Baicalin ameliorates cadmium-induced hepatic and renal oxidative damage in rats

Jicang Wang*, Huali Zhu¹, Cai Zhang¹, Hongwei Wang¹ and Zijun Yang¹

College of Animal Science and Technology, Henan University of Science and Technology, No. 263, Kaiyuan Avenue, 471023, Luoyang, PR China.

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ABSTRACT

Cadmium (Cd)-induced oxidative damage of liver and kidney and the ameliorative impact of baicalein against hepatotoxicity and nephrotoxicity of rats was studied. Male SD rats were handled with either intraperitoneal cadmium (CdCl₂, 2mg/kg) and/or oral baicalein (100 mg/kg) for 4 weeks. The results demonstrated that Cd increased the level of GPT, GOT, BUN in serum and the contents of MDA, GSH, decreased the activities of SOD, CAT, GSH-Px in tissues versus control. Conversely, administration of baicalein restored the changes in these parameters to nearly normal levels. The results suggested that the ameliorative impact of baicalein might be because of its antioxidant properties in combating free radical-induced oxidative stress resulting from cadmium chloride.

Key words: Baicalein, Cadmium, kidney, Liver, Oxidative stress.

INTRODUCTION

With the advancement of industry and agriculture, the convergence of overwhelming metals expanded in the earth in late years (Wang et al., 2017). They were found in each range of advanced consumerism and heedful or accidental permit, increased the exposure (Dhanalakshmi and Gawdaman, 2013). Cadmium (Cd) is an important heavy metal, which is discharged into nature by the mining and smelting operations of cadmium, lead, zinc and copper, the use of phosphate fertilizer, and sewage sludge, burning of metropolitan waste (Edwards et al., 2013). People are exposed to Cd from water, rice, potato, tobacco, soil, sleek seeds, root and leaf of vegetables which were polluted by Cd (Nisha et al., 2015). Furthermore, cadmium accumulates in the biological system because of its long end half-life of 10–30 years. Drawn out presentation to Cd brings to damage to the liver, lungs, kidney and testes (Prabu et al., 2012).

Cadmium possesses cytotoxic, carcinogenic, and mutagenic properties (Du et al., 2015). It causes hepatotoxicity and nephrotoxicity by acute administration (Ezedom and Asagba, 2016). Kidneys are accepted to be the most target organ of Cd toxicity. The mammalian kidney’s proximal tubule cells are the significant targets cells of Cd (Veljkovic et al., 2012). After ingestion, Cd and metallothionein (MT) incorporated Cd-MT complex in the liver, released into the circulation, and taken up by renal tubule cells and initiated nephrotoxicity. Cadmium hindered liver metabolic catalyst frameworks containing sulfhydryl groups and uncoupling of oxidative phosphorylation in the mitochondria. This induces in expanded lipid peroxidation, exhaustion of sulfhydryls, DNA damage, oxidative stress, necrosis, apoptosis, and inflammatory infiltration (Liu et al., 2016). Cadmium is not a redox-dynamic metal and subsequently is not ready to take part directly in Fenton’s reaction and make reactive oxygen species (ROS, mainly O₂⁻, H₂O₂ and ·OH), however it can initiate the generation of ROS through indirect mechanisms. ROS cause lipid peroxidation, membrane protein, DNA harm, apoptosis and calcium homeostasis imbalance (Wang et al., 2014).

Antioxidants restrain lipid peroxidation and other free radicals mediated process as radical scavengers. Numerous substances go about as antioxidants that are scavenging radicals for example flavonoids. Natural plants are broadly devoured by people regularly, these common items have numerous pharmacological and biological properties (Zhang et al., 2016). Baicalein is a flavonoid and its molecular formula is C₁₅H₁₀O₅ and molecular mass is 270.24. Baicalein was separated from the Chinese traditional medicine herb S. baicalensis Georgi. It has been accounted for to show a ability to inhibit inflammatory mediators’ production, such as IL-6, TNF-α, and MCP-1 both in vitro and in vivo (Li et al., 2015). Furthermore, baicalein is the primary part with bioactivity of S. baicalensis and has good antioxidant activities (Li et al., 2009). The aim of this work was to investigate the conceivable ameliorative impact of baicalein on cadmium induced toxicity on SD (Sprague Dawley) rats.

*Corresponding author’s e-mail: wangjicang@126.com
¹College of Animal Science and Technology, Henan University of Science and Technology, No. 263, Kaiyuan Avenue, 471023, Luoyang, PR China.
²Law Hospital, Henan University of Science and Technology, No.263, Kaiyuan Avenue, 471023, Luoyang, PR China.
Results and Discussion

Body weight, relative organ-body weight: The effect of Cd and baicalein on body weight and organ-body weight ratio (%) was presented (Table 1). In Cd-treated rats, body weight gain significantly (P<0.01) decreased when compared with control rats. There are no significant changes between control and baicalein administered rats. Interestingly, baicalein (100 mg/kg) with Cd significantly attenuated the loss of body weight after 4 weeks (P<0.05). In Cd alone treated group of rats, the liver (or kidney)-body weight ratio was increased significantly (P<0.05) when compared with the control rats. Baicalein (100 mg/kg/day) alongside Cd can decrease the relative weight of liver and kidney. But there have no significant difference between baicalein and Cd group (P>0.05). The body weight of the experimental rats decreased significantly during the 4 weeks of treatment with Cd compared to control rats. This observed change is consistent with previously published reports (Josthna et al., 2012). Reduced growth rate is one of the side effects of Cd toxicity in rats (Choi and Rhee, 2001). Weight gain depends on the availability and assimilation of supplements. Cadmium decreased nutrient assimilation and retention through its immediate impact on the intestinal mucosal cells. Additionally, exposure to low levels of heavy metals may do harm to the glucocorticoid system (Akomo1afe et al., 2016). The glucocorticoid hormones assume an indispensable part in glucose regulation except carbohydrate, lipid, and protein metabolism. Weight reduction and weight gain have relationship with the disorder of glucocorticoid system. Consequently, the observed decrease in body weight of Cd treated rats may have come about because of an increase in the degeneration of lipids and proteins subsequently of Cd toxicity or a disabled glucocorticoid system (Erdogan et al., 2005).

Effects on serum hepatic and renal marker enzymes and BUN: The levels of GPT and GOT in serum of the control and other groups were presented in Fig. 1A-B. Compared with control group, a significant (P<0.01) increase in the levels of GPT and GOT in Cd treated rats was observed. The administration of baicalein significantly (P<0.05 or P<0.01) lessened Cd-induced hepatotoxicity and nephrotoxicity as shown by diminished GPT and GOT levels, in this way offering protection against Cd toxicity in rats. Liver damage due to Cd exposure can be explained by the elevation levels of serum hepatic marker enzymes. These elevated enzymes

### Table 1: Effects of exposure of male SD rats to Cd and/or baicalein on body weight, organ-body weight ratio.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Cd</th>
<th>Baicalein</th>
<th>Cd+Baicalein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial (g)</td>
<td>176.92±7.61</td>
<td>172.40±4.55</td>
<td>178.73±5.36</td>
<td>176.72±6.04</td>
</tr>
<tr>
<td>Final (g)</td>
<td>274.37±4.97</td>
<td>232.50±9.65**</td>
<td>278.30±8.09</td>
<td>240.08±5.51*</td>
</tr>
<tr>
<td>liver-body weight ratio (%)</td>
<td>3.12±0.13</td>
<td>3.67±0.19*</td>
<td>3.20±0.09</td>
<td>3.55±0.41</td>
</tr>
<tr>
<td>kidney-body weight ratio (%)</td>
<td>0.82±0.03</td>
<td>0.98±0.05*</td>
<td>0.80±0.04</td>
<td>0.95±0.02</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01 compared with control group (non-Cd exposed group); *P<0.05, ***P<0.01 compared with Cd exposed group.
indicate that cell overflow and destruction of liver membrane structure and thereby function get affected. In the present study, the increased levels of GPT and GOT were discharged into the blood from the membrane of hepatocytes because of the damage to the liver that was induced by chronic exposure to Cd. Significant restoration of GPT and GOT levels were observed in the rats concurrently treated with baicalein offering protection against Cd toxicity. This defensive impact of baicalein might be because of its action by restraining the Cd induced generation of ROS and keep up the structural integrity of the membrane.

Kidney damage due to Cd intoxication could be evaluated by measuring the serum markers of renal functional integrity, which are the biochemical signs of renal tissue damage. BUN is utilized for evaluating renal glomerular function filtration and its concentrations in the serum depend generally on glomerular function. In this study, the serum BUN level in Cd-treated group was higher (P<0.01) than the control rats (Fig 1-C). Significant restoration of BUN was observed in the rats concurrently treated with baicalein offering protection against Cd toxicity in rats (P<0.05). This finding shows that the administration of Cd modified the glomeruli and tubular capacity. A comparable finding was made by Gaurav et al. (2011), who reported that BUN levels were expanded in the serum of Cd-intoxicated rats. However, this finding is not in concurrence with Horiguchi et al. (1996), who observed that administration of Cd in rats did not modify the BUN level. The absence of consistency is likely owing to the course of introduction and dose utilized in their study.

**Effects on oxidative stress markers:** The levels of MDA in the liver and kidney are represented in Table 2. MDA significantly (P<0.05 or P<0.01) increased in liver and kidney of Cd treated rats when compared with control group. However, baicalein treatment significantly decreased Cd induced rise of MDA level (P<0.05 or P<0.01) in both the organs. The mechanism of Cd-induced damage is thought to be identified with increased oxidative stress. It appears that Cd is associated with mitochondrial structures and induced oxygen-free radicals generation increased (Tang and Shaikh, 2001). Researches have demonstrated that Cd presentation is connected with oxidative stress by creating
ROS and lipid peroxidation (Xu et al., 2010). In this study we observed that MDA was markedly increased in rats exposed to Cd, thus proposing an increased oxidative stress. Comparable information had already been reported (Akomolafe et al., 2016). Increased MDA level due to Cd exposure could be because of excessive free radicals formatted which do harm to biological macromolecules (Stoeh et al., 2001). In the present study, Cd intoxicated rats pretreated with baicalein demonstrated a marked decrease in the levels of MDA. This might be because of baicalein is excellent scavengers of free radicals thereby hindering lipid peroxidation and protein carbonylation.

**Effects on non-enzymatic antioxidants:** Alterations in the content of non-enzymatic antioxidant GSH in the liver and kidney are shown (Table 2). A significant increase (P<0.01) in the content of GSH was observed in liver and kidney of Cd intoxicated rats when compared with control rats. Upon pre-administration with baicalein along with Cd for 4 weeks, the levels of the GSH in kidney was significantly (P<0.05) restored to close ordinary content when compared with Cd treated rats. GSH is as a strong endogenous antioxidant (Murugavel and Pari, 2007). It is a tripeptide and a cysteine rich protein that participates in the maintenance of cytoplasmic and membrane thiol status. It is an antioxidant and a powerful nucleophile, critical for cellular protection such as detoxification of ROS. In the current study, Cd increases the contents of GSH in liver and kidney. It could be because of increased use of GSH by the cells act as scavengers of free radicals induced by Cd. Expanded use of GSH for the action of GSH-Px shaping oxidized GSH (GSSG) because of increased generation of ROS. The increase of GSH could be explained by its incitement to neutralize the increased oxygen free radicals production. On the contrary, Akomolafe et al. (2016) watched that Cd prompted GSH level diminished. This may be due to relationship with the given dose and time exposure.

**Effects on enzymatic antioxidants:** The activities of enzymatic antioxidants SOD, CAT, GSH-Px are shown in Table 3. A significant (P<0.05 or P<0.01) decrease in the activities of SOD, CAT, GSH-Px in Cd intoxicated rats was observed. Oral administration of baicalein significantly (P<0.05) restored the activities of these antioxidant enzymes to their close ordinary levels. SOD, CAT and GSH-Px constitute antioxidant defense against ROS. SOD is a metal enzyme that catalyzes the dismutation of superoxide radicals. CAT is a heme protein that catalyses the decrease of H₂O₂ to H₂O and O₂, therefore protects cells from the oxidative damage of H₂O₂ and OH⁻ (Shahat et al., 2017). GSH-Px is a seleno enzyme. It assumes a noteworthy part in the diminishment of hydrogen peroxide and hydroperoxides. In our investigation Cd intoxicated rats demonstrated a critical diminishing in the activities of SOD, CAT and GSH-Px in tissues. It may be because of that Cd leads to the over generation of ROS. It will consume too much SOD, CAT and GSH-Px when cleaning ROS (Amin et al., 2006). Concurrently treated with baicalein in Cd intoxicated rats demonstrate a noteworthy recuperation of hepatic enzymatic antioxidant systems. This may be on account of baicalein have metal chelating property, besides their high antioxidant activity.

**CONCLUSION**

In conclusion, our results showed Cd is able to cause marked oxidative stress in addition to deplete the antioxidants and inhibit the activities of antioxidant enzymes. Baicalein could significantly reduce the Cd induced hepatotoxicity and nephrotoxicity. The result shows baicalein has therapeutic potential to be used as a cost effective safe herbal antioxidative agent in the treatment of Cd toxicity.

**REFERENCES**


