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Original Article

Gallic acid protects against cadmium chloride-induced alterations in Wistar rats via the antioxidant defense mechanism

[El ácido gálico protege contra las alteraciones inducidas por el cloruro de cadmio en ratas Wistar a través del mecanismo de defensa antioxidante]

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Abstract

Context: Cadmium has been considered as one of the most hazardous toxic compounds with harmfully effect on the health of organisms.

Aims: To evaluate the effects of gallic acid (GA) on the cadmium-induced liver and renal oxidative stress in Wistar rats.

Methods: Twenty Wistar rats were grouped into four (A–D) of five rats. Rats in Group A, B, C and D were administered distilled water, 5 mg/kg bw cadmium chloride ($CdCl_2$), $CdCl_2$ + GA concurrently and GA (20 mg/kg bw) respectively and administered for 14 days. Biochemical parameters such as antioxidant enzyme activities, urea, creatinine and myeloperoxidase activity were determined.

Results: In the urea, creatinine and MPO, there was a significant increase in the $CdCl_2$ treated group. In the liver, the $CdCl_2$ treated group reduced significantly the catalase activity and increased the reduced glutathione. The gallic acid group increased in the GSH level, SOD, and CAT activities and it also reduced significantly the MDA level. However, the co-administration of $CdCl_2$ + GA had a considerably increase in the antioxidant enzymes. In the kidney, catalase activity and MDA level significantly decrease and increase respectively. The gallic acid also increases significantly the CAT and SOD activities while the MDA level was reduced. Co-administration of GA + $CdCl_2$ had a substantial increase only in the SOD activity compared to the control.

Conclusions: This study indicates that gallic acid was able to protect the alteration induced by cadmium chloride in the rat kidney and liver.

Keywords: gallic acid; cadmium chloride; antioxidant; nephrotoxicity; hepatotoxicity.

Resumen

Contexto: El cadmio ha sido considerado como uno de los compuestos tóxicos más peligrosos con efectos nocivos para la salud de los organismos.

Objetivos: Evaluar los efectos del ácido gálico (GA) sobre el estrés oxidativo renal y hepático inducido por cadmio en ratas Wistar.

Métodos: Se agruparon veinte ratas Wistar en cuatro (A–D) de cinco ratas. A las ratas de los grupos A, B, C y D se les administró agua destilada, 5 mg/kg de peso corporal de cloruro de cadmio ($CdCl_2$), $CdCl_2$ + GA al mismo tiempo y GA (20 mg/kg de peso corporal) respectivamente y durante 14 días. Se determinaron parámetros bioquímicos como actividad enzimática antioxidante, urea, creatinina y actividad mieloperoxidasa.

Resultados: En el grupo tratado con urea, creatinina y MPO, hubo un aumento significativo en el grupo tratado con $CdCl_2$. En el hígado, el grupo tratado con $CdCl_2$ redujo significativamente la actividad catalasa y aumentó el glutatión reducido. El grupo de ácido gálico aumentó en las actividades de nivel de GSH, SOD y CAT y también redujo significativamente el nivel de MDA. Sin embargo, la coadministración de $CdCl_2$ + GA tuvo un aumento considerable de las enzimas antioxidantes. En el riñón, la actividad de la catalasa y el nivel de MDA disminuyen y aumentan significativamente, respectivamente. El ácido gálico también aumenta significativamente las actividades de CAT y SOD mientras que se redujo el nivel de MDA. La coadministración de GA + $CdCl_2$ tuvo un aumento sustancial solo en la actividad de SOD en comparación con el control.

Conclusiones: Este estudio indica que el ácido gálico fue capaz de proteger la alteración inducida por el cloruro de cadmio en el riñón e hígado de rata.

Palabras Clave: ácido gálico; antioxidante; cloruro de cadmio; hepatotoxicidad; nefrotoxicidad.

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INTRODUCTION

The toxicity of heavy metals has become a public health challenge due to exposure to both occupational and environmental resources. This threat to environmental and public health is due to acute or chronic metal exposure brought about severe organ damage and even death (Ali et al., 2019). Cadmium (Cd) has been established as a known toxic substance abundantly present due to its importance in the industry worldwide. It is not biodegradable and has become a major health hazard as a result of its stretched half-life of about 10-30 years (Anetor et al., 2016). It is found in air, food, water, soil, and tobacco smoke. In occupational settings, its use involves Nickel-Cd battery production, zinc refining, smelting, welding, galvanizing, electroplating and by pigments, and plastics manufacturer (Odewumi et al., 2011). At a lower concentration, Cd induces tissue damage. Cd has been considered as a category I cancer-causing agent by the International Agency for Research on Cancer (IARC, 1993). Cd toxicity has been characterized by proteinuria, bone fractures, severe pain, and osteomalacia, predominantly among women (Rahimzadeh et al., 2017).

Cd ingested is distributed via vital body part, for example, liver, lung, testis, kidney, heart, and brain, and most of it enters and accumulates into the liver and kidneys (Genchi et al., 2020). Cd causes cellular reactive oxygen species synthesis in the kidney by expanding lipid peroxidation. Acute and chronic exposure initiates adjacent tubular dysfunction and leads to nephrotoxicity. Nephrotoxicity induced structural damage of kidneys and clinically observed as aminoaciduria, glycosuria, and proteinuria (Ewere et al., 2016). The liver is one of the key vital organs for the harmfulness of Cd. It tends to be dependent upon particular clinical and morphological modifications under Cd impact. The hepatotoxicity of cadmium induces acute lethality in the body. There has been a strong relationship between the exposures to various environmental chemicals such as Cd and both renal and hepatic damage reported through several epidemiological studies (Rinaldi et al., 2017; Branca et al., 2018).

Several reports established that liver and kidney were the vast majority of delicate natural tissues readily influenced by Cd poisonousness (Ognjanovic´ et al., 2010; Ojo et al., 2014c). The initiation of Cd nephrotoxicity for instance generated through several pathways comprising radicals and cell death (El-Sharaky et al., 2007). Earlier studies focused on the use of metals for example zinc, copper, as antioxidants for defense against Cd toxicity. These inorganic ions were revealed to be involved in the incorporation and transference of Cd constituents inside biological environments via concealing and transferring processes (González-Trujano and Navarrete, 2011). Though, the usage of these ions in extreme portions might trigger severe biological complications.

Gallic acid (GA) is a naturally-occurring polyphenolic constituent present in fruits and several products of the soil plants. GA is an antioxidant found naturally in plants with application in the drug, food, and cosmetics industries (Owumi et al., 2020). GA possess several activities such as anti-mutagenic, antiviral, antifungal, antibacterial, against cancer-causing, anti-allergic, and anti-inflammatory ability through its antioxidant potentials (Olusoji et al., 2017; Zahrani et al., 2020). The scavenging ability of GA has been reported as a plausible component for the decrease of oxidative stress and improvement of degenerative disorders (Oyagbemi et al., 2016). GA also suppresses pro-inflammatory cytokines, reduces IL-6, and TNF-α expression suggesting it possesses anti-inflammatory properties (Mohamed et al., 2016). In this study, we evaluated the defensive and antioxidant impacts of GA against Cd-induced liver and renal stress in Wistar rats.

MATERIAL AND METHODS

Chemicals and reagents

Gallic acid (GA), cadmium chloride ($CdCl_2$), and also commercial assay kits of urea, creatinine,

and myeloperoxidase (MPO) were bought from Sigma–Aldrich Company (St. Louis, MO, USA).

Experimental animals and treatments

Twenty Wistar rats (170-200 g) were procured from the Department of Biochemistry, Landmark University. The animals were allowed to be acclimatized after which they were randomized into four groups (A–D) of five rats. The animals were exposed to light cycle (12h light/12h dark), room temperature of 24-27°C, and fed with commercial rat chow and water *ad libitum*. The experimental dealings on the rats complied with the ethical rules and affirmed by ethical committee (LUAC/2020/0052B) of the Department of Biochemistry, Landmark University, Nigeria.

Animal groupings

Rats in Group A were given distilled water daily, group B rats were orally given 5 mg/kg b.w. cadmium daily, group C rats were given cadmium (5 mg/kg b.w./daily) and GA (20 mg/kg b.w./day) concurrently, group D rats were administered GA (20 mg/kg b.w./daily). $CdCl_2$ and GA were dissolved in distilled water and administered for 2 weeks. Doses for cadmium and GA were selected based on earlier reports by El-Demerdash et al. (2004) for cadmium, and Ola-Davies and Olukole (2018) for gallic acid. It has been shown that the dose selected induces major oxidative stress in different tissues (Ojo et al., 2014a; 2014b; 2014c), while gallic acid was reported to be safe at 20 mg/kg body weight per day (Ola-Davies and Olukole, 2018).

Serum and organ preparation

The rats were anesthetized twenty-four hours after the last treatment under diethyl ether. The blood was collected, left for an hour, and the serum was separated by centrifuging at 1300×*g* for 10 min. The tissues of interest (liver and kidney) were removed, homogenized, and centrifuged at 5000 g for 10 minutes.

Biochemical parameters

The serum samples were utilized for estimation of kidney indices such as serum creatinine (CRE), urea, and myeloperoxidases (MPO) using commercial kits. The malondialdehyde (MDA) level, superoxide dismutase (SOD) and catalase (CAT), and the reduced glutathione (GSH) level were measured in the kidney and liver homogenates. The level of lipid peroxidation by measuring malondialdehyde level was according to Satoh (1978), CAT, SOD, and GSH content were determined according to Misra and Fridovich (1972), Aebi (1974), and Beutler (1963), respectively.

Histopathological study

For proper fixation, a portion of the liver and kidney tissues collected was immersed in 10% buffered formalin. These organs were inserted in paraffin wax using hematoxylin and eosin (H & E) staining, about 5–6 µm of the tissue were stained for histological assessment (Drury et al., 1976). Concisely, fixed liver and kidney tissues were dehydrated in methanol and xylene, respectively. Afterward, tissues sections (5 µm) were made, mounted on glass slides, and stained with stained with H&E. The slides were analyzed under the light microscope (Olympus BX63 with a DP72 camera, Olympus Corporation, Tokyo, Japan) at 400× and sections were observed.

Statistical analysis

Data were analyzed via one-way analysis of variance (ANOVA) along with Tukey's *posthoc* test on GraphPad Prism 8.0 (Version 8.0). Values were expressed as mean ± standard error of mean SEM (n = 5) with p significant at ≤0.05.

RESULTS

Table 1 revealed that $CdCl_2$ treated group produced considerable increment ($p<0.05$) in the concentrations of serum urea, creatinine, and MPO activities. Whereas, in the groups administered with GA alone and co-administration of $CdCl_2$ + GA showed a substantial reduction in the concentrations of urea, creatinine, and MPO activities.

Table 1. Protective impact of gallic acid on cadmium chloride-induced alterations on some selected serum markers.

Parameter	Control	Cadmium chloride treated rats	Cadmium chloride + gallic acid-treated rats	Gallic acid-treated rats
Urea (µmol/L)	22.34 ± 1.11	32.89 ± 1.42**	27.56 ± 1.16*	21.56 ± 1.07*
Creatinine (µmol/L)	0.44 ± 0.02	0.62 ± 0.08**	0.47 ± 0.03*	0.49 ± 0.04*
MPO (µmol/min)	22.45 ± 1.56	45.62 ± 6.43**	28.22 ± 5.48*	21.76 ± 1.89*

Values are expressed as mean ± SEM (n=5). *p<0.05 significant difference compared to control (Group A); **p<0.05 statistically significant differences compared to $CdCl_2$ treated group. Myeloperoxidase (MPO); cadmium chloride ($CdCl_2$).

Fig. 1 displays the levels of enzymatic and non-enzymatic antioxidants in the liver. Hepatic SOD and CAT activities were significantly decreased in $CdCl_2$ treated groups compared to the control. Notwithstanding, SOD, CAT, and GSH levels improved substantially in the gallic acid-treated groups compared to the $CdCl_2$ group. Also, hepatic GSH concentrations was considerably elevated in the $CdCl_2$ group comparable to the control. In contrast, the considerable reduction was observed in the $CdCl_2$ + GA group. Hepatic MDA was expressively elevated in the $CdCl_2$ group compared to control, but considerably reduced in $CdCl_2$ + GA relative to the $CdCl_2$ treated group and gallic acid-treated groups relative to the control.

Fig. 2 reveals the concentrations of antioxidant enzymes and non-enzymatic antioxidants in the kidney. Renal SOD and CAT activities were altogether decreased in $CdCl_2$ groups compared to the control, but significantly increased in $CdCl_2$ + GA and GA treated groups relative to $CdCl_2$ treated and control groups. However, SOD and CAT activities were enhanced considerably in the GA groups compared to the control. Also, renal GSH concentrations were slightly reduced in the $CdCl_2$ treated group compared to the control. Renal MDA was significantly increased in $CdCl_2$ group comparable to the control, but drastically reduced in the $CdCl_2$ + GA relative to $CdCl_2$ treated group and gallic acid groups relative to the control.

The defensive function of gallic acid against $CdCl_2$ toxicity was explored in hepatic and renal tissues via histo-architectural studies as revealed in Figs. 3-4. Normal physiology with no visible lesions was seen in the hepatocytes of control animals (Fig. 3) and gallic acid-treated group alone. In rats treated with $CdCl_2$ revealed mild vascular congestion while groups co-administered with $CdCl_2$ + gallic acid revealed regeneration. In the kidney histology, normal renal cortex, glomeruli, and tubules were seen in the control animals (Fig. 4) and gallic acid-treated group alone. In contrast, mild congestion of blood vessels and dilation of glomeruli were observed in $CdCl_2$-treated rats (Fig. 4). In groups co-administered with $CdCl_2$ + GA, revealed regeneration and restoration of the glomeruli and cells.

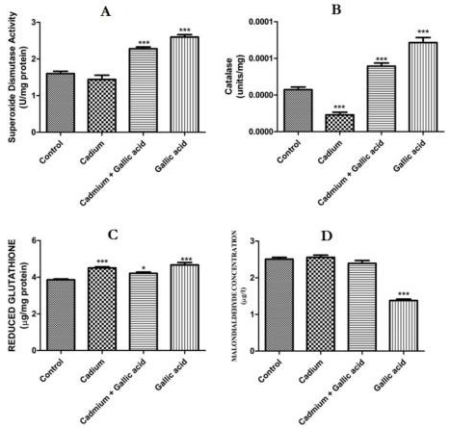

Figure 1. Changes in the level of hepatic antioxidant enzymes and oxidative stress marker.
Values are expressed as mean ± SEM (n = 5). *p<0.05; **p<0.01; ***p<0.001 statistically significant differences versus control.

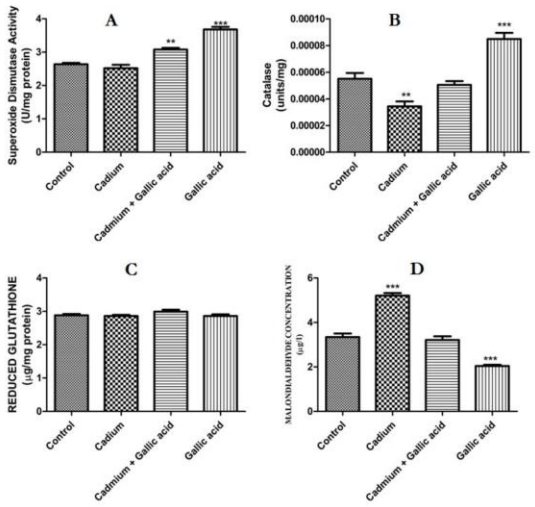

Figure 2. Protective effects of gallic acid on cadmium chloride-induced changes in kidney antioxidant and oxidative stress marker after two weeks.

Values are expressed as mean ± SEM (n = 5). *p<0.05; **p<0.01; ***p<0.001 statistically significant differences versus control.

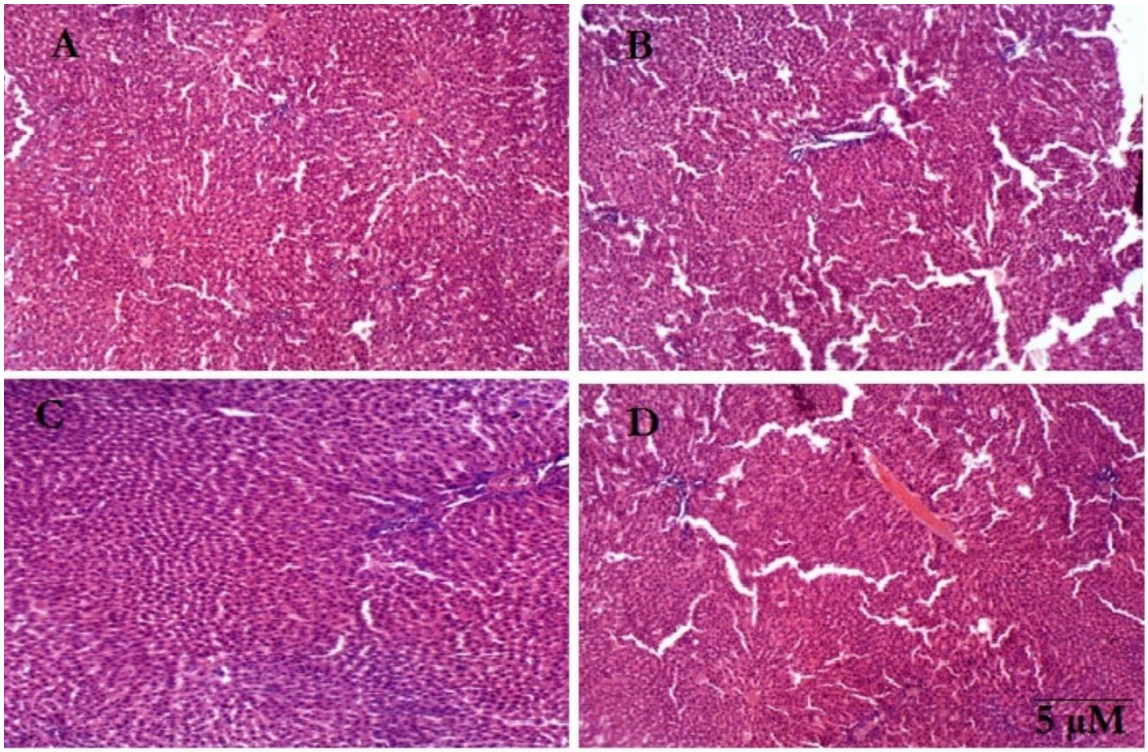

Figure 3. Cross-section of the liver of rats after two weeks.

Group A (Control rats), Group B (cadmium chloride-treated rats), Group C ($CdCl_2$ + GA-treated rats), Group D (gallic acid-treated rats).

(A) Control showing hepatocytes, normal portal tracts and central vein; **(B)** $CdCl_2$ group showing normal hepatocytes, normal portal tracts, and central vein and mild vascular congestion; **(C)** $CdCl_2$ + GA group showing mild vascular congestion; **(D)** GA group reveals normal hepatocytes, normal portal tracts, and central vein.

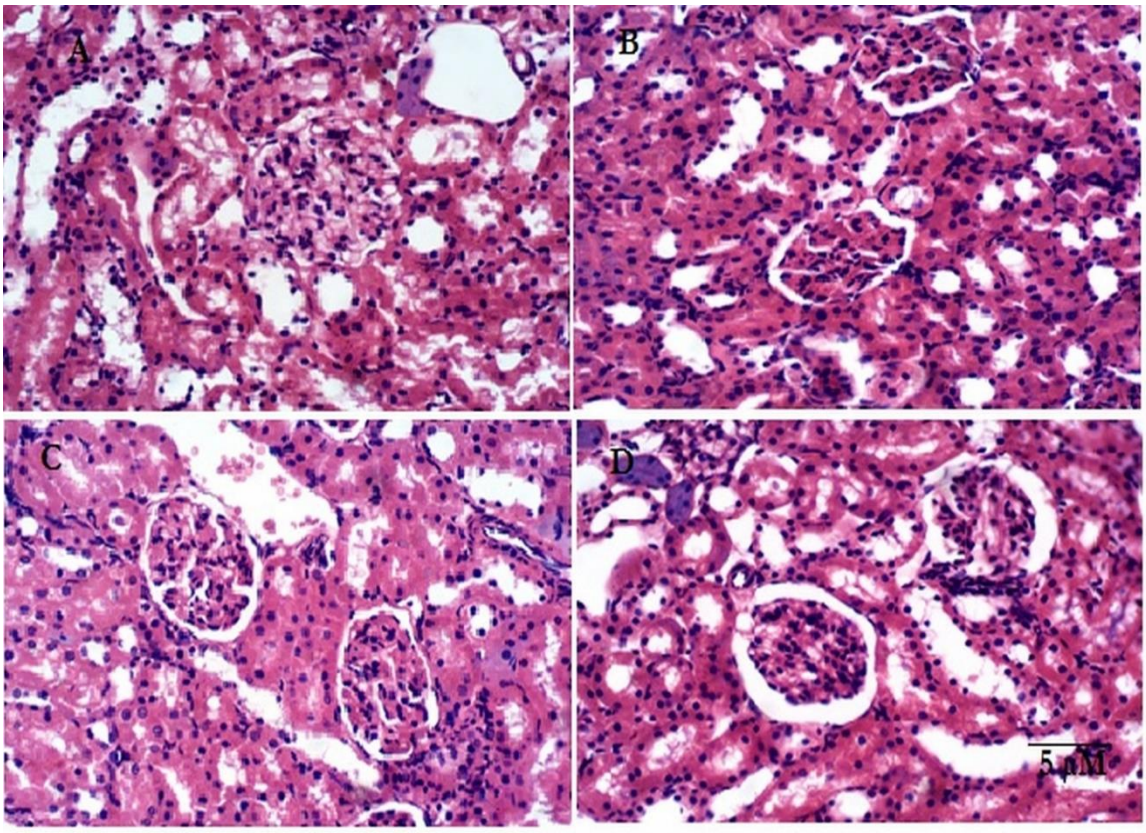

Figure 4. Cross-section of the kidney of rats after two weeks.

Group A (Control rats), Group B (cadmium chloride-treated rats), Group C ($CdCl_2$ + GA-treated rats), Group D (gallic acid-treated rats).

(A) Control revealing typical glomeruli and tubules; **(B)** $CdCl_2$ group revealing mild glomeruli congestion; **(C)** $CdCl_2$ + GA group displaying mildly inflamed glomeruli; **(D)** GA group reveals epithelial with abundant eosinophilic cytoplasm.

DISCUSSION

Cd exposure through contaminated food, water, air, commercial phosphate fertilizer, occupational hazards, and manufactured goods are a major sources of cadmium intoxication (Hayat et al., 2019). It was documented that contact with $CdCl_2$ mixtures exacerbates increment in the production of oxidants, which triggers oxidative injury of numerous natural organs (Liu et al., 2008). The liver and kidney have been described as the greatest delicate tissues to Cd toxicity (Liu et al., 2010; Ojo et al., 2014c). The build-up of $CdCl_2$ in human tissues contributes to several pathological disorders comprising hepatic and renal dysfunction (Ojo et al., 2014a; 2014c). So, evaluating the actions of poisonousness caused by heavy metals and medications urge more researchers to look for natural products with essential antiradical property to shield biological organisms from oxidative injury caused by the generation of radicals (Sarwat et al., 2011). This investigation is meant to assess the effectiveness of gallic acid against cadmium-induced hepato-renal toxicity, via an antioxidant defense system.

In the current investigation, serum urea, creatinine, and MPO were evaluated to survey kidney performance. The information got indicated a huge increment in kidney indices; urea, MPO, and creatinine following $CdCl_2$ exposure. The alterations in the concentrations of serum kidney indices signify kidney injury trigger via $CdCl_2$ as earlier documented by (Purena et al., 2018). The increase in urea and creatinine might also be associated with hypertension-induced renal damage (Abdel-Zaher et al., 2019). These data correlate with other

researchers' work who documented that $CdCl_2$ initiated tube-shaped necrosis or loss of the membrane lining and injury of the kidney (Wang et al., 2009). In addition to that, the elevated serum urea produced by $CdCl_2$ toxicity might be identified with derangement in the catabolism of protein as an aftereffect of the rise in the production of the enzyme arginase implicated in urea generation (Tormanen, 2006). Furthermore, the administration of gallic acid revealed substantial enhancement in renal performance by a decline in the concentrations of urea and creatinine. Thus, the information acquired indicates a fundamental antioxidant property of gallic acid towards $CdCl_2$ toxicity, and that the treatment of gallic acid alone has no impact on the concentrations of kidney indices demonstrating the harmless usage of gallic acid on the liver and kidney.

Cd has been noted to stimulates the production of free radicals for example, hydroxyl radical (^{-}OH), superoxide anion (O_2^{-}), etc. In humans and animals, pathological conditions and oxidative deterioration of macromolecules are initiated by the overwhelming level of free radicals (Rani et al., 2014). Cd is absorbed and rapidly taken from the blood to the liver and kidney majorly, where it concentrates and induces many metabolic and histological changes, altered gene expression, apoptosis, and membrane damage (Matović et al., 2015; Andjelkovic et al., 2019). The efficient pathway of cellular defense and repair occurs via antioxidative protection against oxidant species. Antioxidant enzyme includes SOD and CAT. SOD catalyzes the reduction of O_2^{-} to hydrogen peroxide (H_2O_2) whereas H_2O_2 is additionally separated via catalase to water and oxygen. Several reports in the literature have utilized different chelating agents to ease the harmfulness of Cd by increasing Cd excretion; nonetheless, chelation therapy is controversial in terms of efficiency and safety (Rahimzadeh et al., 2017; Rana et al., 2018; Ojo et al., 2018). Cd shows a high affinity for compounds containing the thiol group. In our study, lipid peroxidation increased with Cd administration while a decrease in catalase which establishes the toxicity already reported in the literature. The group administered with GA increased the antioxidant activities and reduced the lipid peroxidation biomarker. However, the induced toxicity of cadmium was ameliorated by the administration of GA. This supports the claim of GA as an antioxidant agent. GSH is a nucleophilic substance containing sulfur with a high concentration in the liver and kidney. It promotes cellular protection from oxidative stress and other toxic compounds. Cd cytotoxicity has been linked to alteration in the metabolism of cellular GSH and its increase may protect cells from the induced Cd toxicity (Remelli et al., 2016). GA increases the intracellular GSH level by scavenging the reactive oxygen species (Hagar and Al Malki, 2014; Lee et al., 2018).

The build-up of Cd in rat liver caused organ damage (Ojo et al., 2014a). The histology of the hepatocytes in the control group shows normal portal tracts, and central vein while the GA group showing usual hepatocytes, portal tracts and central vein. The induced $CdCl_2$ group showed extensive vascular congestion. However, the $CdCl_2$ + GA group reveals mild vascular congestion. According to the histopathological changes seen in the kidneys, it may be concluded that cadmium harmfulness produced injury through developing tubular harm while the adjacent tubules were delicate to cadmium poisonousness due to their high re-absorptive activity (Ojo et al., 2014c).

CONCLUSIONS

This study indicates that gallic acid was able to protect the alteration induced by $CdCl_2$ in the rat kidney and liver by increasing the anti-oxidative enzymes and restore the histological changes induced by cadmium.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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AUTHOR CONTRIBUTION:

Contribution	Ojo OA	Rotimi D	Bright AE	Kayode O	Ojo AB	Alejolowo O	Ajiboye BO	Oluba OM
Concepts or ideas	x				x			x
Design	x	x		x		x	x	x
Definition of intellectual content	x	x		x	x		x	x
Literature search		x	x		x	x		
Experimental studies		x	x					
Data acquisition		x	x	x	x	x		
Data analysis	x						x	x
Statistical analysis		x	x			x		
Manuscript preparation	x	x		x	x	x		
Manuscript editing	x			x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x

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