Journal of Pharmacovigilance
ISSN: 2329-6887

Kaisar and Cucullo, J Pharmacovigilance 2015, 3:2
DOI: 10.4172/2329-6887.1000e136

Editorial Open Access

OTC Antioxidant Products for the Treatment of Cardiovascular and other Disorders: Popular Myth or Fact?

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Cardiovascular disease (CVD) is the number one cause of mortality worldwide as reported by World Health Organization (WHO), Centers for Disease Control (CDC) and American Heart Association (AHA). The role of micronutrients has been studied extensively as CVD risk minimizing intervention. Among these, dietary supplements antioxidants available over the counter are highly commercialized but scientific evidences and clinical trials supporting their use is not conclusive yet [1]. The beneficial effects of these antioxidants are focused mainly against pathogenesis of atherosclerosis, as the primary contributor to coronary artery disease and resulting cardiovascular complications. Atherosclerosis is chronic inflammatory process of deposition of fatty cholesterol filled plaque in arterial wall which narrows the diameter and obstructs blood flow down the length of coronary artery and throughout its branches. Hyperlipidemia (high HDL: LDL ratio), high blood pressure, toxins from tobacco are assumed to be the major risk factor of atherosclerosis. If plasma LDL exceeds the regulatory capacity of endothelial cells, LDL crosses the endothelial barrier and trapped in sub-endothelial space where they are susceptible for oxidation by reactive oxygen species (ROS) - superoxide anion ($\cdot O_2^-$), hydroxyl radical (OH·), hydrogen peroxide (H_2O_2), reactive nitrogen species (RNS), nitric oxide (NO) and peroxynitrite (ONOO·) released by endothelial cells and macrophages [2]. These modified LDL stimulates endothelial cells to express various cell adhesion molecules (VCAM-I, P-selectin etc.) and chemotactic factors (monocyte chemotactic factor-1, MCP-1) for the recruitment of monocytes. Monocyte attachment is initiated by P-selectin on endothelial cell upon binding with P-selectin glycoprotein ligand-1 (PSGL-1) on the monocytes leading to rolling and prolonging the contact of monocyte on the arterial wall and initiate diapedesis across endothelial layers. Monocytes differentiate into macrophages under the influence of monocyte colony stimulating factor (M-CSF). Oxidized LDL is then engulfed in an unregulated fashion by macrophage scavenger receptor resulting in intracellular accumulation of cholesterol and forms foam cell formation [3,4]. Macrophages are also involved in activation of T cells to amplify the inflammatory response by secreting TNF-α and INF-γ. Finally, smooth muscle cells proliferate and migrate from tunica media and shield the fatty plaque and synthesize collagen to form a fibrous cap [5-7].

Despite the lack of strong biological evidences, widespread consumption of antioxidant supplements by patients suffering from cardiovascular disorders has made antioxidant therapy a multibillion industry. Among these highly advertised and frequently used antioxidants vitamin E (α tocopherol), vitamin C (ascorbic acid), co-enzyme Q-10 CoQ (10), α-lipoic acid (ALA), resveratrol and glutathione (GSH) have received highest attention due to their supposed beneficial effects in reducing the risk of CVD. However, results from randomized clinical trials are still inconclusive to support or disprove these claims [8]. Several in-vitro and in-vivo studies have demonstrated that vitamin E inhibits oxidation of LDL. The antioxidant effect is facilitated by the lipophilic nature of Vitamin E which favor its interaction with the target molecule [9]. In addition to blocking this crucial step of atherosclerosis initiation vitamin E has been proven to inhibit the progression of atherosclerotic inflammatory cascade via intracellular antioxidant effects due to its ability to cross the lipid bilayer of the cellular membranes [10,11]. Cell targets comprise vascular endothelial cells, monocyte/macrophage, platelets and smooth muscle cells. To this end vitamin E negatively modulates their inflammatory response. The downstream effect of inflammatory activity inhibition by vitamin E includes the following: 1) down regulation of the expression of cell adhesion molecules [12-14] which hinders endothelial–monocyte adhesion; 2) decreased cytokine release [15] and repression of monocytes scavenger receptor activity to engulf ox-LDL [16]; 3) inhibition of platelet aggregation [17,18] and smooth muscle cell proliferation (this latter reduced the risk of narrowing of the arterial walls) [18,19]; 4) decreased foam cell formation [20] and monocyte to macrophage differentiation by protected paraoxonase (PON 1) [21]. Detailed molecular studies suggests that the antioxidant and anti-inflammatory activities of this molecule are dependent upon its modulatory influence on a number of intracellular enzymes including phospholipase A2 (PPA2), COX-2, PKC, 5-lipooxygenase, nitric oxide synthase (NOS), NADPH oxidase and superoxide dismutase (SOD). Further, in vitro studies have shown a modulatory effect of Vitamin directed toward gene expression of factors involved in the pathogenesis of atherosclerosis (such as cytokines, selectins, cyclins, etc.) [22].

Regardless of these numerous evidences randomized clinical trial failed to confirm vitamin E supplementation to be beneficial in reducing the risk of cardiovascular complications [23,24]. However, American Heart Association recommends taking balanced diet rich in vitamin E for the better health of heart. Research has also shown that the oxidation and inflammation induced by CS in animals and cells can be reduced by antioxidants [25,26]. Likewise, the Food and Nutrition Board of the National Academy of Sciences has established a higher recommended dietary allowance (RDA) of vitamin C for smokers (over 200 mg/day versus the recommended 90 mg/day for non-smokers). Vitamin C has been shown to act as a dual negative modulator of oxidative stress (as a hydrophilic antioxidant) and production of lymphocytes and cytokines. Vitamin C also inhibits the activity of phagocytes and similarly to vitamin E, the expression of a number of cell adhesion molecules in monocytes [27]. Furthermore, vitamin C seems to prevents histamine release and increases the detoxification of histamine [28]. Inasmuch active and passive smoking is associated with dysfunction of vascular endothelial physiology [29-36] in a causative and dose dependent way

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Received April 15, 2015; **Accepted** April 16, 2015; **Published** April 21, 2015

Citation: Kaisar MA, Cucullo L (2015) OTC Antioxidant Products for the Treatment of Cardiovascular and other Disorders: Popular Myth or Fact? J Pharmacovigilance 3: e136. doi:10.4172/2329-6887.1000e136

[37] that is largely related to the content of reactive oxygen species (ROS) [31,38,39] and pro-inflammatory activity [39,40]. Cigarette smoke (CS) increases the risk of silent cerebral infarction (SCI) [41] and stroke by approximately 50% [42,43] due to its pro-coagulant and atherogenic effects [44,45] and is currently considered a major public health challenge accounting for over 400,000 deaths/year in US alone. Several studies have shown that chronic smokers suffer from antioxidant shortages caused by increased anti-oxidative mobilization that is evoked by CS [46-48]. Similarly to vitamin E, despite the positive in vitro results, vitamin C-based antioxidant therapies show contradicting outcomes in most clinical trials. Therefore, arguing for or against the prophylactic and/or therapeutic use of antioxidants remains a challenging conundrum.

In contrast to other antioxidants Co-enzyme Q10 – CoQ(10) inhibits both the initiation and the promulgation of lipid and protein oxidation and regenerates vitamin E, thereby further inhibiting the propagation steps of oxidative damage to cellular components. In addition, CoQ(10) seems to prevent the oxidation of mitochondrial DNA and LDL and its use is suggested (among others) as mitochondrial medicine in cardiovascular disorder especially in heart failure. CoQ(10) has also been recommended in hypertension and statin myopathy [49] based on the fact that, declined CoQ(10) levels may impair production of bioenergetics molecules (e.g., ATP), thus leading to increase oxidative stress and dysfunction of cardiac muscle resulting in heart failure [50]. Based on these premises from a number of in vitro and in vivo studies, CoQ(10) seems to possess anti-inflammatory, anti-nociceptive and anti-angiogenic activities and several pathological disorders on top of CVD (including Parkinson's and Huntington's diseases) seem to be responsive to CoQ(10) treatment [51,52]. However, a number of clinical trials on CoQ(10) have been published with contradictory results and failed to substantiate any conclusion on the beneficial role of Co-Q10 in primary prevention of cardiovascular disease [53] while other trials claim that long term CoQ(10) adjunct therapy is effective in the treatment of chronic heart failure and consequent cardiovascular complications [54].

α-Lipoic acid (ALA) is a powerful natural antioxidant and essential for the aerobic metabolism and is involved in the recycling of other antioxidants in the body (including vitamins C, E and glutathione) by acting as regenerative substrate. It is commonly present in almost all foods, especially heart, kidney, liver, spinach, broccoli, and yeast. ALA (and its active reduced form, dihydrolipoic acid - DHLA), has been shown to counteract oxidative stress by quenching a variety of ROS and preserve blood-brain barrier (BBB) integrity [55-57]. Differently from vitamin E and C, ALA is amphipathic in nature, thus can act both in lipid and aqueous solutions. In addition to ROS scavenging, ALA has been shown to modulate blood lipid, protect against LDL oxidation and reduce hypertension. These characteristics suggest a potential use for the treatment and/or prevention of CVD as well as other disorders including diabetes, cancer, neurodegenerative, and autoimmune diseases [58-61]. However, despite the numerous studies there is no unanimous consensus on a number of therapeutic parameters including dosage, dose frequency and form of administration.

Glutathione (GSH) is the major endogenous cellular antioxidant which directly participated in the neutralization of free radicals and reactive oxygen compounds and maintains exogenous antioxidants (including vitamins C and E) in their reduced (active) form. Glutathione also plays a central role in the regulation of the nitric oxide cycle, DNA synthesis and repair, protein synthesis, and enzyme activation [62-64]. As a result, the use GSH supplements have been postulated as a useful approach to counteract and/or prevent CVD and stroke, protect the lining of the arteries and reduce LDL oxidation and lower cholesterol by naturally inhibiting its production in the liver [65,66]. However, clinical trials focused on assessing the effects of oral GSH supplementation on systemic oxidative stress did not reveal any significant benefit. The discrepancy between in vivo studies in rodents (rats) and humans could be possibly due to the relative inability of the latter to absorb GSH through the intestinal tract. In fact, while some experimental evidence have suggested an increases in blood and/or intracellular levels of GSH through oral supplementation using reduced GSH in vivo [67]; the absorption of GSH in humans has not been equally confirmed [68,69]. The problem of GSH absorption in human could be complicated by the fact that the human gastrointestinal tract contains substantial amounts of γ-glutamyltransferase (GGT) which recycles GSH precursors and may prevent the oral absorption of intact glutathione itself.

Resveratrol is a natural plant-derived polyphenol which is found in abundance in the skin of grapes, mulberries, raspberries, and blueberries which seems to exert diverse positive biological effects and is currently considered a hot topic in numerous animal and human studies. Anticancer, anti-inflammatory, anti-aging, anti-diabetic and beneficial cardiovascular effects of resveratrol have been reported [70-72] although inconsistently. Not to mention, resveratrol has been shown to have protective effect on the BBB during ischemia [73,74] and in recent years (2003) resveratrol was discovered to be a small molecule activator of Sirtuin 1 (SIRT1), a protein whose activity has been linked to longevity. However, as for now, clinical evidence of these beneficial effects of resveratrol in humans is still lacking. For example, there is no confirmation that resveratrol can benefit patients who already suffer of heart disease [75,76]; although some data support a possible beneficial effect on diabetes [77]; the positive effect on cancer are inconsistent as well [78]. As for the metabolic effects of resveratrol, the clinical data are also inconclusive [79]. Finally, the hoped antiaging effect of resveratrol still remains unclear and yet to be proved [80].

References

1. Tinkel J, Hassanain H, Khouri SJ (2012) Cardiovascular antioxidant therapy: a review of supplements, pharmacotherapies, and mechanisms. Cardiol Rev 20: 77-83.
2. Stocker R, Keaney JF Jr (2005) New insights on oxidative stress in the artery wall. J Thromb Haemost 3: 1825-1834.
3. Kaplan M, Aviram M (1999) Oxidized low density lipoprotein: atherogenic and proinflammatory characteristics during macrophage foam cell formation. An inhibitory role for nutritional antioxidants and serum paraoxonase. Clin Chem Lab Med 37: 777-787.
4. Aviram M (1999) Macrophage foam cell formation during early atherogenesis is determined by the balance between pro-oxidants and anti-oxidants in arterial cells and blood lipoproteins. Antioxid Redox Signal 1: 585-594.
5. Schwartz CJ, Kelley JL, Nerem RM, Sprague EA, Rozek MM, et al. (1989) Pathophysiology of the atherogenic process. Am J Cardiol 64: 23G-30G.
6. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Nerem RM (1991) The pathogenesis of atherosclerosis: an overview. Clin Cardiol 14: 11-16.
7. Schwartz CJ, Valente AJ, Sprague EA (1993) A modern view of atherogenesis. Am J Cardiol 71: 9B-14B.
8. Núñez-Córdoba JM, Martínez-González MA (2011) Antioxidant vitamins and cardiovascular disease. Curr Top Med Chem 11: 1861-1869.
9. Thomas SR, Stocker R (2000) Molecular action of vitamin E in lipoprotein oxidation: implications for atherosclerosis. Free Radic Biol Med 28: 1795-1805.
10. Azzi A, Ricciarelli R, Zingg JM (2002) Non-antioxidant molecular functions of alpha-tocopherol (vitamin E). FEBS Lett 519: 8-10.
11. Zingg JM, Azzi A (2004) Non-antioxidant activities of vitamin E. Curr Med Chem 11: 1113-1133.

12. Chen YH, Lin SJ, Chen YL, Liu PL, Chen JW (2006) Anti-inflammatory effects of different drugs/agents with antioxidant property on endothelial expression of adhesion molecules. Cardiovasc Hematol Disord Drug Targets 6: 279-304.

13. Cominacini L, Garbin U, Pasini AF, Davoli A, Campagnola M, et al. (1997) Antioxidants inhibit the expression of intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1 induced by oxidized LDL on human umbilical vein endothelial cells. Free Radic Biol Med 22: 117-127.

14. Terasawa Y, Manabe H, Yoshida N, Uemura M, Sugimoto N, et al. (2000) Alpha-tocopherol protects against monocyte Mac-1 (CD11b/CD18) expression and Mac-1-dependent adhesion to endothelial cells induced by oxidized low-density lipoprotein. Biofactors 11: 221-233.

15. Jialal I, Devaraj S, Kaul N (2001) The effect of alpha-tocopherol on monocyte proatherogenic activity. J Nutr 131: 389S-94S.

16. Teupser D, Thiery J, Seidel D (1999) Alpha-tocopherol down-regulates scavenger receptor activity in macrophages. Atherosclerosis 144: 109-115.

17. Freedman JE, Keaney JF Jr (2001) Vitamin E inhibition of platelet aggregation is independent of antioxidant activity. J Nutr 131: 374S-7S.

18. Chang CC, Lee JJ, Chiang CW, Jayakumar T, Hsiao G, et al. (2010) Inhibitory effect of PMC, a potent hydrophilic alpha-tocopherol derivative, on vascular smooth muscle cell proliferation: the pivotal role of PKC-alpha translocation. Pharm Biol 48: 938-946.

19. Boscoboinik D, Szewczyk A, Hensey C, Azzi A (1991) Inhibition of cell proliferation by alpha-tocopherol. Role of protein kinase C. J Biol Chem 266: 6188-6194.

20. Huang ZG, Liang C, Han SF, Wu ZG (2012) Vitamin E ameliorates ox-LDL-induced foam cells formation through modulating the activities of oxidative stress-induced NF-κB pathway. Mol Cell Biochem 363: 11-19.

21. Aviram M, Rosenblat M, Billecke S, Erogul J, Sorenson R, et al. (1999) Human serum paraoxonase (PON 1) is inactivated by oxidized low density lipoprotein and preserved by antioxidants. Free Radic Biol Med 26: 892-904.

22. Munteanu A, Zingg JM, Azzi A (2004) Anti-atherosclerotic effects of vitamin E--myth or reality? J Cell Mol Med 8: 59-76.

23. Myung SK, Ju W, Cho B, Oh SW, Park SM, et al. (2013) Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. BMJ 346: f10.

24. Ye Y, Li J, Yuan Z (2013) Effect of antioxidant vitamin supplementation on cardiovascular outcomes: a meta-analysis of randomized controlled trials. PLoS One 8: e56803.

25. Willcox JK, Ash SL, Catignani GL (2004) Antioxidants and prevention of chronic disease. Crit Rev Food Sci Nutr 44: 275-295.

26. Hossain M, Mazzone P, Tierney W, Cucullo L (2011) In vitro assessment of tobacco smoke toxicity at the BBB: do antioxidant supplements have a protective role? BMC Neurosci 12: 92.

27. Preedy VR, Watson RR, Sherma Z (2010) Dietary Components and Immune Function (Nutrition and Health) Humana Press, Totowa, NJ 36.

28. Johnston CS, Martin LJ, Cai X (1992) Antihistamine effect of supplemental ascorbic acid and neutrophil chemotaxis. J Am Coll Nutr 11: 172-176.

29. Adams MR, Jessup W, Celermajer DS (1997) Cigarette smoking is associated with increased human monocyte adhesion to endothelial cells: reversibility with oral L-arginine but not vitamin C. J Am Coll Cardiol 29: 491-497.

30. Hossain M, Sathe T, Fazio V, Mazzone P, Weksler B, et al. (2009) Tobacco smoke: a critical etiological factor for vascular impairment at the blood-brain barrier. Brain Res 1287: 192-205.

31. Naik P, Fofaria N, Prasad S, Sajja RK, Weksler B, et al. (2014) Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? BMC Neurosci 15: 51.

32. Chen HW, Chien ML, Chaung YH, Lii CK, Wang TS (2004) Extracts from cigarette smoke induce DNA damage and cell adhesion molecule expression through different pathways. Chem Biol Interact 150: 233-241.

33. Davis JW (1990) Some acute effects of smoking on endothelial cells and platelets. Adv Exp Med Biol 273: 107-118.

34. Nagy J, Demaster EG, Wittmann I, Shultz P, Raij L (1997) Induction of endothelial cell injury by cigarette smoke. Endothelium 5: 251-263.

35. Noronha-Dutra AA, Epperlein MM, Woolf N (1993) Effect of cigarette smoking on cultured human endothelial cells. Cardiovasc Res 27: 774-778.

36. Raij L, DeMaster EG, Jaimes EA (2001) Cigarette smoke-induced endothelium dysfunction: role of superoxide anion. J Hypertens 19: 891-897.

37. Gill JS, Shipley MJ, Tsementzis SA, Hornby R, Gill SK, et al. (1989) Cigarette smoking. A risk factor for hemorrhagic and nonhemorrhagic stroke. Arch Intern Med 149: 2053-2057.

38. Panda K, Chattopadhyay R, Ghosh MK, Chattopadhyay DJ, Chatterjee IB (1999) Vitamin C prevents cigarette smoke induced oxidative damage of proteins and increased proteolysis. Free Radic Biol Med 27: 1064-1079.

39. Naik P, Fofaria N, Prasad S, Sajja RK, Weksler B, et al. (2014) Oxidative and pro-inflammatory impact of regular and denicotinized cigarettes on blood brain barrier endothelial cells: is smoking reduced or nicotine-free products really safe? BMC Neurosci 15: 51.

40. Arnson Y, Shoenfeld Y, Amital H (2010) Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 34: J258-265.

41. Howard G, Wagenknecht LE, Cai J, Cooper L, Kraut MA, et al. (1998) Cigarette smoking and other risk factors for silent cerebral infarction in the general population. Stroke 29: 913-917.

42. Shinton R, Beevers G (1989) Meta-analysis of relation between cigarette smoking and stroke. BMJ 298: 789-794.

43. Mannami T, Iso H, Baba S, Sasaki S, Okada K, et al. (2004) Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. Stroke 35: 1248-1253.

44. Miller GJ, Bauer KA, Cooper JA, Rosenberg RD (1998) Activation of the coagulant pathway in cigarette smokers. Thromb Haemost 79: 549-553.

45. Mast H, Thompson JL, Lin IF, Hofmeister C, Hartmann A, et al. (1998) Cigarette smoking as a determinant of high-grade carotid artery stenosis in Hispanic, black, and white patients with stroke or transient ischemic attack. Stroke 29: 908-912.

46. Sobczak A, Gołka D, Szołtysek-Bołdys I (2004) The effects of tobacco smoke on plasma alpha- and gamma-tocopherol levels in passive and active cigarette smokers. Toxicol Lett 151: 429-437.

47. Dietrich M, Block G, Norkus EP, Hudes M, Traber MG, et al. (2003) Smoking and exposure to environmental tobacco smoke decrease some plasma antioxidants and increase gamma-tocopherol in vivo after adjustment for dietary antioxidant intakes. Am J Clin Nutr 77: 160-166.

48. Tsuchiya M, Asada A, Kasahara E, Sato EF, Shindo M, et al. (2002) Smoking a single cigarette rapidly reduces combined concentrations of nitrate and nitrite and concentrations of antioxidants in plasma. Circulation 105: 1155-1157.

49. Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, et al. (2007) Coenzyme Q10 in cardiovascular disease. Mitochondrion 7 Suppl: S154-167.

50. Fosslien E (2003) Review: Mitochondrial medicine--cardiomyopathy caused by defective oxidative phosphorylation. Ann Clin Lab Sci 33: 371-395.

51. Quinzii CM, López LC, Gilkerson RW, Dorado B, Coku J, et al. (2010) Reactive oxygen species, oxidative stress, and cell death correlate with level of CoQ10 deficiency. FASEB J 24: 3733-3743.

52. Jung HJ, Park EH, Lim CJ (2009) Evaluation of anti-angiogenic, anti-inflammatory and antinociceptive activity of coenzyme Q(10) in experimental animals. J Pharm Pharmacol 61: 1391-1395.

53. Flowers N, Hartley L, Todkill D, Stranges S, Rees K (2014) Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 12: CD010405.

54. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, et al. (2014) The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2: 641-649.

55. GorÄ ca A, Huk-Kolega H, Piechota A, Kleniewska P, Ciejka E, et al. (2011) Lipoic acid - biological activity and therapeutic potential. Pharmacol Rep 63: 849-858.

56. Wang X, Yu Y, Ji L, Liang X, Zhang T, et al. (2011) Alpha-lipoic acid protects

against myocardial ischemia/reperfusion injury via multiple target effects. Food Chem Toxicol 49: 2750-2757.

57. Erşahin M, Toklu HZ, Cetinel S, Yüksel M, Erzik C, et al. (2010) Alpha lipoic acid alleviates oxidative stress and preserves blood brain permeability in rats with subarachnoid hemorrhage. Neurochem Res 35: 418-428.

58. Bajaj S, Khan A (2012) Antioxidants and diabetes. Indian J Endocrinol Metab 16: S267-271.

59. Rochette L, Ghibu S, Richard C, Zeller M, Cottin Y, et al. (2013) Direct and indirect antioxidant properties of α-lipoic acid and therapeutic potential. Mol Nutr Food Res 57: 114-125.

60. Harding SV, Rideout TC, Jones PJ (2012) Evidence for using alpha-lipoic acid in reducing lipoprotein and inflammatory related atherosclerotic risk. J Diet Suppl 9: 116-127.

61. Midaoui AE, Elimadi A, Wu L, Haddad PS, de Champlain J (2003) Lipoic acid prevents hypertension, hyperglycemia, and the increase in heart mitochondrial superoxide production. Am J Hypertens 16: 173-179.

62. Schulz JB, Lindenau J, Seyfried J, Dichgans J (2000) Glutathione, oxidative stress and neurodegeneration. Eur J Biochem 267: 4904-4911.

63. Mytilineou C, Kramer BC, Yabut JA (2002) Glutathione depletion and oxidative stress. Parkinsonism Relat Disord 8: 385-387.

64. Aquilano K, Baldelli S, Ciriolo MR (2011) Glutathione is a crucial guardian of protein integrity in the brain upon nitric oxide imbalance. Commun Integr Biol 4: 477-479.

65. Johnson WM, Wilson-Delfosse AL, Mieyal JJ (2012) Dysregulation of glutathione homeostasis in neurodegenerative diseases. Nutrients 4: 1399-1440.

66. Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, et al. (2009) Glutathione dysregulation and the etiology and progression of human diseases. Biol Chem 390: 191-214.

67. Favilli F, Marraccini P, Iantomasi T, Vincenzini MT (1997) Effect of orally administered glutathione on glutathione levels in some organs of rats: role of specific transporters. Br J Nutr 78: 293-300.

68. Witschi A, Reddy S, Stofer B, Lauterburg BH (1992) The systemic availability of oral glutathione. Eur J Clin Pharmacol 43: 667-669.

69. Allen J, Bradley RD (2011) Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers. J Altern Complement Med 17: 827-833.

70. Tang Y, Xu J, Qu W, Peng X, Xin P, et al. (2012) Resveratrol reduces vascular cell senescence through attenuation of oxidative stress by SIRT1/NADPH oxidase-dependent mechanisms. J Nutr Biochem 23: 1410-1416.

71. Li H, Xia N, Förstermann U (2012) Cardiovascular effects and molecular targets of resveratrol. Nitric Oxide 26: 102-110.

72. Brasnyó P, Molnár GA, Mohás M, Markó L, Laczy B, et al. (2011) Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br J Nutr 106: 383-389.

73. Simao F, Matte A, Matte C, Soares FM, Wyse AT, et al. (2011) Resveratrol prevents oxidative stress and inhibition of Na(+)K(+)-ATPase activity induced by transient global cerebral ischemia in rats. J Nutr Biochem 22: 921-928.

74. Ren J, Fan C, Chen N, Huang J, Yang Q (2011) Resveratrol pretreatment attenuates cerebral ischemic injury by upregulating expression of transcription factor Nrf2 and HO-1 in rats. Neurochem Res 36: 2352-2362.

75. van der Made SM, Plat J, Mensink RP (2015) Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. PLoS One 10: e0118393.

76. Tomé-Carneiro J, Gonzálvez M, Larrosa M, Yáñez-Gascón MJ, García-Almagro FJ, et al. (2013) Resveratrol in primary and secondary prevention of cardiovascular disease: a dietary and clinical perspective. Ann N Y Acad Sci 1290: 37-51.

77. Hausenblas HA, Schoulda JA, Smoliga JM (2015) Resveratrol treatment as an adjunct to pharmacological management in type 2 diabetes mellitus--systematic review and meta-analysis. Mol Nutr Food Res 59: 147-159.

78. Carter LG, D'Orazio JA, Pearson KJ (2014) Resveratrol and cancer: focus on in vivo evidence. Endocr Relat Cancer 21: R209-225.

79. Poulsen MM, Jørgensen JO, Jessen N, Richelsen B, Pedersen SB (2013) Resveratrol in metabolic health: an overview of the current evidence and perspectives. Ann N Y Acad Sci 1290: 74-82.

80. Fernández AF, Fraga MF (2011) The effects of the dietary polyphenol resveratrol on human healthy aging and lifespan. Epigenetics 6: 870-874.