

Hepatotoxicity of Cadmium and Roles of Mitigating Agents

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Abstract: There are increasing reports on cadmium associated hepatotoxicity, due to these reports this study reviewed relevant literature on cadmium associated hepatotoxicity with emphasis on doses, route of administration, salt forms (cadmium compounds) and the roles of mitigating agents. Reports have shown that continuous exposure of the liver to cadmium has led to hepatotoxicity. Humans are generally exposed to cadmium by two main routes, inhalation and ingestion. In this study, evaluation of relevant literature showed that irrespective of route of administration and salt forms cadmium hepatotoxicity is dose and time dependent. Cadmium associated hepatotoxicity manifested through impaired functions of hepatic biomarkers (transaminases), enzymatic and non enzymatic antioxidants. Histopathological damage to liver architecture manifested as swelling of hepatocytes, focal necrosis, hepatocytes degeneration, dilatation of ribosomes, damage of membrane-bounded lysosomes, nuclear pyknosis and cytoplasm vacuolization. Deterioration of mitochondrial cristae, deposition of collagen fibrils, hypertrophy of kuffer cells, congestion in central veins and sinusoids, infiltration of mixed inflammatory cells and peripheral hemorrhage also occurred. Hepatotoxic effect of cadmium was mitigated by Vitamin C, Vitamin E, Manganese (II) Chloride, N-acetylcysteine and Selenium. Extracts of plant origin including *Solanum tuberosum*, *Calycopteris floribunda* and *Hibiscus sabdariffa* mitigated cadmium induced hepatotoxicity. Chemical substances of animal origin including honey and camel milk were reported to have ameliorated cadmium induced hepatotoxicity. One of the mechanisms of cadmium induced hepatotoxicity is reported to be associated with the up regulation of reactive oxygen species (oxidative stress) which caused oxidative damage to lipid contents of membranes and direct liver injury. Conclusion cadmium is dose and time dependently hepatotoxic irrespective of route of administration, salt form and is ameliorated by some antioxidants and extracts of plant and materials of animal origin which may require further evaluation for clinical application.

Keywords: Cadmium, liver, mechanism, mitigation, route, toxicity

INTRODUCTION

Liver is an abdominal organ which plays a vital role in detoxification and excretion of many endogenous and exogenous substances. The liver is a natural chemical factory which aids in anabolism of complex molecules from simple substances absorbed from the gastro-intestinal tract (GIT). It neutralizes toxins and manufactures bile which aids fat digestion and removes toxins through the bowels (Buraimoh *et al.*, 2011). Continuous exposure and intoxication of liver to different types of exogenous compounds on a daily basis may lead to hepatic dysfunction (Nithya *et al.*, 2012). Hepatic dysfunction due to exposure to environmental toxic agents is increasing worldwide. Cadmium is one of the known environment toxins that is detrimental to liver function on exposure. Cadmium (Cd) is a relatively rare element that occurs naturally in ores together with zinc, lead and copper or is emitted

into the air through volcanic emission. It is put into commercial use in the 20th century due to its agricultural and industrial importance (WHO, 2000; Jarup, 2003). Cadmium is a carcinogenic metal (International Agency for Research on Cancer Monographs, 1993) and it is a serious environmental and industrial pollutant. Cadmium emissions to the atmospheric, aquatic and terrestrial environment have increased during the last century. Since cadmium is not degraded in the environment, the risk of human exposure is constantly increasing as it enters the food chain (ATSDR, 2005). Humans are generally exposed to cadmium by two main routes, inhalation and ingestion. Absorption of Cadmium by skin is relatively insignificant (Mead, 2010). It is reported to be contained in industrial emissions and cigarette, fertilization and cigarette. Occupational exposure to cadmium occurs through working with cadmium containing pigments, plastic, glass, metal alloys and

electrode material in nickel-cadmium batteries. Non occupational exposure occurs through food, water and cigarette smoking (Waisberg *et al.*, 2003).

During exposure, cadmium accumulates predominantly in the liver, kidneys, reproductive organs and tissues (WHO, 1992; Godt *et al.*, 2006; Takamura *et al.*, 2006). Upon acute exposure to cadmium, hepatotoxicity is indicated by changes such as swelling of hepatocytes, fatty changes, focal necrosis, hepatocytes degeneration and impaired functions of biomarkers of liver function. On electron microscopy, changes such as dilatation of ribosomes, damage of membrane-bounded lysosomes, nuclear pyknosis, were reported. The molecular mechanism that may be responsible for the hepatotoxicity of cadmium involves oxidative stress, disturbance of the antioxidant defense system and the generation of reactive oxygen species (Thijssen *et al.*, 2007; Stohs *et al.*, 2001). Due to rising reports on cadmium associated hepatotoxicity in humans and animals, we evaluated past and present cadmium reported hepatotoxicity taking into consideration route of administration, salt forms (different cadmium compounds) and mitigating effects of chemical agents against cadmium induced hepatotoxicity.

CADMIUM HEPATOTOXICITY

Researchers have shown that cadmium has toxicological effect on various cells and organs in both humans and animals. Among its toxicological effects is the impairment of reproductive function as reported by some scholars (Al-Azemi *et al.*, 2010; De Souza Predes *et al.*, 2010; Yang *et al.*, 2006; Adaikpoh and Obi, 2009). Kidney which is an integral part of drug excretion is reported as one of the targets of cadmium toxicity (Obianime and Robert, 2009; Karimi *et al.*, 2012; Onwuka *et al.*, 2010; Lassmi *et al.*, 2012; Abdel-Moneim and Said, 2007). Cadmium is also reported to be detrimental to bone functions (Comelekoglu *et al.*, 2007; Bodo *et al.*, 2010; Brzoska *et al.*, 2005a, b; Åkesson *et al.*, 2006). Structure and functions of blood have been shown to be impaired on exposure to cadmium (Radhakarishan, 2010; Depault *et al.*, 2006). Cadmium is also reported to be injurious to the heart (Gulyasar *et al.*, 2009; Navas-Acien *et al.*, 2004; Waisberg *et al.*, 2005). Inhalation of cadmium causes respiratory stress and injures the respiratory tract. Emphysema and chronic rhinitis have been linked to high cadmium concentrations in polluted air. Reduction in forced expiratory volume and respiratory distress syndrome were reported among people exposed to cadmium (Lampe *et al.*, 2008; El-Sokkary and Awadalla, 2011). Cadmium has been reported to be a hepatotoxic element. It has impaired biomarkers of liver function and induced histopathological changes in the liver of animals and humans. In this review we capture relevant literature on cadmium hepatotoxicity with respect to various routes of administration

(intraperitoneal, oral, subcutaneous, intravenous and *in vitro*). Roles of various agents with mitigating abilities against cadmium toxicological effect on liver function and structure were also evaluated in this study.

Subcutaneous route: Subcutaneous route is one of the essential routes of drug administration, quite a number of researchers have reported cadmium induced hepatotoxicity in animals via this route. Among these researchers are Eybl and Kotyzora. They reported that 24 h after 7 mg/kg bwt of cadmium chloride was injected subcutaneously to mice, cadmium induced hepatic damage was characterized by an increase in hepatic lipid peroxidation in collaboration with the depletion of endogenous antioxidants. Activities of glutathione, glutathione peroxidase and catalase were altered. Pre treatment with 20 mg/kg bwt of MnCl₂ 24 h before cadmium intoxication completely prevented or significantly attenuated these changes. Manganese (II) pretreatment attenuated the interference of cadmium on calcium homeostasis. Manganese is reported to have antioxidant property and is an activator, a constituent of several enzymes. It is an important cofactor of mitochondria superoxide dismutase. These properties must have contributed to its ability in mitigating cadmium toxicity on the liver (Tarasub *et al.*, 2008; Eybl and Kotyzová, 2010).

In an evaluation of cadmium-induced hepatotoxicity and oxidative stress in rats, cadmium chloride 2 mg/kg was administered subcutaneously to male rats. Significant ($p < 0.01$) increment in AST, ALP, ALT, γ -GT, bilirubin and hepatic zinc was reported. Administration of selenium one hour before cadmium intoxication ameliorated the toxic effects of cadmium which could be due to the antioxidant property of selenium as reported. Selenium is an important antioxidant that is present in glutathione peroxidase and thioredoxin reductase which helps in the production of antioxidant enzymes (Alhazzi, 2008).

Bamidele and coworkers administered 2.5 mg/kg bwt of cadmium subcutaneously every other day regularly for six weeks. They observed significant reduction in total proteins and albumin levels while ALT activity was significantly increased. Histopathological observation of the liver of treated rats showed fatty degeneration, cytoplasm vacuolization with focal and diffused hepatocellular necrosis. However, the toxic effect of cadmium was significantly controlled in rats pre-treated with 300 mg/kg body weight of methanolic extract of *Momordica charantia* one hour before subcutaneous 2.5 mg/kg body weight of cadmium was administered (Bamidele *et al.*, 2012).

Bashandy and co researchers administered 2.2 mg/kg of cadmium chloride subcutaneously four times weekly for 2 months to rats. Cadmium was observed to increase GSH levels and decrease hepatic catalase activity significantly. Aspartate aminotransferase and alanine aminotransferase levels were significantly decreased. Alterations of the structure of the liver

manifested as deterioration of mitochondrial cristae, deposition of collagen fibrils and hypertrophy of kuffer cells. They further reported that administration of 2.2 mg/kg of zinc chloride injection subcutaneously four times weekly for 2 months one hour prior to cadmium administration mitigated cadmium induced toxicity (Bashandy *et al.*, 2000).

This is in agreement with the work of Jabeen and Chaudhry, who subcutaneously administered 1 mg/kg bwt of cadmium chloride to rats. This induced hepatotoxicity via significant increase in DNA liver fragmentation, MDA levels with decrease in GSH and CAT levels. Ameliorating effects of 1 mg/kg body weight of selenium ($\text{Na}_2\text{Se}_2\text{O}_3$) in saline solution were observed in pretreated rats. The hepatoprotective effects of selenium against cadmium induced toxicity, oxidative stress and tissue damage in this study could be attributed to its antioxidant and possible chelating effects on cadmium (Jabeen and Chaudhry, 2011).

Administration of 3 mg/kg body weight of cadmium subcutaneously to rats for three weeks showed significant ($p < 0.05$) increase in activities of serum transaminases, alkaline phosphatase, lactate dehydrogenase and lipid peroxidation with significant decrease in the levels of anti oxidant in the liver. Liver histopathological evaluation showed change in liver architecture via macrovascular fatty changes in hepatocytes, periportal inflammation and cell infiltration. Oral administration of silibinin 80 mg/kg bwt significantly normalized the activities of serum hepatic enzymes and reduced the levels of lipid peroxidation and also restored the antioxidant defense in the liver (Srinivasan and Ramprasath, 2012).

Intraperitoneal Route: There are reports of hepatotoxicity via intraperitoneal administration of cadmium; one of these reports can be seen from the work of Amin and colleagues. They exposed rats to 3.5 mg/kg bwt of cadmium via intraperitoneal injection and reported significant ($p < 0.001$) increase in the activities of serum ALT and AST (357 and 126%) with respect to the control. Hepatic MDA level was significantly ($p < 0.01$) increased by 73% and CAT activity was also elevated ($p < 0.05$). SOD and GSH levels were significantly decreased ($p < 0.01$). Histopathological evaluation of the liver of treated rats with 3.5 mg/kg bwt of cadmium showed mild necrosis in the lobule, degenerated cells, karyolysis or pyknosis of nuclei, congestion in central veins and sinusoids and infiltration of mixed inflammatory cells. Pre administration with one gm/kg body weight of Spirulina dissolved in 5 mL distilled water showed marked reduction in serum aminotransferase activities, reduction in lipid peroxidation and recovery of the endogenous levels of antioxidants following cadmium intoxication. Cadmium induced hepatic histopathological changes were also minimized by this extract. This result suggests that Spirulina algae might play a role in mitigating the toxic effect of cadmium (Amin *et al.*, 2006).

Intraperitoneal administration of 0.5 mg/kg cadmium chloride dissolved in saline for 4 weeks to male rats' revealed marked elevation in the levels of free radicals, liver enzymes with decrease in GPx activity and GSH level. Histopathological examination of rat liver revealed different degrees of cell degeneration, necrosis, dilatation and congestion of blood vessels. Depletion of glycogen granules in a rarified vacuolated cytoplasm was also seen in the hepatocytes. Administration of honey to cadmium intoxicated rats led to improvement in all examined parameters. It was noticed that concurrent administration of honey with cadmium improved histopathological changes in liver with respect to cadmium treated rats. It could be concluded that honey via its antioxidant activity has the ability to protect against cadmium induced hepatotoxicity (Abdel-Moneim and Ghafeer, 2007). Similar hepatotoxic effect of cadmium was also reported by some scholars (Borges *et al.*, 2005).

The effect of cadmium on liver regeneration after partial hepatectomy in rats was studied by Tzirogiannis *et al.* (2005). They intraperitoneally administered 2.5 mg and 1.0mg/kg bwt of cadmium chloride and observed that cadmium suppressed the rate of DNA synthesis and delayed the first peak of liver regeneration. The rate-determining enzyme thymidine kinase was suppressed in the liver by cadmium. Margeli *et al.* (1994 a, b) reported similar effect of cadmium on the liver. Possible role of oxidative stress in acute cadmium hepatotoxicity in rats was evaluated by Mladenovi *et al.* (2010) through the administration of 2.5 mg/kg of cadmium intraperitoneally for 24 h. Evaluation of biochemical parameters revealed elevated concentration of malondialdehyde in plasma and liver ($p < 0.01$), significant decrease in superoxide dismutase activity ($p < 0.01$) was also observed. Cadmium caused morphological changes in hepatocytes, such as dilatation of the rough endoplasmic reticulum with loss of ribosome, nuclear condensation, hepatocellular necrosis and apoptosis (Dudley *et al.*, 1984).

Furthermore 4 mg/kg bwt of cadmium chloride administered intraperitoneally every other day for one week to rats showed significant reduction in MDA, GSH and GST activities. Significant increases in levels of serum GOT, GPT, ALP and OGT were observed. These cadmium induced changes in biochemical parameters were normalized by the administration of 250 mg/kg of *Solanum tuberosum* extract (Lawal *et al.*, 2011). Similar observations were also reported by some scholars with respect to cadmium induced changes in biomarkers of liver function (Qu *et al.*, 2005; Lawal and Ellis, 2010).

Ibrahim exposed male rats to intraperitoneal injection of 3.5 mg/kg bwt of cadmium chloride and/or γ -irradiation with 4 Gy. Biochemical analysis showed significant ($p < 0.05$) increase in ALP, AST, ALT and

TBARS levels. Significant decrease in SOD, CAT and GSH contents was observed in treated rats. Administration of 1 mL/Kg of body weight Kombucha Tea Ferment, via gavages, for two weeks before intraperitoneal administration of 3.5 mg/Kg body weight cadmium chloride and irradiation with 4 Gy, resulted in recovery of all the pathological changes induced by cadmium and γ irradiation (Ibrahim, 2013).

Hepatotoxicity of cadmium can also be seen in rats subjected to 30-34% partial hepatectomy, amitotic index, immunochemistry and thymidine kinase activities were used as indices for liver regeneration. Administration of 2.5 mg/kg body weight of cadmium intraperitoneally during the first 24 h after partial hepatectomy arrested liver regeneration. The introduction of Hepatic Stimulator Substance (HSS) restored liver regeneration (Tzirogiannis *et al.*, 2005). These findings are in agreement with other findings with respect to cadmium induced hepatotoxicity (Margeli *et al.*, 1994 a, b).

Oral route: Oral ingestion has been one of the routes of cadmium induce hepatotoxicity; this has been proven in animal studies and humans exposed to cadmium. This can be seen from the work of Tarasub and friends who treated rats orally with 200 mg/kg bwt of cadmium acetate for 24 h and observed significant increase in serum AST ($p < 0.001$), ALT ($p < 0.005$), MDA ($p < 0.01$) and decrease hepatic level of GSH ($p < 0.05$) with respect to the control. Histopathological examination of liver of rats treated with 200 mg/kg bwt of cadmium showed increased cytoplasm hypereosinophilia, hepatic cell damage such as nuclear hyperchromasia, pyknosis and karyorrhexis. It was observed that pre treatment with 250 mg/kg bwt of curcumin before cadmium administration could not prevent cadmium induced oxidative damage in rat liver (Tarasub *et al.*, 2008).

Rajasekaran and Periasamy also orally administered 5 mg/kg bwt of cadmium chloride to rats for four weeks, they observed significant ($p < 0.05$) elevation of hepatospecific serum makers (SGOT, SGPT and ALP) with respect to the control. The blood samples from the animals treated with 200 mg/kg bwt and 400 mg/kg bwt of ethanolic leaf extract of *Calycopteris floribunda* showed significant reduction in the serum markers indicating the effect of the leaf extract in restoring the normal functional ability of the hepatocytes with respect to cadmium treated rats (Rajasekaran and Periasamy, 2012).

Treatment of rats with 5 mg/kg of cadmium via gavage for 27 days resulted in significant increase in lipid peroxidation, metallothioniens expression and significant decrease in glutathione levels. Liver histopathological study showed hepatic damage including necrosis, inflammation, cytoplasm vacuolization and inflammatory cell infiltration. The

treatment of cadmium exposed rats with 200 mg/kg bwt, curcumin, 100 mg/kg bwt and 100 mg/kg bwt of vitamin C alone could not reverse cadmium induced changes. Combined treatment with curcumin 200 mg/kg bwt or 400 mg/kg bwt along with vitamin C 100 mg/kg bwt one hour before cadmium intoxication was more effective in mitigating these changes than the individual agents (Tarasub *et al.*, 2012). Hepatotoxic effect of cadmium was further buttress by the administration of 50 mg/L of cadmium chloride to rats in drinking water for 3 months which resulted in elevation of AST and ALT concentrations (Kowalczyk *et al.*, 2002).

Gathwan *et al.* (2012) orally administered 1-10 mg/kg body wt of cadmium chloride and 1-8 mg/kg body wt of zinc chloride to mice. Histopathological evaluation of the liver of treated rats' revealed necrosis as a feature of cadmium and zinc induce hepatotoxicity. This was characterized by apoptosis and necrosis which was dose dependent, decrease in liver weight was also observed (Gathwan *et al.*, 2012). Previous studies also reported similar observation (Morsey and Protasowicki, 1990; Habeebu *et al.*, 1997; Ersan *et al.*, 2008).

Ige and colleagues orally administered cadmium 1.5 mg/100 kg bwt/day for four weeks to rats, results showed significant decrease in hepatic SOD activity, total serum protein, significant increase in hepatic malondialdehyde (MDA) level, serum ALT and AST activities. Cadmium was observed to impair hepatic architecture through slight decrease in liver weight, cellular degeneration, necrosis and localized fatty degeneration. Pre-treatment with *Allium cepa* extract (1.0 mm/100 kg bwt/day) and post treatment with *Allium cepa* extract (1.5 mg/100 kg bwt/day) for 8 weeks ameliorated cadmium induced changes in biochemical parameters and liver architecture (Ige *et al.*, 2011). Findings associated with cadmium induced hepatotoxicity were also reported by some scholars (Hristo *et al.*, 2008; Shaikh *et al.*, 1999).

Oral administration of 200 mg/kg of cadmium chloride to rats for 30 days impaired biochemical parameters by causing significant increase in serum glucose concentration, alanine aminotransferase glutamate pyruvate transaminase, alanine and alkaline phosphatase activity. Liver glutathione level, catalase and glutathione peroxidase, were significantly decreased. Consequently the observed biochemical changes correlated with the liver alterations such as the presence of cellular debris within the central vein and cytoplasmic vacuolization with increase in liver weight. Administration of vitamin C or vitamin E inhibited cadmium induced hepatotoxicity. Coadministration of vitamin C and E produced synergistic protection against cadmium induced toxicity with respect to individual agents (Layachi and Kechrid, 2012). The mitigating effects of vitamin C and E as exhibited above can be attributed to their water and lipid soluble antioxidants

properties respectively. Vitamin E prevents ROS induce damage in polyunsaturated fatty acid and acts as a membrane stabilizing agent by breaking antioxidants chain. Vitamin C protects biomembranes against peroxidative damage in aqueous phase. In addition both agents form synergy because the both inhibit ROS generation. Vitamin C is known to cause regeneration of oxidized vitamin E molecule and both vitamins have sparing effect on each other (Obianime *et al.*, 2010). Previous histopathological study of the liver of rats administered cadmium was characterized by cellular hypertrophy, enlarge nuclei, hepatocytes necrosis, hepatocytes vacuolization and hepatocytes with dilated central vein (Brzóška *et al.*, 2002).

Administration of 5 mg/kg of oral cadmium to rats for four weeks enhanced significant lipid peroxidation and significantly reduced non enzymatic antioxidants. Enzymatic antioxidants like superoxide dismutase, catalase and glutathione-s-transferase were significantly reduced. Two different doses of rustin (80 and 200 mg/kg bwt) were administered, it was observed that 80mg/kg of rustin resulted in significant decrease in lipid peroxidase ($p < 0.001$) and significant positive change in SOD, CAT and GSH activities ($p < 0.001$) (Miran *et al.*, 2012).

Administration of oral 10 mg/kg bwt of cadmium to rats was reported to alter some biochemical parameters. Significant increases in serum activities of ALT, AST and ALP were observed. Administration of 2.5 and 4.6 g/kg bwt of calyx extract of *Hibiscus sabdariffa* normalized some of these cadmium induced changes (Muhammad and Charles, 2008). Similar observation was documented by Al-Hashem *et al.* (2009) who administered oral 10 mg/kg body weight of cadmium to rats for 21 days and observed elevated levels of AST, ALT and ALP. The addition of Camel's milk to cadmium chloride normalized albumin, hemoglobin, calcium, serum alanine aminotransferase, aspartate aminotransferase and serum alkaline phosphatase levels. Hydroperoxides, superoxide dismutase, catalase and glutathione levels were also normalized with respect to cadmium treated rats (Al-Hashem *et al.*, 2009). The above report is in agreement with other observations (Nigma *et al.*, 1999; Chwelatiuk *et al.*, 2006; Rikans and Yamano, 2000; Tzirogiannis *et al.*, 2003).

Oral administration of 5mg/kg bwt of cadmium for four weeks to rats significantly ($p < 0.05$) elevated the levels of serum hepatic markers such as serum AST, ALT, ALP, LDH, GGT and TBRNS. Significantly it increased oxidative stress markers viz, thiobarbituric acid reaction substances, lipid hydroperoxidase, protein carbonyls and conjugated diene. Enzymatic antioxidants viz. glutathione dismutase, catalase, glutathione peroxides, glutathione s-transferase, glutathione reductive and glucose-6-phosphite were reduced. Non-enzymatic antioxidants viz. glutathione,

total sulthydryls, vitamin C and vitamin E in the liver were also significantly reduced. Histopathological findings in cadmium treated rats showed peri portal inflammation, degeneration of hepatocytes, necrosis, micro vascular steatosis and balloon degeneration. Pre-oral supplementation with 200 mg/kg bwt of *Piper betle* leaf extract in cadmium intoxicated rats normalized the above mention biochemical indices and pathological changes induced by cadmium (Prabu *et al.*, 2012).

Intravenous route: Intravenous route has been one of the known routes of drug administration and research has shown that exposure of animals to cadmium via this route has caused tremendous toxicity. This can be seen from a study which exposed rats to a single intravenous injection of 4 mg/kg body weight cadmium. Significant elevated levels of ALT, AST and lactate dehydrogenase (LDH) were reported. Histopathology evaluation of cadmium treated liver showed central lobular necrosis around central veins, peripheral hemorrhage around portal triads. Pretreatment with 50, 100 mg/kg/day of licorice extract normalized ALT, AST and LDH levels. In histopathological analysis, licorice decreased the central necrosis around central veins, the peripheral hemorrhage around portal triads, the percentage of degenerative hepatic regions and the number of degenerative hepatic cells. Licorice also inhibited the increment of Bad (a BH 3 domain containing protein) translocation by cadmium in liver cells (Lee *et al.*, 2009).

In vitro: Cadmium has been reported to impair cellular activities via cell damage in prepared liver cells (cell lines). This can be seen from the reports of Yazihan *et al.* (2008) who evaluated the effect of 0.5-1-5-10 $\mu\text{g/mL}$ of cadmium on human hepatoma cell line (Hep3B). The effects of exogenously applied 250-5000 pg/mL midkine and/or 5 $\mu\text{g/mL}$ cadmium were also evaluated. Cadmium induced cellular damage include decrease living cell number, cellular damage in a dose and time dependent manner, increased apoptosis, which was confirmed with increase in caspase-3 levels and decrease in LDH release in the Hep3B cells. They were able to show that midkine secretion from Hep3B cells during cadmium exposure protected liver cells from cadmium induced cellular damage. Also exogenous midkine treatment caused proliferation of Hep3B cells, in a dose and time dependent manner and prevented cell death, induced by cadmium even with the lowest dosages. Midkine has an ant-apoptotic and cytoprotective role during cadmium toxicity (Yazihan *et al.*, 2008).

Odewumi and her colleagues reported cadmium induced damage in cultured rat normal liver cells. They treated rats liver cells with 150 Mm of cadmium chloride, results showed decrease in cell viability, catalase enzyme, glutathione peroxidase enzyme, glutathione reductase and increased cell cycle arrest.

Two hours pre simultaneous or 2 h post-treatment for 24 h with 5 mM of N-Acetylcysteine (NAC) mitigated cadmium associated changes in the liver (Odewumi *et al.*, 2011). NAC is an antioxidant with direct and indirect activities. NAC is said to act directly when its thiol group reacts with the electrophilic group of ROS. NAC acts indirectly by providing intracellular cysteine for the production of glutathione (Dekhuijzen, 2004).

Exposure of murine hepatocytes *in vitro* to 5, 10, 25 μ M of cadmium chloride showed a dose-dependent decrease in hepatocytes viability and an elevated aspartate aminotransferase (AST) activity in the culture medium. Significant increase in lactate dehydrogenase (LDH) activity, decreased albumin content, decrease in calcium concentration in the culture medium of cadmium chloride exposed hepatocytes was observed (Wang *et al.*, 2007).

The exposure of hepatoma cell line Hep G2 to 5, 10 and 50 μ M of cadmium chloride showed decrease in cell viability. There was significant increase in lactate dehydrogenase leakage, DNA damage, malondialdehyde and antioxidant enzymes activities. Significant decreases in ATP production were also observed at all cadmium concentrations in HepG2. ROS levels significantly increase and GSH/GSSG ratio significantly decrease. These effects were reported to be attenuated by the presence of N-Acetylcysteine (NAC) (Lawal and Ellis, 2010; Oh and Lim, 2006).

MECHANISMS OF CADMIUM HEPATOTOXICITY

Several mechanisms have been suggested for the induction of cadmium-associated hepatotoxicity. One of the reported mechanisms of cadmium induced liver toxicity is mediated by the upregulation of reactive oxygen species (hydroxyl groups, superoxides and hydrogen peroxides) which cause oxidative damage to lipid contents of membranes (Packer and Cadenas, 2002; Shaikh *et al.*, 1999). Over-production of ROS normally induces oxidative stress unless it was scavenged with endogenous antioxidants. Thus, overproduction of ROS could be attributed to the depletion of antioxidants or to the direct action of cadmium on peroxidation reaction and iron-mediated peroxidation (Pillai and Gupta, 2005; Casalino *et al.*, 2002, 1997).

Primary injury of cells resulting from binding of cadmium to sulphhydryl groups in mitochondria and secondary injury initiated by the activation of kupffer cells have also been mentioned as possible mechanisms of toxic effect of cadmium on the liver (Rikans and Yamano, 2000). Inactivation of sulphhydryl groups causes oxidative stress, mitochondrial permeability transition and mitochondrial dysfunction (Jurczuk *et al.*, 2004). It is also suggested that kupffer cells release proinflammatory cytokines and chemokines which stimulate the migration and accumulation of neutrophils and monocytes in the liver (Dudley *et al.*, 1984).

Dudley also suggested that hepatocytes injury may be caused by ischemia due to sinusoidal endothelial cell dysfunction. Cadmium has been found to accumulate in endothelial cells leading to necrosis and denudation of hepatic sinusoids. The hepatotoxicity of cadmium has also been attributed to the formation of toxic metabolites when it is activated by hepatic cytochrome P 450 (Wong *et al.*, 1981) to a highly active metabolite N-acetyl-P-benzoquinone imine (Savides and Oehne, 1983).

Furthermore, interference with essential metals could be one of the mechanisms employed by cadmium mediated toxicological effects. Cadmium may interact with elements like zinc, iron, magnesium, manganese, calcium and selenium and cause their secondary deficit thereby disrupting metabolism, resulting in the final morphological and functional changes in many organs (Sarkar *et al.*, 2013). Cadmium has been reported to be involved in the disruption of signaling and biomembranes. This could occur through interaction with cellular components even without entering the cell, by interaction with receptors on their surface. Cadmium forms covalent and ionic bonds with atoms of sulfur, oxygen and hydrogen present in the sulphhydryl groups, disulfide, carboxyl, imidazole or multiple amino compounds present in the cells, causing significant disruption of their homeostasis (Bertin and Averback, 2006). Cadmium interferes with the reception and processing in the cells where the external signals reach and prevent their proper functioning. Cadmium may interfere with cell signaling at every stage of signal transduction and can act on receptors, second messengers and transcription factors (Jing *et al.*, 2012). These mechanisms could be employed by cadmium in the induction of hepatotoxicity.

CONCLUSION

In this study cadmium salts which include cadmium acetate, cadmium chloride and cadmium sulphate are dose and time dependently hepatotoxic. All possible routes of drug administration have confirmed the hepatotoxic effects of cadmium. It was observed that some antioxidants, plant extracts and substances of animal origin were able to mitigate cadmium induced hepatotoxicity through normalization of biochemical parameters and histopathological changes induced by cadmium. There is need for further evaluation of these chemical agents if they could be of clinical applications.

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