ISSN (Online) 2249-6084 (Print) 2250-1029

International Journal of Pharmaceutical and Phytopharmacological Research (eIJPPR)
[Impact Factor – 0.7826]

Journal Homepage: www.eijppr.com

Review Article

An Emerging Role of Natural Antioxidants in Hypertension

Sonu, Satbir Singh, Gaurav Sharma, Vineet Sharma, Ankur Rohilla*, Ashok Kushnoor
Department of Pharmaceutical Sciences, Shri Gopichand Group of Institutions, Baghpat-250609, UP, India.

Article info

Article History:
Received 10 June 2013
Accepted 29 June 2013

Keywords:
Cardiovascular diseases, Hypertension, Oxidative stress, Antioxidants

Abstract

The prevalence of cardiovascular diseases (CVD) like hypertension (HT) is increasing worldwide at an alarming rate. A direct relationship occurs between blood pressure (BP) and the risk of CVD, with oxidative stress as the prime culprit. The evidence which implicates the role of oxidative stress in the pathogenesis and complications of HT suggests the beneficial role of antioxidants in the treatment and prevention of HT. Ample of studies suggest that supplementation with antioxidants play a vital role in order to delay, prevent or remove oxidative damage. Natural substances like Vitamin A, C, and E, L-arginine, Coenzyme Q and α-lipoic acid show potent antioxidant and antihypertensive effects, resulting in the suppression of elevated BP. The purpose of the present review article is to examine the mechanisms whereby natural antioxidants reduce BP in patients presented with HT.

1. INTRODUCTION

Several risk factors for cardiovascular diseases (CVD) like coronary heart disease (CHD) and myocardial infarction (MI) have been reported worldwide. Hypertension (HT) represents one of the major factors for the development and progression of CVD[1-2]. Numbers of evidences suggest that reactive oxygen species (ROS) play an important role in the pathogenesis of HT and along with MI, and thus, the adverse effects of ROS on biological systems have become an important area for focus on current biomedical research.[3-4] Various reports demonstrated the involvement of oxygen free radicals (OFRs) and lipid peroxides (LP) in the pathogenesis of many diseases, including diabetes mellitus (DM), cancer, HT, rheumatoid arthritis (RA), systemic lupus erythematosus, atherosclerosis and aging[2,5-7]. The antioxidant vitamins have been suggested to exert potential effects against the development and progression of various CVD, including HT[8-9]. In addition, data from several observational epidemiologic studies have reported that the agents with antioxidant properties like dietary antioxidants ß-carotene, vitamin C, and vitamin E play a vital role in reducing the risk of CVD by significantly lowering the blood pressure (BP) [10-12]. Moreover, the anti-oxidant enzymes, which dispose, scavenge and suppress the formation of free radicals, have been noted to produce an important defense mechanism against oxidative stress[13-15]. The present review article aims to discuss the potential role of various antioxidants in the treatment and prevention of HT.

2. PATHOPHYSIOLOGY OF HYPERTENSION

The exact pathophysiology of HT has not been understood completely, but a number of pathophysiological mechanisms have been reported from time to time. The rise in peripheral resistance in established HT has been suggested to be attributed to the structural narrowing of small arteries and arterioles[16]. In addition, decrease in the number and density of capillaries has also been noted to be part of the cause[17-18]. Further, HT has been linked with reduced peripheral venous compliance, enhancing the venous return and cardiac preload, ultimately causing diastolic dysfunction[19]. Moreover, occurrence of high pulse pressure in geriatric patients presented with HT or isolated systolic HT has been suggested to be caused due to increased arterial stiffness associated with aging[20]. Furthermore, other mechanisms have also been denoted for the development of increased peripheral resistance in HT which includes disturbances in renal salt and water management, particularly abnormalities in the intra-renal renin-angiotensin system, and dysfunctioning of the sympathetic nervous system[21-22]. Additionally, various evidences have suggested that endothelial dysfunction and vascular inflammation also contribute to enhanced peripheral resistance and vascular damage in HT[23-25] (Fig. 1).

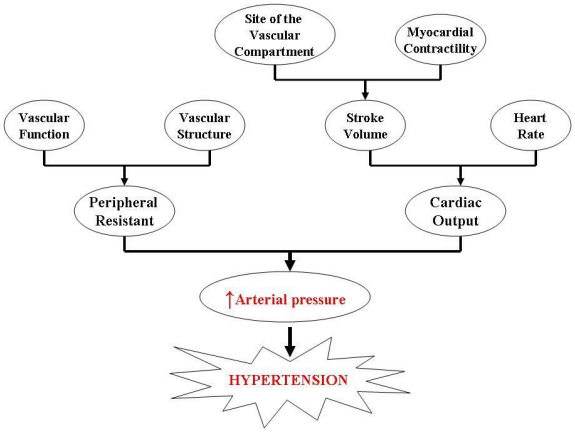

Fig.1. Pathophysiology of Hypertension

3. ROLE OF NATURAL ANTIOXIDANTS (VITAMINS) IN TREATMENT OF HT

Various antioxidant vitamins show antihypertensive effects by different mechanisms, but the mechanisms have not been apparent. A number of antioxidant vitamins have been suggested for the treatment and prevention of the HT which include Vitamin A,

Corresponding Author:
Ankur Rohilla, M.Pharm
Assistant Professor of Pharmacology,
Department of Pharmaceutical Sciences,
Shri Gopi Chand Group of Institutions,
Baghpat-250609, UP, India.
Mobile: +91-9896561778
E-mail: ankurrohilla1984@rediffmail.com

C, E, Coenzyme Q10 (CoQ-10), L-arginine, α-lipoic acid and flavonoids[2,11-12, 26]. Vitamin A, commonly known as retinoids, contains a β-ionone ring attached to an isoprenoid carbon chain. Vitamin A is derived from certain plant pigments called as carotenoids (Pro-vitamin A). The four components of pro-vitamin A are: α-carotene, β-carotene, γ-carotene and cryptoxanthine. The rich dietary sources of vitamin A includes fish liver oils, egg yolk, cheese, butter, liver, potato, carrot, pumpkin, spinach and broccoli leaf. It has been suggested that free radicals are responsible for the development and progression of CVD such as heart attack, HT, and atherogenesis. Vitamin A has been noted to neutralize the free radicals and prevent these complications by significantly decreasing the enhanced plasma levels in order to decrease BP in a clinical study[26-27]. However; the adverse mortality data with respect to β-carotene has limited interest in this compound as an effective antihypertensive agent[28]. Lycopene, which is synthesized from vitamin A derivatives, have also been noted to show potent antioxidant effects[29]. This contention is supported by the fact that tomato-extract based invention showed significant decrease in BP in patients presented with stage-I hypertension[30-31].

Vitamin C, commonly known as ascorbic acid, has been reported to possess potent antioxidant effects. It has a six-carbon lactone ring and exerts a structure similar to L-glucose[32]. Good dietary sources of Vitamin C include citrus fruits like lemon and orange; berries; melons; leafy vegetables; cabbages; tomatoes; and rose hips. L-ascorbic acid has been the biologically active form of Vitamin C which represents the primary antioxidant defense in blood[33]. it has been strongly suggested that Vitamin C reacts with the oxygen species, and terminates free radical chain reactions, and thus, acts as a strong antioxidant agent. In addition, Vitamin C also has crucial interactions with a numbers of other antioxidants, and is crucial for the regeneration of lipid-bound Vitamin E[26]. Furthermore, the antihypertensive potential of Vitamin C has been evaluated in multiple studies which evidenced the fact that a significant reductions in BP is achieved in both normotensive and hypertensive populations[34-35]. Moreover, it has been demonstrated that Vitamin C supplementation showed a significant decline in both systolic and diastolic BP which may persist for prolonged period. In addition, Vitamin C has been suggested to act more than an antioxidant and its effects on neurotransmitters lead to its antihypertensive activity[36]. This contention is supported by the fact that Vitamin C interferes with the production of free oxygen radicals and peroxides and stimulates the synthesis of prostaglandins (PGs), which produces a vasodilatory effect, ultimately leading to the treatment and prevention of HT[36]. Other mechanisms supporting the protective antioxidant potential of Vitamin C in HT suggest that the effect is caused by restoring vasodilatory activity of nitric oxide (NO) and by improving Ang-II induced endothelium-dependent vasodilation[37]. In addition, Vitamin C has been reported to reduce insulin resistance which in turn causes endothelium-dependent and NO-mediated vasodilation[38-39].

Vitamin E, commonly known as tocopherol, is the principal lipid-soluble antioxidant, which was discovered in 1936[40]. The four naturally occurring tocopherols are alpha, beta, gamma and delta consisting of a six-chromanol ring or head with a phytyl side chain[41]. It has been suggested that dietary Vitamin E is mostly absorbed in the small intestine, and thus, severe pancreatic, biliary dysfunction or fat malabsorption have been noted to affect the absorption of Vitamin E[42]. The rich dietary sources of Vitamin E includes wheat germ oil, milk, butter, rice, salad, cooking oils, peanuts, tree nuts, mayonnaise and other oil based dressings and some vegetables, asparagus, leafy green vegetables, higher derived from fats and oils[11, 26, 43]. Further, the cardio-protective potential of Vitamin E has been attributed to its potent antioxidant action. This contention is supported by the fact that α-tocopherol shows antioxidant potential by donating hydrogen radical to remove the free lipid radicals, reacting with it to form non-radical products, or trapping of lipid radicals[44]. In addition, cardioprotective potential of Vitamin E has been attributed to its potential in decreasing platelet adhesion, inhibiting Vitamin K dependent clotting factors, and stimulating NO formation by the endothelial cell[11].

CoQ-10, commonly known as ubiquinone, is a naturally occurring antioxidant, have been demonstrated to be widely distributed throughout the human body[18, 45]. CoQ-10 is a lipid soluble pro-vitamin, structurally similar to vitamin K[46]. CoQ-10 has been noted to be present in a wide variety of foods, mainly supplied by biosynthesis, and is also responsible for the cholesterol synthesis[47]. The CoQ-10 has been reported to show its action by various mechanisms. The CoQ-10 has been noted to be involved in oxidative phosphorylation, as a coenzyme for three critical mitochondrial enzyme systems including complex-I, II, and III[48]. In addition, it has been noted to act by enhancing the production and improving the energy function in tissues with high oxidative demands. Moreover, the CoQ-10 also serves to restore oxidized α-tocopherols levels, and thus, play a vital role for the function of its antioxidant effect[49]. Furthermore; it may also act due to its lipid solubility; as it is present in the cell membrane phospholipid layer and thus, influences membrane stability as well; further evidencing the role of CoQ-10 as an antioxidant.

L-arginine, an amino acid, is the main substrate for the production of NO from eNOS, in a reaction which is dependent on tetrahydrobiopterin[50-51]. The potential dietary source of L-arginine includes milk products, wheat germ, nuts, beef and soybeans. Numbers of studies have suggested and reported the low cellular levels of L-arginine in the progression and development of human HT[52-53]. Thus, it can be suggested that L-arginine supplementation could theoretically reduced BP by allowing restorations in normal NO bioavailability. Further; the antihypertensive potential of L-arginine has been evidenced by its supplementation in salt-sensitive rats, healthy human volunteers, hypertensive diabetics, patients with chronic kidney disease, and diabetic patients in combination with N-acetylcysteine[51, 54]. It has been reported that treatment with L-arginine showed suppressive effects on Ang II levels and potentiating insulin levels[55]. Various evidences have been demonstrated which suggest a potential role for neutralizing the eNOS-related antioxidant effects of L-arginine in patients presented with HT[7, 56].

Flavonoids, like quercetin, are polyphenolic compounds, which have been suggested to possess a prime role in the treatment and prevention of HT. Rich dietary sources of quercetin includes apples, onions, berries, red wine, red grapes, dark chocolate, flowers, citrus fruits, capers, and cocoa powder[57-58]. However; various epidemiological studies denote an inverse relationship between dietary quercetin and CVD. Conversely, other studies have been reported a reduction in BP with quercetin supplementation provided to hypertensive animals and humans[26]. Furthermore; quercetin showed antihypertensive effects by various proposed mechanisms like reduction in oxidative stress, quenching of ACE (Angiotensin converting enzyme) activity, and by improving endothelial function. Additionally, quercetin has been reported to decrease the prevalence of CVD alongwith protective effects in a variety of disorders such as allergies, asthma, bacterial infections, arthritis, gout, eye disorders, HT and neurodegenerative diseases.[59-60] Furthermore, the potential of quercetin in the treatment and prevention of HT is supported by the fact that short duration of dark chocolate therapy found to have BP lowering effects in patients presented with HT[61-64]. Moreover, in certain population, tea intake has been noted to show BP lowering effects, which further evidenced the potential of flavonoids in the treatment and prevention of HT[61]. In addition, various epidemiological studies suggested that other potential natural antioxidants such as garlic, glutamate, N-acetylcysteine, sour milk, and vitamin D show antihypertensive effect by quenching the sources of excessive ROS through antioxidant mechanisms[53, 65].

4. CONCLUSION

The wide-reaching prevalence of chronic CVDs like HT is on an all-time rise, resulting in increased mortality and morbidity. Moreover, it constitutes the major cause of death globally, mainly associated with oxidative stress. Thus, the antioxidant vitamins find the ceiling scope in the treatment and prevention of patients presented with HT. numbers of dietary antioxidants such as vitamin C, vitamin E and beta carotene have been suggested to might play a potential role in decreasing BP. However, the studies investigating the effect of natural antioxidants on oxidative stress in HT have been at a relatively early stage, and hence further studies are needed in order to completely explore the benefits of other potent antioxidants in the treatment and prevention of patients presented with HT.

REFERENCES

1. Farmer JA, Gotto AM Junior “Dyslipidemia and other risk factors for coronary artery disease” In heart disease. *A Textbook of Cardiovascular Medicine*. 1997; 5:1126–60.

2. Rohilla A, Sonu "Hypertension: sources and treatments". *Int J Res Pharm Biomed Sci,* 2013; 4; 94-99.
3. Loeper J "Lipid peroxidation and protective enzymes during myocardial infarction". *Clin Chim Acta,* 1991; 196: 119-26.
4. Kamat JP, Devasagayam TPA "Oxidative damage to mitochondria in normal and cancer tissues, and its modulation" *Toxicology*, 2000; 155:73–82.
5. Kiziltunc A "Oxidant/antioxidant status in serum of patients with Behçet's disease". *Ann Clin Lab Sci*, 2002; 32: 377–82.
6. Cogalgil S, Taysi S "Levels of antioxidant proteins and soluble intercellular adhesion molecule-I in serum of patients with rheumatoid arthritis". *Ann Clin Lab Sci*, 2002; 32: 264–70.
7. Jahangir E "The effect of l-arginine and creatine on vascular function and homocysteine metabolism" *Vasc Med* 2009; 14: 239–48.
8. Greenberg ER, MB "Antioxidant vitamins, cancer, and cardiovascular disease" *N Engl J Med* 1996; 334: 1189–90.
9. Miller ER "The effect of antioxidant vitamin supplementation on traditional cardiovascular risk factors". *J Cardiovasc Risk*. 1997; 4:19–24.
10. Jialal I, Devaraj S "Vitamin E supplementation and cardiovascular events in high-risk patients" *N Engl J Med* 2000; 342: 1917–8.
11. De Gaetano G "Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice". *Lancet*.2001; 357:89–95.
12. Mezzetti A "Vitamin E and lipid peroxide plasma levels predict the risk of cardiovascular events in a group of healthy very old people". *J Am Geriatr Soc*. 2001; 49:533–7.
13. Cotgreave IE, Moldeus P, Orrenius E "Host biochemical defence mechanism against prooxidants". *Annu Rev Pharmacol Toxicol*. 1988; 28: 189–212.
14. Chobanian AV "Clinical practice. Isolated systolic hypertension in the elderly". *N. Engl. J. Med* 357: 789–96.
15. Widder JD "Attenuation of angiotensin II-induced vascular dysfunction and hypertension by overexpression of Thioredoxin 2. Hypertension". 2009 August; 54(2):338–344.
16. Desir GV "Human renalase: a review of its biology, function, and implications for hypertension". *J Am Soc Hypertens* 2012; in press.
17. Chen X "Antioxidant effects of vitamins C and E are associated with altered activation of vascular NADPH oxidase and superoxide dismutase in stroke-prone SHR". Hypertension. 2001; 38:606–611.
18. Montezano AC, Touyz RM "Oxidative stress, Noxs, and hypertension: experimental evidence and clinical controversies". *Ann Med* 2012; 44: S2-16.
19. Abad-Cardiel M "Hypertension Caused by Primary Hyperaldosteronism: Increased Heart Damage and Cardiovascular Risk". *Rev Esp Cardiol 2012; in press*.
20. Zieman SJ, Melenovsky V, Kass DA "Mechanisms, pathophysiology, and therapy of arterial stiffness". Arterioscler. *Thromb. Vasc. Biol*, 25: 932–43.
21. Navar LG "Counterpoint: Activation of the intrarenal renin-angiotensin system is the dominant contributor to systemic hypertension". *J. Appl. Physiol*. 109 (6): 1998–2000.
22. Lambert E "Point: Chronic activation of the sympathetic nervous system is the dominant contributor to systemic hypertension". *J. Appl. Physiol*. 109: 1996–8.
23. Versari D "Endothelium-dependent contractions and endothelial dysfunction in human hypertension". *Br. J. Pharmacol* 2009; 157 (4): 527-36.
24. Marchesi C "Role of the renin-angiotensin system in vascular inflammation". *Trends Pharmacol. Sci*. 29 (7): 367–74.
25. Wolin MS "ROS and the control of vascular function". *Am J Physiol Heart Circ Physiol*. 2009 March; 296(3):H539–H549.
26. Tinoy J. Kizhakekuttu "Natural Antioxidant and Hypertension: promise and challenges". *Cardiovasc Ther. Author manuscript*; 2011 [August].
27. Stamler J "Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients". *Hypertension. 2002 May*; 39(5):1000–1006.
28. Augustin W "Beta-carotene cleavage products induce oxidative stress in vitro by impairing mitochondrial respiration". *FASEB J. 2002* August; 16(10):1289–1291.
29. Sutherland WH "Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes". *Diabetes Care. 2000* June; 23(6):733–738.
30. Ried K "Dark chocolate or tomato extract for prehypertension: a randomized controlled trial". *BMC Complement Altern Med*. 2009; 9:22.
31. Engelhard YN "Natural antioxidants from tomato extract reduces blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study". *Am Heart J.* 2006 January.151 (1):100.
32. Hendler SS"PDR for Nutritional Supplements". *Montvale, NJ: Medical Economics Company;* 2001.
33. Gey KF. "Vitamins E plus C and interacting conutrients required for optimal health. A critical and constructive review of epidemiology and supplementation data regarding cardiovascular disease and cancer". *Biofactors* 1998; 7(1-2):113-74.
34. Muhlhofer A "High-dose intravenous vitamin C is not associated with an increase of pro-oxidative biomarkers". *Eur J Clin Nutr*. 2004 August; 58(8):1151–1158.
35. Mullan BA. "Ascorbic Acid reduces blood pressure and arterial stiffness in type 2 diabetes". *Hypertension. 2002* December; 40(6):804–809.
36. Brody S "A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress". *Psychopharmacology (Berl)* 2002; 159:319-24.
37. Hirooka Y "Vitamin C improves attenuated angiotensin II-induced endothelium-dependent vasodilation in human forearm vessels". *Hypertens Res* 2003; 26:953-9.
38. Hirashima O "Improvement of endothelial function and insulin sensitivity with vitamin C in patients with coronary spastic angina: possible role of reactive oxygen species". *J Am Coll Cardiol* 2000; 35:1860-6.
39. Hernandez-Guerra M "Ascorbic acid improves the intrahepatic endothelial dysfunction of patients with cirrhosis and portal hypertension". *Hepatology* 2006; 43:485-91.
40. Greenberg ER. Sporn MB. "Antioxidant vitamins, cancer, and cardiovascular disease". *N Engl J Med*. 1996; 334: 1189–90.
41. Ward NC "The effect of vitamin E on blood pressure in individuals with type 2 diabetes: a randomized, double-blind, placebo-controlled trial". *J Hypertens*. 2007 January; 25(1):227–234.
42. Sesso HD "Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial". *JAMA*. 2008 November 12; 300(18):2123–2133.
43. Dhalla NS "Role of oxidative stress in cardiovascular diseases". *J Hypertens* 2000; 18:655-73.
44. Choi H. "Mechanism of angiotensin IIinduced superoxide production in cells reconstituted with angiotensin type 1 receptor and the components of NADPH oxidase". *J Biol Chem* 2008; 283:255-67.
45. Jabecka A "Oral L-arginine supplementation in patients with mild arterial hypertension and its effect on plasma level of asymmetric dimethylarginine, L-citruline, L-arginine and antioxidant status". *Eur Rev Med Pharmacol Sci* 2012; 16:1665-74.
46. Graham D "Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. Hypertension". 2009 August; 54(2):322–328.
47. Ono K, et al., (2005) "Performed beta-amyloid fibrils are destablished by coenzyme Q-10 in vitro". *Biochem Biophys Res commun*. 330:111-116.
48. Muralikrishnan Dhanasekaran and Jun Ren (2005). "The emerging role of coenzyme Q-10 in aging, neurodegeneration, cardiovascular diseases, cancer and diabetes mellitus".
49. McDonald SR, et al., (2005) "Concurrent administration of coenzyme Q-10 and Alpha-tocopherol improves learning in aged mice". *Free Radic Biol* Med 38:729-36.

50. Tiefenbacher CP. “Tetrahydrobiopterin: a critical cofactor for eNOS and a strategy in the treatment of endothelial dysfunction?” *Am J Physiol Heart Circ Physiol.* 2001 June; 280(6):H2484–H2488.
51. Martina V “Long-term N-acetylcysteine and L-arginine administration reduces endothelial activation and systolic blood pressure in hypertensive patients with type 2 diabetes”. *Diabetes Care*. 2008 May; 31(5):940–944.
52. Wang D “Asymmetric dimethylarginine, oxidative stress, and vascular nitric oxide synthase in essential hypertension”. *Am J Physiol Regul Integr Comp Physiol*. 2009 February; 296(2):R195–R200.
53. Stamler J “Glutamic acid, the main dietary amino acid, and blood pressure: the INTERMAP Study (International Collaborative Study of Macronutrients, Micronutrients and Blood Pressure)”. *Circulation*. 2009 July 21; 120(3):221–228.
54. Siani A “Blood pressure and metabolic changes during dietary L-arginine supplementation in humans”. *Am J Hypertens*. 2000 May; 13(5 Pt 1):547–551.
55. Gokce N“L-arginine and hypertension”. *J Nutr.* 2004 October.134 *(10 Suppl)* 2807S–28011S.
56. Tyagi N “Mechanisms of homocysteine-induced oxidative stress”. *Am J Physiol Heart Circ Physiol*. 2005 December; 289(6):H2649–H2656.
57. Peters U “Does tea affect cardiovascular disease? A meta-analysis”. *Am J Epidemiol*. 2001 September 15; 154(6):495–503.
58. Bazzano LA “Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Followup Study”. *Am J Clin Nutr*. 2002 July; 76(1):93–99.
59. Geleijnse “Inverse association of tea and flavonoid intakes with incident myocardial infarction: The Rotterdam Study”. *Am. J. Clin. Nutr.* 2002, 75, 880–886.
60. Lotito SB, Frei B “Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon?” *Free Radic Biol Med.* 2006 December 15; 41(12):1727–1746.
61. Taubert D “Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial”. *JAMA.* 2007 July 4; 298(1):49–60.
62. Taubert D “Effect of cocoa and tea intake on blood pressure: a metaanalysis”. *Arch Intern Med*. 2007 April 9; 167(7):626–634.
63. Grassi D “Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming highpolyphenol dark chocolate”. *J Nutr*. 2008 September; 138(9):1671–1676.
64. Ried K. “Dark chocolate or tomato extract for prehypertension: a randomized controlled trial”. *BMC Complement Altern Med.* 2009; 9:22.
65. El MA. “Comparative effects of N-acetyl-Lcysteine and ramipril on arterial hypertension, insulin resistance, and oxidative stress in chronically glucose-fed rats”. *Can J Physiol Pharmacol*. 2008 November; 86(11):752–760.