**EFFECT OF GALLIC ACID ON LIPID PROFILE AND ANTIOXIDANT STATUS IN CADMIUM CHLORIDE TREATED RATS**

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**ABSTRACT**

This study was aimed to explore the role of gallic acid (GA) in ameliorating in reducing adverse effects of cadmium chloride (CdCl₂) on antioxidant status and lipid profile in adult male rats. Twenty-eight (28) adult male rats were divided randomly into four equal groups; they were daily handled for 30 days, as follows: control group (C), received tap water only, (G1), received 100ppm of CdCl₂ in drinking tap water, animals in proceeding groups were given in addition to CdCl₂ in drinking water the following: intraperitoneal injection of GA 100 mg/kg, daily (G2) group and the combination of GA and CdCl₂ were given to rats in group (G3) in the same pattern. At the end of the experiment, fasting blood samples were collected and serum was isolated for measuring of antioxidant status and lipid profile. The results showed that administration CdCl₂ (G1 group) caused a case of dyslipidemia illustrated by significant elevation in serum cholesterol concentration in lipoprotein low density lipoprotein-cholesterol (LDL-C) and very low-density lipoprotein-cholesterol (VLDL-C), total cholesterol (TC), triglyceride (TAG) and non-HDL-C accompanied with significant decrease in cholesterol of high density lipoprotein (HDL-C) concentrations. The results also revealed a significant elevation in lipid indices including, coronary risk index (CRI), and cardiovascular risk index (CVRI) in CdCl₂ exposed rats. While significant elevation in malondialdehyde (MDA) and reduction in (GSH) concentrations observed in the same group comparing to gallic acid and control group indicating a case of oxidative stress. The current results also recorded that intraperitoneal injection of GA against CdCl₂ caused amelioration of all previously estimated parameters.

Key Words: GSH, MDA, Dyslipidemia, Lipoproteins, Oxidative stress.

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**Efecto del ácido gallico sobre el perfil lipídico y el estado antioxidante en ratas tratadas con cloruro de cadmio**

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B. Najim Al-Okaily

**Resumen**

Este estudio tuvo como objetivo explorar el papel del ácido gallico (GA) en el amelioración en la reducción de los efectos adversos del cloruro de cadmio (CdCl₂) sobre el estado antioxidante y el perfil lipídico en hembra de ratas adultas. Veinte y ocho (28) ratas macho adultas fueron divididas al azar en cuatro grupos iguales; se les manejaron diariamente durante 30 días, de la siguiente manera: grupo de control (G1), recibió agua corriente solo, grupo (G2) recibió 100 ppm de CdCl₂ en agua corriente, animales en grupos siguientes recibieron adicionalmente a CdCl₂ en agua corriente la siguiente: inyección intraperitoneal de GA 100 mg/kg, diariamente (G3) y la combinación de GA y CdCl₂ fueron administradas a ratas en el grupo (G4) en el mismo patrón. Al finalizar el experimento, se recogieron muestras de sangre de ayunas y se aisló la sangre para la medición del estado antioxidante y del perfil lipídico. Los resultados mostraron que la administración de CdCl₂ (G1 grupo) causó un caso de dislipidemia ilustrado por un aumento significativo en la concentración de colesterol del lipoproteína de baja densidad (LDL-C) y de muy baja densidad (VLDL-C), colesterol total (TC), triglicéridos (TAG) y no-HDL-C acompañado con un decremento significativo en el colesterol de la lipoproteína de alta densidad (HDL-C). Los resultados también revelaron un aumento significativo en los índices lipídicos incluyendo, índice de riesgo coronario (CRI), e índice de riesgo cardiovascular (CVRI) en ratas expuestas a CdCl₂. Mientras que se observó una elevación significativa en el malondialdehído (MDA) y una reducción en la concentración de GSH en el mismo grupo comparado con el ácido gallico y el grupo control, indicando un caso de estrés oxidativo. Los resultados actuales también registraron que la inyección intraperitoneal de GA contra CdCl₂ causó amelioración de todos los parámetros estimados previamente.

Palabras clave: GSH, MDA, Dismetilipemia, Lipoproteínas, Estrés oxidativo.

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**効果ギャリック酸による脂質パターンと抗酸化状態の変動についての研究**

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K. Khadim Khudair  
B. Najim Al-Okaily

**要約**

この研究の目的は、ギャリック酸（GA）がカドミウム塩化物（CdCl₂）による抗酸化状態と脂質パターンを改善する作用について検討することでした。28匹の成年雄ラットを4つの等しい群に分け、実験が行われました。コントロール群（G1）、水のみを給与。G2群にCdCl₂を100ppm添加し、G3群にG2群に加えてGAを50ppm添加。G4群にG2群に加えてCdCl₂を100ppm添加しました。実験終了時、空腹時血漿サンプルを採血、抗酸化状態と脂質パターンを測定しました。結果、CdCl₂摂取（G1群）により高コレステロール血症（Dyslipidemia）が観察され、LDL-C、VLDL-C、TC、TAG、および非HDL-Cの濃度に有意な増加が認められました。一方、HDL-Cの濃度に有意な有意な低下が観察されました。また、MDAの濃度が上昇し、GSHの濃度が低下しました。これらの結果は、GAの併用がCdCl₂摂取による酸化ストレスの抑制に寄与することを示唆しています。この研究の結果は、GAの投与がCdCl₂摂取による脂質パターンの変動を改善する可能性を示しています。
INTRODUCTION
Cadmium (Cd) is regarded as environmental heavy toxic metals and a common industrial pollutant (28). Excessive release of Cd to the environment have increase the risk of human exposure via inhalation and ingestion, attributed to its presence in air, food as well as tobacco leaves (38). Hepatic and renal dysfunction were observe after prolong exposure to Cd (10,13). Besides, vascular damage (18), testicular toxicity (27) anemia, osteoporosis, and bone fractures (11) were also reported. Toxicity of Cd has been associated with oxidative stress via it high affinity to thiol group specially of GSH which result in alteration in intracellular redox status, releasing of lipid peroxides (LPO) products such as MDA and hydroperoxides that stimulating deleterious effect on essential biochemical processes (3). Gallic acid (GA) is a natural phenolic acid percent in different plant including; grapes, pomegranate and green tea (22). GA and its derivatives possess numerous uses in the food, cosmetic, printing, pharmaceutical and dyeing industries (29). It has been documented that consumption of foods rich in GA, induced hypoglycemia and attenuate the health hazard effects in obese individuals (36). GA has been implicated as antioxidant (34), antibacterial (21) and antitumor (23) agents. In addition to its protection against myocardial infarction (19). Besides, protective role of GA on testicular damage (1) and DNA fragmentation against cyclophosphamid was recorded in mice (25).

MATERIALS AND METHODS
A total of 28 adult Wistar male rats were randomly divided into four equal groups and were treated daily for 30 days as follows: Group C: Rats of this group were allowed to ad libitum supply of drinking water (control group), Group G1: Rats of this group were allowed to ad libitum supply of drinking water containing 100 ppm of CdCl2; animals in proceeding groups were given in addition to CdCl2 in drinking water, intraperitoneal (i/p) injection of 100 mg/kg/day/ of GA (G2group), while the combination of both GA and CdCl2 were given to animal in group (G3), in the same previous mentioned doses and method of administration. Fasting blood (for 8-12 hrs.) samples were collected (by cardiac puncture technique) at the end experiment, centrifuged at 2500rpm for 15 minutes, and then serum samples were liquefied and frozen at -20 °C until analysis. Serum lipid profile including: TAG, TC, HDL-C were measured using enzymatic kits (Linear chemicals, Barcelona /Spain); LDL-C, VLDL-C and non-HDL-C concentrations according to Friedewald et al., (12). Atherogenic index (AI), coronary risk index (CRI) and cardiovascular risk index (CVRI) were measured according to Abbott et al., and Alladi et al., (2,6). Serum GSH and MDA concentrations were measured using ELISA kits (My BioSource, USA) according to Burtis and Ashwood (8). Statistical analysis of data was performed on the basis of One-Way Analysis of Variance (ANOVA) using a significant level of (P ≤ 0.01). Specific group differences were determined using least significant differences (LSD) as described by Snedecor and Cochran (37).

RESULTS AND DISCUSSION
The mean values of serum lipid profile concentrations in the control and treated groups at zero and after 30 days of treatment were clarified in Table 1. The result showed that i/p injection of gallic acid (G2) or combination of both (G3) for 30 days caused significant (P ≤ 0.01) decrease in serum TC, TAG, VLDL-C and LDL-C concentration comparing to the values in G1 group that received CdCl2 alone. Furthermore, serum HDL-C concentrations decreased significantly (P ≤ 0.05) in the G1 treated group as compared to the control and other treated groups. Cardiovascular risk index (CVRI) and Atherogenic index (AI) (Table 2), non HDL-C and coronary risk index (CRI) (Table 3) showed a significant elevation (P ≤ 0.01) in CdCl2 group comparing to GA and control groups.
Dyslipidemia and oxidative stress were the major deleterious effects induced by Cd administration in the current study. It has been documented that several enzymes correlate with lipid metabolism has been inhibited by Cd leading to dyslipidemia and atherosclerosis. An elevation in serum hepatic activity hydroxyl methyl glutaryl-CoA reductase (HMG-CoA) was observed after Cd administration, which can alter cholesterol synthesis and lipid metabolisms (5). The results also showed dyslipidemia caused by Cd in the current study was accompanied with reduction in antioxidant status, documented that oxidative stress induced by Cd could be a mechanism for its dyslipidemic effect (35). In the present study restoration of lipid profile by GA indicating its hypolipidemic effect. The inhibitory effect of gallic acid-derivatives rich fruit, pomegranate (Punica granatum) extracts on α-amylase, lipase, α-glycosidase and trypsin enzyme activities (40) has been reported. Another mechanism for hypolipidemic effect of GA could be due to its inhibitory effect on the rate limiting enzymes (HMG-CoA reductase) in cholesterol synthesis (4), in addition to its hypoglycemic effect (33), that lead to decrease in TAG formation (16). Lipid indices evaluation (AI, CRI and CVRI) is used to document the role of lipid profile as risk factor for cardiac vascular diseases (15,39). Their elevation by CdCl₂ indicating its cardiotoxic effects. While, reduction in these indices by GA indicating its effect.

Table 1. Effect of gallic acid on serum lipid profile concentrations in normal and cadmium chloride treated rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>VLDL-C</th>
<th>Total Cholesterol</th>
<th>Triglyceride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>59.93 ±0.67 b</td>
<td>42.06 ±0.65 b</td>
<td>19.04 ±0.17 b</td>
<td>121.03 ±0.35 b</td>
<td>95.21 ±0.87 b</td>
</tr>
<tr>
<td>G1: CdCl₂</td>
<td>86.78 ±0.78 a</td>
<td>29.87 ±0.26 d</td>
<td>25.74 ±0.32 a</td>
<td>142.40 ±0.73 a</td>
<td>128.72 ±1.60 a</td>
</tr>
<tr>
<td>G2: Gallic acid</td>
<td>31.67 ±0.82 c</td>
<td>54.41 ±0.53 a</td>
<td>14.47 ±0.19 d</td>
<td>100.56 ±0.51 d</td>
<td>72.39 ±0.98 d</td>
</tr>
<tr>
<td>G3: CdCl₂ + Gallic acid</td>
<td>59.89 ±1.60 b</td>
<td>36.07 ±0.44 c</td>
<td>18.06 ±0.16 c</td>
<td>114.02 ±1.42 c</td>
<td>90.30 ±0.84 c</td>
</tr>
<tr>
<td>LSD value</td>
<td>3.0349 **</td>
<td>1.455 **</td>
<td>0.655 **</td>
<td>2.503 **</td>
<td>3.275 **</td>
</tr>
</tbody>
</table>

Means having with the different letters in same column differed significantly ** (P≤0.01).

Values are expressed as mean ± SE. n= 7 / each groups. C: Control group rats were given normal water, G1: received 100ppm of CdCl₂ in drinking tap water, G2: Rats were injection intraperitoneally (i/p) of 100 mg/kg/day/ of GA, G3: rats were given combination of GA and CdCl₂ for 30 day.

Table 2. Effect of gallic acid on coronary vascular risk index (CVRI) and Atherogenic index in normal and cadmium chloride treated rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SE (ratio)</th>
<th>Coronary vascular risk index (CVRI)</th>
<th>Atherogenic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.26 ±0.03 c</td>
<td>1.420 ±0.04 c</td>
<td></td>
</tr>
<tr>
<td>G1: CdCl₂</td>
<td>4.31 ±0.08 a</td>
<td>2.90 ±0.05 a</td>
<td></td>
</tr>
<tr>
<td>G2: Gallic acid</td>
<td>1.33 ±0.02 d</td>
<td>0.578 ±0.02 d</td>
<td></td>
</tr>
<tr>
<td>G3: CdCl₂ + Gallic acid</td>
<td>2.50 ±0.04 b</td>
<td>1.66 ±0.06 b</td>
<td></td>
</tr>
<tr>
<td>LSD value</td>
<td>0.156 **</td>
<td>0.129 **</td>
<td></td>
</tr>
</tbody>
</table>

Means having with the different letters in same column differed significantly ** (P≤0.01).

Values are expressed as mean ± SE. n= 7 / each groups. C: Control group rats were given normal water, G1: received 100ppm of CdCl₂ in drinking tap water, G2: Rats were injection intraperitoneally (i/p) of 100 mg/kg/day/ of GA, G3: rats were given combination of GA and CdCl₂ for 30 day.

Table 3. Effect of gallic acid on non HDL-C and CRI in normal and cadmium chloride treated rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>non HDL-C (mg/dl)</td>
<td>CRI (ratio)</td>
</tr>
<tr>
<td>Control</td>
<td>78.97 ±0.64 b</td>
</tr>
<tr>
<td>G1: CdCl₂</td>
<td>112.52 ±0.95 a</td>
</tr>
<tr>
<td>G2: Gallic acid</td>
<td>47.49 ±1.81 c</td>
</tr>
<tr>
<td>G3: CdCl₂ + Gallic acid</td>
<td>77.95 ±1.72 b</td>
</tr>
<tr>
<td>LSD value</td>
<td>4.017 **</td>
</tr>
</tbody>
</table>

Means having with the different letters in same column differed significantly ** (P≤0.01).

Values are expressed as mean ± SE. n= 7 / each groups. C: Control group rats were given normal water, G1: received 100ppm of CdCl₂ in drinking tap water, G2: Rats were injection intraperitoneally (i/p) of 100 mg/kg/day/ of GA, G3: rats were given combination of GA and CdCl₂ for 30 day.
beneficial supplement in improving lipid profile and cardiovascular risk. The result in Table 4 showed significant (P ≤ 0.01) elevation in serum GSH concentration and decrease in serum MDA in G2 and G3 group comparing to G1 treated group at the end of the experiment.

Table 4. Effect of gallic acid on serum glutathione (GSH) and malondialdehyde (MDA) concentrations in normal and cadmium chloride treated rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SE (umol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25.05 ±0.35 b</td>
</tr>
<tr>
<td>G1: CdCl₂</td>
<td>18.20 ±0.27 c</td>
</tr>
<tr>
<td>G2: Gallic acid</td>
<td>35.89 ±0.76 a</td>
</tr>
<tr>
<td>G3: CdCl₂ + Gallic acid</td>
<td>24.87 ±0.37 b</td>
</tr>
<tr>
<td>LSD value</td>
<td>1.406 **</td>
</tr>
<tr>
<td>p value</td>
<td>0.721 **</td>
</tr>
</tbody>
</table>

Values are expresses as mean ± SE. n= 7 / each groups. C: Control group rats were given tap water, G1: received 100ppm of CdCl₂ in drinking tap water, G2: Rats were injection intraperitoneally (i/p) of 100 mg/kg/day/ of GA, G3: rats were given combination of GA and CdCl₂ for 30 day. The results of current study also indicated elevation in serum MDA and depletion in GSH concentration in CdCl₂ treated group which documented that oxidative stress is possible mechanism for Cd toxicity (7,26). Cadmium being a Fenton metal (24), decrease the activity of antioxidant enzyme, bind to thiol groups of GSH, caused its depletion (9,30), this further weakened the body antioxidant defense system causing over production of reactive oxygen species, with subsequent enhancing of LPO followed by elevation in MDA level (32) as documented in this study. Besides, inhibiting pancreatic lipase activity, improving glucose uptake, and adipogenesis blocking by GA (17) could be a mechanism. Our findings showed that GA administration caused a rise in GSH and decrease in MDA levels indicating its antioxidant activity (31). It has characteristics of the strong free radical scavenging and antioxidant activities, boosting the concentrations of non-enzymatic antioxidant system, such as GSH and it can protect different organs and tissues from injury and damages induced by oxidative stress (14,20). In conclusion, the present study the beneficial role of GA as antioxidant and hypolipidemic effect against Cd exposure in rats.

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