

The DASH diet is very effective in controlling blood pressure. Sacks et al. (*17*) studied the effect of different levels of dietary sodium, in conjunction with the DASH diet, in patients both with and without hypertension and discovered that a reduction of sodium intake to levels below the current recommendation of 2400 mg per day and the DASH diet both lower blood pressure

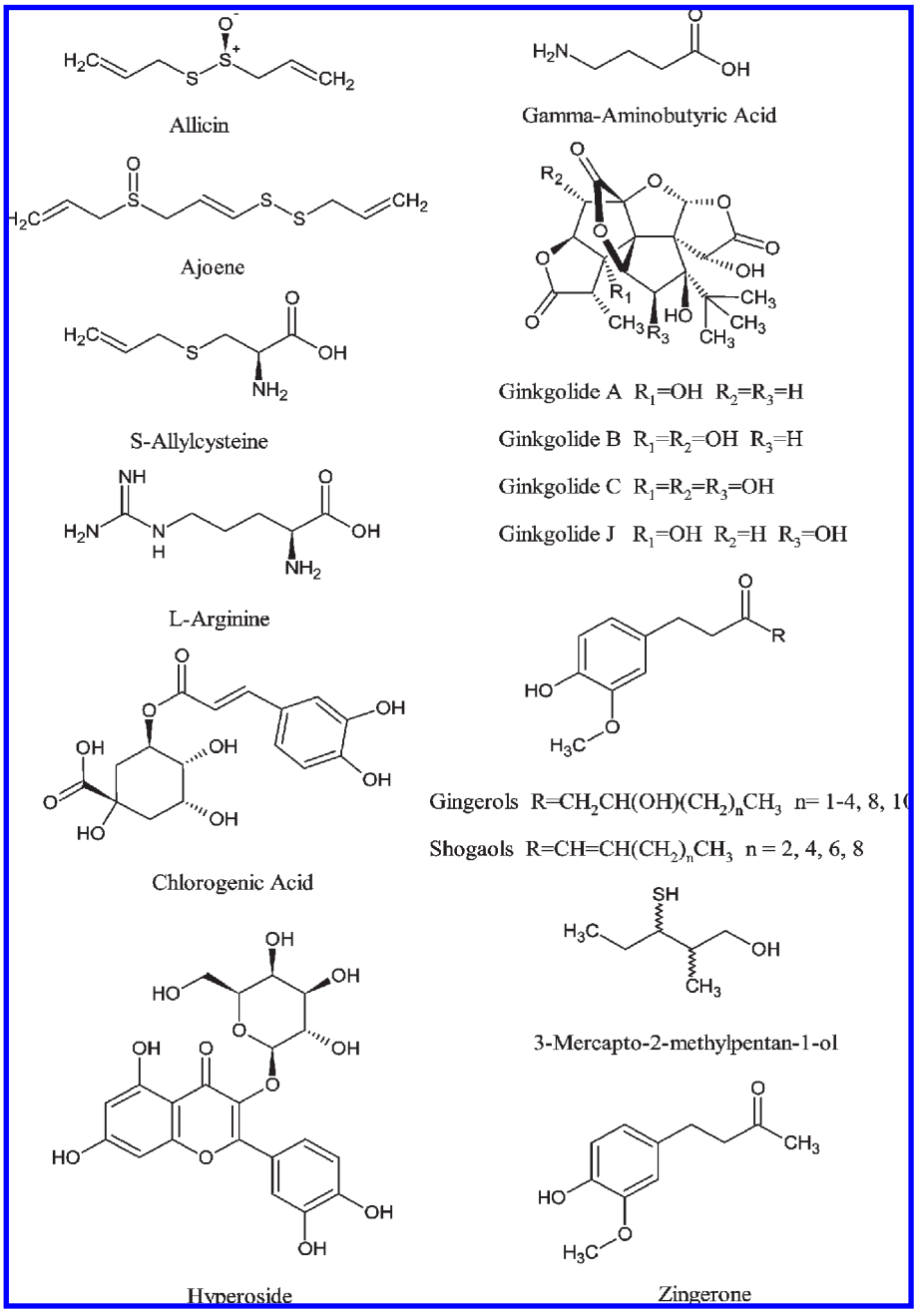

Figure 3. Structures of selected natural anti-hypertensive compounds.

substantially and that the effect is greater when the two are combined. A study conducted by Appel et al. (*18*) enrolled 459 adults with systolic blood pressures of < 160 mmHg and diastolic blood pressures of 80−95 mmHg and randomly assigned them into three groups that received, respectively, a control diet, a diet rich in fruits and vegetables, and a DASH diet. It was found that the DASH diet was most effective in reducing blood pressure. The DASH diet has been shown not only to lower blood pressure but also to reduce the risk of CHD and stroke among middle-aged women during 24 years of follow-up (*19*). The success of the DASH diet in controlling blood pressure is an excellent example of how diet plays an important role in general health and management of diseases.

L-Arginine Supplementation. L-Arginine has become increasingly popular as a health supplement for hypertensive patients (**Figure 3**). It is a nonessential amino acid because L-arginine can be endogenously synthesized from three amino acids (glutamine, glutamate, and proline) in humans. L-Arginine is a precursor to NO, which is a key component in endothelium-dependent relaxation (**Figure 2**). In addition, L-arginine is metabolically involved in the formation of urea and creatine. L-Arginine has been also associated with immunity enhancement, release of growth hormone, and attenuation of atherosclerosis. It is estimated that consumption of L-arginine by humans is 3−6 g/day and the observed safe level is 20 g/day (*20*). Theoretically, L-arginine supplementation can boost production of NO, improve the function of blood vessels, and lower blood pressure as it is a substrate for NO synthesis.

L-Arginine has been extensively studied for its function in improvement of endothelial function and reduction of blood pressure in both animals and humans. A number of animal studies have found that L-arginine lowers blood pressure. For example, L-arginine supplementation decreased hypertension, proteinuria, and ADMA levels in stress-induced pre-eclamptic rats, indicating that taking L-arginine is beneficial in pre-eclampsia treatment (*21*). The administration of tap water containing

L-arginine at a concentration of 1.5% not only lowered blood pressure but also normalized the abnormality of renal hemodynamics accompanying salt-induced hypertension in salt-sensitive rats (*22*).

Loss of NO bioactivity is a main feature of endothelial dysfunctions in hypertension. Therefore, supplementation of L-arginine should boost the production of NO. In fact, L-arginine supplementation improves endothelium-dependent dilation and reduces blood pressure in humans. Most clinical trials have shown that either intravenous injection or oral intake of L-arginine reduces blood pressure and improves endothelial function (*23*−*26*). As a result, most clinical trials have also indicated that L-arginine produces a modest decrease in blood pressure in both normotensive individuals and hypertensive patients (*27*).

Chlorogenic Acid (CGA). CGA refers to a family of esters formed between *trans*-cinnamic acids and quinic acid (**Figure 3**). Specifically, the commonest chlorogenic acid is formed between caffeic acid and quinic acid. CGA is widespread in plants, fruits, and vegetables such as coffee beans, apples, pears, tomatoes, blueberry, potatoes, peanuts, Chinese parsley, and eggplants, and its chemistry has been well documented (*28*−*30*). It is estimated that humans consume up to 1 g of CGA per day (*31*). In addition to its reported anti-hypertensive activity, CGA also possesses carcinostatic, hypoglycemic, and antioxidant activities.

A number of animal studies have indicated that CGA is hypotensive. A single ingestion of CGA (30−600 mg/kg) could reduce blood pressure in spontaneously hypertensive (SHR) rats (*31*). When SHR rats were fed diets containing 0.5% CQA for 8 weeks, the development of hypertension was inhibited compared with the control diet group (*31*). In another SHR rat experiment, a single oral ingestion (50−200 mg/kg) of 5-CGA dose-dependently decreased blood pressure. When given intravenously at concentrations of 2.5, 5, and 10 mmol/kg of body weight, caffeic acid or ferulic acid, metabolites of CGA, were hypotensive. Ferulic acid was stronger than caffeic acid, suggesting that it is an anti-hypertensive candidate component (*32*).

The blood pressure-lowering activity of CGA is also pronounced in humans. When mildly hypertensive subjects were randomized to receive treatment with CGA (140 mg/day) isolated from green coffee bean extracts or placebo, blood pressure (systolic and diastolic) decreased significantly in the CGA group but not in the placebo group (*33*). Coffee is rich in CGA, and hydroxyhydroquinone produced by roasting green coffee beans counteracts the activity of CGA. It was found that CGA in hydroxyhydroquinone-free coffee had an anti-hypertensive effect in a dose-dependent manner (*34*). However, it should be pointed out that consumption of high doses of chlorogenic acid might raise plasma total homocysteine concentration, which is a risk factor for coronary heart disease in humans (*35*).

The mechanism for the blood pressure-lowering activity of CGA is partially known. First, CGA is an antioxidant and its consumption is significant. It is believed that the superoxide radical is involved in hypertension by destroying NO by forming peroxynitrite in vascular walls. CGA can increase NO bioavailability by inhibiting the reactive oxygen species-generating enzymes including DAD(P)H and xanthine oxidase and reducing the formation of peroxynitrite (*31*, *36*). Second, CGA-induced anti-hypertensive activity is thought to be associated with its protective role in eNOS (**Figure 2**). This is supported by the observation that addition of a NOS inhibitor, *N*(G)-nitro-L-arginine methyl ester (L-NAME), blocked the anti-hypertensive response of CGA in SHR rats (*31*). It is known that blood pressure is negatively correlated with the plasma level of NO metabolites. In this regard, CGA intake increased the urinary NO metabolites in SHR rats, although it was unable to affect the NOS expression level (*31*).

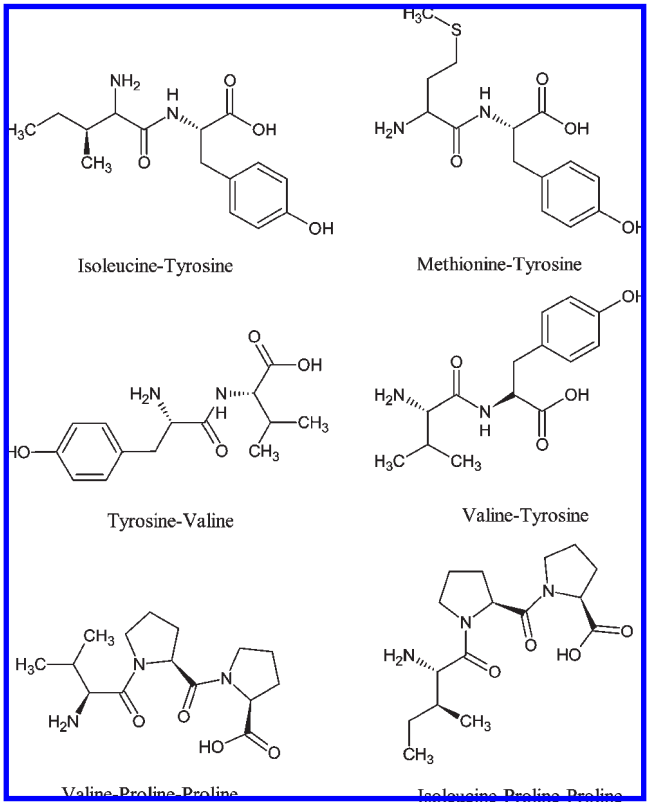

Figure 4. Structures of selected anti-hypertensive peptides.

Fermented Milk. Several studies have established the effect of drinking milk, particularly fermented dairy products, on blood pressure (*37*). First, epidemiological studies have demonstrated that people with higher milk intakes have a more desirable blood pressure than those who drink lesser milk (*38*). This is largely attributable to a number of components in milk that have blood pressure-lowering activity. These may include the minerals calcium, magnesium, and potassium, which are rich in milk and have anti-hypertensive activities, although the underlying mechanism remains poorly understood. Second, anti-hypertensive activity of fermented milk and dairy products is more pronounced than that of nonfermented products. Several anti-hypertensive peptides produced by fermentation with lactic acid bacteria have been identified.

The chemistry and biochemistry of milk and fermented milk have been well studied. Fermentation-derived anti-hypertensive peptides have been of particular interest. Two of the most studied peptides in fermented milk are the tripeptides valine−proline−proline (VPP) and isoleucine−proline−proline (IPP) (**Figure 4**), which were first identified by Nakamura et al. (*39*). These two peptides possess a strong ACE inhibiting activity. The commercial products Evolus, made in Finland, and Calpis, made in Japan, are good examples of these products fermented by *Lactobacillus helveticus* and contain significant amounts of these two peptides.

The blood pressure-lowering activity of VPP and IPP has been demonstrated in a number of animal studies. A single oral administration of sour milk (5 mL/kg of body weight) containing 0.6 mg/kg VPP or 0.3 mg/kg IPP significantly decreased the systolic blood pressure from 6 to 8 h after administration; blood pressure returned to the initial level at 24 h after administration in SHR rats (*40*). Long-term administration of

fermented milk or VPP and IPP was also effective in reducing significantly systolic blood pressure in SHR rats (*41*, *42*). The underlying molecular mechanism by which VPP and IPP inhibit ACE activity has been attributed to their unique binding mode to the active site of ACE (*43*).

Data from most studies on the blood pressure-lowering activity of fermented milk in humans are promising. In a randomized, double-blind placebo-controlled parallel group study, 94 hypertensive patients not receiving any drug treatment were given 150 mL twice daily of fermented milk containing 7 mg of IPP and 10 mg of VPP per 100 g. It was found that the fermented milk containing these two bioactive peptides in daily use lowered the blood pressure (*44*). In another randomized, placebo-controlled, double-blind study, the effect and safety of powdered fermented milk with *L. helveticus* CM4 on subjects with high−normal blood pressure or mild hypertension were evaluated. It was found that daily ingestion of the tablets containing powdered fermented milk reduced elevated blood pressure and had no adverse effects (*45*). When milk fermented by *L. helveticus* was given for a relatively longer time of 21 weeks, there were mean differences of 6.7 mmHg in systolic blood pressure and 3.6 mmHg in diastolic blood pressure between the test and control hypertensive patients (*46*). However, a study of 135 Dutch subjects with elevated systolic blood pressure demonstrated that fermented milk containing lactotripeptides did not significantly change systolic blood pressure or diastolic blood pressure (*47*). Although a definite conclusion cannot be reached, the evidence of most clinical trials appears to find blood pressure reductions of 5−10 mmHg in systolic and diastolic blood pressure following fermented milk intervention.

Garlic. Garlic (*Allium sativum* L.) belongs to the family Alliaceae. Garlic has been long used as both a foodstuff and a medicine by many cultures due to its characteristic pungent and spicy flavor and the health benefits associated with its consumption. Garlic has been claimed to possess antioxidant properties, to help prevent heart disease including atherosclerosis, to reduce both plasma cholesterol level and blood pressure, and to prevent the development of cancer as well as cold and flu symptoms through immune enhancement (*48*). When crushed, garlic produces a number of sulfur-containing compounds that give it its characteristic flavor. Although thiosulfinates such as allicin have been long considered to be active compounds, other compounds such as ajoene, *S*-allylcysteine, and saponin in garlic may synergistically contribute to the essential biological activities of garlic (*49*) (**Figure 3**). In addition, garlic is rich in other bioactive compounds, namely, polyphenols, flavonoids, flavanols, anthocyanins, tannins, and ascorbic acid (*50*). However, the active ingredients have been shown to be subjected to degradation caused by cooking (*51*).

Garlic appears to play an important dietary role in the management of hypertension (*52*). Animal studies have suggested that the consumption of garlic is able to reduce blood pressure. In rats, it was found that aged garlic and its most abundant organosulfur compound, *S*-allylcysteine, had anti-hypertensive and renoprotective activity (*53*). Similarly, allicin in garlic reduced not only blood pressure but also blood cholesterol in rats (*54*). In two-kidney−one-clip (2K1C) hypertensive rats, a negative correlation between the consumption of garlic and blood pressure was seen (*55*). It appeared that aged garlic extract was safer than raw garlic because raw garlic might have harmful effects including a decrease in erythrocytes, an increase in reticulocytes, and generation of papilloma in the forestomach (*56*). The anti-hypertensive effect of garlic is at its strongest 2−6 h after administration, but a residual effect can continue for up to 24 h (*57*).

Animal studies have consistently suggested that garlic reduces blood pressure, but human studies have generated mixed results. In this regard, a recent systematic review and meta-analysis was performed to test the associations between blood pressure outcomes and duration of treatment, dosage, and blood pressure at the start of garlic treatment (*52*). A mean decrease of 4.6 mmHg for SBP was found in the garlic group compared to the placebo group ($n = 10$; $p = 0.001$), whereas the mean decreases in the hypertensive subgroup were 8.4 mmHg for SBP ($n = 4$; $p < 0.001$) and 7.3 mmHg for DBP ($n = 3$; $p < 0.001$). The superior performance of the garlic treatment to the placebo in this meta-analysis indicates that garlic preparations definitely help to reduce blood pressure in individuals with hypertension (*52*). To examine the effect of garlic on blood pressure in patients with and without elevated SPB, another meta-analysis of randomized controlled trials was recently conducted (*58*). It found that garlic reduced SBP by 16.3 mmHg and DBP by 9.3 mmHg compared with placebo in patients with elevated SBP. However, the use of garlic did not reduce SBP or DBP in patients without elevated SBP (*58*). These meta-analyses prove that garlic is able to reduce blood pressure in patients with an elevated SBP, although its effect on those without elevated SBP is not significant.

Although it remains largely unclear how garlic lowers blood pressure, some evidence suggests that the anti-hypertensive activity of garlic is probably mediated by one or a combination of the following mechanisms. First, lower ACE activity in serum and different tissues was found to be associated with the consumption of garlic in 2K1C rats, suggesting that the blood pressure-lowering effect is partially mediated by its inhibition on ACE (*55*). Second, garlic treatment could reduce significantly production of thromboxane-B2 and prostaglandin-E2 in 2K1C rats, indicating that the blood pressure-lowering effects of garlic might have been induced partially by a greater reduction in the synthesis of vasoconstrictor prostanoids (*59*). Third, garlic and the active metabolite allicin have been shown to elicit an NO-dependent relaxation in rat isolated pulmonary arteries, and this response was probably mediated via garlic activation of NO formation (*60*, *61*). Finally, *S*-allylcysteine present in garlic has been found to be a peroxynitrite radical scavenger (*62*). Peroxynitrite, a reaction product of superoxide and NO, could oxidize (BH_4), a crucial cofactor for NOS, leading to endothelial dysfunction and elevation of blood pressure. It is concluded that garlic is anti-hypertensive in subjects with hypertension, possibly mediated by its effect on multiple metabolic sites in the regulation of blood pressure.

Onion. The onion (*Allium cepa*, also known as the garden onion or bulb onion) is one of the oldest vegetables known in human diets and is found in many recipes and preparations around the world. It can be consumed either fresh or frozen, or canned, pickled, powdered, chopped, or dehydrated. Like garlic, onions are rich in thiosulfinates and volatile pungent sulfur compounds (*63*). In addition to these low molecular weight compounds, onions are also rich in phenolic compounds (*64*, *65*). These compounds are believed to be responsible for the health benefits associated with the consumption of onions.

Onion has been shown to be anti-hypertensive in most animal studies. In L-NAME-induced hypertensive rats and stroke-prone spontaneously hypertensive rats (SHRSP) rats, dried onion was able to reduce blood pressure when it was added into diet at 5% (*66*). Green-leafy type but not white-sheath type Welsh onion has been reported to lower the blood pressure of rats fed a high-fat and high-sucrose diet (*67*). Interestingly, only raw Welsh onion but not cooked onion was capable of lowering the resting blood pressure in rats (*67*), suggesting the thermal destruction of the active ingredients in onion. Although the active

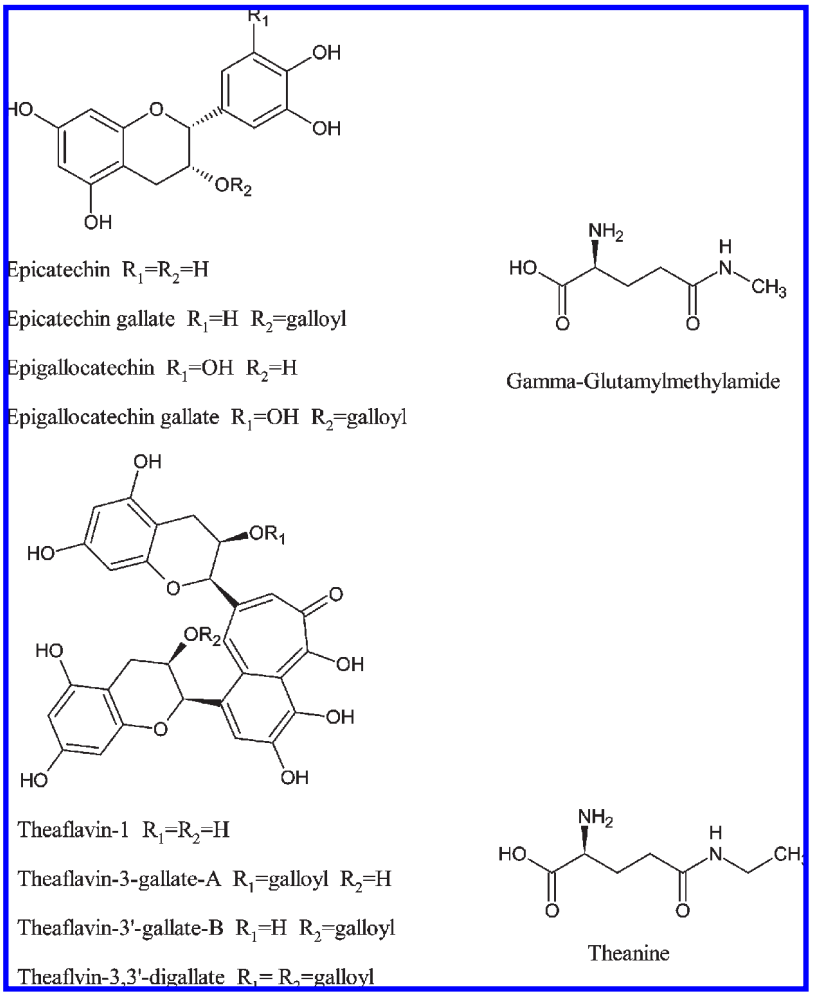

Figure 5. Structures of the anti-hypertensive compounds in tea.

ingredients responsible for the blood pressure-lowering activity of onion are not yet fully understood, some evidence suggests that they reduce blood pressure probably by the following mechanisms. First, the anti-hypertensive effect of onion probably involves the saving of NO, as dietary onion increased the nitrate/nitrite metabolites in urine and the NOS activity in the kidney of SHRSP rats (*66*). It has also been shown that 3-mercapto-2-methylpentan-1-ol (3-MP), a constituent in onion, was able to scavenge the peroxynitrite radical in vitro (*69*). Second, the anti-hypertensive activity of onion is believed to be mediated by its inhibition of the production of angiotensin II, because rats fed a high-fat−high-sucrose diet containing onion not only had a higher level of NO metabolites but also suppressed angiotensin II production (*67*). Third, onion exhibits and attenuates the hypertension possibly via inhibition of calcium influx independent of its effect on NO, cGMP, endothelium, and prostaglandins (*70*).

Data regarding the effect of onion on blood pressure in humans are scarce. One characteristic of the Mediterranean diet is to use onion and olive oil as the crucial ingredients. Kalus et al. (*71*) conducted a randomized, placebo-controlled, double-blind, and crossover study to investigate the effect of an onion−olive oil maceration capsule formulation on arterial blood pressure. They found that it produced a decrease in arterial blood pressure. It is known that onion is rich in a flavonoid called quercetin, which is believed to be one of the active ingredients responsible for the anti-hypertensive activity of onion. One study investigated the efficacy of quercetin supplementation in lowering blood pressure in hypertensive humans and demonstrated that 730 mg of quercetin per day could reduce SBP by 7 mmHg, DBP by 5 mmHg, and mean arterial pressures by 5 mmHg in stage 1 hypertensive patients (*72*). However, effect of onion on blood pressure in humans with or without hypertension cannot be warranted until more randomized and double-blind experiments are conducted.

Tea. The blood pressure-lowering activity of tea has been extensively investigated. Tea, derived from the leaves of *Camellia sinensis*, is the world's most popular and widely consumed beverage. On the basis of distinct manufacturing processes and chemical composition, tea can be classified into three main types: green tea, oolong tea, and black tea (*73*). Green tea is nonfermented, whereas black tea generally refers to the fermented products and oolong tea is a partially fermented type of tea. Green tea catechins (GTCs), a group of polyphenols, remained unchanged in green tea, but by the process of fermentation in black tea they are oxidized and polymerized to the "pigments" called theaflavins (TF) and thearubigins (TR). Green tea contains four major GTC derivatives, namely, (−)-epicatechin (EC), (−)-epicatechin gallate (ECG), (−)-epigallocatechin (EGC), and (−)-epigallocatechin-gallate (EGCG), whereas in addition to GTCs, black tea and oolong tea also contain theaflavin (TF1), theaflavin-3-gallate (TF2A), theaflavin-3′-gallate (TF2B), and theaflavin-3,3′-digallate (TF3) (**Figure 5**). Tea is also known to contain caffeine, γ-glutamylmethylamide (GMA), and theanine.

GTCs have been shown to lower blood pressure in most animal studies. When SHRSP rats were given water containing green tea polyphenols and black tea polyphenols, systolic and diastolic

blood pressure were significantly lowered compared with the control group (*74*). Oral administration of tea-leaf saponin appeared to decrease mean blood pressure very effectively at a dose of 100 mg/kg of body weight in SHR rats (*75*). In type 2 diabetic Goto−Kakizaki (GK) rats, dietary catechins tended to maintain blood glucose and systolic blood pressure at lower levels than the control diet (*76*). Cell culture and animal experiments suggest that GTCs reduce blood pressure probably by the following mechanisms. First, GTCs are ACE inhibitors. When cultured endothelial cells from human umbilical veins were incubated with green tea, black tea, and four individual catechins (EC, EGC, ECG, and EGCG) for 10 min, a significant and dose-dependent inhibition of ACE activity was seen (*77*). Second, the anti-hypertensive activity of GTCs is probably mediated by its action on endothelial NO production (*77*). When the effects of green and black tea on NO production and vasodilation were compared in bovine aortic endothelial cells, both green and black tea stimulated eNOS activity and phosphorylation as well as vasorelaxation in rat aortic rings to a similar extent (*78*). In green tea, it was found that EGCG was potent, whereas TF and TR in black tea had equally potent effects on pronounced NO production and NO-dependent vasorelaxation in aortic rings (*78*). Third, it has been shown that tea catechin-induced endothelium-dependent relaxation is primarily mediated by nitric oxide and partially through nitric oxide-dependent activation of iberiotoxin-sensitive K^+ channels (*70*). Fourth, GTE has been shown to cause a dose-dependent depressor action in anesthetized rats at least partly through the blockade of adrenergic α1-receptors (*80*). Finally, tea contains GMA and theanine, which are known to have some anti-hypertensive activity (*81*, *82*). However, the underlying mechanisms associated with actions of these two compounds remain poorly understood.

Data from tea studies on blood pressure in humans are not consistent. In a 1996 study in Taiwan, Yang et al. (*83*) examined the effect of tea drinking on the risk of newly diagnosed hypertension in 1507 subjects with no hypertensive history. After carefully adjusting for age, sex, socioeconomic status, family history of hypertension, body mass index, waist−hip ratio, and lifestyle factors, they found that compared with nonhabitual tea drinkers, the risk of developing hypertension decreased by 46% for those who drank 120−599 mL/d and was further reduced by 65% for those who drank 600 mL/d or more. One observational study found that both tea and a tea-derived biomarker, 4-*O*-methylgallic acid in urine, were negatively associated with blood pressure in older women (*84*). Another study investigated the relationship of tea to systolic blood pressure and mortality from coronary heart diseases and demonstrated that systolic blood pressure was inversely related to tea with drops of 2.1 mmHg in men and 3.5 mmHg in women (*85*). However, some studies did not observe a favorable effect. For instance, the results from a clinical trial did not demonstrate that drinking tea for 6 weeks was associated with any favorable change in blood pressure compared with placebo (*86*). Taubert et al. (*87*) summarized the findings of five studies of tea consumption involving a total 343 subjects with a median duration of 4 weeks and concluded that tea intake had no significant effects on blood pressure. Furthermore, tea may have an acute blood pressure-raising effect as demonstrated from one study which found that blood pressure was significantly increased by tea alone in comparison to each of three other groups: water alone, meal with water, and meal with tea beverage (*88*). The effect is probably attributable to caffeine, which is known to have a mild hypertensive effect for a few hours after use (*89*). It therefore appears that tea has both anti-hypertensive and hypertensive components. The former include tea catechins, theaflavins, GMA, and theanine, whereas caffeine is an important hypertensive component. As the evidence for the blood pressure-lowering activity of tea in humans is mixed, further additional clinical randomized, double-blind crossover studies are needed to resolve the issue.

Soybean Protein and Peptides. Soy products have received considerable attention as anti-hypertensive functional foods. Soy foods are popular in many cultures and are consumed as tofu, soy milk, soy flour, soy protein isolate, tempeh, and miso. The chemistry of soybean and its active ingrediets isoflavones has been well documented (*90*, *91*). Yang et al. (*92*) have found that rats fed a diet containing soy protein and soy protein hydrolysate as the protein source had better blood pressure control and renal function and lower circulating ACE activity and renal tumor necrosis factor-α (TNF-α) concentration than rats fed a casein protein diet. A similar result was seen in a study comparing the effects of soy- and casein-based diets on blood pressure and cardiovascular functions in male and female SHR rats. The study found that the development of hypertension was weaker in both female and male rats fed a soy protein diet than a casein diet (*93*). In a long-term study of 12 weeks of feeding, it was found that administration of soybean hydrolysate in SHR rats was capable of retarding the development of hypertension (*94*).

Anti-hypertensive activity of soy products on blood pressure has been also investigated in humans. Welty et al. (*95*) found that substituting soy nuts for non-soy protein lowered blood pressure and low-density lipoprotein cholesterol levels in hypertensive women, suggesting that soy is cardioprotective. A randomized, double-blind, controlled trial in 302 mildly hypertensive subjects aged 35−64 years demonstrated that 40 g of daily isolated soybean protein supplements per day resulted in reductions of 7.9 mmHg for SBP and 5.3 mmHg for DBP (*96*). Yang et al. (*97*) demonstrated that consumption of soy foods at the usual intake level could also reduce both SBP and DBP, particularly among elderly women. When the anti-hypertensive potential of soy milk (500 mL twice daily) was compared with cow's milk in a 3 month double-blind randomized study of 40 men and women with mild to moderate hypertension, chronic soy milk consumption had modest, but significant, anti-hypertensive action in essentially hypertensive subjects (*98*). However, the anti-hypertensive activity of soy products and proteins was not found in other studies (*99*, *100*). Instead, one study found that soy protein might increase systolic blood pressure (*101*). These conflicting findings indicate that additional clinical trials are required to determine the anti-hypertensive activity of soy proteins.

It has been hypothesized that anti-hypertensive activity of soybean protein is mediated by its production of ACE inhibitory short peptides during enzymatic hydrolysis in the gastrointestinal tract in animal studies, although human trials have produced mixed results. In this regard, several peptides including Val-Leu-Ile-Val-Pro, Tyr-Leu-Ala-Gly-Asn-Gln, Phe-Phe-Leu, Ile-Tyr-Leu-Leu, and Val-Met-Asp-Lys-Pro-Gly (**Figure 4**) that possessed ACE inhibitory activity have been isolated (*102*−*104*). Natto is a traditional Japanese fermented food made by fermenting boiled soybeans with *Bacillus natto*. Two groups of ACE inhibitors with a high molecular weight and a low molecular weight were detected and exhibited competitive or noncompetitive inhibition against the hydrolysis of Bz-Gly-His-Leu by ACE (*105*). A γ-aminobutyric acid (GABA)-enriched tempeh-like fermented soybean (GABA-tempeh) was found to prevent the elevation of systolic blood pressure in SHR rats, as GABA is a depressive neurotransmitter and is able to depress the elevation of blood pressure (*106*). Although agreement has yet to be reached on this point, it has been suggested that phytoestrogens present in soybean protein may also be partially responsible for the anti-hypertensive activity (*107*). In general, most animal studies have

found soybean protein to be anti-hypertensive, and the active ingredients are the soy protein-derived ACE inhibitory peptides upon hydrolysis.

Ginger. Ginger refers to the underground stem of the plant *Zingiber officinale*. It has a long history of cultivation and is used as both a spice for cooking and a medicinal herb by many cultures. Ginger root is characterized by its unique odor and flavor, which are attributable to a mixture of compounds called zingerone, shogaols, gingerols, and volatile oils (**Figure 3**). Ginger has a number of health benefits, demonstrating immunomodulatory, antitumorigenic, anti-inflammatory, antiapoptotic, antihyperglycemic, antilipidemic, and antiemetic action, and research in both animals and humans suggests that ginger also exerts direct and indirect effects on the blood pressure and heart rate (*108*).

Animal studies mainly in rats have demonstrated that ginger root is anti-hypertensive. Ginger crude extract could induce a dose-dependent fall in the arterial blood pressure of anesthetized rats (*109*). In the cardiovascular system, both (6)-shogaol and (6)-gingerol, two active components in ginger, produced depressor response at lower doses on the blood pressure (*110*). At high doses, they showed a triphasic response, which comprised a rapid fall followed by a rise and a delayed fall (*111*). Data regarding the effect of ginger consumption on blood pressure in humans are, however, scarce.

The underlying mechanism by which ginger and its active components lower blood pressure remains poorly understood. In guinea pig paired atria, ginger crude extract exhibited a cardiodepressant activity on the rate and force of spontaneous contractions, whereas in rabbit thoracic aorta preparation, ginger crude extract relaxed the phenylephrine-induced vascular contraction at a dose 10 times higher than that required against K^+ (80 mM)-induced contraction (*109*). Ca^{2+} channel-blocking activity was confirmed when ginger crude extract shifted the Ca^{2+} dose−response curves to the right, similar to the effect of verapamil, suggesting that the blood pressure-lowering effect of ginger is mediated through a blockade of the voltage-dependent calcium channel (*109*). In addition, zingerone, an active ingredient in ginger, is able to efficiently scavenge native ONOO(−) as well as ONOO(−) derived from the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1), thus improving the functionality of endothelium (*112*).

Hawthorn. Hawthorn (*Crataegus*) is widely distributed throughout the northern temperate regions of the world, with approximately 280 species primarily in East Asia, Europe, and North America. *Crataegus pinnatifida* and *Crataegus cuneata* are the two major species found in China, where their fruits are named Shanzha and commonly used to cure scurvy, constipation, and stomach ailment. Consumption of hawthorn fruit is also associated with the reduction of hypertension and long-term medicinal benefits to the cardiovascular system. The chemical composition of hawthorn fruits has been a subject of extensive studies (*113*). The major components, including fructose, flavonoids, proanthocyanidins, triterpenes, chlorogenic acid, vitamins, and minerals, vary with species, geographic locations, and time of harvest.

Hawthorn has been shown to be capable of decreasing blood pressure in rats. One study investigated the blood pressure and the structure of the coronary arterial wall of L-NAME-induced hypertensive rats given an aqueous leaf extract of hawthorn (100 mg/kg) for 4 weeks via gavage, finding that the extract, especially the hyperoside (one of the active ingredients, **Figure 3**) fraction, prevented L-NAME-induced hypertension and had beneficial effects on the cardiovascular system (*114*). It was also demonstrated that bolus injection of hawthorn extracts caused a significant reduction in the blood pressure and exhibited a potential anti-arrhythmic action on ischemic myocardium in male Wistar rats (*115*). In humans, patients with type 2 diabetes given daily 1200 mg of hawthorn extract showed greater reductions in blood pressure than the placebo group (*116*). In a double-blind, placebo-controlled clinical trial, a total of 92 men and women with primary mild hypertension, aged 40−60 years, received either hydroalcoholic extract of hawthorn or placebo three times daily, and statistical analysis showed a significant decrease in both SBP and DBP after 3 months associated with the consumption of hawthorn extract (*117*).

Anti-hypertensive activity of hawthorn is probably mediated by the following mechanisms. First, hawthorn is able to induce endothelium-dependent, NO-mediated vasorelaxation via eNOS phosphorylation (*118*). It was previously shown that pretreatment of the arterial tissues with L-NAME inhibited the relaxation induced by hawthorn extract, whereas indomethacin (10 μM) had no effect. L-Arginine (3 mM) did not affect the relaxation induced by hawthorn extract but partially reversed the effect of 10 μM L-NAME (*119*). Second, hawthorn is rich in a flavonoid known as hyperoside. It is hypothesized that hyperoside has a strong free radical scavenging activity which can save NO from attack by superoxide radicals and scavenge peroxynitrite radicals (*114*, *120*). Third, procyanidins in hawthorn extract may be responsible for the endothelium-dependent nitric oxide-mediated relaxation in isolated rat aorta, via activation of tetraethylammonium-sensitive K^+ channels (*121*). Finally, flavonoids and proanthocyanidins present in hawthorn may have ACE inhibitory activity (*122*).

Gingko Leaves. Ginkgo has been used in China for centuries and has become popular in Europe because it has a potent vasodilating activity. Ginkgo active ingredients are attributable to two types of components, namely, flavone glycosides and terpene lactones (*123*). The former consists of kaempferol, quercetin, and isorhamnetin, whereas the latter contains ginkgolides A, B, C, and J and bilobalide (**Figure 3**). It is believed that terpene lactones are able to dilate blood vessels, therefore improving blood flow through the body and reducing blood pressure. Most studies have demonstrated that gingko leaf extract (GLE) has modest improvement in blood flow in patients having memory impairment, dementia, and peripheral vascular diseases (*124*).

Studies using animal models have demonstrated that GLE not only improves the blood circulation by causing the dilation of vascular vessels but also reduces blood pressure. To test the effect of dietary administration of GLE on the blood pressure and vascular tone of hypertensive, Dahl salt-sensitive (Dahl) rats were fed an 8.0% NaCl diet or an 8.0% NaCl plus 0.5% GLE diet for 24 days. It was found that GLE did not change the heart rate, but it significantly decreased systolic salt-related elevation of blood pressure (*125*). When SHR and Wistar Kyoto rats were fed either a control diet or a diet containing 0.05−0.5% ginkgo for 30 days, it was found ginkgo did not change systolic blood pressure in Wistar Kyoto rats, but significantly decreased systolic blood pressure in SHR rats (*126*). One study examined the effects of GLE on the development of hypertension, platelet activation, and renal dysfunction in deoxycorticosterone acetate-salt hypertensive rats, demonstrating that development of hypertension was attenuated in rats fed a 2% GLE diet (*127*). In addition, an increase in heart weight, an indicator of sustained high BP, was inhibited significantly when animals were fed the GLE diet (*127*). However, GLE feeding did not affect blood pressure, but significantly reduced heart rate and blood flow velocity in tail arteries of aged SHR rats (*128*). Furthermore, GLE feeding did not affect contractile response to phenylephrine, relaxation responses to not only sodium nitroprusside but also acetylcholine,

and protein levels of endothelium nitric oxide synthase and soluble guanylate cyclase in aortas of aged SHR rats, suggesting that long-term GLE feeding impairs peripheral circulation in aged SHR rats (*128*).

Studies of the effect of gingko on blood pressure in humans have produced inconsistent results. Two studies have been documented to demonstrate that gingko reduces blood pressure. The first study evaluated the effects of gingko extract on blood pressure responses during stress in healthy young volunteers ($n = 70$) in a double-blind placebo-controlled design and found that a single treatment with gingko extract (120 mg) reduced stress-induced rise in blood pressure without affecting the heart rate (*129*). The second study was to determine the effect of GLE on glucose-stimulated pancreatic β-cell function in 20 normal glucose-tolerant individuals given 120 mg/day at bedtime for 3 months, finding that GLE caused decreases in systolic blood pressure from 125 to 118 mmHg ($p < 0.05$) and in diastolic blood pressure from 86 to 68 ($p < 0.01$) (*130*). In contrast, other studies have found that gingko has no effect on blood pressure (*131*−*133*).

The underlying mechanism by which ginkgo reduces blood pressure is probably attributable to its effect on calcium level in endothelium. It has been shown that ginkgo enhances endothelium-dependent vasodilation and elevation of the endothelial intracellular $Ca0^{(2+)}$ level, resulting in hypotension. This accelerative effect of ginkgo on $Ca^{(2+)}$ mobilization seemed to be associated with restoration of impaired dilatory function induced by acetylcholine in endothelial cells (*126*). In addition, ginkgo extract is able to up-regulate eNOS in rats. When the ginkgo extract was administered orally to SHRSP rats at 60 and 120 mg/kg each day for 3 weeks from the age of 7 weeks, the age-related increase in blood pressure observed in SHRSP rats was suppressed significantly at both doses 3 weeks after treatment (*134*). This was accompanied by a significant increase in urinary NO metabolites, nitrite/nitrate, and up-regulation of expression of eNOS mRNA compared with the control values.

Bioactive Peptides from Hydrolysis of Fish Protein. Hydrolysis of fish proteins or other proteins has been documented to produce the short bioactive peptides that possess potent inhibitory activity against ACE (*135*). Sardine peptides are a typical example. The efficacy of these peptides has been proved, and they are sold as a blood pressure-lowering functional foods in Korea and Japan. These peptides usually consist of two to three amino acid residues. Among them, Val-Tyr, Met-Tyr, Ala-Pro, Lys-Pro, Agr-Pro, and Arg-Val-Tyr have been athe subject of some in vivo or in vitro investigations (**Figure 4**).

Results from animal studies on anti-hypertensive activity of fish protein-derived peptides are promising. In one study, the depressor action of Val-Tyr was investigated in transgenic mice carrying the human renin gene cross-mated with mice bearing the human angiotensinogen gene. It was found that a single oral administration of Val-Tyr (0.1 mg/g) resulted in a prolonged reduction of blood pressure for up to 9 h (*136*). In 18-week-old SHR rats, similar results were seen when a single oral administration of Val-Tyr (10 mg/kg) resulted in a prolonged reduction of SBP for up to 9 h (*137*). It was found that Val-Tyr showed a vascular relaxation effect in KCl-induced contraction of thoracic aorta rings from 18-week-old SHR rats among dipeptides of Val-Tyr, Ile-Tyr, and Tyr-Val irrespective of their angiotensin I-converting enzyme inhibitory activity (*138*). Met-Tyr, which is also an ACE inhibitory dipeptide derived from sardine muscle, protected endothelial cells from oxidative stress via induction of HO-1 and ferritin but independent of its ACE inhibitory properties (*139*). In addition, three ACE inhibitory peptides, Ala-Pro, Lys-Pro, and Arg-Pro, were isolated from fermented fish sauce (*140*).

Three clinical trials have proved that Val-Tyr is effective in reducing blood pressure in hypertensive patients. A randomized double-blind placebo-controlled study was carried out in 29 volunteers given orally a 100 mL drink containing 3 mg of Val-Tyr or a 100 mL placebo drink, demonstrating that in the Val-Tyr group, reductions in systolic and diastolic blood pressures were 9.7 and 5.3 mmHg ($P < 0.001$) at week 1 and 9.3 and 5.2 mmHg ($P < 0.001$) at week 4, respectively, whereas neither systolic nor diastolic blood pressure changed in the placebo group (*141*). The second randomized double-blind placebo-controlled study was conducted in 63 subjects given a vegetable drink containing Val-Tyr. As a result, a significant decrease of blood pressure was observed in the hypertension, mild hypertension, and high-normal blood pressure groups without any observed adverse effects (*142*). The third trial was to investigate the change in plasma level of Val-Tyr after a single oral administration of a Val-Tyr-drink at doses of 0, 6, or 12 mg in mildly hypertensive subjects (*143*). It was found that the maximal increment of plasma Val-Tyr level was observed over the second hour postprandially and the plasma Val-Tyr level increased with the Val-Tyr dosage. However, no marked blood pressure change was observed with the increase of plasma Val-Tyr level, suggesting that Val-Tyr did not exert an acute anti-hypertensive effect (*143*).

Fish Oil and Omega-3 Polyunsaturated Fatty Acids (PUFA). Fish oil has been shown to influence blood pressure in both humans and animals. To test whether different edible oils are either beneficial or harmful to blood pressure and cardiac and aortic structures, six groups of 3-month-old male SHR rats were given fish, canola, palm, olive, and soybean oils of 1.5 g/kg per day or a placebo (water) by gavage for 13 weeks. It was found that fish oil could decrease blood pressure (*144*). When the effect of fish oil on blood pressure in SHR rats was compared with that in SHRSP rats, the results indicated that the blood pressure lowering effect of fish oil when administered during the period of development of hypertension was much greater in the SHR than in the SHRSP (*145*). One study investigated the effects of diets containing fish oil or pectin on blood pressure and lipid metabolism in the deoxycorticosterone acetate-salt hypertensive rats and found that the systolic blood pressure of rats fed fish oil was significantly lower than that of rats fed the control diet and that dietary fish oil attenuated the development of deoxycorticosterone acetate-salt hypertension (*146*). In humans, results from most clinical trials suggest that supplementation of diet with fish oils may reduce blood pressure. However, these clinical trials of fish oil or omega-3 PUFA supplementation were on a relatively small scale, and it was not possible to use them as the basis of firm conclusions on their blood pressure-lowering activity. In this regard, a meta-analysis of 17 controlled clinical trials of fish oil or omega-3 PUFA supplementation was conducted and concluded that a diet supplemented with a relatively high dose of omega-3 PUFA, generally >3 g/day, could lead to clinically relevant reduction in blood pressure in individuals with untreated hypertension (*141*). In the low dose of <3 g/day, fish oil or omega-3 PUFA was not effective (*148*). The ability of fish oil to modulate blood pressure is attributable to its two constituent fatty acids, namely, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (*149*, *150*).

Although the mechanisms responsible for the blood pressure-lowering activity of fish oil and omega-3 PUFA are not yet fully understood, some evidence suggests that they probably reduce blood cholesterol level by their effect on eNOS. One study tested the ability of fish oil to prevent vascular dysfunction in fructose-fed rats, a model of insulin resistance and hypertension. It was found that systolic blood pressure increased significantly in the fructose-fed rats but fell to control levels when fish oil was added

to the diet. This was accompanied by reduction of eNOS in the fructose-fed rats but up-regulation in the fish oil-fed group (*151*). The second mechanism associated with reduction in blood pressure by fish oil is probably linked to its effect on altered biosynthesis of eicosanoids. To test this hypothesis, blood pressure and eicosanoid production during supplementation of dietary fat for 4 weeks in 32 men with mild essential hypertension were measured. It was found that the formation of vasodilatory prostacyclins (PGI_2 and PGI_3) increased initially and then decreased as blood pressure fell, whereas the level of vasoconstrictor thromboxane A2 (TXA_2) metabolites fell in the groups receiving fish oil (*152*) (**Figure 2**). The third principal mechanism is that n-3 fatty acids can suppress the synthesis and release of TNF-α and interleukin-1 (IL-1), modulate the hypothalamic−pituitary−adrenal anti-inflammatory responses, and increase the release of acetylcholine (*153*). It is known that TNF-α increases insulin resistance and blood pressure, whereas acetylcholine relaxes the vessel and lowers blood pressure. The fourth possible mechanism by which fish oil and omega-3 PUFA reduce blood pressure is mediated by reducing blood triacylglycerols and viscosity (*154*). The fifth possible mechanism is that oral EPA supplementation may alter the activities of the membrane sodium transport systems. One study showed that EPA supplementation increased membrane EPA content, decreased intracellular sodium concentration, and reduced blood pressure in patients with essential hypertension (*155*). Finally, fish oil and omega-3 PUFA are unique among the anti-hypertensive functional foods because they are able to suppress the formation of plasma ADMA, which is an endogenous NOS inhibitor and a strong predictor for coronary heart diseases. To determine whether ADMA reduction contributed to EPA and DHA beneficial effects on the cardiovascular system, plasma ADMA levels in aged SHR rats supplemented for 8 weeks with EPA and DHA were measured, and it was found that EPA and DHA reduced plasma ADMA and arachidonate levels without affecting DDAH, which is an enzyme metabolizing ADMA (*156*). In this regard, it is worth studying whether supplementation of omega-3 PUFA is associated with down-regulation of PRMT I, an enzyme responsible for endogenous synthesis of ADMA.

FUTURE PERSPECTIVE

Blood pressure-lowering nutraceuticals and functional foods play an important role in the treatment of hypertension and reduction of the risk of cardiovascular diseases. This review suggests that the efficacy and action mechanisms for favorable reduction in blood pressure vary with individual nutraceuticals and functional foods. In general, these nutraceutials and functional foods reduce blood pressure, and this effect is most likely mediated by inhibiting ACE activity, modulating NO production, scavenging free radicals, and improving endothelial function. However, development of these nutraceuticals faces some challenges. Some of the most important issues are related to the safety, effectiveness, regulation, and health claims of these nutraceuticals. In addition, application of these nutraceuticals to foods is technically difficult. For example, ACE inhibitory peptides are bitter and fish oil causes rancidity, whereas phenolics can become insoluble and cause astringency. Thus, the end products naturally containing these nutraceutials or supplemented with them should have a more balanced finish of color, flavor, and taste in addition to the health benefits.

ABBREVIATIONS USED

AC, adenylate cyclase; ACE, angiotensin I-converting enzyme; ADMA, asymmetric dimethylarginine; BH4, tetrahydrobiopterin; cAMP, cyclic adenosine monophosphate; CGA, chlorogenic acid; CHD, coronary heart disease; cGMP, cyclic guanosine monophosphate; COX, cyclooxygenase; DALYS, disability-adjusted life years; DASH, dietary approaches to stop hypertension; DBP, diastolic blood pressure; DDAH, dimethylarginine dimethylaminohydrolase; DHA, docosahexaenoic acid; EC, epicatechin; ECG, (−)-epicatechin gallate; EGC, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-gallate; eNOS, endothelial nitric oxide synthase; EPA, eicosapentaenoic acid; GABA, γ-aminobutyric acid; GLE, gingko leaf extract; GTC, green tea catechins; GMA, γ-glutamylmethylamide; iNOS, inducible nitric oxide synthase; IPP, isoleucine−proline−proline; GC, guanylate cyclase; L-NAME, *N*(G)-nitro-L-arginine methyl ester; L-NMMA, N^G-monomethyl-L-arginine; NO, nitric oxide; nNOS, neuronal nitric oxide synthase; PKA, cAMP-dependent protein kinase; PKG, cGMP-dependent protein kinase; PRMT I, protein arginine methyltransferase I; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SBP, systolic blood pressure; SHR, spontaneously hypertensive rats; SHRSP, stroke prone spontaneously hypertensive rats; SVMC, smooth vascular muscle cells; TF, theaflavin; TF1, theaflavin; TF2A, theaflavin-3-gallate; TF2B, theaflavin-3′-gallate; TF3, theaflavin-3,3′-digallate; TNF-α, tumor necrosis factor-α; VGCC, voltage-gated calcium channels; VPP, valine−proline−proline.

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