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Protective Effect of Rutin Against Cadmium Induced Hepatotoxicity in Swiss Albino Mice

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ABSTRACT

Cadmium is an extremely toxic metal which has no known necessary function in the body. Industrial use and agricultural fertilizers are the major source of its environmental contamination. It principally affects lung, liver, kidney and testes following acute intoxication. The present study pertains to the protective role of rutin against cadmium (Cd)-induced hepatotoxicity in mice. Rutin is a naturally occurring citrus flavanone which has been reported to have a wide range of pharmacological properties. In the present investigation cadmium (5 mg kg^{-1}) was administered orally for 4 weeks to induce hepatotoxicity. Cadmium treatment enhanced the lipid peroxidation in liver significantly ($p<0.001$). Cadmium treatment also decreased the amount of non-enzymatic antioxidant viz., reduced glutathione (GSH) significantly. Cadmium treatment decreased the level of enzymatic antioxidant enzymes viz., super oxide dismutase (SOD), catalase (CAT) and Glutathione-S-Transferase (GST). Two different doses of rutin (80 and 20 mg kg^{-1} b.wt.) were given to the mice along with the cadmium. High dose treatment of rutin (80 mg kg^{-1} b.wt.) resulted in significant decrease in lipid peroxidation ($p<0.001$). It also restored the amount of reduced glutathione significantly ($p<0.001$). Administration of high dose of rutin also brought the activities of cellular antioxidant enzymes viz., SOD ($p<0.001$), CAT ($p<0.01$) and GST ($p<0.001$) significantly to normal. The study result suggested that rutin may be beneficial in ameliorating the cadmium-induced oxidative damage in the liver of mice.

Key words: Rutin, cadmium, hepatotoxicity, catalase, oxidative damage

INTRODUCTION

Cadmium (Cd) is highly toxic heavy metal which is used in smelting, electroplating and in the manufacturing of batteries, dyes, paints and plastics (Al-Khedhairy *et al*., 2001; Natzir, 2004; Kaplan *et al*., 2011). Industrial use and agricultural fertilizers are the major source of its environmental contamination (Hashem and Abed, 2007; Eriyamremu *et al*., 2006). Animals including human beings are exposed to cadmium through food, water and some time through contaminated soil. Lipid peroxidation is considered as the primary mechanism for Cd-induced toxicity though it indirectly involved in the generation of free radicals (Bagchi *et al*., 1996; Dabak *et al*., 2009; Cinar *et al*., 2011; Eneman *et al*., 2000). Cadmium exerts its toxic effects via oxidative damage to cellular organelles by inducing the generation of Reactive Oxygen Species (ROS) (Stohs *et al*., 2001), which consist mainly of $O_2^{\bullet}$, H_2O_2 and $OH^{\bullet}$. The molecular mechanism by which the generation of free radicals are far from being understood but reports have indicated that cadmium does this via an indirect phenomenon (Stohs and Bagchi, 1995; Yiin *et al*., 1999).

Reactions of these ROS with cellular biomolecules have been shown to lead to lipid peroxidation, membrane protein damage, altered anti-oxidant system, DNA damage, altered gene expression and apoptosis (Stohs and Bagchi, 1995; Stohs *et al*., 2001). In addition to that depletion of glutathione and other endogenous antioxidants may also contribute significantly to the development of cadmium-induced toxic oxidative stress (Bagchi *et al*., 1996). As Cadmium indirectly induces the generation of free radicals so it is possible to treat the cadmium toxicity by antioxidants. There are many reports in which naturally occurring phytochemicals having antioxidant properties were used against Cd-induced hepatotoxicity (Choi *et al*., 2003; Gramza-Michalowska and Korczak, 2007; Vincente-Sanchez *et al*., 2008). Among those, flavonoids are one of the most numerous and widespread group of naturally occurring antioxidants and as potent inhibitors of lipid peroxidation in a biological membrane. Rutin, a citrus flavonoid glycoside present mainly in buckwheat, has antioxidant, antiallergic, anti-inflammatory, antiangiogenic and antiviral properties because of its superoxide radical scavenging nature (Guruvayoorappan and Kuttan, 2007; Kamalakkannan and Prince, 2006; Bishnoi *et al*., 2007). It showed many pharmacological benefits including anti-tumor (Deschner *et al*., 1991), anti-diarrhoeal (Di Carlo *et al*., 1993) and myocardial protecting (Pozin *et al*., 1996), immunomodulator (Chen *et al*., 2000). Many people have shown the antioxidant properties of rutin in different experimental models (Alsaif, 2009; Gao *et al*., 2002; Nagasawa *et al*., 2003). Taking the above into account, present work was carried out to assess the efficacy of rutin on Cd-induced hepatotoxicity protection in mice.

MATERIALS AND METHODS

Chemicals: Oxidized and reduced glutathione (GSSG and GSH), reduced nicotinamide adenine dinucleotide (NADPH), potassium dichromate, dithionitrobenzene (DTNB), 1-chloro-2,4-dinitrobenzene (CDNB), Reduced Glutathione(GSH), Thiobarbituric acid (TBA),Trichloroacetic acid (TCA 10%), physiological normal saline (0.9%), Formalin (4%), Sulphosalicylic acid (4%), Glycine were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals and reagents used were of highest purity commercially available.

Animal maintenance: Swiss albino male mice of 6-8 weeks weighing 30-35 g were housed in groups of six in polypropylene cages. Lighting was regulated to provide equal hours of light and dark. Animals were obtained from the central animal house facility of Jamia Hamdard, New Delhi, India. The animals were acclimatized to standard laboratory conditions (temperature 25±10°C, relative humidity 50±15%) 1 week prior to the actual commencement of the experiment. They were provided with standard food pellets (Hindustan Lever Ltd., India) and tap water ad libitum. The study was approved from the Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA). CPCSEA guidelines were followed for animal handling and treatment.

Experimental design: Twenty five Swiss albino mice were divided in to five groups. Group I served as control g roup and received vehicle i.e olive oil. Group II received cadmium (5 mg kg^{-1} b.wt.) for four weeks. Group III received cadmium along with low dose of rutin (20 mg kg^{-1} b.wt.). Group IV received cadmium along with high dose of rutin (80 mg kg^{-1} b.wt.). Group V received only rutin (80 mg kg^{-1} b.wt.).

Preparation of homogenates: At the end of potassium dichromate exposure, liver was excised under anesthesia. The organs were washed thoroughly in ice-cold physiological saline and weighed. A 10% homogenate of each tissue was prepared separately in 0.1 M phosphate buffer (pH 7.4) using a motor driven Teflon-pestle homogenizer (Fischer) and centrifugation at 4000 rpm for 5 min at 4°C. The supernatant obtained was called "homogenate" and used for the assays.

Preparation of PMS (post mitochondrial supernatant): The homogenate was centrifuged at 12000 rpm for 20 min at 4°C. The supernatant fraction obtained was called "PMS" and used for the assays.

Biochemical estimations

Determination of lipid peroxidation: Briefly, 0.6 mL of homogenate was mixed with 0.4 mL of phosphate buffer pH 7.4 and 1 mL 10% trichloroacetic acid (TCA) and finally kept for 5 min at room temperature (Wright *et al*., 1981). Then 1 mL 0.67% thiobarbituric acid (TBA) was mixed and tubes were placed in boiling water bath at 90°C for 45 min and on ice bath for 15 min. Tubes were centrifuged at 2500 xg for 10 min. Pellet was discarded and supernatant was collected to measure the absorbance at 535 nm in spectrophotometer. The result was expressed in nmoles of TBARS formed min^{-1} g^{-1} tissue at 37°C by using a molar extinction coefficient of 1.56×10^{5} M^{-1} cm^{-1}.

Determination of reduced glutathione (GSH): 1.0 mL of PMS fraction (10%) was mixed with 1.0 mL of sulphosalicylic acid (4%) (Jollow *et al*., 1974). The samples were incubated at 4°C for at least 1 h and then subjected to centrifugation at 1200×g for 15 min at 4°C. The assay mixture contained 0.4 mL filtered aliquot, 2.2 mL phosphate buffer (0.1 M, pH 7) and 0.4 mL DTNB (4 mg mL^{-1}) in a total volume of 3.0 mL. The yellow colour developed was read immediately at 412 nm on spectrophotometer (Milton Roy Model-21 D). The GSH concentration was calculated as nmoles GSH formed g^{-1} tissue using a molar extinction coefficient of $1.36\times10^{4.}$

Assay of catalase: In brief, the assay mixture consisted of 1.950 mL phosphate buffer (0.1 M, pH 7), 1 mL hydrogen peroxide (0.34%) and 0.05 mL of PMS (10%) in a final volume of 3.0 mL (Claiborne, 1985). Change in absorbance was recorded at 240 nm. The catalase activity was calculated in terms of nmoles H_2O_2 consumed min^{-1} mg^{-1} protein using a molar extinction coefficient of 43.6 M^{-1} cm^{-1}.

Assay of super oxide dismutase (SOD): The reaction mixture consisted of 1.6 mL hot glycine buffer (50 mM, pH 10.4), 0.2 mL of PMS (10%) and 0.04 mL of chilled epinephrine in a final volume of 1.84 mL (Stevens *et al*., 1980). The change in absorbance was recorded at 480 nm and the enzymatic activity was calculated as nmol of epinephrine protected from oxidation mg^{-1} protein min^{-1} using a molar extinction coefficient of 4.02×10^{3} M^{-1} cm^{-1}.

Assay of glutathione S-transferase (GST): The reaction mixture consisted of 2.4 mL phosphate buffer (0.1 M, pH 6.5), 0.2 mL reduced glutathione (1.0 mM), 0.2 mL CDNB (1.0 mM) and 0.2 mL of cytosolic fraction in a total volume of 3.0 mL (Habig *et al*., 1974). The changes in absorbance were recorded at 340 nm and the enzymatic activity was calculated as nmol CDNB conjugate formed min^{-1} mg^{-1} protein using a molar extinction coefficient of 9.6×10^{3} M^{-1} cm^{-1}.

Statistical analysis: Data from experiments were compared by one-way ANOVA followed by Turkey's t-test. All values were reported as Mean±SE for each group. The significant level was showed as $p<0.001$, $p<0.01$ and $p<0.05$.

RESULTS

Rutin attenuated cadmium induced lipid peroxidation (LPO) in liver: Thiobarbituric acid reactive substances (TBARS) are measured to evaluate the extent of lipid peroxidation induced by cadmium in the liver tissue homogenate of mice. Results indicate that cadmium (Cd) treatment increased TBARS level significantly ($p<0.001$) in liver (Table 1). Co-administration of rutin with cadmium caused significant decrease in TBARS content as compared to control group. High dose (80 mg kg^{-1}) of rutin ($p<0.01$) showed better protection as compared to low dose (20 mg kg^{-1}; $p<0.05$).

Rutin reinstated cadmium induced depletion in cellular reduced glutathione content (GSH): GSH, a non-enzymatic cellular anti-oxidant is estimated in PMS of liver. The content of GSH was significantly ($p<0.001$) decreased in liver of mice treated with cadmium as compared to control (Table 2). Treatment with low dose of rutin (20 mg kg^{-1}) did not show any change significant change in GSH content. But high dose of rutin (80 mg kg^{-1}) restores the reduced GSH content of the liver significantly ($p<0.001$).

Rutin restored cadmium induced changes in cellular enzymatic antioxidants: SOD, CAT and GST were measured as an index of antioxidant status of liver tissues. Significantly lower liver SOD ($p<0.001$), CAT ($p<0.001$) and GST ($p<0.001$) activity were observed in cadmium treated group as compared to the normal control group (Table 3). Treatment of high dose rutin restored the activities of SOD ($p<0.001$), CAT ($p<0.001$) and GST ($p<0.001$) significantly (Table 3). High dose of rutin showed better restoration as compared to low dose.

Table 1: Effect of rutin on cadmium induced alterations in lipid peroxidation in liver

Treatment	LPO (liver)
Control	3.047±0.196
Cadmium (5 mg kg^{-1})	4.973±0.297###
Cadmium+rutin (L)	3.549±0.459*
Cadmium+rutin (H)	3.293±0.180**
Rutin	3.605±0.193

Values are Mean±SE of five mice per group, Lipid peroxidation (LPO) is expressed as nmoles of TBARS formed min^{-1} g^{-1} of tissue, Values are significant at ###$p<0.001$, (compared with Group I) and **$p<0.01$, (compared with Group II), L: Low dose, H: High dose

Table 2: Effect of rutin on cadmium induced alterations in cellular GSH content

Treatment	GSH (liver)
Control	3.401±0.042
Cadmium (5 mg kg^{-1})	2.962±0.020###
Cadmium+rutin (L)	2.841±0.019
Cadmium+rutin (H)	3.444±0.023***
Rutin	3.225±0.020

Values are Mean±SE of five mice per group, GSH is expressed as nmoles of GSH formed g^{-1} tissue, Values are significant at ###$p<0.001$, (compared with Group I) and ***$p<0.001$ (compared with Group II), L: Low dose with, H: high dose, GSH: Reduced glutathione

Table 3: Effect of rutin on cadmium induced changes on enzymatic antioxidants of liver

Treatment	SOD	CAT	GST
Control	46.66±3.39	1.688±0.0478	0.217±0.0052
Cadmium (5 mg kg^{-1})	17.96±2.86$^{\#\#}$	0.768±0.0562$^{\#\#\#}$	0.167±0.0055$^{\#\#\#}$
Cadmium+rutin (L)	28.28±4.36	0.906±0.0436	0.211±0.0059***
Cadmium+rutin (H)	52.49±6.54***	1.456±0.0288***	0.243±0.0039***
Rutin	57.34±4.87	1.272±0.0126	0.231±0.0035

Values are Mean±SE of five mice per group, Values are significant at *(compared with Group I) and *(compared with Group II), L: Low dose, H: High dose, SOD: Superoxide dismutase (nmol of epinephrine protected from oxidation mg^{-1} protein), GST: Glutathione-S-transferase (mmol CDNB conjugate formed min^{-1} mg^{-1} protein), CAT: Catalase (mmoles H_2O_2 consumed min^{-1} mg^{-1} protein)

DISCUSSION

Different people have explained the mechanism of cadmium-induced hepatotoxicity which includes lipid peroxidation and interaction with membrane components (Bagchi *et al*., 1996). It induces oxidative stress and lipid peroxidation by depleting GSH or by inhibition of antioxidant enzymes (Bagchi *et al*., 1996). Because of its oxidative stress inducing nature the Cd-induced toxicity can be restored by the treatment of various antioxidants (Eriyamremu *et al*., 2006; Karbownik *et al*., 2001). Corroborating to these findings the present study also confirmed that the administration of rutin (80 mg kg^{-1}) significantly restored the liver enzymatic and non-enzymatic antioxidants against the toxicities induced by cadmium. Cd gets accumulated in the liver and causes tissue damage (Stohs and Bagchi, 1995). Cd indirectly generates various radicals like superoxide, hydroxyl and nitric oxide and induces oxidative stress and tissue damage (Stohs *et al*., 2001). These reactive oxygen species generated indirectly by Cd, attack on the cell membrane and cause destabilization and disintegration of the cell membrane resulting in lipid peroxidation (Shakun and Vysotski, 1982; Kaplan *et al*., 2011). In this study, Cd intoxication induced elevation of hepatic LPO, lipid hydroperoxides contents was similar to other reports (Santos *et al*., 2005). Cd-intoxication is also characterized by the depletion of tissue and circulating non-enzymatic antioxidants including GSH, vitamin E and vitamin C (Hossain and Bhattacharya, 2006). Because of sulfhydryl group in GSH it works as a first line of defense against oxidative stress by acting as a non-enzymatic antioxidant. It can also be involved in the enzymatic detoxification reaction of ROS as a cofactor or as a coenzyme (Sunitha *et al*., 2001). Our GSH result is in consistent with the other reports in which GSH concentration is decreased during Cd administration (Pari and Murugavel, 2005). Pretreatment of rutin in Cd-intoxicated mice reinstated the reduced GSH level. CAT, GST and SOD, represent commonly a helpful array of protection against Reactive Oxygen Species (ROS). In our study the decreased level of SOD, CAT and GST on Cd-intoxication are in consistence with the previous study (Tang *et al*., 1998; Whanger, 1979) and that may either be due to the direct binding of the metal to the enzyme-active site or because of its increased usage in free radical scavenging (Waisberg *et al*., 2003). Co-administration of rutin restored the activities of SOD, CAT and GST in the liver of Cd-intoxicated mice to normal level which might be due to the capability of rutin to decrease the gathering of free radicals generated during lipid peroxidation induced by cadmium.

CONCLUSION

In conclusion findings of the present study indicates that the administration of rutin in cadmium treated animals counteracted the oxidative hepatic dysfunction attributed by cadmium. Co-administration of rutin substantially diminished the abnormal changes because of Cd-

intoxication and restored the hepatotoxicity to near normal. This was contributed by the augment in the activities of antioxidant enzyme cascade, enhancement in the levels of non-enzymatic antioxidants along with the attenuation of TBARS contents in liver. In the light of this study, it can be concluded that rutin played an important role of an antioxidant which may be due to its free radical scavenging and metal-chelating property and there by improved the damaging state of liver cells which tattered its use as a possible soothing agent in cadmium-induced hepatotoxicity.

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REFERENCES

Al-Khedhairy, A.A., S.A. Al-Rokayan and F.A. Al-Misned, 2001. Cadmium toxicity and cell stress response. J. Medical Sci., 1: 39-43.

Alsaif, M.A., 2009. Combined treatment of rutin and vitamin C improves the antioxidant status in streptozotocin-induced diabetic rats. J. Med. Sci., 9: 1-9.

Bagchi, D., M. Bagchi, E.A. Hassoun and S.J. Stohs, 1996. Cadmium induced excretion of urinary lipid metabolites, DNA damage, glutathione depletion and hepatic lipid peroxidation in Sprague-Dawley rats. Biol. Trace Elements Res., 52: 143-154.

Bishnoi, M., K. Chopra and S.K. Kulkarni, 2007. Protective effect of rutin, a polyphenolic flavonoid against haloperidol-induced orofacial dyskinesia and associated behavioural, biochemical and neurochemical changes. Fundam. Clin. Pharmacol., 21: 521-529.

Chen, S., J. Gong, F. Liu and U. Mohammed, 2000. Naturally occurring polyphenolic antioxidants modulate IgE-mediated mast cell activation. Immunology, 100: 471-480.

Choi, J.H., I.K. Rhee, K.Y. Park, J.K. Kim and S.J. Rhee, 2003. Action of green tea catechin on bone metabolic disorder in chronic cadmium poisoned rats. Life Sci., 73: 1479-1489.

Cinar, M., A.A. Yigit, I. Yalcinkaya, E. Oruc, O. Duru and M. Arslan, 2011. Cadmium induced changes on growth performance, some biochemical parameters and tissue in broilers: Effects of vitamin C and vitamin E. Asian J. Anim. Vet. Adv., 6: 923-934.

Claiborne, A., 1985. Catalase Activity. In: CRC Handbook of Methods of Oxygen Radicals Research, Greenwald, R.A. (Ed.). CRC Press, Boca Raton, FL., pp: 283-284.

Dabak, J.D., S.Y. Gazuwa and G.A. Ubom, 2009. Hepatoprotective potential of calcium and magnesium against cadmium and lead induced hepatotoxicity in Wistar rats. Asian J. Biotechnol., 1: 12-19.

Deschner, E.E., J. Ruperto, G. Wong and H.L. Newmark, 1991. Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. Carcinogenesis, 12: 1193-1196.

Di Carlo, G., G. Autore, A.A. Izzo, P. Maiolino and N. Mascolo *et al.*, 1993. Inhibition of intestinal motility and secretion by flavonoids in mice and rats: Structure activity relationships. J. Pharm. Pharmacol., 45: 1054-1059.

Eneman, J.D., R.J. Potts, M. Osier, G.S. Shukla, C.H. Lee, J.F. Chin and B.A. Hart, 2000. Suppressed oxidant-induced apoptosis in cadmium adapted alveolar epithelial cells and its potential involvement in cadmium carcinogenesis. Toxicology, 147: 215-228.

Eriyamremu, G.E., M.A. Adaikpoh and F.O. Obi, 2006. Pretreatment of Rats with α-tocopherol alter liver and kidney protein, alkaline phosphatase activity and phospholipid profile after 24 h intoxication with cadmium. J. Medical Sci., 6: 615-620.

Gao, Z., H. Xu and K. Huang, 2002. Effects of rutin supplementation on antioxidant status and iron, copper and zinc contents in mouse liver and brain. Biol. Trace Elem. Res., 88: 271-279.

Gramza-Michalowska, A. and J. Korczak, 2007. Polyphenols-potential food improvement factor. Am. J. Food Technol., 2: 662-670.

Guruvayoorappan, C. and G. Kuttan, 2007. Antiangiogenic effect of rutin and its regulatory effect on the production of VEGF, IL-1β and TNF-α in tumor associated macrophages. J. Boil. Sci., 7: 1511-1519.

Habig, W.H., M.J. Pabst and W.B. Jakoby, 1974. Glutathione transferase: A first enzymatic step in mercapturic acid formation. J. Biol. Chem., 249: 7130-7139.

Hashem, A.R. and K.F. Abed, 2007. Aluminum, cadmium and microorganisms in female hair and nails from Riyadh, Saudi Arabia. J. Med. Sci., 7: 263-266.

Hossain, S.K.U. and S. Bhattacharya, 2006. Prevention of cadmium induced lipid peroxidation, depletion of some antioxidative enzymes and glutathione by a series of novel organoselenocyanates. Environ. Toxicol. Pharmacol., 22: 298-308.

Jollow, D.J., S.S. Thogeirsson, W.Z. Potter, M. Hashimoto and J.R. Mitchell, 1974. Acetaminophen-induced hepatic necrosis. VI. Metabolic disposition of toxic and nontoxic doses of acetaminophen. Pharmacology, 12: 251-271.

Kamalakkannan, N. and P.S.M. Prince, 2006. Rutin improves the antioxidant status in streptozotocin-induced diabetic rat tissues. Mol. Cell Biochem., 293: 211-219.

Kaplan, O., N.C. Yildirim, N. Yildirim and M. Cimen, 2011. Toxic elements in animal products and environmental health. Asian J. Anim. Vet. Adv., 6: 228-232.

Karbownik, M., E. Gitto, A. Lewinsky and R.J. Reiter, 2001. Induction of lipid peroxidation in hamster organs by the carcinogen cadmium: Amelioration by melatonin. Cell Biol. Toxicol., 17: 33-40.

Nagasawa, T., N. Tabata, Y. Ito, N. Nishizawa, Y. Aiba and D.D. Kitts, 2003. Inhibition of glycation reaction in tissue protein incubations by water soluble rutin derivative. Mol. Cell. Biochem., 249: 3-10.

Natzir, R., 2004. Discovery of the α-1 microglobulin complex in urine sample patients with cadmium intoxication. J. Med. Sci., 4: 198-202.

Pari, L. and P. Murugavel, 2005. Role of diallyl tetrasulfide in ameliorating the cadmium induced biochemical changes in rats. Environ. Toxicol. Pharmacol., 20: 493-500.

Pozin, V.M., S.G. Skuratovskaia and G.A. Pocheptsova, 1996. Changes in the vascular wall and ischemic damages to the myocardium in reversible episodes of heart muscle ischemia. Fiziologicheskii Zhurnal, 42: 10-16.

Santos, F.W., G. Zeni, J.B.T. Rocha, S.N. Weis, J.M. Fachinetto, A.M. Favero and C.W. Nogueira, 2005. Diphenyl diselenide reverses cadmium-induced oxidative damage on mice tissues. Chem. Biol. Interact., 151: 159-165.

Shakun, N.P. and I.I.U. Vysotski, 1982. Effect of tetracycline antibiotics on lipid peroxidation. Antibiotiki, 27: 684-687.

Stevens, D.G., A.V. Nebeker and R.J. Baker, 1980. Avoidance responses of salmon and trout to air-supersaturated water. Trans. Am. Fish. Soc., 109: 751-754.

Stohs, S.J. and D. Bagchi, 1995. Oxidative mechanisms in the toxicity of metal ions. Free Radic. Biol. Med., 18: 321-336.

Stohs, S.J., D. Bagchi, E. Hassoun and M. Bagchi, 2001. Oxidative mechanisms in the toxicity of chromium and cadmium ions. J. Environ. Pathol. Toxicol. Oncol., 20: 77-88.

Sunitha, S., M. Nagaraj and P. Varalakshmi, 2001. Hepatoprotective effect of lupeol and lupeol linoleate on tissue antioxidant defence system in cadmium-induced hepatotoxicity in rats. Fitoterapia, 72: 516-523.

Tang, W., S. Sadovic and Z.A. Shaikh, 1998. Nephrotoxicity of cadmium-metallothionein: Protection by zinc and role of glutathione. Toxicol. Applied Pharmacol., 151: 276-282.

Vincente-Sanchez, C., J. Egido, P.D. Sanchez-Gonzalez, F. Perez-Barriocanal, J.M. Lopez-Novoa and A.I. Morales, 2008. Effect of the flavonoid quercetin on cadmium induced hepatotoxicity. Food Chem. Toxicol., 46: 2279-2287.

Waisberg, M., P. Joseph, B. Hale and D. Beyersmann, 2003. Molecular and cellular mechanisms of cadmium carcinogenesis. Toxicology, 192: 95-117.

Whanger, P.D., 1979. Cadmium effects in rats on tissue iron, selenium and blood pressure: Blood and hair cadmium in some oregon residents. Environ Health Perspect., 28: 115-121.

Wright, J.R., H.D. Colby and P.R. Miles, 1981. Cytosolic factors which affect microsomal lipid peroxidation in lung and liver. Arch. Biochem. Biophys., 206: 296-304.

Yiin, S.J., C.L. Chern, J.Y. Sheu, W.C. Tseng and T.H. Lin, 1999. Cadmium induced renal lipid peroxidation in rats and protection by selenium. J. Toxicol. Environ. Health A, 57: 403-413.