Please cite this article as:

hypothesis

Haleh Vaez et al. Potential of *Cydonia oblonga* leaves in cardiovascular disease. *Hypothesis* 2014, **12**(1): e4, doi:10.5779/hypothesis.v12i1.356

Potential of *Cydonia oblonga* leaves in cardiovascular disease

Haleh Vaez[1,2*], Samin Hamidi[1,3], Sanam Arami[1,4]

[1]Student Research Committee, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Department of Pharmacology, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

[3]Department of Medicinal Chemistry, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

[4]Department of Biotechnology, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

*Correspondence:
vaezh@tbzmed.ac.ir

Received: 2013/11/10; Accepted: 2013/11/19;
Posted online: 2014/07/18

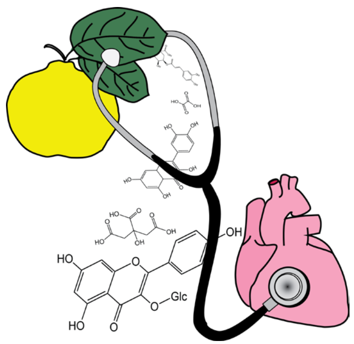

Illustration by Eloïse Kremer

ABSTRACT Nowadays plant-based medicine or herbal medicine research is becoming more prevalent all over the world, presumably due to natural accessibility and fewer adverse effects. Quince (*Cydonia oblonga* Miller), a plant in the Rosaceae family, is considered to be a good and cheap natural source for potent antioxidants including phenolic acids and flavonoids. There have been limited investigations on the efficacy of quince leaves in heart function. The potential for prophylactic and therapeutic effects of quince leaves in reducing cardiovascular disease is discussed based on its beneficial constituents. The review covers the findings from traditional medicines and various actions of effective constituents demonstrated in other investigations including antioxidant, antiatherogenic, anti-inflammation, antihypertensive and vasodilatory effects, which all are in accordance with the hypothesis of a beneficial role of quince in cardiovascular health.

INTRODUCTION Quince (*Cydonia oblonga* Miller), the sole member of the genus *Cydonia* of the Rosaceae family, is a small, deciduous tree, 5–8 m tall and 4–6 m wide, with bright yellow pome-like fruits 7–12 cm long and 6–9 cm broad. The leaves are simple, elliptical, 6–11 cm long with fine white hairs. The white or pink flowers 5 cm across are produced in spring[1]. It is cultivated from prehistoric periods in countries extending from Iran to India[2]. Quince is considered a safe plant and toxicity is only proposed for seeds if they are eaten in large quantities because of their nitrile content. Nitrile is a common agent in seeds of Rosaceae and when hydrolyzed, produces hydrogen cyanide in the body[3]. For the other parts of this plant, especially the leaves, which are our targeted segment, toxicity is not claimed. In various studies the quince fruit is recognized as a source of health-promoting natural compounds, due to its antioxidant, antimicrobial (antibacterial and anti-influenza virus) and anti-ulcerative properties, which are mainly attributed to phenolic compounds[4-9].

Traditional drugs have an important role in drug research, resulting in the discovery of novel agents. In folk medicine, the decoction of quince leaves is used as a treatment for cough, cold, bronchitis, abdominal pain, diarrhea, nervousness, insomnia and dysuria for its sedative, antipyretic, anti-diarrheal and antitussive properties and for the treatment of various skin diseases[10-11]. Also, anti-hemolytic, anti-diabetic and anti-lipoperoxidative effects and the ability to reduce lipid levels have been attributed to quince leaf[12]. The extract of quince leaf also possesses concentration-dependent antiproliferative effects on colon (Caco-2) cancer cell lines[13]. The sugar lowering potency of quince leaves is revealed to be the same as that of standard antidiabetic drugs[10]. In addition, in hypercholesterolemia-induced renal injury, the quince leaf decoction showed probable protective effects which are attributed to both its antioxidants and lipid-lowering characteristics[12]. Recently, an anti-inflammation role of quince extract was reported in a study of colitis and inflammatory bowel disease[14].

The Hypothesis

CARDIOVASCULAR DISEASE Cardiovascular diseases (CVD) contribute a major and increasing health burden in developed countries. Despite huge advances in treatment, traditional medicine is used all over the world and this points to the importance of research in natural compounds used in folk medicine.

Oxidative stress has a central role in the pathogenesis of CVDs and is associated with several pathological states, including atherosclerosis, hypertension, heart failure, stroke, diabetes and inflammation[15-18]. Among the cardiovascular risk factors, it is recognized that high blood pressure, arterial stiffness, atherosclerosis, easy blood clotting and heart inflammation can lead to catastrophic events such as heart attack and stroke. Oxidative stress plays a key role in all of these different pathophysiological processes. Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen and highly reactive due to the presence of unpaired electrons. An increased generation of ROS along with reduction of nitric oxide (NO) amounts causes vascular wall damage and shifting of the cell towards oxidation of DNA, lipids and proteins associated with cell death and cardiac injury[19,20]. In different studies the relation of oxidative stress and various cardiovascular risk factors has been demonstrated (summarized in Table 1). In addition, in Table 2 a list of important cardiovascular diseases related to ROS and oxidative stress is presented briefly.

It has been demonstrated that by means of specific antioxidants, mitochondrial respiration and ROS production can be modulated in a way to protect mitochondria against oxidative stress in CVDs[108]. Antioxidants, by potentiating endothelial nitric oxide levels as well as inhibiting vascular inflammation, lipid peroxidation, platelet aggregation and oxidation of LDL, can also contribute to preventing endothelial dysfunction. Fruits and vegetables are one of the main sources of antioxidants in our diets[109,110]. Various studies have recognized that there is a clear affiliation between intake of these beneficial agents and reduced rate of heart disease, different cancers and other degenerative diseases[5]. This affiliation is often attributed to the antioxidant compounds present in these natural agents, primarily to phenolic compounds such as phenolic acids and flavonoids[6]. With antioxidant properties of these agents, the cells would be capable of scavenging free radicals and surviving destructive injuries.

Costa et al.[111] studied the phenolic profile of quince and compared the antioxidant potential of quince leaf with that of green tea (*Camellia sinensis*). Their results point out that quince leaf may have applications as a preventive or therapeutic agent in diseases in which free radicals are involved and according to this point, the antihemolytic activities of the quince leaf also have been confirmed[111,112]. Among different parts of the plant *C. oblonga*, the total phenolic content of leaves was reported as much higher than that found in pulps, peels and seeds, which may indicate that the leaves of the tree can be much more interesting in terms of health-promoting constituents[113].

CONSTITUENTS AND BIOACTIVITY As a source of phenolic compounds, especially flavonoids, which are considered potent

RISK FACTORS OF CARDIOVASCULAR DISEASE	EXISTING EVIDENCE OF ASSOCIATION OF OXIDATIVE STRESS AND CARDIOVASCULAR RISK FACTORS			
Atherosclerosis	"…increased free radical production and impaired antioxidant protection are relevant to plaque activation"[21]. "Increased levels of O_2^- generation and attenuated NO mediated responses [have been] demonstrated in cholesterol-fed rabbits"[22,23].	"Chronic and acute overproduction of reactive oxygen species (ROS) form an integral part of the development of cardiovascular diseases (CVD), and in particular atherosclerosis"[24]. O_2^-levels are raised in WHHL (Watanabe heritable hyperlipidemic) rabbits[25].	Mitochondrial dysfunction and increased ROS production has been shown to associate with early atherosclerotic lesion formation[26]. Free oxygen radicals increase adhesion molecule expression in endothelial cells[27]. In monkeys with atherosclerosis, disease severity is related to O_2^- levels[28].	"ROS trigger extracellular matrix remodeling through regulation of collagen resorption, resulting in compromised plaque stability"[27,29]. "…antioxidant therapy has been shown to exert beneficial effects in hypertension, atherosclerosis, ischemic heart disease, cardiomyopathies and congestive heart failure"[30].
Smoking	"…atherogenic effects of smoking are mediated in part by free radical damage to lipids and possible breakdown of antioxidant status in cigarette smoking"[21].	"Cigarette smoke exposure increases oxidative stress as a potential mechanism for initiating cardiovascular dysfunction"[31,32].	"…smoking led to blunted hypertension, endothelial dysfunction, leukocyte activation with ROS generation, decreased NO bioavailability and mild cardiac hypertrophy in mice…"[33].	"…endothelial dysfunction in chronic smokers is at least in part mediated by enhanced formation of oxygen-derived free radicals"[34].

Table 1 | Existing evidence of association of oxidative stress and cardiovascular risk factors

RISK FACTORS OF CARDIOVASCULAR DISEASE	EXISTING EVIDENCE OF ASSOCIATION OF OXIDATIVE STRESS AND CARDIOVASCULAR RISK FACTORS			
Endothelial dysfunction	"…endothelial dysfunction correlates with increased local ROS production and reduced superoxide dismutase activity"[34].	Atherosclerosis and lipid peroxidation in coronary arteries even at early stages are associated with evidence of endothelium dysfunction[35].	"…free radical stress can lead to cardiovascular disease by influencing the endothelial function"[36].	"Supplementation of antioxidant superoxide dismutase has been shown to improve endothelium dependent vasodilatation of coronary arteries"[37].
Hypertension	Increasing levels of oxidative stress by glutathione depletion can cause hypertension[38]. "Oxidative stress may play a significant role in the development of arterial stiffness" and remodeling in hypertensive subjects[39]. Hypertension is associated with increased vascular oxidative stress in a number of animal models of hypertension[40].	Increased ROS production is seen in patients with essential hypertension, renovascular hypertension, malignant hypertension and pre-eclampsia[41-44]. "In hypertension, lipid peroxidation by-products have been shown to be elevated, whereas levels/activity of anti-oxidant systems has been reported to be decreased"[45,46].	Several studies have shown an increase in O_2^- levels in hypertension[47,48]. "…classical antihypertensive agents such as ß-adrenergic blockers (Carvedilol), ACE inhibitors, AT_1 receptor antagonists, and Ca_2^+ channel blockers may be mediated, in part, by decreasing vascular oxidative stress"[49-51].	"…many of the adverse effects of hypertension on endothelial function may be reversed by intra-arterial infusion of anti-oxidants, such as vitamin C"[52]. Consistent with increased ROS production being a key feature of hypertension, treatment with antioxidants and SOD mimetics, attenuated endothelial dysfunction and lowered blood pressure[53,54].
Diabetes	A role for ROS in the endothelial dysfunction associated with diabetes was proposed in the early 1990s[55]. As a consequence of the overproduction of ROS, diabetes is related to oxidative stress[56].	"Hyperglycemia induces the overproduction of oxygen free radicals and consequently increases the protein oxidation and lipid oxidation;" thereby therapeutic interventions with antioxidants will be efficient[57]. People with diabetes have decreased levels of antioxidants[58-60]. Normalizing mitochondrial O_2^- has been shown to block pathways involved in hyperglycemic damage[61].	"…oxidative status and nitric oxide metabolism are affected in type II DM patients"[62] "…there is reduced antioxidative defense in type 2 diabetics with prominent cardiovascular complications"[63]. "Many biochemical pathways strictly associated with hyperglycemia can increase the production of free radicals"[64-66].	"Free radical reactions and non-enzymatic glycosylation may play important roles not only in the development of diabetes but also in its complications"[67]. "…chronic hyperglycemia can influence the generation of free radicals, which may lead ultimately to increased lipid peroxidation and depletion of antioxidants"[68].
Hyperhomocysteinaemia	"Patients with hyperhomocysteinaemia exhibit endothelial dysfunction and elevated oxidative stress"[69,70].	Hyperhomocysteinemia causes reduction of NO bioavailability through the generation of superoxide[71,72].	One of the primary causes of cardiovascular alterations characteristic of hyperhomocysteinemia is its oxidative stress production[73].	"Acute hyperhomocysteinemia impairs endothelial function and increases arterial stiffness"[74].

Table 1 | Existing evidence of association of oxidative stress and cardiovascular risk factors (con't)

CARDIOVASCULAR DISEASE	EXISTING EVIDENCE OF ASSOCIATION OF OXIDATIVE STRESS AND CARDIOVASCULAR DISEASE			
Myocardial infarction and cardiac ischemia-reperfusion	Reactive oxygen species (ROS) may play important roles in the pathogenesis in myocardial infarction[75]. Evidence showed an imbalance between oxidant and antioxidant molecules in acute myocardial infarction (AMI)[76]. Increased production of ROS, decreased endothelium-dependent relaxation and NO bio-availability have been observed in the vasculature of rats after myocardial infarction[77,78].	Significant increase in malondialdehyde and conjugated dienes in patients with acute myocardial infarction was observed[79]. "In addition to the decrease of nonenzymatic antioxidant defenses, the increase in oxidative stress was probably a result of the elevation in ROS production due to the ischemic/reperfusion event of AMI"[80].	"Blood sample from patients with ischemic heart disease has been shown to contain evidence of oxidative stress"[81]. "In myocardial ischemia, hypoxia and re-oxygenation induces an increase in free radical production in cardiac tissues [which cause] reperfusion injury" and inflammation[82]. "Oxidative stress contributes critically to the pathogenesis of ischemia-reperfusion injury"[83].	"Myocardial ischemia/reperfusion promotes excess generation of highly ROS and causes oxidative stress"[84]. "A consequence of ischemia-reperfusion is mitochondrial oxidative stress…harbingers to the activation of cell death apoptotic pathways"[85]. "…increased oxidative stress, which oxidizes biological macromolecules and impairs cell functions, is a major pathogenic factor in MI/R injury"[86].
Cardiac hypertrophy, cardiomyopathy & heart failure	"Increase in ROS is responsible for impaired endothelial regulation of left ventricular relaxation observed in moderate pressure overload left ventricular hypertrophy"[87,88]. "Myocardial remodeling in congestive heart failure has been attributed to ROS production by the mitochondrial, xanthine oxidase, nitric oxide synthetase and NADPH oxidase pathways"[89,90]. "ROS activate a broad variety of hypertrophy signaling kinases and transcription factors"[91]. "ROS have potent effects on the extracellular matrix, stimulating cardiac fibroblast proliferation"[92].	"Investigations aimed at prevention of hypertrophy should address reduction of oxidative stress"[93]. "Treatment with the antioxidant vitamin C produced a significant inhibition of oxidative stress, an improvement in endothelial function, and a reduction of cardiac hypertrophy"[94]. "More specific targeting of the source of oxidative stress, such as recoupling of NOS or enhancing intrinsic antioxidants, may ultimately provide more effective approaches to reversing cardiac remodeling"[95]. "[O_2^-] contributes to impaired endothelium-dependent relaxation in coronary arteries of…cardiomyopathic hamsters"[96].	"The level of oxidative stress significantly increased and was positively correlated with the degree of myocardial damage in patients with cardiomyopathy"[97]. Hyperhomocysteinemia (HCM) is characterized by enhanced oxidative stress[98]. "Oxidative stress was elevated in myocardia of [hypertrophic cardiomyopathy] patients and the levels were correlated with left ventricular dilatation and systolic dysfunction"[99]. "…supplementation with antioxidants in the treatment of idiopathic dilated cardiomyopathy (IDC) may be helpful to these patients"[100].	"…heart failure under acute as well as chronic conditions is associated with reduced antioxidant reserve and increased oxidative stress"[101,102]. "…oxidative stress contributes to the exaggerated muscle reflex in heart failure"[103]. "Level and activity of xanthine oxygenase [an important cardiovascular source of ROS] increased in heart failure"[104]. Levels of ROS are elevated in heart failure and cardiac protection is observed with antioxidant treatment [105-107].

Table 2 | Existing evidence of association of oxidative stress and cardiovascular disease

antioxidants, *Cydonia* species are excellent low-cost natural health promoting compounds[6,11,113,114]. Various studies were performed to evaluate phenolic compounds and organic acids of quince[115-117]. For example, the influence of jam processing upon the contents of these constituents of quince fruit was assessed and the antioxidant activity of the methanolic extracts of quince jam was reported[6,118].

The most abundant compound in quince leaves is 5-*O*-caffeoylquinic acid (neochlorogenic acid or 5-CQA), followed by quercetin-3-O-rutinoside[119]. 5-CQA, a major antioxidant in quince leaves, is an isomer of chlorogenic acid, which refers to a family of esters of hydroxycinnamic acids (caffeic acid, ferulic acid and p-coumaric acid) with quinic acid. These agents are classified in phenol groups with the property of inhibiting excessive production of ROS in vessels and thereby decreasing oxidative stress and improving nitric oxide bioavailability, leading to attenuation of endothelial dysfunction, hypertension and vascular hypertrophy[120,121]. As well as antioxidant activity, strong anti-inflammatory effects which can inhibit edema, inflammation, neutrophil migration and TNF-α expression are reported[122]. In a study of the effects of coffee consumption, it is documented that biological effects such as antioxidation, antimutation, anticarcinogenesis, antibiotic, antihypercholesterolemia, antihypertension and anti-inflammatory actions are due to relatively large amounts of chlorogenic acid in this useful beverage[123]. Therefore, it is possible that all or at least some of these beneficial effects of chlorogenic acid can also be demonstrated in quince.

Astragalin (kaempferol-3-O-glucoside) and quercetin, which belong to flavonoid groups, are the other beneficial constituents of quince leaf. In comparison with other parts of quince, the leaves presented the highest relative contents of kaempferol derivatives, especially of kaempferol-3-O-rutinoside, which represented 12.5% of the total phenolic content[119]. But these contents are variable according to geographical origin and collection month, especially the 3-O-caffeoylquinic and 3,5-O-dicaffeoylquinic acid contents, which indicates a possible use of them as markers of samples with different geographical origins and/or physiological maturities[113].

In various studies of flavonoids, antiallergic, anti-inflammatory[124], anti-microbial[125,126], anti-cancer[127], anti-diarrheal[128] and antioxidant activities[129] of this major class of phytochemicals were demonstrated[130]. Several epidemiological studies have examined the relationship between flavonoids and heart disease[131,132]. An inverse correlation between dietary flavonoid intake and the incidence of coronary artery disease (CAD) in elderly men has been shown by Hertog et al.[133]. Dietary flavonoids, mainly quercetin, were inversely associated with stroke incidence and the claimed reasons for this effect were the possibility of storing certain flavonoids in blood vessels and exertion of their antiatherogenic effects[133]. In a study of the mechanism of antiatherogenic effects of quercetin and phenolic compounds of red wine, impairing of copper ion-catalyzed oxidation of LDL was demonstrated[134]. Vasodilatory effects of flavonoids also have been shown[135]. The potential utility of flavonoids as a means of enhancing myocardial ischemic tolerance or resistance to reperfusion injury by diminishing detrimental ROS production was also reported[136]. Flavonoids constitute a more stable form of free radicals with lower toxicity. Besides, they can chelate Fe^{2+} and prohibit the effects of free radicals[130]. A protective effect of quercetin by its preventive effect on the decrease of xanthine dehydrogenase/oxidase ratio was observed during ischemia-reperfusion in the rat[137]. The enzyme xanthine oxidase is formed from dehydrogenase and is a source of ROS in oxidative tissue injury[138]. The inhibition of xanthine oxidase activity by flavonoids has been described[139]. By antioxidant activity, flavonoids could be important in protecting LDL from oxidation, thus reducing their atherogenicity. In a Japanese study an inverse correlation between flavonoid intake and total plasma cholesterol concentration was reported[140]. Thereby, flavonoids could potentially influence disease states in which lipid peroxidation products are involved, especially vascular disorders and coronary artery disease. Considering the relevance of inflammatory process and

ORGANIC ACID PROFILE	PHENOLIC PROFILE
Oxalic acid	*3*-O-caffeoylquinic acid
Citric acid*	4-O-caffeoylquinic acid
Malic acid	5-O-caffeoylquinic acid*
Quinic acid*	3,5-O-dicaffeoylquinic acid
Shikimic acid	quercetin-3-Ogalactoside
Fumaric acids	quercetin-3-O-rutinoside*
	kaempferol-3-O-glycoside
*Quinic acid was the major compound (72.2%), followed by citric acid (13.6%).	kaempferol-3-O-glucoside
	kaempferol-3-O-rutinoside
	*5-O-caffeoylquinic acid was the major phenolic compound (36.2%), followed by quercetin 3-O-rutinoside (21.1%).

Table 3 | Antioxidant profile of *Cydonia oblonga*

cardiovascular disease, the ability of flavonoids in modulation of inflammation by inhibitory effect on mast cells, T cells, B cells, interferons, NK cells, basophils and neutrophils provides protective evidence in cardiovascular disease treatment[141,142].

The organic acids, which are primary compounds found in great amounts in all plants, may also have a protective role against various diseases due to their antioxidant properties (Table 3). Citric, malic and tartaric acids are commonly found in fruits, while oxalic acid is present in higher amounts in green leaves. Quince leaves contain an organic acid profile composed of six constituents: oxalic, citric, malic, quinic, shikimic and fumaric acids. These structures behave as antioxidants because they also have the ability to chelate metals[6,11,143].

CONCLUSION In conclusion, the possible efficacy of phenols, flavonoids and other constituents of quince as protective agents in CVD is described. This protective ability could arise by influencing several processes, such as 1) antioxidant action and inhibitory effect on xanthine oxidase and ability to chelate metals, 2) enhancing myocardial ischemic tolerance to reperfusion injury, 3) decrease in LDL oxidation by antioxidant property and increase in HDL levels, mainly due to flavonoids, 4) antiatherogenic effects in vessels, 5) improving nitric oxide bioavailability and attenuation of endothelial dysfunction, hypertension and vascular hypertrophy by vasodilatory effects and 6) reduction of cardiac mast cell mediator release and decrease in cardiovascular inflammation. Traditional natural compounds have an important role in drug research, and may result in the discovery of novel molecules. Therefore more study is needed in this context to demonstrate each possible effective pathway in quince. In other natural compounds like honey and grape seed, the cardioprotective effects were attributed to various available polyphenols and flavonoids in these agents[144,145]. These findings suggest a novel path in quince research to study these compounds further. To evaluate the validity of our hypothesis, we propose the use of isolated rat hearts to assess cardiac function in the presence of different doses of the extract.

Finally, this study suggests that leaves from *C. oblonga* can be used as a great natural and cheap source of bioactive compounds with primary antioxidative properties along with other mechanisms of action. By modulating various cardiovascular risk factors such as atherosclerosis, smoking, endothelial dysfunction, hypertension, diabetes and hyperhomocysteinaemia, quince leaf extract may have relevance in the prevention and treatment of different pathological states of ischemic, inflammatory and hypertrophic heart disease.**H**

ACKNOWLEDGEMENTS The authors thank the Faculty of Pharmacy of Tabriz University of Medical Sciences, Tabriz, Iran.

CONFLICTS OF INTEREST Authors declare no conflicts of interest.

ABOUT THE AUTHORS Haleh Vaez is a pharmacist who received a PharmD degree in 2011 from Tabriz Medical University and now is educating in pharmacology at the PhD level and studying different natural extractions' effects on the heart using an isolated heart system.

Samin Hamidi is studying medicinal chemistry at the PhD level and concentrates on the chemistry of various constituents of natural extracts.

Sanam Arami is a pharmacist and received a PharmD degree in 2009 from Tabriz Medical University and now is educating in biotechnology at the PhD level and studying the development of new drugs.

REFERENCES

1 Gholgholab H. Ghiah (in Farsi). Tehran: Tehran University Press; 1961.

2 Yildirim A, Oktay M, Bulaloulu V. The Antioxidant Activity of the Leaves of *Cydonia vulgaris*. Turk J Med Sci. 2001;31:23-27.

3 Huxley A, Griffiths M, Levy M, editors. The new RHS dictionary of gardening. London: Grove's Dictionaries; Paper and slipcase edition 1999.

4 Osman AGM, Koutb M, Sayed AE-DH. Use of hematological parameters to assess the efficiency of quince (*Cydonia oblonga* Miller) leaf extract in alleviation of the effect of ultraviolet–A radiation on African catfish *Clarias gariepinus* (Burchell, 1822). J Photochem Photobiol B. 2010;99:1-8.
http://dx.doi.org/10.1016/j.jphotobiol.2010.01.002

5 Fattouch S, Caboni P, Coroneo V, Tuberoso CI, Angioni A, Dessi S, et al. Antimicrobial activity of Tunisian quince (*Cydonia oblonga* Miller) pulp and peel polyphenolic extracts. J Agric Food Chem. 2007;55:963-969.
http://dx.doi.org/10.1021/jf062614e

6 Silva BM, Andrade PB, Valentao P, Ferreres F, Seabra RM, Ferreira MA. Quince (*Cydonia oblonga* Miller) fruit (pulp, peel, and seed) and Jam: antioxidant activity. J Agric Food Chem. 2004;52:4705-4712.
http://dx.doi.org/10.1021/jf040057v

7 Hamauzu Y, Yasui H, Inno T, Kume C, Omanyuda M. Phenolic profile, antioxidant property, and anti-influenza viral activity of Chinese quince (*Pseudocydonia sinensis* Schneid.), quince (*Cydonia oblonga* Mill.), and apple (*Malus domestica* Mill.) fruits. J Agric Food Chem. 2005;53:928-934.
http://dx.doi.org/10.1021/jf0494635

8 Hamauzu Y, Inno T, Kume C, Irie M, Hiramatsu K. Antioxidant and antiulcerative properties of phenolics from Chinese quince, quince, and apple fruits. J Agric Food Chem. 2006;54:765-772.
http://dx.doi.org/10.1021/jf052236y

9 Wang X, Jia W, Zhao A. Anti-influenza agents from plants and traditional Chinese medicine. Phytother Res. 2006;20:335-341.
http://dx.doi.org/10.1002/ptr.1892

10 Aslan M, Orhan N, Orhan DD, Ergun F. Hypoglycemic activity and antioxidant potential of some medicinal plants traditionally used in Turkey for diabetes. J Ethnopharmacol. 2010;128:384-389.
http://dx.doi.org/10.1016/j.jep.2010.01.040

11 Oliveira AP, Pereira JA, Andrade PB, Valentao P, Seabra RM, Silva BM. Organic acids composition of *Cydonia oblonga* Miller leaf. Food Chem 2008;111:393-399.
http://dx.doi.org/10.1016/j.foodchem.2008.04.004

12 Jouyban A, Shoja MM, Ardalan MR, Khoubnasabjafari M, Sadighi A, Tubbs RS, et al. The effect of quince leaf decoction on renal injury induced by hypercholesterolemia in rabbits: A pilot study. J Med Plants Res. 2011;5:5291-5295.

13 Carvalho M, Silva BM, Silva R, Valentao P, Andrade PB, Bastos ML. First report on *Cydonia oblonga* Miller anticancer potential: differential antiproliferative effect against human kidney and colon cancer cells. J Agric Food Chem. 2010;58:3366-3370.
http://dx.doi.org/10.1021/jf903836k

14 Minaiyan M, Ghannadi A, Etemad M, Mahzouni P. A study of the effects of *Cydonia oblonga* Miller (Quince) on TNBS-induced ulcerative colitis in rats. Res Pharm Sci. 2012;7:103-110.

15 Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: Part II: animal and human studies. Circulation. 2003;108:2034-2040.

http://dx.doi.org/10.1161/01.CIR.0000093661.90582.c4

16 Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol. 2005;25:29-38.

17 Mueller CF, Laude K, McNally JS, Harrison DG. ATVB in focus: redox mechanisms in blood vessels. Arterioscler Thromb Vasc Biol. 2005;25:274-278.
http://dx.doi.org/10.1161/01.ATV.0000149143.04821.eb

18 Pashkow FJ. Oxidative Stress and Inflammation in Heart Disease: Do Antioxidants Have a Role in Treatment and/or Prevention? Int J Inflam. 2011;2011:514623.

19 Lee R, Margaritis M, Channon KM, Antoniades C. Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. Curr Med Chem. 2012;19:2504-2520.
http://dx.doi.org/10.2174/092986712800493057

20 Channon KM, Guzik TJ. Mechanisms of superoxide production in human blood vessels: relationship to endothelial dysfunction, clinical and genetic risk factors. J Physiol Pharmacol. 2002;53:515-524.

21 Pasupathi P, Rao Y, Farook J, Saravanan G, Bakthavathsalam G. Oxidative Stress and Cardiac Biomarkers in Patients with Acute Myocardial Infarction. Eur J Sci Res. 2009;27:275-285.

22 Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. J Clin Invest. 1993; 91: 2546-2551.
http://dx.doi.org/10.1172/JCI116491

23 Mugge A, Brandes RP, Boger RH, Dwenger A, Bode-Boger S, Kienke S, et al. Vascular release of superoxide radicals is enhanced in hypercholesterolemic rabbits. J Cardiovasc Pharmacol. 1994;24:994-998.
http://dx.doi.org/10.1097/00005344-199424060-00019

24 Victor VM, Apostolova N, Herance R, Hernandez-Mijares A, Rocha M. Oxidative stress and mitochondrial dysfunction in atherosclerosis: mitochondria-targeted antioxidants as potential therapy. Curr Med Chem. 2009;16:4654-4667.
http://dx.doi.org/10.2174/092986709789878265

25 Miller FJ, Jr., Gutterman DD, Rios CD, Heistad DD, Davidson BL. Superoxide production in vascular smooth muscle contributes to oxidative stress and impaired relaxation in atherosclerosis. Circ Res. 1998;82:1298-1305.
http://dx.doi.org/10.1161/01.RES.82.12.1298

26 Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res. 2000;86:494-501.
http://dx.doi.org/10.1161/01.RES.86.5.494

27 Heymes C, Bendall JK, Ratajczak P, Cave AC, Samuel JL, Hasenfuss G, et al. Increased myocardial NADPH oxidase activity in human heart failure. J Am Coll Cardiol. 2003;41:2164-2171.
http://dx.doi.org/10.1016/S0735-1097(03)00471-6

28 Hathaway CA, Heistad DD, Piegors DJ, Miller FJ, Jr. Regression of atherosclerosis in monkeys reduces vascular superoxide levels. Circ Res. 2002;90:277-283.
http://dx.doi.org/10.1161/hh0302.104724

29 Maytin M, Siwik DA, Ito M, Xiao L, Sawyer DB, Liao R, et al. Pressure overload-induced myocardial hypertrophy in mice does not require gp91phox. Circulation. 2004;109:1168-1171.
http://dx.doi.org/10.1161/01.CIR.0000117229.60628.2F

30 Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens. 2000;18:655-673.
http://dx.doi.org/10.1097/00004872-200018060-00002

31 Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43:1731-1737.
http://dx.doi.org/10.1016/j.jacc.2003.12.047

32 Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis. 2003;46:91-111.
http://dx.doi.org/10.1016/S0033-0620(03)00087-2

33 Talukder MA, Johnson WM, Varadharaj S, Lian J, Kearns PN, El-Mahdy MA, et al. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. Am J Physiol Heart Circ Physiol. 2011;300:H388-396.
http://dx.doi.org/10.1152/ajpheart.00868.2010

34 Heitzer T, Just H, Munzel T. Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. Circulation. 1996;94:6-9.
http://dx.doi.org/10.1161/01.CIR.94.1.6

35 Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation. 1993;88:2149-2155.
http://dx.doi.org/10.1161/01.CIR.88.5.2149

36 Wilson SH, Best PJ, Edwards WD, Holmes DR, Jr., Carlson PJ, Celermajer DS, et al. Nuclear factor-kappaB immunoreactivity is present in human coronary plaque and enhanced in patients with unstable angina pectoris. Atherosclerosis. 2002;160:147-153.
http://dx.doi.org/10.1016/S0021-9150(01)00546-9

37 Nisoli E, Tonello C, Cardile A, Cozzi V, Bracale R, Tedesco L, et al. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science. 2005;310:314-317.
http://dx.doi.org/10.1126/science.1117728

38 Vaziri ND, Wang XQ, Oveisi F, Rad B. Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats. Hypertension. 2000;36:142-146.
http://dx.doi.org/10.1161/01.HYP.36.1.142

39 Klima L, Kawecka-Jaszcz K, Stolarz-Skrzypek K, Menne J, Fijorek K, Olszanecka A, et al. Structure and function of large arteries in hypertension in relation to oxidative stress markers. Kardiol Pol. 2013;71:917-923.
http://dx.doi.org/10.5603/KP.2013.0226

40 Zeiher AM, Schachlinger V, Hohnloser SH, Saurbier B, Just H. Coronary atherosclerotic wall thickening and vascular reactivity in humans. Elevated high-density lipoprotein levels ameliorate abnormal vasoconstriction in early atherosclerosis. Circulation. 1994;89:2525-2532.
http://dx.doi.org/10.1161/01.CIR.89.6.2525

41 Zheng JS, Yang XQ, Lookingland KJ, Fink GD, Hesslinger C, Kapatos G, et al. Gene transfer of human guanosine 5'-triphosphate cyclohydrolase I restores vascular tetrahydrobiopterin level and endothelial function in low renin hypertension. Circulation. 2003;108:1238-1245.
http://dx.doi.org/10.1161/01.CIR.0000089082.40285.C3

42 Higashi Y, Sasaki S, Nakagawa K, Matsuura H, Oshima T, Chayama K. Endothelial function and oxidative stress in renovascular hypertension. N Engl J Med. 2002;346:1954-1962.
http://dx.doi.org/10.1056/NEJMoa013591

43 Lip GY, Edmunds E, Nuttall SL, Landray MJ, Blann AD, Beevers DG. Oxidative stress in malignant and non-malignant phase hypertension. J Hum Hypertens. 2002;16:333-336.
http://dx.doi.org/10.1038/sj.jhh.1001386

44 Lee VM, Quinn PA, Jennings SC, Ng LL. Neutrophil activation and production of reactive oxygen species in pre-eclampsia. J Hypertens. 2003;21:395-402.
http://dx.doi.org/10.1097/00004872-200302000-00032

45 Koska J, Syrova D, Blazicek P, Marko M, Grna JD, Kvetnansky R, et al. Malondialdehyde, lipofuscin and activity of antioxidant enzymes during physical exercise in patients with essential hypertension. J Hypertens. 1999;17:529-535.
http://dx.doi.org/10.1097/00004872-199917040-00011

46 Yasunari K, Maeda K, Nakamura M, Yoshikawa J. Oxidative stress in leukocytes is a possible link between blood pressure, blood glucose, and C-reacting protein. Hypertension. 2002;39:777-780.
http://dx.doi.org/10.1161/hy0302.104670

47 Lacy F, O'Connor DT, Schmid-Schonbein GW. Plasma hydrogen peroxide production in hypertensives and normotensive subjects at genetic risk of hypertension. J Hypertens. 1998;16:291-303.
http://dx.doi.org/10.1097/00004872-199816030-00006

48 Mehta JL, Lopez LM, Chen L, Cox OE. Alterations in nitric oxide synthase activity, superoxide anion generation, and platelet aggregation in systemic hypertension, and effects of celiprolol. Am J Cardiol. 1994;74:901-905.
http://dx.doi.org/10.1016/0002-9149(94)90583-5

49 Ghiadoni L, Magagna A, Versari D, Kardasz I, Huang Y, Taddei S, et al. Different effect of antihypertensive drugs on conduit artery endothelial function. Hypertension. 2003;41:1281-1286.
http://dx.doi.org/10.1161/01.HYP.0000070956.57418.22

50 Yoshida J, Yamamoto K, Mano T, Sakata Y, Nishikawa N, Nishio M, et al. AT1 receptor blocker added to ACE inhibitor provides benefits at advanced stage of hypertensive diastolic heart failure. Hypertension. 2004;43:686-691.
http://dx.doi.org/10.1161/01.HYP.0000118017.02160.fa

51 Paravicini TM, Touyz RM. NADPH oxidases, reactive oxygen species, and hypertension: clinical implications and therapeutic possibilities. Diabetes Care. 2008;31 Suppl 2:S170-180.
http://dx.doi.org/10.2337/dc08-s247

52 Taddei S, Virdis A, Ghiadoni L, Magagna A, Salvetti A. Vitamin C improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential hypertension. Circulation. 1998;97:2222-2229.
http://dx.doi.org/10.1161/01.CIR.97.22.2222

53 Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci U S A. 1991;88:10045-10048.
http://dx.doi.org/10.1073/pnas.88.22.10045

54 Schnackenberg CG, Wilcox CS. Two-week administration of tempol attenuates both hypertension and renal excretion of 8-Iso prostaglandin f2alpha. Hypertension. 1999;33:424-428.
http://dx.doi.org/10.1161/01.HYP.33.1.424

55 Langenstroer P, Pieper GM. Regulation of spontaneous EDRF release in diabetic rat aorta by oxygen free radicals. Am J Physiol. 1992;263:H257-265.

56 Victor VM, Rocha M, Herance R, Hernandez-Mijares A. Oxidative stress and mitochondrial dysfunction in type 2 diabetes. Curr Pharm Des. 2011;17:3947-3958.
http://dx.doi.org/10.2174/138161211798764915

57 Ramakrishna V, Jailkhani R. Evaluation of oxidative stress in Insulin Dependent Diabetes Mellitus (IDDM) patients. Diagn Pathol. 2007;2:22.
http://dx.doi.org/10.1186/1746-1596-2-22

58 Polidori MC, Mecocci P, Stahl W, Parente B, Cecchetti R, Cherubini A, et al. Plasma levels of lipophilic antioxidants in very old patients with type 2 diabetes. Diabetes Metab Res Rev. 2000;16:15-19.
http://dx.doi.org/10.1002/(SICI)1520-7560(200001/02)16:1<15::AID-DMRR71>3.0.CO;2-B

59 Martin-Gallan P, Carrascosa A, Gussinye M, Dominguez C. Estimation of lipoperoxidative damage and antioxidant status in diabetic children: relationship with individual antioxidants. Free Radic Res. 2005;39:933-942.
http://dx.doi.org/10.1080/10715760500156751

60 Quilliot D, Walters E, Bonte JP, Fruchart JC, Duriez P, Ziegler O. Diabetes mellitus worsens antioxidant status in patients with chronic pancreatitis. Am J Clin Nutr. 2005;81:1117-1125.

61 Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 2000;404:787-790.
http://dx.doi.org/10.1038/35008121

62 Aydin A, Orhan H, Sayal A, Ozata M, Sahin G, Isimer A. Oxidative stress and nitric oxide related parameters in type II diabetes mellitus: effects of glycemic control. Clin Biochem. 2001;34:65-70.
http://dx.doi.org/10.1016/S0009-9120(00)00199-5

63 Colak E, Majkic-Singh N, Stankovic S, Sreckovic-Dimitrijevic V, Djordjevic PB, Lalic K, et al. Parameters of antioxidative defense in type 2 diabetic patients with cardiovascular complications. Ann Med. 2005;37:613-620.
http://dx.doi.org/10.1080/07853890500330193

64 Abou-Seif MA, Youssef AA. Oxidative stress and male IGF-1, gonadotropin and related hormones in diabetic patients. Clin Chem Lab Med. 2001; 39:618-623.
http://dx.doi.org/10.1515/CCLM.2001.099

65 Matkovics B, Kotorman M, Varga IS, Hai DQ, Roman F, Novak Z. Pro-, antioxidant and filtration changes in the blood of type 1 diabetic patients. Acta Physiol Hung. 1997;85:99-106.

66 Ruiz C, Alegria A, Barbera R, Farre R, Lagarda MJ. Lipid peroxidation and antioxidant enzyme activities in patients with type 1 diabetes mellitus. Scand J Clin Lab Invest. 1999;59:99-105.
http://dx.doi.org/10.1080/00365519950185823

67 Hayakawa M, Kuzuya F. [Free radicals and diabetes mellitus]. Nihon Ronen Igakkai Zasshi. 1990;27:149-154. Japanese.

68 Whiting PH, Kalansooriya A, Holbrook I, Haddad F, Jennings PE. The relationship between chronic glycaemic control and oxidative stress in type 2 diabetes mellitus. Br J Biomed Sci. 2008;65:71-74.

69 Kanani PM, Sinkey CA, Browning RL, Allaman M, Knapp HR, Haynes WG. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocyst(e)inemia in humans. Circulation. 1999;100:1161-1168.
http://dx.doi.org/10.1161/01.CIR.100.11.1161

70 Lee I, Lee H, Kim JM, Chae EH, Kim SJ, Chang N. Short-term hyperhomocysteinemia-induced oxidative stress activates retinal glial cells and increases vascular endothelial growth factor expression in rat retina. Biosci Biotechnol Biochem. 2007;71:1203-1210.
http://dx.doi.org/10.1271/bbb.60657

71 Suematsu N, Ojaimi C, Kinugawa S, Wang Z, Xu X, Koller A, et al. Hyperhomocysteinemia alters cardiac substrate metabolism by impairing nitric oxide bioavailability through oxidative stress. Circulation. 2007;115:255-262.
http://dx.doi.org/10.1161/CIRCULATIONAHA.106.652693

72 Becker JS, Adler A, Schneeberger A, Huang H, Wang Z, Walsh E, et al. Hyperhomocysteinemia, a cardiac metabolic disease: role of nitric oxide and the p22phox subunit of NADPH oxidase. Circulation. 2005;111:2112-2118.
http://dx.doi.org/10.1161/01.CIR.0000162506.61443.15

73 Kolling J, Scherer EB, da Cunha AA, da Cunha MJ, Wyse AT. Homocysteine induces oxidative-nitrative stress in heart of rats: prevention by folic acid. Cardiovasc Toxicol. 2011;11:67-73.
http://dx.doi.org/10.1007/s12012-010-9094-7

74 Doupis J, Eleftheriadou I, Kokkinos A, Perrea D, Pavlatos S, Gonis A, et al. Acute hyperhomocysteinemia impairs endothelium function in subjects with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes. 2010;118:453-458.
http://dx.doi.org/10.1055/s-0030-1248290

75 Loeper J, Goy J, Rozensztajn L, Bedu O, Moisson P. Lipid peroxidation and protective enzymes during myocardial infarction. Clin Chim Acta. 1991;196:119-125.
http://dx.doi.org/10.1016/0009-8981(91)90064-J

76 Elahi MM, Kong YX, Matata BM. Oxidative stress as a mediator of cardiovascular disease. Oxid Med Cell Longev. 2009;2:259-269.
http://dx.doi.org/10.4161/oxim.2.5.9441

77 Wiemer G, Itter G, Malinski T, Linz W. Decreased nitric oxide availability in normotensive and hypertensive rats with failing hearts after myocardial infarction. Hypertension. 2001;38:1367-1371.
http://dx.doi.org/10.1161/hy1101.096115

78 Bauersachs J, Bouloumie A, Fraccarollo D, Hu K, Busse R, Ertl G. Endothelial dysfunction in chronic myocardial infarction despite increased vascular endothelial nitric oxide synthase and soluble guanylate cyclase expression: role of enhanced vascular superoxide production. Circulation. 1999;100:292-298.
http://dx.doi.org/10.1161/01.CIR.100.3.292

79 Kumar A, Sivakanesan R, Gunasekera S. Oxidative stress and antioxidant status in normolipidemic AMI patients. Indian J Clin Biochem. 2008;23:296-298.

80 Bagatini MD, Martins CC, Battisti V, Gasparetto D, da Rosa CS, Spanevello RM, et al. Oxidative stress

versus antioxidant defenses in patients with acute myocardial infarction. Heart Vessels. 2011;26:55-63. http://dx.doi.org/10.1007/s00380-010-0029-9
81 Ross R. Atherosclerosis–an inflammatory disease. N Engl J Med. 1999;340:115-126. http://dx.doi.org/10.1056/NEJM199901143400207
82 Gutteridge JM, Halliwell B. Free radicals and antioxidants in the year 2000. A historical look to the future. Ann N Y Acad Sci. 2000;899:136-147. http://dx.doi.org/10.1111/j.1749-6632.2000.tb06182.x
83 Daffu G, Del Pozo CH, O'Shea KM, Ananthakrishnan R, Ramasamy R, Schmidt AM. Radical Roles for RAGE in the Pathogenesis of Oxidative Stress in Cardiovascular Diseases and Beyond. Int J Mol Sci. 2013;14:19891-19910. http://dx.doi.org/10.3390/ijms141019891
84 Zweier JL, Talukder MA. The role of oxidants and free radicals in reperfusion injury. Cardiovasc Res. 2006;70:181-190. http://dx.doi.org/10.1016/j.cardiores.2006.02.025
85 Loor G, Kondapalli J, Iwase H, Chandel NS, Waypa GB, Guzy RD, et al. Mitochondrial oxidant stress triggers cell death in simulated ischemia-reperfusion. Biochim Biophys Acta. 2011;1813:1382-1394. http://dx.doi.org/10.1016/j.bbamcr.2010.12.008
86 Ji L, Fu F, Zhang L, Liu W, Cai X, Zhang L, et al. Insulin attenuates myocardial ischemia/reperfusion injury via reducing oxidative/nitrative stress. Am J Physiol Endocrinol Metab. 2010;298:E871-880. http://dx.doi.org/10.1152/ajpendo.00623.2009
87 MacCarthy PA, Grieve DJ, Li JM, Dunster C, Kelly FJ, Shah AM. Impaired endothelial regulation of ventricular relaxation in cardiac hypertrophy: role of reactive oxygen species and NADPH oxidase. Circulation. 2001;104:2967-2974. http://dx.doi.org/10.1161/hc4901.100382
88 MacCarthy PA, Shah AM. Impaired endothelium-dependent regulation of ventricular relaxation in pressure-overload cardiac hypertrophy. Circulation. 2000;101:1854-1860. http://dx.doi.org/10.1161/01.CIR.101.15.1854
89 Cave A, Grieve D, Johar S, Zhang M, Shah AM. NADPH oxidase-derived reactive oxygen species in cardiac pathophysiology. Philos Trans R Soc Lond B Biol Sci. 2005;360:2327-2334. http://dx.doi.org/10.1098/rstb.2005.1772
90 Zhang GX, Lu XM, Kimura S, Nishiyama A. Role of mitochondria in angiotensin II-induced reactive oxygen species and mitogen-activated protein kinase activation. Cardiovasc Res. 2007; 76:204-212. http://dx.doi.org/10.1016/j.cardiores.2007.07.014
91 Sabri A, Hughie HH, Lucchesi PA. Regulation of hypertrophic and apoptotic signaling pathways by reactive oxygen species in cardiac myocytes. Antioxid Redox Signal. 2003;5:731-740. http://dx.doi.org/10.1089/152308603770380034
92 Cheng TH, Cheng PY, Shih NL, Chen IB, Wang DL, Chen JJ. Involvement of reactive oxygen species in angiotensin II-induced endothelin-1 gene expression in rat cardiac fibroblasts. J Am Coll Cardiol. 2003;42:1845-1854. http://dx.doi.org/10.1016/j.jacc.2003.06.010
93 Purushothaman S, Renuka Nair R, Harikrishnan VS, Fernandez AC. Temporal relation of cardiac hypertrophy, oxidative stress, and fatty acid metabolism in spontaneously hypertensive rat. Mol Cell Biochem. 2011;351:59-64. http://dx.doi.org/10.1007/s11010-011-0711-y
94 Bell JP, Mosfer SI, Lang D, Donaldson F, Lewis MJ. Vitamin C and quinapril abrogate LVH and endothelial dysfunction in aortic-banded guinea pigs. Am J Physiol Heart Circ Physiol. 2001;281:H1704-1710.
95 Blau N, Erlandsen H. The metabolic and molecular bases of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. Mol Genet Metab. 2004;82:101-111. http://dx.doi.org/10.1016/j.ymgme.2004.03.006
96 Gutierrez JA, Clark SG, Giulumian AD, Fuchs LC. Superoxide anions contribute to impaired regulation of blood pressure by nitric oxide during the development of cardiomyopathy. J Pharmacol Exp Ther. 1997;282:1643-1649.
97 Pei J, Fu W, Yang L, Zhang Z, Liu Y. Oxidative Stress Is Involved in the Pathogenesis of Keshan Disease (an Endemic Dilated Cardiomyopathy) in China. Oxid Med Cell Longev. 2013;2013:474203. http://dx.doi.org/10.1155/2013/474203
98 Dimitrow PP, Undas A, Wolkow P, Tracz W, Dubiel JS. Enhanced oxidative stress in hypertrophic cardiomyopathy. Pharmacol Rep. 2009;61:491-495. http://dx.doi.org/10.1016/S1734-1140(09)70091-X
99 Nakamura K, Kusano KF, Matsubara H, Nakamura Y, Miura A, Nishii N, et al. Relationship between oxidative stress and systolic dysfunction in patients with hypertrophic cardiomyopathy. J Card Fail. 2005;11:117-123. http://dx.doi.org/10.1016/j.cardfail.2004.05.005
100 Demirbag R, Yilmaz R, Erel O, Gultekin U, Asci D, Elbasan Z. The relationship between potency of oxidative stress and severity of dilated cardiomyopathy. Can J Cardiol. 2005;21:851-855.
101 Singh N, Dhalla AK, Seneviratne C, Singal PK. Oxidative stress and heart failure. Mol Cell Biochem. 1995;147:77-81. http://dx.doi.org/10.1007/BF00944786
102 Nakamura K, Miura D, Matsubara H, Ito H. Oxidative stress and calcium overload in heart failure. Nihon Yakurigaku Zasshi. 2012;140:265-269. http://dx.doi.org/10.1254/fpj.140.265
103 Koba S, Gao Z, Sinoway LI. Oxidative stress and the muscle reflex in heart failure. J Physiol. 2009;587:5227-5237. http://dx.doi.org/10.1113/jphysiol.2009.177071
104 Warnholtz A, Nickenig G, Schulz E, Macharzina R, Brasen JH, Skatchkov M, et al. Increased NADH-oxidase-mediated superoxide production in the early stages of atherosclerosis: evidence for involvement of the renin-angiotensin system. Circulation. 1999;99:2027-2033. http://dx.doi.org/10.1161/01.CIR.99.15.2027
105 Cargnoni A, Ceconi C, Bernocchi P, Boraso A, Parrinello G, Curello S, et al. Reduction of oxidative stress by carvedilol: role in maintenance of ischaemic myocardium viability. Cardiovasc Res. 2000;47:556-566. http://dx.doi.org/10.1016/S0008-6363(00)00082-1
106 Ide T, Tsutsui H, Kinugawa S, Suematsu N, Hayashidani S, Ichikawa K, et al. Direct evidence for increased hydroxyl radicals originating from superoxide in the failing myocardium. Circ Res. 2000;86:152-157. http://dx.doi.org/10.1161/01.RES.86.2.152
107 Lang D, Mosfer SI, Shakesby A, Donaldson F, Lewis MJ. Coronary microvascular endothelial cell redox state in left ventricular hypertrophy: the role of angiotensin II. Circ Res. 2000;86:463-469. http://dx.doi.org/10.1161/01.RES.86.4.463
108 Rocha M, Apostolova N, Hernandez-Mijares A, Herance R, Victor VM. Oxidative stress and endothelial dysfunction in cardiovascular disease: mitochondria-targeted therapeutics. Curr Med Chem. 2010;17:3827-3841. http://dx.doi.org/10.2174/092986710793205444
109 Murcia MA, Jimenez AM, Martinez-Tome M. Evaluation of the antioxidant properties of Mediterranean and tropical fruits compared with common food additives. J Food Prot. 2001;64:2037-2046.
110 Garcı, amp, x, a-Alonso M, amp, x, et al. Evaluation of the antioxidant properties of fruits. Food Chemistry. 2004;84:13-18. http://dx.doi.org/10.1016/S0308-8146(03)00160-2
111 Costa RM, Magalhaes AS, Pereira JA, Andrade PB, Valentao P, Carvalho M, et al. Evaluation of free radical-scavenging and antihemolytic activities of quince (*Cydonia oblonga*) leaf: a comparative study with green tea (*Camellia sinensis*). Food Chem Toxicol. 2009;47:860-865. http://dx.doi.org/10.1016/j.fct.2009.01.019
112 Oliveira AP, Costa RM, Magalhães AS, Pereira JA, Carvalho M, Valentão P, et al. Targeted metabolites and biological activities of *Cydonia oblonga* Miller leaves. Food Res Int. 2012;46:496-504. http://dx.doi.org/10.1016/j.foodres.2010.10.021

113 Oliveira AP, Pereira JA, Andrade PB, Valentao P, Seabra RM, Silva BM. Phenolic profile of *Cydonia oblonga* Miller leaves. J Agric Food Chem. 2007;55:7926-7930.
http://dx.doi.org/10.1021/jf0711237

114 Silva BM, Andrade PB, Ferreres F, Seabra RM, Oliveira MB, Ferreira MA. Composition of quince (*Cydonia oblonga* Miller) seeds: phenolics, organic acids and free amino acids. Nat Prod Res. 2005;19:275-281.
http://dx.doi.org/10.1080/14786410410001714678

115 Silva BM, Andrade PB, Ferreres F, Domingues AL, Seabra RM, Ferreira MA. Phenolic profile of quince fruit (*Cydonia oblonga* Miller) (pulp and peel). J Agric Food Chem. 2002;50:4615-4618.
http://dx.doi.org/10.1021/jf0203139

116 Silva BM, Andrade PB, Seabra RM, Ferreira MA. Determination of selected phenolic compounds in quince jams by solid-phase extraction and HPLC. J Liq Chromatogr R T. 2001;24:2861-2872.
http://dx.doi.org/10.1081/JLC-100106954

117 Silva BM, Casal S, Andrade PB, Seabra RM, Oliveira MB, Ferreira MA. Development and evaluation of a GC/FID method for the analysis of free amino acids in quince fruit and jam. Anal Sci. 2003;19:1285-1290.
http://dx.doi.org/10.2116/analsci.19.1285

118 Silva BM, Andrade PB, Goncalves AC, Seabra RM, Oliveira MB, Ferreira MA. Influence of jam processing upon the contents of phenolics, organic acids and free amino acids in quince fruit (*Cydonia oblonga* Miller). Eur Food Res Technol. 2004;218:385-389.
http://dx.doi.org/10.1007/s00217-003-0845-6

119 Khoubnasabjafari M, Jouyban A. A review of phytochemistry and bioactivity of quince (*Cydonia oblonga* Mill.). J Med Plants Res. 2011;5:3577-3594.

120 Suzuki A, Yamamoto N, Jokura H, Yamamoto M, Fujii A, Tokimitsu I, et al. Chlorogenic acid attenuates hypertension and improves endothelial function in spontaneously hypertensive rats. J Hypertens. 2006;24:1065-1073.
http://dx.doi.org/10.1097/01.hjh.0000226196.67052.c0

121 Sato Y, Itagaki S, Kurokawa T, Ogura J, Kobayashi M, Hirano T, et al. In vitro and in vivo antioxidant properties of chlorogenic acid and caffeic acid. Int J Pharm. 2011;403:136-138.
http://dx.doi.org/10.1016/j.ijpharm.2010.09.035

122 Chagas-Paula DA, Oliveira RB, da Silva VC, Gobbo-Neto L, Gasparoto TH, Campanelli AP, et al. Chlorogenic acids from *Tithonia diversifolia* demonstrate better anti-inflammatory effect than indomethacin and its sesquiterpene lactones. J Ethnopharmacol. 2011;136:355-362.
http://dx.doi.org/10.1016/j.jep.2011.04.067

123 Yukawa GS, Mune M, Otani H, Tone Y, Liang XM, Iwahashi H, et al. Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. Biochemistry (Mosc). 2004;69:70-74.
http://dx.doi.org/10.1023/B:BIRY.0000016354.05438.0f

124 Yamamoto Y, Gaynor RB. Therapeutic potential of inhibition of the NF-kappaB pathway in the treatment of inflammation and cancer. J Clin Invest. 2001;107:135-142.
http://dx.doi.org/10.1172/JCI11914

125 Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents. 2005; 26:343-356.
http://dx.doi.org/10.1016/j.ijantimicag.2005.09.002

126 Cushnie TP, Lamb AJ. Recent advances in understanding the antibacterial properties of flavonoids. Int J Antimicrob Agents. 2011;38:99-107.
http://dx.doi.org/10.1016/j.ijantimicag.2011.02.014

127 de Sousa RR, Queiroz KC, Souza AC, Gurgueira SA, Augusto AC, Miranda MA, et al. Phosphoprotein levels, MAPK activities and NFkappaB expression are affected by fisetin. J Enzyme Inhib Med Chem. 2007;22:439-444.
http://dx.doi.org/10.1080/14756360601162063

128 Schuier M, Sies H, Illek B, Fischer H. Cocoa-related flavonoids inhibit CFTR-mediated chloride transport across T84 human colon epithelia. J Nutr. 2005;135:2320-2325.

129 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;41:1727-1746.
http://dx.doi.org/10.1016/j.freeradbiomed.2006.04.033

130 Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr. 2001;74:418-425.

131 Samman S, Wall P, Cook N. Flavonoids and coronary heart disease: Dietary perspectives. In: Rice-Evans C, Packer L, editors. Flavonoids in Health and Disease. New York: Marcel Dekker; 1998. p. 469–481.

132 Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. BMJ. 1996;312:478-481.
http://dx.doi.org/10.1136/bmj.312.7029.478

133 Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet. 1993;342:1007-1011.
http://dx.doi.org/10.1016/0140-6736(93)92876-U

134 Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. Lancet. 1993;341:454-457.
http://dx.doi.org/10.1016/0140-6736(93)90206-V

135 Duarte J, Vizcaino FP, Utrilla P, Jimenez J, Tamargo J, Zarzuelo A. Vasodilatory Effects of Flavonoids in Rat Aortic Smooth Muscle. Structure-Activity Relationships. Gen Pharmacol. 1993;24:857-862.
http://dx.doi.org/10.1016/0306-3623(93)90159-U

136 Ning XH, Ding XX, Childs KF, Bolling SF, Gallagher KP. Flavone Improves Functional Recovery after Ischemia in Isolated Reperfused Rabbit Hearts. J Thorac Cardiovasc Surg. 1993;105:541-549.

137 Sanhueza J, Valdes J, Campos R, Garrido A, Valenzuela A. Changes in the xanthine dehydrogenase/xanthine oxidase ratio in the rat kidney subjected to ischemia-reperfusion stress: preventive effect of some flavonoids. Res Commun Chem Pathol Pharmacol. 1992;78:211-218.

138 Chambers DE, Parks DA, Patterson G, Roy R, McCord JM, Yoshida S, et al. Xanthine oxidase as a source of free radical damage in myocardial ischemia. J Mol Cell Cardiol. 1985;17:145-152.
http://dx.doi.org/10.1016/S0022-2828(85)80017-1

139 Iio M, Ono Y, Kai S, Fukumoto M. Effects of flavonoids on xanthine oxidation as well as on cytochrome c reduction by milk xanthine oxidase. J Nutr Sci Vitaminol (Tokyo). 1986;32:635-642.
http://dx.doi.org/10.3177/jnsv.32.635

140 Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr. 2000;130:2243-2250.

141 Middleton E, Jr., Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol Rev. 2000;52:673-751.

142 Middleton E, Jr., Kandaswami C. Effects of flavonoids on immune and inflammatory cell functions. Biochem Pharmacol. 1992;43:1167-1179.
http://dx.doi.org/10.1016/0006-2952(92)90489-6

143 Showkath AM, Regu K, Rajendran R, Mohanan MK, Ganesh B. Awareness of health personnel about lymphatic filariasis and mass drug administration in Kerala State. J Commun Dis. 2008;40:37-40.

144 Najafi M, Zahednezhad F, Samadzadeh M, Vaez H. Zero Flow Global Ischemia-Induced Injuries in Rat Heart Are Attenuated by Natural Honey. Advanced Pharmaceutical Bulletin. 2012;2:165-171.

145 Najafi M, Vaez H, Zahednezhad F, Samadzadeh M, Babaei H. Study of the effects of hydroalcoholic extract of grape seed (*Vitis vinifera*) on infarct size and cardiac arrhythmias in ischemic-reperfused isolated rat heart. Pharmaceutical Sciences. 2010;16:187-194.