REVIEW PAPER

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THE ROLE OF WELL-KNOWN ANTIOXIDANT VITAMINS IN THE PREVENTION OF CADMIUM-INDUCED TOXICITY

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Abstract
Long-term exposure to cadmium (Cd) leads to the development of a number of conditions associated with liver and kidney damage, reproductive and cardiovascular disorders, in addition to visual impairment, blindness and hearing loss, among others. Cadmium has been classified as a human carcinogen by the International Agency for Research on Cancer. The toxicity of Cd is related to its pro-oxidant properties and the associated increase in oxidative stress. Antioxidant ingredients may be helpful in preventing the adverse effects of Cd. The effect of well-known antioxidant vitamins (E, C, A and β-carotene) in the prevention of Cd-induced toxicity is presented in this study. Numerous studies in animal models have shown that the effects of vitamins: E, C, A, and β-carotene were effective in reducing Cd concentrations in organs and tissues and reduced Cd-induced changes in liver, kidney, and reproductive, circulatory, nervous, immune, and respiratory systems. In contrast, the limited number of human studies does not allow to accurately determine the role of these nutrients in reducing Cd-induced toxicity, indicating the need for further studies clarifying the role of antioxidant vitamins in reducing Cd-induced toxicity. However, it seems reasonable to promote the consumption of natural food products that are sources of antioxidant vitamins in groups of people with occupational and environmental exposure to Cd. Int J Occup Med Environ Health. 2022;35(4):367–92

Key words:
vitamin A, β-carotene, vitamin E, vitamin C, oxidative stress, cadmium exposure

INTRODUCTION

The cadmium (Cd) content in the environment is constantly increasing, which is related to human activities and natural processes occurring in nature. The increase in Cd content associated with human factor is due to the use of this metal in many industries, including the construction of nickel-cadmium batteries, in galvanizing steel, paint pigments, and in agriculture for the production of phosphate fertilizers, while natural sources of Cd are mainly volcanic eruptions and rock weathering [1].

Cadmium enters the human body mainly through the oral route, through respiratory tract and absorption through the skin is negligible. The highest exposure to Cd occurs during occupational exposure and concerns workers in the electroplating, battery manufacturing and pigment industries. Smoking is an important source of chronic environmental exposure to Cd. Cadmium is also found in some foods, which include algal formulations, cocoa-based products, crustaceans, edible offal, fungi, oilseeds, seaweeds and water mollusks. However, the highest amounts of dietary Cd come from products that are consumed in large quantities, such as grains and grains products, vegetables and vegetables products and starchy roots and tubers. Based on total diet studies con-

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ducted in such countries as the United States, Australia, Sweden, France, Chile, Spain, Serbia and Denmark, it was estimated that 40–60% of total dietary Cd intake comes from rice, potatoes and wheat [2].

The harmful effects of Cd at high doses have long been known. Epidemiological studies also indicate significant toxicity at long-term exposure to relatively low doses of Cd. Long-term exposure to Cd is associated with dysfunction of such system as: urinary (glomerular and tubular damage, kidney stones), digestive (hepatic dysfunction), respiratory (pneumonitis, destruction of mucous membranes), cardiovascular (coronary heart disease, stroke, peripheral artery disease and changes in lipid profile, hypertension), skeletal (loss of bone density and mineralization, Itai-Itai disease), reproductive (testicular necrosis, estrogen-like effects, affection of steroid-hormone synthesis). Cadmium has also been shown to have teratogenic and carcinogenic effects. The International Agency for Research on Cancer has classified Cd as a group 1 carcinogen based on data obtained from occupational exposure in humans [1].

The toxic effects of Cd result from various mechanisms, but the most significant is the impairment of the antioxidant system and the associated increase in the concentration of reactive oxygen species. Moreover, Cd induces tissue injury through epigenetic changes in DNA expression. Other mechanisms include inhibition of heme synthesis, and impairment of mitochondrial function which is potentially connected with inducing apoptosis. The toxic effect of Cd is also associated with the inhibition of the activity of antioxidant enzymes as a result of the formation of bonds with the -SH groups of cell membranes and cytoplasmic proteins. Moreover Cd may interfere with the physiologic action of Zn or Mg.

Various nutrients are involved in reducing the severity of oxidative stress, and in particular the benefits and function of the well-known antioxidants such as vitamin: E, C, A and β-carotene and also lesser-known antioxidants – vitamin: D, K and folic acid were examined. The protective properties of vitamins may be due to activation of antioxidant enzymes and reduction of reactive oxygen species. Studies on the reduction of oxidative stress intensity focus mainly on the antioxidant effect of vitamin E, C and A and β-carotene [3].

In this review, the results of animal and human studies analyzing the effects of well-known antioxidant vitamins such as vitamin E, C, A and β-carotene on the reduction of Cd induced toxicity are discussed.

METHODS

In this review, electronic database PubMed were used. Articles relevant for the study were searched for using the following keywords: cadmium and vitamin E, cadmium and vitamin C, cadmium and vitamin A, cadmium and β-carotene. Antioxidant vitamins were included because they may be helpful in preventing the adverse effects of Cd. As a result of the search 310 articles were collected. The following inclusion criteria were used:

- written in English,
- full text article,
- publication date: January 1, 1980–April, 30, 2021 (73.6% of those were published after 2000),
- topic: exposure to Cd and use of antioxidant vitamins.

The analysis eventually included 57 original, reviewed articles in English (50 *in vivo* in animal models studies, and 7 human studies), in which a potentially modulating effect of antioxidant vitamins on Cd-induced toxicity has been studied (Figure 1).

RESULTS

Vitamin E

The effects of vitamin E on reducing the effects of Cd-induced toxicity were analyzed *in vivo* in animal models and in 2 human studies. Different doses of vitamin E and varying exposure times were used in the animal model studies. The results of the analyzed studies on the protec-

tive role of vitamin E during Cd exposure are presented in Table 1.

Studies on animal models exposed to Cd have shown a beneficial effect of vitamin E supplementation on the gastrointestinal tract, which was associated with a reduction in the severity of oxidative stress in the liver [4–10]. In studies on rats exposed to Cd, vitamin E also contributed to an increase in intracellular liver calcium and reversal of morphological changes in this organ [4], caused a reduction in histological changes in the liver [11], and in addition, an increase in animal body weight and liver weight [5], as well as a reduction in histopathological [5,7], and morphological changes of liver cells [12], and in Cd accumulation [5,6], and addition an increase in vitamin E concentration in the liver [5,13] were observed. In a study on fish exposed to Cd, a positive effect of vitamin E on liver function parameters was also observed – reduction of alanine aminotransferase (ALT) activity in the blood [14]. Decrease of liver enzymes activity was also shown in studies conducted on broiler chicks, fish and rats exposed to Cd [12,15–18]. Vitamin E also contributed to the reduction of glucose levels in the blood in fish and rats exposed to Cd [16,17]. In one study conducted on fish exposed to Cd, no effect of vitamin E was observed on the concentration of Cd in the liver [7].

The beneficial effect of vitamin E in animals exposed to Cd was also associated with increased protein and mRNA expressions of Nrf 2-related molecules (heme-oxygenase-1, NADPH quinine-oxidoreductase-1, glutamylcysteine ligase catalytic subunit, glutamate cysteine ligase modifier subunit, glutathione S transferase) [5]. The protective effect of vitamin E on animals exposed to Cd was also due to reducing the apoptosis of liver cells by regulating apoptosis-related gene expression [7]. In another study in rats exposed to Cd, vitamin E did not affect gene expression of tumor necrosis factor α and c-fos [9].

Several studies have analyzed the beneficial effect of vitamin E on the urinary system of animals exposed to Cd.

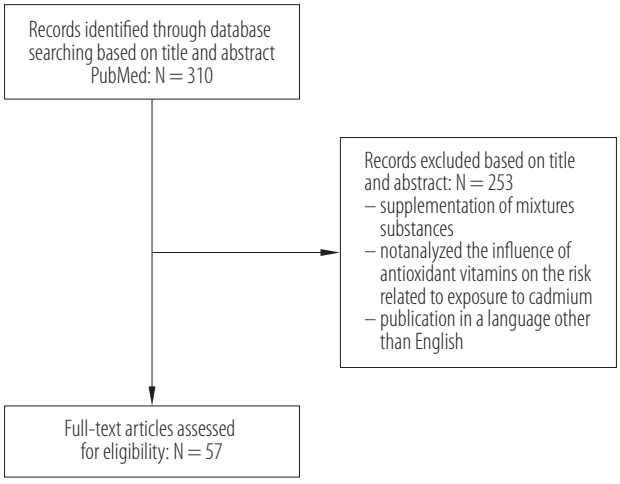

Figure 1. The procedure of inclusion of studies in the review in animal models on vitamin E treatment and relationship between Cd exposure and vitamin E in blood concentration in human studies, collected on PubMed in May 2021

Vitamin E helped to reduce inflammation in kidney [19]. In other studies conducted on fish, rabbits and rats exposed to Cd, a reduction in the severity of oxidative stress [6,10,13,20] and histopathological changes in the kidney were observed [19,20]

A decrease in lactate dehydrogenase activity in urine was observed in a study by Shaikh et al. [10]. Vitamin E at a higher dose (400 mg/kg of diet) also alleviated functional and structural damage in kidney tissue (including decreased β2 microglobulin in urine, improved glomerular filtration rate, decreased edema in renal tissue) of rats exposed to Cd [21]. An improvement in renal function parameters and a decrease in malondialdehyde levels, an increase in reduced glutathione, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), total antioxidant capacity in the kidney was demonstrated. Vitamin E also contributed to the reduction of the renal cell apoptosis and the mRNA and protein expression levels of renal cell apoptotic regulatory molecules (Bax, Caspase-3, GRP94, GRP78, Caspase-8) [22]. The beneficial effect of vitamin E on renal function parameters by lowering creatinine and urea in serum was observed in a study on rats

Table 1. Results of studies in animal models with cadmium (Cd) exposure and vitamin E treatment and relationship between Cd exposure and vitamin E in blood concentration in human studies, collected on PubMed in May 2021

Reference	Research model	Study description	Main results
4	Rats, Wistar	– CG (N = 8) – Cd (15 mg/kg b.w. orally) – G1 (N= 8) – Cd (15 mg/kg b.w. orally) and vitamin E (300 mg/kg b.w. for 3 weeks)	G1 vs. CG – liver: weight↑, calcium↑, MDA↓, POD↓, CAT↑ SOD↑, morphological changes↓
5	Rats, Sprague Dawley	– CG (N = 8) – $CdCl_2$ (5 mg/kg b.w. intragastric administration for 4 weeks) – G1 (N = 8) – $CdCl_2$ (5 mg/kg b.w. intragastric administration for 4 weeks) and vitamin E (100 mg/kg b.w. intragastric administration for 4 weeks)	G1 vs. CG – liver: weight↑, histopathological changes↓, Cd↓, vitamin E↑, ALT↓, AST↓, MDA↓, GSH↑, T-AOC↑, SOD↑, CAT↑, GPx↑, protein and mRNA expression levels of: Nrf2↑, HO-1↑, NQO-1↑, GCLC↑, GCLM↑, GST↑ – body: weight↑
6	Rats, Charles Foster	– CG (N = 5) – $CdCl_2$ (0.05 mg/kg b.w. by gavage for 30 days) – G1 (N = 5) – $CdCl_2$ (0.05 mg/kg b.w. by gavage for 30 days) and vitamin E (0.4 IU/100 g b.w. by gavage for 30 days)	G1 vs. CG – liver: Cd↓, MDA↓, GSH↑, GSSG↑ – kidney: Cd↓, MDA↓, GSH↑, GSSG↑
7	Fish (*Ctenopharyngodon idellus)*	– CG (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected intraperitoneally) – G1 (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected intraperitoneally) and vitamin E (20 IU/kg b.w. were given 4 days post Cd injection)	G1 vs. CG – liver: Cd↔, histopathological changes↓, MDA↓, apoptotic percentage↓, caspase-3↓, caspase-8↔, caspase-9↓, Grp78↔, Bax↓, AIF↓, Bcl-2↑
8	Broiler chicks, Cobb strain	– CG (N = 10) – Cd (100 ppm in fed for 6 weeks) – G1 (N = 10) – Cd (100 ppm in fed for 4 weeks) and vitamin E (300 ppm in feed for 2 weeks) – G2 (N = 10) – Cd (100 ppm in fed for 6 weeks) and vitamin E (300 ppm in feed for 6 weeks)	G1, G2 vs. CG – blood: CAT↓, SOD↓ – liver: TBARS↓, GSH↑
9	Rats, Sprague Dawley	– CG (N = 10) – $CdCl_2$ (20 µmol/kg b.w. intraperitoneally administred single dose) – G1 (N = 10) – $CdCl_2$ (20 µmol/kg b.w. intraperitoneally administred single dose) and vitamin E (50 mg/100g b.w. intragastrically, pretreatment)	G1 vs. CG – liver: MDA↓, GSH↔, gene expression (TNF-α and c-fos)↔
10	Rats, Sprague Dawley	– CG (N = 6) – $CdCl_2$ (5 µmol/kg b.w. 5 times/week for 22 weeks) – G1 (N = 6) – $CdCl_2$ (5 µmol/kg b.w. 5 times/week for 22 weeks) and vitamin E (100 mg/kg b.w. 5 times/week for week 13 and 150 mg/kg b.w. from week 16 to 22)	G1 vs. CG – serum: ALT↓, LDH↓ – liver: GSH↔, MDA↓ – kidney: GSH↔, MDA↓ – urine: LDH↓, protein↓
11	Rats, Wistar	– CG (N = 5) – Cd (2 mg, single dose, intraperitoneally) – G1 (N = 5) – Cd (2 mg, single dose, intraperitoneally) and vitamin E (1.5 mg/kg)	G1 vs. CG – serum: urea↓, creatinine↓, ALP↔, AcP_T↓, AcP_P↓ – liver: histological changes↓ – kidney: histological changes↓ – testes: histological changes↓

12	Fish, grass carp (*Ctenopharyngodon idellus*)	– CG (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) – G1 (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) and vitamin E (20 IU/kg b.w. were given 4 days post Cd injection)	G1 vs. CG – liver: morphological changes↓, AST↓, ALT↓, CAT↑, SOD↑, GPx↑, CAT mRNA expression↑, SOD mRNA expression↑, GPx mRNA expression↑
13	Rabbits, New Zealand White	– CG (N = 8) – $CdCl_2$ (1 g/l water for 30 days) – G1(N = 8) – $CdCl_2$ (1 g/l water for 30 days) and vitamin E (100 mg orally for 30 days)	G1 vs. CG – plasma: vitamin E↑, TBARS↓ – RBC: TBARS↓, GPx↑, GSH↔ – liver: vitamin E↑, TBARS↓, GPx↑, GSH↔ – kidneys: vitamin E↑, TBARS↓, GPx↑, GSH↔
14	Fish, Nile tilapia (*Oreochromis niloticus*)	– CG (N = 20) – Cd (50 mg/kg diet for 12 weeks) – G1 (N = 20) – Cd (50 mg/kg diet for 12 weeks) and vitamin E (50 mg/kg diet for 12 weeks)	G1 vs. CG – blood: total protein↔, albumin↔, creatinine↓, urea↔, ALT↓, AST↔, Hb↔, RBC↔, WBC↔ – body: weight↔, Cd residue↓
15	Broiler chicks, Cobb strain	– CG (N = 10) – Cd (100 ppm in fed for 6 weeks) – G1 (N = 10) – Cd (100 ppm in fed for 4 weeks) and vitamin E (300 ppm in feed for 2 weeks) – G2 (N = 10) – Cd (100 ppm in fed for 6 weeks) and vitamin E (300 ppm in feed for 6 weeks)	G1, G2 vs. CG – serum: ALT↓, ALP↓, creatinine↓, urea↓
16	Fish, Nile tilapia *(Oreochromis niloticus)*	– CG (N = 14) – Cd (4.64 mg/l for 30 days) – G1 (N = 10) – Cd (4.64 mg/l for 30 days) and vitamin E (50 mg/kg b.w. for 30 days)	G1 vs. CG – blood: RBC↑, Hb↑, Htc↑, MCV↑, MCH↑, MCHC↑, glucose↓, TP↑, TL↓, AST↓, ALT↓, LPO↓, DNA↓ – condition factor: ↔
17	Rats, Sprague Dawley	– CG (N = 7) – $CdCl_2$ (5 mg/kg b.w. orally for 30 days) – G1 (N = 7) – $CdCl_2$ (5 mg/kg b.w. orally for 30 days) and vitamin E (100 mg/kg b.w. orally for 15 days)	G1 vs. CG – plasma: TBARS↓, GST↑, AST↓, ALT↓, AlP↑, AChE↑, TP↔, globulin↔, albumin↑, glucose↓, bilirubin↓, urea↓, creatinine↓ – blood: Hb↑, TEC↑, TLC↓, Htc↑ – liver: TBARS↓, GST↑, AST↔, ALT↔, AlP↑, protein↔ – testes: TBARS↔, GST↔, AST↓, ALT↓, protein↔ – brain: TBARS↓, GST↔, AChE↑, protein↔ – sperm: concentration↑, motility↑, dead↓, abnormal↓
18	Rats, Wistar	– CG (N = 8) – Cd (0.4 mg/kg b.w., injected intraperitoneally) – G1 (N = 8) – Cd (0.4 mg/kg b.w., injected intraperitoneally) and vitamin E (20 UI/kg b.w. single intramuscularly dose)	– G1 vs. CG – blood: RBC↑, Hb↑, Htc↑, WBC↓, PLT↑ – serum: TP↑, TL↓, ALT↓, AST↓ – plasma: vitamin E↑, vitamin C↑, coenzyme Q_{10}↑ – erythrocytes: LPO↓, GSH↑, GSSG↓, SOD↑, CAT↑, GPx↑, GR↑
19	Fish, grass carp (*Ctenopharyngodon idellus*)	– CG (N = 3) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) – G1 (N = 3) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) and vitamin E (20 IU/kg b.w. were given 4 days post Cd injection)	– blood: Cd↔, RBC↔, Hb↔, apoptosis↔, leukocytes↔, lysozyme↔ – trunk kidney: Cd↔, histopathological changes↓, apoptosis↔, expression of CD 4 L and CD 8β mRNA↔

Table 1. Results of studies in animal models with cadmium (Cd) exposure and vitamin E treatment and relationship between Cd exposure and vitamin E in blood concentration in human studies, collected on PubMed in May 2021 – cont.

Reference	Research model	Study description	Main results
20	Rats, Wistar	– CG (N = 6) – $CdCl_2$ (20 mg/kg/b.w. by orally for 30 days) – G1 (N = 6) – $CdCl_2$ (20 mg/kg/b.w. by orally for 30 days) and vitamin E (20 mg/kg/b.w. by orally for 30 days)	G1 vs. CG – kidney: Mn-SOD↑, Cu/Zn-SOD↑, CAT↑, GPx↑, GR↑, GST↓, LPx↓, histopathological changes↓
21	Rats, Sprague Dawley	– CG (N = 10) – Cd (50 ppm in the drinking water for 20 weeks) – G1 (N = 10) – Cd (50 ppm in the drinking water for 20 weeks) and vitamin E (40 mg/kg of diet for 20 weeks) – G2 (N = 10) – Cd (50 ppm in the drinking water for 20 weeks) and vitamin E (400 mg/kg of diet for 20 weeks)	G1 vs. CG – serum: ACE↓ – blood: pressure↓ – kidney: GFR↑, morphological changes↔ – urine: $\beta_2$microglobulin↔ G2 vs. CG – serum: ACE↓ – blood: pressure↓ – kidney: GFR↑, morphological changes↓ – urine: $\beta_2$microglobulin↓
22	Rats, Sprague Dawley	– CG (N = 8) – $CdCl_2$ (5 mg/kg b.w. intragastric administration for 4 weeks) – G1 (N = 8) – $CdCl_2$ (5 mg/kg b.w. intragastric administration for 4 weeks) and vitamin E (100 mg/kg b.w. intragastric administration for 4 weeks)	G1 vs. CG – serum: BUN↓, creatinine↓ – kidney: vitamin E↑, Cd↔, MDA↓, GSH↑, SOD↑, CAT↔, GPx↑, T-AOC↑, renal cell apoptosis↓, histopathological changes↓, Bcl-2↑, Bax↓, caspase-3↓, Grp94↓, Grp78↓, caspase-8↓ – weight: body↑, kidney↑
23	Fish, grass carp (*Ctenopharyngodon idellus)*	– CG (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) – G1 (N = 6) – $CdCl_2$ (20 µmol/kg b.w. single dose injected) and vitamin E (20 IU/kg b.w. were given 4 days post Cd injection)	– head kidney: Cd↔, histopathological changes↓, apoptosis↔, expression of CD 4 L and CD 8β mRNA↔ – spleen: Cd↔, histopathological changes↓, apoptosis↔, expression of CD 4 L and CD 8β mRNA↔
24	Rats, Sprague Dawley	– CG (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) – G1 (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) and vitamin E (150 mg/kg chow for 3 days) – G2 (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) and vitamin E (300 mg/kg chow for 3 days)	G1, G2 vs. CG – serum: testosterone↑ – testis: StAR mRNA↑, 3β-HSD↑, 17β-HSD↑, MDA↓, SOD↑, GPx↑
25	Mice, Swiss albino	– CG (N = 24) – $CdCl_2$ (1 mg/kg b.w. intraperitoneal injection) – G1 (N = 24) – $CdCl_2$ (1 mg/kg b.w. intraperitoneal injection) and vitamin E (100 mg/kg b.w. intraperitoneal injection)	G1 vs. CG – testes: LPP↓, ascorbic acid↑, SOD↔, CAT↑, GSH↑ – sperm: abnormality↓, count↔

26	Rats, Sprague Dawley	– CG (N = 5) – CdCl2 (0.2 mg/kg b.w. subcutaneously for 15 days) – G1 (N = 5) – CdCl2 (0.2 mg/kg b.w. subcutaneously for 15 days) and vitamin E (75 mg/kg b.w. by gastric intubation for 15 days)	G1 vs. CG – testis: protein content↑, CAT↑, POD↑, SOD↑, TBARS↓, GR↑ – prostate: CAT↔, POD↑, SOD↔, TBARS↓, GR↑ – seminiferous tubules: epithelial height↑, diameter↑, spermatogonia↑, primary spermatocytes↑, secondary spermatocyte, spermatids↑, histological changes↓
27	Rats, Wistar	– CG (N = 8) – $CdCl_2$ (0.4 mg Cd/kg b.w., intraperitoneally, single dose) – G1 (N = 8) – $CdCl_2$ (0.4 mg Cd/kg b.w., intraperitoneally, single dose) and vitamin E (20 UI/kg b.w., single dose)	G1 vs. CG – testes: LPO↓, SOD↑, CAT↑, GPx↑, GR↑, GST↑, vitamin C↑, vitamin E↑
28	Rats, Sprague Dawley	– CG (N = 5) – $CdCl_2$ (0.2 mg/kg b.w. subcutaneously for 15 days) – G1 (N = 5) – $CdCl_2$ (0.2 mg/kg b.w. subcutaneously for 15 days) and vitamin E (75 mg/kg b.w. by gastric intubation for 15 days)	G1 vs. CG – plasma: testosterone↑, Cd↓, Zn↔ – sperm: daily production↑, efficiency of production↑ – testis: Cd↓, Zn↑ – body weight: initial↔, final↑
29	Rats, Wistar	– CG (N = 8) – Cd (2 mg/kg b.w. for 28 days) – G1 (N = 8) – Cd (2 mg/kg b.w. for 28 days) and vitamin E (100 IU/kg b.w. for 28 days)	G1 vs. CG – testes: weight↔, Mfn1↑, Mnf2↑, Bcl-2↑, Bax↓, caspase-9↓, caspase 3/7↓
30	Rats, Wistar	– CG – $CdCl_2$ (2.18 mM/kg b.w. for 3 days) – G1 – $CdCl_2$ (2.18 mM/kg b.w. for 3 days) and vitamin E (250 mg/kg b.w. pretreatment, twice a week for 1 month)	G1 vs. CG – erythrocytes: SOD↑, CAT↑, GSH↑, GSH-R↔, GST↓
31	Rats, Wistar	– CG (N = 8) – cigarette smoke exposed (for 1 h each day over 90 days) – G1 (N = 8) – cigarette smoke exposed (for 1 h each day over 90 days) and vitamin E (10 mg/kg b.w. intramuscular over 90 days)	G1 vs. CG – lens: Cd↔, Fe↓, pathological changes↓
32	Rats, Albino	– CG (N = 5) – Cd (0.4 mg/kg b.w. for 30 days) – G1 (N = 5) – Cd (0.4 mg/kg b.w. for 30 days) and vitamin E (5 mg/kg b.w. on alternate days for 30 days)	G1 vs. CG – cerebellum: GSH↑, GSSG↓, GSH/GSSG↑, GR↔, GPDH↔ – cerebral hemispheres: GSH↑, GSSG↓, GSH/GSSG↑, GR↑, GPDH↑ – brain stem: GSH↑, GSSG↔, GSH/GSSG↔, GR↔, GPDH↔
33	Rats, Albino	– CG (N = 10) – Cd (0.4 mg/kg b.w. for 30 days) – G1 (N = 10) – Cd (0.4 mg/kg b.w. for 30 days) and vitamin E (5 mg/kg b.w. on alternate days for 30 days)	G1 vs. CG – cerebellum: SOD↑, lipofuscin↓ – cerebral hemispheres: SOD↑, lipofuscin↓ – brain stem: SOD↑, lipofuscin↓
34	Broiler chicks	– CG (N = 7) – $CdCl_2$ (2.5 mg/kg b.w. for 15 days) – G1 (N = 7) – $CdCl_2$ (2.5 mg/kg b.w. for 15 days) and vitamin E (5 mg/kg b.w. for 15 days)	G1 vs. CG – serum: T3↑, T4↔ – liver: 5'D-I↑, LPO↓, SOD↔, CAT↔

Table 1. Results of studies in animal models with cadmium (Cd) exposure and vitamin E treatment and relationship between Cd exposure and vitamin E in blood concentration in human studies, collected on PubMed in May 2021 – cont.

Reference	Research model	Study description	Main results
35	Japanese quail chicks	– CG (N = 54) – Cd (120 mg/kg diet for 6 weeks) – G1 (N = 54) – Cd (120 mg/kg diet for 6 weeks) and vitamin E (250 mg/kg diet for 6 weeks)	G1 vs. CG – liver: Cd↓ – muscle: Cd↓ – mortality rate: ↓ – weight: body↔, gain↔
36	Smoking patients, male, 44–55 years	– CG (N = 15) – non smokers – G1 (N = 15) – light smokers – G2 (N = 15) – moderate smokers – G3 (N = 15) – heavy smokers	G1, G2, G3 vs. CG – serum: vitamin E↓ – blood: Cd↑ – lenses: Cd↑ – in G1, G2, G3 – vitamin E serum level and blood Cd concentration – negative correlation
37	People, ≥20 years	– G1 (N = 7826)	in G1 – blood: cadmium with leukocyte telomere length inverse associated – serum: α-tocopherol with leukocyte telomere length – marginally positive association – γ-tocopherol with leukocyte telomere length – inverse association

17β-HSD – 17β hydroxysteroid dehydrogenase; 3β-HSD – 3β hydroxysteroid dehydrogenase; 5′D-I – 5′-deiodinase; ACE – angiotensin-converting enzyme; AChE – acetylocholinesterase; AcP_P – prostatic acid phosphatase; AcP_T – total acid phosphatase; ALP – alkaline phosphatase; AIF – apoptosis inducing factor; ALT – alanine aminotransferase; AST – aspartate aminotransferase; Bax – Bcl-2 associated X; Bcl-2 – B-cell lymphoma 2; BUN – blood urea nitrogen; CAT – catalase; Cd – cadmium; CD 4 – cluster of differentiation 4-like; CD 8β – cluster of differentiation 8β; CG – control group; CG1 – control group 1; CG2 – control group 2; Cu/Zn-SOD – copper zinc superoxide dismutase; DNA – deoxyribonucleic acid; Fe – ferrum; G1 – group 1; G2 – group 2; G3 – group 3; GCLC – glutamylcysteine ligase catalytic subunit; GCLM – glutamate cysteinę ligase modifier subunit; GFR – glomerular filtration rate; GPDH – glucose-6-phosphate dehydrogenase; GPx – glutathione peroxidase; GR – glutathione reductase; Grp78 – glucose-regulated protein 78; Grp94 – glucose-regulated protein 94; GSH – reduced glutathione; GSH-R – erythrocyte glutathionereductase; GSSG – oxidized glutathione; GST – glutathione-S-transferase; Hb – haemoglobin; HO-1 – heme-oxygenase-1; Htc – haematocrit value; LDH – lactate dehydrogenase; LPO – lipid peroxidation; LPP – lipid peroxidation potential; LPx – lipid peroxidase; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular hemoglobin concentration; MCV – mean corpuscular volume; MDA – malondialdehyde; Mfn 1 – mitofusin 1; Mfn 2 – mitofusin 2; Mn-SOD – manganase superoxide dismutase; mRNA – messenger ribonucleic acid; NQO-1 – NADPH quinine-oxidoreductase-1; Nrf2 – nuclear factor erythroid 2-related factor 2; PLT – platelets; POD – peroxidase; RBC – red blood cells; SOD – superoxide dismutase; StAR – steroidogenic acute regulatory protein; T3 – triiodothyronine; T4 – thyroxine; T-AOC – total antioxidant capacity; TBARS – thiobarbituric acid reactive substances; TEC – total erythrocytic count; TL – total lipids; TLC – total leukocyte count; TNF-α – tumor necrosis factor α; TP – total protein; WBC – white blood cells; Zn – zinc.
↑ – significant increase; ↓ – significant decrease; ↔ – no significant changes.

and broiler chicks exposed to Cd [11,15]. A reduction in creatinine in blood was also demonstrated in a study on fish exposed to Cd. However, there was no change in urea concentration in blood [14] and no decrease in cytotoxicity in the kidney of fish exposed to Cd [19].

Vitamin E could potentially be an agent to help reduce Cd accumulation in the kidney, as observed in a study on rats exposed to Cd [6]. However, in a study on fish exposed to Cd, the effect of vitamin E on renal Cd concentration was not confirmed [19,23].

The protective role of vitamin E in Cd-induced toxicity also affected the reproductive system. In a study conducted by Sen Gupta et al. [24] on rats exposed to Cd, an increase in steroidogenic acute regulatory protein (StAR) mRNA levels and activity of steroidogenic enzymes (17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase) in the testis and an increase in serum testosterone levels were demonstrated. A reduction in the severity of oxidative stress in the testis was observed in several studies [25,26]. The beneficial effect of vitamin E on the reproductive system of rats exposed to Cd involving also changes in the activity of enzymatic (increase in the activity of testicular SOD, CAT, GPx, glutathione reductase (GSH)) and non-enzymatic (glutathione, vitamin C, vitamin E in testes) antioxidant defense system was demonstrated in the study by Ognjanović et al. [27].

An increase in the concentration of ascorbic acid in testes and a decrease in the percentage of sperm abnormality were observed [25]. The effect of vitamin E on the reproductive function of rats exposed to Cd by increasing plasma testosterone concentration, daily sperm production and efficiency, decreasing Cd concentration in plasma and testis, increasing final body weight of animals and zinc concentration in plasma was shown in the study of Jahan et al. [28]. A decrease in histological changes in seminiferous tubules, as well as an effect on morphometric results (improvement in the tubular diameter and epithelial height of seminiferous tubules) and number of different cell types in the seminiferous tubule was demonstrated in a study conducted on rats exposed to Cd [26]. Additionally in the study of Amanpour et al. [29] vitamin E had a protective effect on the reproductive system of rats exposed to Cd by decreasing apoptosis in rat testes. The beneficial effect of vitamin E on the improvement of semen quality (an increase in sperm concentration and motility and a decrease in the number of dead and abnormal sperm) was shown in the study by El-Demerdash et al. [17].

The protective effect of vitamin E also included the blood system of animals exposed to Cd. In several studies, vitamin E contributed to an improvement of hematological parameters, i.e., increase in red blood cell number, hemoglobin and hematocrit concentrations in animals exposed to Cd [16,18]. In a study conducted on rats, an increase in vitamin E, vitamin C and coenzyme Q10 concentrations in plasma and additionally an increase in glutathione concentration, an increase in SOD, CAT, GPx, GSH activity, and a decrease in lipid peroxidation in the erythrocytes of rats were observed [18,30]. In a study by Choi et al. [21], vitamin E contributed to lower blood pressure and vitamin E reduced the rate of decrease in blood hemoglobin concentration. However, it did not reduce Cd concentrations or cytotoxicity and immunotoxicity (no effect on the number of leukocytes and lysozyme content) in the blood of fish exposed to Cd [19]. But in a study on fish exposed to Cd, no effect of vitamin E on hemoglobin concentration and number of red blood cell was observed [14,19].

One of the studies concerned the protective effect of vitamin E on spleen of animals exposed to Cd. A decrease in histological changes in this organ was observed. However, there was no decrease in Cd concentration, cytotoxicity and immunotoxicity in the spleen of fish exposed to Cd [23].

Vitamin E can also help to reduce negative changes in the organ of vision and the nervous system. A beneficial effect of vitamin E on the organ of vision of animals

exposed to cigarette smoke was observed including prevention of pathological changes and limitation of iron accumulation in the rat lenses. However, no changes in the concentration of Cd in the lens of the eye of animals exposed to cigarette smoke were observed [31]. In a study by Shukla et al. [32] on rats exposed to Cd, vitamin E reduced the adverse effects of Cd by affecting the increase in glutathione concentration and enzyme activity in different brain areas (cerebellum, cerebral hemispheres and brain stem). In another study on rats exposed to Cd, vitamin E contributed to a decrease in lipofuscin concentration in different brain regions (cerebellum, cerebral hemisphere and brain stem). An increase in SOD activity in the same brain regions was also observed [33].

Protective effect of vitamin E on thyroid of chickens exposed to Cd by restored thyroid function (increase of triiodothyronine concentration, restoration of 5'-monodeiodinase activity) was demonstrated [34].

In a study conducted on Japanese quails exposed to Cd, vitamin E decreased mortality rate and Cd accumulation in the muscle and liver [35].

Two studies on the role of vitamin E in Cd-induced toxicity have been conducted with humans environmentally exposed to Cd. A study with cataractous patients showed higher Cd concentration in blood and lenses and lower vitamin E concentration in serum in light, moderate and heavy smokers in comparison with non-smokers. Moreover, a negative correlation between blood Cd concentration and vitamin E concentration was observed in all groups of smokers (light, moderate and heavy). This relation was not significant in the group of non-smokers [36]. In turn, a study with participation of general US adult population demonstrated inverse association between γ-tocopherol and leukocyte telomere length (LTL) and positive association with α-tocopherol and LTL (marginally significant). However, serum vitamin E concentration (γ-tocopherol and α-tocopherol) did not modify blood Cd and LTL associations [37].

Studies on animal models showed beneficial effect of vitamin E in decreasing Cd-induced toxicity in gastrointestinal, urinary, reproductive, circulatory, immune and respiratory systems, in decreasing genotoxicity, cytotoxicity and decreasing Cd concentration in serum and tissues of animals exposed to Cd. These beneficial effects were observed during different ways of administration (orally, intragastric, intraperitoneally, intramuscularly), different time (for 3, 4, 15, 30 days, 2, 3, 4, 6, 12 or 20 weeks) and different doses of vitamin E (1.5, 5, 10, 20, 50, 75, 100, 150, 250, 300 mg/kg b.w./day; 0.4 IU/100 g b.w./day; 20, 100 IU/kg b.w./day; 300 ppm in feed; 40, 150, 300, 400 mg/kg diet) as well as Cd (time: for 30 days, for 3, 4, 6, 12 weeks, doses: 2 mg; 0.05, 0.2, 0.4, 1, 2, 5, 15 mg/kg b.w., 5, 20 μmol/kg b.w., 2.18 mM/kg b.w. 0.2 mg/100 g b.w.; 100 ppm in fed; 50 ppm in drinking water, 1 g/l water; 4.64 mg/l water; 50, 120 mg/kg diet).

Several studies show a neutral effect of vitamin E in animals exposed to cadmium. In 3 studies on fish, the ineffectiveness of the use of vitamin E at a dose of 20 IU/kg b.w. for 4 days post Cd injection (20 μmol/kg b.w. single dose injected intraperitoneally) on the reduction of Cd concentration in tissues and organs was confirmed, which could be caused by the time of vitamin E administration. Others studies carried out on fish did not indicate changes in aspartate aminotransferase (AST) activity in the blood, hemoglobin concentration and red blood cell count which may have been due to the long exposure to Cd (12 weeks). Moreover, vitamin E did not contribute to decrease in cytotoxicity and immunotoxicity of fish exposed to Cd and gene expression of tumor necrosis α and c-fos in rats exposed to Cd. Application the various modes of administration, exposure time and dose of vitamin E (injection, intragastrically, with diet, intramuscular; for 4 days or 12 weeks; 20 μmol/kg b.w., 50 mg/100 g b.w., 50 mg/kg diet) and Cd (injection, intraperitoneally, cigarette smoke exposed; single dose, for 12 weeks; 20 μmol/kg b.w., 50 mg/kg diet) may have influenced the obtained results.

The type of animal model was also important. Most of the studies that did not show a beneficial effect of vitamin E in exposed to Cd animals have looked at fish. This may be due to mechanisms of heavy metal excretion, deposition and detoxification which in fish are not capable of handling heavy metals in short time frames. Heavy metals tend to accumulate specifically in metabolically active tissues and organs. Moreover metal accumulation rates in animals vary with species and among individuals in a population. They also depend upon the age, size, feeding status and sex of the organism.

In turn, the study with participation of cataractous patients demonstrated negative correlation between blood Cd concentration and vitamin E concentration in all examined groups of smokers. However, serum vitamin E concentration did not modify blood Cd and LTL associations in the general US adult population.

Vitamin C

Vitamin C is another component with potential protective effects on Cd exposure. Table 2 shows the results of animal models studies and human studies that analyzed the effect of vitamin C in reducing Cd-induced toxicity.

The protective effect of vitamin C on the gastrointestinal tract of animals exposed to Cd including improvement of liver function parameters (reduction of AST, ALT, gamma glutamyl transferase, lactate dehydrogenase activity and bilirubin concentration) was demonstrated in the study by Mumtaz et al. [38]. Reduction of ALT activity in blood also occurred in a study on fish exposed to Cd. In this study, however, no beneficial changes in other parameters describing liver function (AST, total protein, albumin) were noted in these animals [14]. In another study on fish exposed to Cd, a decrease in lipid peroxidation (decrease in thiobarbituric acid reactive substances) and oxidative stress intensity (increase in CAT activity, decrease in SOD activity) in the liver was observed as a result of vitamin C activity [39]. The beneficial effect of vitamin C on the liver of animals exposed to Cd by inhibiting histological changes was demonstrated in studies on rats exposed to Cd [11,40]. Vitamin C also contributed to an increased mRNA expression of the hepatic antioxidant genes (metallothionein, glutathione S-transferase, GPx) and inhibition of toxicopathic lesions in fish exposed to Cd [41]. In contrast, a study by Tarasub et al. [42] did not show a protective effect of vitamin C on the liver of rats exposed to Cd. No reduction in lipid peroxidation level and oxidative stress was observed in experimental animals. Vitamin C did also have no significant effect in prevention against liver damages.

The protective effects of vitamin C also included urinary system of animals exposed to Cd. In a study conducted by Ali et al. [43], supplementation of vitamin C to animals exposed to Cd contributed to improvement of renal function parameters (reduction of creatinine, cystathion C, uric acid levels, reduction of alkaline phosphatase activity). In a study on fish exposed to Cd, the effect of vitamin C on lowering creatinine in blood was observed [14]. The improvement of kidney function parameters (reduction of creatinine and urea level in serum) and reduction of histopathological changes in this organ were also demonstrated in the study performed on guinea pigs [44] and rats exposed to Cd [11]. A reduction in histological changes in kidney was observed in a study by El-Rafaiy et al. [40]. On the other hand, in a study on fish exposed to Cd, there was a reduction in lipid peroxidation and oxidative stress severity in the kidney as a result of vitamin C activity [39].

Another system that was affected by the beneficial effects of vitamin C in animals exposed to Cd was the reproductive system. In a study on mice and rats exposed to Cd, there was a reduction in oxidative stress [24,25], as well as an increase in ascorbic acid content in testes [25]. Vitamin C also caused an increase in sperm count profile and a decrease in the percentage of sperm abnormality [25]. In a study by Sen Gupta et al. [24], vitamin C

Table 2. Results of studies in animal models with Cd exposure and vitamin C treatment and relationship between Cd exposure and vitamin C in blood concentration in human studies, collected on PubMed in May 2021

Reference	Research model	Study description	Main results
38	Rabbits (*Oryctolagus cuniculus*)	– CG (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) – G1 (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) and vitamin C (150 mg/kg b.w. orally for 28 days)	G1 vs. CG – liver: ALT↓, total protein↑, bilirubin↓, LDH↓, AST↓, GGT↓, Cd↓
14	Fish, Nile tilapia (*Oreochromis niloticus)*	– CG (N = 20) – Cd (50 mg/kg diet for 12 weeks) – G1 (N = 20) – Cd (50 mg/kg diet for 12 weeks) and vitamin C (100 mg/kg diet)	G1 vs. CG – blood: total protein↔, albumin↔, creatinine↓, urea↔, ALT↓, AST↔, Hb↔, RBC↔, WBC↔ – body: weight:↔, Cd residue↓
39	Fish, Nile tilapia (*Oreochromis niloticus)*	– CG (N = 15) – $CdCl_2$ (10 ppm for 21 days) – G1 (N = 15) – $CdCl_2$ (10 ppm for 21 days) and vitamin C (10 ppm in tank water for 21 days)	G1 vs. CG – liver: TBARS↓, CAT↑, SOD↓, Cd↓ – kidney: TBARS↓, CAT↑, SOD↔, Cd↓ – muscle: Cd↔ – gills: Cd↓
11	Rats, Wistar	– CG (N = 5) – Cd (2 mg, single dose, intraperitoneally) – G1 (N = 5) – Cd (2 mg, single dose, intraperitoneally) and vitamin C (0.0015 mg/kg)	G1 vs. CG – serum: urea↓, creatinine↓, ALP↔, AcP_T↓, AcP_P↓ – liver: histological changes↓ – kidney: histological changes↓ – testes: histological changes↓
40	Rats, Sprague Dawley	– CG (N = 10) – $CdCl_2$(3 mg/kg b.w. orally for 90 days) – G1(N = 10) – $CdCl_2$ (3 mg/kg b.w. orally for 90 days) and vitamin C (2g/l in distilled water for 90 days)	G1 vs. CG – liver: histopathological changes↓, collagen fibres↓, DNA content↑ – kidney: histopathological changes↓, collagen fibres↓, DNA content↑ – testis: histopathological changes↓, collagen fibres↓, DNA content↑ – lung: histopathological changes↓, collagen fibres↓, DNA content↓ – bone marrow cells: chromosomal aberration↓, frequency of total chromosomal aberration↓
41	Fish, Nile tilapia (*Oreochromis niloticus)*	– CG (N = 30) – Cd (5 mg/l drinking water for 45 days) – G1 (N = 30) – Cd (5 mg/l drinking water for 45 days) and vitamin C (500 mg/kg diet for 45 days)	G1 vs. CG – liver: MT↓, GST↑, GPx↑, histopathological changes↓
42	Rats, Wistar	– CG (N = 8) – $CdCl_2$ (5 mg/kg b.w. by gavage for 27 days) – G1 (N = 8) – $CdCl_2$ (5 mg/kg b.w. by gavage for 27 days) and vitamin C (100 mg/kg b.w. for 1 h prior to Cd)	G1 vs. CG – liver: MDA↔, GSH↔, MT↔, histological changes↔
43	Rabbits (*Oryctolagus cuniculus)*	– CG (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) – G1 (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) and vitamin C (150 mg/kg b.w. orally for 28 days)	G1 vs. CG – serum: creatinine↓, cystation C↓, uric acid↓, ALP↓ – kidney: Cd↓

44	Guinea pigs, Velaz, Prague	– CG (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (2 mg/animal for 12 weeks) – G1 (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (100 mg/animal for 12 weeks)	G1 vs. CG – kidney: weight↔, histomorphological changes (epithelial proximal tubules vacuolization, interstitium edema dilatation of veins, paravenous lymphatic infiltrates) ↓, lymphatic elements in interstitium↔ – serum: creatinine↓, urea↓
24	Rats, Sprague Dawley	– CG (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) – G1 (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) and vitamin C (500 mg/l drinking water for 3 days)	G1 vs. CG – testis: StAR mRNA↑, 3β-HSD↑, 17β-HSD↑, MDA↓, SOD↑, GPx↑ – serum: testosterone↑
25	Mice, Swiss albino	– CG (N = 24) – $CdCl_2$ (1 mg/kg b.w. intraperitoneal injection) – G1 (N = 24) – $CdCl_2$ (1 mg/kg b.w. intraperitoneal injection) and vitamin C (10 mg/kg b.w. intraperitoneal injection)	G1 vs. CG – testes: LPP↓, ascorbic acid↑, SOD↔, CAT↑, GSH↑, – sperm: abnormality↓, count↑
45	Rabbits (*Oryctolagus cuniculus)*	– CG (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. by oral gavage for 28 days) – G1 (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. by oral gavage for 28 days) and vitamin C (150 µg/g b.w. by oral gavage for 28 days)	G1 vs. CG – serum: cholesterol↓, HDL↑, LDL↑, TnT↓, creatinine kinase↓ – heart: Cd↓
46	Rabbits (*Oryctolagus cuniculus*)	– CG (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) – G1 (N = 6) – $CdCl_2$ (1.5 mg/kg b.w. orally for 28 days) and vitamin C (150 mg/kg b.w. orally for 28 days)	G1 vs. CG – serum: T3↑, T4↑, TSH↓, TG↓, Hb↑, MCHC↑, Htc↑ – liver: Cd↓ – kidney: Cd↑ – heart: Cd↓ – lungs: Cd↓
47	Guinea pigs, Velaz Praha	– CG (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (2 mg/animal for 12 weeks) – G1 (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (100 mg/animal for 12 weeks)	G1 vs. CG – phagocytic activity of polymorphonuclears and monocytes↑ – weight: body↔, spleen↓
48	Rats, Wistar	– CG (N = 45) – $CdCl_2$ (1.0 – 1.2 mg Cd/kg b.w. intragastrically for 28 days) – G1 (N = 45) – $CdCl_2$ (1.0 – 1.2 mg Cd/kg b.w. intragastrically for 28 days) and vitamin C (1.25 g/rat for 28 days)	G1 vs. CG – liver: Cd↓ – kidneys: Cd↓ – testicles: Cd↓ – muscles: Cd↓
49	Japanese quails (*Coturnix japonica*)	– CG (N = 10) – $CdCl_2$ (100 µCi/kg of diet during 7–14 days) – G1 (N = 10) – $CdCl_2$ (100 µCi/kg of diet during 7–14 days) and 0.5% ascorbic acid (during 7–14 days)	G1 vs. CG – liver: Cd↔ – kidney: Cd↓ – duodenum: Cd↓ – jejunum-ileum: Cd↓ – body weight: ↔

Table 2. Results of studies in animal models with Cd exposure and vitamin C treatment and relationship between Cd exposure and vitamin C in blood concentration in human studies, collected on PubMed in May 2021 – cont.

Reference	Research model	Study description	Main results
		– CG (N = 10) – $CdCl_2$ (3.4 µCi/kg – single dose given at 9 days) – G1 (N = 10) – $CdCl_2$ (3.4 µCi/kg – single dose given at 9 days) and 0.5% ascorbic acid (7–16 days)	G1 vs. CG – liver: Cd↓ – kidney: Cd↓ – duodenum: Cd↓ – jejunum-ileum: Cd↓ – body weight: ↔
		– CG (N = 10) – $CdCl_2$ (3.4 µCi/kg – single dose given at 9 days) – G1 (N = 10) – $CdCl_2$ (3.4 µCi/kg – single dose given at 9 days) and 0.5% ascorbic acid (for 16 days)	G1 vs. CG – liver: Cd↓ – kidney: Cd↓ – duodenum: Cd↓ – jejunum-ileum: Cd↓ – body weight: ↔
50	Guinea pigs, Velaz, Prague	– CG (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (2 mg/animal for 12 weeks) – G1 (N = 8) – Cd Cl_2 (1 mg/animal for 12 weeks) and vitamin C (100 mg/animal for 12 weeks)	G1 vs. CG – serum: zinc↔, copper↓ – kidney: zinc↔, copper↔ – liver: zinc↑, copper↑ – testes: zinc↔, copper↓ – heart: zinc↔, copper↔ – brain: zinc↔, copper↓
36	Smoking patients, male, 44–55 years	– CG (N = 15) – nonsmokers – G1 (N = 15) – light smokers – G2 (N = 15) – moderate smokers – G3 (N = 15) – heavy smokers	G1, G2, G3 vs. CG – serum: vitamin C↓ – blood: Cd↑ – lenses: Cd↑ in G1, G3: – vitamin C serum level and blood Cd concentration – negative correlation in G2: – vitamin C serum level and blood Cd concentration – positive correlation

51	People, ≤58 years	– CG 1 (N = 5) – nonsmokers with cataract (40–50 years) – G1 (N = 3) – smokers with cataract (40–50 years) – CG 2 (N = 6) – nonsmokers with cataract (51–55 years) – G2 (N = 6) – smokers with cataract (51–55 years) – CG 3 (N = 26) – nonsmokers with cataract (56–58 years) – G3 (N = 23) – smokers with cataract (56–58 years) – CG (N = 21) – nonsmokers without cataract (30–40 years) – G1 (N = 19) – smokers without cataract (30–40 years)	G1, G2, G3 vs. CG1, CG2, CG3 – blood: vitamin C↔ – lens: Cd↑ G1 vs. CG1 – blood: Cd↔ G2, G3 vs. CG2, CG3 – blood: Cd↑ G1 vs. CG – blood: Cd↑, vitamin C↔
52	Men, 29–64 years	– CG – fructose placebo for 1 month – G1 – vitamin C (500 mg) for 1 month – G2 – vitamin C (1000 mg) for 1 month	G1 and G2 vs. CG – blood: Cd↔ – hair: Cd↔
53	Pregnant women	– G1 (N = 381) – dietary intake was assessed using 24-hour recall questionnaire	in G1: – blood Cd level with ascorbic acid – negative association

ATP – adenosine triphosphate; CG3 – control group 3; FPMS – fast progressive motile spermatozoa; GGT – gamma glutamyl transferase; HDL – high-density lipoprotein; LDH – lactate dehydrogenase; LDL – low-density lipoprotein; MT – metallothionein.
Other abbreviations as in Table 1.

increased testis StAR mRNA levels and activity of steroidogenic enzymes (17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase). Increased serum testosterone levels were also observed. A protective effect of vitamin C including reduction of histological changes in the testis was observed in rats exposed to Cd [11,40].

Beneficial changes in biochemical and hematological parameters were also observed with Cd exposure and vitamin C supplementation. A study by Ali et al. [45] showed beneficial effects of this vitamin including improvement in blood biochemical parameters (e.g., reduction in cholesterol, troponin T and creatinine kinase levels and an increase in high-density lipoprotein levels). The positive effect of vitamin C on blood biochemical parameters was also demonstrated in a study on rabbits exposed to Cd. Vitamin C contributed to a decrease in triglycerides and an increase in serum hemoglobin, hematocrit, mean corpuscular hemoglobin concentration [46]. The effect of vitamin C on hematological blood parameters (hemoglobin concentration, total erythrocytes and leukocytes) was not demonstrated in a study on fish exposed to Cd [14].

The protective effects of vitamin C also included other tissues and systems of animals exposed to Cd. In a study conducted by Kubova et al. [47] on guinea pigs exposed to Cd, an increase in phagocytic activity of polymorphonuclear leucocytes was observed when vitamin C was applied at a dose of 100 mg/animal. However, this effect was not observed with a lower dose of vitamin C (2 mg/animal).

In another study on rats exposed to Cd a reduction in genotoxicity was demonstrated. Vitamin C caused an increased DNA content and decreased chromosomal aberrations [40].

One study showed a beneficial effect of vitamin C on the respiratory system of rats exposed to Cd. A reduction in histopathological changes in the lungs was observed, including no inflammatory cells and improvement of the bronchiole [40].

In a study by Khan et al. [46], vitamin C had beneficial effects on parameters related to pituitary-thyroid axis function (increased blood levels of triiodothyronine and thyroxine, and decreased thyroid-stimulating hormone levels) in rabbits exposed to Cd.

The protective effect of vitamin C in animals exposed to Cd was also associated with reduction of Cd accumulation in tissues and organs. In the study conducted by Grosicki [48], vitamin C contributed to a decrease in Cd concentration in liver, kidneys, testicles and muscles. Similar effects were shown in a study on fish – there was a reduction in Cd concentration in kidney, liver and gills, but no effect of vitamin C on Cd concentration in the muscles of fish was noted [39]. In another study on fish, a reduction in Cd residues in fish bodies was observed [14]. In turn, a reduction in Cd levels in duodenum, jejunum-ileum, and kidney was demonstrated in a study on Japanese quails exposed to Cd [49]. A reduction in kidney Cd concentration was also confirmed in a study on rabbits exposed to Cd [43], while another study on rabbits exposed to Cd showed an increase in kidney Cd concentration and a reduction in Cd concentration in heart, liver and lungs [46].

In a study conducted by Kadrabova et al. [50], the effect of vitamin C on zinc and copper concentrations in the tissues and serum of guinea-pigs exposed to Cd was evaluated. It was shown that vitamin C administered in high dose (100 mg/animal/day) can contribute to a decrease in copper concentration in the testes, brain and serum of animals exposed to Cd. The effect of vitamin C on copper concentration in kidneys and heart as well as on zinc concentration in these organs and serum of guinea-pigs exposed to Cd was not observed.

Several studies on the protective role of vitamin C have been conducted with humans environmentally exposed to Cd. A study involving cataractous patients showed higher Cd concentrations in blood and lenses and lower vitamin C concentrations in serum in light, moderate and heavy smokers compared with non-smokers. Moreover, a negative correlation between blood Cd and vitamin C concentration at light and heavy smokers and a positive correlation between blood Cd and vitamin C concentration at moderate smokers was observed [36]. Higher Cd concentration in the lenses in smokers in comparison with non-smokers was also shown in a study conducted by Ramakrishnan et al. [51] involving cataractous patients in 3 age groups (40–50, 51–55, 56–58 years). An increase in Cd concentration in the blood of smokers in comparison with non-smokers was also observed in 2 age groups (51–55 and 56–58 years). An increase in the concentration of Cd in the blood was not demonstrated in the group belonging to the age range of 40–50 years. There was also no change in vitamin C concentration in the blood in any of the studied groups of patients with cataract. However, in patients without cataract, an increase in Cd concentration in the blood was observed in smokers in comparison with non-smokers, whereas no change in vitamin C concentration in the blood was found. On the other hand, in a study conducted by Calabrese et al. [52] involving a population nonoccupationally exposed to Cd, it was shown that vitamin C supplementation administered in different doses (500 mg/day and 1000 mg/day) had no effect on Cd content in human hair and blood. In a study conducted with pregnant women, a negative association was observed between high vitamin C intake and blood Cd levels in the third trimester of pregnancy [53].

Studies on the role of vitamin C in reducing Cd-induced toxicity showed positive effects of this vitamin on the gastrointestinal, genitourinary, circulatory, and immune systems, as well as reducing genotoxicity and Cd accumulation in tissues and organs of animals exposed to Cd. The beneficial effect was observed regardless of the method of administration (orally, intragastrically, intraperitoneally, subcutaneously), time of administration (for 3, 7, 10, 16, 21, 27,

28, 45, 90 days, 12 weeks) and dose of both vitamin C (10, 100, 150 mg/kg b.w., 150 μg/g b.w., 100 mg/kg diet, 10 ppm in tank water, 0.5, 2 g/l water, 500 mg/kg diet, 2, 100 mg/animal, 1.25 g/animal) as well as Cd (for 7, 9, 21, 27, 28, 45, 90 days, 12 weeks, single dose; 1.0, 1.2, 1.5, 5.0 mg/kg b.w., 0.2 mg/100 g b.w., 3.4 μCi/kg, 50 mg/kg diet 100 μCi/kg diet, 10 ppm in water, 5 mg/l drinking water, 1, 2, 3 mg/animal). Beneficial effects have been observed in various animal models (rabbits, fish, rats, guinea pigs, mice, Japanese quails).

In contrast, in a study on fish and rats exposed to Cd, there was no beneficial effect of vitamin C on the liver, or on hematological parameters of blood of fish exposed to Cd. Vitamin C also failed to reduce the accumulation of Cd in the muscle of rats. However, in 1 study, an increase in kidney Cd concentration was observed in rabbits exposed to Cd. Lack of protective effect of vitamin C in animals could be caused by long exposure to Cd (21 days, 27 days, 28 days and 12 weeks) as well as too low dose of vitamin C, method of administration (simultaneously in 3 studies and prior to Cd in one study) and the experimental model used.

The protective role of vitamin C has also been demonstrated in human studies. A negative association between high intake of vitamin C and blood Cd levels was observed in pregnant women. Negative correlation between blood Cd and vitamin C concentration was also observed in a study conducted with cataractous patients in light and heavy smokers. However, in a study involving 3 age groups of cataractous patients divided into smokers and non-smokers as well as in patients without cataract, significant differences in blood Cd concentrations were found between the analyzed groups, while vitamin C concentrations in blood in the analyzed groups did not differ significantly. On the other hand, in population environmentally exposed to Cd it was shown that vitamin C supplementation did not influence Cd concentration in human hair and blood.

Vitamin C and vitamin E

Two studies investigated the protective effect of vitamins E and C administered simultaneously on the reproductive system (Table 3).

These vitamins contributed to reduction of adverse effects of Cd on body weight of animals exposed to Cd, improvement of semen parameters (among others sperm count, sperm viability and sperm motility), decrease of histopathological and apoptotic changes in testicular tissue and an increase in testosterone serum concentration [54]. In a study by Sen Gupta et al [24], vitamins C and E had a beneficial effect on the reproductive system of rats exposed to Cd by increasing testis StAR mRNA levels and the activity of steroidogenic enzymes (17β-hydroxysteroid dehydrogenase, 3β-hydroxysteroid dehydrogenase) in the testis. Increased serum testosterone levels and increased activity of testicular antioxidant enzymes – SOD, GPx in the testis were also observed.

In the case of simultaneous supplementation of vitamin E and C and exposure to Cd, the beneficial effects were observed regardless of the administration protocol used. Vitamin C and vitamin E were administered orally, while Cd was orally or subcutaneously. Both the 21-day and the 3-day period and various doses of the vitamins in question (vitamin E and vitamin C combination 200 mg/kg b.w.; vitamin C in dose 500 mg/l drinking water and vitamin E in dose 150 mg/kg chow) reduced the adverse effects of Cd on animals.

Vitamin A

The effects of vitamin A on reducing the effects of Cd-induced toxicity have been studied on animal models (*in vivo)* and human studies. For the animal model studies, different doses of vitamin A and varying exposure times to Cd were used. A summary of the results of the studies is presented in Table 4.

In a study by Sauer et al. [55], beneficial effects of vitamin A on the liver of animals exposed to Cd were dem-

Table 3. Results of studies in animal models with Cd exposure and vitamin C and vitamin E treatment, collected on PubMed in May 2021

Reference	Research model	Study description	Main results
54	Mice, BALB/c, male	– CG (N = 6) – $CdCl_2$ (2 mg/kg b.w. orally for 21 days) – G1 (N = 6) – $CdCl_2$ (2 mg/kg b.w. orally for 21 days) and vitamin E and C combination (200 mg/kg b.w. orally for 21 days)	G1 vs. CG – serum: testosterone↑ – body weight gain: ↑ – sperm: count↑, viability↑, anomaly↓, FPMS↑, SPMS↑, NPMS↓, NMS↓ – testis: histopathological changes↓, NOS2↓, apoptotic changes↓
24	Rats, Sprague Dawley	– CG (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) – G1 (N = 8) – $CdCl_2$ (0.2 mg/100 g b.w., single dose subcutaneously) and vitamin C (500 mg/l drinking water for 3 days) and vitamin E (150 mg/kg chow for 3 days)	G1 vs. CG – serum: testosterone↑ – testis: StAR mRNA↑, 3β-HSD↑, 17β-HSD↑, MDA↓, SOD↑, GPx↑

FPMS – fast progressive motile sperm; mRNA – messenger ribonucleic acid; NMS – nonmotile spermatozoa; NOS2 – nitric oxide synthase 2; NPMS – nonprogressive progressive motile sperm; SPMS – slow progressive motile sperm.
Other abbreviations and explanations as in Table 1.

onstrated, associated with a decrease in ALT activity and inhibition of inflammatory response and hepatocellular necrosis. In addition, beneficial effects of vitamin A were observed in other tissues, including an increase in metallothionein levels in the liver and pancreatic cells. In a study performed on rats exposed to Cd, decreases in AST, ALT, acid phosphatase, and alkaline phosphatase activities were observed in the serum, heart, and liver of animals. Moreover the positive effect of vitamin A on behavioral and biochemical changes of animals exposed to Cd was demonstrated. Vitamin A increased spontaneous motor activity and rota-rod endurance time [56]. In contrast, a study by Asagba et al. [57] showed a decrease in vitamin A concentration in the eyes of rats exposed to Cd. In addition, beneficial effects of vitamin A were demonstrated in the lungs (decreased inflammation), kidney (decreased histopathological changes) and testis (decreased damage within germinal epithelium) and decreased Cd concentration in these organs [55].

In turn, a study involving a group of women did not show any association between serum retinol and urinary Cd concentrations. However, it was observed that serum retinol tended to be positively associated with bone mineral density (BMD). Moreover, BMD was higher among women with high serum retinol and low urinary Cd compared to the reference category with low serum retinol and high urinary Cd and therefore the authors suggest that adequate vitamin A status may counteract the adverse association between Cd and BMD [58]. Positive association was observed between serum vitamin A and LTL. However, vitamin A did not affect the association between Cd exposure (measurement as Cd concentration in the blood) and LTL in the general US adult population [37].

In summary, the in vivo studies in a animal model have shown positive effects of vitamin A on the reduction of toxicity caused by Cd mainly by lowering Cd concentration and changes of biochemical parameters in tissues

Table 4. Results of studies in animal models with Cd exposure and vitamin A treatment and relationship between Cd exposure and vitamin A in blood concentration in human studies, collected on PubMed in May 2021

Reference	Research model	Study description	Main results
55	Rats, Sprague Dawley	– CG – $CdCl_2$ (2.5 – 4.0 mg/kg b.w. single injection) – G1 – $CdCl_2$ (2.5 – 4.0 mg/kg b.w. single injection) and vitamin A (75 mg/kg/day by oral gavage for 7 days pretreatment)	– plasma: ALT↓ – kidney: histopathological changes↓ – testis: damage within germinal epithelium↓ – lungs: inflammatory response↓
		– CG – $CdCl_2$ (2 mg/kg b.w. single injection) – G1 – $CdCl_2$ (2 mg/kg b.w. single injection) and vitamin A (75 mg/kg/day by oral gavage for 7 days pretreatment)	– liver: MT↑, Cd↑ – kidney: MT↔, Cd↔ – lung: MT↔, Cd↓ – testis: MT↔, Cd↓ – pancreas: MT↑
56	Rats, Wistar	– CG – $CdCl_2$ (1 mg Cd/kg b.w./day for 21 days) – G1 – $CdCl_2$ (1 mg Cd/kg b.w./day for 21 days) and vitamin A (500 IU/kg b.w./day for 21 days simultaneous) – G2 – $CdCl_2$ (1 mg Cd/kg b.w./day for 21 days) and vitamin A (500 IU/kg b.w./day for 21 days post-treatment)	G1, G2 vs. CG – serum: AST↓, ALT↓, ACP↓, ALP↓ – liver: AST↓, ALT↓, ACP↓, ALP↓ – heart: AST↓, ALT↓, ACP↓, ALP↓ – behavioral effects: SMA↑, RRE↑
57	Rats, Wistar	– CG (N = 7) – deionized water for 1 month – G1 (N = 7) – Cd (100 ppm in drinking water for 1 month)	G1 vs. CG – rats: body weight↓ – eyes: weight↑, TBARS↑, vitamin A↓
58	Women, 54–64 years, Sweden	– G1 – women with high serum retinol and low urinary Cd	in G1: – BMD↑
37	People, ≥20 years	– G1 (N = 7826)	in G1: – blood: cadmium with leukocyte telomere length – inverse association – serum: vitamin A with leukocyte telomere length – positive association

ACP – acid phosphatase; BMD – bone mineral density; MT – metallothionein; RRE – rota-rod endurance time; SMA – spontaneous motor activity.
Other abbreviations as in Table 1.

and organs, beneficial effects on lungs, kidney and testis, and effects on behavioral and biochemical changes of animals exposed to Cd. The beneficial effect was observed regardless of the method of administration, time of administration and dose both vitamin A (orally; for 7, 21 days, 1 month; 75 mg/kg b.w./day, 500 IU/kg b.w./day) as well as Cd (injection, orally; single dose, 1 mg/kg b.w./day; 1.0, 2.5–4.0 mg/kg b.w., 100 ppm in drinking water). The protective effect was observed both when administering vitamin A pretreatment and simultaneously with Cd. However, it is not known whether supplementation with this vitamin would be equally effective in studies in other animal models.

In human studies, there was no association of serum retinol with urinary Cd concentration. This could be due to, the use of serum retinol as a marker of vitamin A status it may not necessarily reflect subtle variations in status or the status at the time period relevant for affecting the integrity of bone. The bone turnover markers are, in contrast to BMD, indicators of short-term bone metabolism and may be influenced by within-day and day-to-day-variation. Moreover serum vitamin A concentration did not modify blood Cd and LTL associations in the general US adult population.

Beta-carotene

Several studies on animal models and human studies have investigated the potentially protective role of β-carotene in Cd-induced toxicity. The results of these studies are presented in Table 5.

In a rat study, β-carotene supplementation decreased the levels of free radicals and increased glutathione S-transferase and alkaline phosphatase activities in the liver. In contrast, there were no changes in AST and ALT activities or protein concentrations in the liver. The effects of β-carotene on the reproductive system included a significant increase in semen quality [17] and a decrease in oxidative stress in the testis of rats exposed to Cd [59]. The beneficial effects of β-carotene were also associated with improved hematological blood parameters, while the effects of this compound on the nervous system were due to a decrease in oxidative stress [59] and an increase in acetylcholinesterase activity in the brain [17].

A study conducted with cataractous patients showed higher Cd concentration in blood and lenses and lower β-carotene concentration in serum in light, moderate and heavy smokers compared to non-smokers. A negative correlation between blood Cd concentration and serum β-carotene level was also observed in all groups of smokers, but this relationship was not significant in heavy smokers [36]. In the general US adult population, a positive association of β-carotene with LTL was observed. However, β-carotene concentration did not modify the relationship between LTL and blood Cd [37]. In contrast, Zhuang et al. [60] observed a positive association between peripheral arterial disease and urinary Cd and an inverse association between serum β-carotene and peripheral arterial disease. Moreover, an inverse association between urinary Cd and serum β-carotene concentration was observed.

In studies on animals exposed to Cd, the beneficial effects of β-carotene included the liver, reproductive, circulatory and nervous systems. The beneficial effect in the study on the rat model was observed regardless of the experimental protocol. Beta-carotene was given orally in dose 10 mg/kg b.w. or 250 IU/kg b.w. for 30 days or every other day for 6 weeks whereas Cd was given orally or intragastrically in dose 5 or 2 mg/kg b.w. simultaneously with β-carotene. The studies were carried out only on the rat model, therefore it is not known the effectiveness of carotene in relation to other animal models.

In human studies, a negative correlation of urinary Cd concentration with serum β-carotene concentration was observed in patients with peripheral arterial disease. A negative correlation between blood Cd concentration and serum β-carotene concentration was observed in

Table 5. Results of studies in animal models with Cd exposure and β-carotene treatment and relationship between Cd exposure and β-carotene in blood concentration in human studies, collected on PubMed in May 2021

Reference	Research model	Study description	Main results
17	Rats, Sprague Dawley	– CG (N = 7) – $CdCl_2$ (5 mg/kg b.w. orally for 30 days) – G1 (N = 7) – $CdCl_2$ (5 mg/kg b.w. orally for 30 days) and β-carotene (10 mg/kg b.w. orally for 15 days)	G1 vs. CG – plasma: TBARS↓, GST↑, AST↔, ALT↓, ALP↑, AChE↑, TP↔, globulin↔, albumin↑, glucose↓, bilirubin↓, urea↓, creatinine↓ – blood: Hb↑, TEC↑, TLC↓, PCV↑ – liver: TBARS↓, GST↑, AST↔, ALT↔, ALP↑, protein↔ – testes: TBARS↔, GST↔, AST↓, ALT↓, protein↔ – sperm: concentration↑, motility↑, dead↓, abnormal↓ – brain: TBARS↓, GST↔, AChE↑, protein↔
59	Rats, albino	– CG (N = 12) – $CdCl_2$ (2 mg/kg b.w. 3 times/week, every other day for 6 weeks) – G1 (N = 12) – $CdCl_2$ (2 mg/kg b.w. 3 times/week, every other day for 6 weeks) and β-carotene (250 IU/kg b.w. 3 times/week, every other day for 6 weeks)	G1 vs. CG – brain: TBARS↓, GSH↑, SOD↑, GST↑, LDH↓, ATPase↑ – testis: TBARS↓, GSH↑, SOD↑, GST↑, LDH↓, ATPase↑
36	Smoking patients, male, 44–55 years	– CG (N = 15) – non smokers – G1 (N = 15) – light smokers – G2 (N = 15) – moderate smokers – G3 (N = 15) – heavy smokers	G1, G2, G3 vs. CG – serum: β-carotene↓ – blood: Cd↑ – lenses: Cd↑ – β-carotene serum level and blood Cd concentration – negative correlation
37	People ≥20 years	– G1 (N = 7826) – people exposed to Cd as one of environmental factors (2001–2002)	in G1: – blood: cadmium with leukocyte telomere length – inverse association – serum: β-carotene with leukocyte telomere length – positive association
60	People >40 years	– G1 (N = 6819) – people exposed to Cd as one of environmental factors	in G1: – urinary cadmium with PAD – positive association – serum β-carotene with PAD – inverse association – urinary cadmium and serum β-carotene – inverse association

PAD – peripheral arterial disease; PCV – packed cell volume.
Other abbreviations and explanations as in Table 1.

studies involving cataractous patients. In contrast, serum β-carotene concentration did not modify blood Cd and LTL associations in the general US adult population.

CONCLUSIONS

The results of most animal studies showed the beneficial effect of antioxidant vitamins in terms of reducing Cd-induced toxicity. The spectrum of action of these vitamins was very wide and included reduction of the severity of adverse changes in the gastrointestinal, urinary, reproductive, circulatory, nervous and respiratory systems. Improvements in hematological blood parameters and lipid metabolism parameters have also been shown. However, some studies on animal models did not confirm the beneficial role of antioxidant vitamins in reducing Cd-induced toxicity in the gastrointestinal, circulatory and urinary systems.

Human studies, to date, are limited. These studies have focused on analyzing the relationship between serum vitamin concentration/dietary intake of antioxidant vitamins and blood/urinary Cd concentration. The blood concentration and intake of antioxidant vitamins were associated with reduction in adverse health effects. However results are inconclusive and this signals the need for a more detailed analysis of the effect of these dietary components in population exposed to Cd. In addition, in human studies, it would be important to take into account various factors that may affect the test results (including body mass index, diet, comorbidities, exposure to other toxic factors).

In this situation it seems reasonable to promote the consumption of natural food products as a source of antioxidant vitamins in groups of people with occupational and environmental exposure to Cd. Products providing well-known antioxidant vitamins are mainly plant oils (vitamin E), food of plant origin, mainly citrus and soft fruits and leafy green vegetables (vitamin C), dairy products, fortified margarine, liver and fish oils (vitamin A), as well as yellow and green vegetables and yellow fruits (β-carotene).

REFERENCES

1. International Agency for Research on Cancer (IARC). Cadmium and cadmium compounds. In: IARC. Arsenic, metals, fibres, and dusts volume 100 C. A review of human carcinogens. Lyon. 2012. p. 121-41.
2. European Food Safety Authority. Cadmium dietary exposure in the European population. EFSA J. 2012; 10:2551. https://doi.org/10.2903/j.efsa.2012.2551.
3. Nair A, DeGheselle O, Smeets K, Van Kerkhove E, Cuypers A. Cadmium-Induced Pathologies: Where Is the Oxidative Balance Lost (or Not)? IJMS. 2013;14(3):6116-43. https://doi.org/10.3390/ijms14036116.
4. Bahri S, Kaddour H, Karoui D, Bouraoui S, Amri M, Mokni M. Protective role of vitamin E against cadmium induced oxidative stress into the rat liver. Tunis Med. 2019;97(1):100-5.
5. Fang J, Yin H, Yang Z, Tan M, Wang F, Chen K, et al. Vitamin E protects against cadmium-induced sub-chronic liver injury associated with the inhibition of oxidative stress and activation of Nrf2 pathway. Ecotoxicol Environ Saf. 2021; 208:111610. https://doi.org/10.1016/j.ecoenv.2020.111610.
6. Rana SVS, Verma S. Protective effects of GSH, vitamin E, and selenium on lipid peroxidation in cadmium-fed rats. Biol Trace Elem Res. 1996;51(2):161-8. https://doi.org/10.1007/BF02785435.
7. Duan Y, Duan J, Feng Y, Huang X, Fan W, Wang K, et al. Hepatoprotective Activity of Vitamin E and Metallothionein in Cadmium-Induced Liver Injury in Ctenopharyngodon idellus. Oxid Med Cell Longev. 2018:1-12. https://doi.org/10.1155/2018/9506543.
8. Swapna G, Reddy AG, Reddy AR. Cadmium-induced Oxidative Stress and Evaluation of Embilica Officinalis and Stressroak in Broilers. Toxicol Int. 2010;17(2):49-51. https://doi.org/10.4103/0971-6580.72669.
9. Wu X, Lu Z, Chen J, Wang J, Huang F. Hepatic c-fos Expression Is Independent of Oxidative Stress and Inflammation Induced by Acute Cadmium Exposure in Rats. Ann Nutr Metab. 2007;51(3):258-63. https://doi.org/10.1159/000105446.

10. Shaikh ZA, Vu TT, Zaman K. Oxidative Stress as a Mechanism of Chronic Cadmium-Induced Hepatotoxicity and Renal Toxicity and Protection by Antioxidants. Toxicol Appl Pharmacol. 1999;154(3):256-63. https://doi.org/10.1006/taap.1998.8586.
11. Obianime AW, Roberts II. Antioxidants, cadmium-induced toxicity, serum biochemical and the histological abnormalities of the kidney and testes of the male Wistar rats. Niger J Physiol Sci. 2009;24(2):177-85. https://doi.org/10.4314/njps.v24i2.52910.
12. Feng Y, Huang X, Duan Y, Fan W, Duan J, Wang K et al. The Effect of Vitamin E and Metallothionein on the Antioxidant Capacities of Cadmium-Damaged Liver in Grass Carp Ctenopharyngodon idellus. BioMed Res. 2018;2018: 1-8. https://doi.org/10.1155/2018/7935396.
13. Beytut E, Yuce A, Kamiloglu NN, Aksakal M. Role of dietary vitamin E in cadmium-induced oxidative damage in rabbit's blood, liver and kidneys. Int J Vitam Nutr Res. 2003;73(5):351-55. https://doi.org/10.1024/0300-9831.73.5.351.
14. Ayyat MS, Mahmoud HK, El-Hais AE-AM, Abd El-Latif KM. The role of some feed additives in fish fed on diets contaminated with cadmium. Environ Sci Pollut Res. 2017;24(30):23636-45. https://doi.org/10.1007/s11356-017-9986-1.
15. Reddy G, Swapna G. Effect of cadmium on organ biomarkers and evaluation of certain adaptogens in broilers. Toxicol Int. 2011;18(1):47. https://doi.org/10.4103/0971-6580.75856.
16. Mekkawy IAA, Mahmoud UM, Wassif ET, Naguib M. Effects of cadmium on some haematological and biochemical characteristics of Oreochromis niloticus (Linnaeus, 1758) dietary supplemented with tomato paste and vitamin E. Fish Physiol Biochem. 2011;37(1):71-84. https://doi.org/10.1007/s10695-010-9418-3.
17. El-Demerdash FM, Yousef MI, Kedwany FS, Baghdadi HH. Cadmium-induced changes in lipid peroxidation, blood hematology, biochemical parameters and semen quality of male rats: protective role of vitamin E and beta-carotene. Food Chem Toxicol. 2004;42(10):1563-71. https://doi.org/10.1016/j.fct.2004.05.001.
18. Paunović MG, Matić MM, Ognjanović BI, Saičić ZS. Antioxidative and haematoprotective activity of coenzyme Q10 and vitamin E against cadmium-induced oxidative stress in Wistar rats. Toxicol Ind Health. 2017;33(10):746-56. https://doi.org/10.1177/0748233717725480.
19. Huang X, Xiong G, Feng Y, Fan W, Yang S, Duan J, et al. Protective effects of metallothionein and vitamin E in the trunk kidney and blood of cadmium poisoned Ctenopharyngodon idellus. Fish Physiol Biochem. 2020;46(3):1053-61. https://doi.org/10.1007/s10695-020-00771-2.
20. Adi PJ, Burra SP, Vataparti AR, Matcha B. Calcium, zinc and vitamin E ameliorate cadmium-induced renal oxidative damage in albino Wistar rats. Toxicology Reports. 2016;3:591-7. https://doi.org/10.1016/j.toxrep.2016.07.005.
21. Choi J-H, Rhee S-J. Effects of vitamin E on renal dysfunction in chronic cadmium-poisoned rats. J Med Food. 2003;6(3): 209-15. https://doi.org/10.1089/10966200360716625.
22. Fang J, Xie S, Chen Z, Wang F, Chen K, Zuo Z et al. Protective Effect of Vitamin E on Cadmium-Induced Renal Oxidative Damage and Apoptosis in Rats. Biol Trace Elem Res. Published online February 9, 2021. https://doi.org/10.1007/s13011-021-02606-4.
23. Huang X, Feng Y, Fan W, Duan, J, Duan Y, Xiong G, et al. Potential ability for metallothionein and vitamin E protection against cadmium immunotoxicity in head kidney and spleen of grass carp (Ctenopharyngodon idellus). Ecotoxicol Environ Saf. 2019;170:246-52. https://doi.org/10.1016/j.ecoenv.2018.11.134.
24. Sen Gupta R, Sen Gupta E, Dhakal BK, Thakur AR, Ahnn J. Vitamin C and vitamin E protect the rat testes from cadmium-induced reactive oxygen species. Mol Cells. 2004;17(1):132-9.
25. Acharya UR, Mishra M, Patro J, Panda MK. Effect of vitamins C and E on spermatogenesis in mice exposed to cadmium. Reprod Toxicol. 2008;25(1):84-8. https://doi.org/10.1016/j.reprotox.2007.10.004.

26. Jahan S, Zahra A, Irum U, Iftikhar N, Ullah H. Protective effects of different antioxidants against cadmium induced oxidative damage in rat testis and prostate tissues. SBiRM. 2014;60(4):199-205. https://doi.org/10.3109/19396368.2014.912363.
27. Ognjanović BI, Marković SD, Đorđević NZ, Trbojević IS, Štajn AŠ, Saičić ZS. Cadmium-induced lipid peroxidation and changes in antioxidant defense system in the rat testes: Protective role of coenzyme Q10 and Vitamin E. Reprod Toxicol. 2010;29(2):191-7. https://doi.org/10.1016/j.reprotox.2009.11.009.
28. Jahan S, Khan M, Ahmed S, Ullah H. Comparative analysis of antioxidants against cadmium induced reproductive toxicity in adult male rats. SBiRM. 2014;60(1):28-34. https://doi.org/10.3109/19396368.2013.843039.
29. Amanpour P, Khodarahmi P, Salehipour M. Protective effects of vitamin E on cadmium-induced apoptosis in rat testes. Naunyn-Schmiedeberg's Arch Pharmacol. 2020;393(3):349-58. https://doi.org/10.1007/s00210-019-01736-w.
30. Sarkar S, Yadav P, Bhatnagar D. Cadmium-Induced Lipid Peroxidation and the Antioxidant System in Rat Erythrocytes: the Role of Antioxidants. J Trace Elem Med Biol. 1997;11(1):8-13. https://doi.org/10.1016/S0946-672X(97)80002-8.
31. Avunduk AM, Yardimci S, Avunduk MC, Kurnaz L. Cadmium and iron accumulation in rat lens after cigarette smoke exposure and the effect of vitamin E (a-tocopherol) treatment. Cur Eye Res. 1999;18(6):403-7. https://doi.org/10.1076/ceyr.18.6.403.5268.
32. Shukla GS, Srivastava RS, Chandra SV. Prevention of cadmium-induced effects on regional glutathione status of rat brain by vitamin E. J Appl Toxicol. 1988;8(5):355-9. https://doi.org/10.1002/jat.2550080504.
33. Shukla GS, Hussain T, Chandra SV. Protective Effect of Vitamin E on Cadmium-Induced Alterations in Lipofuscin and Superoxide Dismutase in Rat Brain Regions. Pharmacol Toxicol. 1988;63(4):305-6. https://doi.org/10.1111/j.1600-0773.1988.tb00958.x.
34. Gupta P, Kar A. Cadmium induced thyroid dysfunction in chicken: hepatic type I iodothyronine 5'-monodeiodinase activity and role of lipid peroxidation. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1999;123(1):39-44. https://doi.org/10.1016/S0742-8413(99)00007-9.
35. Abou-Kassem DE, Mahrose KhM, Alagawany M. The role of vitamin E or clay in growing Japanese quail fed diets polluted by cadmium at various levels. Animal. 2016;10(3):508-19. https://doi.org/10.1017/S1751731115002578.
36. Mosad SM, Ghanem AA, El-Fallal HM, El-Kannishy AM, El Baiomy AA, Al–Diasty AM, et al. Lens Cadmium, Lead, and Serum Vitamins C, E, and Beta Carotene in Cataractous Smoking Patients. Cur Eye Res. 2010;35(1):23-30. https://doi.org/10.3109/02713680903362880.
37. Nomura SJ, Robien K, Zota AR. Serum Folate, Vitamin B-12, Vitamin A, γ-Tocopherol, α-Tocopherol, and Carotenoids Do Not Modify Associations between Cadmium Exposure and Leukocyte Telomere Length in the General US Adult Population. J Nutr. 2017;147(4):538-48. https://doi.org/10.3945/jn.116.243162.
38. Mumtaz S, Ali S, Khan R, Andleeb S, Ulhaq M, Khan M, et al. The protective role of ascorbic acid in the hepatotoxicity of cadmium and mercury in rabbits. Environ Sci Pollut Res. 2019;26(14):14087-96. https://doi.org/10.1007/s11356-019-04620-5.
39. Al-Anazi MS, Virk P, Elobeid M, Siddiqui MI. Ameliorative effects of Rosmarinus officinalis leaf extract and Vitamin C on cadmium-induced oxidative stress in Nile tilapia Oreochromis niloticus. J Environ Biol. 2015;36(6):1401-8.
40. El-Refaiy AI, Eissa FI. Histopathology and cytotoxicity as biomarkers in treated rats with cadmium and some therapeutic agents. Saudi J Biol Sci. 2013;20(3):265-80. https://doi.org/10.1016/j.sjbs.2013.02.004.
41. El-Sayed YS, El-Gazzar AM, El-Nahas AF, Ashry KM. Vitamin C modulates cadmium-induced hepatic antioxidants' gene transcripts and toxicopathic changes in Nile tilapia, Oreochromis niloticus. Environ Sci Pollut Res. 2016;23(2):1664-70. https://doi.org/10.1007/s11356-015-5412-8.

42. Tarasub N, Junseecha T, Tarasub C, Na Ayutthaya WD. Protective Effects of Curcumin, Vitamin C, or their Combination on Cadmium-Induced Hepatotoxicity. J Basic Clin Pharm. 2012; 3(2):273-81. https://doi.org/10.4103/0976-0105.103821.
43. Ali S, Hussain S, Khan R, Mumtaz S, Ashraf N, Andleeb S et al. Renal toxicity of heavy metals (cadmium and mercury) and their amelioration with ascorbic acid in rabbits. Environ Sci Pollut Res Int. 2019;26(4):3909-20. https://doi.org/10.1007/s11356-018-3819-8.
44. Nagyova A, Galbavy S, Ginter E. Histopathological evidence of vitamin C protection against Cd-nephrotoxicity in Guinea pigs. Exp Toxicol Pathol. 1994;46(1):11-4. https://doi.org/10.1016/S0940-2993(11)80005-9.
45. Ali S, Awan Z, Mumtaz S, Shakir HA, Ahmad F, Ulhaq M, et al. Cardiac toxicity of heavy metals (cadmium and me rcury) and pharmacological intervention by vitamin C in rabbits. Environ Sci Pollut Res Int. 2020;27(23):29266-79. https://doi.org/10.1007/s11356-020-09011-9.
46. Khan R, Ali S, Mumtaz S, Andleeb S, Ulhaq M, Tahir H M, et al. Toxicological effects of toxic metals (cadmium and mercury) on blood and the thyroid gland and pharmacological intervention by vitamin C in rabbits. Environ Sci Pollut Res. 2019;26(16):16727-41. https://doi.org/10.1007/s11356-019-04886-9.
47. Kubová J, Tulinská J, Štolcová E, Mošaťová A, Ginter E. The influence of ascorbic acid on selected parameters of cell immunity in guinea pigs exposed to cadmium. Z Ernährungswiss. 1993;32(2):113-20. https://doi.org/10.1007/BF01614754.
48. Grosicki A. Influence of vitamin C on cadmium absorption and distribution in rats. J Trace Elem Med Biol. 2004;18(2): 183-7. https://doi.org/10.1016/j.jtemb.2004.06.003.
49. Fox MR, Jacobs RM, Jones AO, Fry BE, Stone CL. Effects of vitamin C and iron and cadmium metabolism. Ann N Y Acad Sci. 1980;355:249-61. https://doi.org/10.1111/j.1749-6632.1980.tb21343.x.
50. Kadrabová J, Madaric A, Ginter E. Zinc and copper in the tissues and serum of cadmium intoxicated guinea-pigs: influence of vitamin C. Physiol Res. 1993;42(4):261-6.
51. Ramakrishnan S, Sulochana KN, Selvaraj T, Abdul Rahim A, Lakshmi M, Arunagiri K. Smoking of beedies and cataract: cadmium and vitamin C in the lens and blood. Br J Ophthalmol. 1995;79(3):202-6. https://doi.org/10.1136/bjo.79.3.202.
52. Calabrese EJ, Stoddard A, Leonard DA, Dinardi SR. The Effects of Vitamin C Supplementation on Blood and Hair Levels of Cadmium, Lead, and Mercury. Ann NY Acad Sci. 1987;498(1 Third Confere):347-53. https://doi.org/10.1111/j.1749-6632.1987.tb23773.x.
53. Suarez-Ortegón MF, Mosquera M, Caicedo DM, De Plata CA, Méndez F. Nutrients intake as determinants of blood lead and cadmium levels in Colombian pregnant women: Nutrients Intake and Levels of Lead and Cadmium. Am J Hum Biol. 2013;25(3):344-50. https://doi.org/10.1002/ajhb.22375.
54. Güner Ö, Güner A, Yavaşoğlu A, Karabay Yavaşoğlu NÜ, Kavlak O. Ameliorative effect of edible Halopteris scoparia against cadmium-induced reproductive toxicity in male mice: A biochemical and histopathologic study. Andrologia. 2020;52(6):e13591. https://doi.org/10.1111/and.13591.
55. Sauer J-M, Waalkes MP, Hooser SB, Baines AT, Kuester RK, Sipes IG. Tolerance Induced by All-trans-Retinol to the Hepatotoxic Effects of Cadmium in Rats: Role of Metallothionein Expression. Toxicol Appl Pharmacol. 1997;143(1):110-9. https://doi.org/10.1006/taap.1996.8050.
56. Sujatha R, Jayakumar AR, Krishnamoorthy MS, Paul V, Jayakumar R. Behavioural and biochemical changes after simultaneous and post-treatment of vitamin A and D on cadmium toxicity. Environ Toxicol Pharmacol. 1999;7(3):189-97. https://doi.org/10.1016/S1382-6689(99)00013-7.
57. Asagba SO, Isamah GK, Ossai EK, Ekakitie AO. Effect of oral exposure to cadmium on the levels of vitamin A and lipid peroxidation in the eye. Bull Environ Contam Toxicol. 2002; 68(1):18-21. https://doi.org/10.1007/s00128-001-0213-9.
58. Engström A, Håkansson H, Skerfving S, Bjellerup P, Lidfeldt J, Lundh T, et al. Retinol May Counteract the Negative Effect of Cadmium on Bone. J Nutr. 2011;141(12):2198-203. https://doi.org/10.3945/jn.111.146944.

59. El-Missiry MA, Shalaby F. Role of beta-carotene in ameliorating the cadmium-induced oxidative stress in rat brain and testis. J Biochem Mol Toxicol. 2000;14(5):238-43. https://doi.org/10.1002/1099-0461(2000)14:5<238::AID-JBT2>3.0.CO;2-X.
60. Zhuang X, Ni A, Liao L, Guo Y, Dai W, Jiang Y, et al. Environment-wide association study to identify novel factors associated with peripheral arterial disease: Evidence from the National Health and Nutrition Examination Survey (1999–2004). Atherosclerosis. 2018;269:172-7. https://doi.org/10.1016/j.atherosclerosis.2018.01.006.