Botanicals and Nutritional Compounds for Endothelial and Cardiovascular Health

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Discussion

ARTERIAL HEALTH INFLUENCES CARDIOVASCULAR HEALTH

Cardiovascular disease (CVD) is the leading cause of debility and death worldwide. Hypertension is a worldwide health challenge and a major risk factor for CVD and cerebrovascular disease. According to 2012 figures, about 30% of the U.S. adult population suffers from high blood pressure and incidence increases with age. Risk factors include genetic, environmental, dietary, and lifestyle factors including diabetes, smoking, obesity, and dyslipidemia.[1-6]

With over 2 million new diagnoses of hypertension each year, billions of dollars are spent on this condition. It is a leading cause of disability and death from stroke, heart disease, heart failure, and kidney failure.[7,8] Hypertension is associated with many conditions including atherosclerosis, peripheral artery disease, coronary artery disease, kidney damage, and dementia.[1] Despite treatment advances and research, clinical reports find that deaths from CVD increase each year.[9]

Hypertension is characterized by dysregulation of factors that maintain arterial health. This influences large and small arteries along with microcirculation.[1] Cardiovascular health is directly related to multiple factors that influence the resilience and elasticity of the blood vessel walls. This includes the ability of the arterial walls to expand and contract in response to dynamic pressure changes created by the heart's forceful pumping. The intrinsic elasticity of the vessel walls is a key factor in measuring pulse wave velocity (PWV) -- the pressure wave through the arterial tree which increases as the arteries stiffen. PWV is considered an independent predictor of CVD and mortality.[10] Systolic pressure, in particular, is influenced by arterial stiffness. Studies find that systolic and pulse pressure play a more important role than diastolic pressure alone. Pulse pressure (PP) refers to the difference between systolic and diastolic pressure.[11]

Arterial wall health is influenced by its composition of structural proteins, lipid accumulation, inflammatory processes, structural changes of collagen fibers (particularly collagen cross-linking caused by AGEs – advanced glycation end-products), and calcium deposits. These factors combine to form complex plaque structures leading to arterial stiffness. Conditions such as hyperlipidemia, diabetes mellitus, elevated body mass index, obesity, smoking, and others are also found to accelerate arterial stiffening. As arteries stiffen, PP increases, which adversely affects the micro vessels, especially of the brain and kidneys. PP is found to correlate more closely to cardiovascular events than systolic or diastolic blood pressure alone and is found to be the main cause of age-related increase in hypertension.[10]

Epigenetic processes are found to play a key role in CVD, including atherosclerosis and hypertension, primarily through DNA methylation. Studies find that diets deficient in methyl donors contribute to dysregulation of metabolic and cardiovascular function. These methyl donors include betaine, choline, folate, and methionine.[12]

VASCULAR HOMEOSTASIS AND THE ENDOTHELIUM

Endothelial dysfunction is found to be linked with all risk factors associated with the acceleration of atherosclerotic vascular disease.[11] The endothelial cell layer that covers the internal surface of blood vessels is recognized as a living entity that plays a significant role in multiple aspects of homeostasis within the cardiovascular network. It has the ability to sense changes in hemodynamic signals and to release modulating compounds that maintain a balance between relaxing and contracting factors in order to maintain vascular homeostasis.[1,11]

When homeostasis is disrupted, the vasculature becomes prone to vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, pro-oxidation, thrombosis, impaired coagulation, vascular inflammation, and atherosclerosis.[11] Increased oxidative stress contributes to the inflammatory process, triggers plaque formation, contributes to endothelial dysfunction, and progresses to hypertension.[1]

The transcription factor NFKB (nuclear factor kappa B) and other factors also play key roles in the mediation

and maintenance of blood pressure. NFKB is found to induce endothelial cell dysfunction, oxidative stress, and inflammation as it promotes the release of pro-inflammatory cytokines along with other actions.[1]

BOTANICALS FOR CARDIOVASCULAR HEALTH

A vast cornucopia of plants and herbs have been used worldwide as food and medicine for millennia. Reports from the World Health Organization (WHO) estimate that about 80% of the global population still rely on or choose to use botanicals for their health needs.[14]

Botanicals are extensively researched for their potential to address hypertension and hypermethylation, to restore epigenetic processes, and to treat CVD and many other health conditions. Usage of herbal medicines for CVD is increasing worldwide.[12] Studies find that diet, exercise, stress management, micronutrients, and herbs effectively and safely help reduce high blood pressure.[6]

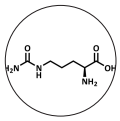
There is a large body of research on the connection between micronutrients and heart disease. Micronutrients include vitamins, minerals, amino acids, flavonoids, and coenzymes.[13] Multiple studies report that diets featuring an abundance of vegetables and fruits along with a balanced intake of legumes, whole grains, fish and other natural foods benefit heart health.[7,15]

This is largely attributed to the fact that vegetables, fruits, and many botanical medicines are high in flavonoids. Research consistently reports that the risk of coronary artery disease is significantly lessened with high dietary flavonoids.[3] Flavonoids are known to be powerful free-radical scavengers with the ability to prevent oxidation of LDL cholesterol. They also enhance endothelial derived NO (nitric oxide) activity, inhibit endothelial activation, and inhibit platelet aggregation.[3,16]

Flavonoids, including the OPCs (oligomeric proanthocyanadins), contribute to the strength and integrity of vascular walls.[3,17] They also support the natural cross-linking of collagen; the matrix of connective tissue. This function enhances tissue healing and supports connective tissue health including vascular integrity.[16]

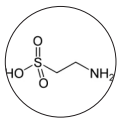
Studies report that herbal remedies are effective to help restore endothelial homeostasis. A wide range of plant and herbal extracts and their metabolites are found to modulate signaling cascades essential to the health of the cardiovascular system. Some herbs are found to be vasculo-protective, offering the potential to reverse the changes of hypertension and to restore homeostasis and the balance of pro-and antioxidants.[1]

Botanicals and Nutritional Compounds for Endothelial and Cardiovascular Health



L-Citrulline

The amino acid citrulline is well-absorbed while safely and directly raising plasma levels of arginine (for which it is a precursor).[19] Citrulline supports healthy plasma arginine levels, flow-mediated vasodilation, and other cardiovascular markers.[18] Both citrulline and arginine contribute directly to healthy levels of NO (nitric oxide), which promotes arterial relaxation, elasticity, and resilience.[20] L-citrulline is found to reduce peripheral blood pressure through enhancing aortic relaxation in rats.[19]



L-Taurine

Taurine is a sulfur-containing amino acid that is conditionally-essential because diet is the main source of taurine for humans.[21] Taurine is highest in animal foods while dairy contains only small amounts.[15,21] Small amounts of taurine are synthesized in the liver from methionine and cysteine.[15] Deficiency of B6 is shown to impair taurine synthesis.[21,22]

Taurine is found to act as a growth modulator and is essential for mammalian development. It is present in high concentrations in human mother's milk and then decreases significantly over the first few months of the infant's life.[21] Low levels are associated with cardiomyopathy and other syndromes, especially if there is deficiency during development. Taurine plays a key role in multiple physiological functions. It conjugates bile acids, helps modulate cellular calcium levels, and plays a role in cellular membrane stabilization and osmoregulation.[15,22]

Taurine occurs in many tissues including the brain, skeletal system, and most abundantly in cardiac muscle and the retina.[15,22] Considered to be cardio-protective,[21] taurine comprises over 50% of the heart's total free amino acid pool.[22] Studies conclude that taurine plays a significant role in reducing the risk of heart disease in humans.[15] Taurine is found to help normalize heart function including EKG abnormalities.[22] Studies find it significantly decreases dyspnea, palipitation, heart crackles, and edema in

congestive heart failure. It also contributes to increased exercise capacity.[21]

Studies report that taurine supplementation significantly decreases high blood pressure and exerts a beneficial influence on cardiac and arterial health.[7,21,23] Taurine may decrease high blood pressure through several pathways including modulation of angiotensin II signaling and promotion of pathways in the kidney that facilitate vasodilation. It is found to decrease epinephrine levels (which increases heart rate) and norepinephrine (which influences vasoconstriction).[7,15]

Taurine is found to be preventive against hypertension, stroke, CVD, and atherosclerotic arterial disease. Its preventive mechanisms are ascribed to sympathetic-modulating activity that reduces blood pressure and exerts an anti-inflammatory influence. Many findings are confirmed epidemiologically by WHO-coordinated studies on 61 populations in the world over 25 years.[24]

Taurine supports cell membrane stabilization through several mechanisms. While accumulation of calcium contributes to cell injury and death, taurine is found to be an intra-and extracellular calcium regulator. It helps regulate osmotic pressure in the cell, helps maintain intracellular ion homeostasis, and inhibits phosphorylation of membrane proteins.[21]

Taurine exerts antioxidant influence and prevents lipid peroxidation.[13,21-23] It is found to influence the LDL receptors and play a role in regulating LDL cholesterol.[15]

Hawthorn (*Crataegus spp.*)

The fruit, leaves, flowers, and bark of the hardy Hawthorn shrub have been used as food and medicine for millennia.[1,7] It is revered as a medicinal herb for cardiovascular health in many cultures.[1,25] The Europeans used Hawthorn to strengthen heart health and function and the American Eclectic physicians esteemed it above other herbal remedies for cardiac conditions.[26]

The cardio-protective activity of Hawthorn is attributed primarily to the flavonoid and OPC (oligomeric proanthocyanadin) content which is especially concentrated in its leaves and flowers.[1,14,17,27,29] Hawthorn contains an abundance of flavonoids including catechins, triterpene saponins, and OPCs. OPCs are known as powerful free radical scavengers and with such an abundance of flavonoids, including OPCs, Hawthorn exerts potent antioxidant activity.[1,14,27,28] Hawthorn has the ability to scavenge reactive oxygen species, up-regulate antioxidant enzymes, including SOD (super oxide dismutase), and to enhance GSH (reducing glutathione) concentration.[1]

Hawthorn is found to support blood vessel integrity and to enhance coronary blood flow and oxygen utilization. In studies, the flavonoids from Hawthorn show diversified action, exerting multiple influences on the heart that suggest a modulatory influence. In studies with human subjects, Hawthorn was found to significantly improve cardiac function.[14] Studies report that Hawthorn is able to improve the energy dynamics of the heart muscle, particularly in ischemic conditions.[14] Studies find that extract of Hawthorn influences the refractory phase of the heart (opposite to digoxin) thus reducing the risk of arrhythmias.[14]

Hawthorn is reported to exert a hypotensive effect, lowering high blood pressure.[7,30] It is also found to increase coronary blood flow[27] and to enhance oxygen flow and utilization by the heart.[31] The antihypertensive influence of Hawthorn is attributed to its abundance of flavonoids and OPCs. Quercetin, a major polyphenolic flavonoid in Hawthorn, exerts wide influence including antioxidant, anti-inflammatory and vasorelaxant. Hawthorn extract is shown to affect both VSMCs (vascular smooth muscle cells) and endothelial cells, as they increase NOS activity and NO release.[1]

Studies report Hawthorn exerts a beneficial influence on blood lipid profiles.[14] Hawthorn can help prevent elevated plasma lipids, including total cholesterol, triglycerides, LDL- and VLDL-fractions in animal studies.[32] Hawthorn works through multiple pathways to prevent elevated plasma lipids. It upregulates hepatic LDL-receptors and prevents accumulation of cholesterol in the liver through enhancing cholesterol degradation. It also promotes bile flow and suppresses cholesterol biosynthesis.[33]

Hawthorn is found to inhibit human neutrophils elastase (HNE) which increases under ischemic conditions and may be partly responsible for myocardial damage along with free radicals. It is thought that the cardio-protective ability of Hawthorn is due to its free radical scavenging ability along with the ability of its OPCs to inhibit HNE. Another flavonoid extracted from Hawthorn is also found to have potent anti-ischemic activity.[14]

Arjuna (*Terminalia arjuna*)

Arjuna bark, highly valued in Ayurvedic medicine for treatment of cardiovascular conditions, has a history of over 2500 years of usage as a cardio-protective and cardio-tonic botanical.[3,7]

Arjuna bark contains tannins, triterpenoid saponins, flavonoids, gallic acid, ellagic acid, OPCs, and phytosterols.

It also contains the minerals calcium, magnesium, zinc, and copper.[1,3] Arjuna contains high levels of flavonoids including arjunolone, flavones, baicalein, quercetin, and others.[3] Arjuna's high flavonoid and OPC components contribute to vascular integrity and strength and offer potent antioxidant activity.[14]

The pleiotropic influence and multiple benefits of Arjuna bark are reported in both in vivo and in vitro studies of this ancient botanical medicine. It is found to be anti-atherogenic, hypotensive, anti-inflammatory, and antioxidative. Studies report that Arjuna's actions benefit many cardiovascular disorders.[34]

Arjuna is noted as a cardio tonic with anti-ischemic and potent antioxidant activity. It is found to prevent LDL cholesterol oxidation and to help reduce lipid levels. Studies find Arjuna is cardio-protective and aids reperfusion in ischemic injury to the heart.[3,35] It is found to benefit those with cardiac disorders including congestive heart failure and coronary artery disease. Studies report that Arjuna benefits those with angina and significantly helps reduce angina episodes.[7]

Many components of Arjuna are noted to exert powerful influence on cardiovascular health. It is high in tannins which are known to enhance NO synthesis and relax vascular segments pre-contracted with norepinephrine. Hence the tannins may contribute to the hypotensive influence of Arjuna bark.[3] Recently two new cardenolide cardiac glycosides were isolated from the root and seeds of Arjuna. These are found to increase the force of cardiac contraction through raising intracellular sodium and calcium.[3] The saponin glycosides in Arjuna are thought to contribute to its benefit to cardiac muscle function.[14]

The triterpenoid saponin arjunolic acid is found to be cardio-protective and cardio-tonic.[3,36] It helps prevent damage caused by myocardial necrosis, prevent platelet aggregation, and normalize heart blood pressure.[3,36] Arjunolic acid influences electrocardiographic changes, serum marker enzymes, antioxidant status, lipid peroxide, and other markers.[3,36] Significant research suggests that ROS (reactive oxidative species) plays a strong role in the development and progression of many types of heart disease. Studies find that arjunolic acid is also a potent antioxidant.[3,36]

Arjuna is noted in research for its beneficial actions in treatment of coronary artery disease, heart failure, and ability to relieve angina pain.[14] Clinical studies report about 50% reduction in angina episodes in patients with both stable and unstable angina after three months of taking Arjuna. In addition, increased exercise tolerance and improved treadmill test results were significant in those with stable angina. There was also significant reduction in systolic blood pressure.[14]

Olive Leaf (*Olea europea*)

Olive leaf is a traditional remedy used since ancient times to lower high blood pressure and to treat atherosclerosis, blood sugar issues, and other conditions. Modern research bears out these ancient medicinal traditions and finds high efficacy and safety in using olive leaf.[5,37] Studies indicate that the benefits seen with the use of olive leaf extract are found to exceed the benefits of lifestyle changes alone.[5]

Olive leaves contain about 20% oleuropein, which is considered their main active constituent. Oleuropein is a complex structure of flavonoids, esters, and iridoid glycosides. These compounds are found to exert a vasodilatory influence and to significantly lower blood pressure in human studies.[5,7] As a flavonoid, oleuropein exerts potent antioxidant influence.[5]

Olive leaf extract is shown to significantly reduce triglyceride levels, total cholesterol, and LDL-cholesterol levels.[5] It is found to benefit both systolic and diastolic blood pressure, lowering both in those with stage-1 hypertension.[5]

Grape Seed (*Vitis vinifera*)

Grape seeds and grape seed extract (GSE) are widely-renowned and highly-studied because of their phenolic compounds, which demonstrate numerous health benefits. Phenolic compounds, abundant in vegetables and fruits, are known to exert potent antioxidant effects.[38]

Phenolic compounds from grape seeds are shown to benefit endothelial health and function.[38] They activate responses in the endothelium that cause endothelium-dependent relaxation (EDR) of blood vessels, which supports healthy blood pressure and healthy blood circulation.[39,40] GSE is shown to exert an immune-modulatory influence in those with hypertension where it is demonstrated to downregulate inflammatory factors.[12]

Grape seed contains an abundance of flavonoids including catechins, epicatechin, anthocyanadins, proanthocyanidins, and OPCs.[41] Grape seed flavonoids are anti-inflammatory and help prevent the release and synthesis of inflammatory compounds including prostaglandins, histamines, and other compounds.[16]

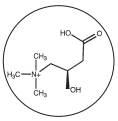
OPCs are widely known for their antioxidant activity and are also noted for their anti-inflammatory, antibacterial, anti-allergic, and vasodilatory actions.[42] OPCs are found to inhibit lipid peroxidation and platelet aggregation. They support

healthy capillary permeability and strength.[42,43]

In studies where animals were fed GSE a significant decrease in arterial pressure and oxidative factors was noted.[38] In a small study that included adults with metabolic syndrome, GSE given at a dose of 150mg/d to 300mg/day reduced systolic and diastolic BP.[39]

A specialized, patented form of GSE, called MegaNatural®-BP, is found to contain about 94% polyphenolic compounds, particularly catechin, epicatechin, tannins, and OPCs.[39,44] It is extracted with a proprietary process and is made in California with a special blend of grape seeds from unfermented varietal wine and juice grapes. After the seeds are extracted in hot water, the extract is purified, concentrated and spray-dried, which concentrates the natural grape phenolics.

MegaNatural®-BP GSE has been clinically studied. Studies done on this unique compound find that the extract is readily absorbed into the systemic circulation.[39] Two placebo-controlled human clinical studies were conducted by researchers at the University of California Davis School of Medicine, Department of Preventative Cardiology. They found that MegaNatural®-BP Grape Seed Extract supports healthy blood pressure within the normal range.[44]



L-Carnitine

L-carnitine plays a key role in energy production and specifically influences lipid metabolism. In the human body it is synthesized from the amino acids lysine and methionine.[45,46] Carnitine transports long-chain acyl groups from fatty acids into the mitrochondrial matrix so they can be broken down to acetyl-CoA to enter the citric acid cycle for production of cellular energy.[47-49]

Studies report that carnitine benefits cardiac and cardiovascular health. It is found to enhance heart muscle health and function. Carnitine exerts a positive influence to help lower triglyceride and cholesterol levels, while benefiting healthy HDL (high-density lipoprotein) levels.[50]

Carnitine benefits mitochondrial health, cellular respiration, and improves cell membrane potential. It exerts potent antioxidant activity with the ability to stabilize cell membrane activity. Carnitine is found to possess trophic (restorative) benefits and demonstrates the ability to activate DNA repair enzymes and to enhance antioxidant status.[46,51]

In a review of controlled trials involving 3,629 patients, supplementation with carnitine was found to significantly improve the cardiac health of patients after a heart attack. Analysis found great reduction in ventricular arrhythmia (65%) and angina attacks (40%) following heart attack, compared to placebo or control.[52]

Rauwolfia (*Rauwolfia serpentina*)

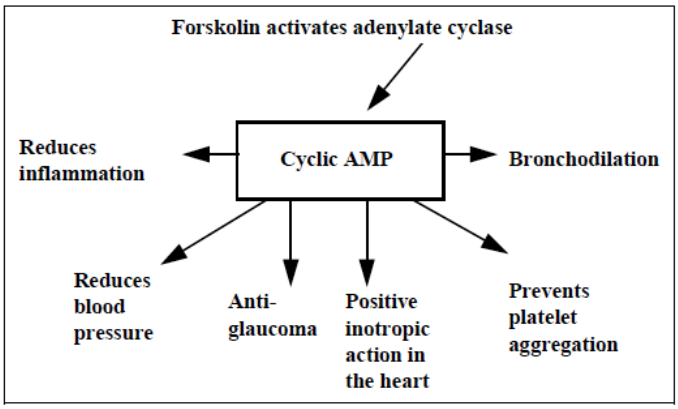
Rauwolfia root is famous worldwide in ancient and modern medicine. It has been used for centuries in India and Africa for a variety of disorders including hypertension, insomnia, and for its calming influence.[53] Rauwolfia root was used by many physicians in India during the 1940s. With the publication of a 1949 paper by a famous Indian cardiologist, Rauwolfia root became recognized worldwide in the 1950s as a successful agent to lower high blood pressure.[54,55]

Rauwolfia contains 30 or more alkaloids, including reserpine, many of which are found to be beneficial in treating hypertension. They are found to control nerve impulses along pathways that influence the heart and blood vessels. Clinical studies find that Rauwolfia reduces diastolic blood pressure and exerts significant anti-arrythmic influence.[7]

Coleus forskohlii

Coleus root is traditionally used in Ayurvedic medicine for a number of conditions including cardiovascular disease and hypertension. Its diterpene isolate, forskolin, exerts a hypotensive and anti-spasmodic action, influencing relaxation of arterial smooth muscle.[7,12,56] Studies find that it lowers blood pressure in animals and in humans.[12] Forskolin influences calcium uptake by heart muscles[7] and it is also found to act as a vasodilator and to exert anti-inflammatory influence.[56-59]

Spectrum of Potential Therapeutic Activities of Forskolin



Source: *See reference #60*

Forskolin is a potent activator of adenylyl cyclase, the enzyme specific for production of cAMP (cyclic adenosine monophosphate), which is active in metabolic processes. Forskolin increases intracellular cAMP levels, leading to the activation of protein kinase A, which promotes relaxation of the vascular smooth muscle cells. This is one way that forskolin contributes to lowering blood pressure. Cyclic AMP also helps

reduce inflammation and decrease platelet aggregation.[12,59-61]

Green Coffee Bean (*Coffea robusta*)

Green coffee beans contain an array of the protective antioxidative polyphenols. One of these, chlorogenic acid (CGA), is found to influence NO in the vascular endothelium to induce vaso-relaxation and help improve vasoreactivity.[62,63]

Green coffee bean extract (GCE) is found to be anti-hypertensive with the ability to lower high blood pressure in animal and human studies.[62,63] In a human study, those drinking GCE were noted to have significantly decreased levels of serum homocysteine.[63]

Ginger (*Zingiber officinale*)

This world-renowned and well-loved herb has been used as cooking spice, herbal remedy, and revered medicine for centuries. Ginger acts as a gentle diffusive stimulant on circulation and has a mild relaxing effect. Herbalists also use Ginger to enhance the digestion of other herbs in a formula.[64]

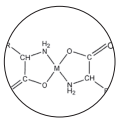
Ginger demonstrates impressive antioxidant[65-67] and anti-inflammatory activity[68,69] and is found to modulate lipid peroxidation.[65] Ginger influences prostaglandin metabolism, is a potent inhibitor of thromboxane synthesis, and is found to significantly inhibit platelet aggregation and inflammation.[70-72]

Studies find that Ginger significantly reduces serum and hepatic cholesterol levels. It possesses potent cardio-tonic activity.[73,74] Studies also report that Ginger, used traditionally for hypertension, exerts some calcium channel-blocking activity along with a vasodilatory influence.[75]

Celery (*Apium graveolens*)

Today's celery originates from wild celery native to the Mediterranean region. Celery seeds are highly valued for their culinary and medicinal properties.[4] Folk medicine has long used celery and celery seeds for their anti-hypertensive effects. Celery demonstrates antioxidant, hypolipidemic, and anti-inflammatory activity.[76]

Studies find Celery seeds to significantly reduce systolic and diastolic blood pressure. The compound which gives Celery its characteristic odor, 3nB (3 n-butyl phthalaide), is found to lower blood pressure in animal studies. Studies report it lowers blood pressure through its diuretic and vasodilator effects. 3nB is shown to lower blood cholesterol, to help reduce formation of arterial plaque, and to increase blood vessel elasticity.[4] In animal studies, Celery seed is found to significantly enhance neurological and brain function recovery in post-stroke conditions.[4,76]



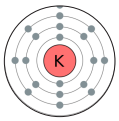
Magnesium and Vitamin C

Magnesium, a vital mineral, is a cofactor in over 350 enzymatic reactions in human physiology, most of which are related to energy metabolism. As the second most abundant intracellular cation in the body (after potassium), it is vital to multiple cellular functions and metabolic pathways. About 33% of the body's magnesium is distributed in the cardiac and skeletal muscles and in the liver.[77]

Magnesium is a key major mineral necessary for bone and muscle strength, heart health, central nervous system function, correct assimilation of calcium and potassium, and efficient enzymatic function. Magnesium is essential for neuromuscular activity, muscular relaxation, and strength. A contributing factor to heart muscle strength, it supports a regular heartbeat.[77-79] Magnesium can be helpful to relax smooth muscles of the blood vessels and lower blood pressure.[7]

Magnesium influences mitochondria, membrane receptors, and enzymes. It plays a major role in ATP synthesis and exerts a regulatory role in energy metabolism.[77-79] Magnesium is a catalyst in the synthesis of taurine that occurs in the liver, where it catalyzes the methylation of methionine to form homocysteine.[15]

The magnesium ascorbate form of magnesium offers a small amount of buffered Vitamin C that is easily absorbed. The water-soluble vitamin C is known as a powerful antioxidant. Vitamin C modulates NO and can impact defective endothelium-dependent vasodilation.[7]



Potassium

Potassium, an essential nutrient, plays vital roles in electrolyte balance, maintenance of total body fluid volume, and normal cell function.[80] Low potassium levels are associated with hypertension and stroke. Increased dietary potassium is found to be protective against these conditions.[80] In 22 randomized, controlled trials with 1606 people it was found that increased potassium intake helps reduce systolic and diastolic blood pressure in those with hypertension but not in those with normal blood pressure.[80]

Generally, diets low in potassium and high in sodium are associated with hypertension. Potassium is found to significantly reduce blood pressure in people consuming high-salt diets. Regulation of plasma potassium is regulated through homeostatic control mechanisms.[7,81,82]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

References

1. Al Disi, SS, Anwar MA, Eid AH. *Anti-hypertensive herbs and their mechanisms of action: Part I*. Frontiers in Pharmacology. 2016 January. 6(article 323).
2. Nwankwao T, Yoon SS, et al. *Hypertension Among Adults in the United States: National Health and Nutrition Examination Survey, 2011–2012*. NCHS Data Brief No. 133. October 2013. http://www.cdc.gov/nchs/products/databriefs/db133.htm
3. Arman RS, Mahtab AS. *Unani drugs in the management of cardiovascular diseases: a review on pharmacological studies on arjun and zafran*. Int J Res Ayurveda Pharm. 2013 May-June. 4(3):doi: 10.7897/2277-4343.04332
4. Madhavi D, Kagan D, et al. *A pilot study to evaluate the antihypertensive effect of celery extract in mild to moderate hypertensive patients*. Natural Medicine Journal. 2013 April. 5(4)
5. Susalit E, Agus N, et al. *Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril*. Phytomedicine. 2010. doi:10.1016/j.phymed.2010.08.016
6. Xi L, Hao YC, et al. *Associations between serum potassium and sodium levels and risk of hypertension: a community-based cohort study*. J Geriatr Cardiol. 2015. 12: 119-126. doi:10.11909/j.issn.1671-5411.2015.02.009
7. Khosh F, Khosh M. *Natural approach to hypertension*. Alt Med Rev. 2001. 6(6):590=600.
8. Arbuto NJ. *Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses*. BMJ. 2013. doi: 10.1136/bmj.f1378 (Published 5 April 2013)
9. Upadhyay RK. *Emerging risk biomarkers in cardiovascular diseases and disor*ders. J Lipids. 2015. Article ID 971453. 50 pages. http://dx.doi.org/10.1155/2015/971453
10. Cecilja M, Chowienczyk. *Role of arterial stiffness in cardiovascular disease*. JRSM Cardiovas Dis. 2012 July. 1(4): cvd.2012.012016. doi: 10.1258/cvd.2012.012016
11. Anderson TJ. *Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk*. Can J Cardiol. 2006 Feb. 22(Suppl B): 72B-80B.
12. Anwar MA, Al Disi, SS, Eid AH. *Anti-hypertensive herbs and their mechanisms of action: Part II*. Frontiers in Pharmacology. 2016 March. 6(article 323)
13. Miller AL. *Cardiovascular disease – toward a unified approach*. Alt Med Rev. 1996. 1(3):132-147.
14. Mahmood ZA, Sualeh M, et al. *Herbal treatment for cardiovascular disease. The evidence based therapy*. Pak J Pharm Sci 2010 Jan. 23(1):119-124. Paper 20
15. Wojcik OP, Koenig KL, et al. *The potential protective effects of taurine on coronary heart disease*. Atherosclerosis. Jan 2010. 208(1):19 doi: 10.1016/jatherosclerosis.2009.06.002
16. Shi J, Yu J, et al. *Polyphenolics in grape seeds-biochemistry and functionality*. J Med Food. 2003 Winter. 6(4):291-299.
17. Gabor M. *Pharmacological effects of flavonoids on blood vessels*. Angiologica. 1972. 9:355-374.

L-Citruline

18. Schwedhelm, E, Mass, R, Freese, R, Jung, D, et al. *Pharmacokinetic and pharmacodynamics properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism*. Br J Clin Pharmacol. 2008 January; 65(1): 51-59.
19. Figueroa A, Trivino JA, et al. *Oral L-citrulline supplementation attenuates blood pressure response to cold pressor test in young men*. Am J Hypertension. 2009.
20. Ochiai, M, Hayashi, T, Morita, et al. *Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men*. Int J Cardiol (2010) doi:10,1016/j.ijcard.2010.10.0004

Taurine

21. *Taurine Monograph*. Alt Med Rev. 2001. 6(1):78-82.
22. Birdsall TC. *Therapeutic applications of taurine*. Alt Med Rev. 1998. 3(2):128-136.
23. Zulli A. *Taurine in cardiovascular disease*. Curr Opin Clin Nutr Metab Care. 2010 Oct 30.
24. Yamori Y, Taguchi T, et al. *Taurine in health and diseases: consistent evidence from experiemental and epidemiological studies*. J Biomed Sci. 2010. 17(Suppl 1):S6.

Hawthorn

25. Chang WT, Dao J, Shao ZH. *Hawthorn: potential roles in cardiovascular disease*. Am J Chin Med. 2005. 33(1):1-10. Review.
26. Ellingwood F. *American Materia Medica, Therapeutics and Pharmacognosy*. 1919. Cincinnati, Ohio. p217-220.
27. Rakotoarison DA, Gressier, et al. *Antioxidant activities of polyphenolic extracts from flowers, in vitro callus and cell suspension cultures of Crataegus monogyna*. Pharmazie 1997. 52:60-64.
28. Schussler M, Holzl J, Fricke U. *Myocardial effects of flavonoids from Crataegus species*. Arzneimittelforschung. 1995. 45:842-845.
29. Rewerski VW, Piechocki T, et al. *Some pharmacological properties of oligomeric procyanidin isolaled from hawthorn (Crataegus oxyacantha)*. Arznemittforschung Drug Res. 1967:17:490-491.
30. Walker AF, Marakis G, et al. *Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial*. Br J Gen Pract. 2006. June. 56(527):437-443.
31. Popping S, Rose H, et al. *Effect of a hawthorn extract on contraction and energy turnover of isolated rat cardiomyocytes*. Arzneimittelforschung. 1995. 45:1157-1161.
32. Shanthi S, Parasakthy K, et al. *Hypolipidemic activity of tincture of Crataegus in rats*. Indian J Biochem Biophys. 1994. 31:143-146.
33. Rajendran S, Deepalakshmi PD, et al. *Effect of tincture of Crataegus on the LDL-receptor activity of hepatic plasma membrane of rats fed an atherogenic diet*. Atherosclerosis. 1996.123:235-241.

Arjuna Bark

34. Kapoor D, Vijayvergiya R, Dhawan V. *Terminalia arjuna in coronary artery disease: ethnopharmacology, pre-clinical, clinical & safety evaluation*. J Ethnopharmacol. 2014 Sep 11. 155(2):1029-1045. doi: 10.1016/j.jep.2014.06.056. Epub 2014 Jul 8.
35. Dwivedi S. *Terminalia arjuna Wight & Arn.- a useful drug for cardiovascular disorders*. J Ethnopharmacol. 2007 Nov 1. 114(2):114-129. Epub 2007 Aug 10.
36. Hemalatha T, Pulavendran S, et al. *Arjunolic acid: a novel phytomedicine with multifunctional therapeutic actions*. Indian J Exp Biol. 2010 Mar. 48(3):238-247.

Olive Leaf

37. Gilani AH, Khan AU, et al. *Blood pressure lowering effect of olive is mediated through calcium channel blockade*. Int J Food Sci Nutr. 2005 Dec. 56(8):613-620.

Grape Seed

38. Peng N, Clark JT, et al. *Antihypertensive and cognitive effects of grape polyphenols in estrogen-depleted, female, spontaneously hypertensive rats*. Am J Phys Regul Integr Comp Physiol. 2005. 289:R771-R775.
39. Sivaprakasapillai B, Edirisinghe I. *Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome*. Metabolism Clinical and Experimental. 2009. 58:1743-1746.
40. Edirisinghe I, Burton-Freeman B, Tissa Kappagoda C. *Mechanism of the endothelium-dependent relaxation evoked by a grape seed extract*. Clin Sci. 2008 Feb. 114(4):331-337.

41. Lee JH, Talcott ST. *Fruit maturity and juice extraction influences ellagic acid derivatives and other antioxidant polyphenolics in muscadine grapes*. J Agric Food Chem. 2004 Jan 28. 52(2):361-366.
42. Fine AM. *Oligomeric proanthocyanidin complexes: history, structure, and phytopharmaceutical appli*cations. Altern Med Rev. 2000 Apr. 5(2):144-151.
43. Teixeira S. *Bioflavonoids: proanthocyanidins and quercetin and their potential roles in treating musculoskeletal conditions*. J Orthop Sports Phys Ther. 2002. 32:357-363.
44. Robinson M, Lu B, et al. *Effect of grape seed extract on blood pressure in subjects with pre-hypertension*. J Pharm Nutr Sci. 2012. (2):155-159.

Carnitine

45. Murray MT, Pizzarno JE. *Textbook of Natural Medicine*. V: Carnitine.
46. Kidd, PM. *A review of nutrients and botanicals in the integrative management of cognitive dysfunction.* Alt Med Rev. 1999. 4:144-161.
47. Arsenian MA. *Carnitine and its derivatives in cardiovascular disease.* Progress in Cardiovascular Diseases. 1997 Nov/Dec. 40 (3):265–286.
48. Mingrone G, Greco A, et al. *L-Carnitine Improves Glucose Disposal in Type 2 Diabetic Patients*. J Am Coll Nutrition. 1999 Feb 1. 18 (1):77–82.
49. Malaguarnera M, Cammalleri L, et al. *L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial*, Am J Clin Nutr. 2007 Dec. 86(6):1738-1744.
50. Pauly DF, Pepine CJ. *Ischemic heart disease: metabolic approaches to management*. Clin Cardiol. 2004 Aug. 27(8):439-441.
51. Sethumadhavan S, Chinnakannu P. *Carnitine and lipoic acid alleviates protein oxidation in heart mitochondria during aging process*. Biogerontology. 2006 Apr. 7(2):101-109.
52. DiNicolantonio JJ, Lavie CJ, et al. *L-Carnitine in the Secondary Prevention of Cardiovascular Disease: Systematic Review and Meta-analysis*. Mayo Clinic Proceedings. 2013 June. 88(6). DOI: 10.1016/j.mayocp.2013.02.007

Rauwolfia

53. Jerie P. *Milestones of cardiovascular therapy. IV. Reserpine*, Cas Lek Cesk. 2007. 146(7):573-577.
54. Isharwal S, Gupta S. *Rustom Jal Vakil: his contributions to cardiology*. Tex Heart Inst J. 2006. 33(2):161-170.
55. Lobay D. *Rauwolfia in the treatment of hypertension*. Integr Med (Encinitas). 2015 June. 14(3):40-46.

Coleus

56. Jaqtap M, Chandola HM, et al. *Clinical efficacy of Coleus forskohlii (Willd.) Briq. (Makandi) in hypertension of geriatric population*. Ayu. 2011 Jan-Mar. 32(1):59-65. doi: 10.4013/0974-8520.85729.
57. Metzger H, Lindner E. *The positive inotropic-acting forskolin, a potent adenylate cyclase activator*. Arzneimittelforschung. 1981. 31(8):1248-1250.
58. Hayashida N, et al. *Antiinflammatory effects of colforsin daropate hydrochloride, a novel water-soluble forskolin derivative*. Ann Thorac Surg. 2001. 71(6):1931-1938.
59. Christenson JT, Thulesius O, Nazzal MM. *The effect of forskolin on blood flow, platelet metabolism, aggregation and ATP release*. Vasa. 1995. 24(1):56-61.
60. Majeed M, Prakash L. *Coleus forskohlii exract (95% forskolin): Monograph*.
61. Schlepper M, Thormann J, et al. *Cardiovascular effects of forskolin and phosphodiesterase-III inhibitors. Inotropic Stumulation and Myocardial Energetics*. H. Just et al. (eds.) Springer-Verlag Berlin Heidelberg. 1989

Green Coffee Bean

62. Ochiai R, Jokura H, et al. *Green coffee bean extract improves human vasoreactivity*. Hypertens Res. 2004 Oct. 27(10):731-737.
63. Watanabe T, Arai Y, et al. *The blood pressure-lowering effect and safety of chlorogenic acid from green coffee bean extract in essential hypertension*. Clin Exp Hypertens. 2006 Jul. 28(5):439-449.

Ginger

64. Duke JA, Ayensu ES. *Medicinal Plants of China. Medicinal Plants of the World*. Vol. 1. Algonac, MI:Reference Publications, Inc, 1985. 362.
65. Sujatha R, Srinivas L. *Modulation of lipid peroxidation by dietary componenets*. Toxicology in vitro. 1995. 9:231-236.
66. Zhou Y, Xu R. *Antioxidative effect of Chinese drugs*. Chung Kuo Chung Yao Tsa Chih 1992. 17:368-369, 373 inside backcover.
67. Cao ZF, Chen ZG, et al. *Scavenging effects of ginger on superoxide anion and hydroxyl radical.* Zhongguo Zhong Yao Za Zhi. 1993 Dec. 18(12):750-751, 764.
68. Kim SO, Chun KS, et al. *Inhibitory effects of [6]-gingerol on PMA-induced COX-2 expression and activation of NF-kappaB and p38 MAPK in mouse skin. Biofactors*. 2004:21(1-4):27-31.
69. Kim SO, Kundu JK, et al. *Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin*. Oncogene. 2005 Apr. 7:24(15):2558-67.
70. Kiuchi F, Shibuya M, Sankawa U. *Inhibitors of prostaglandin biosynthesis from ginger*. Chem Pharm Bull. Tokyo. 1982. 30:754-7.
71. Flynn D, Rafferty M, Boctor A. *Inhibition of human neutrophil 5-liopxygenase activity by gingerdione, shogaol, capsaicin and related pungent compounds*. Prostaglandins Leukotrienes Med. 1986. 24:195-198.
72. Srivastava KC. *Isolation and effects of some ginger components of platelet aggregation and eicosanoid biosynthesis. Prostaglandins.* Leukot Med. 1986. 25:187-198.
73. Kobayashi M, Ishida Y, et al. *Cardiotonic action of [8]-gingerol, an activator of the Ca++-pumping adenosine triphosphatase of sarcoplasmic reticulum, in guinea pig atrial muscle*. J Pharmacol Exp Ther. 1988. 246:667-673.
74. Shoji N, Iwasa A, et al. *Cardiotonic principles of ginger (Zingiber officinale Roscoe).* J Pharm Sci. 1982. 71:1174-1175.
75. Ghayur MN, Gilani AH. *Ginger lowers blood pressure through blockade of voltage-dependent calcium channels*. J cardiovasc Pharmacol. 2005 Jan. 45(1):74-80.

Celery Seed

76. Moghadam MH, Imenshahidi M, et al. *Antihypertensive effect of celery seed on rat blood pressure in chronic administration*. J Med Food. 2013. 16(6):558-563.

Magnesium & Vitamin C

77. *Magnesium Monograph*. Alt Med Rev. 2002. p251-260.
78. Faryadi Q. *The Magnificent Effect of Magnesium to Human Health: A Critical Review*. Int J App Sci Tech. 2012 March. 2(3):118-126
79. Dominguez LJ, Barbagallo M, et al. *Magnesium and muscle performance in older persons: the InCHIANTI study*. Am J Clin Nutr 2006 August. 84(2):419-426.

Postassium

80. Arbuto NJ. *Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses*. BMJ. 2013. doi: 10.1136/bmj.f1378 (Published 5 April 2013)
81. van Bommel E, Cleophas T. *Potassium treatment for hypertension in patients with high salt intake: a meta-analysis*. Int J Clin Pharmacol Ther. 2012 Jul. 50(7):478-482. doi: 10.5414/CP201724
82. Treasure J, Ploth D. *Role of dietary potassium in the treatment of hypertension*. Hypertension. 1983 Nov/Dec. 5(6):864-872.