PROTECTIVE EFFECT OF CORIANDER SATIVUM L. ON CADMIUM INDUCED TOXICITY IN ALBINO RATS

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ABSTRACT

Background: Cadmium is a environmental and occupational hazard that causes various degree of damage in target cells mainly in the liver and kidney. It is found in drinking water, atmospheric air, and even in food. Objective: The present study has been undertaken to evaluate the protective effect of Coriandrum sativum L in cadmium chloride induced toxicity in albino rats. Methods: Wistar strains of albino rats were used and the experimental animals were divided into five groups each consisted six animals. In experimental design, group I is served as normal control, group II is served as disease control (intraperitoneally administered with cadmium (6mg/kg of bw) as CdCl₂ for 15 days).

Group III and IV is induced with CdCl₂ and aqueous extract of Coriandrum sativum L (100 and 200 mg/kg of bw). Group V was treated with plant alone. Result: Oral administration of cadmium as cadmium chloride showed a significant increase in the marker enzymes (Alanine transaminase, Aspartate transaminase, Alkaline Phosphatase, Acid phosphatase) and Cholesterol in serum and Lipid Peroxide in liver tissue. After the treatment with aqueous extract of Coriandrum sativum L of 100,200mg/kg of bw produced a well pronounced protective effect in response to these parameters in cadmium intoxicated rats. The treatment with cadmium caused a concomitant reduction in the enzymatic and non enzymatic antioxidants like Superoxide Dismutase, Catalase, Reduced Glutathione and serum protein respectively, while treatment with aqueous extract of Coriandrum sativum L at the dose levels of 100 and 200mg/kg of bw resulted in the marked improvement in the antioxidants and protein compared to control rats. Conclusion: The above results concludes that the treatment with aqueous extract of Coriandrum sativum L produced a significant protective effect against cadmium-induced toxicity in albino rats.
INTRODUCTION

Trace elements are known to have a variety of important biological functions and in many instances, they may have adverse effects on biological system \(^{1, 2, 3}\). In this respect, cadmium is one of the ubiquitous environmental pollutant and 7th most hazardous substance \(^{4}\) and is also a carcinogen \(^{5}\). In the body, cadmium produces toxic effects by a mechanism related to its ability to generate free radicals at range high enough to overwhelm the natural antioxidant defense system of the body and results in the condition known as oxidative stress \(^{6}\). Free radicals are evolved at the early stages of cadmium intoxification \(^{7, 8}\). Cadmium toxic effects on biological systems have been extensively reported \(^{9}\). For the general population, cadmium is mainly exposed by oral and inhalation routes, kidneys and liver are considered the most susceptible organs in the case of exposure to cadmium \(^{10, 11, 12}\). Chronic exposure to cadmium can induce severe nephropathy in humans \(^{13}\) and animals \(^{14}\). Several mechanisms have been proposed to explain the toxic effect of cadmium on renal cells. Cadmium may cause nephrotoxicity by generating free radicals \(^{15}\) and by inducing necrosis and apoptosis \(^{16}\).

Several Indian plants are considered as potential sources of antioxidants which can diminish the peroxidative stress in biological system due to several stresses, including heavy metals, pesticides, and mycotoxins \(^{17}\). Biological compounds with antioxidants properties contribute to the protection of cells and tissues against deleterious effects of reactive oxygen species and other free radicals. Protective agents from plant origin with anti peroxidative and antioxidant properties play an important role in protecting the liver against toxicity \(^{18}\). Various methodologies are being devised to combat cadmium induced toxicity with a focus on herbal formulations. The use of herbal medicine increases every day and still finds a wide use worldwide.

*Coriander sativum* L. is an annual herb belonging to the family Apiaceae. It has long been used in traditional Chinese and Indian systems of medicine, for the treatment of digestive disorders, hepatitis, ulcerative colitis etc. Thus, the present study has been undertaken to evaluate hepatoprotective effect of *Coriander sativum* L. on cadmium induced toxicity in animal models.
MATERIALS AND METHODS

Collection of plant material
Plant source selected for the present study is Coriander sativum L. Aerial parts of the selected plant were collected from in and around Trichy, identified with the help of Flora of Presidency of Madras. The plant was authenticated with the specimen deposited at RAPINAT Herbarium, Department of Botany, St, Joseph’s college, Trichy.

Preparation of Aqueous Plant Extract
The plant material was shade dried and coarsely powdered with electrical blender. 200gm of Coriander sativum L. was mixed with 1200 ml of water. Then it was boiled until it was reduced to one third and filtered. The filtrate was evaporated to dryness. Paste form of the extract obtained was subjected to screen its hepatoprotective activity.

Experimental Animals
Healthy adult Wistar strain of albino rats of both sexes, two to three months old and weighing 150g-200g were obtained from Tamilnadu Veterinary and Animal Sciences University, Chennai. The animals were allowed to acclimatize under laboratory conditions for a period of 5 days prior to the experiment. Animals were housed in standard polypropylene cages. Six animals were housed per cage, so as to provide them with sufficient space, and to avoid unnecessary morbidity and mortality. Animals were maintained under standard condition of 12: 12- hours light/ dark cycle and at an ambient temperature at 23 ± 2°C, with 65 ± 5 % humidity. Animals were fed with standard rat chow pellet obtained from Sai Durga Foods and Feeds, Bangalore, India and water ad libitum. All the studies were conducted according to the ethical guidelines of CPCSEA after obtaining necessary clearance from the committee (Approval No: 790/03/ac/CPCSEA).

Experimental Design
The experimental animals were divided into five groups each consisted of six animals. Group I was served as normal control and group II was served as disease control (Intraperitoneal administration of Cadmium as CdCl₂ (6mg/Kgbw) for 15 days. Group III and IV was induced with CdCl₂ and followed by treated with ACSE at the doses of (100 and 200mg/kg of bw). Group Group V was treated with plant alone.

Statistical Analysis
All the results were expressed as mean ± S.E . The data were statistically analyzed by one –
way analysis of variance (ANOVA) followed by Duncan multiple range test. Statistical presentations were organized using statistical package for social sciences (SPPS), windows version 17.0.2008. SPPS Inc., New York. Inter group comparison were carried out and P values <0.05 and P<0.01 were considered as significant.

Biochemical observations

After the experimental period of 15 days, animals were sacrificed by cervical dislocation. Blood and tissue samples were collected and serum was separated by centrifuging the blood at 3000 rpm for 10 minutes and subjected for the determination of Serum enzymes like Alanine transaminase (ALT)\(^{19}\), Acid phosphatase (ACP)\(^{19}\), Alkaline phosphatase (ALP)\(^{19}\), Aspartate transaminase (AST)\(^{19}\). Tissue was homogenized and used for determination of Enzymatic and non enzymatic antioxidants like superoxide dismutase\(^{20}\), Catalase\(^{21}\), Reduced glutathione\(^{22}\), lipid peroxide\(^{23}\). Biochemical parameters like serum protein\(^{24}\) and serum cholesterol\(^{25}\) were determined using appropriate methods.

RESULTS

Table 1. Levels of Antioxidants and Lipid per oxide in Experimental Animals

<table>
<thead>
<tr>
<th>Groups</th>
<th>Lipid per oxide  (nM of MDA/g tissue)</th>
<th>Catalase  (µmol of H(_2)O(_2) hydrolyzed/min/mg protein)</th>
<th>Reduced Glutathione  (mg/g tissue)</th>
<th>Superoxide Dismutase  (mM of epinephrine oxidized/min/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>525.45±0.02*, #</td>
<td>72.80±0.50*, #</td>
<td>41.9±0.60*, #</td>
<td>21.34±0.17*, #</td>
</tr>
<tr>
<td>Group II</td>
<td>958.36±0.04*, **</td>
<td>48.30±0.25*, **</td>
<td>21.56±0.98*, **</td>
<td>10.00±0.15*, **</td>
</tr>
<tr>
<td>Group III</td>
<td>889.88±0.02</td>
<td>52.92±0.40</td>
<td>32.10±0.95</td>
<td>15.16±0.18</td>
</tr>
<tr>
<td>Group IV</td>
<td>744.46±0.02**</td>
<td>65.80±0.10**</td>
<td>36±0.18**</td>
<td>20.74±0.18**</td>
</tr>
<tr>
<td>Group V</td>
<td>633.36±0.02#</td>
<td>70.20±0.30#</td>
<td>40.20±1.00#</td>
<td>20.90±0.19#</td>
</tr>
</tbody>
</table>

* - Significant at P<0.05 when compared between Group I and Group II (n=6)
** - Significant at P<0.05 when compared between Group II and Group IV (n=6)
# - Non-significant at P-0.05 when compared between Group I and Group V (n=6)

Table 2. Levels of Serum Enzymes in Experimental Animals

<table>
<thead>
<tr>
<th>Groups</th>
<th>SGPT (IU/L)</th>
<th>SGOT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>ACP (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>49.05±0.30*, #</td>
<td>69.58±0.40*, #</td>
<td>75.7±1.20*, #</td>
<td>25.63±0.12*, #</td>
</tr>
<tr>
<td>Group II</td>
<td>70.96±0.70*, **</td>
<td>92.96±0.60*, **</td>
<td>110.9±2-80*, **</td>
<td>69.48±0.80*, **</td>
</tr>
<tr>
<td>Group III</td>
<td>65.08±0.60</td>
<td>84.28±0.50</td>
<td>95±1.60</td>
<td>45.10±0.50</td>
</tr>
<tr>
<td>Group IV</td>
<td>56.07±0.50**</td>
<td>73.47±0.58**</td>
<td>80±0.50**</td>
<td>38.90±0.20**</td>
</tr>
<tr>
<td>Group V</td>
<td>46.40±0.20#</td>
<td>67.46±0.30#</td>
<td>75±0.85#</td>
<td>21.05±0.08#</td>
</tr>
</tbody>
</table>

* - Significant at P<0.05 when compared between Group I and Group II (n=6)
** - Significant at P<0.05 when compared between Group II and Group IV (n=6)
# - Non-significant at P-0.05 when compared between Group I and Group V (n=6)
Table 3. Levels of Serum Cholesterol and Serum Protein in Experimental Animals

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum Cholesterol (mg/dl)</th>
<th>Protein (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>110±1.03*, #</td>
<td>4.8±0.02*, #</td>
</tr>
<tr>
<td>Group II</td>
<td>145±1.20*, **</td>
<td>3.15±0.07*, **</td>
</tr>
<tr>
<td>Group III</td>
<td>132±0.80</td>
<td>3.98±0.05</td>
</tr>
<tr>
<td>Group IV</td>
<td>120.30 ±0.98**</td>
<td>4.10±0.02**</td>
</tr>
<tr>
<td>Group V</td>
<td>103.19±0.50*</td>
<td>4.30±0.03*</td>
</tr>
</tbody>
</table>

* - Significant at P<0.05 when compared between Group I and Group II (n=6)
** - Significant at P<0.05 when compared between Group II and Group IV (n=6)
# - Non-significant at P>0.05 when compared between Group I and Group V (n=6)

In the present study, the results clearly indicate that the Cadmium intoxication leads to an elevated lipid peroxidation with a subsequent decrease in the antioxidant status. Treatment with the Coriander sativum L. in the dose of 100 and 200mg/kg bw improved the antioxidant status (Table 1). And the activity of serum marker enzymes and the levels of serum cholesterol and protein were shown in Table 2 and 3. Administration of cadmium showed an elevated level of serum marker enzymes and serum cholesterol and reduction on serum protein compared to normal rats, which might be due to the severe hepatic damage. Oral administration of Coriander sativum L. in the dose of 100 and 200mg/kg bw showed a significant reduction (P<0.05) in serum marker enzymes and serum cholesterol, when compared with cadmium induced rats. Serum protein level was also restored to near normal.

DISCUSSION

Cadmium is an environmental and occupational hazard that causes various degree of damage to target cell mainly in the liver and kidney. Inhibition of protein synthesis by cadmium has been reported both in systems (invivo) and in isolated profused hepatocytes. Reduction in protein synthesis could be described to dysfunction at the level of transcription and translation as cadmium is known to bind the in specific site in chromatin, which might interfere with transcription of mRNA [26]. Moreover concurrent administration of cadmium and aqueous extract of Coriander sativum L. improved the protein levels compared to disease control. Similar observations are recorded in earlier work [27]. Administration of aqueous extract of Coriander sativum L at the dose level of 100 and 200mg/kg bw per day significantly increased the total protein level.

Increased activity of serum enzymes such as Alanine transaminase, Aspartate transaminase, Alkaline Phosphatase and Acid phosphatase in Group II rats may be due to the impact of cadmium on liver tissue of the animals. Administration of cadmium as cadmium chloride
caused degeneration of liver cells that resulted in the leakage of cytosolic enzymes into circulation. Thus, the levels of liver enzymes were found to be higher in the cadmium-induced rats (28). Alkaline Phosphatase is a group of glycoprotein enzymes and its activity is found virtually all tissues, particularly bone, liver, kidney, intestine, adrenal and placenta. It has been hypothesized that alkaline phosphatase is in liver found at two distinct sites on the sinusoidal surface of hepatocytes and in the microvilli of the bile canaliculi and has been hypothesized earlier (29). During obstruction of bile passages (cholestasis) the plasma alkaline phosphatase level rises. This is mainly due to the increased synthesis of alkaline phosphatase, but the obstruction itself also play a part by causing regurgitation of the enzyme back in to the blood stream and also the level was elevated in acute hepato cellular disease. Administration of cadmium also causes assimilation of fat in the liver, leading to increased acid phosphatase activity this may due to the lysosomal imbalance in the destruction of the intact membrane (30). Alkaline Phosphatase has been reported to be the marker enzyme for plasma membrane (31) and is required in certain amounts for proper functioning of organs (32). Increase in the acid phosphatase and alkaline phosphatase activities indicated the increased permeability, damage, and /or necrosis of cells.

Increase in Lipid per oxide results in changes in intracellular stability, DNA damage and apoptosis (33). Cadmium may induce oxidative damage in different tissues by enhancing peroxidation of membrane lipids in tissue and altering the antioxidant systems of the cells. The peroxidative damage to cell membrane may cause injury to cellular components due to interaction of metal ions and cell organelles (34). The tissue peroxidation induced by cadmium leads to liver and kidney dysfunction which has reflected in alterations in various functional markers in serum. These alterations consisted of significant decrease in serum protein and increase in Alanine transaminase, Aspartate transaminase, Alkaline Phosphatase and Acid phosphatase levels indicating hepatic toxicity (35).

Superoxide dismutase, Reduced Glutathione and Catalase are metallo proteins accomplishing their antioxidant functions by enzymatically and non-enzymatically detoxifying peroxides. Decreased in the activities of antioxidant enzymes in liver tissue of cadmium treated rats may be due to the inhibition of these enzymes by H₂O and nitric oxide. And also these enzymes play an important role in cadmium chloride induced liver injury (36, 37). The enzymes constitute the first line of defense against free radical induced damage and the restoration of these enzyme activity by aqueous extract of Coriander sativum L. may account for their protective
effect. GSH is a cellular antioxidant defenses against free radical over production, and decreases its cellular concentrations impairs cellular defenses against oxidative stress (38). Cadmium depletes glutathione and protein bound sulfhydryl groups resulting in enhanced production of reactive oxygen species such as superoxide ions, hydroxyl radicals and hydrogen peroxide. These oxygen species result in lipid peroxidation. Cadmium has a high affinity on reduced glutathione and causes the irreversible excretion of glutathione tripeptides (39) that toxic to the bile.

Cadmium increased the level of cholesterol significantly in liver tissue. Cadmium administration is also associated with significant increase in plasma cholesterol, plasma low-density lipoprotein (LDL) and reduced plasma high-density lipoprotein (HDL) which was reported by earlier workers (40, 41, 42). Cadmium mediated development of hypercholesterolemia that involves the activation of cholesterol biosynthetic enzymes and simultaneous suppression of cholesterol catabolic enzymes.

CONCLUSION
Cadmium is one of the most dangerous occupational and environmental toxic metal producing organometallic toxicity especially liver. Cadmium induction resulted in the production of Lipid per oxide and abnormalities in the antioxidants (enzymatic and non enzymatic) which would be normalized by the synergestic treatment with aqueous extract of Coriander sativum L. in cadmium induced hepatotoxic rats. The results concludes that the plant Coriander sativum L. possess a potent organoprotective effect against metal induced toxicity.

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