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Protective effect of curcumin on oxidative stress and DNA fragmentation against lambda cyhalothrin-induced liver damage in rats

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ABSTRACT

LCT is a synthetic pyrethroid, developed as an insecticide for agricultural and public health applications. The purpose of this study was to investigate the adverse effects of LCT on rat liver and to elucidate hepatoprotective ability of CMN against LCT. Liver injury in male rats was induced by oral administration of LCT at a dose of 0.6 mg/kg/day for 4 weeks. CMN (200 mg/kg/day by oral administration) was used as a protective agent for the same period as LCT. Serum and liver samples were collected from all groups at the end of the experimental period. LCT-intoxication elicited significant elevations in hepatic markers enzymes (ALT and AST) and MDA concomitant with significant declines in the antioxidant enzymes (GPx, GST and GR), GSH and TP levels. In addition, it was noted that LCT-intoxicated group exhibited a degree of liver DNA fragmentation. Oral intake of CMN to LCT-intoxicated rats exhibited significant decrease in liver enzymes activities and lipid peroxidation, significant increase in antioxidant enzymes activities and partial inhibition in DNA fragmentation. Therefore, it was concluded that CMN has the ability to scavenge free radicals, protect against oxidative stress and prevent DNA fragmentation induced by LCT intoxication.

INTRODUCTION

Pesticides are used for welfare of human beings but their adverse impacts on non-target organisms are significant. Pesticides are one of the most potentially harmful chemicals introduced into the environment and indiscriminate use of it is on increase. In the last years, the use of pyrethroids has been increasing since restrictions have been placed on many of the organophosphorus insecticides (Soderlund et al., 2002). Pyrethroids chemically are the structural derivatives of naturally occurring pyrethrins and have greater potency. Synthetic pyrethroids account for more than 30% of insecticides used worldwide in agricultural, domestic and veterinary applications (Prasanth and Rajini, 2005). It has become an economically and environment friendly group of insecticides as these possess low mammalian toxicity, rapid decomposition in soil, leave no residue in biosphere and are stable in sunlight (Kale et al., 1999).

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However, these insecticides have proved to be detrimental to human beings, fish and domestic animals by altering various metabolic activities (Adhikari et al., 2006). Lambda-cyhalothrin (LCT), a synthetic type II pyrethroid insecticide has extensive uses as an agro-pesticide (Fetoui et al., 2009). LCT is widely used in Egypt and valued for its broad-spectrum control on a wide range of pests in a variety of applications such as the protection of cotton, cereals and vegetables as well as in public health application against insect, ticks and flies which may act as disease vectors (Abdel Aziz and Abdel Rahem, 2010). Residues of LCT have been reported in vegetables and fruits (Turgut et al., 2011), milk and blood of dairy cows (Bissacot and Vassilieff, 1997) and also in cattle meat (Muhammad et al., 2010). Placental transfer of LCT has been observed in goats (Oliveira et al., 2000). Consistent with its lipophilic nature (Michelangeli et al., 1990) LCT has been found to accumulate in biological membranes leading to oxidative damage. It was reported that LCT caused oxidative stress by altering antioxidant systems and increasing lipid peroxidation in mammals (El-Demerdash, 2007; Fetoui et al., 2008, 2009).

Other possible mechanisms of cytotoxicity of LCT could be nitric oxide production or DNA single strand breaks (Righi and Palermo-Neto, 2005). Although the organism has several biological defence mechanisms against intracellular oxidative stress such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione-S-transferase (GST), non-enzymatic antioxidants such as caratenoids, vitamin E, vitamin C and glutathione, can also act to overcome the oxidative stress (Evans and Halliwell, 2001). A positive correlation has been established between dietary supplementation with certain vegetables and plant products and the reduction of toxic effects of various toxicants and environmental contaminants (Nandi et al., 1997). During the last decades, phenolic compounds have received considerable attention due to their antioxidant properties (Gil-Izquierdo et al., 2001). Curcumin (CMN), a phenolic phytochemical responsible for the yellow colour of turmeric (*Curcuma longa*), has been designated to be a forceful anti-inflammatory, anti-cancer and antioxidant agent, and is under preclinical trial for cancer prevention (Strimpakos and Sharma, 2008). It also has potential therapeutic effects against neurodegenerative, cardiovascular, pulmonary, metabolic and autoimmune diseases (Aggarwal and Harikumar, 2009). In addition, CMN exerted hepatoprotective effects in various animal models of liver injury such as carbon tetrachloride (Fu et al., 2008), endotoxin (Kaur et al., 2006) and thioacetamide (Shapiro et al., 2006). There is evidence that CMN enhances liver detoxification by increasing the activity of glutathione-S-transferase, an enzyme which conjugates glutathione with a wide variety of toxins to facilitate their removal from body (Piper et al., 1998). Recently, CMN has been reported to ameliorate lindane-induced oxidative damage in rat liver (Singh and Sharma, 2011) and ameliorate cypermethrin-induced oxidative stress in liver, kidney and brain of Wistar rats (Sankar et al., 2012). Therefore, the aim of the concurrent study was to assess the effects of LCT on liver enzymes [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], lipid peroxidation (LPO), antioxidant enzymes (GPx, GST and GR), GSH content and DNA fragmentation in male rats. Also, this study aimed to determine the potency of CMN to modulate hepatic damage induced by LCT.

MATERIALS AND METHODS

Chemicals

LCT ($C_{23}H_{19}ClF_3NO_3$) and CMN were obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All other chemicals used were of the finest analytical grade.

Animals

Twenty four adult male albino rats (*Rattus norvegicus*), weighing 120-150 g were used in this study. The animals were obtained from the National Research Centre, Dokki, Egypt. Rats were housed in wire-floored cages under standard laboratory conditions of 12 h/12 h light/dark, 25±2^{o}C with free access to food and water. All animals were acclimatized to laboratory condition for a week before commencement of experiment.

Experimental design

The animals were randomly divided into four groups of six rats each. The LCT and CMN were orally administered daily for 4 weeks.

Group (I): Normal untreated rats served as control.

Group (II): Rats were administered CMN at 200 mg/kg/day (Fu et al., 2008). CMN was suspended in sterile PBS.

Group (III): Rats were received LCT in a dose of 0.6 mg/kg/day (Sharma et al., 2010).

Group (IV): Animals were received LCT (0.6 mg/kg/day) and CMN (200 mg/kg/day).

At the end of the experiment, all animals were killed under light ether anesthesia. Animals were rapidly dissected and blood was collected by cardiac puncture and serum was obtained by blood centrifugation at 1500 × g for 10 min, at 4°C. Livers were quickly excised, washed in ice-cold saline, weighed and homogenized in ice-cold physiological saline. Liver homogenate was divided into portions and stored at –70°C until analyzed.

Preparation of tissue homogenate

The liver was homogenated (10% w/v) in Tris-HCl (0.1 M, pH 7.4). Homogenates were centrifuged at 1000×g for 10 min at 4°C.

Assessment of Liver Function

Liver functions were assayed by measuring serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzyme activities according to Reitman and Frankel (1957).

Determination of lipid peroxidation

Lipid peroxidation (LPO) levels were measured in tissue homogenates as thiobarbituric acid reactive substance (TBARS). TBARS was estimated as malondialdehyde (MDA) by using the method of Ohkawa et al. (1979).

Determination of antioxidant enzymes

GST activity was estimated by determining the rate of formation of glutathione (GSH) and 1-chloro-2, 4, dinitrobenzene (CDNB) conjugates. The conjugate was measured colorimetrically at 340 nm (Habig, et al., 1974).

GR activities were assessed by measuring the reduction of oxidized glutathione to reduced glutathione by NADPH at 340 nm (Horn, 1971).

GPx catalyses the oxidation of glutathione by cumene hydroperoxide in the presence of glutathione reductase and NADPH, the oxidized glutathione is immediately converted to the reduced form with a concomitant oxidation of NADPH to NADP+ (Matkovics et al., 1998). The decrease in absorbance of NADPH was measured at 340 nm.

Determination of glutathione and total protein

GSH content was assayed by the method of Ellman (1959). The method utilized metaphosphoric acid for protein precipitation and 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) for color development and its density was measured at 412 nm. The concentration of proteins was determined by the procedure of Lowry et al. (1957) using bovine serum albumin as standard.

DNA fragmentation analysis

Genomic DNA was isolated from liver homogenate with the Qiamp DNA mini kit according to the manufacturer's instructions and electrophoresed on a 2% agarose gel stained with ethidium bromide (Sambrook et al., 1989).

The gel was then photographed under ultraviolet luminescence. In these conditions, damaged DNA appears as a ladder consisting of DNA fragments, whereas intact DNA is high molecular weight and does not migrate very far into the gel.

Statistical analysis

Data are presented as means ± SE and were analyzed by ANOVA using the SPSS version 13 statistical program. Hypothesis testing methods included one-way analysis of variance (ANOVA) followed by least significant difference (LSD).

RESULTS

Four weeks CMN treatments did not induce relevant alterations in the rats in such a way that no differences were observed between this group and the control one.

Effect of CMN on LCT-induced alteration in ALT and AST

ALT and AST levels from rats exposed to LCT and/or CMN are presented in Table 1. There were differences in the enzymes activities among the different treatment groups.

Table 1: Influence of oral administration of CMN on serum hepatic enzymes (ALT and AST) of LCT-treated rats.

Groups	ALT (IU/L) M ± SE	AST (IU/L) M ± SE
Control	28.73 ± 0.71	49.32 ± 0.99
CMN	28.01 ± 0.92 ^{b***}	48.37 ± 1.42 ^{b***}
LCT	68.82 ± 2.41 ^{a***}	87.50 ± 1.04 ^{a***}
LCT + CMN	33.20 ± 1.28 $^{a*/b***}$	51.20 ± 0.92 ^{b***}

All data are expressed as means (M) of six rats ± standard error (SE). ^{a*} Significant as compared to control group at P< 0.05, ^{a**} highly significant as compared to control group at P< 0.01, ^{a***} very highly significant as compared to control group at P< 0.001. ^{b*} Significant as compared to LCT group at P< 0.05, ^{b**} highly significant as compared to LCT group at P< 0.01, ^{b***} very highly significant as compared to LCT group at P< 0.001.

Oral administration of LCT significantly elevated serum concentrations of ALT and AST compared to control rats. CMN combination treatment to LCT-treated rats significantly reduced the activities of AST and ALT enzymes compared with those of LCT-treated rats.

Effect of CMN on LPO and antioxidant enzymes in LCT-treated rats

LPO level in liver was significantly increased in LCT-treated animals when compared to normal. Treatment with CMN at 200 mg/kg showed significant decrease in LPO level when compared to LCT-treated group (Table 2). The activities of antioxidant enzymes (GPx, GST and GR) were significantly reduced than the control group. All these mentioned changes were significantly increased as compared to LCT-treated rats upon administration of CMN (Table 2).

Effect of CMN on LCT-induced hepatic GSH and TP

Administration of LCT to rats for 4 weeks led to a significant decrease in liver GSH and TP levels as compared to normal control rats. Treatment with CMN attenuated the LCT-induced decrease in GSH and TP.

Effect of CMN on liver genomic DNA in LCT-treated rats

Results presented in figure 1 showed marked DNA laddering induced by LCT compared with control. CMN administration to LCT-treated animals showed a marked decrease in DNA laddering.

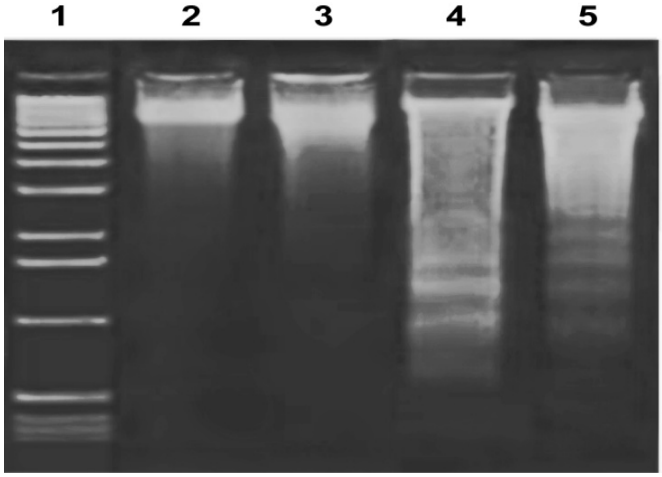

Fig. 1: DNA fragmentation was assessed in rat liver of all experimental groups. Lane 1: DNA molecular weight marker; lane 2: control group; lane 3: CMN-treated rats; lane 4: LCT-treated rats; lane 5: rats treated with LCT plus CMN.

Table 2: Influence of oral administration of CMN on LPO, GPx, GST and GR of LCT-treated rats.

Groups	LPO (nmol/mg) M ± SE	GPx (U/mg) M ± SE	GST (nmol/min/mg) M ± SE	GR (nmol/min/mg) M ± SE
Control	1.59 ± 0.03	2.38 ± 0.08	407.50 ± 1.34	127.83 ± 2.94
CMN	1.51 ± 0.05 ^{b***}	2.48 ± 0.07 ^{b***}	412.83 ± 1.74 ^{b***}	133.83 ± 1.43 ^{b***}
LCT	4.48 ± 0.13 ^{a***}	1.76 ± 0.09 ^{a***}	323.17 ± 2.71 ^{a***}	99.93 ± 1.21 ^{a***}
LCT+CMN	1.88 ± 0.04 $^{a*/b***}$	2.04 ± 0.03 $^{a**/b**}$	401.33 ± 0.99 $^{a**/b***}$	113.71 ± 2.21 $^{a***/b***}$

All data are expressed as means (M) of six rats ± standard error (SE). ^{a*} Significant as compared to control group at P< 0.05, ^{a**} highly significant as compared to control group at P< 0.01, ^{a***} very highly significant as compared to control group at P< 0.001. ^{b*} Significant as compared to LCT group at P< 0.05, ^{b**} highly significant as compared to LCT group at P< 0.01, ^{b***} very highly significant as compared to LCT group at P< 0.001.

Table. 3: Influence of oral administration of CMN on GSH and TP of LCT-treated rats.

Groups	GSH (nmol/mg) M ± SE	TP (g/100g) M ± SE
Control	35.10 ± 0.62	6.20 ± 0.09
CMN	36.95 ± 1.26 ^{b***}	6.24 ± 0.27 ^{b***}
LCT	19.89 ± 0.92 ^{a***}	4.82 ± 0.19 ^{a***}
LCT + CMN	30.27 ± 1.05 $^{a**/b***}$	5.66 ± 0.21 ^{b**}

All data are expressed as means (M) of six rats ± standard error (SE). ^{a*} Significant as compared to control group at P< 0.05, ^{a**} highly significant as compared to control group at P< 0.01, ^{a***} very highly significant as compared to control group at P< 0.001. ^{b*} Significant as compared to LCT group at P< 0.05, ^{b**} highly significant as compared to LCT group at P< 0.01, ^{b***} very highly significant as compared to LCT group at P< 0.001.

DISCUSSION

The present study was conducted in order to investigate the role of CMN in alleviating oxidative stress in rat livers produced by LCT treatment that produces liver injury and DNA fragmentation. Liver is the site of biotransformation by which a toxic compound has been transformed to a less harmful form to reduce toxicity (Hodgson, 2004). However, this will damage the liver cells and produce hepatotoxicity. The most prominent result of liver damage is the release of intracellular enzymes such as ALT and AST into the blood stream, therefore serum ALT and AST levels can serve as indicators of liver status (Ogunlade et al., 2012).

Concurrently, the increase in ALT and AST levels indicated that LCT could induce hepatic dysfunction. These findings were in accordance with Yousef et al. (2006) and Fetoui et al. (2009) who declared that pyrethroids exposure can produce hepatic injury, causing increased serum ALT and AST activities. CMN supplemented to normal rats showed unchanged transaminase activity (Kaur et al., 2006). Moreover, CMN showed a protective effect against LCT-induced hepatic dysfunction through decreasing the levels of ALT and AST towards their respective normal value that is an indication of stabilization of plasma membrane as well as repair of hepatic tissue damage caused by LCT. These results were in agreement with Sankar et al. (2012), who reported that liver enzymes were significantly improved after CMN administration to cypermethrin-intoxicated rats.

Pesticides induce oxidative stress which leading to the generation of free radicals, changes in antioxidants levels and lipid peroxidation (Ender and Onder, 2006). Although LCT itself does not generate free radicals directly, it indirectly generates various radicals such as superoxide radical (O_2^-), and hydroxyl radical ($OH^{\cdot}$) thus causing damage to proteins, lipids and DNA by oxidation (Kale et al., 1999). The level of TBARS presently was significantly elevated in liver tissue of LCT-intoxicated rats. In accordance with the data obtained from this study, El-Demerdash, 2007 and Fetoui et al., 2009, reported that LCT administration resulted in a significant increase in TBARS production. Lipid peroxidation arises from the reaction of free radicals with lipids and this is considered to be an important feature of the cellular injury brought by free radical attack (Hoek and Pastorino, 2002).

Administration of CMN significantly reduced the levels of LPO. This observation demonstrates the anti-peroxidative effect of CMN on LCT toxicity. The presence of π-conjugation in CMN makes it more hydrophobic, which promotes its localization in the lipid bilayer membrane and lipid solubility. This allows the reaction of CMN with the lipid peroxyl radicals and it acts as a chain terminating antioxidant (Sankar et al., 2010).

In the present study, the activities of antioxidant enzymes (GPx, GST and GR) and GSH were decreased significantly in LCT-treated rats. In consistent with these results, the decreased activities of antioxidant enzymes were observed in rat liver (Fetoui et al., 2009), in rat kidney (Fetoui et al., 2010) and in fish liver (*Oreochromis niloticus*) (Piner and Üner, 2012). They indicated the failure of antioxidant defense system to overcome the influx of ROS induced by LCT exposure. LCT toxicity might be due to the release of cyanohydrins, which are unstable under physiological conditions and further decompose to cyanides and aldehydes which in turn could act as a source of free radicals (World Health Organization, 1990). Depletion of tissue GSH is one of the major factors that permit lipid peroxidation and subsequent tissue damage (Huang et al., 2003). GSH is known to function as a substrate for GPx and GST (Darbar et al., 2010). The activities of GPx and GST in this study were reduced as a result of LCT treatment, which may be attributed to the unavailability of GSH. CMN worked as an antioxidant and its administration to LCT-treated rats increased the levels of non-enzymatic antioxidant GSH, enzymatic antioxidants GPx, GST and GR and protein levels in animals exposed to LCT. CMN reduces the oxidative stress in animals, by its high ROS scavenging capacity and by protecting the antioxidant enzymes from being denatured. Protective role of CMN has been reported by other investigators using paracetamol (Piper et al., 1998; Yousef et al., 2010) and aflatoxin (Verma and Mathuria, 2008) induced liver damage models.

DNA fragmentation observed in the present study is the normal consequence of oxidative stress that was demonstrated through elevation in LPO, reduction in antioxidant enzymes (GPx, GST and GR) and glutathione content in rat liver. This is also consistent with previous studies where DNA fragmentation was induced by LCT in rat lymphocytes (Sharma et al., 2010) and by cypermethrin in rat brain (Hussien et al., 2011). CMN supplementation to LCT-treated group produced low DNA fragmentation when compared to the LCT-treated group. This effect can emerge the benefit of CMN supplementation to minimize the risk of DNA fragmentation caused by LCT toxicity. These results coincide with that of Siddique et al. (2010) who stated that CMN inhibits the generation of ROS that are responsible for the DNA damage. Also, this action of CMN was explained by Piwocka et al. (2001) who stated that CMN leads to attenuated DNA fragmentation due to the elevation of GSH. In conclusion, the present study authenticates the importance of CMN in protecting animals against LCT-induced hepatotoxicity through attenuating lipid peroxidation, increasing the activities of antioxidant enzymes and alleviating DNA fragmentation.

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