Flavonoids fractions of Adansonia digitata L. fruits protects adult Wistar rats from mercury chloride-induced hepatorenal toxicity: histopathological and biochemical studies

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ABSTRACT
Mercury chloride is a common heavy metal found in the environment, and it endangers both the environment and living organisms. The study aimed to show whether Flavonoids Fractions of Adansonia digitata (FAD) could protect rats from HgCl2-induced hepatorenal toxicity. Thirty (30) rats were randomly assigned to one of six groups. The first group was given no HgCl2 as a control, while the second group was given a single daily dose of HgCl2 (0.5 mg/kg). The treatment groups (III, IV, and V) received a single daily dose of HgCl2 (0.5 mg/kg) along with 25 mg/kg, 50 mg/kg, and 75 mg/kg of FAD, respectively. HgCl2 (0.5 mg/kg) was given to Group VI, along with Ascorbic Acid (200 mg/kg) as a standard control. After the administration, the blood serum of the experimental rats was used for biochemical analysis. The liver and kidney organs were obtained for histological examination. AST, ALP, ALT, urea, creatinine, and MDA levels all increased in rats given HgCl2 (group II), with decreased SOD, CAT, and GSH levels (p < 0.001), whereas FAD was able to prevent the upsurge of ALT, AST, ALP, creatinine, Urea, and MDA. It also increased SOD, CAT, and GSH levels in the body. FAD protected the glomerulus from degeneration and prevented histological liver steatosis.

Introduction
Heavy metals pollute the environment and are toxic to living organisms, and in their various forms, they exhibit distinct biological behavior, pharmacokinetics, and clinical manifestations [1–3]. It is commonly found in the environment and is linked to severe health issues in mammals, and exposure to mercury chloride (HgCl2) is via products like batteries, pesticides, and paints [1,4,5]. Mercury poisoning affects the nervous system, liver, kidney, and digestive system [6]. It is primarily metabolized in the liver before accumulating in the kidneys. As a result, the liver and kidneys are the organs most affected [7]. Mercury chloride poisoning has previously been shown to occur via several routes, including inhalation, ingestion, and
Flavonoids are phenolic metabolites that occur naturally in all plant materials and are secondary plant metabolites [23]. Flavonoids are famous for their anti-inflammatory, antiallergic, antiviral, antibacterial, and antioxidant properties [22,24]. Flavonoids have various biological activities, including cell proliferation inhibition, enzyme inhibition, and antioxidant effects [17]. According to previous studies, flavonoids have anti-atherosclerotic, anti-inflammatory, and antioxidant properties [25]. This study set out to investigate the protective effects of flavonoid fractionate from Adansonia digitata fruit against hepatorenal damage caused by mercury chloride in rats.

Methods

Materials

Mercury chloride (BDH Chemicals Ltd, England) was used as a hepatorenal toxicity. Vitamin C (Ascorbic Acid; 70 mg/tablet) produced by Micro Labs Limited with NAFDAC number A4-6634 was obtained from a reputable pharmaceutical store (M.U.B Pharmaceutical Enterprises Ltd.) in Sabon Gari, Zaria, Kaduna state, and was used as a standard drug for Antioxidant. Phosphate Buffer Saline (PBS), 70% Ethanol (Sigma-Aldrich Co. LLC St. Louis, USA). The anaesthetic agent used in the study was ketamine hydrochloride (Sigma-Aldrich Co. LLC St. Louis, USA). Colourimetric diagnostic kits (Randox kits) for ALT, ALP, AST, urea, and creatinine were also used. Using laboratory diagnostic kits (Biodiagnostic Co., Cairo, Egypt), antioxidant enzyme activities (SOD, CAT, and GSH) and MDA content in blood serum were determined.

Plants collection and authentication

The fruit of Adansonia digitata L. was obtained from the Sabo market of Kaduna State’s Sabo Gari local government. The fruit
was identified and authenticated using standard botanical monographs. The Botany Department, Faculty of Life Sciences, Ahmadu Bello University Zaria, Nigeria, confirmed them further. The plant’s specimen voucher number (2512).

**Extraction**

The dried fruit pulps were ground into a coarse powder, and the powdered sample was kept in an airtight container until needed. The fruit pulp of Adansonia Digitata L. was extracted with water in a soxhlet apparatus for 10 hours according to the Association of Official Analytical Chemists [26] procedure. The methods of Won et al. [27], was used whereby Adansonia digitata’s crude extract was dissolved in n-hexane, the insoluble residue was then suspended in distilled water, and diethyl ether was added to it. After that, n-butanol was used to partition the distilled water fraction. After that, the water portion was discarded. The first n-butanol fraction was obtained by treating the n-butanol fraction with 1% KOH and then separating it (saponins). To obtain the second n-butanol fraction, conc. HCl was added to the remaining 1% KOH portion, which was then partitioned with n-butanol until exhaustion (flavonoids). The final product used in this study was the crude Flavonoids fraction. A total of 6 kg of Adansonia digitata fruit were used. The flavonoids yielded a total of 1,020 mg.

**Experimental animals**

Thirty (30) Wistar rats of both sexes with weights ranging from 130 g to 220 g were purchased from the Human Anatomy Animal House at Ahmadu Bello University’s Faculty of Basic Medical Sciences in Zaria, Kaduna State, Nigeria. The animals were housed in the Department of Human Anatomy’s animal house and kept at room temperature in standard laboratory conditions. The animals were fed a standard feed grower mash diet and were given free access to water. The animals were given two weeks to acclimate before the administration began. The study was approved by the Ahmadu Bello University Zaria Animal Use and Care Committee (ABUCAUC/2018/088) and carried out in accordance with the ARRIVE guidelines.

**Experimental procedure**

Thirty (30) Wistar rats were divided into six groups (A-F), consisting of five rats. Group A served as control received distilled water (2 ml/kg); while Groups B, C, D, E and F were treatment groups. Group B – mercuric chloride treated rats (0.5 mg/kg BW per day in distilled water); Group C – Flavonoid fraction plus mercuric chloride (25 mg/kg BW + 0.5 mg/kg BW per day, respectively); Group D – Flavonoid fraction plus mercuric chloride (50 mg/kg BW + 0.5 mg/kg BW per day, respectively); Group E – Flavonoid fraction plus mercuric chloride (75 mg/kg bw + 0.5 mg/kg BW per day, respectively); Group F – Ascorbic Acid plus mercuric chloride (200 mg/kg BW + 0.5 mg/kg BW per day, respectively) for a period of 28 days. The mercury chloride doses were selected based on previous research [28]. The route of mercury chloride administration was via intraperitoneal injection, while for the flavonoids and ascorbic acid was via oral gavage. Before and during the study, the experimental animals were weighed weekly.

**Sampling procedure**

Following ketamine anesthesia (75 mg/kg: intraperitoneally) at the end of the study, all rats were humanely sacrificed. Blood samples were taken from each rat in a plain tube, and the blood samples were
spun at 3000 rpm for 5 minutes in a centrifuge machine to obtain the serum for the biochemical studies.

Biochemical studies

The activities of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), urea, and creatinine in the serum were determined using commercially available kits and following the manufacturer’s instructions. Randox Laboratories Limited (United Kingdom) produced the ALT, AST, ALP, urea and creatinine test kits. The method described by Akanji et al. [29] was used to measure lipid peroxidation. The method described by Aebi [30] was used to determine CAT activity, and Fridovich’s [31] method was used to determine SOD activity, while GSH concentration was determined according to the method described by Rajagopalan et al. [32].

Histological studies

The rats were dissected after being euthanized; the liver and kidneys were removed and fixed in neutral buffered formalin before being dehydrated in graded alcohol, embedded in paraffin wax, cleared in xylene, sectioned at 5 μm, and stained with hematoxylin-eosin (H & E) for general histology.

Statistical analysis

The data from these studies were analyzed using the Statistical Package for Social Science (SPSS) software, version 20 (IBM, USA), with one-way ANOVA and Turkey’s multiple comparison post hoc test, which compared the significance level between the control and test groups. All data were presented as mean SEM, with p < 0.05 considered significant.

Results

Liver function parameters

When HgCl₂-treated rats were compared to control rats and FAD-treated rats a significant rise in ALT, ALP and AST was observed in the HgCl₂-treated rats. ALT, ALP, and AST levels increased significantly (p < 0.0001). (See Figure 1). Treatment with FAD at all doses was found to be effective. ALP, ALT, and AST levels did not differ significantly (p > 0.05) between control and FAD-treated and Ascorbic Acid-treated rats (Figure 1).

Parameters of kidney function

When compared to control and FAD/Ascorbic acid-treated rats, the serum levels of urea and creatinine in rats treated only with HgCl₂ increased significantly (p < 0.0001) (Figure 2). Between control and FAD-treated rats (all dosages) and Ascorbic Acid-treated rats (200 mg/kg), there was no significant difference in creatinine levels (p > 0.05). (Figure 2).

Oxidative stress biomarkers

When HgCl₂ control rats were compared to control and FAD-treated rats, the levels of catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH) in their serum significantly decreased (p < 0.0001) (Figure 3). Treatment with FAD (75 mg/kg) was found to be more effective. SOD, CAT, and GSH levels did not differ significantly (p > 0.05) between control and FAD (500 mg/kg) treated rats (Figure 3). In the case of MDA, rats cotreated with FAD (75 mg/kg) and ascorbic acid showed a significant decrease (p < 0.05) when compared to HgCl₂ control rats.

Histological study

A photograph of the liver of a healthy control rat revealed normal hepatocytes, central veins, and sinusoids (Figure 4a). In their livers, rats
exposed only to HgCl₂ had degenerated hepatocytes, steatosis, and fat hepatocellular vacuoles (Figure 4b). The livers of rats given HgCl₂ (5 mg/kg) and FAD (25, 50 and 75 mg/kg, respectively) showed mild steatosis and some microvesicular fatty droplet formation (Figure 4c, d, e). HgCl₂ (5 mg/kg) and ascorbic acid (200 mg/kg) treatment caused mild inflamed in rats’ livers (Figure 4f). Normal control rats’ kidneys showed a typical histological structure, including normal renal tubules and glomeruli (Figure 5a). The kidneys of HgCl₂-treated rats showed focal renal tubular degeneration (Figure 5b). The kidneys of rats given HgCl₂ (5 mg/kg) + FAD at doses of 25, and 50 mg/kg, respectively, revealed a mildly

**Figure 1.** Bar charts of the liver enzymes parameters ((a) ALP, (b) AST, and (c) ALT) after 4 weeks of the experiment. Data were analyzed using one way ANOVA, followed with Tukey post hoc test. *P < 0.033; ** P < 0.002; *** P < 0.0001 indicates a significant difference when compared to normal control; #P < 0.03; ## P < 0.002; ### P < 0.0001, indicates a significant difference when compared to HgCl₂ control group.

**Figure 2.** Bar charts of kidney function parameters (a) urea, and (b) creatinine) after 4 weeks of the experiment. Data were analyzed using one way ANOVA, followed with Tukey post hoc test. *P < 0.033; ** P < 0.002; *** P < 0.0001 indicates a significant difference when compared to normal control; #P < 0.03; ## P < 0.002; ### P < 0.0001, indicates a significant difference when compared to HgCl₂ control group.
obliterative form of a glomerulus (Figure 5c, d, e). FAD at 75 mg/kg-treated rats’ kidneys and Ascorbic acid-treated rats’ kidneys had a mildly normal glomerulus (Figure 5f).

**Discussion**

HgCl$_2$ produces free radicals, which increases oxidative stress and causes nephrotoxicity and elevate hepatotoxicity [33]. The adverse effects of HgCl$_2$ could be prevented by flavonoids treatment, most likely due to their vigorous free radical scavenging activity, which protects cells from oxidation and necrosis [34].

In this study, the kidney and liver functions of HgCl$_2$-treated rats were negatively altered, resulting in hepatorenal degeneration as evidenced by a significant increase in ALP, ALT, and AST enzyme activities, as well as urea and creatinine levels. The upsurge of both liver and kidney function parameters by the HgCl$_2$
explains the severity of hepatic and renal damage induced by the HgCl₂ might be linked to the degree of intracellular and extracellular oxidative stress, which is caused by excessive free radical production combined with low antioxidant concentrations [35]. The pathogenesis of various liver and kidney diseases has been linked to free radical-induced lipid peroxidative damage (Muhammad et al., 2016). Nabil et al. [36] reported similar findings. Rats given HgCl₂ and flavonoids showed significant improvements in ALP, ALT, and AST enzyme activities, as well as urea and creatinine levels, which could be attributed to the antioxidant activity of the flavonoid fractions from Adansonia digitata [37].

HgCl₂ significantly reduces the activities of the antioxidant enzymes SOD, CAT, and GSH in the current study, whereas the end-product of lipid peroxidation (MDA) was significantly increased in rats treated with only HgCl₂. This could be due to HgCl₂’s ability to initiate the formation of highly reactive substances such as oxidative stress, and as a result, lipid peroxidation increased while antioxidant enzyme activity decreased [38]. Several experiments have produced similar results [39,40]. Coadministration of flavonoids fractions + HgCl₂, on the other hand, revealed a significant modulation in the activities of SOD, CAT, and the levels of GSH and MDA toward normal. This could be due to Flavonoids’ ability to act as exogenous antioxidants by directly oxidizing radicals to form less reactive species through four mechanisms: inhibition of nitric-oxide synthase activity, inhibition of xanthine oxidase activity, modulation of channel pathways, and interaction with other enzyme systems [34]. Furthermore, flavonoid metabolites have been linked to the induction of antioxidant defense mechanisms via antioxidant response elements (AREs), which induce the expression of antioxidant enzymes [41]. Flavonoids react with the radical’s reactive compound to stabilize reactive oxygen species. Radicals are rendered inactive due to the high reactivity of the flavonoids’ hydroxyl group [42].

The histopathological study revealed the architectural changes (liver and kidney) of the flavonoid’s fractions and HgCl₂ administered rats (Figures 4 and 5). As previously stated, HgCl₂ causes oxidative stress in the liver and kidney, resulting in pathological changes [43]. Mercury chloride transport in
the kidney has been studied, and it has been discovered that it is taken up by proximal tubular cells [44]. Also, in this study, rats exposed to only HgCl₂ developed renal tubular damage, as well as vascular congestion and mild Bowman’s space enlargement. Flavonoid has been shown to preserve histological integrity in damaged renal tissue with necrosis in the renal parenchyma, and tubular dilatations [45]. The PPARs appear to be promising targets for treating liver disease. Nuclear receptors known as PPARα are involved in mitigating liver inflammation by inhibiting NF-κB and reducing C-reactive protein expression [46]. PPARα stimulation is expected to reduce steatosis by stimulating β-oxidation and reducing inflammation by inhibiting NF-κB [47]. Flavonoids have been shown to stimulate PPAR in several studies [48,49]. Other studies have found that flavonoids increase the PPAR gene expression and protein expression [50,51]. Furthermore, Flavonoids have renoprotective effects [52] by modulating the Nrf2 signaling pathway, which favors the translocation of the transcription factor Nrf2 to the nucleus, where it binds to AREs and activates the transcription of genes encoding phase II antioxidant and detoxifying enzymes [53]. The vital histological findings of this study were that flavonoids treatment resulted in hepatic and renal architecture recovery.

Conclusion

In this study, flavonoids fractions of Adansonia digitata fruit reduces the toxic effect of HgCl₂ on hepatorenal functions.

Limitations of the Study

The antioxidant potential of FAD fruit is thought to play a role in hepatorenal protection. However, at the conclusion of the experiments, this study did not estimate the level of gene expression disruption and the ultrastructural interference in mitochondria metabolism.

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Authors’ contributions

All authors contributed to the conceptualization and design. Wusa Makena, Yomi Samson Aribiyun and Aisha Aminu provide study materials. Barka Ishaku, Wusa Makena and Yomi Samson Aribiyun collected the data. All authors contributed to the interpretation and analysis of the data. Wusa Makena, Ekwere Eke Inemesit, Ayuba Yohana and Aisha Aminu wrote the first draft of the manuscript. Wusa Makena, Ayuba Yohana, Aisha Aminu, Ekwere Eke Inemesit, and Barka Ishaku provided critical feedback on the manuscript. All authors gave their final approval to the manuscript.

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Ethical considerations & guidelines

The Ahmadu Bello University, Zaria, Committee on Animal Use and Care has given its approval to all animal-related experimental protocols, with the number ABUCAUC/2018/088.
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