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Evaluating the Ameliorative Effect of Glycine on Cadmium-Induced Kidney Damage in Adult Wistar Rats

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ABSTRACT: The escalating exposure to heavy metals due to industrialization and anthropogenic activities has led to adverse health effects. Cadmium is one such heavy metal that can accumulate in biological organisms and disrupt cellular functions. Glycine, an amino acid and a neurotransmitter in the brain, has anti-oxidant and anti-inflammatory properties which have been studied by some researchers. Hence the objectives of this paper was to evaluate the ameliorative effects of glycine on cadmium-induced kidney damage in adult Wistar rats using standard technique. There was significant decrease ($P<0.05$) in body weight of rats treated with 10 mg/kg body weight of cadmium when compared to control. No significant change ($P>0.05$) in serum Na^+, K^+ and Cr levels in both Cadmium and Glycine treated groups when compared to control. However, administration of Cadmium showed features of tubular necrosis, interstitial infiltration of inflammatory cells, vascular hypertrophy and interstitial congestion in treated rats which were reversed with treatment with Glycine. Focal tubular necrosis was seen in kidney of rat treated with Cadmium and 1000 mg/kg body weight of Glycine. This study demonstrates that Glycine at a dose of 500 mg/kg body weight has an ameliorative and anti-oxidant effect against Cadmium-induced kidney damage in adult Wistar rats.

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The extensive exposure to heavy metals, facilitated by industrialization and anthropogenic activities, poses significant health risks, affecting both the environment and biological organisms (Bradl, 2005; Briffa *et al*., 2020). The biological activities of metals are linked to their chemical properties and their ability to react with biological systems; this occurs through the loss of one or more electrons to form metal cations with high affinity to the nucleophilic sites of essential macromolecules (Balali-Mood *et al*., 2021). Reports indicate that the resultant effects of metal toxicity include gastrointestinal, kidney and immune dysfunction, skin lesions, birth defects, cancer and nervous system disorders (Balali-Mood *et al*., 2021).

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Cadmium, a group 12 element, shares similarities with zinc and mercury, demonstrating an oxidation state of +2 in most compounds. Discovered in 1817, cadmium's average concentration in the Earth's crust is 0.1 to 0.5 ppm (Morrow, 2010). Glycine, the simplest amino acid, is crucial in protein structure, collagen formation, and serves as an inhibitory neurotransmitter (Taghavinejad, 2008). It functions as a bidentate ligand for metal ions and is involved in various chemical processes (Ingersoll *et al*., 1932; Herbst and Shemin, 1939). Glycine, although non-essential in the human diet, acts as a precursor to proteins, with collagen being a notable exception, containing about 35% glycine (Nelson and Cox, 2005; Szpak, 2011). It

has industrial applications in herbicide production, including glyphosate (Stahl, 2016; Drauz *et al*., 2007). The metabolic capacity for glycine biosynthesis may influence collagen synthesis, as indicated by some publications (Meléndez-Hevia *et al*., 2009). Overall, metal toxicity, cadmium properties, and glycine's multifaceted roles underscore the intricate interactions in biological and chemical systems. As a result, utilizing Sodium ion, Potassium ion and Creatinine levels as indicators as well as histopathological features for cadmium-induced damage in kidney is very essential hence the objective of this paper was to evaluate the ameliorative effect of glycine on cadmium-induced kidney damage in adult Wistar rats.

MATERIALS AND METHODS

Experimental rats: Thirty Wistar rats of weight between 120g and 170g were used. The rats were given a two-week acclimatization period before the administration method begun. They were given free access to conventional rat feed and water. The research ethics committee's guidelines for animal treatment at the University of Benin's College of Medicine were espoused and fully implemented. The experimental protocol is presented as follows:

Group A: Served as control and were fed with Animal feed and water.
Group B: Received 10mg/kg body weight of cadmium for 14 days.
Group C: Received 500mg/kg body weight of glycine for 14 days.
Group D: Received 1000mg/kg body weight of glycine for 14 days.
Group E: Received 10mg/kg body weight of cadmium for 14 days and 500mg/kg body weight of glycine for 14 days
Group F: Received 10mg/kg body weight of cadmium for 14 days and 1000mg/kg body weight of glycine for 14 days

Administration: The glycine and cadmium were given using a garage with an orogastric tube. The rats were carefully handled to minimize oral or oesophageal injuries. All administrations were done by gavage and lasted for fourteen (14) and twenty-eight (28) days respectively.

Tissue collection, processing and staining, histopathology: The rats were sacrificed and the Kidneys were taken at the end of the two weeks and four weeks study. Bloods (5 mL) was collected in sterile bottles for analysis of serum Na^+, K^+ and creatinine levels and were immediately sent to the University of Benin Teaching Hospital's Chemical Pathology department for biochemical analysis. The kidney tissues were preserved for 24 hours in 10% buffered formalin before being histologically processed and stained with Haematoxylin and Eosin using standard procedures (Drury *et al*., 1976). The sections obtained were examined and photomicrographs were taken using a Leica DM750 research microscope with an attached digital camera (Leica CC50). The tissues were photographed digitally at magnifications of x100.

Statistical analysis: Results obtained were expressed as Mean ± SEM (standard error of means). Differences between the means were determined by one-way analysis of variance (ANOVA). Values were considered statistically significant if P value is less than 0.05 ($p < 0.05$). LSD Post Hoc test was used to determine where the significance lay. Statistical package Graph Pad Prism Version 9.0 for Windows (GraphPad Software Inc.) was used to analyze the data obtained in this study.

RESULTS AND DISCUSSION

There was statistically significant decrease ($P<0.05$) in body Weight (g) for rats given 10 mg/kg body weight of cadmium only and a significant increase in body weight for rat given 500 mg/kg body weight of glycine when compared to control. Cadmium, a toxic heavy metal, poses significant health risks to the body. Upon exposure, it can induce oxidative stress within cells, leading to damage of essential molecules (Muthukumar, 2010). Administration of cadmium has been reported in different studies to induce weight loss. In this study, there was significant reduction in body weight in cadmium treated rats (Fig 1).

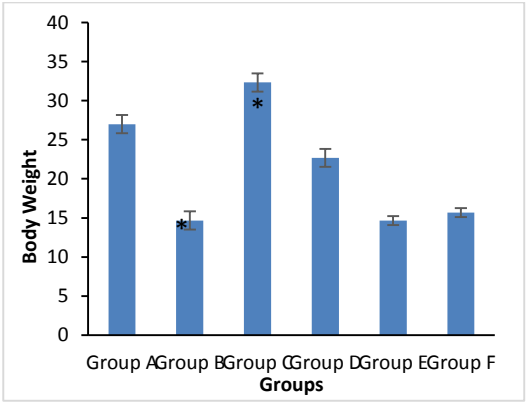

Fig 1: Changes in body weight (g) of rats in control and treated groups

Rencuzogullari and Erdogan, (2007) reported a similar weight loss in cadmium treated rats but this effect was reversed with lycopene administration in their study. Glycine administration in this present study significantly increased the body weight of rats but did

not reverse the weight loss in cadmium treated rats (Fig 1). Although there was no significant change in the serum levels of Na^+, K^+ and Cr of Cadmium treated rats when compared to control in this study (Figs 2, 3 and 4), studies have shown that cadmium preferentially accumulates in the kidneys, with potential adverse effects on kidney function (Lane *et al*., 2000).

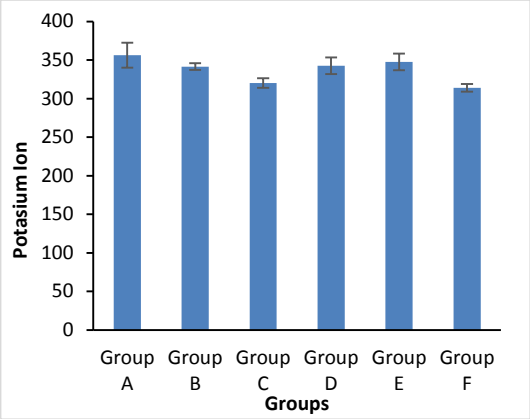

Fig 2: Changes in Potassium ion level of rats in control and treated groups there was no statistically significant change (P>0.05) in the Potassium ion (Mmol/L) levels across the groups.

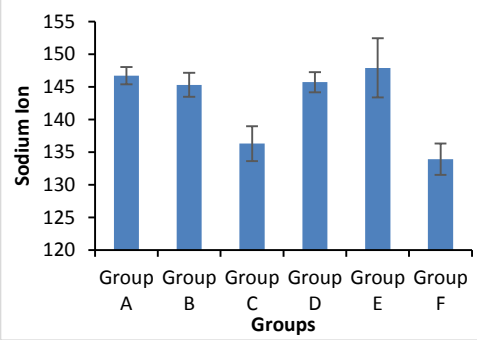

Fig 3: Changes in Sodium ion level of rats in control and treated groups There was no statistically significant change (P>0.05) in the Sodium ion (mg/l) levels across the groups.

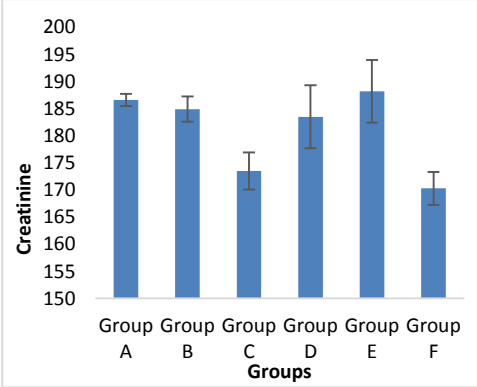

Fig 4. Changes in Creatinine Level of rats in control and treated groups there was no statistically significant change (P>0.05) in Creatinine (mg/dL) level across the groups.

However, long-term exposure to cadmium is linked to increased risk of cancer, heart and kidney diseases, and osteoporosis. (Luevano and Damodaran, 2014; Rahim *et al*., 2013; Tellez-Plaza *et al*., 2010; James and Meliker, 2013).

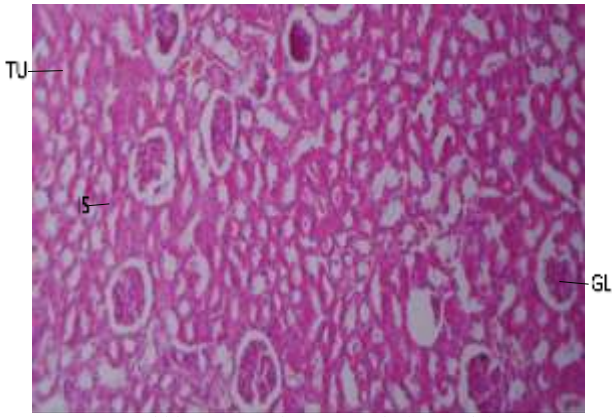

Plate 1. Rat kidney. Control. Composed of normal tissue architecture: Tubules (TU), interstitial space (IS), glomeruli (GL) : H and E x100

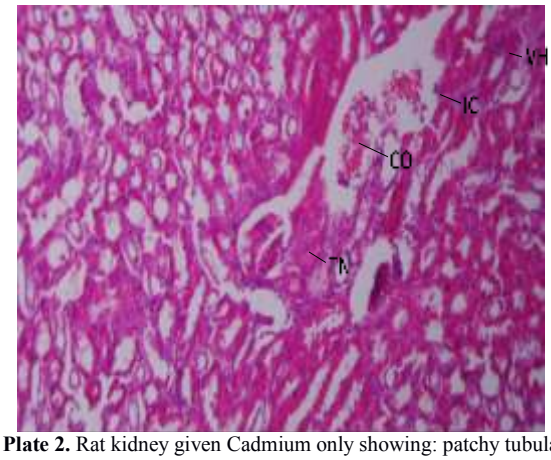

Plate 2. Rat kidney given Cadmium only showing: patchy tubular necrosis (TN), interstitial infiltrates of inflammatory cells (IC), vascular hypertrophy; (VH) interstitial congestion (CO): H and E x100

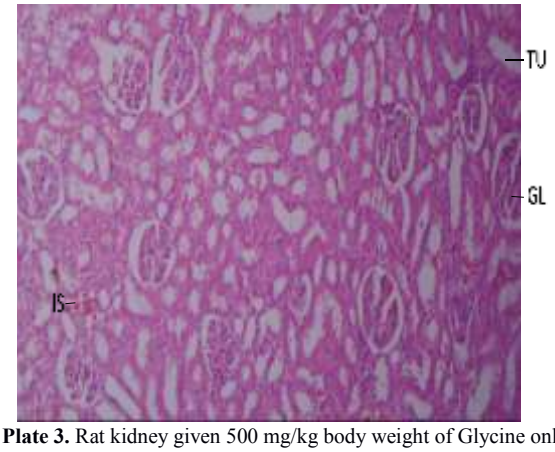

Plate 3. Rat kidney given 500 mg/kg body weight of Glycine only showing normal architecture: tubules (TU), interstitial space (IS), glomeruli (GL): H and E x100

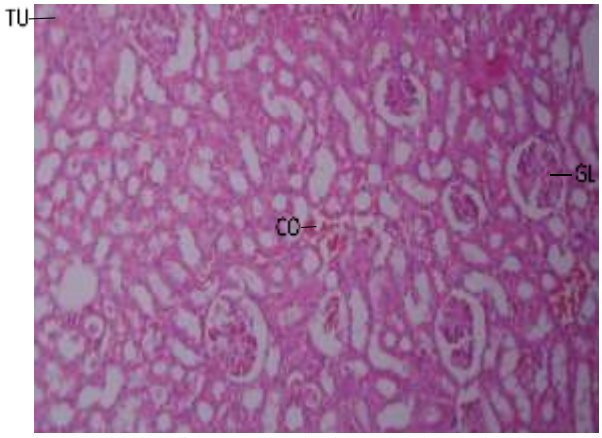

Plate 4. Rat kidney given 1000 mg/kg body weight of Glycine only showing normal architecture: tubules (TU), active interstitial congestion (CO), glomeruli (GL): H and E x100

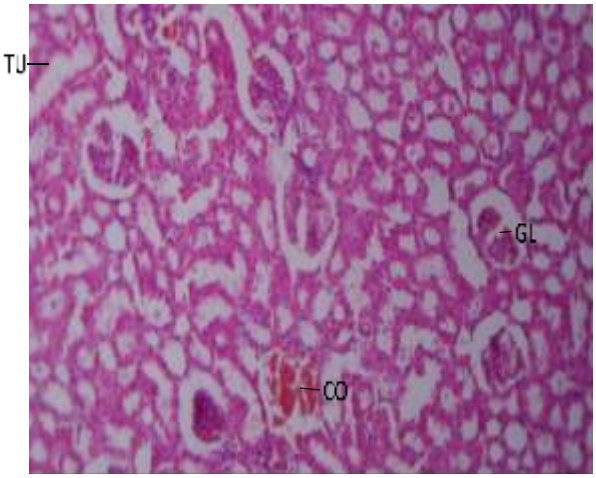

Plate 5. Rat kidney given Cadmium + 500 mg/kg body weight of Glycine showing normal architecture: tubules (TU), glomeruli (GL), active interstitial congestion (CO): H and E x100

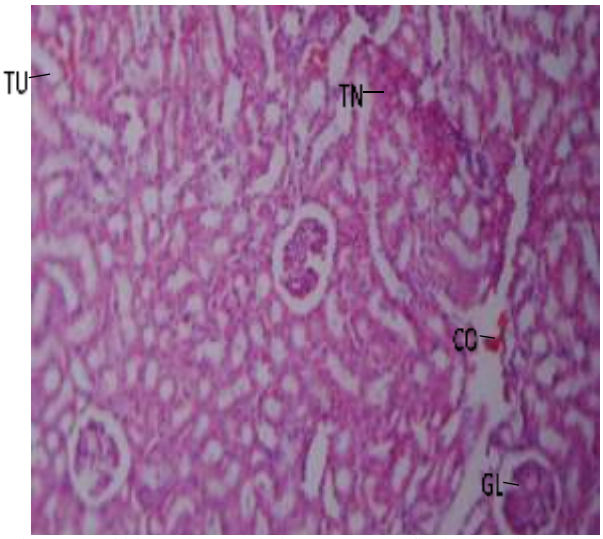

Plate 6. Rat kidney given Cadmium + 1000 mg/kg body weight of Glycine showing: tubules (TU), active interstitial congestion (CO), normal glomeruli (GL), focal tubular necrosis (TN): H and E x100

Even at lower doses of cadmium inhalation during childhood and adolescence, there is significant kidney uptake (Lane *et al*., 2000). Thus, understanding the deleterious effects of cadmium is crucial for implementing measures to mitigate its potential harm to the body. Histological findings in this study showed normal features in the control group that were not treated (Plate 1). Cadmium treated groups showed features of tubular necrosis, interstitial infiltrate of inflammatory cells, vascular hypertrophy and interstitial congestion in rats kidney treated with Cadmium only (Plate 2). These features are consistent with acute kidney injury. Tubular necrosis can lead to acute kidney injury (AKI) and impairment in the kidney's ability to filter and regulate bodily fluids and electrolytes (Watanabe *et al*., 1994). This finding is also consistent with report of Yu *et al*., 1993, who reported a similar findings of vascular hypertrophy in cadmium treated rats. The interstitial infiltrates of inflammatory cells induced by Cadmium treatment in this study could possibly be a cause of interstitial nephritis. Boucher *et al*, 1986 suggested that this condition of interstitial nephritis could also be induced by other factors including infections, autoimmune reactions, and certain medications. Glycine administration to rats showed normal kidney architecture (Plate 3 and 4). However, glycine at 1000 mg/kg body weight showed active interstitial congestion in rats' kidney (Plate 4), an indication that chronic administration of glycine at 1000 mg/kg body weight may potentially induce kidney injury. Administration of glycine at 500 mg/kg body weight to cadmium treated rats potentially reversed the cadmium-induced kidney injury in rats evident by normal tubular and glomerular architecture (Plate 5). Infiltration of inflammatory cells were also absent in this group (Plate 5 and 6). However, glycine at both 500 and 1000 mg/kg body weights were unable to reverse the interstitial congestion induced by cadmium treatment after two weeks of administration (Plate 5 and 6). The 1000 mg/kg dose of glycine had a reduced ameliorative potential in cadmium treated rats as features of focal tubular necrosis were evident (Plate 6)

Conclusion: Glycine has anti-inflammatory and ameliorative potential against Cadmium-induced acute kidney injury with the 500 mg/kg dose having more positive outcomes than the 1000 mg/kg dose.

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