

Invited Review

Oxidative Stress and Cardiovascular Dysfunction Associated with Cadmium Exposure: Beneficial Effects of Curcumin and Tetrahydrocurcumin

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Cadmium (Cd) is a non-essential heavy metal with high toxicity potential. Humans are exposed to Cd present in diet, polluted air, and cigarette smoke. Cd exposure has been associated with increased risk of chronic diseases, including hypertension, atherosclerosis, diabetes, and nephropathy, all of which could be attributable to dysfunctional endothelial and smooth muscle cells. Cd toxicity is correlated with increased reactive oxygen formation and depletion of antioxidants, resulting in an oxidative stress. Chelation of Cd has proved useful in the removal of the Cd burden. However, several chelating agents cause side effects in clinical usage. Recent studies have shown that the antioxidant compounds curcumin and tetrahydrocurcumin can alleviate vascular dysfunction and high blood pressure caused by Cd toxicity. In chronic Cd exposure, these antioxidants protect vascular endothelium by increasing nitric oxide (NO•) bioavailability and improving vascular function. Antioxidant activity against Cd intoxication results directly and/or indirectly through free radical scavenging, metal chelation, enhanced expression of the antioxidant defense system, regulation of inflammatory enzymes, increase in NO• bioavailability, and reduction of gastrointestinal absorption and tissue Cd accumulation. This review summarizes current knowledge of Cd-induced oxidative stress and cardiovascular dysfunction and a possible protective effect conferred by the antioxidants curcumin and tetrahydrocurcumin.

Keywords: cadmium; cardiovascular dysfunction; curcumin; oxidative stress; tetrahydrocurcumin

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Introduction

Cadmium (Cd) is one of several toxic heavy metals that have no known physiological function in the body. Cd is found naturally in the earth's crust associated with zinc, lead, and copper ores. The health hazard from exposure to Cd has long been recognized, both in and outside of the workplace. Cd is toxic at very low levels and has acute and chronic effects on health. The most dangerous characteristic of Cd is that it accumulates throughout one's lifetime. Cd has a long biological half-life of 17-30 years in humans. Evidence suggests that food and cigarette smoke are the major sources of non-occupational Cd exposure in the general population (Jarup and Akesson 2009). Occupational exposure results mainly from Cd fume inhalation in the cadmium-nickel battery industry, as well as from coating and plating of metals and in the production of stabilizers for plastic and paint pigments (ATSDR, Agency for Toxic Substances and Disease Registry 2012). Cd has been impli-

cated in the pathogenesis of age-related macular degeneration and hearing loss (Erie et al. 2007; Satarug et al. 2010; Chantarawong et al. 2014). The most commonly affected organ systems are the kidney, lung, bone and skeletal, cardiovascular, and nervous systems (Jaishankar et al. 2014). Observational studies indicate that chronic Cd exposure is associated with an increased risk of cardiovascular disease, including hypertension, atherosclerosis, nephropathy, and diabetes (Puri 1999; Satarug et al. 2005; Eum et al. 2008; Prozialeck et al. 2008; Messner and Bernhard 2010; Alissa and Ferns 2011; ATSDR 2012; Satarug and Moore 2012).

Cadmium: route and patterns of exposure

Cd (atomic number, 48; relative atomic mass, 112.41) is a soft, silver-white metal. Cd is not usually present in the environment as a pure metal but rather as a complex oxide, sulphide and carbonate in zinc, lead and copper ore (IUPAC, International Union of Pure and Applied Chemistry 2002; ATSDR 2012). Cd is released into soil, water, and air by

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mining and refining of non-ferrous metals, manufacture and use of phosphate fertilizers, combustion of fossil fuel, and incineration and disposal of waste (ATSDR 2012). Moreover, Cd can accumulate in aquatic and agricultural crops. Cd is ingested by breathing, eating, and drinking. In the general population, the primary sources of Cd exposure are cigarette smoke, food (especially shellfish, organ meats, leafy vegetables, grains, and crustaceans), drinking water and ambient air, particularly in urban and industrial areas (IUPAC 2002; Satarug et al. 2004; ATSDR 2012). Cigarette smoke is also a source of Cd exposure. Cd is either released into the air by tobacco smoke or is retained in cigarette ash. The amount of Cd inhaled by smokers is approximately 10% of the total Cd content of the cigarette, and non-smokers may passively inhale significant amounts of Cd as well. A study by Satarug et al. (2013) to estimate the relative level of Cd exposure from both diet and cigarette smoke in a low exposure area (Bangkok) and a high exposure area (Mae Sot) found that the overall Cd exposure levels in Mae Sot were three to four times greater than in Bangkok. People in Mae Sot are much heavier smokers than those in Bangkok. However, estimates of Cd exposure from the toxicokinetic model revealed that dietary exposure was the major source of body Cd, and smoking was only a minor source of exposure in people from Mae Sot (Satarug et al. 2013).

The impact of cadmium on human health in Asia

The effect of Cd-induced lung damage in workers was first reported in the 1930s and later, and the effects of Cd on bone proteinuria were reported in the 1940s (Nordberg 2004). After World War II, a form of Cd-induced renal osteomalacia called itai-itai disease and characterized by fractures and severe pain was identified in the Cd-polluted Jinzu River basin in Toyama, Japan (Osawa et al. 2001; Aoshima 2012). Subsequently, international warnings of health risks from cadmium pollution were issued in the 1970s. In the 1990s, the toxic effect of Cd on skeletal, renal and reproductive systems was reported in Chinese populations who were exposed to Cd via consumption of contaminated rice (Cai et al. 1990). Long-term environmental exposure to Cd was also reported to cause renal dysfunction, which occurred initially as tubular damage, followed by glomerular damage. World Health Organization (WHO) confirmed that the kidney is the most important target organ for Cd toxicity, and a crude quantitative evaluation was conducted in 1992 (WHO 1992). Previous studies showed a relationship between dietary Cd contaminated rice and the presence of chronic renal failure (Hochi et al. 1995; Noonan et al. 2002; Satarug and Moore 2004; Simmons et al. 2005). A high concentration of Cd in the urine was detected in non-smoking farmers who worked on sludge farms in Hyderabad, India (Srikanth et al. 1994). Osteoporosis and nephropathy caused by Cd exposure were found in populations living in polluted areas of southeast China (Jin et al. 2004). A high prevalence of renal failure

was also detected among the farmers in the agricultural area under irrigation in the North Central Province, Sri Lanka (Bandara et al. 2011). Chronic Cd toxicity is a significant health concern among workers engaged in zinc smelting, battery production and silver jewellery industries, particularly in developing countries. In Thailand, environmental Cd contamination was first reported in some rural villages of Mae Sot District, Tak Province, Northwestern Thailand (Swaddiwudhipong et al. 2007; Limpatanachote et al. 2009). This issue has become a public health concern, and Cd toxicity is now monitored in residents living in contaminated areas. Cd contamination in these areas is primarily associated with mining of zinc ores. In particular, Cd contamination may result from irrigation of paddy fields by two creeks (Mae Tao and Mae Ku) which pass through an area where a zinc mine has actively operated for more than 20 years (Songprasert et al. 2015). People who live in contaminated areas are likely to be exposed to Cd via consumption of rice and other crops that are grown locally in these areas (Swaddiwudhipong et al. 2007). A significantly high level of urinary Cd excretion was observed in subjects residing in Mae Sot District (Apinan et al. 2009). In comparison to the general Thai population, Mae Sot residents have a higher incidence of nephrosis/nephritis, osteoporosis, bone mineral loss, cancer, hypertension, and heart diseases (Abu-Hayyeh et al. 2001; Swaddiwudhipong et al. 2007, 2015; Teeyakasem et al. 2007; Limpatanachote et al. 2009; Honda et al. 2010).

Induction of oxidative stress by cadmium

Oxidative stress mechanism

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS)/reactive nitrogen species (RNS) and a biological system's ability to detoxify these reactive intermediates. ROS and RNS induce biochemical alterations (Taniyama and Griendling 2003; Wu et al. 2004), which in turn produces lipid peroxidation, protein oxidation, and DNA damage (Bertin and Averbeck 2006).

There are several mechanisms that generate oxidative stress in vascular tissue, including activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and xanthine oxidase, mitochondrial electron leakage, and uncoupling of endothelial nitric oxide synthase (eNOS) (Lee and Griendling 2008) (Fig. 1). NADH/NADPH oxidases are membrane-bound enzymes that produce superoxide anion ($O_2^{\bullet-}$) by electron transfer from NADPH to molecular oxygen. NADH/NADPH oxidases are the major sources of ROS in vascular tissues and cardiac cells (Ungvari et al. 2003). Increased expression and activity of NADPH oxidase or its subunits have been described in many animal models of hypertension (Fukui et al. 1997; Zalba et al. 2000; Beswick et al. 2001). Xanthine dehydrogenase/xanthine oxidase is an important regulator of cellular redox state. Xanthine oxidase is derived from xanthine dehydrogenase during oxidative stress (McNally et al. 2003). It is expressed mainly in the endothelium and its

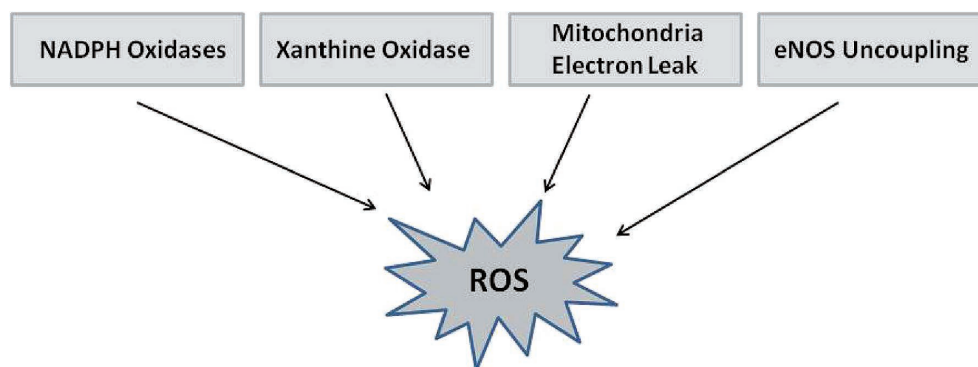


Fig. 1. The major sources of ROS generation in the vasculature.

ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; eNOS, endothelial nitric oxide synthase.

level is increased by angiotensin II or oscillatory shear stress in a NADPH oxidase-dependent manner (McNally et al. 2003; Landmesser et al. 2007). In experimental atherosclerosis caused by diet induced hypercholesterolemia, excess $O_2^{\bullet-}$ production was inhibited by oxypurinol, a xanthine oxidase inhibitor (Sumi et al. 2001). The mitochondrial electron transport chain generates $O_2^{\bullet-}$ as a by-product of electron transport during oxidative phosphorylation. In physiological conditions, most $O_2^{\bullet-}$ is generated inside the mitochondrial matrix and scavenged by Mn-SOD and glutathione peroxidase. If $O_2^{\bullet-}$ generation is excessive, H_2O_2 and $O_2^{\bullet-}$ can escape to the inter-membrane space and to cytosol via anion channels (Aon et al. 2004). The rate of mitochondrial respiration and ROS formation is mostly influenced by the coupling state of the mitochondria, and in turn by factors such as internal and external calcium levels and antioxidant activity. It was found that mitochondrial ROS is linked to vascular cell pathology from hyperglycemia-induced glycation and protein kinase C activation (Du et al. 2001). In normal conditions, eNOS produces NO^{\bullet} by oxidizing L-arginine to L-citrulline. The function of eNOS requires the substrate L-arginine and essential cofactors such as tetrahydrobiopterin (BH_4). In the deficit of L-arginine or BH_4 , eNOS produces $O_2^{\bullet-}$ instead of NO^{\bullet} , which is referred to as “uncoupling” of eNOS (Vasquez-Vivar et al. 1998). The reaction of $O_2^{\bullet-}$ and NO^{\bullet} to form peroxynitrite ($ONOO^-$) is extremely rapid, whereas formation of $ONOO^-$ reduces the NO^{\bullet} bioavailability and produces a more damaging radical ($ONOO^{\bullet}$). Therefore, imbalance between endothelial NO^{\bullet} and ROS production is one of the major contributors to vascular endothelial dysfunction (Schulz et al. 2008), which plays an important part in cardiovascular disease.

Cadmium-induced oxidative stress

Many studies have connected Cd toxicity with oxidative stress. Several lines of evidence indicate that ROS and RNS formed in the presence of Cd may be responsible for its toxic effects in many organs (Wang et al. 2004; Watjen and Beyersmann 2004). Involvement of ROS in Cd toxic-

cology has been observed in a variety of cell culture systems (Liu et al. 1990; He et al. 2008) and in intact animals through all routes of exposure (Kayama et al. 1995; Amara et al. 2008). Since Cd is a non-Fenton metal, it is unable to generate ROS directly (Cuypers et al. 2010). However, Cd induces oxidative stress indirectly by at least four mechanisms (Thevenod 2009; Cuypers et al. 2010; Nair et al. 2013). First, Cd liberates redox-active metals such as iron and copper from tightly bound storages. Cd can replace iron and copper in a number of cytoplasmic and membrane proteins, including ferritin, which in turn can release and increase the concentrations of unbound iron ions. These free ions cause oxidative stress via the Fenton reactions (Casalino et al. 1997; Waisberg et al. 2003). Secondly, Cd inhibits the electron transport chain resulting in uncoupled electron flow and ROS formation. Cd inhibits the activity of complex II and complex III in mitochondria isolated from the liver, brain, and heart of male Dunkin-Hartley guinea pigs (Wang et al. 2004). The impairment of electron transfer through the complex III by Cd may be due to the binding of Cd with semi-ubiquinone and cytochrome b of complex III, resulting in accumulation of unstable semi-ubiquinone, thereby causing electron leakage to molecular oxygen to form $O_2^{\bullet-}$ (Wang et al. 2004). Thirdly, Cd depletes antioxidant scavengers. Glutathione (GSH) is a primary target of Cd. It was found that Cd toxicity is normally involved with the depletion of cellular GSH and protein-bound sulfhydryl groups, resulting in disturbance of the cellular redox balance which leads to enhanced production of ROS such as $O_2^{\bullet-}$, H_2O_2 , and OH^{\bullet} (Bagchi et al. 1997; Liu and Jan 2000). Finally, Cd exposure suppresses antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). However, the changes in these antioxidant enzymes depend on the duration and concentrations of exposure to Cd (Casalino et al. 1997; Waisberg et al. 2003; Wang et al. 2004). Zota et al. (2015) found a strong and independent association between environmental exposure to Cd and a shortening of peripheral blood leukocyte telomere length. Telomeres are particularly sensitive to damage by oxidative

stress because of the high guanine content in telomere sequences. Therefore, chronic exposure to Cd at the levels observed in the U.S. population may cause oxidative stress (Zota et al. 2015). In another U.S. population study, Colacino et al. (2014) found Cd exposure is associated with elevated oxidative stress markers, namely C-reactive protein, γ glutamyl transferase and alkaline phosphatase. Pizzino et al. (2014) also found an increased oxidative DNA damage and impaired the expression of DNA repair and detoxification genes in adolescents who live in the Sicily, Italy and exposed to Cd.

Cadmium-induced cardiovascular dysfunction

In the cardiovascular system, the effects of Cd on the heart can be divided into two types: (1) effect on tissue structure and integrity, and (2) effect on the cardiac conduction system (Messner and Bernhard 2010). A number of publications in experimental animals have suggested that Cd-induced cardiac damage is associated with alteration of antioxidant defense by increased generation of ROS (Zikic et al. 1998; Wang et al. 2004), reduced coronary blood flow (Kisling et al. 1993), and inhibition of the electron transport chain in cardiomyocytes (Wang et al. 2004). The vascular endothelium is thought to be the main site at which the deleterious effects of high blood pressure, high plasma lipid concentrations, and high glucose levels in diabetes lead to the impairment of endothelial function. Therefore, the endothelium is probably affected by Cd. Several lines of evidence reviewed by Prozialeck et al. (2006) suggest that vascular endothelium is an important target of Cd toxicity. The cellular mechanisms by which Cd might contribute to the development of hypertension include Cd-stimulated release of proinflammatory mediators (e.g. tumor necrosis factor- α) and antithrombotic agents (e.g. plasminogen activator inhibitor-1) from vascular endothelial cell culture (Yamamoto et al. 1993; Szuster-Ciesielska et al. 2000). Cd also facilitates the adhesion of peripheral human polymorphonuclear leukocytes to the endothelium (Hernandez and Macia 1996). It was reported that Cd stimulates the secretion of endothelin-1 and angiotensin II from the cultured coronary microvascular endothelial cells (Kusaka et al. 2000). Regarding the microvascular effect of Cd, it was found that Cd alters the function of a Ca^{2+} -dependent cell adhesion molecule, the so-called vascular endothelial-cadherin (VE-cadherin), thereby leading to a disruption of endothelial barrier integrity (Prozialeck and Niewenhuis 1991; Prozialeck 2000; Prozialeck et al. 2006). The effect of Cd on VE-cadherin has been suggested to be involved in the development of atherosclerosis (Pereira et al. 2007). The other mechanism of Cd-induced hypertension suggested by Satarug et al. (2006) is that Cd deposited in human kidney leads to alterations in metal homeostasis and redox state, changes in gene expression profiles, and ultimately tubular injury. Increased risk of hypertension is found in humans with nephropathy caused by environmental Cd exposure (Satarug et al. 2005).

There are several pieces of evidence obtained from the cell culture and animal studies indicating that Cd alters NO• metabolism through direct or indirect mechanisms involving oxidative stress, which causes a reduction in NO• bioavailability resulting in endothelial dysfunction (Kishimoto et al. 1994; Bilgen et al. 2003; Skoczynska and Martynowicz 2005; Kukongviriyapan et al. 2014). Endothelial dysfunction is associated with loss of vasodilation, increased platelet aggregation, and inflammation. Data obtained from cultured vascular smooth muscle cells revealed that Cd enhances the production of extracellular matrices, especially glycosaminoglycans, which alters the vascular structure (Fujiwara et al. 1998). In addition, alterations to sub-endothelial matrix and endothelial cells caused by Cd may lead to the formation of atherosclerotic plaques (Thyberg et al. 1990; Koyama et al. 1996). Washington et al. (2006) suggested that Cd-induced increased protein kinase C activity in vascular smooth muscle of spontaneously hypertensive rats may contribute to vascular dysfunction (Washington et al. 2006). Yooan et al. (2008) reported that subchronic exposure to Cd via drinking water for three months increased systolic blood pressure and reduced acetylcholine (ACh)-induced vascular relaxation in rats. A study by our group found that mice that received CdCl_2 (100 mg/L) via drinking water for eight weeks showed increase in blood pressure and impairment of vascular responsiveness to vasoactive agents (Sompamit et al. 2010). Interestingly, decreased eNOS expression was found to be associated with increased blood pressure and impaired ACh-dependent vasorelaxation in rats and mice exposed to Cd (Yooan et al. 2008; Kukongviriyapan et al. 2014). Furthermore, inhibition of NO• production via inhibiting eNOS phosphorylation might further induce endothelial dysfunction (Majumder et al. 2008). An accumulation of Cd in target tissues including kidney, liver, heart, and aorta was also found in mice after exposure to Cd (Kukongviriyapan et al. 2014). We proposed that Cd content in the aorta might induce aortic weakening through the adverse effects on smooth muscle cell metabolism and the attenuation of vascular reactivity to vasoactive agents. A combination of these effects results from long-term damage of endothelial and vascular smooth muscle cells caused by Cd intoxication (Kukongviriyapan et al. 2014; Sangartit et al. 2014). We also found that Cd promotes vascular smooth muscle growth and proliferation, enhances vascular remodeling, and increases arterial stiffening (Sangartit et al. 2014). Altogether, the hypertensive effect of Cd results from complex actions on vascular endothelium, vascular smooth muscle and vascular extracellular matrix. The putative mechanisms by which cadmium-induced endothelial dysfunction and vascular remodeling mediated at least in part through oxidative stress are summarized in Fig. 2.

It is well documented that oxidative stress plays a major role in vascular dysfunction. GSH is an important intracellular antioxidant that protects the body systems from the damaging effects of oxidative stress. Normally, more

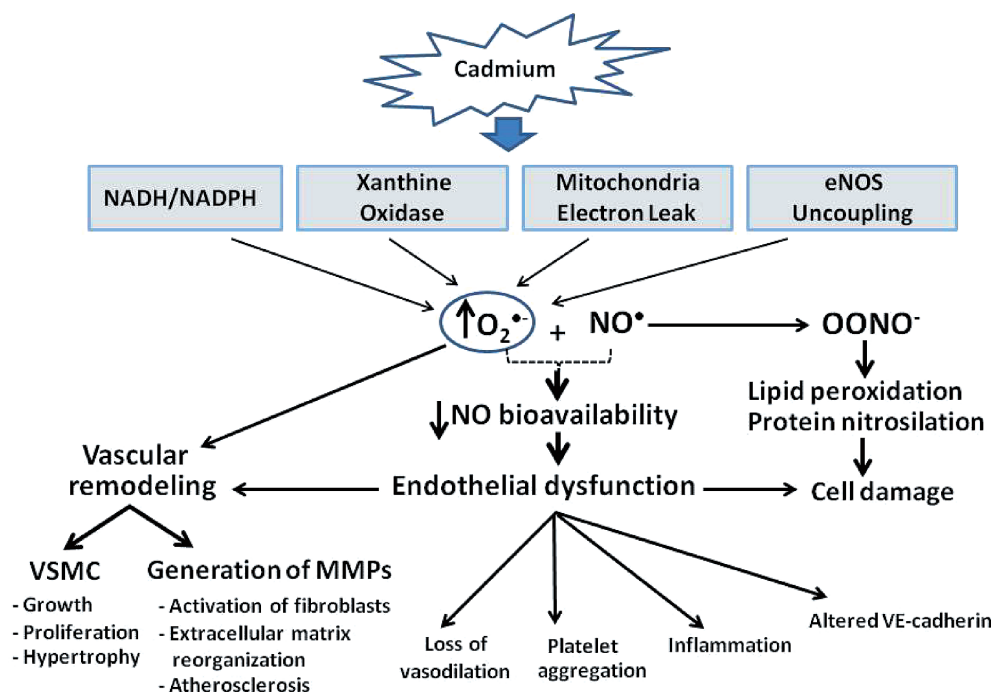


Fig. 2. The putative mechanisms for cadmium exposure-induced endothelial dysfunction and vascular remodeling mediated through oxidative stress.

NO^{\bullet} , nitric oxide; $O_2^{\bullet-}$, superoxide anion; $ONO_2^{\bullet-}$, peroxynitrite.

than 95% of the total GSH is in the reduced form (GSH) and less than 5% is in the disulfide form (GSSG). Therefore, the decreased ratio of GSH to GSSG within cells is indicative of an imbalance in redox state and can be used as a measure of cellular toxicity. It was found that Cd causes a depletion of GSH and an increase in oxidation of GSH to GSSG, thereby reducing the redox ratio of GSH/GSSG in the cell (Kukongviriyapan et al. 2014). The depletion of the GSH defense system after Cd exposure may allow free radicals such as OH^{\bullet} and $O_2^{\bullet-}$ to induce oxidative damage via lipid peroxidation, protein oxidation, and DNA damage in tissues (Stohs and Bagchi 1995). Significant Cd-induced increases in the levels of malondialdehyde (MDA) and protein carbonyl have been reported in cell cultures and animals exposed to Cd (Lopez et al. 2006; Donpunha et al. 2011).

Chelating agents, antioxidants and cadmium toxicity

Chelating agents are organic or inorganic compounds capable of binding metal ions to form complex ring-like structures called chelates (Flora and Pachauri 2010). Normally, electron-donor atoms on the chelating molecule include sulphur, nitrogen, and/or oxygen (Sears 2013). During Cd exposure, thiols or organic sulfhydryl compounds are primarily involved in mobilizing and detoxifying Cd through the formation of Cd-thiol complexes inside the cell (Cuyper et al. 2010). Interestingly, Cd can form complexes with endogenous binding proteins, particularly metallothionines (MT). The resulting Cd-MT complex likely protects tissues from Cd toxicity (Klaassen et al.

1999). After Cd absorption, it is taken up firstly by the liver, where it binds with GSH and MT. It is then either excreted into the bile, or released into the blood stream in the form of Cd-glutathione-S conjugates (Ercal et al. 2001). On the other hand, in the liver, kidneys, and some other tissues, Cd induces the synthesis of MT and Cd is stored primarily in Cd-MT complexes (Klaassen et al. 1999). Cd-MT may be released from the liver and subsequently transported into the kidney, where the complex is degraded and Cd is released. Free Cd within renal cells may thereby cause renal toxicity (Yang and Shu 2015).

Numerous studies have investigated the use of chelating agents or chelators to reduce Cd toxicity by either single or combination therapy. Ideally, the functional chelators should have high water solubility, low toxicity, high affinity for the toxic metal, high ability to penetrate cell membranes, and the ability to rapidly eliminate metal (Flora and Pachauri 2010). One agent used as a chelator is dimercaprol (also known as British Anti-Lewisite or BAL). Dimercaprol is highly effective in the treatment of human arsenic and mercury poisoning. Meso-2,3-dimercaptosuccinic acid (DMSA) is a modified form of BAL that produces fewer side effects. Another agent, dithiol sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), is also used as a mercury-chelating agent. There is no specific guideline for treatment of Cd toxicity. BAL is more toxic than its derivatives, DMPS and DMSA, and is rarely used clinically. It is clear that ethylene diamine tetraacetic acid (EDTA) (Kelley 1999; Waters et al. 2001), DMPS (Tandon et al. 2002) and DMSA increase urinary excretion of Cd. In comparison

with dithiol chelators in animals, DMSA is superior in removal of methylmercury from animal brains. In contrast, DMPS has no effect in the brain, but removes methylmercury from the kidneys (Aposhian 1983). In mice, Cd was removed more effectively by DMSA than DMPS (Andersen and Nielsen 1988). DMSA contains two sulfhydryl groups, which makes it a more effective chelator (Miller 1998). Moreover, DMSA is water soluble, orally administered, low in toxicity, and causes no redistribution of toxic metals from one organ to another (Aposhian et al. 1995). It has been demonstrated in animal experiments that DMSA is a powerful chelator (Jones et al. 1992). Accordingly, our previous study showed that DMSA attenuated Cd-induced hypertension and vascular dysfunction in mice with sub-chronic exposure to Cd (Sompamit et al. 2010).

Several antioxidants are also used to reduce metal toxicities. The most powerful enzymatic antioxidants are SOD, CAT and GPx (Mates et al. 1999). Non-enzymatic antioxidants used to reduce metal toxicity include vitamin C (ascorbic acid), vitamin E, carotenoids, thiol antioxidants (GSH, N-acetylcysteine, thioredoxin and lipoic acid), and melatonin (Sharma et al. 2014). Because Cd is a highly toxic metal that indirectly generates free radicals such as $O_2^{\bullet-}$, OH^{\bullet} , and NO^{\bullet} , the search for antioxidants that are natural, effective, nontoxic and have antioxidant and chelating properties has been heightened in recent years. In particular, curcumin and its metabolites have received considerable attention and have become one of the most cited antioxidants, due to its beneficial health effects in animals and humans (Sharma et al. 2005; Aggarwal et al. 2007; Aggarwal and Sung 2009). However, there is little information regarding the protective effect of curcumin and one of its major metabolites, tetrahydrocurcumin, against the toxicity of heavy metals. Therefore, this review will focus on the protective effects of curcumin and tetrahydrocurcumin on cardiovascular disease and against Cd toxicity.

Curcumin

Curcumin or diferuloylmethane, the major active component of turmeric, is extracted from the dry rhizome of *Curcuma longa* Linn (Zingiberaceae). *C. longa* is a perennial herb and is widely cultivated in tropical regions of Asia. The most important chemical components of turmeric are a group of compounds called curcuminoids, which include curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin. Curcumin is commonly used as a spice to give flavor and yellow color to food. In many countries in Asia including India and Thailand, fresh turmeric rhizomes are widely used in many types of cuisine, particularly in southern Thai dishes such as yellow curry and turmeric soup. Curcumin is a hydrophobic polyphenol compound. Chemically, curcumin is a bis- α,β -unsaturated β -diketone (commonly called diferuloylmethane). The presence of phenolic, β -diketone and the methoxy groups contributes to the free radical-scavenging activity of curcumin. Curcumin exists mostly in two tauto-

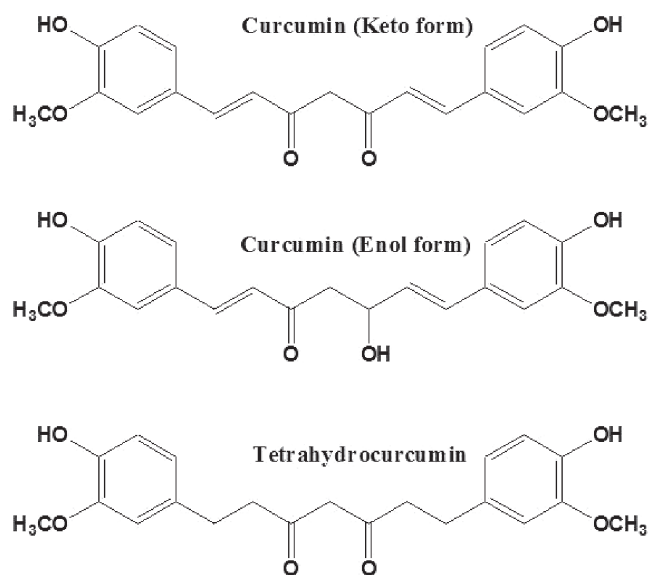


Fig. 3. Chemical structures of the keto and enol forms of curcumin and the tetrahydrocurcumin. Curcumin has α,β -unsaturated carbonyl group, but tetrahydrocurcumin lacks α,β dienes.

meric forms, keto and enol (Fig. 3). The tautomeric equilibrium is dependent upon the polarity and the pH value of the solvent. In acidic and neutral media, the keto form dominates and acts as a proton donor, whereas at alkaline medium the enol form predominates and serves as an electron donor (Wang et al. 1997). The enol form of curcumin is an ideal chelator of positively charged metals (Garcia-Nino and Pedraza-Chaverri 2014).

Curcumin and turmeric products have been characterized as safe by the Food and Drug Administration (FDA) in the USA, the Natural Health Products Directorate of Canada and the joint FAO/WHO Expert Committee on Food Additives of the Food and Agriculture Organization/WHO (NCI, DCPC 1996). Generally, the bioavailability of curcumin is low due to poor intestinal absorption, rapid metabolism in liver and rapid systemic elimination (Anand et al. 2007; Aggarwal and Sung 2009). A study by Pan et al. (1999) in mice revealed that 99% of curcumin in plasma was present as glucuronide conjugates (e.g. curcumin-glucuronoside, dihydrocurcumin-glucuronoside, tetrahydrocurcumin-glucuronoside), and tetrahydrocurcumin is major metabolite of curcumin *in vivo*. In human and rat intestine, curcumin is metabolized into curcumin glucuronide, curcumin sulphate, tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin (Ireson et al. 2002; Sharma et al. 2004; Vareed et al. 2008). The systemic clearance of curcumin from the body is also an important factor, which determines its relative biological activity. An early study by Wahlstrom and Blennow (1978) reported that after oral administration of 1 g/kg curcumin to rats, more than 75% of curcumin was excreted in feces and negligible amount was detected in urine. Further in a human clinical trial, 3.6 g of curcumin via oral route was found to produce a plasma

curcumin level of 11.1 nmol/L after an hour of dosing (Sharma et al. 2004). These results indicate that curcumin is absorbed after oral dosing in humans and can be detected as glucuronide and sulfate conjugates in plasma.

Despite its low bioavailability, curcumin has entered scientific clinical trials at the phase I, II and III levels and is used at doses as high as 12 g/day for three months without overt toxicity (Hsu and Cheng 2007). Curcumin is therapeutically effective against various diseases, including cancer, Alzheimer's disease, diabetes, hypertension, hypercholesterolemia, inflammatory diseases, liver injury, asthma, psoriasis, neurological diseases, and immunodeficiency (Sharma et al. 2005; Aggarwal et al. 2007; Aggarwal and Sung 2009; Nakmareong et al. 2011; Garcia-Nino and Pedraza-Chaverri 2014). Curcumin is a potent scavenger of ROS including $O_2^{\bullet-}$, OH^{\bullet} and singlet oxygen. It has been suggested that a diketone group of curcumin can react with OH^{\bullet} and H_2O_2 whereas the two phenyl methoxy groups of curcumin suppress NF- κ B activation (Singh and Aggarwal 1995; Sandur et al. 2007; Somporn et al. 2007). Treatment with curcumin, a known activator of Nrf2-antioxidant response element (ARE) pathway, may suppress oxidant formation by up-regulation of antioxidant enzymes (Heiss et al. 2009). Oral administration of curcumin at a dose of 3.6 g/day for seven days in cancer patients reduces oxidative DNA adduct levels, thereby lowering the risk of mutations and other genetic damage (Garcea et al. 2005). Curcumin exerts a protective effect against myocardial ischemia in rats, and also possesses an antioxidant effect and an inhibitory effect on xanthine oxidase/xanthine dehydrogenase conversion, leading to a decrease in $O_2^{\bullet-}$ generation (Manikandan et al. 2004). Pretreatment of curcumin alleviates hepatic lipid peroxidation and increases GSH and GPx hepatic activity in a mouse model of Cd-induced oxidative damage (Eybl et al. 2006). Curcumin also inhibits lipid peroxidation in the red blood cells and in the liver of high fat-fed hamsters (Jang et al. 2008). The decrease in lipid peroxidation in liver microsomes and mitochondria is protective in atherosclerotic rabbits (Quiles et al. 2002). In addition, oral administration with curcumin at a dose of 50 mg/kg for 3 days before a single dose of Cd injection results in a reduction of Cd accumulation in liver and brain in mice. The authors suggest that curcumin may reduce Cd load in the body by a possible metal-ligand interaction (Eybl et al. 2006).

Motterlini et al. (2000) found that curcumin upregulates endothelial heme oxygenase-1 (HO-1) protein expression and increase heme oxygenase activity in bovine endothelial cells. Moreover, a study in human bile duct cancer cells suggested that curcumin can induce Nrf2 protein expression, upregulate gamma-glutamylcysteine ligase mRNA, and increase cellular GSH level (Suphim et al. 2010). Similar effects of curcumin on antioxidant enzymes have been reported. The activities of antioxidant enzymes such as glutathione transferases and GPx are also increased with curcumin treatment in high fat-fed rats (Manjunatha

and Srinivasan 2007). Curcumin attenuates LPS-induced vascular dysfunction in mice, as shown by improvement in hemodynamics and vascular responsiveness resulting from a decrease in oxidative stress and preservation of GSH levels (Sompamit et al. 2009). In addition to direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of GSH.

In the vascular system, curcumin causes relaxation of isolated porcine coronary arteries in a concentration-dependent manner through a mechanism involving NO \bullet , cGMP, and adrenergic β -receptor (Xu et al. 2007). It has been reported that curcumin increases the effect of vitamin C in protecting endothelial function through its antioxidant, hypoglycemic, and hypolipidemic actions in streptozotocin-induced diabetic rats (Patumraj et al. 2006). Curcumin exhibits hypotensive and protective effects on vascular endothelium in spontaneously hypertensive rats and its mechanism is thought to be caused by its radical scavenging effect (Goto et al. 2005). Moreover, curcumin also protects against homocysteine-induced endothelial dysfunction in porcine coronary arteries (Ramaswami et al. 2004). This effect may contribute to the suppression of lipid peroxidation and prevention of down regulation of eNOS (Ramaswami et al. 2004). Nakmareong et al. (2011) demonstrated that curcumin (50 or 100 mg/kg) prevents the development of hypertension, improves hemodynamic status, and restores vascular function in L-NAME-induced hypertensive rats.

Tetrahydrocurcumin

Tetrahydrocurcumin was identified as one of the major colorless metabolites of curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)heptane-3,5-dione) by Holder in 1978 (Holder et al. 1978). Tetrahydrocurcumin is useful as a colorless additive to food and cosmetics. Structurally, tetrahydrocurcumin contains similar diketone structures and phenolic groups as curcumin, but tetrahydrocurcumin lacks double bonds (Fig. 3) (Okada et al. 2001; Anand et al. 2008). It has been suggested that the beta-diketone moiety of tetrahydrocurcumin causes antioxidant activity by cleavage of the C-C bond at the active methylene carbon between two carbonyls in the beta-diketone moiety (Sugiyama et al. 1996). Compared with curcumin, tetrahydrocurcumin is more soluble in aqueous media, more easily absorbed through the gastrointestinal tract, and more stable in physiological conditions (Okada et al. 2001; Wu et al. 2014). Tetrahydrocurcumin displays the same physiological and pharmacological properties as curcumin, and in some aspects it may exert greater antioxidant (Aggarwal et al. 2015) and pharmacological activity than curcumin (Sugiyama et al. 1996; Pari and Amali 2005; Somporn et al. 2007). In some systems, tetrahydrocurcumin is a more potent free radical scavenger of tert-butoxyl, peroxy and DPPH radicals than other curcuminoids. Further, tetrahydrocurcumin is more effective in inhibiting red blood cell

hemolysis and reducing lipid peroxidation in rabbit erythrocyte membrane ghosts and rat liver microsomes (Osawa et al. 1995; Sugiyama et al. 1996). In cholesterol-fed rabbits, tetrahydrocurcumin inhibits oxidative modification of LDL and shows protective effects against oxidative stress (Naito et al. 2002). Tetrahydrocurcumin administered orally (80 mg/kg) to diabetic rats for 45 days showed a significantly beneficial effect on erythrocyte membrane bound enzymes and antioxidant defenses, in addition to its antihyperglycemic activity (Murugan and Pari 2007). Moreover, it was found that combined administration of chlorogenic acid (5 mg/kg) and tetrahydrocurcumin (80 mg/kg) for 45 days remarkably reduced the streptozotocin-induced changes in lipids, lipoproteins, and lipid metabolizing enzymes in diabetic rats (Karthikesan et al. 2010). It has been reported that tetrahydrocurcumin possesses hepatoprotective effects against chloroquine-induced hepatotoxicity in rats by decreasing the levels of enzymatic and non-enzymatic antioxidant activities (Murugavel and Pari 2004; Pari and Amali 2005). In neurodegenerative disorders, tetrahydrocurcumin increases the level of dopamine through the inhibition of monoamine oxidase activity in an animal model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Rajeswari and Sabesan 2008). Moreover, tetrahydrocurcumin reduces amyloid- β -induced oxidative stress and neurotoxicity by regenerating the mitochondrial membrane potential and inhibiting ROS generation and caspase-3 activity in rat hippocampal and human neuronal cells (Mishra et al. 2011). However, tetrahydrocurcumin was shown to be less effective than curcumin in TNF-induced NF- κ B activation and COX2 expression (Sandur et al. 2007).

In comparison with curcumin, there is limited information about the effect of tetrahydrocurcumin on cardiovascular function. A study by Ali et al. (2009) reported the cardioprotective effect of tetrahydrocurcumin on ischemic-reperfusion induced myocardial infarction in rats. Previous studies by our group have demonstrated the protective and therapeutic effects of tetrahydrocurcumin (50 and 100 mg/kg) against development of hypertension and vascular dysfunction induced by L-NAME administration in rats, and that the effects are associated with alleviation of oxidative stress (Nakmareong et al. 2011, 2012). The antihypertensive effect and some antioxidant effects of tetrahydrocurcumin are apparently more potent than those of curcumin (Nakmareong et al. 2011).

Mitigation of cadmium toxicity with curcumin and tetrahydrocurcumin

There are several studies in *in vitro* and rodent models which show that curcumin protects against Cd-induced immunotoxicity (Pathak and Khandelwal 2008; Alghasham et al. 2013), nephrotoxicity (Deevika et al. 2012), neurotoxicity (Daniel et al. 2004), lung toxicity (Rennolds et al. 2012), reproductive toxicity (Aktas et al. 2012; Oguzturk et al. 2012), hepatotoxicity (Eybl et al. 2004; Tarasub et al.

2012; Garcia-Nino and Pedraza-Chaverri 2014), and cardiovascular toxicity (Kukongviriyapan et al. 2014). The data acquired from our experiments provide evidence that curcumin has a significant ability to protect against vascular dysfunction induced by Cd in mice (Kukongviriyapan et al. 2014). A synopsis of proposed mechanisms by which curcumin and tetrahydrocurcumin mitigate Cd-induced endothelial dysfunction, vascular remodeling, and oxidative stress is shown in Fig. 4. Treatment with curcumin (50 or 100 mg/kg) restores blood pressure to nearly normal values, especially with high doses of curcumin. Moreover, curcumin improves vascular responses to vasoactive agents, including ACh, phenylephrine, and sodium nitroprusside. We found that Cd exposure induces down-regulation of eNOS protein expression, and this is associated with increased blood pressure and impaired ACh-dependent vasorelaxation (Kukongviriyapan et al. 2014). A previous report by Yoo et al. (2008) also found a decrease in eNOS protein levels in rats exposed to Cd. As discussed earlier, curcumin might also suppress $O_2^{\bullet-}$ and increase NO \bullet formation, thereby preventing ONOO $^-$ production and increasing NO \bullet bioavailability (Fig. 4) (Kukongviriyapan et al. 2014). Curcumin also reduces Cd accumulation in blood, liver, and kidney, probably caused by its chelating activity (Kukongviriyapan et al. 2014). Based on electrochemical studies in mice, it has been suggested that there might be a metal-ligand interaction between Cd and curcumin, thereby reducing heavy metal load in the body (Eybl et al. 2006), and mitigating any toxic effects of Cd. Therefore, the chelating effect of curcumin might contribute to a decrease in blood pressure and vascular function in Cd-treated mice.

The impact of tetrahydrocurcumin on Cd-induced hypertension and vascular dysfunction was reported by our group (Sangartit et al. 2014). We found that tetrahydrocurcumin (50 and 100 mg/kg) significantly decreases blood pressure, improves vascular responsiveness, and reverses structural and mechanical alterations of the aorta, including collagen and elastin deposition in mice that received Cd (100 mg/L) in drinking water (Sangartit et al. 2014). The ameliorative effect of tetrahydrocurcumin is associated with upregulated eNOS and down-regulated iNOS protein expression, increased nitrate/nitrite level, alleviation of oxidative stress and enhanced antioxidant GSH. Moreover, tetrahydrocurcumin also reduces the accumulation of Cd in the blood and tissues. Our results suggest that tetrahydrocurcumin ameliorates Cd induced hypertension, vascular dysfunction, and arterial stiffness in mice by enhancing NO \bullet bioavailability, attenuating oxidative stress, improving vascular remodeling, and decreasing Cd accumulation in other tissues (Sangartit et al. 2014). The results of our study suggest a beneficial effect of tetrahydrocurcumin in reducing the vascular alterations associated with Cd exposure.

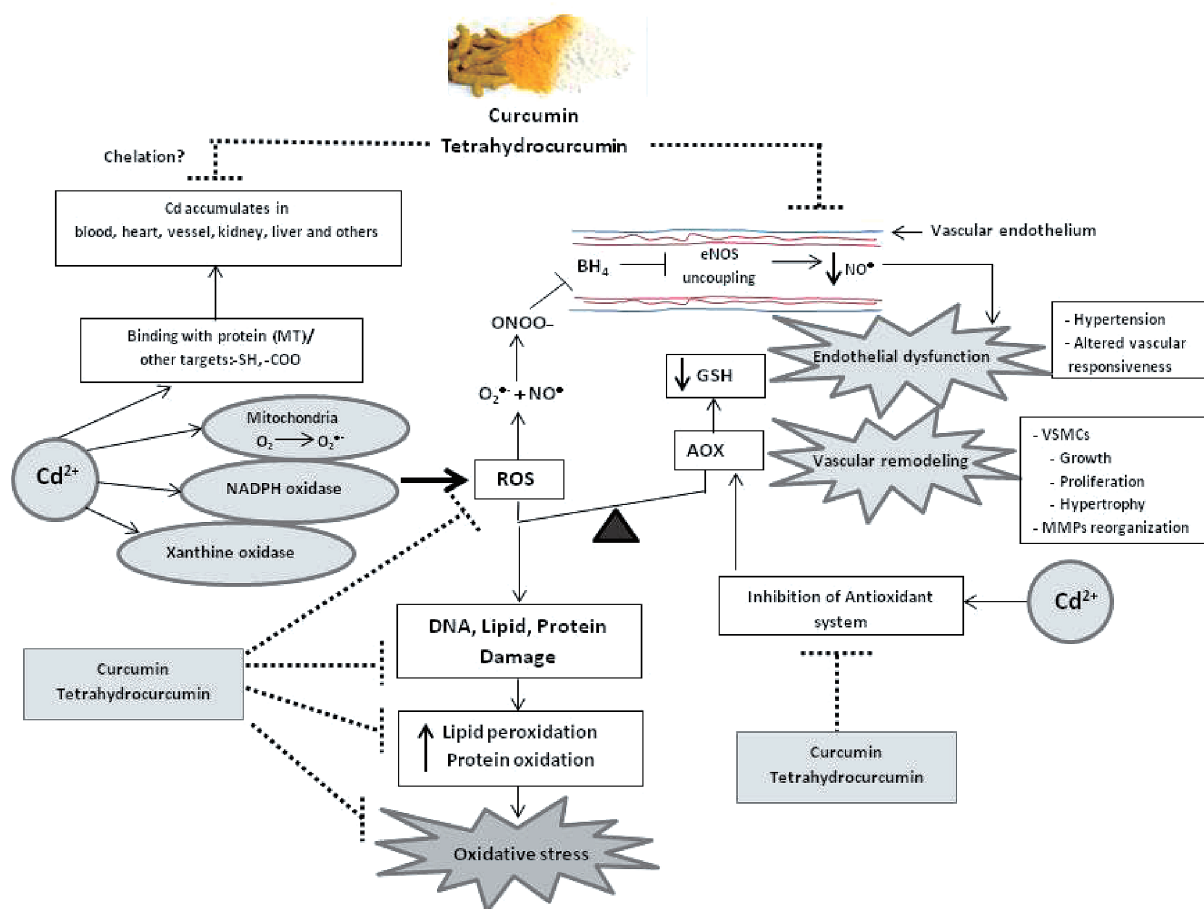


Fig. 4. A synopsis of proposed mechanisms by which curcumin and tetrahydrocurcumin mitigate the effect of cadmium on endothelial dysfunction, vascular remodeling, and oxidative stress.

ROS, reactive oxygen species; AOX, antioxidant; BH₄, tetrahydrobiopterin; NO•, nitric oxide; O₂•⁻, superoxide anion; ONOO⁻, peroxynitrite; GSH, glutathione; MT, metallothioneine; MMPs, matrix metalloproteinases.

Conclusion

Because Cd is not degraded in the environment and enters the food chain, the risk of human exposure to Cd and toxicity is constantly rising. Cd is a persistent and widespread pollutant that affects the structure and function of several organs by generating oxidative stress. This review provides an insight into the role of reactive species in Cd-induced toxicity. Metal-induced oxidative damage is driven by the formation of ROS/RNS, including O₂•⁻, OH•, NO• and ONOO⁻. The sources of free radicals within vascular cells are NADPH oxidases, xanthine oxidase, mitochondrial electron leakage, and uncoupled eNOS. Cd exposure increases risk of cardiovascular diseases including hypertension, atherosclerosis, nephropathy, and diabetes. Cd affects the cardiovascular system by altering cardiovascular structure and function. Endothelial and vascular smooth muscle cells are the major targets of Cd toxicity. Cd chelation has been suggested to be of use in the treatment of Cd toxicity. However, most chelators have severe adverse effects and inconvenient modes of administration. Combined therapy with more than one chelator and/or with

antioxidants may be more effective in reducing Cd toxicity. Recent studies provide evidence that curcumin and tetrahydrocurcumin, polyphenol compounds with strong antioxidant activities, can protect against hypertension, vascular dysfunction, arterial stiffness, and vascular remodeling during Cd intoxication in mice. The mechanisms contributing to their effectiveness are their free radical scavenging effect, alleviation of oxidative stress, restoration of the antioxidant GSH, and probable chelation effect resulting in reduction of Cd load in tissues. All of these effects lead to a reduction of high blood pressure and improvement of vascular function in our study. Although curcumin and tetrahydrocurcumin protect against Cd toxicity, the therapeutic effect of these two compounds after Cd exposure is another important aspect and merits further detailed investigation. In conclusion, the results from previous studies, together with the findings presented here, suggest a beneficial effect of curcumin and tetrahydrocurcumin. These two antioxidants may be used as a dietary supplement following heavy metal exposure, or as a complimentary chelating agent to increase the efficacy of chelators in order to minimize metal toxicity. However, evidence to support the use of natural

antioxidants in clinical treatment is still lacking. Therefore, further studies are needed to explore the exact mechanisms underlying the vascular protective effects of these antioxidants, and also to define the proper dosage and duration of treatment in humans.

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Conflict of Interest

The authors declare no conflict of interest.

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