Ameliorating Efficacy of Curcumin on Cadmium Induced Thyroid Dysfunction in Albino Rats

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Available online at: www.isroset.org

Received: 10/Feb/2019, Accepted: 22/Feb/2019, Online: 28/Feb/2019

Abstract—Cadmium (Cd) is one of the hazardous heavy metals as it causes various forms of physiological and hormonal imbalances. The aim of the present study was to investigate pharmacological effects of curcumin, a derivative of Curcuma longa Linn., in the prevention of oxidative stress induced by CdCl₂ on the thyroid gland of albino rats. In this study, rats were divided into 5 groups (n=5). Group 1 rats kept as control. Group 2 rats administered a single oral dose of 50mg/kg body weight of CdCl₂ on day 1 and left for 30 days. Group 3 rats were given an oral dose of 150mg/kg body weight of curcumin daily for 30 days and kept as a positive control. Group 4 rats, acted as a post-treated group, administered a single oral dose of 50mg/kg body weight of CdCl₂ on day 1 and 150mg/kg body weight of curcumin daily for the next 30 days. Group 5 rats, acted as a pretreated group, were given an oral dose of 150mg/kg body weight of curcumin daily for 30 days and 50 mg/kg body weight of CdCl₂ on last day. In rats, acute CdCl₂ treatment caused increased oxidative stress, decreased SOD, CAT and irregularities in normal levels of serum hormones (T3, T4, and TSH). In curcumin supplemented rats, level of Cd-induced lipid peroxidation was significantly lowered, the activity of SOD and CAT were significantly increased and improved serum hormone levels were noticed, which shows that curcumin to some degree could alleviate the toxic effects of CdCl₂.

Keywords—Cadmium, Curcumin, Thyroid, T3, T4, TSH, Oxidative Stress

I. INTRODUCTION

Environmental pollution is considered as man’s greatest crime against himself as pollution of the ecosystem with industrial, agricultural and sewage effluents results in contamination of air, food and water with some toxic agents such as heavy metals which constitute a major public threat. Some metals are essential for life, others have unknown biological functions and some others have the potential to cause toxicity [1]. Heavy metals are persistent environmental contaminants since they cannot be degraded or destroyed easily from living systems.

Among the various heavy metals, Cadmium (Cd), 48th element in the periodic table with an atomic weight of 112.4, is one of the hazardous metals that is not physiologically or biochemically essential to organisms and is present in all components of our environment i.e. air, water and soil. It is unique among all the heavy metal toxicants because of its low dosage toxicity, long biological half-life and low rate of excretion from the body [2].

International Agency for Research on Cancer has classified Cd as a group I human carcinogen [3,4]. It is largely used in cadmium-based products such as nickel-cadmium batteries, television phosphors, stabilizer for polyvinyl chloride etc. Due to its brilliant orange color, it is extensively used as a pigment in paints, plasters and plastics [5]. It is known to be the most harmful heavy metal as it causes various forms of diseases such as osteomalacia, osteoporosis, hypertension, arteriosclerosis, anemia and cancer [6,7].

Cadmium, as an environmental pollutant, affects various tissues and organs. Once absorbed, Cd is rapidly cleared from blood but remains in various tissues [8]. It can accumulate in the body over many years because the body doesn't possess a homeostatic mechanism to keep Cd at constant level [9]. Long exposure to high or low doses of cadmium may cause biochemical and functional changes in some critical organs [10], where it causes many metabolic and histopathological changes, leading to various possible pathological conditions in both animals and human populations culminating in infertility and cancer of the reproductive tissues [11-13].

Thyroid gland, is an endocrine gland, whose follicular and parafollicular cell synthesize and secrete important regulatory hormones such as thyroxine (T4) and triiodothyronine (T3) which are necessary to maintain the
metabolism of the cells [14]. Cd as a potential pollutant and an endocrine disrupting compound (EDC) [15,16], affect thyroid gland by accumulating in the mitochondria of thyroid follicular epithelial cells and inhibiting the synthesis and release of its hormones. Cd appears to be the largest single contributor to auto-immune thyroid disease [17-19].

In recent years, much attention has been given on the use of herbal medicines and their derivatives in healing different conditions related to toxicity [20]. There has been considerable public and scientific interest in the use of phytochemicals especially polyphenols derived from dietary components to combat human diseases due to their antioxidant, anti-inflammatory, anti-bacterial, anti-mutagenicity and anti-cancer properties [21].

Turmeric (Curcuma longa Linn.) belonging to family Zingiberaceae, is an imperative spice present in every Indian kitchen. It is traditionally used in India as a coloring and flavoring agent in food as well as for medicinal purposes [22]. It is usually used in most of the cooked preparations and is generally believed to fend off several ailments. It exhibits antitumor, anti-inflammatory and anti-infectious activities [23,24].

Curcumin (Cur), a derivative of Curcuma, is the main active component of turmeric. Curcumin is among the best characterized natural polyphenols and is the prime yellow pigment extracted from turmeric. Curcumin has been given the designation of super antioxidant and has shown to possess a broad spectrum of biological and pharmacological activities, anti-inflammatory, antineoplastic, anti-mutagenic and anticancer effects [25]. It is found to be effective against several disorders including anorexia, coryza, cough, hepatic diseases and sinusitis [26,27]. The most important feature of curcumin is that it has no side effects despite being a therapeutic and antioxidant agent with multiple beneficial functions [28,29]. So, the aim of the present study is to evaluate the protective role of curcumin in Cd- induced oxidative stress on thyroid gland activity.

Rest of the paper is organized as follows, Section I contains the introduction of the study. Section II contains materials purchased and methods applied for the experiment. Section III contains the output of the experiment in the form of results with graphs. Section IV describes the discussion with reference to previous work done. Section V concludes research work and Section VI contains the acknowledgment.

II. MATERIALS AND METHODS

2.1 Source of Chemicals: Cadmium chloride (CdCl2) and Curcumin (Cur) were purchased from Himedia Laboratories Pvt. Ltd., Mumbai. CdCl2 was dissolved in distilled water and administered to rats by oral gavage. An aqueous suspension of curcumin was made and administered orally to rats [30].

2.2 Procurement of Animals: 25 male wistar albino rats weighing 100-200 grams were purchased from Disease Free Animal House, LUVAS, Hisar. Rats were housed in plastic cages with soft wood chips for bedding, acclimatized to the laboratory conditions for 15 days and fed with the standard rat feed in the form of pellets purchased from M/S Aashirwad Industries, Ltd., Chandigarh and water ad libitum.

2.3 Experimental Design: In the present study, Wistar albino rats were divided into 5 groups (n=5) and kept as designed protocol as follows:

- **Group 1 (Control):** Rats were kept as control.
- **Group 2 (Cd):** Rats were administered a single oral dose of 50mg/kg body weight of CdCl2 on day 1 and left for 30 days.
- **Group 3 (Cur):** Rats were given an oral dose of 150mg/kg body weight of curcumin daily for 30 days and kept as a positive control.
- **Group 4 (Cd+Cur):** Rats were given a single oral dose of 50mg/kg body weight of CdCl2 on day 1 and 150mg/ kg body weight of curcumin daily for next 30 days and served as a post-treated group.
- **Group 5 (pre Cur+Cd):** Rats were given an oral dose of 150mg/kg body weight of curcumin daily for 30 days and 50 mg/kg body weight of CdCl2 on the last day which served as a pre-treated group.

2.4 Serum Collection: 24 hours after the administration of the last dose, 2 ml of blood from each rat was collected via retro-orbital venous plexus in clean dry centrifuge tubes, left for 20 minutes at room temperature to clot, centrifuged at 3000 rpm for 5 minutes for separation of blood serum and quickly frozen at -20°C till the assessment of various hormones (T3, T4 and TSH). Meanwhile, the animals were sacrificed by cervical dislocation. The thyroid gland was removed, freed of adipose tissue, blotted dry, weighed separately and processed for biochemical (MDA, SOD and CAT) investigations.

2.5 Estimation of T3, T4 and TSH: Serum total T3 (triiodothyronine), T4 (thyroxine) and TSH (thyroid stimulating hormone) were assessed by ELISA reader using kits provided by Calbiotech Inc. USA according to the manufacturer’s instruction [31].

2.6 Determination of MDA: The level of malondialdehyde (MDA), the end product of lipid peroxidation was evaluated by the method described [32].

2.7 Assay of Superoxide dismutase and Catalase Activity: Superoxide dismutase (SOD) and Catalase (CAT) activity were estimated according to previously described methods [33,34].

2.8 Statistical analysis: Data was subjected to one-way analysis of variance (ANOVA) by using GraphPad PRISM
version 7.03. Results are expressed as mean ±S.D. Values were considered statistically significant at \( p \leq 0.05 \).

### RESULTS

#### 3.1 Body and organ weight
As evaluated from the present findings, body weight of the experimental animals gradually increased in all the treated groups but lesser weight gain was observed in Cd-exposed rats G2 as compared to control. Overall, the weight of the thyroid gland exhibited a significant decrease \( (p<0.001) \) in all the treated groups compared to control group. Co-administration of curcumin with cadmium in post-treated and pre-treated rats revealed significantly higher values \( (p<0.001) \) when compared to intoxicated group G2. Positive control rats G3 revealed almost similar results compared to control (Fig. 1).

#### 3.2 Hormonal Analysis
In the present study, 30 days after the acute exposure to 50mg/kg body weight of Cd, serum analysis revealed a significant decrease \( (p<0.0001) \) in T3 and T4 levels in Cd treated G2 group in comparison to control G1. On the other hand, T3 and T4 levels were increased significantly with \( p<0.0001 \) in case of curcumin post-treated and pre-treated groups (G4 and G5) as compared to Cd treated G2 (Fig. 2 and 3).

The serum concentration of TSH was increased significantly \( (p<0.0001) \) in case of Cd treated group when compared to control group. The higher plasma level of TSH was decreased significantly \( (p<0.0001) \) in groups G4 and G5 treated with curcumin as compared to Cd treated G2 group (Fig. 4).

Curcumin administered (G4 and G5) rats showed almost normal T3 levels \( (p>0.05) \) when compared to control. G5 rats showed a normal serum T4 level \( (p>0.05) \) when compared to control but a significant difference in plasma T4 \( (p<0.001) \) concentration was observed in G4 rats as compared to control (Fig. 2 and 3). However, treatment with curcumin in G4 and G5 rats did not normalize serum TSH levels compared to control group but co-administration of curcumin could slightly decrease the elevated TSH levels in these groups (Fig. 4).

#### 3.3 Biochemical Analysis
MDA concentration in the thyroid tissue was used as a measure of lipid peroxidation. The results of the present study showed a significant increase \( (p<0.0001) \) in MDA content in the thyroid tissue of Cd-exposed rats (G2) when compared to control. But the values of MDA content in case of G4 and G5 rats exhibited a significant decrease \( (p<0.0001) \) when compared with Cd treated rats G2. (Fig. 5).

Cd-exposed rats G2 expressed a significant decrease in the activity of antioxidant enzymes SOD \( (p<0.0001) \) and CAT \( (p<0.0001) \) in thyroid in comparison to control. A significant increase \( (p<0.0001) \) was observed in SOD and CAT activity in curcumin supplemented groups when compared to Cd-exposed group (Fig. 6 and 7).

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**Figure 1.** Mean weight of thyroid gland in control and experimental rats. Results are expressed as mean±S.D.

\( ^*p≤0.05\ vs\ control, \ ^*#p≤0.05\ vs\ 50\text{mg/kg Cd group} \)

S.D.= Standard Deviations; \( p=\)probability
Figure 2. Serum T3 concentration in control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D. = Standard Deviations; p=probability

Figure 3. Serum T4 concentration in control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D. = Standard Deviations; p=probability

Figure 4. Serum TSH concentration in control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D. = Standard Deviations; p=probability
Figure 5. Lipid peroxidation, expressed as MDA content, in the thyroid homogenates of the control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D.= Standard Deviations; p=probability

Figure 6. Superoxide dismutase (SOD) activity in the thyroid homogenates of the control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D.= Standard Deviations; p=probability

Figure 7. Catalase (CAT) activity in the thyroid homogenates of the control and experimental rats. Results are expressed as mean±S.D. (*p≤0.05 vs control, #p≤0.05 vs 50mg/kg Cd group). S.D.= Standard Deviations; p=probability
IV. DISCUSSION

Human beings are mostly exposed to cadmium through industrial aerosols, waste waters from extraction mines, cigarette smoke, phosphate-based fertilizers and accidental ingestion of contaminated dust or soil [35]. Through the process of bioaccumulation and due to the long half-life of the Cd, which requires 20 years to completely metabolize in humans [36], acute or chronic exposure to Cd can lead to oxidative stress in organs such as liver, kidney, bone and testes in experimental animals [37-39]. Oxidative stress occurs when there are too many free radicals and too much cellular damage which exceeds the body's natural defense systems. Antioxidants are natural substances which clean up free radicals within the cells. Some studies have reported that non-enzymatic polyphenolic antioxidants such as curcumin could alleviate oxidative stress [40]. The purpose of the present study was to find out the efficacy of curcumin against CdCl2 induced oxidative stress in the thyroid gland of albino rats.

For maintaining important bodily functions such as metabolism, growth, reproduction etc., thyroid hormones play an essential role and are regulated by pituitary and hypothalamus [41]. For instance, when the level of thyroid hormones falls in the blood, hypothalamus secretes thyrotropin releasing hormone (TRH) which in turn stimulates anterior pituitary to release thyroid stimulating hormone (TSH) which further controls the secretion of triiodothyronine (T3) and thyroxine (T4) [42]. Some studies reported alteration in the activities of thyroid and parathyroid glands as well as disruption in the secretion of their hormones after accumulation of Cd in them [43].

In the present study, Cd-exposed rats (G2) experienced hypothyroidism which was evidenced biochemically by significant decrease in serum T3 and T4 levels and significant increase in serum TSH level when compared to control. Many studies have shown the production of reactive oxygen species (ROS) in hypothyroidism [44,45], which may be the principal cause of low T3 and T4. Cd accumulates in the mitochondria of follicular epithelial cells of thyroid tissue, disturbing oxidative phosphorylation and due to low energy production, inhibits the synthesis and release of thyroid hormones [46].

The results of the present study are in agreement to the results of previous studies who reported that precursor of the thyroid hormones T3 and T4 is a glycoprotein called thyroglobulin which is synthesized by the follicular cells and stored in the lumen of the follicles [47]. Cadmium accumulation in these cells may interfere with the release of T3 and T4. Other studies suggested that low T3 and T4 levels occur due to reduction in the activity of the enzyme called ‘ORD’ (Outer Ring Deiodinase) present in liver cells, which convert T4 into more biologically active form, T3 [48]. Lower activity of this enzyme could play a critical role in normal circulating serum T3 and T4 levels.

Further, a significant higher serum concentration of TSH was found in Cd-exposed rats (G2) which was not able to produce enough T3 and T4. Studies suggested that Cd induces irregularities in the synthesis of thyroid hormones at pituitary level which produces more TSH in response to low serum concentration of T3 and T4 [49].

In the present study, a significant elevation in MDA concentration and significant reduction in the activities of SOD and CAT were observed in Cd treated rats (G2) when compared to control rats (G1) which indicates that thyroid antioxidant defense mechanism fails to protect the thyroid gland from oxidative stress produced by Cd. Oxidative stress occurs due to an imbalance between intracellular production ROS and cellular antioxidant defense system [50]. Cells protect themselves against oxidative damage by network of enzymes such as superoxide dismutase (SOD) that catalyzes the breakdown of superoxide anion into oxygen (O2) and hydrogen peroxide (H2O2) [51,52]. Further, catalase converts H2O2 into oxygen and water thereby protecting the cells from the oxidative damage [53]. Since, Cd produces its toxicity by interacting with lipid membranes which caused high concentration of MDA in the thyroid gland [54]. The reduction in the activities of SOD and CAT could be due to the production of free radicals in the Cd-exposed rats and due to the replacement of zinc (Zn) or magnesium (Mg) of the enzyme SOD by Cd, changing its structure from Cu/Zn-SOD to Cu/Cd-SOD, creating an inactive form of this enzyme [55,56], which may have failed to protect the cells from oxidative damage.

Hypothyroidism, is frequently treated with iodine supplements or thyroid hormone replacement therapy. Naturally occurring substances reinforce thyroid activity either by increasing the production of thyroid hormones or screening it from injury. In our experiment, post and pre-treated group of rats (G4 and G5) with curcumin revealed significant higher serum values of T3, T4 and significant lower values of TSH when compared to Cd-exposed rats (G2) which shows that curcumin has the ability to reverse the toxic effects of Cd to some extent and prevents oxidative damage by free radical trapping capacity. Moreover, two methoxylated phenols and enol form of β-diketone in the curcumin are responsible for free radical quenching ability which in turn acts as a chain-breaking antioxidant [57].

In Cd-induced toxicity, lipid peroxidation is the main event which give rise to ROS. But in curcumin treated rats G4 and G5, a significant decrease in the MDA content and significant increase in SOD and CAT activity were observed when compared to Cd-exposed group G2 which confirms curcumin to be an effective antioxidant against Cd-induced tissue damage. Furthermore, studies suggested that curcumin scavenges lipid peroxyl radicals before they damage lipid membranes or by modifying the process of lipid peroxidation and boosting the activities of antioxidant enzymes [58,59].
V. CONCLUSION

We undertook the present study to evaluate the efficacy of curcumin in Cd-induced oxidative stress in thyroid gland activity. Our results indicate that oral administration of an acute dose of CdCl₂ could inhibit the release of T3 and T4 even in the presence of elevated TSH which could be due to the enhanced generation of ROS resulting in depletion of antioxidant enzymes SOD and CAT causing failure of thyroid antioxidant defense system. However, supplementation of curcumin ameliorates CdCl₂ induced thyroid dysfunction to some extent.

VI. ACKNOWLEDGEMENT

The authors gratefully acknowledge the Institutional Ethical committee for permitting the research work on rats. Also, the facilities provided by the Department of Zoology and Environmental Sciences, Punjabi University, Patiala, to carry out the research studies are truly appreciated.

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