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Protective and Therapeutic Effects of Aqueous Leaf Extract Of *Nephrolepis Biserrata* on Cadmium-Induced Hepatorenal Toxicity in Male Wistar Rats

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ABSTRACT: *Nephrolepis biserrata*, commonly known as giant sword fern, has been recognized for its medicinal value in traditional medicine across various countries. Cadmium chloride ($CdCl_2$), a toxic environmental pollutant, poses significant threats to liver and kidney function through oxidative stress and inflammation. Hence the objective of this paper is to evaluate the protective and therapeutic effects of aqueous leaf extract of *Nephrolepis biserrata* on cadmium induced hepatorenal toxicity in male Wistar rats using appropriate standard methods by assessing Liver and kidney function biomarkers (ALT, AST, ALP, TB, TP, albumin, urea, creatinine, electrolytes. Data obtained shows that the levels of phytochemical were alkaloids (106.21), flavonoids (272.70), saponins (80.86), phenols (120.01), steroids (66.76), tannins (280.75) and terpenoids (74.62)**.** Cadmium exposure significantly elevated ALT, AST, ALP, total bilirubin, urea, and creatinine, while reducing albumin, total protein, and electrolyte levels. Treatment with *N. biserrata* significantly ameliorated these alterations in a dose dependent manner. The extract exhibited strong antioxidant, anti -inflammatory, and membrane stabilizing properties attributed to its rich phytochemical content, including flavonoids, alkaloids, saponins, and polyphenols. Aqueous leaf extract of *Nephrolepis biserrata* demonstrated hepatorenal potential against cadmium induced toxicity in Wistar rats. Its therapeutic efficacy supports its potential as a natural remedy for managing environmental heavy metal toxicity like cadmium.

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Cadmium chloride toxicity severely impacts liver and kidney function, causing oxidative stress, enzymatic dysfunction, and cellular damage (Rahimzadeh *et al.*, 2017; Arroyo *et al.*, 2012). This study investigates the protective effects of *Nephrolepis biserrata*, a fern with bioactive compounds such as flavonoids, alkaloids, polyphenols, and terpenoids, known for their antioxidant and anti-inflammatory properties Fajuke *et al.*, 2018; Mirkov *et al.*, 2020). The extract enhances hepatorenal defense mechanisms, restoring enzymatic balance and mitigating inflammation. (Oyawaluja *et al.*, 2024) Consequently, the objective of this paper is to evaluate the protective and therapeutic effects of aqueous leaf extract of Nephrolepis biserrata on cadmium induced hepatorenal toxicity in male Wistar rats aqueous *Nephrolepis biserrata* leaf extract to cadmium-induced Wistar rats and observed reduced liver enzyme levels (AST, ALT, ALP), normalized bilirubin metabolism, improved renal function

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markers (urea and creatinine), and increased total protein and albumin levels. (Monago-Ighorodje and Peters,2024; Habashy *et al.,* 2021); Belinskaia *et al.,* 2021) provide an integrative analysis of albumin in biochemical and pathophysiological contexts. Sodium and chloride levels rose due to renal tubular reabsorption influenced by the bioactive compounds, while bicarbonate concentrations declined post-cadmium exposure (Benet *et al.,* 1996); Ginès *et al.,* 2021). These findings align with previous research, confirming *Nephrolepis biserrata*'s hepatoprotective, nephroprotective, antioxidant, and chelating properties Srivastav and Prajapati, 2023); Oladele *et al.,* 2017).

MATERIALS AND METHODS

Collection and Identification of Plant Material and Experimental Animals: Fresh Nephrolepis biserrata leaves were collected from Choba riverbank, Rivers State, Nigeria, and processed into an aqueous extract following Sofowara's (1993) method. The study involved 25 adult male Wistar rats (180–220g) obtained from the University of Port Harcourt's Faculty of Basic Medical Sciences. The rats were fed a standard chow and acclimatized for two weeks before the experiment.

Ethical Approval: The study adhered to the ARRIVE guidelines and the Laboratory Animal Care standards outlined in NIH Publication 1996, No. 85-23. The experimental protocol was thoroughly reviewed and approved by the University of Port Harcourt Ethical Committee, with reference no UPH/CEREMAD/REC/MM98/050.

Phytochemical Screening of the Plant: The fresh leaves of the plant were subjected to phytochemical analysis according to the method outlined by (Rahimzadeh *et al.,*, 2017; Arroyo *et al.*,,2012).The phytochemical analysis was done to detect the presence of secondary metabolites, such as alkaloids, glycoside, saponins, tannins, flavonoids, phenolic compounds, steroids, polyphenols, cardiac glycosides and terpenes.

Experimental Design: Twenty-five adult male Wistar rats (8–10 weeks old, weighing 180–220g) were randomly divided into five groups (n=5). The rats were induced with 5mg/kg body weight of cadmium chloride ($CdCl_2$) for 14 days, followed by plant extract administration starting on day 15 and continuing for another 14 days. Group A served as the normal control, receiving standard feed and water. Group B was given 5mg/kg $CdCl_2$. Group C received 100mg/kg of the plant extract, Group D received 200mg/kg, and Group E was administered 300mg/kg of the extract.

Collection and Analysis of Liver and Kidney Parameter: At the end of the 28-day experiment, blood samples were collected via cardiac puncture from anesthetized rats. Serum extraction was conducted by centrifugation at 3000rpm for 20 minutes. Biochemical analyses using a spectrophotometer measured electrolyte levels (Na^+, K^+, Cl^-, HCO_3^-), renal markers (Urea, Creatinine), and liver enzymes (AST, ALT, ALP, TP, TB). Reagent kits from Effective Medical, Port Harcourt, were used following manufacturer guidelines and Ghazal *et al.,* 2021) methodology.

Statistical Analysis: Data collected were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's (HSD) multiple comparison test in Statistical Package for Social Sciences (SPSS for Windows Version, 23.0). The significance of the data was assessed using a *P*-value of less than 0.05 and reported as Mean ± Standard Error of Mean (SEM).

RESULTS AND DISCUSSION

Phytochemical Composition of the Leaves of Nephrolepis biserrata: The phytochemical analysis showed the presence of the following phytochemicals-alkaloids, flavonoids, saponins, phenols, steroids, tannins and terpenoids.

Table 1: Quantitative Phytochemical Composition of Nephrolepis biserrata Leaves (ppm)

Phytochemical	Concentration(ppm)
Alkaloids	106.21
Flavonoids	272.70
Saponins	80.86
Phenols	120.01
Steroids	66.76
Tannins	280.75
Terpenoids	74.62

Effect of Aqueous Leaf Extract of Nephrolepis biserrata on cadmium chloride induced Wistar rats: The administration of Nephrolepis biserrata aqueous leaf extract significantly reduced the activities of hepatic enzymes AST, ALT, and ALP in cadmium chloride–induced Wistar rats. As illustrated in Figure 1 below, the enzyme levels in treatment groups C, D, and E showed a notable decline compared to the negative control (Group B), suggesting a hepatoprotective effect of the extract, protecting against oxidative stress and hepatorenal damage. Its flavonoids, phenolic compounds, and tannins counteracted toxicity, supporting liver and kidney function. These findings align with Mirkov *et al.*,, 2020). and Oyawaluja *et al.*,, 2024, reinforcing its therapeutic potential. This is as a result of the

bioactive components like flavonoids, polyphenols, and vitamins contained in Nephrolepis biserrata which neutralizes reactive oxygen species (ROS) from cadmium chloride exposure. Its antioxidant activity reduces ALT, AST, and ALP release, counteracts oxidative damage to hepatocytes and renal cells, restores membrane integrity by stabilizing membrane permeability, and preserving the liver and kidney function thereby highlighting the hepatoprotective and nephroprotective effects against cadmium toxicity (Monago-Ighorodje and Peters, 2024).

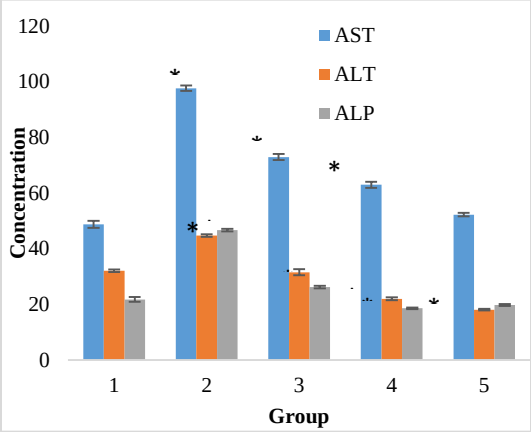


Fig 1: Effect of Aqueous Leaf Extract of Nephrolepis biserrata on Serum AST, ALT, and ALP Levels in Cadmium Chloride–Induced Wistar Rat

*Values are reported as Mean ± Standard Error of Mean (M±SEM) (n =5). Values with character * indicate statistical significance difference (p<0.05) when compared with the normal control (group A).*

Effect of aqueous leaves extract of Nephrolepis biserrata on total protein and albumin: The result shows that aqueous *Nephrolepis biserrata* leaf extract increased total protein and albumin levels in cadmium-induced Wistar rats (Groups C, D, and E), while the negative control (Group B) showed a significant decline as shown in Fig 2 below. No notable difference was found between treated groups and the normal control (A). This finding supports the extract's protective and antioxidant effects of Flavonoids, tannins, and polyphenols found in the liver and kidney function, reinforcing its therapeutic potential (Habashy *et al.*, 2021; Belinskaia *et al.*, 2021). Treated groups showed increased total protein and albumin levels, confirming its hepatoprotective, nephroprotective, antioxidant, and anti-inflammatory effects. When compared to the negative control (B) group, the concentration of albumin and total protein increased significantly ($p<0.05$) in the experimental groups C, D and E). The results show no significant difference between the normal control group A and the experimental groups.

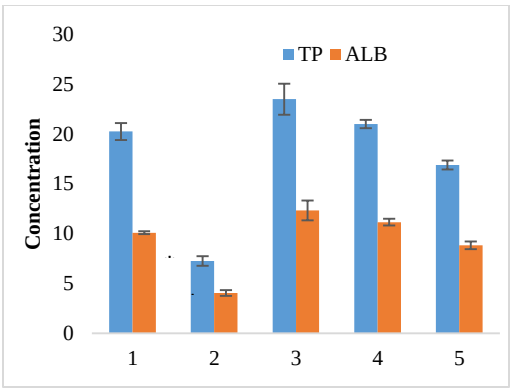


Fig 2: Effect of aqueous leaves extract of Nephrolepis biserrata on total protein and albumin levels in Cadmium Chloride–Induced Wistar Rat

*Values are reported as Mean ± Standard Error of Mean (M±SEM) (n =5). Values with character * indicate statistical significance difference (p<0.05) when compared with the normal control (group A).*

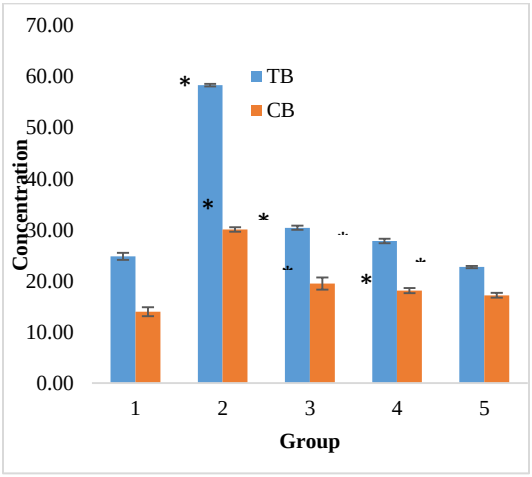


Fig 3: Effect of aqueous leaves extract of Nephrolepis biserrata on total bilirubin and conjugated bilirubin levels in cadmium induced Wistar rats.

*Values are reported as Mean ± Standard Error of Mean (M±SEM) (n =5). Values with character * indicate statistical significance difference (p<0.05) when compared with the normal control (group A)*

Effect of aqueous leaves extract of Nephrolepis biserrata on total bilirubin and conjugated bilirubin: Nephrolepis biserrata reduced total and conjugated bilirubin levels in experimental groups compared to the negative control, which exhibited elevated concentrations. The decrease is attributed to its hepatoprotective, antioxidant, and chelating properties, aiding in cadmium detoxification and liver regeneration. Normalized liver enzyme levels (ALT, AST, ALP) improved bilirubin processing, further lowering its concentration. These findings align with research by Oloyede *et al.*, (2019). In comparing with the normal control (A) group, the concentration of total bilirubin and conjugated bilirubin decreased across all the experimental groups except in group B

where its concentration increased significantly as shown in Fig 3.

Effect of Aqueous Leaf Extract of Nephrolepis biserrata on Sodium, Potassium and Bicarbonate Levels: A decrease in bicarbonate (HCO_3^-) concentration was observed across all experimental groups treated with the aqueous leaf extract of *Nephrolepis biserrata* following cadmium chloride-induced hepatorenal damage. The levels of sodium and chloride significantly decreased in all experimental groups (C, D and E) when compared to normal control group (A). The levels of bicarbonate show a significant difference in all experimental groups (C, D and E) when compared to the normal control group (A) as shown in Fig 4. However, an there was a significant increase in serum sodium and chloride levels. This effect is linked to bioactive compounds that enhance renal reabsorption and Aquaporin regulation (Benet *et al.*,,1996). The extract counteracted cadmium-induced membrane disruption, facilitating cellular repair and ionic redistribution, leading to temporary sodium and chloride elevations. These findings align with Oyawaluja *et al.*,, 2024; Ginès; Krag *et al.*,, 2021)

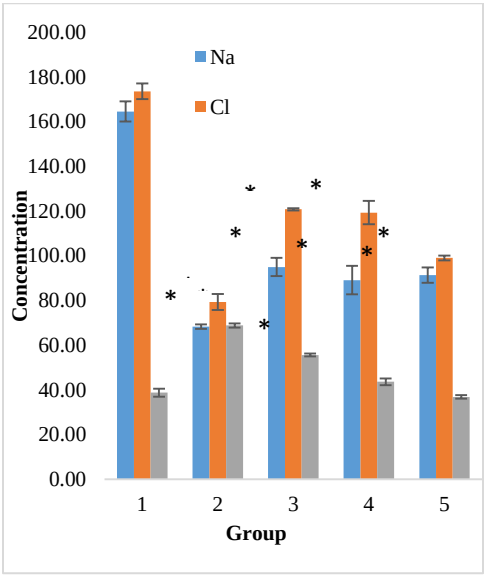


Fig 4: Effect of Aqueous Leaf Extract of Nephrolepis biserrata on Sodium, Potassium and Bicarbonate Levels in cadmium induced Wistar rats

*Values are reported as Mean ± Standard Error of Mean (M±SEM) (n =5). Values with character * indicate statistical significance difference (p<0.05) when compared with the normal control (group A).*

Effect of Aqueous Leaf Extract of Nephrolepis biserrata on Creatinine and Urea Concentration: Urea and creatinine concentrations decreased significantly in all experimental groups treated with the plant extract after cadmium chloride induction. These results conform with the research conducted by Koriem *et al.*, 2009), strongly suggesting restored renal function and the nephroprotective effects of *Nephrolepis biserrata*. In Fig 5 it can be observed that urea and creatinine levels significantly increased in the negative control group (B) when compared to all the experimental groups (C, D and E) and the normal control group (A).

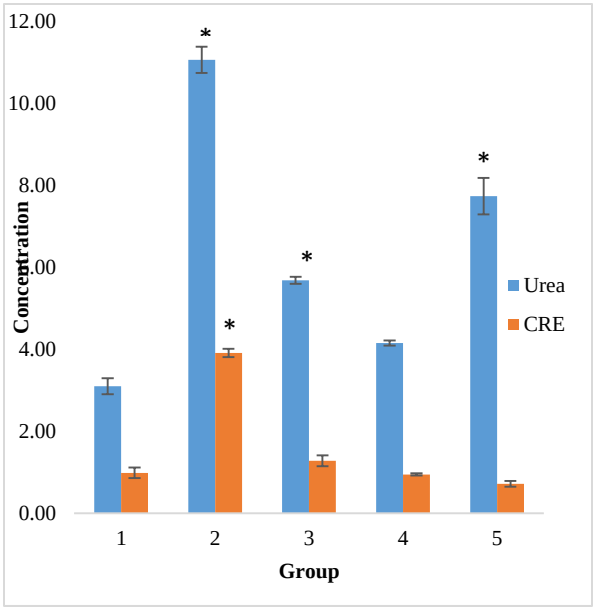


Fig 5: Effect of Aqueous Leaf Extract of Nephrolepis biserrata on Creatinine and Urea Concentration Levels in Cadmium induced Wistar rats.

*Values are reported as Mean ± Standard Error of Mean (M±SEM) (n =5). Values with character * indicate statistical significance difference (p<0.05) when compared with the normal control (group A).*

Cadmium chloride induces renal tubular necrosis and glomerular dysfunction, leading to impaired filtration of creatinine and urea and causes elevation of blood urea nitrogen (BUN) and creatinine levels. The use of *Nephrolepis biserratea* extract likely facilitates renal tissue repair and restoration of glomerular filtration rate (GFR), which helps to improve excretion of nitrogenous wastes and normalize blood levels of urea and creatinine. The extract is rich in flavonoids, polyphenols, and other antioxidants (Chettri, U *et al.*,, 2020), which scavenge free radicals generated by cadmium and reduce oxidative stress in renal cells. This protects or regenerates nephron structure and prevents further damage and enhances the excretory function of the kidneys, leading to reduced accumulation of waste products like urea and creatinine.

Conclusion: This study has demonstrated that aqueous leaf extract of *Nephrolepis biserrata*

significantly mitigates the hepatotoxic and nephrotoxic effects of cadmium chloride in Wistar rats. The extract effectively restored liver and kidney biomarkers, improve protein and electrolytes balance. These therapeutic effects are largely attributed to its abundant phytochemical constituents such as flavonoids, alkaloids, saponins, and polyphenols, which possess antioxidant, anti-inflammatory, and membrane stabilizing activities. The observed biochemical recovery indicates that *Nephrolepis biserrata* can be used as a natural therapeutic agent in the treatment of cadmium induced organ damage.

Declaration of Conflict of Interest: The authors declare that no known conflict of interest or personal relationships that could have influence the work reported in this paper.

Declaration of Data Availability: Data are available upon request from the corresponding author

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