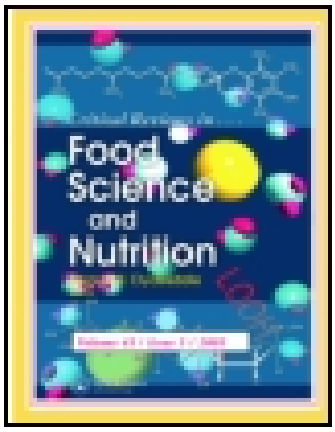

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Are Food Compounds Able to Modulate Noxious Activities Induced by Cadmium Exposure?

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Accepted author version posted online: 09 Mar 2015.

Are Food Compounds Able To Modulate Noxious Activities Induced by Cadmium Exposure?

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Abstract

Cadmium is one of the most toxic environmental and industrial pollutants and is able to induce severe injury because it is poorly excreted, accumulating in various organs. This common pollutant is responsible for serious damage in lung, brain, testis, kidney, liver, blood system and bone. Food compounds, such as flavonoids, represent the most abundant polyphenols in human dietary and comprise thousands of substances, which are freely available as high-dose dietary supplements. The mechanism of action of these ones consists in free radical scavenging and metal sequestration. The interaction of metal ions with flavonoids leads to chelation formation and the using of these natural compounds is better than the synthetic ones due to their lower toxic effects. The aim of this review is to describe the role of some food compounds, focusing flavonoids for modulating noxious biological activities induced by cadmium exposure.

Key words: flavonoids; cadmium; toxicity; nutrition

INTRODUCTION

In the last decades, chemoprevention has emerged as a novelty in controlling several chronic diseases, such as cardiovascular disease, renal dysfunction, lung, kidney and gastrointestinal damage, neuro-degeneration and cancer (Del Rio et al., 2013; Bishayee et al., 2011; Nordberg, 2009; Arora et al., 2008; Borges et al, 2008).

The understanding of the mechanisms of action involving chemoprotective compounds has been addressed by observing possible therapies against the toxic effects of heavy metals such as cadmium (Lawal & Ellis, 2011). Biologically, such metals participate in various signaling and metabolic pathways (Flora et al., 2013) and they are potentially toxic, mainly due to oxidative stress (Nwokocha et al., 2012).

Several metals and metalloids have been classified as being carcinogenic by the International Agency for Research on Cancer (Ziech et al., 2010; Mena et al., 2009). The potential of different metals on generating reactive oxygen species (ROS) is considered the main mechanism of metal-induced carcinogenesis since they are capable of changing the redox mechanism in the eukaryotic cells (Lee et al., 2012). Numerous studies have shown an increase in the incidence of cancer associated with chronic exposure to heavy metals (Arita & Costa, 2009).

Cadmium is one of the most toxic environmental and industrial pollutants and is able to induce severe injuries. It is poorly excreted and accumulates in various organs, being responsible

for serious damages in lung, brain, testis, kidney, liver, blood system and bone (El-Refaiy & Eissa, 2013; Anetor, 2012). Diet is the main source of environmental exposure to cadmium in non-smokers; it is present in practically every food type (Engström et al., 2011; Satarug et al., 2010; Jarup & Akesson, 2009; Panjehpour & Bayesteh, 2008; Brzóska et al., 2003). According to Nasreddine & Parent-Massin (2002), two thirds of the cadmium exposure through the diet is attributed to contaminated vegetables and the one third to animal products. The World Health Organization states that the human daily intake of cadmium ranges from 40 mg in non-polluted regions to 200 mg for contaminated areas (Ivanova et al., 2013). Moreover, smoking rises cadmium exposure in active and passive smokers (Satarug, 2012).

Studies have demonstrated that cadmium is absorbed by the gastrointestinal tract and by pulmonary exposure, being carried via blood bonded to albumin (Nordberg, 2009; Sánchez-González et al., 2006). On the liver, this complex inhibits liver enzymes promoting increased lipid peroxidation, congestion, ischemia and hypoxia (Sánchez-González et al., 2006). Concomitantly, it induces the synthesis of metallothionein (MT), a chain of aminoacids with a binding site for metals. The cadmium-MT complex is filtered by the renal glomeruli and reabsorbed by the proximal tubules. There, digestive enzymes act on the protein, releasing the cadmium ions restarting the synthesis of new MT. When the levels of free cadmium exceed the production of MT, extensive damage in the kidney cell membranes occurs and, consequently, renal insufficiency takes place (Sanchez-Gonzalez et al., 2006. Zhao et al., 2010; Nordberg, 1984).

In the lungs, the absorption and accumulation of cadmium are responsible for the development of diseases such as emphysema, bronchitis and cancer (Panjehpour & Bayesteh, 2008). Zhao and colleagues (2010) argued that there is an increase of MT response in the lungs, possibly as a defense mechanism against the presence of cadmium in the tissue.

Regardless of the affected tissue, toxicity triggered by cadmium is initially characterized by oxidative damage (Eybl et al., 2006). Studies have suggested that the mechanism of acute toxicity by cadmium involves depletion of glutathione and proteins bound to a sulfhydryl group. The result is in an increase of reactive oxygen species, which, in turn, promotes lipid peroxidation, leading to DNA damages (El-Refaiy & Eissa, 2013; Liu et al., 2009).

In view of the extensive human exposure to cadmium (through environmental, occupational and food contamination, as well as smoking habits) studies demonstrating the effectiveness of food compounds in reducing or reversing the damage are welcome.

Numerous food compounds have been tested for this purpose. Flavonoids represent the most abundant polyphenols in human diet, comprising thousands of compounds (de Moura et al., 2013), which are also freely available as dietary supplements (Flora et al., 2013). Biologically, the mechanism of action attributed to polyphenols is of free radical scavenging and metal sequestration (Flora et al., 2013; Fraga et al., 2010). The inactivation of free radicals occurs when an antioxidant reacts with the free radical and even when the reaction leads to the formation of another, less active, radical (Leopoldini et al., 2011).

In spite of the therapeutic interventions using potent chelating agents for cadmium intoxication-treatment, an effective chelation therapy has not yet been established (Flora & Pachauri, 2010). Nevertheless, great efforts have been made in order to test the use of antioxidants for treating genomic instability syndromes induced by cadmium (Anetor, 2012, (Ramesh & Satakopan, 2010). Therefore, it is believed that the use of natural antioxidant compounds is one way to attenuate the damage caused by cadmium intoxication (Renugadevi & Prabu, 2010a).

Regarding the chelation mechanism, chelating agents are able to remove toxic metals, forming a stable complex. The metal is then removed from the biological chelator and this new complex, non-toxic, can be transported across physiological barriers, facilitating cadmium excretion not only from the site of deposition, but also from the body (Flora et al., 2013).

Several natural compounds have been described in the literature due to chelating roles (Sears, 2013). Chelators are able of mobilize metals in the tissues and maintain the chelate moiety during circulation to the kidneys (for excretion in the urine) and to the liver (for excretion in the bile) (Sears, 2013).

The aim of this review is to describe the role of food components in modulating noxious activities induced by cadmium exposure.

Studies involving the use of food components and cadmium exposure

Since 1980, polyphenols have been tested as chelator agents. The interaction of metal ions with flavonoids forms complexes with the advantage of showing lower toxic effects in comparison with synthetic chelators (Smith, 2013; Symonowicz & Kolanek, 2011; Malešev & Kunti 2007). Recently Gollücke et al. (2013) revised recent uses of polyphenols against diseases and discussed several possible mechanisms.

Quercetin, a biologically active and common dietary flavonoid present in fruits and vegetables, is known by its antioxidant activity. It has been reported that the substance is able to prevent oxidative injury and cell death by chelating metal ions, scavenging oxygen radicals, and protecting against lipid peroxidation (Unsal et al., 2014; Bu et al., 2011; Malešev & Kunti, 2007). Unsal and colleagues (2014) evaluated the neuroprotective effect of quercetin against cadmium exposure. The authors injected cadmium chloride (2 ml/kg/day for 30 days) in Sprague-Dawley rats, and the quercetin-treated group received 15mg/kg once a day intraperitoneally (ip) starting 2 days prior to cadmium injection. After the experimental period enzymatic antioxidants (superoxide dismutase, glutathione peroxidase and catalase) and lipid peroxidation levels were evaluated. The authors concluded that quercetin was effective in combating cadmium-induced neurotoxicity.

Wang and colleagues (2013) studied quercetin effects on cadmium-induced cytotoxicity in proximal tubular cells (1µg/mL quercetin; 2.5 or 5µmol/L cadmium) and showed that this compound had a protective effect in the cell against cadmium damages, inhibiting apoptosis, attenuating lipid peroxidation and renewing mitochondrial function by elevation of antioxidant

levels. Bu et al. (2011) also used quercetin in treating germ cells after cadmium intoxication, with 4 mg/kg of body weight of cadmium to mice, daily, during 2 weeks. Animals exposed to cadmium and treated with quercetin had the structure of the seminiferous epithelium and the antioxidant status restored to normal. These effects were confirmed by evaluating glutathione and superoxide dismutase status, as well as verifying the suppression of apoptosis of germ cells.

Renugadevi and Prabu (2010b) demonstrated that quercetin provided protective effect against oxidative damage induced by cadmium in the kidney tissue of rats (5mg/kg $CdCl_2$, 50mg/kg quercetin, for 4 weeks). The substance was able to re-establish the levels of the enzymatic antioxidants catalase, superoxide dismutase, glutathione peroxidase, S-transferase and reductase, and of non-enzymatic antioxidants (vitamins C and E and reduced glutathione) in the kidney, diminishing the lipid peroxidation and some other biochemical parameters, such as urea, uric acid and creatinine. Furthermore, quercetin also ameliorated the tubular necrosis, tubular degeneration, desquamation and thickening of basement membrane. In the heart, pre-treatment with quercetin prevented oxidative impairment in rats exposed to cadmium reducing the activities of the cardiac enzymes (creatinine kinase, lactate dehydrogenase, alkaline phosphatase, aspartate transaminase and alanine transaminase) restoring to normal levels. The authors attribute the positive results to the anti-lipoperoxidative, anti-oxidant and membrane stabilizing properties of quercetin. Moreover, this food compound normalized serum lipids inhibiting the accumulation of cholesterol and consequently hypercholesterolemia and atherosclerosis. Histologically, quercetin was capable of preventing miofibrile damage induced by cadmium. Taken together, quercetin supplements protected cardiac tissue against heavy metals (Prabu et al., 2011).

Regardless of all the protective effects demonstrated by quercetin in cadmium-induced damage, discussed above, it was not able to protect hepatotoxicity according to Vicente-Sanchez and colleagues (2008). The authors showed that quercetin was not a metal chelator, although it prevented oxidative stress, increased metallothionenin and eNOS expression. They also suggested that lipid peroxidation may contribute to the liver damage produced by acute cadmium administration, but that is not the major toxic mechanism.

Naringenin, a flavonone found in citrus and grape fruits, was employed in cadmium-induced hepatotoxicity (5mg/kg $CdCl_2$, 50mg/kg naringenin, for 4 weeks). The results showed that naringenin significantly reversed the activities of serum hepatic marker enzymes to their near-normal levels, reduced lipid peroxidation, restored the levels of antioxidant defense in the liver and preserved the normal histological architecture of the tissue (Renugadevi & Prabu, 2010a). The association of naringenin with vitamins C and E accelerated the detoxication of cadmium in the liver tissue, inhibiting oxidative stress, improving antioxidant status and reducing histopathological changes (Prabu et al., 2011).

Many researchers indicate that honey has functional properties in human health which is mainly credited to the presence of flavonoid compounds (Abdelaziz et al., 2013). Honey was evaluated against cadmium exposure using rabbit's haematological parameters (Abdelaziz et al, 2013). Animals received 3mg/kg of cadmium (ip) and cadmium chloride in tap water (100mg/L). The results showed that the group receiving cadmium had an increase in glucose, total cholesterol and triglycerides levels at the end of the experiments, when compared to the control group. When the animals were treated with honey, these parameters were attenuated when

compared to the intoxicated animals but still higher than the control group. Serum transaminases (aspartate aminotransferase, AST, and alanine aminotransferase, ALT), bilirubin and serum alkaline phosphatase (ALP) were also evaluated and they were ameliorated after the honey intake, as well as urea, uric acid and creatinine levels. The authors concluded that honey was effective in providing recoveries in the altered blood parameters.

Zingiberofficinale is a herb used for culinary purposes which is also used therapeutically. It is known for anti-inflammatory and antioxidant potentials, including against metal toxicity, as a chelator agent. With regards to this property, Nwokocha et al. (2012) analyzed the hepatoprotection of *Zingiberofficinaleto against heavy metals accumulation. This herb was mixed in rat chow (7% w/w) and fed to the animals exposed to cadmium (200 ppm in tap water). The results showed that Zingiberofficinale affected the bioavailability, kinetics and assimilation of heavy metals as well as its uptake and excretion in a time-dependent manner, mainly acting as a hepatic protection against cadmium.*

The most widely consumed beverage in the world, black tea, is rich in catequins that, when oxidized and polymerized, result in aflavin. This compound was tested for its protective effects against damages caused by cadmium in spermatogenesis (Wang et al., 2012). The authors applied 0.4 mg/kg of cadmium, once a day, during five weeks and treated the rats with 50, 100 or 200mg/kg of aflavin for the same period. The results showed that aflavin presented a dose-dependent response in most of the parameters, ameliorating sperm concentration, mobility and malformation, DNA damage of testicular cells, antioxidants enzyme levels (glutathiones and superoxide dismutase) and lipid peroxidation. The aflavins also had chelant action, diminishing

cadmium-concentration in the liver, testis and blood level, while cadmium levels increased in urine and feces. In a similar manner, Wang and colleagues concluded that flavins were beneficial in the treatment of cadmium-induced testicular toxicity. When long-term grape juice concentrate consumption rich in polyphenols was tested, the results revealed that this compound was able to protect the reproductive parameters of cadmium-exposed male rats (Pires et al., 2013).

Curcumin and resveratrol were also studied by Ebyl et al. (2006) in a 3 day oral pre-treatment on cadmium-induced oxidative damage and cadmium distribution. According to the authors, the interaction between cadmium and curcumin reduced heavy metal load in the body and, resveratrol was able to inhibit lipid peroxidation. The data showed that both compounds completely prevented lipid peroxidation in the liver, but were not able to prevent glutathione depletion. Both curcumin and resveratrol prevented cadmium-induced inhibition of glutathione peroxidase, while resveratrol alone was effective against catalase activity inhibition. Conversely, none of the xenobiotics was able to reduce cadmium concentrations in biological tissues.

In 2002, Casalino and colleagues reported the effects of hydroxytyrosol (2-3,4-dihydroxyphenyletanol, DPE), a compound present in extra-virgin olive oil, combined with manganese (Mn^{2+}) in the liver of rats exposed to cadmium. The results showed that twenty four hours following cadmium intoxication, liver glutathione levels increased 30.4% in non-treated animals and similar result was observed with administration of a low concentration of Mn^{2+}(32.9%). The treatment of cadmium-exposed rats with Mn^{2+} alone failed to restore the liver activities of CuZn-SOD, Mn-SOD and catalase. Animals exposed to cadmium (2.5mg/kg, ip) and treated with DPE (9mg/kg, ip) and Mn^{2+}(2mg/kg, ip) were able to maintain the lipid peroxidation

The authors concluded that the exposure to cadmium stimulated endogenous defense in liver cells and that DPE was able to modulate this outcome.

Two widely accepted foodstuffs are recognized for their culinary and medicinal properties: onion and garlic (Suru, 2008). *Allium cepa* (onion) and *Allium sativum* (garlic) are rich in antioxidant compounds and their protection potential against cadmium exposure has been documented (Ige et al., 2009). Ola-Mudathir and colleagues (2008) showed that onion and garlic extracts partially protects the testis and spermatozoa against cadmium toxicity by reduction in the level of lipid peroxidation as well as enhanced levels of glutathione, superoxide dismutase and catalase in the testis. The impairment in sperm characteristics was markedly restored with a corresponding increase in the weight of the testis. *Allium cepa* extract diminished superoxide dismutase and catalase enzymes as well as lipid peroxidation level. The extract was also able to decrease cadmium levels in urine of treated rats, preventing renal tubular damage. (Ige et al., 2011; Ige et al., 2009). Suru (2008) also obtained positive results for renal damage induced by cadmium and treated with *Allium cepa* or *Allium sativum*. Onion and garlic had protective effects on cadmium induced oxidative stress by reduction of lipid peroxidation and by sparing the depletion of endogenous glutathione, superoxide dismutase and catalase. Onion and garlic intake offered a consistent protection against cadmium induced oxidative damage in the kidney.

Concluding remarks

In this article, we have showed recent studies focusing the modulatory activities exerted by food compounds against cadmium exposure using experimental test systems. Although these data have revealed important mechanisms of action much remains to be examined. More adequately powered, randomised, placebo controlled human studies are needed better understanding the role of these food compounds on human health. Therefore, this area warrants intensive investigation as a new way of knowledge, which would apply foods as promising therapeutic agent against human diseases..

Acknowledgments

This study was supported by CNPq and CAPES.

Conflict of Interest

None declared.

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