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Nephroprotective Effect of D-Ribose-L-Cysteine (DRLC) On Renal Oxidative Stress and Proinflammatory Markers in Lead Acetate-Treated Mice

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ABSTRACT

Lead exposure is known to cause damage to several body organs, including the kidney. In this study, the protective effect of D-Ribose-L-Cysteine (DRLC) on renal oxidative stress and proinflammatory markers in lead acetate-treated mice was investigated. Thirty-six (36) male Swiss albino mice were equally grouped into; 1 (Normal control); 2 (Negative control administered 100mg/kg of lead acetate only); 3 (Mice co-administered 100mg/kg of lead acetate and 50mg/kg of DLRC daily); 4 (Mice co-administered 100mg/kg of lead acetate and 100mg/kg of DRLC daily). The mice were treated, and sacrificed after 21 days. The kidney was excised and used to prepare homogenates for biochemical assay of glutathione (GSH), Catalase, Malondialdehyde (MDA), Myeloperoxidase (MPO) and Total protein. Results obtained revealed that the level of the oxidative stress marker, MDA, was significantly ($p<0.05$) elevated in the negative control group. However, coadministration of lead with DRLC led to significantly ($p<0.05$) reduced MDA levels when compared to the negative control group. The antioxidants (GSH levels and Catalase activity) were significantly ($p<0.05$) reduced following lead exposure, but coadministration with DRLC significantly ($p<0.05$) improved antioxidant defense in the kidneys of the mice. Also, exposure to lead increased inflammation in the mice as evidenced by significantly ($p<0.05$) increased MPO activity and Total protein levels, but coadministration with DRLC significantly ($p<0.05$) decreased MPO and total protein in comparison to the negative control group. This study suggests that DRLC possesses significant nephroprotective potential in lead-exposed mice by mitigating the inflammation and oxidative stress induced by lead.

Keywords: *Antioxidants, D-Ribose-L-Cysteine, Inflammation, Kidneys, Lead toxicity, Oxidative stress.*

1.0 INTRODUCTION

Lead (Pb) is a common natural element found in the environment. It is one of the environment's most prevalent and persistent pollutants [1]. Lead is used to produce many industrial products, such as paints, printing, gasoline, batteries, water pipes, ceramic glazing, cosmetics, brass faucets, tank linings and toys [2]. Exposure to lead from several sources, including air, water, and food, can have negative effects on all biological systems due to its harmful cumulative effect on the environment. Lead can move up the food chain and harm humans and other living things. According to Duruibe and researchers [3], it is one of the most hazardous metals found in the environment and negatively affects most of the human body's organs. Numerous physiological, morphological, and biochemical changes are linked to lead toxicity, including abnormal glucose metabolism [4, 5], haematological disorders [6], liver dysfunction [7], impaired renal system functions [8], and nervous system disturbances [9]. The kidneys are essential organs that control fluid and electrolyte levels, remove waste, and preserve general physiological balance. Unfortunately, lead exposure severely damages this vital organ, leading to decreased renal function and the development of crippling kidney disorders [10]. Oxidative stress and inflammation, two known major contributors to the illness, lie at the heart of the process of lead-induced

nephrotoxicity. Oxidative stress results from a delicate balance between the production of reactive oxygen species (ROS) and the body's capacity to combat them with antioxidant defences [11]. This balance is upset by lead exposure, which causes a rise in ROS generation and significant cellular damage to the vulnerable renal tissue. In addition to directly harming the renal tissues, this elevated oxidative stress triggers a series of inflammatory reactions [12]. A key factor in the development of lead-induced kidney damage is the kidneys' inflammatory processes, which are marked by immune cell activation and the release of proinflammatory mediators. Interestingly, proinflammatory indicators including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) aid in the recruitment of immune cells and the exacerbation of the inflammatory response in the renal tissue [13]. Renal injury is made worse by the ongoing inflammatory cascade, which ultimately results in a crippling reduction in kidney function. Recognizing the serious health consequences of lead-induced nephrotoxicity, there is an urgent need to investigate potential interventions capable of mitigating the adverse effects of lead exposure on renal health. D-ribose L-cysteine (DRLC) is a compound with remarkable antioxidant and anti-inflammatory properties. D-Ribose, which is a naturally occurring carbohydrate, serves as an important structural component of macromolecules like RNA and DNA [14]. L-cysteine is a precursor of glutathione that is essential for detoxifying cellular oxidant molecules [14]. This study was designed to carefully assess the efficacy of D-ribose L-cysteine (DRLC) in alleviating oxidative stress and inflammation caused by lead exposure in the kidneys. Hence, we determined the levels of malondialdehyde (a marker for oxidative stress), activity of catalase and levels of reduced glutathione (antioxidants), total protein and myeloperoxidase (a pro-inflammatory marker) in the kidneys of lead-treated mice.

2.0 MATERIALS AND METHODS

2.1 Chemicals and Reagents

All the chemicals and reagents used for this study were of analytical grade.

2.2 Experimental animals

Thirty-six (36) male Swiss albino mice with an average weight of 24.0 ± 2.0 g were used for this study. The mice were procured from the Central Animal House situated within the Faculty of Basic Medical Sciences at Delta State University, Abraka. The animals were kept in plastic cages under controlled condition of 12 hrs light / 12 hrs dark cycle and allowed access to standard rat feed and water *ad libitum*. The maintenance of the animals was following approved guidelines by the Animal Ethics Committee, Delta State University, Abraka, Nigeria.

2.3 Preparation of D-ribose L-cysteine

The required amounts of D-ribose L-cysteine (DRLC) for this study were weighed using a sensitive electrical weighing balance. Then, the weighed DRLC were dissolved in 100 mL of distilled water prior to administration. The dose (mg/kg) was converted to volume for easy administration as follows using equation 1:

$$\boldsymbol{Volume(ml)} = \frac{Dose\left(\frac{mg}{kg}\right) X\ Body\ weight\left(\frac{mg}{kg}\right)}{Concentration\left(\frac{mg}{mL}\right)} \quad \textbf{(1)}$$

2.4 Experimental design

The mice were caged into four groups with nine (9) mice in each group. The mice were grouped as follows:
Group 1: Normal control (Given only standard feed and water).
Group 2: Negative control (administered 100mg/kg of lead acetate only).
Group 3: Experimental 1 (administered 100mg/kg of lead acetate and 50mg/kg of DLRC daily)
Group 4: Experimental 2 (administered 100mg/kg of lead acetate and 100mg/kg of DRLC daily).
The lead acetate was administered to the mice via the intraperitoneal route, while the D-ribose L-cysteine was administered as a single dose via the oral route according to the body weights of the experimental mice for twenty- one days.

2.5 Sample collection

After the last day of administration, the experimental mice were sacrificed by cervical decapitation following an overnight fast. Laparotomy was conducted on the mice to gain access to the kidney. Kidneys were excised and a uniform portion of 0.5 g was weighed and homogenized in 4.5 mL of buffer. The homogenate was then centrifuged and supernatant collected for the biochemical assessment of glutathione (GSH), malondialdehyde (MDA) levels, Myeloperoxidase (MPO), Catalase and Total protein.

2.6 Biochemical Analysis

The biochemical investigations were carried out using standard procedures. Assessment of GSH was determined using Ellman's method [15]. MDA levels was determined according to the method described by Niehaus and Samuelsson [16]. MPO activity was determined according to the method of Desser *et al*. [17]. Catalase activity was determined by the method of Kaplan *et al.* [18]. The method of Tietz [19] was used for the assay of total protein.

2.7 Statistical Analysis

The results obtained were expressed as Mean ± SD for n = 9 mice/group. The data were evaluated using one-way analysis of variance (ANOVA), and post-hoc analysis using the Least Significant Difference (LSD) test. Results were considered statistically significant at $p < 0.05$. SPSS statistical package version 23 was used for data analysis.

3.0 RESULTS AND DISCUSSION

Lead exposure remains a serious public health concern, as it is associated with negative effects on several body organs and systems. The kidneys are

particularly vulnerable to lead toxicity due to their involvement in filtration and excretion of chemicals. In this present study, exposure of experimental animals to lead caused significant alterations in proinflammatory and oxidative stress markers. However, coadministration of lead acetate with DRLC led to significant dose-dependent amelioration of lead-induced kidney toxicity in experimental mice (Table 1).

Table 1: Results of the effect of DRLC on renal oxidative stress and proinflammatory markers in lead acetate treated mice

Group	MPO(U/mg)	GSH (U/mg)	MDA (U/mg)	Catalase Activity (U/L)	Total Protein (g/dL)
1	10.41±2.34[a]	41.94±0.09[a]	0.78±0.22[a]	59.51±7.28[a]	10.62±0.75[a]
2	16.52±1.73[b]	22.04±0.12[b]	2.25±1.07[b]	38.10±2.40[b]	16.19±0.38[b]
3	12.43±0.52[c]	32.27±0.09[c]	1.11±0.10[c]	51.75±5.50[c]	13.83±0.85[c]
4	8.76±0.68[d]	33.09±0.11[c]	0.62±0.29[a]	60.23±3.07[a]	12.22±0.79[c]

*Values are expressed as Mean±SEM.
Values not sharing a common superscript differ significantly ($p<0.05$)
Group 1: Normal control (standard feed and water only)
Group 2: Negative control (administered 100 mg/kg of lead acetate only)
Group 3 Experimental 1 (administered 100 mg/kg lead acetate + 50mg/kg of DRLC)
Group 4 Experimental 2 (administered 100 mg/kg lead acetate + 100mg/kg of DRLC)

Malondialdehyde (MDA) levels significantly increased in the lead-induced group compared to the normal control ($p < 0.05$). The elevation of Malondialdehyde (MDA) levels in the lead-exposed group indicated increased lipid peroxidation, a marker of oxidative stress, in the kidney of the experimental mice. The relationship between oxidative stress and organ-induced damage has been reported in previous studies [20, 21, 22]. Co-administration with varying doses of DRLC significantly reduced MDA levels in a dose-dependent manner. The decrease in MDA levels at 100mg/kg of DRLC was comparable to the level for mice in normal control group. The significant increase in malondialdehyde (MDA) levels, a marker of lipid peroxidation and oxidative damage, underlines lead's ability to induce oxidative stress. Lead's pro-oxidant properties may trigger lipid peroxidation, resulting in higher MDA levels [23]. By reducing MDA levels, DRLC could potentially mitigate lipid peroxidation, thereby protecting the kidneys of the animals from oxidative damage.

Reduced glutathione (GSH) activity significantly decreased in the group administered lead acetate only (negative control) when compared to the normal control ($p < 0.05$). The reduction in glutathione (GSH) concentration in response to lead exposure underlines the oxidative stress induced by lead toxicity. Treatment with varying doses of DRLC (50mg/kg and 100mg/kg) alongside lead acetate administration significantly ($p < 0.05$) improved the concentrations of GSH when compared to the negative control. The significant decrease in glutathione (GSH) concentration, a crucial antioxidant defense molecule, suggests an increase in the level of renal oxidative stress in the experimental mice following exposure to lead acetate, thereby depleting the concentration of GSH. The significant increase in GSH concentration following DRLC co-administration indicates the potential of DRLC in restoring antioxidant defenses. DRLC has been known to help cells in the production of glutathione [24, 25] which could explain the improved GSH concentrations in the DRLC co-administered groups.

The activity of catalase, an essential antioxidant enzyme, was significantly ($p < 0.05$) decreased upon lead exposure in comparison to the normal control, further signifies the ability of lead to disrupt the antioxidant defense system in the kidney of the experimental mice. DRLC co-administration, however, significantly ($p < 0.05$) improved catalase activity in a dose-dependent manner when compared to the negative control group. The significant elevation in catalase activity following DRLC co-administration further suggests that DRLC could potentially improve the antioxidant enzyme's activity, which indicates its protective effect.

Myeloperoxidase (MPO) activity in the lead-induced group considerably increased in comparison to the normal control ($p < 0.05$). MPO, which is an enzyme that is increased during inflammation, as well as oxidative stress, is considered a biomarker of inflammation [26, 27]. The significantly increased MPO following lead exposure thereby suggests increased inflammation in the kidney of the mice along with the increased oxidative stress. Co-administration with DRLC however caused dose-dependent significant decrease ($p < 0.05$) in MPO activity in comparison to the negative control group. This therefore suggests that DRLC could help mitigate the lead-induced inflammation to the

kidneys of the experimental animals, thereby protecting the kidneys from toxicity.

Total Protein levels significantly increased in the lead-induced group compared to the normal control ($p < 0.05$). Coadministration of DRLC, however significantly ($p < 0.05$) decreased the level of total protein in a dose-dependent manner when compared to the negative control group. The rapid increase in total protein levels in the lead-induced group indicates the potential kidney damage or altered protein metabolism due to lead exposure. The kidneys play a vital role in protein metabolism, and lead-induced nephrotoxicity may disrupt this process. Also, high levels of total protein have been associated with inflammation [28], and could thus be a marker of inflammation in the experimental animals. The mitigating effect of DRLC on total protein levels could, therefore, further support its anti-inflammatory effect in the kidneys of mice exposed to lead-induced toxicity.

This present study therefore agrees with some previous studies which have reported oxidative stress and inflammation as important mechanisms of nephrotoxicity in experimental animals following exposure to lead [29, 30, 31]. The study contributes to the increasing pool of knowledge on the potent antioxidant and anti-inflammatory activity of DRLC [32, 33, 34]. The results obtained from this present study show that the administration of DRLC could be beneficial in protecting individuals from lead-induced renal injury.

4.0 CONCLUSION

The findings from this study revealed that the administration of DRLC produced a significant protective effect on the kidneys of lead-exposed mice by mitigating inflammation and oxidative stress induced by lead toxicity. These findings provide a solid foundation for further research, fostering a thorough investigation of D-Ribose-L-Cysteine's therapeutic potential and the underlying mechanisms by which DRLC counters the adverse effects of lead exposure on renal function.

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