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Research Article

CURCUMIN PROTECTION AGAINST CADMIUM-INDUCED OXIDATIVE STRESS IN PANCREAS OF SWISS ALBINO MICE

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ABSTRACT

Objective: This study was planned to explore the protective efficacy of *Curcuma longa* (curcumin) against cadmium chloride ($CdCl_2$)-induced oxidative stress in pancreatic tissue of albino mice.

Methods: A total of 40 albino mice were equally divided into eight groups (five mice for each). The mice were kept on standard feed and water *ad libitum*. Control Groups 1 and 5 mice were given equal amount of distilled water, Groups 2 and 6 mice received 1 mg/kg body weight of $CdCl_2$ on alternate days, and Group 3 and 7 received 1 mg/kg body weight of $CdCl_2$ on alternate days and 100 mg/kg body weight of curcumin every day. Groups 4 and 8 received 100 mg/kg body weight of curcumin daily and were kept as positive control. Autopsies were done on 15 and 45 days post-treatment. The pancreas was collected from each mouse and homogenized for biochemical study.

Results: The results of the present study revealed that Cd-induced oxidative stress depleted the antioxidant scavenger system and curcumin showed free radical scavenging potential. The activities of antioxidant enzymes, i.e., superoxide dismutase, catalase, glutathione peroxidase were observed to be significantly decreased, and methylenedioxyamphetamine concentration was increased in $CdCl_2$-treated group which was restored to normal level after curcumin treatment.

Conclusion: It can be concluded that curcumin acts as a powerful and beneficial antioxidant against oxidative stress by scavenging the free radicals produced by $CdCl_2$.

Keywords: Cadmium chloride, Curcumin, Oxidative stress, Glutathione peroxidase, Pancreas.

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INTRODUCTION

Heavy metals represent an environmental pollutant with toxicity to biota. Since the late 19th century, heavy metals have accumulated in the environment by the mining and industrial waste. Cadmium (Cd) is one of the most toxic heavy metals ingested by animals and humans. The biological half-life of Cd is very long in animals [1]. Cd is largely used in Ni-Cd batteries, plastics manufacturing, and electroplating of steel. Cd is an extremely toxic heavy metal that can lead to acute and chronic Cd poisoning by accumulation in mammals, birds, and fishes through the food chain [2,3]. Cd has been reported to increase the impairment of pancreatic functions by causing structural deformation in the pancreatic α- and β-cells [4]. Cd also damages the liver, kidney, bones, nerves, and other organs [5,6]. Cd affects both endocrine and exocrine part of the pancreas, and its accumulation is reported even in those populations which are not directly exposed to Cd [7,8].

The various toxic effects induced by Cd in biological systems have been linked to increased lipid peroxidation and reduced antioxidant reserves of the body. Cd toxicity leads to enhanced lipid peroxidation and alterations in the antioxidant defense system which includes enzymes such as glutathione peroxidase (GPx), glutathione-S-transferase (GST), superoxide dismutase (SOD), catalase (CAT), and non-enzymatic molecule like glutathione, which normally protect against free radical toxicity [9]. Chopra *et al.* [10] also reported that Cd significantly enhanced lipid peroxidation and declined the levels of antioxidant, namely reduced glutathione, GST, SOD, and CAT activity.

The pancreas is more susceptible organ to oxidative stress than other tissues and organs because pancreatic islet cells show extremely weak manifestation of antioxidative enzymes [11]. Cd directly affects carbohydrate metabolism by injuring the islet of Langerhans and reducing the insulin secretion [12]. Cd in pancreas of rats is generally bound to metallothionein (MT). However, MT in pancreas is extremely susceptible to oxidative reactions as compared to MT in the liver, spleen, and kidneys [13]. Cd toxicity involves the reduction of glutathione and sulfhydryl groups, resulting in the enhanced production of various reactive oxygen species (ROS) such as superoxide ion, hydrogen peroxide, and hydroxyl radicals [14]. The levels of ROS are regulated by a variety of cellular defense mechanisms consisting of enzymic and non-enzymic antioxidants [15]. The primary scavenger enzymes involved in detoxification of ROS in mammalian systems are CAT, SOD, GPx, and GST [16]. Long exposure to Cd leads to necrosis, degeneration, and degranulation of β-cells, causing an increase in the serum glucose level and decrease in plasma insulin concentration causing alteration in blood and urine glucose level [17].

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a yellow phenolic compound present in turmeric (*Curcuma longa*) a commonly used spice in Indian food. Curcumin has a significant antioxidant activity in both *in vitro* and *in vivo* studies [18-21]. Curcumin is also reported to have anticarcinogenic [22-24], anticataractogenic [25-27], anti-inflammatory [28], antidiabetic/hypoglycemic [29], and antiglycating [30,31] activities. Curcumin also has a positive effect on blood glucose in diabetics and increases gastric mucosal secretion in rabbits [32]. Curcumin is a potent antioxidant agent and free radical scavenger [33]. It is also an inhibitor of lipid peroxidation [32] and also reduces the overexpression of nitric oxide synthase [34,35]. Similarly, Kalpana and Polasa [36,37] also reported that curcumin scavenges oxygen free radicals, inhibits lipid peroxidation, and protects cellular macromolecules including deoxyribonucleic acid from oxidative damage.

METHODS

Animals

4-weak-old male Swiss albino mice weighing 20 ± 2 g were used and purchased from the Central Research Institute, Kasauli (H.P). The animals were housed under standardized environmental conditions during experimental period. The pellet diet (obtained from Hindustan Liver Limited, Mumbai, India) and tap water were given *ad libitum.* All experiments were conducted in the Department of Zoology and Environmental Sciences, Punjabi University, Patiala, with the approval of the Institutional Animal Ethical Committee.

Chemicals

Cd chloride ($CdCl_2$) and curcumin powder were obtained from Hi-Media Laboratories Pvt., Ltd., Mumbai. Cd and curcumin were dissolved in distilled water and administered to mice orally. An aqueous suspension of curcumin was made according to Kamel *et al.* [38].

Experimental design

Mice were divided into following eight groups and five mice were kept in each group. Groups 1 and 5 were kept as control and tap water was given *ad libitum.* Groups 2 and 6 mice were administered $CdCl_2$ orally at a dose of 1 mg/kg body weight on alternate days for 15 and 45 days. Groups 3 and 7 were given 1 mg/kg body weight of $CdCl_2$ orally on alternate days and 100 mg/kg body weight of curcumin daily for 15 and 45 days, respectively. Groups 4 and 8 mice were administered orally 100 mg/kg body weight of curcumin daily for 15 and 45 days, respectively, and were kept as positive control. Autopsies were done on 15 and 45 days post-treatment.

Biochemical analysis

The pancreatic tissue was collected after autopsies from each group and washed with ice-cold saline to remove the blood. Tissue was minced and homogenized in 3 ml of phosphate buffer (pH - 7.2) and centrifuged (×3000 g for 10 min). The clear supernatant was used for various biochemical analyses.

Measurement of oxidative stress markers

Lipid peroxidation was measured by estimating the malondialdehyde-thiobarbituric acid reactive substances in pancreatic homogenate using the method [39].

Estimation of antioxidant enzymes

SOD was determined by the method [40]. CAT activity was assayed by the method [41]. GPx in pancreatic homogenate was quantified by the method of Ahrens [42].

Statistical analysis

The data were statistically analyzed by two-way analysis of variance followed by Student's t-test. The difference among means was analyzed by Tukey's t-test. The data reported in this study are considered statistically significant at *p<0.05 levels.

RESULTS

Fig. 1 showed statistically significant (*p<0.05) increase in methylenedioxyamphetamine (MDA) level in Groups 2 and 6 ($CdCl_2$) in comparison to control groups (1 and 5) at both the intervals, i.e. 15 and 45 days. Group 3 (Cd + Cur) showed statistically non-significant (p>0.05) increase in MDA content and Group 7 (Cd + Cur) showed statistically significant (*p<0.05) rise in MDA concentration as compared to control mice. The MDA content in antioxidant-treated Groups 4 and 8 (+ve Cur) showed statistically non-significant (p>0.05) elevation in MDA content as comparison to control. The SOD activity showed a statistically significant (*p<0.05) decline in Cd-treated mice (Groups 2 and 6) as compared to control Groups 1 and 5 (Fig. 2). Group 3 (Cd + Cur) showed statistically non-significant (p>0.05) decrease in SOD value and Group 7 (Cd + Cur) showed very statistically significant (*p<0.05) reduction in SOD activity with respect to control group. The SOD activity in antioxidant supplemented Groups 4 and 8 (+ve Cur) showed statistically non-significant (p>0.05) elevation in comparison to control value. Fig. 3 showed a statistically significant (*p<0.05) decrease in CAT activity in Cd-treated groups (2 and 6) in comparison to control Groups 1 and 5. Group 3 (Cd + Cur) showed statistically non-significant (p>0.05) decrease in CAT activity and Group 7 (Cd + Cur) showed very statistically significant (*p<0.05) reduction in CAT activity with respect to control group. Groups 4 and 8 (+ve Cur) showed non-significant increase in CAT activity. Fig. 4 depicts that the Cd administration in Group 2 and 6 showed statistically non-significant (p>0.05) decrease and statistically significant decrease in the GPx activity, respectively, as compared to control at 15 and 45 days. A non-significant (p>0.05) decrease was observed in Groups 3 and 7 with respect to control value. Groups 4 and 8 (+ve Cur) showed non-significant increase in GPx activity as compared to control mice.

DISCUSSION

Pancreatic cells are observed to be susceptible to oxidative damage because of the two reasons: One is their lower antioxidant defense machinery and other is the overproduction of ROS within the cell due to the exposure of the general population to the toxic substances in the daily life [43]. Cd is a toxic metal but is unable to generate ROS directly. However, Cd-induced oxidative stress is a common phenomenon observed in several studies [14]. It is already proved that oxidative stress plays an important role in Cd poisoning [44]. Cd exposure could trigger significant increase in blood glucose concentration and lipid peroxidation and significant decrease in body weight, blood insulin level, GSH, and activity of antioxidant enzymes in pancreatic tissue [45].

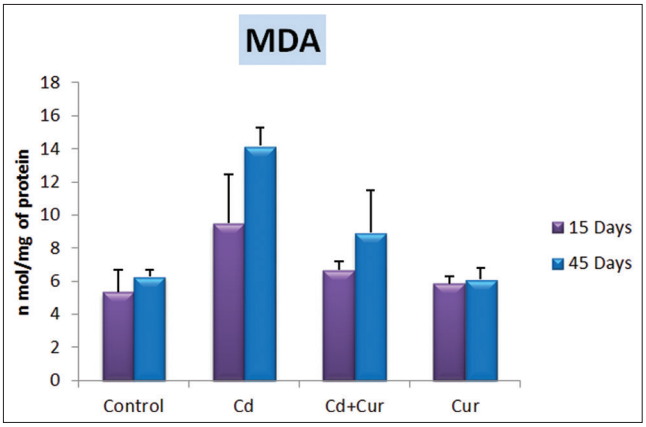

Fig. 1: Effect of curcumin on cadmium-induced changes in methylenedioxyamphetamine concentration in pancreatic tissue in the control and experimental mice. Values are given as mean±standard deviation from five mice in each group

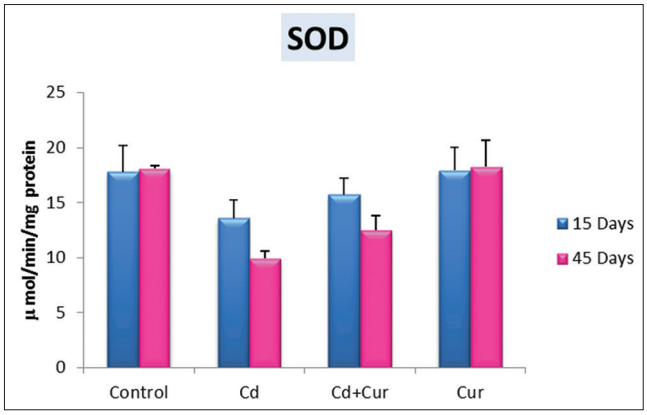

Fig. 2: Effect of curcumin on cadmium-induced changes in superoxide dismutase level in pancreatic tissue in the control and experimental mice. Values are given as mean±standard deviation from five mice in each group

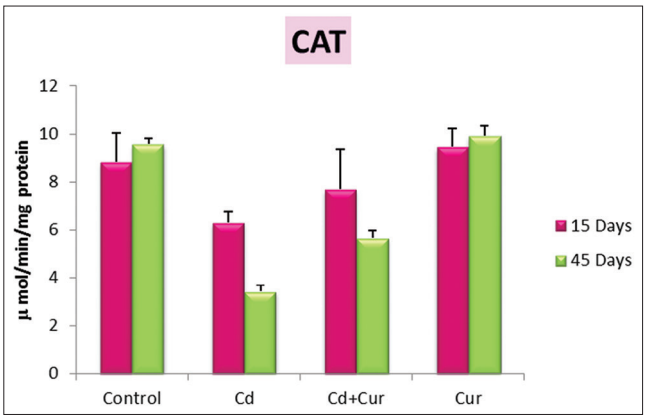

Fig. 3: Effect of curcumin on cadmium-induced changes in catalase level in pancreatic tissue in the control and experimental mice. Values are given as mean ± standard deviation from five mice in each group

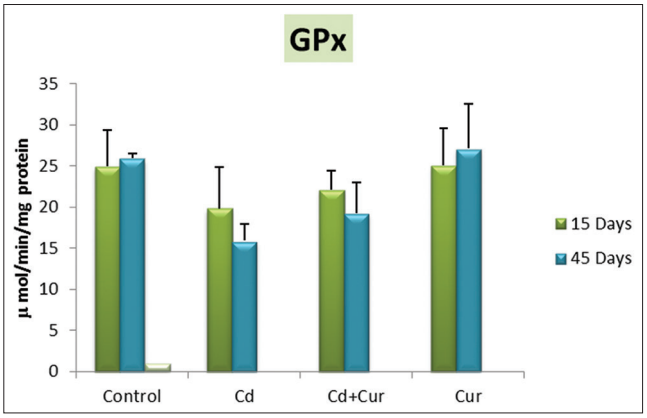

Fig. 4: Effect of curcumin on cadmium-induced changes in glutathione peroxidase level in pancreatic tissue in the control and experimental mice. Values are given as mean±standard deviation from five mice in each group

Liu [46] found that Cd concentration and MDA content were elevated and antioxidant activity markers (CAT, SOD, GSH-Px, and T-AOC) were decreased in pancreas of chickens exposed to Cd. Similarly, Cd treatment elevated the MDA concentration and decreased levels of GSH, SOD, and CAT in male Wistar albino rats [47].

The results of the present study showed significant decrease in the level of antioxidant enzymes in pancreas of Cd intoxicated mice which may be due to direct binding of Cd to the active sites of the enzymes and increased MDA level because of the accumulation of lipid peroxidation substances produced by Cd intoxication [48,49]. On the other side, curcumin supplementation resulted in decrease in lipid peroxidation and showed significant elevation in SOD, CAT, and GPx in pancreatic tissue, indicating the protective effect of curcumin against Cd toxicity. This work is in agreement with the results of Lyons, and Suryanarayana *et al.* [50,51] as they reported a significant elevation in concentration of thiobarbituric acid reactive substances (TBARS) in various tissues of Wistar rats such as liver, kidney, heart, pancreas, and RBCs indicating elevated oxidative stress, but they found significant decline in TBARS in the liver, kidney, heart, pancreas, and RBCs of curcumin/turmeric-treated groups as compared to untreated diabetic group, showing inhibition of hyperglycemia-induced oxidative stress. Similarly, Aziz reported significant decreased levels of MDA in pancreas, liver, and aorta treated with the novel water-soluble curcumin [52]. Sharma [21] also reported the significant decreased level of MDA in pancreas of Swiss albino mice when exposed to Cd.

Oxidative stress is an important mechanism of Cd toxicity and might alter antioxidant defense system and stimulates the formation of ROS such as hydroxyl radicals and singlet oxygen. Cd accumulation in pancreas is possibly caused due to its role in detoxification. MT present in pancreas contains a significant amount of cysteine amino acid. Cysteine contains sulfhydryl group that has high affinity toward Cd, thus it could tolerate high Cd concentration [49]. Lipid peroxidation is considered to be a cellular deteriorating process induced by oxidative stress that occurs readily in the tissues rich in highly oxidizable polyunsaturated fatty acids which impairs cell membrane fluidity resulting in alteration in the malfunctioning of membrane-bound enzymes and receptors [53]. Similarly, Sarkar [54] reported that Cd poisoning affects polyunsaturated fatty acids of biofilms, causing lipid peroxidation and membrane damage. Lipid peroxidation is commonly considered as a biomarker of cell oxidative damage. MDA is a secondary product of lipid peroxidation that reflects the degree of ROS attack and can be used to indicate the oxidation of membranes [55,56]. The cellular defense system to combat free radicals includes SOD, CAT, and GPx [57]. SOD can instantly convert harmful oxygen free radicals into H_2O_2 or peroxide. CAT can transform H_2O_2 into H_2O and O_2, while GPx decomposes peroxides such as H_2O_2 [58]. Casalino [59] suggested that Cd-induced displacement of Zn, Mn from the active sites of SOD, resulting in its decreased activity [59,60].

The antioxidant action of curcumin is attributed to its conjugated structure which includes two methoxylated phenols and an enol form of β-diketone. The structure is shown to have a distinctive radical trapping capacity as a chain-breaking antioxidant [61]. Dinokova and Talalay [62] also found that curcumin is a bifunctional antioxidant because of its ability to react directly with ROS and to induce an upregulation of various cytoprotective and antioxidant proteins. Treatment of curcumin significantly declined the level of TBARS (*$p<0.05$) and increased the activity of GSH and SOD (*$p<0.05$) [63]. Curcumin has a property to prevent the islets β-cells damage, decline the insulin resistance and oxidative stress [64]. The administration of curcumin to diabetic rats significantly normalized their blood sugar level, TBARS value, and elevated the activities of antioxidant enzymes such as SOD and GPx [65]. Similar results were obtained in streptozotocin-induced diabetic rats treated with turmeric [66-68]. Further, curcumin was found to be effective in decreasing oxidative damage induced by Cd which resulted in lower MDA concentration, it was observed to be capable of inhibiting the formation of ROS and induced high antioxidant activity [69-71]. Curcumin protection against Cd-induced oxidative stress was observed by significantly increased GPx activity and decreased MDA concentration in blood of rats [72]. The amelioration by curcumin is observed in diabetic rats with significant improvement in MDA, SOD, and CAT enzymes as compared to untreated group [73]. Similar results were also reported by Lyons, Adhikari *et al.*, Hussein and EL-Maksoud, and Seo *et al.* [50,64,74,75].

CONCLUSION

Cd induced oxidative stress in pancreas of albino mice. The results of the present study suggest that administration of curcumin though significantly improves but were not able to completely prevent oxidative stress in Cd-induced toxicity in pancreatic tissue of albino mice. Curcumin at a dose of 100 mg/kg gives encouraging results by enhancing antioxidant activity and shows a rise in endogenous defense directly by decreasing lipid peroxides in Cd-treated as well as only curcumin-treated mice (+ve control).

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AUTHORS' CONTRIBUTION

We declare that this work was done by the authors named in this article. Suman Sharma designed the experiment and edited the manuscript.

Anu performed the experiment, interpreted the data, and prepared the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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