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Review

Organosulfur compounds and cardiovascular disease

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ABSTRACT

Epidemiological studies have shown an inverse relationship between consumption of fruits and vegetables and the risk of cardiovascular disease. Phytochemicals are non-nutritional chemical compounds found in small quantities in fruits and vegetables with known health benefits. Among them, organosulfides are present mainly in garlic and onion characterized by their antioxidant and anti-inflammatory properties, and isothiocyanates in cruciferous vegetables have anticarcinogenic effects in experimental models. In this review, we are focusing on the main biological studies regarding the beneficial effect of organosulfur compounds on their protection against cardiovascular disease.

Contents

1. Organosulfur compounds from vegetables and health

Dietary factors play a key role in the development or prevention of various human diseases, including cardiovascular disease. Epidemiologic studies have shown an inverse relationship between diets rich in fruits, vegetables and spices, and risk of all-cause cancer and cardiovascular-disease death (Genkinger et al., 2004). These foods contain phytochemicals that have beneficial properties in cardiovascular disease. One source of such phytochemicals is organosulfur compounds whose role in cardiovascular disease protection has been extensively studied. Organosulfur compounds have been shown to exert diverse biological effects such as antioxidant effects, anti-inflammatory properties, inhibition of platelet aggregation, reduction of systolic blood pressure, and reduction of cholesterol levels (Rose et al., 2005). The organosulfur compounds best studied in cardiovascular protection are those found in alliums mainly garlic and onion. On the other hand, the isothiocyanates, particularly sulforaphane (best known for its anticancer properties) have recently been attributed antioxidant and anti-inflammatory properties in cardiovascular disease.

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1.1. Isothiocyanates

Isothiocyanate is the chemical group –N=C=S, formed by substituting sulfur for oxygen in the isocyanate group. Many natural isothiocyanates from plants are produced by enzymatic conversion of metabolites called glucosinolates. When the raw vegetables are damaged or chewed, the plant cells are broken and the enzyme myrosinase hydrolyses the glucosinolates into isothiocyanates. These compounds can be found in cruciferous vegetables such as broccoli, cauliflower, brussels sprouts and cabbage. Isothiocyanates, such as phenethyl isothiocyanate and sulforaphane, have been shown to inhibit carcinogenesis through inhibition of cytochrome P450 enzymes. Sulforaphane is an organosulfur compound obtained when the enzyme myrosinase transforms glucoraphanin, a glucosinolate, into sulforaphane. Young sprouts of broccoli and cauliflower are particularly rich in glucoraphanin. Recent studies have shown that sulforaphane is an indirect antioxidant that acts by inducing transcription factor NF-E2-related factor 2 (Nrf2)-dependent phase 2 enzymes. The transcription factor Nrf2 regulates the gene expression through the promoter antioxidant response element (ARE) that transcriptionally regulates genes encoding detoxification enzymes and antioxidant proteins playing an important role in cellular defense system, such as glutathione S-transferase(GST), heme oxygenase-1 (HO-1), quinone reductase (QR), UDP-glucuronosyltransferase (UGT). Sulforaphane have anti-inflammatory properties in vascular endothelial cells (Chen et al., 2009; Zakkar et al., 2009) and in macrophages stimulated with LPS-induced inflammation via activation of Nrf2 (Lin et al. 2008). Proinflammatory mediators influence atherosclerosis by inducing adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells via signaling intermediaries including p38-MAP kinase. This was confirmed by Zakkar et al. (2009) were sulforaphane suppresses endothelial cell activation by inhibiting p38-VCAM-1 signaling through the transcription factor Nrf2 in wild-type, but not in Nrf2(−/−) animals. Also, sulforaphane protects the heart against ischemia–reperfusion injury in rats through an increase in the antioxidant enzyme levels of Mn-superoxide dismutase, catalase and heme oxygenase-1 blocked by pretreatment with 5-hydroxydecanoic acid, a mitochondrial K(ATP) channel blocker (Piao et al., 2010). In other study, sulforaphane through Nrf2 activation prevents the biochemical dysfunction of endothelial cells induced by hyperglycemia (Xue et al., 2008). In this study the concentration of sulforaphane used (4 μmol/l) was related to thus found in plasma after consumption of 200 g of raw broccoli (Song et al., 2005). Is important to note that cooking by steaming, microwaving and stir-fry did not produce significant loss of glucosinolates, whereas boiling showed significant losses by leaching into cooking water, therefore avoiding boiling of vegetables is the best way to increase bioavailability of dietary isothiocyanates (Song and Thornalley, 2007).

The study of isothiocyanates in cardiovascular disease is still largely unexplored area. Therefore it is necessary to evaluate the potential beneficial effect of these compounds on cardiovascular health in humans.

Fig. 1 shows the effect of sulforaphane on Nrf2 activation.

1.2. Organosulfur compounds from alliums

The biological properties of garlic and onion are mainly attributed to their high content of organosulfur compounds (Lancaster and Boland, 1990). The most important organosulfur compounds in alliums are the cysteine sulfoxides and the gamma-glutamylcysteines. When the tissues of alliums are disrupted, the enzyme allinase hydrolyses the flavor precursors

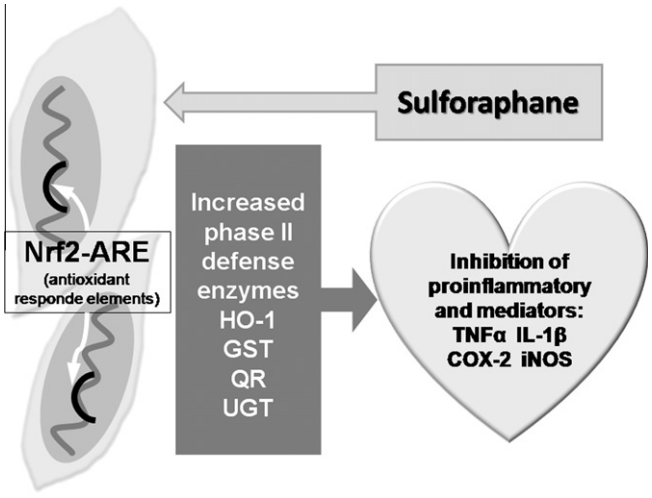

Fig. 1. Mechanisms of action of sulforaphane on cardiovascular system. Sulforaphane is an activator of transcriptional factor Nrf2 that regulates gene expression through the promoter antioxidant response element (ARE). Nrf2 regulates the transcription of a battery of protective and metabolic enzymes. COX-2 cyclooxygenase 2; GST, glutathione S-transferase; HO-1, heme oxygenase-1; IL-1β, interleukine 1 beta; iNOS, inducible nitric oxide synthase; QR, quinone reductase; TNFα, tumor necrosis factor alpha; UGT, UDP-glucuronosyltransferase.

S-alk(en)yl-L-cysteine sulfoxides (ACSOs), giving rise to the flavor and pungency characteristic of the *Allium* plants. There are four different ACSOs identified in *allium* species: (+)-S-allyl-L-cysteine sulfoxide known as alliin (2-PCSO), (+)-S-2-methyl-L-cysteine sulfoxide or methiin (MCSO), S-propyl-L-cysteine sulfoxide or propiin (PCSO) and (+)-S-trans-1-propenyl-L-cysteine sulfoxide or isoalliin (TPCSO) (Randle and Lancaster, 2002; Rose et al., 2005). The characteristic flavor of each allium species depends on the quantitative and qualitative differences of these ACSOs. For example, isoalliin is the major sulfoxide present in onion tissues responsible for its flavor and lachrymatory effect, while the flavor of garlic is due to its high alliin content (Block, 1992; Lancaster and Boland, 1990). The result of the interaction of enzyme allinase and flavor precursors is a wide range of reactive organosulfur compounds. Allicin (allyl-2-propenethiosulfinate), formed from the precursor alliin is the predominant garlic thiosulfinate (Keusgen, 2002). Allicin is relatively unstable and decomposes into a variety of organosulfur compounds depending on the type of solvent used. For example, garlic oil extract is characterized by a high content of vinyldithiins, mainly 2-vinyl-4-H-1,3-dithiin, whereas aqueous garlic juice primarily contains alkenyl sulfides, such as diallyl disulfide and diallyl trisulfide. When ethanol is used as solvent, allicin is converted to ajoene (Keusgen, 2002). Alternatively, aged garlic extract (AGE) is an odorless product resulting from prolonged extraction of fresh garlic at room temperature in which water-soluble S-allylcysteine and S-allylmercaptocysteine, the most important organosulfur compounds, have potent antioxidant activity (Ide and Lau, 1997). Furthermore, AGE contains lipid-soluble compounds such as diallyl sulfide, triallyl sulfide, diallyl disulfide, diallyl polysulfides and others (Borek, 2001). Although a number of biological activities have been attributed to various allicin and allicin-derived compounds, including diallyl sulfides, ajoene, and vinyldithiins, these compounds have never been detected in human blood, urine, or stool, even after consuming large amounts of fresh crushed garlic (25 g) or pure allicin (60 mg). These findings suggest that allicin and allicin-derived compounds are rapidly metabolized. The concentration of allyl methyl sulfide in the breath has been proposed as an indicator of the bioavailability of allicin and allicin-derived compounds (Lawson and Wang, 2005). By contrast, onion is usually consumed fresh, in powder or as an essential oil, and its commercial products are less abundant than those of garlic.

2. Effects of organosulfur compounds from garlic on animal experimental models of cardiovascular disease and human disease

There are several risk factors for cardiovascular disease, including hypertension, hyperlipidemia, diabetes, metabolic syndrome, increased platelet activity, and obesity. Oxidative stress and vascular inflammation are involved in many of these risk factors. The effect of organosulfur compounds of some of these biological variables related with cardiovascular disease will be reviewed. Many studies have drawn the attention to the antioxidant properties of organosulfur compounds, since reactive oxygen species (ROS) play a physiological role in the vessel wall. ROS, especially superoxide anion ($O_2^{\cdot-}$), inactivate nitric oxide ($NO^{\cdot}$) forming peroxynitrite (ONOO–) that constitutes a strong oxidant molecule affecting proteins, lipids and nucleic acids (Beckman and Koppenol, 1996). The major sources of ROS in vascular tissue are membrane associated NAD(P)H-oxidase (Cruzado et al., 2005; Fortuño et al., 2005). The beneficial effects of aqueous garlic extract in the prevention of oxidative stress associated with their organosulfur compounds through reduced aortic NAD(P)H-oxidase activity and lipid peroxidation had been recently demonstrated in an experimental model of metabolic syndrome induced by fructose administration (Vazquez-Prieto et al., 2010). In vitro, the antioxidant effect of AGE or their major compound, S-allylcisteine was evaluated in pulmonary artery endothelial cells pre-treated with oxidized LDL-induced injury. Both compounds prevented the depletion of intracellular GSH and removed peroxides. S-allylcyesteine also inhibited $H_2O_2^{\cdot-}$ or TNF-α–induced NF-kB activation (Ide and Lau, 2001). Kim et al. (2001) showed that garlic extract and S-allylcysteine inhibits $NO^{\cdot}$ production by iNOS expression through suppression of NF-kB activation in macrophage cell line, while in endothelial cells increase the bioavailability of $NO^{\cdot}$ synthesized by endothelial nitric oxide synthase (eNOS) attributed to their antioxidant effect. The effect of organosulfur compounds on reduced hypertension has been studied. The allicin and organosulfur compounds from aqueous garlic extract administration reduced the systolic blood pressure in fructose-fed rats (Elkayam et al., 2001; Vazquez-Prieto et al., 2010) and in spontaneously hypertensive rats (Harauma and Moriguchi, 2006). The same effect on systolic blood pressure was observed when the allicin from garlic powder was administered to rats fed with a high cholesterol diet (Ali et al., 2000). One of the antihypertensive mechanisms can probably be attributed to its prostaglandin-like effects, which decreases peripheral vascular resistance (Rashid and Khan, 1985) or due to its antioxidant properties of some organosulfur compounds either protecting the bioavailability of NO· or scavenging ROS such as ($O_2^{\cdot-}$), H_2O_2, hydroxyl radicals ($OH^{\cdot}$), and $ONOO^-$ (Keusgen, 2002; Kim et al., 2001). Other authors have shown that garlic compounds inhibit angiotensin-converting enzyme in vitro (Sendl et al., 1993). In male Wistar rats garlic increases nitric oxide synthase and blocks the effect of L-nitro arginine methyl ester, an inhibitor of nitric oxide synthesis that induced hypertension (Pedraza-Chaverrí et al., 1998). S-allylcysteine and aged garlic extract showed antihypertensive and renoprotective effects in nephrectomized rats associated with its antioxidant properties that produced a decrease in inducible nitric oxide synthase (iNOS), p22phox, gp91phox (subunits of NAD(P)H oxidase enzyme), and increased superoxide dismutase activity, an antioxidant enzyme (Cruz et al., 2007). In a meta-analysis published in 1994 reported promising results in subjects with mild hypertension but found insufficient evidence to recommend garlic for clinical therapy (Silagy and Neil 1994a). However, in a more recent meta-analysis where eleven randomized controlled trials and non-placebo controlled trials were evaluated from 1995 to 2007, found that garlic supplementation exerts a hypotensive effect compared to placebo, in individuals with high blood pressure. Most of these studies evaluated used raw garlic powder containing 600–900 mg per day, providing 3.6–5.4 mg of allicin (Ried et al., 2008).

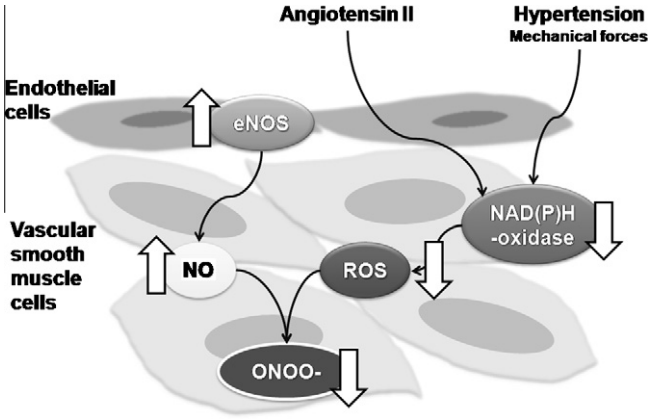

Fig. 2. Beneficial effects of allium organosulfides on vascular wall indicated by arrows. eNOS, endothelial nitric oxide synthase; NAD(P)H-oxidase, nicotinamide adenine dinucleotide phosphate-oxidase; NO, nitric oxide; ROS, reactive oxygen species; ONOO–, peroxynitrite.

Numerous studies have shown the anti-inflammatory effect of organosulfur compounds in vitro and in vivo (Dirsch et al., 1998; Ide and Lau, 2001; Kim et al., 2001; Lei et al. 2008; Son et al., 2006). ROS also induce the expression of different molecules in the endothelial cell surface such as VCAM-1, which stimulates monocyte binding and subsequent macrophage differentiation favoring the atherosclerosis process. Allicin inhibits the expression of intracellular cell adhesion molecule (ICAM) through downregulation of intracellular transduction signal pathways like AP-1 and c-Jun NH2-terminal kinase (JNK) (Son et al., 2006). Additionally, allicin and ajoene reduced the expression of iNOS, an enzyme induced by an inflammatory environment, and which was shown to promote peroxynitrite formation in atherosclerotic lesions (Dirsch et al., 1998). Lei et al. (2008) showed that diallyl disulfide or diallyl trisulfide were able to suppress E-selectin and VCAM-1 expression and decreased monocyte adhesion to endothelial cells stimulated with oxidized LDL likely via the protein kinase B and A signaling pathway, respectively. Furthermore, 1,2-vinyldithiin reduced lipid accumulation in preadipocytes and reduced the secretion of inflammatory molecules such as interleukin-6 and monocyte chemoattractant protein-1 induced by macrophage-secreted factors (Keophiphath et al., 2009). Although these in vitro studies strongly suggest a beneficial effect of organosulfur compounds in cardiovascular disease prevention, there is no evidence that these compounds are present in the blood after being consumed, therefore these effects must be confirmed in vivo studies.

Metabolic syndrome, characterized by hypertension, hyperglucemia, hyperlipidemia, is another well-known risk factor for cardiovascular disease (Isomaa et al., 2001; Miatello et al., 2004). Oxidative stress and vascular remodeling is also reported in this model (Miatello et al., 2005; Renna et al., 2009). In a recent study, aqueous garlic extracts were able to prevent vascular remodeling in arcuate arteries related to their organosulfur content (Vazquez-Prieto et al., 2010). In vitro, allyl methyl sulfide and diallyl sulfide inhibited aortic smooth muscle cell angiotensin II-stimulated cell-cycle progression and migration in cultured aortic smooth muscle cells isolated from spontaneously hypertensive rats. This effect was associated to the prevention of the cell-cycle inhibitor p27Kip1 (p27) downregulation and the reduction of extracellular signal-regulated kinase 1/2 phosphorylation. Additionally, both organosulfur compounds inhibited angiotensin II-reactive oxygen species generation, suggesting that these organosulfur compounds could be effective antioxidants targeted at the arterial remodeling seen in hypertension (Castro et al., 2009). The lipid-lowering properties of organosulfur compounds from allium have been assessed in human and animal models (Ali et al., 2000; Augusti and Mathew, 1974; Steiner et al., 1996; Yeh and Liu, 2001). Although the mechanism(s) is not completely elucidated, the in vitro data suggest that organosulfur compounds from garlic reduced cholesterol biosynthesis in hepatocytes by inhibiting enzymes, such as HMG-CoA reductase, in the cholesterol pathway (Gebhardt, 1993; Gebhardt and Beck, 1996; Yeh and Liu, 2001). However, in a recent clinical trial, the administration of raw garlic, powdered or aged garlic extract supplement during six month did not modify the lipid concentrations in adults with moderate hypercholesterolemia (Gardner et al., 2007). Differences in garlic preparations containing different constituents and methodological differences could account, in part, for the inconsistent findings (Silagy and Neil, 1994b). Platelet aggregation has been implicated in cardiovascular disease. Evidence from several studies in vitro showed that organosulfur compounds inhibit platelet aggregation by multiple mechanisms: (a) inhibiting cyclooxygenase activity, (b) suppressing Ca^{2+} mobilization within platelets, (c) increasing cAMP levels, (d) increasing availability of platelet $NO^{\cdot}$, and (e) interacting directly with the fibrinogen receptor GPIIb/IIIa and inhibiting its exposure to fibrinogen (Rahman, 2007).

Fig. 2 shows the effects of organosulfides from alliums on vascular wall.

3. Conclusions and further considerations

There is much evidence from in vitro and in vivo studies supporting the beneficial effects of organosulfide consumption in the prevention of cardiovascular disease. Existing evidence to date suggests that organosulfides have the ability to prevent

ROS production, increase antioxidant status, increase the bioavailability of nitric oxide, prevent vascular inflammation, reduce lipid content and inhibit platelet aggregation. The results obtained in human are inconsistent, probably due to differences in garlic preparations, unknown active constituents and their bioavailability, differences in the population selected and duration of trials. Also, organosulfur compounds from alliums and cruciferous vegetables are usually cooked before being consumed, and it is known that cooking inactivates the enzyme and thus the production of its bioactive constituents (Cavagnaro et al., 2007; Hecht, 2000; Song and Thornalley 2007). Therefore, it is also important apply the best cooking conditions in order to prevent the loss of the bioactive compounds.

In conclusion, the proposed mechanisms in vitro and/or in animal models should be verified in further human studies in order to establish a causative link between some molecular properties and the role in cardiovascular disease prevention of these compounds.

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