Pertanika J. Trop. Agric. Sci. 44 (1): 83 - 105 (2021)

PERTANIKA JOURNALS

TROPICAL AGRICULTURAL SCIENCE

Journal homepage: http://www.pertanika.upm.edu.my/

Review Article

Review of Antioxidant-rich Natural Dietary Products as Protective and Therapeutic Factors against Cadmium Toxicity in Living Organisms

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ABSTRACT

Advances in civilization processes and industrialization have doubled the release of toxic heavy metals into the environment, consequently elevating their presence in the food chains. Cadmium (Cd) is one of the severe toxic metals widely present in the atmosphere. The major route of animal or human exposure to Cd is through water or food ingestion and inhalation of particles or inhalation of fumes during various industrial processes. Continuous exposure to low levels of Cd results in a gradual deposition in different tissues of the body, causing toxic effects on the liver, kidneys, testes, and other vital organs. The beneficial effect of natural antioxidants against chemical induced toxicity is receiving more attention. Antioxidant-rich dietary products and their function in tempering free radicals produced in the body under different pathological conditions is an active research field. In the current review, we attempted to highlight the current research progress in the field of using antioxidant-rich natural dietary products and their function in mitigating or

ARTICLE INFO

Article history:
Received: 08 July 2020
Accepted: 27 August 2020
Published: 24 February 2021

DOI: https://doi.org/10.47836/pjtas.44.1.05

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ISSN: 1511-3701
e-ISSN: 2231-8542

preventing health issues and tissue damage associated with Cd induced toxicity along with its mechanism.

Keywords: Cadmium toxicity, dietary products, mechanisms, natural antioxidants

INTRODUCTION

The incidence of several adverse health effects in humans and animals associated with exposure to toxic heavy metals in the environment is a general issue and a matter of grave concern (Vardhan et al., 2019). In recent years the concentration of heavy metals in the environment has increased abundantly; industries have played a major role in this regard (H. Zhang & Reynolds, 2019). Cd is one of the severe toxic metals widely present in the atmosphere (Ataei et al., 2019; Lane et al., 2015; Patra et al., 2011; Satarug et al., 2010). It is extensively present in the environment. Advances in civilization processes and industrialization have doubled the increase in Cd level in the environment consequently elevating its presence in the food chains and risking human and animal health (World Health Organization [WHO], 2010). Cd is present in PVC pipes, phosphatic fertilizers, and color pigments, with few of Cd containing products recycled (Järup & Åkesson, 2009). Cigarette smoke and food are the most important sources of Cd exposure in the human population (Piasek et al., 2001), while animals are exposed through several other sources (H. Zhang & Reynolds, 2019). It can enter the body via daily eating, which contains a considerable amount of Cd in normal condition (X. Wang et al., 2021). Cd causes damage to various tissues and vital organs such as the kidney, liver, lungs, bones, and brain (Geng & Wang, 2019). Endocrine modulative properties of Cd have been suggested by several studies, and therefore, it has been included in the category of endocrine disruptors (WHO, 2017). In the case of acute Cd poisoning, the liver is the main target organ of toxicity resulting in hepatotoxicity that can lead to Cd caused lethality (Rikans & Yamano, 2000). Several studies also showed an association between chronic Cd-toxicity and nephrotoxicity (El-Demerdash et al., 2004). Various studies on female rats revealed that Cd, a heavy metal with a considerably long half-life, accumulates in the female reproductive organ (S. Wang et al., 2019). Oxidative stress plays an important role in Cd-induced toxicity in the brain, kidneys, liver, bone, testes, and ovarian tissues. Oxidative stress is recognized as one of the many mechanisms of Cd toxicity which involves stimulating the synthesis of reactive oxygen species (ROS), thus causes oxidative disruption in RBCs and several other tissues, resulting in loss of membrane function (Nasiadek et al., 2014). Thus, Cd can cause oxidative damage in various tissues by increasing the peroxidation of membrane lipids and interfering with the antioxidant mechanistic of the cells. Cellular components may lead to disruption due to the damage caused by the peroxidation of cellular membrane and interference of metal ions with organelles (Sarkar et al., 2013).

The beneficial effects of natural antioxidants against chemically induced toxicity are receiving more attention (Mężyńska & Brzóska, 2019; Spencer, 2003). Research on naturally occurring antioxidants and their function in tempering free radicals produced in the body under different pathological conditions has remained to be a focus point (Flora et al., 2012). Dietary and supplementary antioxidants may inhibit carcinogenesis (Calabrese, 2002). Various naturally occurring compounds are reported to show a protective role against oxidative stress such as ROS lipid peroxidation (Dailiah Roopha & Padmalatha, 2012). The understanding of oxidative stress as an active mechanism by which Cd causes its toxic effect indicates that naturally occurring antioxidants can play a role in the treatment of Cd poisoning (Abdelaziz et al., 2013). The main purpose of this review is, therefore, to highlight the ongoing development in the area of research related to the use of naturally occurring antioxidant-rich sources against heavy metal toxic agents especially Cd and to point out possible knowledge gaps and future directions.

In preparation of this review, we searched for the data in bibliographic databases like Elsevier, Scopus, Medline, and Google Scholar using keywords such as natural antioxidants, bio elements, honey, green tea, cadmium/Cd, exposure, adverse effects, kidney damage, ginger, hepatotoxicity, and mechanism of Cd toxicity, green tea, reproductive toxicity, curcumin, and preventive measures.

MECHANISMS OF Cd TOXICITY

Various mechanisms are responsible for Cd toxicity. The main mechanisms reported include oxidative stress, DNA damage and apoptosis. Synergism of several mechanisms is responsible for the entire effect of Cd on any tissue or cell (Figure 1) (Khan et al., 2019; Rani et al., 2014; Thompson & Bannigan, 2008).

Oxidative Stress

Oxidative stress is the outcome of the imbalance between the generation of oxidants and their elimination systems (Puppel et al., 2015). Oxidative stress plays a vital role in Cd-induced toxicity in the brain, kidneys, liver, bone, testes, and ovarian tissues. It is recognized as one of the many mechanisms of Cd toxicity mediated by stimulating the synthesis of reactive oxygen species (ROS), thus causing oxidative disruption in RBCs and in several other tissues, resulting in membrane function loss (Giaginis et al., 2006; Nasiadek et al., 2014). Cd causes oxidative stress and induces lipid peroxidation by either inhibiting the antioxidant enzymatic system or through depletion of glutathione (GSH) (Rikans & Yamano, 2000). ROS are produced during the metabolism of mitochondria and in cell responses to xenobiotics (S. Wang et al., 2019). ROS are often responsible for the Cd-induced detrimental health effects. There is direct evidence of the free radicals generation in animals following acute Cd exposure and indirect evidence of ROS responsible for chronic Cd toxicity and carcinogenesis (Patra et al., 2011). Cd

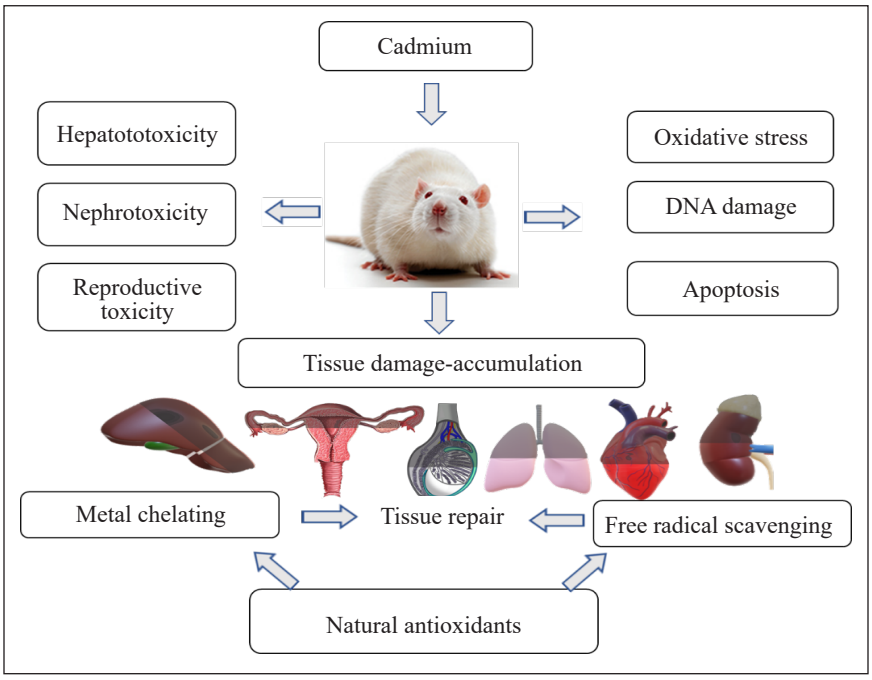

Figure 1. The possible biological pathways of Cd-induced oxidative injury and tissue damage

can cause oxidative damage in various tissues by increasing the peroxidation of membrane lipids and interfering in the antioxidant mechanistic of the cells. Cellular components may lead to disruption due to the damage caused by the peroxidation of cellular membrane and interference of metal ions with organelles (Sarkar et al., 2013).

DNA Damage

Cd is responsible for the disruption of DNA synthesis, cell cycle progression, cell proliferation and differentiation, and other various cellular processes (Aimola et al., 2012). The inhibition of the DNA repair mechanism may be another impact of Cd toxicity (Giaginis et al., 2006). Furthermore, several other possible indirect mechanisms have also been proposed to elucidate Cd carcinogenesis, including oxidative stress, alteration of DNA methylation, protooncogene activation, and dysregulated gene expression (Beyersmann & Hechtenberg, 1997). *In vitro* experiments demonstrate clearly that Cd induces oxidative stress, damage to the DNA and programmed cell death in cells containing human liver carcinoma (Skipper et al., 2016). In a study conducted by J. M. Yang et al., (2003), cadmium was found to be directly toxic to primary Leydig cells, and the decreased percentage of normal cells and increased levels of DNA damage in cadmium exposed Leydig cells was evident. Lysosome is one of the main targets for cadmium toxicity and can be responsible for other cellular events, including DNA damage (Fotakis et al., 2005).

Apoptosis

Among the various harmful responses, apoptosis is also responsible for the Cd toxicity effect. As a primary defense mechanism against the free pre-filtering transformed or mutated cells, apoptosis that is usually found in Cd-exposed cells supposed to have an anti-cancer function (Ospondpant et al., 2019). Some studies have shown that only a proportion of Cd-exposed cells in a population die by apoptosis, while the remaining can become apoptosis-resistant (S. Wang et al., 2019; Waisberg et al., 2003). Moreover, it has been observed that resistance to apoptosis is enhanced in Cd-adapted or transformed cells (Hart et al., 2001). Disturbance in the apoptosis mechanism is considered crucial in tumor development, acquired resistance to apoptosis, and malignant progression is a common sign of cancer (van der Wall, 2010).

Cd-INDUCED ORGAN TOXICITY

Nephrotoxicity

The kidney is the main target organ in chronic Cd exposure. It has been long observed that Cd-Metallothionein (MT) complex mediates the Cd-induced nephrotoxicity (Klaassen et al., 2009). Accumulation of Cd in the kidney found in human population studies indicates that a considerable number of people may have toxic levels of Cd in their kidneys (Satarug et al., 2000). Several studies showed evidence of an association between chronic Cd exposure and nephrotoxicity. Initial stages of Cd nephrotoxicity include specific disruptions in proximal tubule cell adhesion, cellular signaling, cascade, and autophagic response that occur before the occurrence of apoptosis or necrosis of proximal tubule cells (Prozialeck & Edwards, 2012). A high degree of Cd exposure can result in interference of calcium metabolism and formation of kidney stones, osteoporosis, and softening of the bones, which have been observed in human individuals living or working in Cd-abundant areas or exposed groups (WHO, 2010). Cd induces renal damage, characterized by proximal re-absorptive tubular dysfunction (Järup & Åkesson, 2009).

Hepatotoxicity

In the case of acute Cd-poisoning, the liver is the main primary organ of toxicity, and hepatotoxicity can also lead to lethality (Klaassen et al., 2009). Cd is delivered to target organs via pulmonary or gastrointestinal absorption into the systemic circulation. The liver receives much of the Cd absorbed in the intestines through the portal circulation, bound mainly to albumin, where it reaches to hepatocytes from sinusoidal capillaries (Figure 2) (DelRaso et al., 2003). Cd-induced damage occurs to all liver cells; the Cd-induced inflammatory response generates an infiltration and activation of phagocytic cells that generates more inflammatory mediators including cytokines or ROS (Arroyo et al., 2013). Cd hepatotoxicity is closely associated with inflammation. Following acute exposure, the damaged liver is often intruded by polymorphonuclear neutrophils (PMN), which along with damage to Kupfer cells;

contribute to the hepatotoxicity by elevating inflammatory mediators and promoting necrosis. Two pathways induce the hepatotoxicity; the early injury resulted from the direct effects of the metal deposit and the other injury that follows the inflammatory process (Rikans & Yamano, 2000).

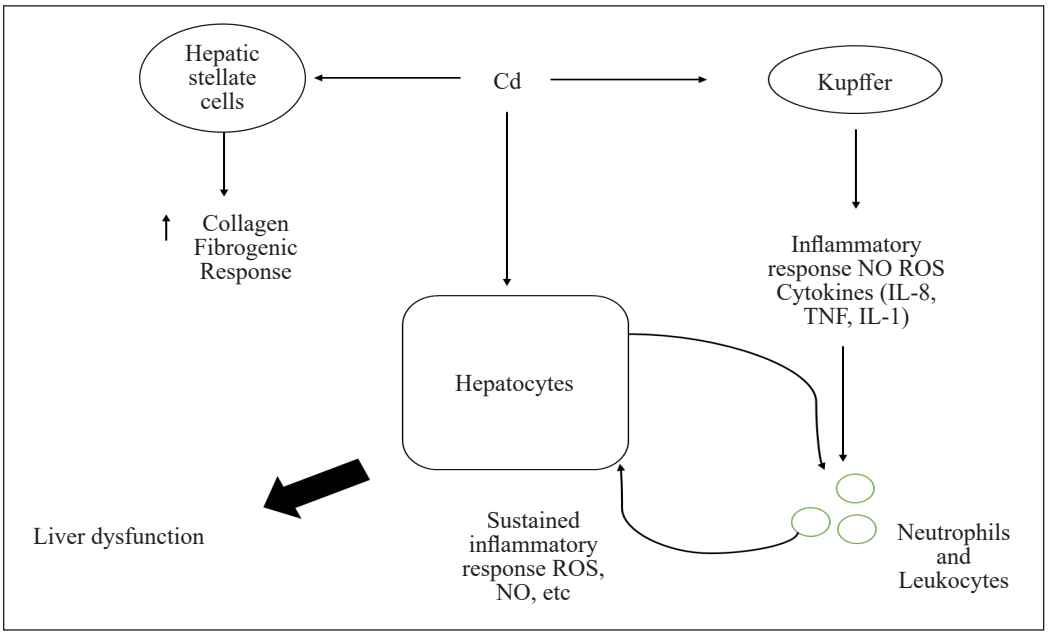

Figure 2. General pathway of Cd-induced liver dysfunction. Cd toxic reaction involves different types of hepatic cells, resulting in liver damage (Arroyo et al., 2013)

Reproductive Toxicity

Cd exposure is linked with several toxic effects on the mammalian reproductive system, thereby affecting the normal reproductive functions. It has been placed under the list of recognized endocrine-disrupting chemicals (EDCs) due to its defined ability to disturb the rates of placental and ovarian steroidogenesis process (Chedrese et al., 2008; Nna et al., 2017). For example, progesterone biosynthesis in human luteal cells is either enhanced or inhibited due to the accumulation of Cd, therefore, affecting reproductive morphology. Additionally, premature birth and decreased birth weights were reported to have been associated with Cd exposure in women (Miceli et al., 2005).

Moreover, Cd is known to cause blockage of the pathway that delivers cholesterol precursors for steroidogenesis from the maternal peripheral circulation due to an increase in placental low-density lipoprotein receptor. Another possible potential mode of actions by which Cd may disrupt steroidogenesis includes alteration of the DNA bind zinc through the replacement of Cd for Zn (Henson & Chedrese, 2004). Cd persuades expression of estrogen target genes in mammalian cell culture, thus

initiating activation of cytoplasmic kinases (W. Zhang & Jia, 2007). Cd accumulation in embryos increases from the four-cell stage ahead, and blastocyst stage development is inhibited by high dose exposure, which can cause decompaction and degeneration in blastocysts. Besides, Cd has also been incorporated in the chromatin structure of developing gametes. Ovarian tissues accumulate high amount of Cd over a span of time and with increasing age, consequently leading to deterred progression of oocyte growth from the primary to the secondary stage and failure to ovulate. Another mechanism by which ovulation is considered ineffective is the failure of tubal cilia to pick up the oocytes (Thompson & Bannigan, 2008). Incidences of reproductive anomalies linked with Cd exposure are higher in women as shown in different studies (Akesson et al., 2002; Berglund et al., 1994; Järup, 2003). Nevertheless altered testicular function associated with Cd exposure has also been reported in men (Amit et al., 2019; de Angelis et al., 2017; T. Zhang et al., 2019). Mechanisms of deleterious effects due to Cd exposure in the testis include impairment to Sertoli and Leydig cells, intercellular connections, vascular endothelium, oxidative stress induction, interference in antioxidant defense system, and interference in the inflammatory responses, which leads to functional and morphological changes like impairment of spermatogenesis and inhibition of testosterone synthesis (Figure 3) (Taha et al., 2013). Cd also disrupts prostate function by altering its secretion, hormonal activity, and consequently leads to infertility problems in men (Sarkar et al., 2013).

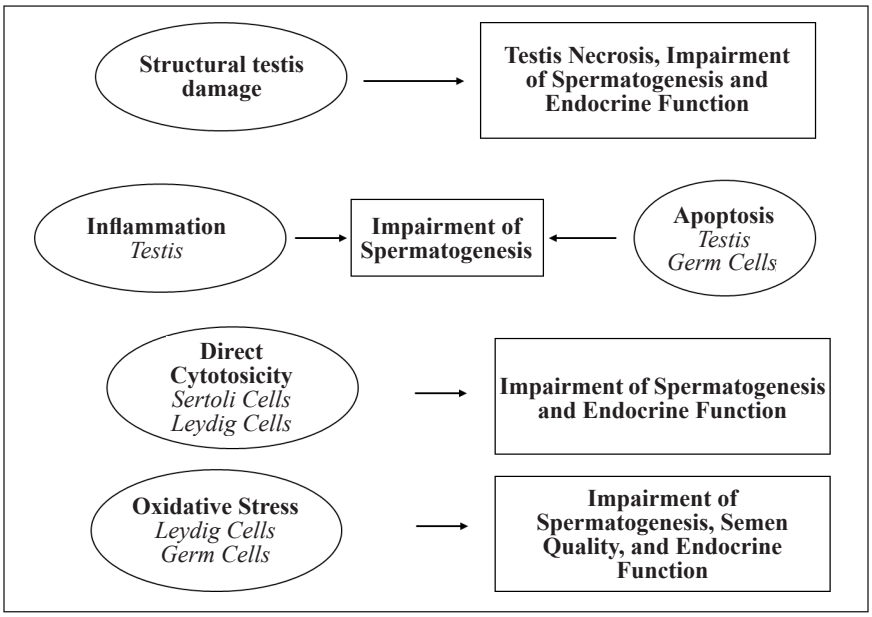

Figure 3. Overview of main proposed pathways of Cd-induced reprotoxicity

NATURALLY OCCURRING ANTIOXIDANT SUBSTANCES AND THEIR AMELIORATING EFFECTS ON Cd TOXICITY

Nowadays, natural antioxidants and their protective effects against chemically induced toxicity are receiving more and more attention (Mężyńska & Brzóska, 2019). Naturally occurring antioxidants and their function in tempering free radicals produced in the body under different pathological conditions are also active research fields (Flora et al., 2012). Dietary and supplementary antioxidants have been believed to inhibit carcinogenesis (Calabrese, 2002). Consequently, a great deal of attention has been given towards the biochemical functions of natural substances in biological systems (Matés et al., 2010). Various naturally occurring substances are reported to show a protecting role against ROS and lipid peroxidation (Table 1) (Alkhedaide et al., 2016; Amamou et al., 2015; J. J. Kim et al., 2019; Nna et al., 2017) and below are some of them considered in this review.

Curcumin

Curcumin, a turmeric plant's active component, is an efficient antioxidant against oxidative tissue damage because it significantly hampers the formation of both *in vitro* and *in vivo* ROS (K. S. Kim et al., 2018). It was revealed by Eybl et al. (2006) that pre-treatment of curcumin effectively protected against Cd-induced lipid peroxidation and ameliorated Cd adverse effects in mice. Attia et al. (2014a) carried out a study on rats, and their research finding suggested that curcumin increased the antioxidant glutathione peroxidase (GPx) activity of Cd-exposed rats and decreased lipid peroxidation and hemolysis of erythrocytes (Attia et al., 2014a). $CdCl_2$ decreases sperm motility, reduces sperm density, and the amount of serum testosterone, it also decreased glutathione peroxidase (GSH-Px), testicular total superoxide dismutase (T-SOD), and glutathione (GSH), and increased malondialdehyde (MDA) levels, while all of these parameters were ameliorated by the supplementation of curcumin (S. H. Yang et al., 2019). A study conducted by Abu-Taweel (2016) in mice showed that curcumin improved both behavioral and biochemical parameters of blood analyzed and decreased the Cd toxicity effect also in a dose-dependent manner (Abu-Taweel, 2016). Blood indices such as red and white blood cells, platelets, hemoglobin, and packed cell volume were reduced in Cd exposed mice but remained at normal levels in mice treated with nanoparticles of curcumin (Ahmad et al., 2018). Curcumin treatment significantly reduced the urinary excretion of kidney damaging molecules-1 (Kim-1), osteopontin (OPN), metalloproteinases tissue inhibitor 1 (TIMP-1), neutrophil gelatinase-associated lipocalin (GRL), and netrin-1 in comparison with $CdCl_2$ group treatments (K. S. Kim et al., 2018).

Honey

In addition to its sugar component, honey also includes numerous bioactive

Table 1
Different natural antioxidants and their effect on tissues

Natural substance	Dosage/Route of exposure of Cd	Studied animal	Exposure length	Target tissue	Mechanism of action	References
Curcumin	25 mg/kg b.w./P.O.	Sprague Dawley male rats	7 days	Kidney	Curcumin treatment significantly improved the biomarkers associated with nephrotoxicity compared with that in the $CdCl_2$-treated group	K. S. Kim et al. (2018)
	7 mg/kg b.w./SQ	Male CD mice	3 days	Liver, Kidney, Testes, Brain	Curcumin pretreatment effectively protected against Cd-induced lipid peroxidation and improved the negative impact of cadmium on antioxidant status without reducing tissue cadmium rates	Eybl et al. (2006)
	10 mg/kg b.w./P.O.	Male albino rats	24 days	Blood	Curcumin due to its antioxidant mechanisms had a protective role against cadmium-induced hematotoxicity in rats, and may have therapeutic relevance	Attia et al. (2014a)
	2 mg/kg b.w./IP	Mice	5 days	Male reproductive system	By activating the Nrf2/ARE (antioxidant responsive element) signaling pathway, curcumin may protect against Cd-induced testicular injury	S. H. Yang et al. (2019)
Honey	0.5 mg/kg b.w./IP	Male albino Wistar rats	30 days	Liver and Kidney	Honey administration with Cd induced improvement in all parameters examined.	Abdel-Moneim and Ghafeer (2007)
	0.67 mg/kg b.w./IP	Male albino mice	8 days	Male reproductive system	Honey administration improved the level of Cd-induced chromosomal aberrations and sperm abnormalities	Asmaa et al. (2016)
	200 mg/kg b.w./ P.O.	Albino rats	21 days	Liver	Honey found protective against cadmium-induced liver cell injury as evidenced by the ability of each test substance to minimize increased liver enzyme plasma activity and total liver function marker concentration of bilirubin	Anyia (2016)

Table 1 *(continue)*

Natural substance	Dosage/Route of exposure of Cd	Studied animal	Exposure length	Target tissue	Mechanism of action	References
Green tea extract (GTE)	3 µmoles/kg b.w./P.O.	Wistar rats	6 months	Liver	Green tea extract significantly increased the activity of enzymatic antioxidants in rat's liver compared to those treated with cadmium alone	Hamden et al. (2009)
	1.25 mg/kg b.w./IP	Male albino rats	Not defined	Liver	Hepatoprotective effect of green tea in cadmium chloride toxicated rats is reported	
	6 mg/L P.O.	Albino rats	10 days	Liver and kidney	GTE intake can effectively reduce Cd-induced cell injury in liver and kidney tissues	Hussain and Al-taee (2014)
Olive	5 mg/kg b.w./P.O.	Albino rats	4 weeks	Kidney and brain	Olive oil administration with $CdCl_2$ has been effective in improving the altered biochemical and oxidative-antioxidant parameters as well as the percentage of DNA fragmentation to almost those of the control group	E. Mohammed et al. (2014)
	50 mg/L P.O.	Wistar rats	8 weeks	Liver	Olive oil co-treatment significantly improved Cd oxidative damage. The potential for antioxidants in plasma and liver was significantly restored and MDA levels also significantly decreased	Amamou et al. (2015)
	1.8 mg/kg b.w./ P.O.	Swiss Albino mice	28 days	Kidney	The treatment with olive oil significantly protected the cadmium-induced oxidative stress	Wani et al., (2018)
Grape seed extract (GSE)	5 mg/kg b.w./P.O.	Male Wistar rats	4 weeks	Liver, kidney, brain, and testes	GSE enhanced antioxidant potential in all tissues, and reduced blood plasma and liver MDA levels	Evcimen et al. (2018)
	5 mg/kg b.w./P.O.	Kunming mice	30 days	Kidney	GSE administration attenuated Cd-induced lipid peroxidation, and antagonized renal apoptosis, possibly associated with Bax and Bcl-2 expression	Chen et al. (2013)
	60 mg/L P.O.		20 weeks	Prostate	The prostatic oxidative stress and fibrosis caused by $CdCl_2$ were improved by the GSE	Lei et al. (2017)

Table 1 *(continue)*

Natural substance	Dosage/Route of exposure of Cd	Studied animal	Exposure length	Target tissue	Mechanism of action	References
Rosemary	30 mg/kg b.w./P.O.	Albino rat	8 weeks	Liver	The toxic effects of $CdCl_2$ on the liver were improved by rosemary aqueous extract demonstrated by histological observation, decreased MDA and increased CAT, SOD, and GSH in the liver	Sakr et al. (2015)
	5 mg/kg b.w./P.O.	Guinea pigs	28 days	Liver	The serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activity, as well as complete and direct serum bilirubin, were increased due to Cd-induced toxicity, all these parameters were declined by co-administration of rosemary extract	Albasha (2014)
	15 mg/kg b.w./P.O.	Wistar rats	4 weeks	Kidney and liver	Cd-induced cellular disorganization of the kidney and liver has been restored through the co-treatment of rosemary extract.	Virk et al. (2013)
Ginger	5 mg/kg b.w./P.O.	Wistar albino rats	30 days	Kidney	Enhancement of the kidney tissue in histological examinations reflects improvements in functional kidney markers and significantly supports the possible protective role of ginger against renal toxicity due to cadmium	Gabr et al. (2019)
	200 mg/kg b.w./ P.O.	Rabbits	12 weeks	Kidney and liver	Caspase3 and MKI67's immunohistochemical expression was high in hepatocytes and tubular epithelium in (Cd) group, while hepatocytes and tubular epithelium were slightly stained in cadmium and ginger group, suggesting ginger's protective effect against cadmium toxicity	Baiomy and Mansour (2016)
	10 mg/kg b.w./P.O.	Female albino rats	26 days	Blood	Cd-exposed animals with ginger decreased the concentration of MDA and hemolysis by 20% and 17%, respectively	Attia et al. (2014b)

Note. b.w. = Body weight; P.O. = *per os* (Orally); SQ = Subcutaneous; IP = Intraperitoneal

compounds such as phenolic compounds, flavonoids, and carotenoids, which act as antioxidants and scavenging free radicals (Elmenoufy, 2012). A study conducted by Abdel-Moneim and Ghafeer (2007) in male albino rats showed that honey in combination with Cd reduced its hazards. It was also revealed in the same research that honey could protect against Cd-induced oxidative stress by reducing free radicals and increasing antioxidant levels (Abdel-Moneim & Ghafeer, 2007). According to Abdelaziz et al. (2013), honey treatment is reported to be the most effective as compared to vitamin C and B complex in recovering the affected blood parameters in Cd-exposed rabbits. Asmaa et al. (2016) revealed that the administration of honey improved the chromosomal aberration rate and sperm abnormality caused by Cd. Among the beneficial effects of honey reported also include the capability to prevent oxidative damage, protect the liver and kidney tissues and restore the natural metabolic processes (Elmenoufy, 2012). Furthermore, honey with Kola seed was shown to have an anti-hepatotoxic function and decreased plasma total bilirubin concentration and enzyme activity in rats exposed to Cd acetate (Anyia, 2016).

Green Tea Extract

Green tea intake is correlated with various health-promoting properties (Venables et al., 2008). It helps detoxify heavy metals by inhibiting absorption and promoting excretion (El-Shahat et al., 2009). According to Hamden et al (2009), oral administration of green tea with Cd improves liver dysfunction and oxidative stress in rats. A study conducted by Kumar et al. (2010) showed that green tea extract (GTE) had hepatoprotective effects on the liver of Cd-exposed rats. As discussed before, Cd has cytotoxic effects on rat liver and kidney cells, and according to Hussain et al. (2014), GTE intake can minimize cell damage in these tissues effectively. GTE supplement also showed protective effects on testes against Cd through inhibition of oxidative damage and apoptosis (Abdelrazek et al., 2016). The ameliorating effect of GTE against Pb and Cd-induced testicular toxicity in rats was also proven by Hussein et al. (2014). Supplementing rats with GTE along with Cd boosts the antioxidant or detoxification process, thus reducing oxidative stress in rat testes (Hussein et al., 2014). The study conducted by Mahmood et al. (2015) in female Wistar rats showed ameliorating effects of GTE on gonadotropin hormones (FSH and LH) against Cd-induced toxicity. It was found by Singh et al. (2013) that GTE, due to its antioxidant properties, reversed changes in hematological parameters of rats, thus reducing the toxic effects of Cd. According to Z. I. Mohammed (2014), GTE's phenolic compound protects the kidney tissue against Cd toxicity.

Onion and Garlic

Onion and garlic are essential bioactive natural ingredient sources, including polyphenols and organosulfur compounds (Mężyńska & Brzóska, 2019). Garlic and garlic extracts have been reported to

defend body against free radical damage (Chung, 2006). An investigation carried out by Massadeh et al. (2007) demonstrated that Cd-induced immunosuppression in mice was substantially reversed by garlic extract. According to Ola-Mudathir et al. (2008), garlic extract offers protection against Cd-induced oxidative damage and spermiotoxicity in rats possibly through reduction of the peroxidation of lipids and enhance the antioxidant protection mechanism (Ola-Mudathir et al., 2008). It was revealed by Lawal et al.(2011) that garlic extract had positive actions in 1321N1 human astrocytoma cells and HEK 293 human embryonic kidney cells to combat the Cd-induced toxicity, and these include membrane damage prevention and lipid peroxidation reduction. Garlic and onion extracts are suggested to have their protective effects by reducing lipid peroxidation and enhancing antioxidant resistance (Suru, 2008). Upon Cd exposure in rats, histological abnormalities including myofibril degradation, cytoplasm vacuolization, and myofibril irregularity were observed in cardiac tissue. These histological changes were successfully mitigated by onion extract (Alpsoy et al., 2014).

Olive Oil

There has been considerable interest in the antioxidant ability of phenolic compounds in olive oil (Owen et al., 2000). Administration of olive oil with $CdCl_2$ has successfully enhanced and improved altered biochemical and oxidative- antioxidant parameters and fragmentation of DNA (E. Mohammed et al., 2014). Consumption of olive oil or colocynth oil protected rat liver against Cd-induced injury by increasing enzyme activity and reducing oxidative stress (Amamou et al., 2015). It was found that serum creatinine, blood urea, and the antioxidant markers (glutathione peroxidase, superoxide dismutase, and catalase) levels were decreased in Cd-exposed rats while these parameters were improved in olive oil-treated groups (Wani et al., 2018). In addition to a reduction in the number of chromosomes, several chromosomal anomalies in albino rats were caused by $CdCl_2$, while olive oil supplementation reversed these chromosomal shifts (Aly et al., 2018).

Rosemary

Results from several studies showed that the rosemary essential oil had antimicrobial, antioxidant, anti-carcinogenic, and cognitive effects, it was mostly researched in light of its anti-cancer, antioxidant, and anti-infectious properties, covering 55% of the studies (Andrade et al., 2018; Sakr et al., 2015). According to a research conducted by Sakr et al. (2015), administration of rosemary extract in rats exposed to $CdCl_2$ showed that the concentration of GSH and the activity of catalase (CAT) and superoxide dismutase (SOD) were elevated while a decrease in malonaldehyde MDA were noticed as compared with the rats treated with the metal alone (Sakr et al., 2015). In Cd-exposed guinea pigs, aspartate aminotransferase, serum alanine aminotransferase, glutamyl

transferase, and alkaline phosphatase, serum total, and specific bilirubin were elevated. The fenugreek, rosemary, and cinnamon co-administration considerably improved structural changes in the liver and significantly reduced all of the biochemical parameters described above (Albasha, 2014). It was found that with the co-treatment of the rosemary, Cd-induced cell disorganizations of the kidney and liver were restored, SOD and CAT were elevated while MDA levels were lowered (Virk et al., 2013).

Ginger

Ginger has been reported to have antioxidant activity driven by the removal of free radicals (Maisuthisakul et al., 2007). Ginger's pharmacological activities are primarily due to its active phytocompounds; 6-gingerol is the abundant bioactive compound with numerous pharmacological effects, including analgesic, anti-inflammatory, antipyretic, and antioxidant properties (Ali et al., 2018). According to Gabr et al. (2019), Cd intoxicated rats display renal dysfunction, damage to the kidney tissue and an oxidative stress effect along with a decline in the total antioxidant status (TAC) and DNA content. Meanwhile, treatment with ginger leads to significant recovery of biomarkers of renal function, TAC, molecular DNA, and histological improvements, which may occur via free radical scavenging and regenerative mechanisms. Administration of Cd increased the mRNA expression of the observed apoptotic cells, the proliferation of MKI67, antioxidant (GST) expressions whereas decreased anti-apoptotic expression (Bcl2). The effect of Cd was counteracted by the administration of the ginger extract, resulting in the down-regulation of the previously mentioned upgraded genes (Baiomy et al., 2016). Cd exposure in rats resulted in an elevation of parameters of liver function. However, ginger-containing treatment reduced ALT and normalized the other liver function parameters. The altered renal total serum cholesterol parameters were returned to near typical values after treatment (Ugwuja et al., 2016). It was found that ginger treatment of Cd-exposed rats increased hemoglobin content compared to Cd alone group. Ginger treatment also increased Glutathione Peroxidase (GPx) activity of Cd-exposed rats compared to Cd alone group (Attia et al., 2014b).

Grape Seed Extract

The grape seed extract (GSE) has shown to have excellent antioxidant potential and a greater scavenging capability of free radicals (Evcimen et al., 2018). According to Chen et al. (2013), Cd causes a decrease in GSH and SOD activities, and elevation in MDA level, induces renal apoptosis in mice. Co-administration of GSE, however, mitigates Cd-induced lipid peroxidation and antagonized renal apoptosis, possibly associated with Bax and Bcl-2 expression. GSE is also reported to improve prostatic oxidation stress and fibrosis induced by $CdCl_2$. It inhibits the over-generation of prostatic expressions of transforming

growth factors. According to Bashir et al. (2016), increasing levels of proinflammatory cytokines, lowers levels of cell defense proteins, and glucose transporters, as well as enhancing rates of signals of apoptosis molecules, observed in pancreas of Cd-intoxicated rats. Blood and liver MDA levels in Cd-treated rats were increased relative to controls. GSE improved the antioxidant potential in all tissues and decreased blood plasma and liver MDA levels (Evcimen et al., 2018). It was found that Cd treatment increased MDA and decreased Monoamine oxidase-A(MAO-A), acetylcholinesterase, and glutathione reductase (GR), while the GSE treatment caused improvements in those parameters (El-Tarras et al., 2016).

CONCLUSION AND FUTURE PERSPECTIVES

Since environmental and occupational exposure to Cd remains a serious health issue (Gaur & Agnihotri, 2019; Järup et al.,1998; J. J. Kim et al., 2019; Patra et al., 2011; Sarkar et al., 2013), especially in developing and industrialized countries, it is very important to find an effective solution to protect against adverse effects of Cd-exposure. Antioxidant-rich dietary products seem to be among the potential protective and therapeutic agents. They are particularly more promising in prevention than reversing treating the adverse health effects of the metal poisons in humans. Several experimental studies have shown that antioxidants exert a beneficial action against Cd toxicity in different organs of the body by averting oxidative stress as well as other adverse effects of this xenobiotic. The natural products rich in antioxidants can reduce the Cd-accumulation in tissues and hence humans may benefit from the consumption of these products. The existing literature shows that the researchers have recently focused their attention on ways to mitigate the absorption and accumulation of Cd and improve the organism's resistance to the toxic element. Interest has been given to agents with antioxidant ability, primarily naturally occurring substances. The search for more potent antioxidant-rich natural products is expected to continue with additional, relatively new products coming into the investigation. One of the examples is Edible Bird's Nest (EBN) which is currently under investigation in our laboratory to see its protective role against Cd toxicity. In our recent studies, EBN has been confirmed to play a significant protective role against lead (Pb), another heavy metal toxic agent (Albishtue et al., 2019). More research on the prophylactic and therapeutic use of antioxidant containing natural substances is warranted, as therapeutically active chelation treatment of Cd is currently lacking.

ACKNOWLEDGEMENT

This work was supported by the Ministry of Education Malaysia under the FRGS research grant scheme (No. 5540114/FRGS/1/2018/SKK08/UPM/02/6).

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