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Dose-Dependent Hepatorenal Protection by Aqueous Extract of Watermelon (*Citrullus lanatus*) Seeds Against Lead-Induced Toxicity in Male Wistar Rats

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Abstract: Lead toxicity remains a major public health concern due to its detrimental effects on vital organs, particularly the liver and kidneys. This study evaluated the protective effects of aqueous extracts of watermelon (*Citrullus lanatus*) seeds on hepatic and renal functions in lead-induced Wistar rats. A total of four experimental groups were used: a normal control, a lead-exposed group, and two treatment groups administered 200 mg/kg and 400 mg/kg of watermelon seed extract alongside lead exposure. Liver function markers: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and Alkaline Phosphatase (ALP) as well as renal biomarkers; urea and creatinine were assessed. Results showed that lead exposure significantly elevated AST, ALT, ALP, urea, and creatinine levels, indicating hepatic and renal damage. However, treatment with the aqueous watermelon seed extract produced a dose-dependent improvement. Notably, the 400 mg/kg dose significantly reduced ALP levels and restored AST and ALT values close to normal. Similarly, both treatment groups showed reductions in urea and creatinine levels, although these changes were not statistically significant. These findings suggest that aqueous watermelon seed extract possesses hepatoprotective and nephroprotective properties, likely due to its bioactive phytochemicals with antioxidant potential. The higher dose demonstrated greater efficacy, indicating a dose-dependent therapeutic effect. The findings suggest that the aqueous extract of *C. lanatus* seeds possesses protective and ameliorative effects against lead-induced hepatorenal dysfunction in male Wistar rats. This study highlights the potential of watermelon seed extract as a natural therapeutic for mitigating heavy-metal-induced hepatorenal toxicity, warranting further investigation into its mechanisms of action, safety profile, and potential translational applications in human hepatic and renal health.

Keywords: Lead toxicity; *Citrullus lanatus* seed aqueous extract; Renal biomarkers; Wistar rats; Dose-dependent effect

Introduction: The increase in urbanization and industrialization have contributed greatly to continuous exposure of humans to various toxic environmental pollutants. Lead has a deleterious effect on the well-being of humans. The likelihood of exposure to heavy metals has increased as environmental pollution continues to rise, and because these substances do not break down naturally. Heavy metals can trigger oxidative stress (OS) by promoting the generation of reactive oxygen species (ROS) while simultaneously reducing the body's antioxidant defenses (Karari et al., 2012). Human activities such as mining, industrial processes, and the combustion of fossil fuels significantly contribute to lead exposure. Lead is widely used in the manufacture of products such as car batteries, hair dyes, agricultural equipment, gasoline, paints, ceramics, cosmetics, water pipes, and aircraft components (Seema & Tripathi, 2013; La-Llave-Leon et al., 2016). Humans may be exposed to lead through multiple pathways, including ingestion of contaminated food and water which is often due to leaching from old, corroded pipes as well as inhalation in industrial environments and dermal contact. After absorption through the gastrointestinal tract, lead is distributed to soft tissues such as the kidneys, bone marrow, liver, and brain, while largely accumulating in the blood and bones (Sansar et al., 2012; ATSDR, 2017).

The liver which is a primary organ involved in the biotransformation of xenobiotics is highly exposed to numerous toxic substances, making it particularly vulnerable to various forms of damage, which then results to chemically-induced hepatic disorders (Raj et al., 2013). Liver diseases now constitute major health challenges which have become a great concern to the global world. Globally, in developed regions, around 20,000 deaths are attributed to liver diseases each year, with more than 250,000 new cases reported annually, a situation that is particularly concerning in developing countries (Subramanian et al., 2013). The liver is a primary target of lead toxicity due to its central role in xenobiotic metabolism and detoxification.

In a study conducted by Ekpe et al. (2020), the effects of lead toxicity were evaluated by measuring electrolyte levels, specifically potassium and chloride, as well as renal function indicators such as urea and creatinine, which act as markers of kidney injury. The findings revealed degeneration and damage in kidney tissues, which were associated with the production of reactive oxygen species (Sharma et al., 2012). Lead acetate when administered to rats causes a rise in the concentration of urea and creatinine, which can absolutely be said that the chemical is nephrotoxic. Ekpe et al. (2020) noted in his research that creatinine and urea levels were 2.26 ± 1.33mg/dl and 8.30 ± 1.01 mmol/L was recorded respectively, which was significantly higher than the normal

reference ranges of 0.50–0.90 mg/dL for creatinine and 1.0–1.8 mmol/L for urea. Experimental studies demonstrate that lead exposure induces hepatocellular injury through oxidative stress mediated mechanisms, including excessive generation of reactive oxygen species (ROS). These biochemical disruptions compromise membrane integrity and enzyme function, resulting in elevated serum biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Persistent oxidative insult may further activate inflammatory cascades and apoptotic pathways, aggravating hepatic damage (Sharma et al., 2012). Lead disrupts multiple physiological pathways, notably by increasing oxidative stress and depleting endogenous antioxidants, which leads to cellular damage in organs such as the liver and kidneys. Elevated serum AST and ALT are indicative of hepatocellular disruption, while increased ALP suggests biliary dysfunction or cholestatic injury (Flora et al., 2021).

The use of medicinal plants as phytotherapeutics has increased noticeably as a result of great strides in the field of phytotherapy and their proven therapeutic safety profile and antioxidant properties in protecting against heavy metal toxicity (Mahmoudian-Sano et al., 2017). Some medicinal plants have been found out to be a better alternative to conventional drugs in treating certain diseases (Hassani et al., 2016; Jutte et al., 2017; Yea et al., 2017). The extensive medicinal value of plants is largely attributed to the presence of phytochemicals, which are naturally synthesized to protect them from predators and environmental stress. These compounds contribute to the management and treatment of various diseases, with evidence supporting their potential as effective therapeutic alternatives (Yea et al., 2017). Medicinal plants offer several advantages, including easy accessibility, natural origin, affordability, and significant therapeutic efficacy (Izzo et al., 2016; Larijani et al., 2010).

Citrullus lanatus (watermelon) is a member of the Cucurbitaceae family (Zia et al., 2021). It is a large fruit that may be oblong, ovoid, or round in shape, characterized by a tough green or whitish rind that is often striped or variegated. Its inner flesh is juicy and sweet, typically red, pink, or yellow, and contains numerous seeds. Native to tropical Africa, the fruit consists of approximately 93% water, which explains its common name, watermelon. Watermelon is considered an ancient fruit believed to have originated from the Kalahari Desert in Africa, although it is now widely cultivated and found in many regions. In recent years, C. lanatus has gained increasing scientific attention due to its diverse biological activities (Erhirhie & Ekene, 2013). The seeds are a natural source of some phytochemicals like phenols, tannis, flavonoids, alkaloids (Nwankwo et al., 2014), and a rich source of proteins and minerals and citrulline (Bazabang et al., 2018). Watermelon seeds extracts are antioxidants reservoir and is seen to have the ability to also reduce oxidative stress caused by lead exposure and enhance liver function in rats induced with lead in dose dependent manner. However, the defensive or beneficial effects of watermelon seeds aqueous extract on lead-induced liver and kidney toxic effects observed in male Wistar rats remain underexplored, hence the need to examine the hepatorenal protective effects of Watermelon (*Citrullus lanatus*) seed aqueous extract in lead-induced toxicity in male wistar rats

This present study investigated the effects of the aqueous extracts of water melon (*Citrullus lanatus*) seeds in mitigating the hepatorenal toxic effects of lead exposure in the male wistar rats.

Despite the widespread use of medicinal plants in managing heavy metal toxicity, the hepatorenal protective effects of aqueous extracts of watermelon (*Citrullus lanatus*) seeds against lead-induced damage remain under-explored. Existing studies have focused on other parts of the fruit (e.g., rind or flesh), leaving a gap in knowledge regarding the seed extract's dose-dependent efficacy, particularly in male Wistar rats. This study addresses whether watermelon seed aqueous extract can mitigate lead-induced liver and kidney dysfunction. To determine the effect of lead acetate (50 mg/kg) on serum levels of AST, ALT, and ALP (liver function markers) on urea and creatinine (renal function markers) in male Wistar rats; To assess the dose-dependent protective effects of 200 mg/kg and 400 mg/kg aqueous watermelon seed extract on lead-induced alterations in these biochemical parameters.. To compare the efficacy of low-dose (200 mg/kg) versus high-dose (400 mg/kg) watermelon seed extract in restoring hepatorenal function.

Materials and Methods: Watermelon (*Citrullus lanatus*) seeds was purchased from the Choba market and authenticated by a plant taxonomist.**Preparation of the aqueous extracts of watermelon (*Citrullus lanatus*) seeds.:** The seeds of *C. lanatus* were air - dried and ground into a powdered form with mortar and pestle which was soaked with water for 48 hours. Mixture was stirred and kept for 12 hours and separated through filtration to get the extract which was kept in a storage container and stored in a refrigerator prior to use.**Animals and Experimental Design :** The male Wistar rats were purchased from the Animal farm, University of Port Harcourt, Choba, Rivers State. Twenty-four Wistar rats were weighed and housed in a wire mesh cage in the animal laboratory of Ignatius Ajuru University of Education (IAUE), Rumuolumeni. They were allowed to acclimatize to the laboratory conditions for two weeks prior to the start of the experiment. The rats were fed with rat feed and water; and properly taken care of under a standard hygienic condition. The rats were randomly divided into 4 groups, with 6 rats each. The rats weighed between 120 – 126g.

Group I – Positive Control (Water and feed only).

Group II – Negative Control - Lead (50mg/kg).

Group III - Lead (50mg/kg) + 200mg Watermelon seed aqueous extract.

Group IV - Lead (50mg/kg) + 400mg Watermelon seed aqueous extract.

Lead and Extract Administration: Lead acetate and extracts were given once daily by oral gavage for a period of 14 days. After the treatment period, the animals were fasted for 24 hours before being sacrificed. They were anaesthetized with chloroform and then euthanized the

following day, after which blood samples were collected through cardiac puncture using sterile syringe and needles and dispensed into plain bottles for biochemical analysis.

Biochemical Assays: Blood samples were collected. Serum AST, ALT, ALP, urea, and creatinine were quantified using standard spectrophotometric assay kits. Data are expressed as mean ± SEM.

Statistical Analysis: The data obtained were displayed in tables and reported as mean ± standard deviation. The findings were further subjected to statistical analysis using Analysis of Variance (ANOVA) and the Least Significant Difference (LSD) test with the Statistical Package for the Social Sciences (SPSS) software. Results were regarded as statistically significant at a probability level of $P < 0.05$.

Results: Effect of the aqueous extracts of water melon seeds on liver functions of lead-induced wistar rats : The liver function test results indicated that Group 2 (negative control) exhibited elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) compared to Group 1. In contrast, Group 3 (lead + 200 mg/kg watermelon seed extract) showed a reduction in AST, ALT, and ALP levels. Similarly, Group 4 (lead + 400 mg/kg aqueous watermelon seed extract) produced a more pronounced decrease in AST, ALT, and ALP compared to the lead-only group.

As presented in Table 1, ALP levels showed a significant difference ($P \leq 0.05$) when compared across Groups 1 and 2, while AST and ALT did not differ significantly between these groups. However, when compared with Group 2, ALP levels were significantly reduced following treatment in Group 4.

Effect of the aqueous extracts of water melon seeds on renal functions of lead-induced wistar rats: Results of the renal functions analyzed showed that group 2 (negative control group) elevated the levels of urea (4.80 ± 0.10) and creatinine (2.67 ± 1.16). Group 3 upon administration with the 200mg/kg of watermelon seed extract reduced the levels of urea (3.77 ± 0.17) and creatinine (64.33 ± 4.04) that were caused by lead exposure. Group 4 when administered with 400mg/kg of watermelon seeds reduced the levels of urea (2.43 ± 0.59) and creatinine (57.67 ± 1.77) when compared to the lead group. (Table 2)

Table 2 showed that in comparison to group 1 (normal control), there was a slight increase in urea concentration that was not statistically significant when treated with the extracts (groups 2 and 3). However, when compared when compared with group 2 (negative control), there was a slight reduction that was not statistically significant in the urea concentration when treated with the extracts (groups 1, 3 and 4). Likewise, in comparison to group 1 (normal control), there was a non-significant increase in the creatinine concentration when treated with the extracts (groups 2, 3 and 4). However, when compared with group 2 (negative control), there was a small reduction that was not statistically significant in the creatinine concentration when treated with the extracts (groups 1, 3 and 4)

Discussion of Findings: The activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were significantly elevated ($p < 0.05$) in the negative control group (Group 2) compared to the normal control (Group 1). The increased levels of these liver enzymes in the lead-exposed group, particularly AST, suggest hepatocellular injury caused by lead toxicity. This liver damage may be linked to lead-induced generation of free radicals and other reactive oxygen species, which results in excessive oxidative stress on liver cells, leading to cellular degeneration. Such injury is often reflected in elevated serum liver enzyme levels, as observed in this study. Notably, treatment with the extracts (Groups 3 and 4) reversed these effects in a dose-dependent manner. A progressive reduction in serum AST, ALT, and ALP levels was observed with increasing concentrations of the extract when compared to the negative control group (Group 2). This supports the idea that *Citrullus lanatus* (watermelon) seed extracts may protect or restore liver function against lead-induced inflammation, likely due to their rich phytochemical composition with strong antioxidant activity. This finding is consistent with the report of Ebuehi et al. (2012).

The observed decrease in liver enzyme levels may be attributed to the antioxidant potential of the extract (Heidari et al., 2012), which has been reported to contain bioactive compounds such as alkaloids, glycosides, saponins, flavonoids, phenols, tannins, and terpenes (Saidu et al., 2014). Similarly, previous studies have shown that watermelon contains phytochemicals including phenols, saponins, tannins, flavonoids, alkaloids, as well as carotenoids, lycopene, and citrulline (Nwankwo et al., 2014). These findings are in agreement with those reported by Ibiam et al. (2013). The kidneys play a key role in maintaining physiological balance by regulating body fluids and eliminating metabolic wastes such as urea and creatinine. Blood levels of urea and creatinine are commonly used as indicators of renal function and are sensitive markers of kidney damage (Olubunmi & Adeyemi, 2015). In this study, elevated urea and creatinine levels were observed in the group treated with lead (50 mg/kg) compared to the control group, indicating impaired renal function, consistent with reports by Lepedda et al. (2016). These elevated levels likely reflect kidney damage caused by lead exposure, in agreement with Abdulazeez (2014) and Sharma et al. (2014). Conversely, administration of watermelon seed extracts to lead-exposed male Wistar rats significantly reduced serum urea and creatinine levels in a dose-dependent manner. The reduction in urea may be associated with the extract's ability to improve glucose regulation and enhance insulin activity, thereby reducing protein breakdown, as previously suggested by Umar (2015). Similarly, the decrease in creatinine levels, as reported by Gwana et al. (2014), may be due to the extract's protective effect on the kidneys, enhancing glomerular filtration and overall renal function. The results of this current research is in agreement with the findings of Rabiu et al. (2020) who carried out a research on "Ameliorative Effect of Aqueous Seed Extract of Citrullus lanatus on Liver Function Parameters and Markers of Oxidative Stress in Lead-Treated Rats" and results showed the protective effect of aqueous watermelon seed extract against lead-induced hepatotoxicity in rats. The rats exposed to lead acetate exhibited significant elevations in serum ALT, AST, ALP, indicating liver injury and oxidative stress. Administration of aqueous watermelon seed extract significantly reduced these biochemical alterations and

improved antioxidant enzyme activities. It was then concluded that watermelon seed extract possesses substantial hepatoprotective activity due to its antioxidant constituents. Similarly, Michael et al. (2021) in their research on "Watermelon Rind Ethanol Extract Exhibits Hepatorenal Protection Against Lead-Induced Impaired Antioxidant Defenses in Male Wistar Rats". Although this study used watermelon rind rather than seeds, it is highly relevant because it investigated protection against lead toxicity. Lead acetate significantly increased oxidative stress markers and impaired liver and kidney functions. Treatment with watermelon rind extract restored antioxidant enzyme levels and reduced tissue injury. This attributed the protective effects to the abundant phenolic and flavonoid compounds.

Conclusion: This study demonstrates that aqueous extract of Citrullus lanatus (watermelon) seeds confers significant dose-dependent hepatorenal protection against lead-induced toxicity in male Wistar rats. The higher dose (400 mg/kg) was more effective, restoring AST, ALT, and ALP levels to near-normal values and reducing urea and creatinine levels, although the latter reductions were not statistically significant. The observed protective effects are likely mediated by antioxidant phytochemicals (e.g., flavonoids, alkaloids, phenols) present in the seeds. Thus, watermelon seed extract represents a promising, affordable, and natural therapeutic option for mitigating heavy-metal-induced liver and kidney damage.

Recommendations: Based on the findings of this study, aqueous extract of watermelon seeds shows promising protective actions against lead-induced liver and kidney damage. It is therefore recommended that:**;** Future studies should isolate, characterize, and test individual phytochemicals (e.g., flavonoids, citrulline, lycopene) from watermelon seeds to identify the most active hepatorenal protective agents.**;**Oxidative stress biomarkers (e.g., MDA, SOD, CAT, GSH) and inflammatory markers (e.g., TNF-α, IL-6) should be incorporated to elucidate the exact mechanism of action beyond enzyme assays.**;** Liver and kidney histopathology should performed to correlate biochemical findings with tissue-level structural protection.**;** Treatment period beyond 14 days should be extended and evaluate higher doses to establish a full safety profile and therapeutic window.**;** Pilot studies should be conducted in animal models with chronic low-level lead exposure mimicking human environmental exposure.**;**The efficacy of aqueous extract with standard chelating agents (e.g., EDTA) or known hepatoprotective drugs (e.g., silymarin) should be compared to benchmark therapeutic potential.

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Table 1. Effect of the aqueous extracts of water melon seeds on liver functions of lead-induced wistar rats

Groups	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
1	11.67 ± 0.58	11.67 ± 1.53	145.67 ± 5.03
2	29.33 ± 2.52	28.00 ± 1.00	205.33 ± 5.03
3	21.00 ± 1.73	19.33 ± 2.31	177.00 ± 6.50
4	13.00 ± 1.00	11.00 ± 1.00	138.00 ± 2.00[b]

GRP 1=Normal control; GRP 2= Negative control (Lead 50mg/kg); GRP 3 = lead + 200mg/kg watermelon seed aqueous extract; GRP 4 = lead + 400mg/kg watermelon seed aqueous extract
AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; ALP = Alkaline Phosphatase

Table 2. Effect of the aqueous extracts of water melon seeds on renal functions of lead-induced wistar rats

Groups	Urea (umoI/l)	Creatinine (umoI/l)
1	2.47 ± 0.12	59.00 ± 2.65
2	4.80 ± 0.10	72.67 ± 1.16
3	3.77 ± 0.17	64.33 ± 4.04
4	2.43 ± 0.59	57.67 ± 1.77

GRP 1=Normal control; GRP 2= Negative control (Lead 50mg/kg); GRP 3 = 200mg/kg watermelon seed aqueous extract; GRP 4= 400mg/kg watermelon seed aqueous extract