**Name of journal: World Journal of Hypertension**

**ESPS Manuscript NO: 15932**

**Columns: Review**

**Antihypertensive effects of foods**

Hieda K *et al*. Functional foods with antihypertensive effects

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**Conflicts-of-interest**: There is no conflict of interest in this study.

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**Received:** December 17, 2014

**Peer-review started:** December 18, 2014

**First decision:** January 20, 2015

**Revised:** February 4, 2015

**Accepted:** April 1, 2015

**Article in press:**

**Published online:**

**Abstract**

Hypertension is one of the major risk factors for arteriosclerosis, which leads to cardiovascular disease and stroke. Several clinical trials revealed that control of the blood pressure is useful to reduce the morbidity and mortality associated with these diseases. However, the protective efficacy against these complications still remains at less than 50% even if the high blood pressure is treated by current medical drugs. Healthy diets are expected to not only prevent but also treat lifestyle-related diseases. Improvement of the dietary life, including low-salt diets, appropriate alcohol consumption, and calorie restriction, is important for the prevention of hypertension. In addition, green tea, which has been drunk on a daily basis in Japan and China since ancient times, possesses an antihypertensive effect, and it was revealed that its components with this effect are catechins. Many studies have been performed on the antihypertensive effects of foods. Therefore, functional foods and their ingredients, reported to possess antihypertensive effects in animal experiments and human clinical trials, are summarized in this review. Blood pressure might be controlled by improvement of the daily eating habits based on evidence regarding these functional foods, and a healthy longevity can be expected.

**Key words:** Foods; Hypertension; Antihypertensive effect; Cardiovascular disease; Renin

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**Core tip:** Management of the blood pressure leads to decreases in morbidity and mortality associated with arteriosclerosis-related diseases. It is well known that the improvement of eating habits, including a low-salt diet, appropriate alcohol drinking, and calorie restriction, has marked effects for the prevention of hypertension. In this review, we have summarized functional foods and their components whose antihypertensive effects have already been reported in animal experiments and human clinical trials. The evidence indicates that hypertension could be effectively controlled by daily functional food intake and healthy longevity could be achieved.

Hieda K, Sunagawa Y, Katanasaka Y, Hasegawa K, Morimoto T. Antihypertensive effects of foods. *World J Hypertens* 2015; In press

**Introduction**

Hypertension is one of the major risk factors of cardiovascular disease (CVD), stroke, and renal failure. Therefore, management of the blood pressure decreases the risk of morbidity and mortality. In 2008, approximately 40% of adults aged 25 or older had been diagnosed with hypertension globally; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008[1]. Of the 57 million global deaths in 2008, 36 million (63%) were primarily due to noncommunicable diseases and 17.3 million (30%) were due to CVDs. Death from cardiovascular disease is primarily due to stroke and heart disease, and it has been reported this number will increase to 23.3 million in 2030[2,3].Therefore, it has become a serious global problem. This assessment of the situation shows that CVD has a high rank regarding disease-related mortality in the world. Hypertension is one of the major risk factors for CVD. The heart is one of the target organs of hypertension. Increasing pressure overload leads to coronary artery endothelial dysfunction, cardiac hypertrophy, and myocardial remodeling. They increase the risk of coronary sclerosis and myocardial ischemia. Several large-scale trials targeting cardiovascular high-risk patients revealed that when their systolic blood pressure (SBP) dropped to 160 mmHg and diastolic blood pressure (DBP) to 90 mmHg, the morbidity and mortality due to CVD decreased[4]. Hypertension is defined as 140/90 mmHg or above. The Hypertension Optimal Treatment study revealed that cardiovascular benefit is maximized when the blood pressure drops to 139/83 mmHg. Survey data of clinics targeting the general population have suggested that the lower the blood pressure, the lower cardiovascular event onset rate. Also, it has been estimated that a 5 mmHg reduction in the population average reduces mortality from stroke by 14%, coronary artery disease by 9%, and total mortality by 7%[5]. In this way, hypertension is one of the highest risk factors for CVD and stroke. Control of the blood pressure is indispensable to improve the prognosis. In hypertension guidelines, diet and exercise therapy are important along with drug therapy. In the future, hypertension will be further improvement by consuming functional foods and lifestyle reconsideration.　We expect them to make a contribution to the development of preventive medicine.

Japan has the longest lifespan in the world. One of the reasons is that the balanced diet in Japan is markedly reduces stroke and tuberculosis. Furthermore, Mechnikov, who was awarded the Nobel Prize, reported that large numbers of healthy and long-lived people in the vicinity of Bulgaria may be due to the habit that they have of consuming a large quantity of yogurt. It has also been reported that few Inuk living mainly on a diet of fish contract heart disease or show hardening of the arteries. For these reasons, the diet and healthy longevity are considered to be closely related. Research on the relationship between food and health has been conducted throughout the world. As a result, it has been indicated that the ingredients in some foods have effects on biological regulation, such as on the immune, endocrine, and nervous systems, and also on digestion, absorption, and circulatory systems. That is, in certain foods, there are substances which have significant effects on the regulatory function of the body. It has been clarified that these ingredients have the ability to prevent various diseases developing because of an abnormal biological regulatory system. Foods with effects like this are called functional foods, and they have attracted global attention[6].Diseases such as hypertension, hypercholesterolemia, and hypertriglyceridemia are lifestyle-related diseases. They are caused by inadequate lifestyle, such as an unbalanced diet, lack of exercise, drinking, and insufficient sleep. In developed countries with increasing lifestyle-related diseases and aging of the population, people have an increased awareness of self-medication, the act of taking care of yourself. Attention has been focused on functional foods. Functional foods having particularly beneficial effects on hypertension in animal experiments (Table 1) and human clinical trials (Table 2) are summarized in this paper. This manuscript is focusing on clinical findings than experimental ones. Moreover, we emphasize interventional studies yielded results with statistical significance. Functional foods reduce the blood pressure by different mechanisms, such as rennin-angiotensin-aldosterone system (RAAS) inhibition, antioxidant effect, diuretic effect, NOS production- promoting effect. And there are also some foods with multiple mechanisms (Figure 1).

**Catechins**

Green tea is a beverage that has been found to be useful for maintaining and recovering health. People have continued to drink it on a daily basis from ancient times in East Asia such as Japan and China. Using stroke-prone spontaneously hypertensive rats (SHRSP), treatment of black tea polyphenols or green tea polyphenols showed significant reductions of SBP and DBP. Moreover, several experiments indicated that the regular consumption of black and green tea may also provide some protection against hypertension in humans[7].The major active constituents of tea are polyphenols such as catechins and tannins. In recent years, many studies have reported that catechins have a variety of actions, such as antihypertensive effects[8-10].The action mechanism of catechins for their antihypertensive effect is considered to be through an antioxidant action. That is, reduction of oxidative stress in the vascular endothelium increases the bioavailability of NO, which enhances the vasodilatory action. Also, it is related to the diuretic action of caffeine contained in green tea. Studies on the hypotensive action of green tea have been conducted throughout the world. Clinical trials in humans reported that hypertensive patients with obese who consumed green tea extract for 3 mo showed significant decreases in their SBP and DBP compared with a placebo group[11].In addition to this, it was reported that subjects who were classified as being healthy but had a slightly high blood pressure or mild hypertension consumed Benifuuki tea from a tea bag containing 2 g of Benifuuki leaves (containing 25 mg of epigallocatechin-3-O-(3-O-methyl) gallate, EGCG) for 8 wk, leading to significant decreases in SBP and DBP[12].Overweight or obese male subjects with a BMI of 28-38 who took 400 mg of EGCG twice daily for 8 wk showed a DBP reduction below 2.8 mmHg[10].Mildly hypertensive patients with type 2 diabetes mellitus showed a decreased SBP after drinking green tea three times a day 2 h after each meal for 4 wk[13].No adverse effects were observed either study. From the above, it has been suggested that polyphenols such as catechins contained in green tea have not only a hypotensive action but also improve lifestyle-related diseases. Although the causal relationship is unknown, the elderly in Shizuoka Prefecture, considered the home of green tea in Japan, consume large amounts of green tea and show a healthy longevity that is a longer compared with other prefectures. Green tea may therefore play a role for health and longevity.

**GABA**

GABA is γ-aminobutyric acid, a kind of amino acid, and one of a large number of inhibitory neurotransmittersin the central nervous system such as the brain, cerebellum, and spinal cord. In recent years, GABA has been found to improve blood flow and metabolism in the brain. In addition to being produced by the brain during sleep, GABA can be obtained from food. GABA is included in trace amounts in rice, vegetables, tea, and fermented food. Especially, sprouted brown rice contains about 10 times more GABA than rice. GABA is produced from glutamic acid decarboxylase (GAD) synthesized by lactic acid bacteria. Therefore, it is also abundant in pickles which is a lactic acid fermentation product made from plants[14,15].Antihypertensive mechanisms of GABA have been considered as follow: an inhibitory effect on the sympathetic nervous system and peripheral sympathetic ganglia, a diuretic effect by the inhibition of anti-diuretic hormone secretion, and angiotensin converting enzyme (ACE) activity inhibition[16,17].Some subjects with a high-normal blood pressure were given 100 mL of fermented milk containing 12.3 mg of GABA. They showed significant decreases of SBP after 8 wk and DBP after 12 wk.A reincrease in the blood pressure was observed after 4 wk following the discontinuation of ingestion[17].The same hypotensive effect was observed in a trial of hypertensive patients, and no adverse reactions were observed[18,19]. From these results, the benefits and safety for hypertensive patients of GABA-containing fermentation foods are expected.

**Stevioside**

Stevioside, contained in Stevia which is a perennial plant of the Asteraceae, is a natural sweetener used widely in Japan and South America. It has been traditionally used as a herbal medicine in South America. A variety of physiological activities have been reported, such as improving insulin resistance in type 2 diabetes, an antihypertensive action, a diuretic action, and an antioxidant action[20,21].Antihypertensive action has been indicated by several experiments using different hypertensive rat models[22].The hypotensive effect of stevioside may be mediated by inhibiting Ca2+ influx into blood vessels and vasodilation[23,24].In a human clinical trial, patients with mild to moderate essential hypertension given 250 mg of stevioside showed significantly decreased both SBP and DBP after 3 months, and the effect persisted for one year[25].Patients with mild essential hypertension taking 500 mg of stevioside 3 times daily for 2 years showed significantly decreased SBP and DBP. These hypotensive effects were noted to begin about 1 wk after the start of treatment and persisted throughout the study and no significant adverse effects were noted[26].In a involving the administration of crude stevioside at 15.0 mg/kg per day for 6 wk to patients with essential hypertension, SBP and DBP decreased during the treatment, but a similar effect was observed in a placebo group. Therefore, crude stevioside did not show a significant antihypertensive effect compared to the placebo group[27].These results indicate that stevioside contained in food has an insufficient antihypertensive effect, and so there is a need to take it as a supplement.

**Black vinegar**

Black vinegar is made from rice and produced by fermentation and aging. Since it contains an abundance of amino acids, various physiological activities, including antioxidant activity, have been reported. It has been reported that the activities are due to amino acids, acetic acid, and low-molecular-weight peptides[28].When subjects were given a drink containing 15% black vinegar or 15% apple vinegar (each contains acetic acid at 750 mg/100 mL) for 8 wk, SBP was significantly reduced both at 2 and 10 wk after the intake, and no side effects were observed[29].In another trial involving subjects given a drink containing tomato vinegar (750 mg/100 g per day) for 12 wk, SBP was significantly reduced at 10 and 12 wk after intake compared to a placebo group, and DBP was also reduced at 10 and 12 wk compared to the value before ingestion[30].Moreover, subject given a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk, SBP was decreased from 6 wk after intake of apple vinegar drink, SBP and DBP were decreased from 4 wk after intake of acetic acid drink[31].By experiment using spontaneously hypertensive rats (SHR) rats, the mechanism of this hypotensive action has been suggested to be the inhibitory effect of the renin-angiotensin system, such as the inhibitions of renin activity and ACE activity by peptides present in black vinegar[28,32].Also, it has been reported that acetate has effects on lipid metabolism[33],and that drinking vinegar routinely improves lifestyle-related diseases as well as decreases blood pressures.

**Sesamin**

Sesamin is a kind of lignan compound contained in a small amount of sesame. In recent years, a variety of bioactivities has been reported, such as antioxidant, cholesterol-lowering, lipid metabolism-enhancing, and liver-protective effects. Sesamin is also known for a hypotensive effect. However, there are many unclear points regarding the mechanism of action.Several animal experiments suggest that the hypotensive action of sesamin is involved in the vasodilating effect caused by NOS production enhancement and oxidative stress reduction in blood vessels due to the antioxidant effect[34-36].In human clinical trials, mildly hypertensive subjects taking 60 mg/d of sesamin for 4 wk, showed significantly decreased SBP and DBP. No significant side effects were observed[37].Since sesamin is often used in small amounts in cooking and its calorie content is high, the ingestion of a large amount at one time is difficult. Therefore, it is desirable for the active ingredient of sesamin to be taken as a supplement.

**EPA, DHA**

The results of epidemiological studies in the 1970s showed that people who lived on mainly a diet of fish in Greenland and Canada suffered less from coronary artery disease than Danes eating mainly meat. Human trials have indicated that diet supplementation with fish oil, generally more than 3 g/d, can lead to clinically relevant BP reductions in individuals with untreated hypertension[38,39].Components exhibiting this antihypertensive effect of fish oil have been reported to be EPA and DHA, *n* = 3 fatty acids abundant in fish, and researches on them is progressing. Many animal experiments indicate that daily administration of EPA significantly decreased the development of hypertension in SHR dose dependently, although it did not affect to BP in normotensive rats[40].Patients with uncomplicated mild to moderate essential hypertension treated with EPA (2.7 g/d) for 4 wk showed decreases in SBP and the intraerythrocyte sodium content (R-Na), accompanied by an increase in the erythrocyte membrane EPA content. The decrease in R-Na was correlated positively with the decrease in SBP, and correlated negatively with the change in Na+-K+ ATPase activity. EPA may lower the blood pressure by altering the activities of the membrane sodium transport systems[41].Antihypertensive mechanisms of fish oil, such as EPA and DHA, are considered to explain the decrease in the intercellular sodium concentration[41],increase in eNOS expression, decrease in oxidative stress[42],and altered biosynthesis of eicosanoids[43].In human trials, patients with hyperlipidemia were assigned to receive 1800 mg/d of EPA or 10 mg/d of pravastatin for 3 mo. In the EPA group, the radial augmentation index (AI, a parameter for vascular aging), SBP, DBP, and C-SBP (the systolic pressure at the ascending aortic root, representing the vascular load of the left ventricle afterload), were decreased, respectively. In the pravastatin group, there were no significant changes in brachial BP, AI, or C-SBP. These results suggest that EPA but not pravastatin reduces cardiac afterload by reducing vascular reflected waves and lowering C-SBP[44].On the other hand, subjects with hypertension and/or hypercholesterolemia supplemented with 2 g of DHA for 5 wk showed significantly decreased SBP, DBP, and heart rate[45].

**Garlic**

Garlic preparations contain a wide variety of organosulfur compounds, of which allicin is the most notable, and it is responsible for the characteristic garlic odor. [46] Antihypertensive effects of galic were reported in many studies using hypertensive rat models. The antihypertensive mechanism of garlic is assumed to involve ACE inhibitory effect[46],antioxidant effect[47],activation of NO formation[48],and reduction in the synthesis of vasoconstrictor prostanoids[49].Although SHR fed diets containing either aged garlic extract (AGE) or raw garlic (RG) powder for 10 wk showed a reduction of SBP from 4 wk, Harmful effects were observed in the RG group, including a decrease in erythrocytes, an increase in reticulocytes, and the generation of a papilloma in the forestomach. These findings suggest that the long-term intake of raw garlic can be harmful to health[50].Patients with uncontrolled systolic hypertension were allocated aged garlic extract (240, 480, and 960 mg containing 0.6, 1.2, and 2.4 mg of S-allylcysteine, respectively). SBP was significantly reduced in the 480 mg/d group over 12 wk, and reached borderline significant reduction in the 960 mg/d group at 8 wk, although blood pressure in the 240 mg/d group was not significantly different compared to the placebo group[51].The efficacy of some clinical trials have been reported in addition to these[52-54].Some trials suggested that garlic is associated with blood pressure reductions in patients with elevated SBP, but not in those without SBP elevation[55,56].These reports suggest that the risk of excessive decreases in blood pressure is low when a healthy person ingests garlic.

**Quercetin**

Onion is a vegetable which is used in a variety of dishes in the world and has excellent storage stability. Onion is rich in phenolic compounds such as quercetin, which have an antioxidant effect[57].It is expected to provide considerable health benefits. There are several reports that quercetin shows an antihypertensive effect through the antioxidant activity[58], inhibition of ACE activity[59] and Ca2+ influx[60].It has been considered that these results show synergistic antihypertensive effect. Animal experiment using abdominal aortic constriction rat indicated that quercetin is also useful for preventing cardiovascular disease[61].In human studies, apparently healthy subjects showed decreased arterial blood pressure 5 h after the administration of an onion-olive-oil maceration capsule formulation. In addition to this, a significant reduction in the plasma viscosity and hematocrit were observed[62].Subjects with prehypertension and stage 1 hypertension ingested 730 mg quercetin per day for 28 d, and the blood pressure was not altered in prehypertensive patients after quercetin supplementation. In contrast, reductions in SBP, DBP, and mean arterial pressures were observed in the stage 1 hypertensive patients after quercetin treatment. However, indices of oxidant stress measured in the plasma and urine were not affected by quercetin[63],and so it is considered that components other than quercetin are also involved in the hypotensive effect of onion.

**Pea protein hydrolysate**

Pea protein has been a focus of attention as an important and cheap vegetable protein with high nutritional and functional values and marked potency as an ingredient for the production of bioactive peptides[64].Pea protein hydrolysate (PPH) showed high-level inhibition of ACE and renin activities[65].PPH shows antihypertensive effects by influencing the renin-angiotensin system in rat model[64].In clinical trials, subjects with SBP ranging from 125 to 170 mmHg took 3 g/d of PPH showed significant reductions in SBP of 5 and 6 mmHg in 2 and 3 wk, respectively. None of the participants reported any adverse side effects[64].Beans such as peas, rich in vegetable protein with low lipids and low calories, are very important in health promotion. However, a complex process of protein purification, as described above, is necessary to obtain PPH with a hypotensive action. So, an abundant consumption of peas is not recommended. We expect that it will become possible to control the blood pressure based on these results and further research on bean proteins and the development of PPH supplements.

**Management of hypertension by functional foods**

Besides the foods introduced in this paper, grains, vegetables, fruits, milk, cheese, meat, chicken, wine, mushrooms, lactic acid bacteria, nicotianamine and egg are various food sources with potential antihypertensive effects. Their main bioactive constituents include ACE inhibitory peptides, vitamins C and E, flavonoids, flavanols, catechins, anthocyanins, phenolic acids, polyphenols, tannins, resveratrol, polysaccharides, fiber, saponin, sterols, as well as K, Ca, and P. These functional foods may provide new therapeutic applications for hypertension prevention and treatment, and contribute to a cardiovascularly healthy population[66].In recent years, the DASH (Dietary Approaches to Stop Hypertension) diet has caught attention as a dietary therapy for blood pressure control. The DASH diet is a composite diet that cuts down fat, based on fruits and vegetables, beans, fish, low-fat dairy products, and cereals. It has been frequently reported as useful for lowering the blood pressure[5,67-72]. The mechanism of the the hypotensive action of the DASH diet has been considered mainly through the Na diuretic effect. In addition to this, as it is rich in K, its hypotensive action is particularly effective for blood pressure elevation due to salt overdose. Since Na is added and K is lost during food processing, actively taking K should be recommended in developed countries where processed foods are commonly consumed. It has also been reported that the intake of Mg reduces the onset risk of metabolic syndrome[73].A DASH diet rich in Mg may reduce the risk of obesity.

We have reviewed the functions of foods, but such foods should be taken with care to complement human physiology. For example, there is a risk of causing high K hyperlipidemia in some patients with marked renal failure or who are taking anti-aldosterone drugs, ACE inhibitors, or angiotensin II receptor blocker (ARB). For this reason, such people are not recommended to abundantly consume vegetables and fruits rich in K. Patients with obesity and diabetes who have restricted energy intake should not abundantly consume nuts and fruits containing much sugar. It is necessary for them to avoid excess calorie intake[74].On the other hand, the intake of food with a diuretic effect is suitable for patients with renal failure because it has the action of body fluid volume control and lowering the blood pressure. However, overconsuming certain functional foods with a hypotensive effect may lead to unbalanced nutrition and adverse interaction with antihypertensive agents. Therefore, recommendations of a balanced diet based on functional foods and dietary advice tailored to an individual’s physiology are recommended.

We summarize the functional foods with antihypertensive effects from the evidences in clinical studies. In contradiction to these studies, there are several reports indicating opposite results and many interventional studies with no statistical significance. For example, Green tea consumption was inversely associated with mortality due to all causes and cardiovascular disease[75], and there are a few reports described no effect of EPA on the blood pressure[76,77].So, the potential of clinical applications of functional foods remains undetermined. Randomized controlled trials are needed to establish the clinical applications of functional foods.

**Conclusion**

In addition to drug therapy, the management of high blood pressure is essential for the improvement of lifestyle habits. Simply taking medicine for health is not enough. It is necessary to adopt a balanced diet and regular life with drug therapy. The first dietary step is to take a low-salt diet (optimal value: less than 6 g/d) in order to reduce the load on the kidneys and blood vessels. We hope that you will enjoy a richer dietary life by positively taking functional foods when presented. Also, we expect people to utilize them effectively as a means to practice “self-medication”.

We are confident that in the future, further studies will expand the field of functional foods, and identify more useful functions of other foods,　not only functional fruits and vegetables, for preventing hypertension-related and other diseases.

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**P-Reviewer:** Efstathiou S, Liu C, Patanè S **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 antihypertensive effects of functional foods in animal experiments**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Functional foods** | **Active ingredients** | **Animal experiments** | **Results** | **Ref.** |
| Tea | CatechinFlavonoid | Taking the green tea polyphenol water containing 3.5 g/L catechins, 0.5 g/L flavonols and 1 g/L polymetric flavonoids.to SHRSP. | Decreases in SBP and DBP. | [7] |
| GABA | g-aminobutyric acid（GABA） | Single oral administration of GABA(0.5 mg/kg) to SHR and normotensive Wistar-Kyoto rats | Decrease in SBP in SHR rats, but not in normotensive rats. | [16] |
| Stevia | Stevioside | Intraperitoneally administration of stevioside (50, 100 and 200 mg/kg) to normotensive Wistar-Kyoto rats (NTR), SHR, deoxycorticosterone acetate-salt (DOCA-NaCl) sensitive hypertensive rats (DHR) and renal hypertensive rats (RHR). | Hypotensive effect was noted in different strains of rats at the dose of 50 mg/kg. The dose of 100 and 200 mg/kg caused slow and persistent lowering of blood pressure in SHR and NTR.Blood pressure decreased in a dose-dependent manner in SHR | [22] |
| Black vinegar | Acetic acidBlack vinegar-derived peptides | Single (3 g/kg body weight) and continuous administration (8 wk; 10% (w/w) of diet) of black malt vinegar to SHR | Decrease in SBP in the administration of either. | [32] |
| Goma | Sesamin | Taking a sesamin-containing diets (0.1, 1 w/w% ) to DOCA-salt hypertensive rats for 5 wk. | Decrease in SBP. | [34] |
| Fish oil | EPA・DHA | Daily oral administration of 30 to 300 mg/kg EPA to SHR and normotensive rats for eight weeks | Treatment of 30, 100, and 300 mg/kg EPA decreased mean SBP in SHR | [40] |
| Garlic | S- allyl cysteine(SAC),Allicin | Daily oral administration of 50 mg of aqueous extract of garlic totwo-kidney-one-clip hypertensive rat for 4 wk | SBP and ACE activity in serum and different tissues such as aorta, heart, kidney and lung decreased. | [46] |
| 5/6 nephrectomized rats were treated with SAC (200 mg/kg ip) or aged garlic extract (1.2 ml/kg ip) every other day for 30 d | SBP and renal failure decreased, SOD activity increased. | [47] |
| Onion | Quercetin | Taking a 5% dried onion diet to L-NAME induced-hypertensive rats and SHRSP for 4 wk | SBP decreased from 1 wk in both rats, and TBARS decreased at 4 wk.Urinary nitrite, NOS activity was increased in SHRSP rats. | [58] |
| Pea | Pea protein hydrolysate（PPH） | Oral administration of the PPH to spontaneously hypertensive rats (SHR) at doses of 100 and 200 mg/kg | Decrease in SBP. | [64] |

A list of animal experiments. Hypotensive actions have been confirmed in multiple types of rat, mainly SHR.

**Table 2 antihypertensive effects of functional foods in human clinical trials**

|  |  |  |
| --- | --- | --- |
| **Functional foods** | **Human clinical trials** | Ref. |
| **Targets** | **Study designs** |
| Tea | Obese (BMI ≥ 30), hypertensive subjects | Taking 379 mg of Green Tea extract (including 208 mg of EGCG) for 3 mo. (randomized double-blind, placebo-controlled trial) | [11] |
| Overweight or obese subjects (BMI > 28) | Taking 400 mg of EGCG twice daily for 8 wk. (randomized double-blind, placebo-controlled trial) | [10] |
| GABA | Subjects with high normal blood pressure | Drinking 100 ml of fermented milk containing 12.3 mg of GABA for 12 wk. (randomized double-blind, placebo-controlled trial) | [17] |
| Mildly hypertensive subjects | Drinking 100 ml of fermented milk product containing 10-12 mg of GABA for 12 wk. (randomized single-blind, placebo-controlled trial） | [18] |
| Subjects with high-normal blood pressure | Taking less-sodium soy sauce containing 120 mg of GABA once daily for 12 wk. (double-blind, placebo-controlled trial） | [19] |
| Stevia | Subjects with mild to moderate essential hypertension | Taking 250 mg of stevioside 3 times daily for 1 year. (randomized double-blind, placebo-controlled trial) | [25] |
| Subjects with mild essential hypertension | Taking 500 mg of stevioside 3 times daily for 2 years. (randomized double-blind, placebo-controlled trial) | [26] |
| Black vinegar | Subjects with mild to moderate hypertension | Taking a drink containing 15% black vinegar or 15% apple vinegar for 10 wk. (double-blind, placebo-controlled trial) | [29] |
| Subjects with high normal, mild hypertension | taking a drink containing tomato vinega (750 mg/100 g/d) for 12 wk. (Double-blind placebo-controlled trial) | [30] |
| Subjects with mild to moderate hypertension | Taking a drink containing apple vinegar (acetic acid 0.75 g/100 mL) or acetic acid (acetic acid 1.5 g/100 mL) for 8 wk.(Three groups parallel, placebo-controlled trial) | [31] |
| Goma | Subjects with mild hypertension | Taking 60 mg of sesamin for 4 wk. (double-blind, cross-over, placebo-controlled trial) | [37] |
| Fish oil | Subjects with essential hypertension | Taking 2.7 g of EPA for 8 wk. (randomized double-blind, cross-over, placebo-controlled trial) | [41] |
| Sujects with hypertension and/or hypercholesterolemia | Taking a 2 g of DHA for 5 wk. (randomized double-blind, placebo-controlled trial) | [45] |
| Garlic | Subjects with uncontrolled systolic hypertension (SBP ≥ 140 mmHg) | Taking aged garlic extract (240/480/960 mg containing 0.6/1.2/2.4 mg of S-allylcysteine) for 12 wk. (randomized double-blind, placebo-controlled trial) | [51] |
| Subjects with uncontrolled hypertension | Taking 960 mg of aged garlic extract containing 2.4 mg S-allylcysteine daily for 12 wk. (randomized double-blind, placebo-controlled trial) | [55] |
| Onion | Subjects with prehypertension and stage 1 hypertension | Taking 730 mg quercetin for 4 wk (randomized double-blind, cross-over, placebo-controlled trial) | [63] |
| Pea | subjects with SBP ranging from 125 to 170 mmHg | Taking 1.5 and 3 g of PPH for 3 wk. (randomized double-blind, cross-over, placebo-controlled trial) | [64] |

A list of human clinical trials. We reviewed mainly clinical trials involving hypertensive patients.



**Figure 1 Antihypertensive mechanism of functional foods.** Anti-hypertensive mechanism of functional foods in this paper. There are also some foods with multiple mechanisms. These suggest that they synergistically promote the hypotensive action.