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Protective Effect of *Solanum Macrocarpon* Leaves Extracts on Adenine-Induced Acute Nephrotoxicity in Male Wistar Rat

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Abstract

Adenine causes damage to kidney structure and functions; thus, it affects its excretory functions and metabolism. *Solanum macrocarpon* is a vegetable commonly eaten in Nigeria. This study was designed to examine the potential anti-nephrotoxicity effects of *Solanum macrocarpon* leaves extract on adenine-induced nephrotoxicity in male Wistar rats. A total of thirty (30) rats were obtained from the Department of Animal Science, University of Ibadan, and were divided into six (6) groups with five (5) animals in each group. The animals were fed with standard feed and drinking water, and treated as follows:, Group 1: distilled water, Group 2: 1000 mg/kg of Adenine only, Group 3: Adenine + 1050 mg/kg ethanol extract of *Solanum macrocarpon*, Group 4: Adenine + 1050 mg/kg diethyl ether extract of *Solanum macrocarpon*, Group 5: 1050mg/kg ethanol extract of *Solanum macrocarpon* and Group 6: 1050 mg/kg diethyl ether extract of *Solanum macrocarpon*. Biochemical parameters such as creatine, urea, uric acid, sodium, potassium, phosphorus, bicarbonate, and superoxide dismutase were determined in the plasma using a Spectrophotometer. Data were analyzed using one–way analysis of variance (ANOVA) followed by Tukey's test, with $P < 0.05$ considered significant. The results indicated a significant increase ($P < 0.0$) in SOD, creatinine, potassium, sodium, phosphorus urea and uric acid in the group treated with adenine alone, with a significant decrease of 33.3% in bicarbonate when compared with the control. Histopathological examination showed nephritis, through congestion, hypertrophied glomeruli, vacuolization of the endothelial cells lining the glomerular tuft, and interstitial nephritis by adenine treatment. The elevated creatine, SOD, potassium, sodium, phosphorus, urea and uric acid were significantly improved. In the groups treated with *Solanum macrocarpon* alcoholic extracts. In conclusion, *Solanum macrocarpon* extracts mitigated the nephrotoxicity caused by adenine.

Keywords: Adenine, *Solanum macrocarpon*, nephrotoxicity, histopathology

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Introduction

Chronic kidney disease (CKD) poses a significant global health challenge, characterized by the gradual loss of renal function over time, often culminating in end-stage renal disease (ESRD) (Oboh *et al.,* 2020). The prevalence of CKD has increased dramatically worldwide, placing substantial burdens on healthcare systems already strained by resource limitations (Cockwell and Fisher, 2020). Factors such as aging populations, rising rates of non-communicable diseases like type 2 diabetes mellitus (T2DM), and widespread exposure to nephrotoxic agents contribute to the growing CKD epidemic (Zhang *et al.,* 2020). As CKD progresses, patients face a higher risk of cardiovascular events, hospitalizations, and mortality, highlighting the urgent need for effective therapeutic interventions (Kovesdy, 2020).

Adenine, as a nitrogenous heterocyclic compound of purines, damages kidney structure and function at certain doses and causes impairment of energy metabolism (Li *et al.,* 2021).
Adenine is an important component of biological DNA. If DNA is damaged, it will trigger apoptosis and gene mutation, seriously affecting the organism's normal physiological function. Adenine as a growth regulator can improve the yield and quality of crops. Nuclear Factor Erythroid 2- Related Factor 2 (Nrf2) is the basis of various genes encoding detoxification enzymes, antioxidant proteins, exogenous transporter proteins, and other stress response mediators. It is a major transcriptional regulator that induces the expression of downstream target genes (Shelton *et al.,* 2013).
Administration of adenine leads to the accumulation of 2, 8 - dihydroxyadenine crystals within the renal tubules, resulting in tubulointerstitial nephropathy and impairment of renal function (Diwan *et al.,* 2018). Adenine-induced nephrotoxicity shares several pathophysiological features with human CKD, making it a clinically relevant model for investigating potential therapeutic interventions
Adenine-induced nephrotoxicity primarily results from the formation of insoluble 2,8-dihydroxyadenine (DHA) crystals which precipitate in the renal tubules, leading to tubular obstruction, inflammation, and subsequent renal injury (Choi *et al*., 2014). The accumulation of DHA crystals triggers oxidative stress and inflammatory responses, exacerbating kidney damage (Kim *et al*., 2015). This crystal-induced injury mimics certain aspects of human chronic kidney diseases, making it a valuable model for studying nephrotoxicity and potential therapeutic interventions (Basile *et al*., 2016). Many societies appreciate traditional herbal preparations for their perceived safety, accessibility, and cultural importance. The pursuit of new therapies for CKD and kidney injuries has sparked a growing interest in investigating natural remedies that may offer protective benefits to renal health. *Solanum macrocarpon*, or African eggplant, stands out as a candidate due to its extensive traditional usage and medicinal properties (Olayemi *et al.,* 2021). However, despite promising preclinical evidence, the translational potential of *S. macrocarpon* in clinical settings remains largely unexplored. Clinical trials evaluating the safety, efficacy, and optimal dosing regimens of *S. macrocarpon* preparations are warranted to validate its therapeutic utility in human (Olayemi *et al*., 2021). This study aimed to investigate the nephroprotective properties of *Solanum macrocarpon* leaves.

Materials And Methods

Chemicals

Teco products (Sodium kit, Phosphorus kit, Potassium kit, and Bicarbonate kit), Spectrum products (Uric acid kit, Urea kit, and Creatinine kit), Tris HCL, EDTA, Pyrogallol, Sodium Azide, Hydrogen peroxide, Sodium hydroxide, and Hydrochloric acid.

Materials

Needle and syringe, Eppendorf tubes, surgical gloves, universal bottles, Glassware (Beaker, conical flasks, measuring cylinder, test tubes, dissecting board, dissecting set, EDTA tubes, micropipette and tips. Ultraviolet-visible spectrophotometer, centrifuge, homogenizer, water bath, refrigerator, rotary evaporator, weighing balance, oven.

Method

Extraction of Plant Material

The *Solanum macrocarpon* leaves were purchased from a local market and were identified by a plant taxonomist at the University of Ibadan with authentication number (UIH-23425). The leaves were air dried for two weeks in the absence of sunlight to avoid depletion of their phytochemicals. 84g of the *Solanum macrocarpon* leaves was weighed, and divided into two equal parts. One half (42 g) was macerated in ethanol, while the remaining 42 g was macerated in diethyl ether for 72 hours. The mixtures were filtered with muslin cloth and the filtrate obtained will be re-filtered using Whatman No. 1 filter paper and concentrated using a rotary evaporator to obtain the ethanol and the diethyl ether extract respectively.

Experimental Animals

Thirty (30) male albino Wistar rats (100 – 200 g) was purchased from the University of Ibadan Animal House. The rats were given conventional rat chow and unlimited water during their two-week acclimatization in the Animal House of Augustine University's Department of Chemical Sciences in Ilara-Epe, Lagos State, in compact cages with adequate ventilation.

Experimental Designs

After a two-week acclimatization, the rats were randomly assigned to six groups, with five rats per group. Groups 1 – 3 were given adenine for 2 weeks before treatment as follows: Group 1: distilled water, Group 2: 1000 mg/kg of Adenine only, Group 3: 1000 mg/kg Adenine + 1050 mg/kg ethanol extract of *S. Macrocarpon*, Group 4: 1000 mg/kg Adenine + 1050 mg/kg diethyl ether extract of *S. macrocarpon*, Group 5: 1050 mg/kg ethanol extract of *S.* macrocarpon, Group 6: 1050 mg/kg diethyl ether extract of *S. macrocarpon.* Treatment with *Solanum macrocarpon* extracts was done for 2 weeks. Each group received treatments daily via oral gavage. The body weight and feed intake were evaluated throughout the trial. The rats were fasted overnight, weighed, and anaesthetized using diethyl ether before being sacrificed. Blood samples were collected by cardiac puncture into appropriately labeled EDTA tubes. The blood was then centrifuged for 10 minutes at 3500 rpm to obtain plasma. The supernatants were collected, kept in the refrigerator, and preserved for further biochemical assays.

Plasma biochemical and antioxidant indicators.

Plasma biochemical indicators (Creatinine, urea, uric acid, bicarbonate, phosphorus, sodium, potassium), and plasma antioxidant indicator (SOD) were carried out as specified. using an ultraviolet spectrophotometer.

Statistical Analysis

All values were expressed as mean ± standard error mean (SEM), and the test of significance between groups was done using One-Way Analysis of Variance (ANOVA) with Tukey's post-hoc test, with p-values < 0.05 considered statistically significant.

Results

Effects of S. macrocarpon leaves extracts on plasma creatinine levels of adenine intoxicated male Wistar rats

Adenine intoxication significantly increased ($P < 0.05$) creatinine levels compared to the control group. Treatment with ethanol and diethyl ether extracts significantly decreased ($P < 0.05$) the elevated (Figure 1)

Effects of S. macrocarpon leaves on plasma bicarbonate and potassium levels of adenine intoxicated male Wistar rats

Adenine intoxication significantly increased ($P < 0.05$) bicarbonate and decreased potassium levels compared to the control group. Intervention with extracts did not significantly ($P > 0.05$) affect the bicarbonate level whereas the potassium level was moderately increased (Figure 2)

Effects of S. macrocarpon leaves on plasma sodium land phosphorus levels of adenine intoxicated male Wistar rats

Sodium levels were significantly increased by adenine compared to the control. There was an increase in sodium level in rats treated with diethyl ether extract alone. Rats intoxicated with adenine had a considerable reduction in plasma phosphorus levels. Treatment with the ethanol and diethyl ether extracts significantly increased phosphorus level (Figure 3).

Effects of S. macrocarpon leaves extracts on plasma superoxide dismutase (SOD) levels of adenine-intoxicated male Wistar rats

The extracts significantly lowered the SOD levels elevated by adenine alone (Figure 4).

Effects of S. macrocarpon leaves extracts on plasma urea and uric acid levels of adenine-intoxicated male Wistar rats

Adenine intoxication significantly increased ($P < 0.05$) urea and uric acid levels compared to the control group. Intervention with extracts did not significantly ($P > 0.05$) affect the urea and uric acid level.

Histopathology

Adenine intoxication resulted in severe lesions, including glomerular atrophy, glomerular capsule expansion, interstitial congestion, clear necrosis in epithelial cells within renal tubules, and pyknotic nuclei (Figure 6b). Treatment with both ethanol and diethyl ether extracts of *S. macrocarpon* lead to the recovery of the renal architecture (Figure 6c and d).

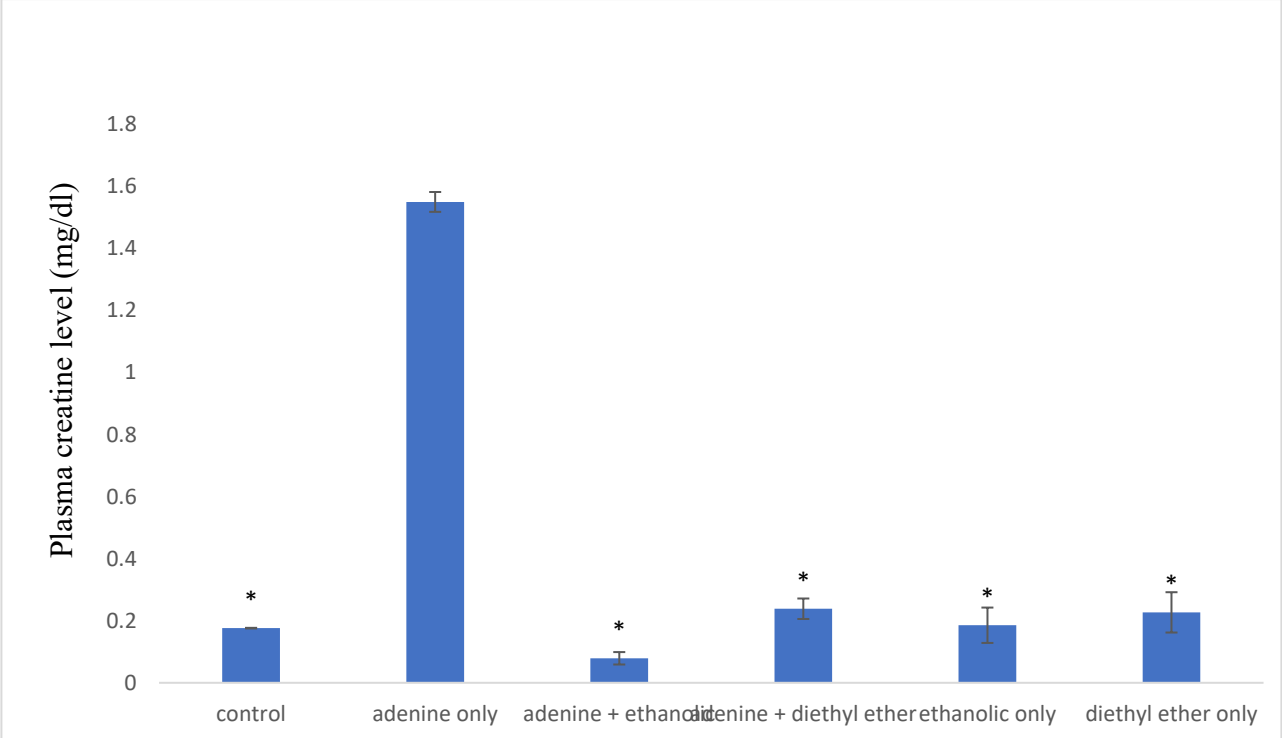


Figure 1: Effect of the extracts on plasma creatinine levels. n =5. *= P < 0.05.

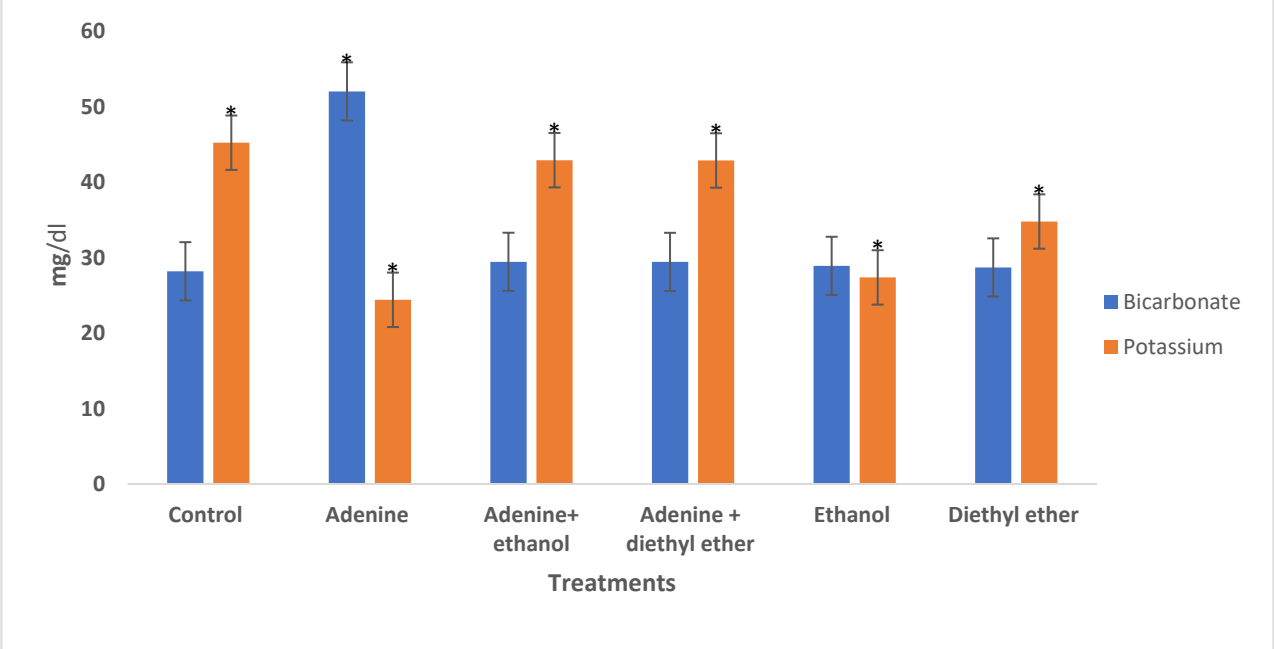


Figure 2: Effect of the extracts on plasma bicarbonate levels. n =5. *= P < 0.05.

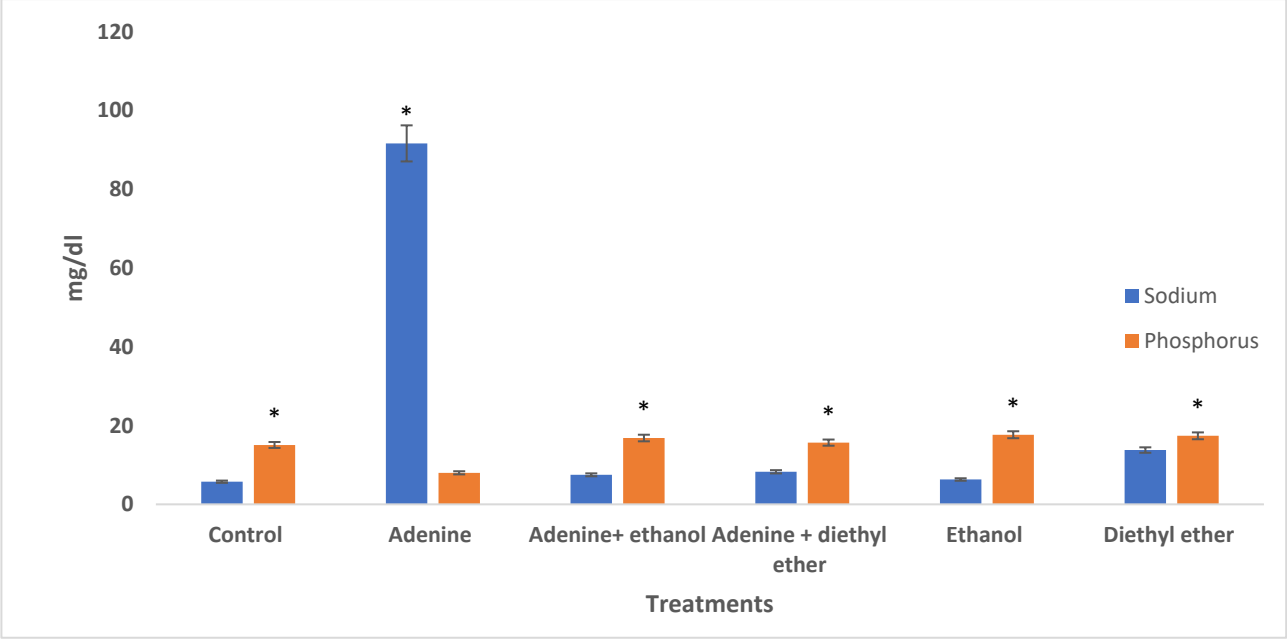


Figure 3: Effect of the extracts on **p**lasma sodium and phosphorus levels. n =5. *= P < 0.05.

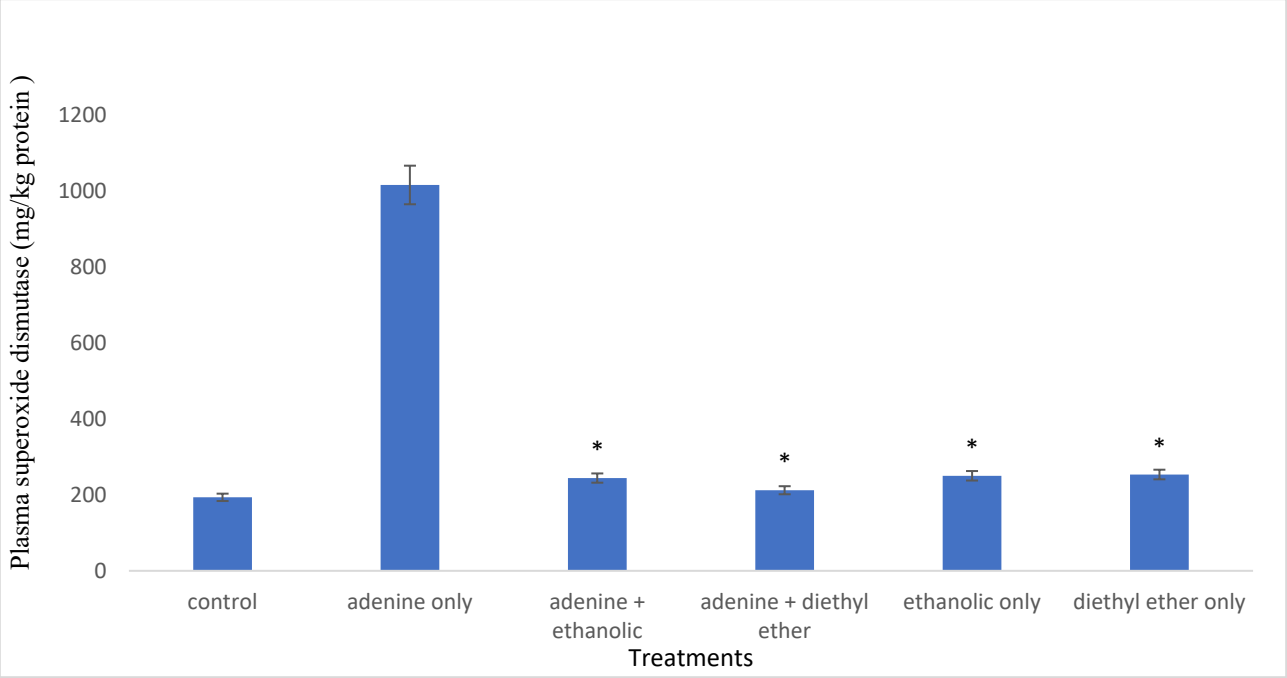


Figure 4: Effect of the extracts on **p**lasma SOD levels. n =5. *= P < 0.05.

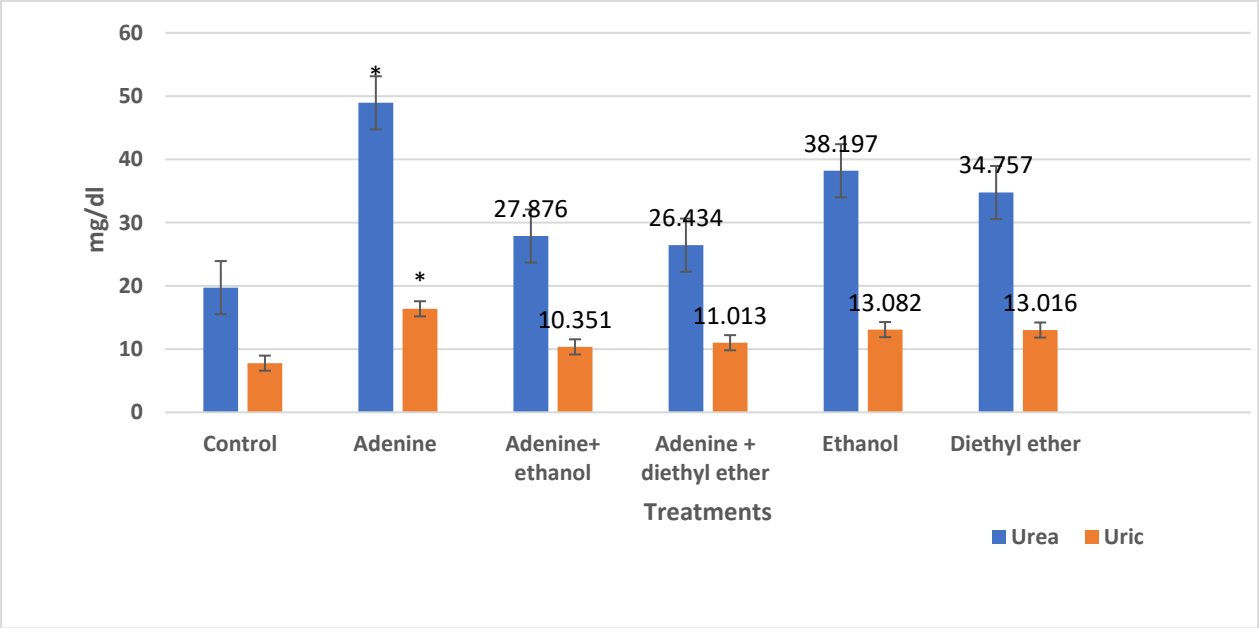


Figure 5: Effect of the extracts on **p**lasma urea and uric acid levels. n =5. *= P < 0.05.

Control

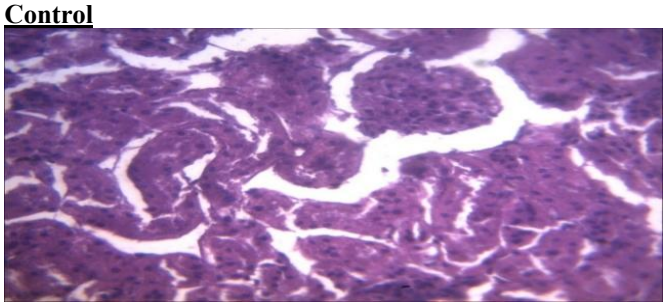


Figure 6a: Histopathology Control group (No visible lesions observed)

Adenine only

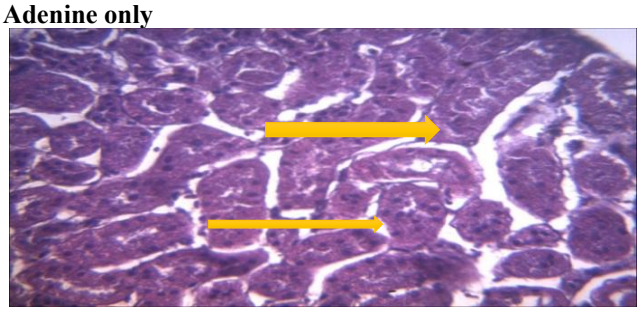


Figure 6b: Histopathology Adenine group (The sinusoids appeared prominent, representing glomerular congestion and hyalinization)

Adenine + Diethyl ether *Solanum macrocarpon* extract (DEESM)

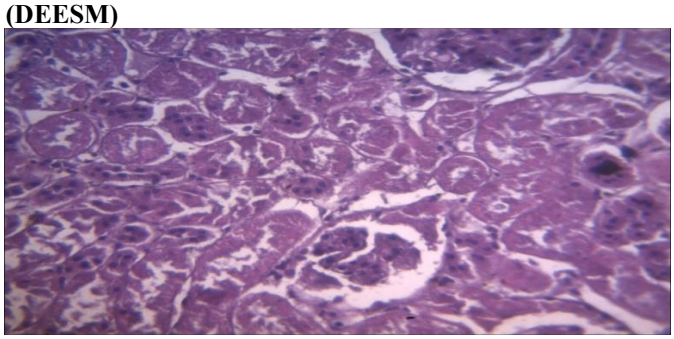
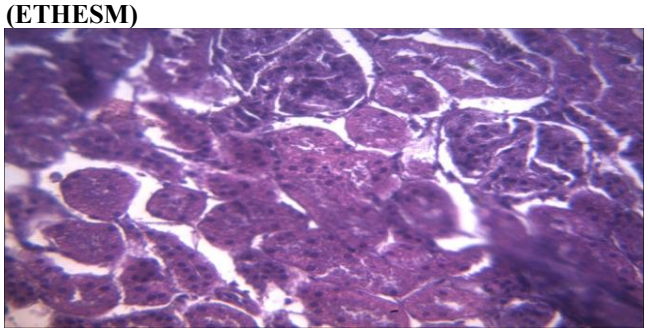


Figure 6c: Histopathology Adenine + DEESM (Several tubules have casts in their lumen, arrows. Represent mesangial necrosis)

Adenine + Ethanol *Solanum macrocarpon* extract (ETHESM)



h 6d: Histopathology Adenine + ETHESM (No visible lesion)

Ethanolic Extract Only

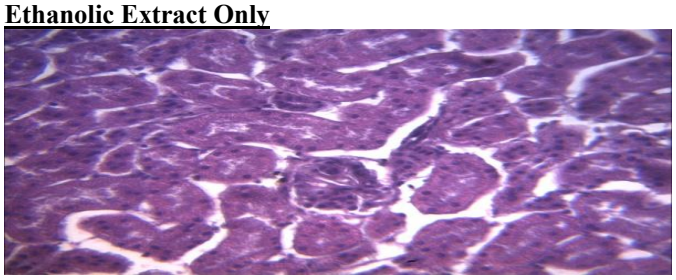


Figure 6e: Histopathology Ethanolic Extract Only **(**No visible lesion)

Diethylether Extract Only

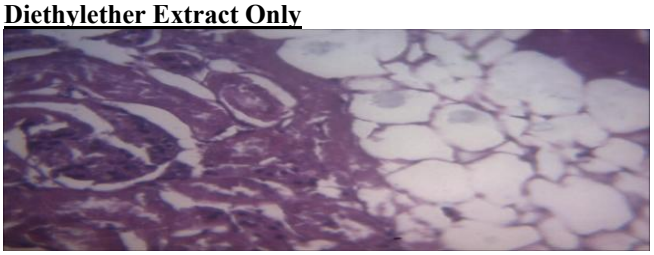


FIGURE 6f: Histopathology Diethyl Ether Extract Only (There is a large, focally extensive area of fatty infiltration into the interstitium (arrows))

Discussion

Kidneys are essential in removing toxins, metabolic products, and other foreign substances from the body (Wang *et al.,* 2019; Kalantar - Zadeh *et al.,* 2021). Renal fibrosis is closely related to the synthesis of mediators and signaling pathways, such as dysregulated uremic toxins, oxidative stress, and Wnt/β catenin (Zhang*, et al.,* 2021; Rao *et al.,* 2021). The present study investigated the protective role of *Solanum macrocarpon* leaves on adenine-induced acute kidney injury. The findings showed that exposure to Adenine evoked a significant increase in creatinine, urea and uric acid levels, indicating renal impairment. Adenine administration is known to cause renal dysfunction by precipitating as 2, 8-dihydroxyadenine crystals in the renal tubules, leading to tubular obstruction and interstitial inflammation. This finding is consistent with earlier results (Chen *et al*., 2017; Diwan *et al.,* 2018; Li *et al*., 2018).

The damage may be attributed to adenine metabolites accumulating in renal tubules, resulting in interstitial inflammation, tubular injury, and fibrosis inducing CKD (Johnson *et al.,* 2013). These renal histological abnormalities produced changes in the glomerular and renal tubules, leading to reduced renal (Ahmed *et al.,* 2019). The administration of ethanol and diethyl ether extract of *S macrocarpon* to adenine intoxicated groups significantly lowered blood concentrations of creatinine, urea, and uric acid, indicating an improved renal excretion of these compounds. These results may be attributed to the inhibition of hepatic xanthine oxidase and xanthine dehydrogenase activity and lowers serum uric acid levels, and/or antioxidative and antihyperuricemic properties of flavanone constituent in the extract (Inami *et al*., 2014). Zhang *et al*. (2020) highlighted the role of flavonoids in protection against adenine-induced nephrotoxicity in rats. Flavonoid-rich extracts could mitigate renal damage by reducing oxidative stress and inflammation. *Solanum macrocarpon* is very rich in polyphenols and flavonoids (Olufunmilayo, 2018), which are known to scavenge free radicals and reduce oxidative stress, a key factor in adenine-induced nephrotoxicity (Nisha *et al*., 2009).

The recovery of kidney function observed in this study is likely due to the clearance of crystals from the tubular lumen, leading to reduced urinary excretion of 2,8-DHA and adenine as well as the compensatory mechanism of the remaining functional nephrons (Atay *et al.,* 2024).

Electrolyte plays a major role in the maintenance of body homeostasis. The outcome of this present research shows that there was a significant increase ($P < 0.05$) in sodium and bicarbonate level in the blood of adenine-treated mice compared to control. This increase in sodium level could align with a diminished expression of the sodium transporters Sodium- Potassium- Chloride cotransporter 2 (NKCC2) and Sodium Hydrogen Exchanger 3(NHE3); however, these transporters may remain unaffected during the recovery phase.

These findings collectively suggest that both sodium transporters and aquaporins (AQPs) may play significant roles in the development of renal injury observed in the adenine-induced CKD model. Hypophosphatemia is also one of the conditions caused by adenine. This condition is often due to renal tubular damage and impaired reabsorption of phosphorus. Wang *et al*. (2015) reported that adenine - induced renal dysfunction in rats resulted in significant hypophosphatemia, attributed to impaired renal tubular function and increased urinary phosphate excretion. Similarly, Li *et al*., (2017) found that rats with adenine-induced nephropathy exhibited significant drops in serum phosphorus levels, highlighting the electrolyte imbalances associated with renal impairment Treatment with *Solanum macrocarpon* extract invariable reverse the damaged caused by the adenine.

Superoxide dismutase (SOD) is a crucial antioxidant enzyme that plays a vital role in defending against oxidative stress in renal tissues. Wang *et al*., (2016) reported that adenine - induced renal dysfunction in rats resulted in significant increase in oxidative stress, reflected by reduced SOD levels as a compensatory response to increased ROS production. Li *et al*. (2017) found that rats with adenine-induced nephropathy exhibited decreased SOD levels, highlighting the enzyme's role in counteracting oxidative damage. Chen *et al*. (2019)

demonstrated that adenine-fed rats showed marked increases in SOD activity, alongside other oxidative stress markers, due to the compromised ability of the kidneys to neutralize ROS. These results are consistent with those of Nemmar *et al.* (2021) and Okokon *et al*. (2017). Meanwhile, the administration of solanum macrocarpon leaves extract resulted in a significant increase in antioxidant markers compared to the adenine-treated group (Campbell *et al.,* 2021).

The potential of various plant extracts to mitigate oxidative stress in renal dysfunction has been explored, with several studies highlighting their antioxidant properties. (Okoye *et al*., 2016) studied the effects of *Solanum nigrum* extract on adenine-induced nephropathy and found that the extract significantly reduced oxidative stress markers, including SOD levels, likely due to its antioxidant effects. (Mahmoud *et al*., 2018) investigated the nephroprotective effects of *Moringa oleifera* leaves against adenine-induced renal dysfunction. Their results showed that the plant extract significantly decreased SOD levels, suggesting reduced oxidative stress. Singh *et al*. (2020) highlighted the role of herbal extracts in managing oxidative stress in renal dysfunction. Their findings indicated that plant extracts rich in antioxidants and anti-inflammatory compounds could mitigate oxidative damage and normalize SOD activity.

Histological examinations of kidney sections showed that rats exposed to adenine had several histopathological changes, including deterioration in hepatocytes, multifocal areas of necrosis, fibrosis, congested blood vessels, and enlargement of adenine deposit. Treatment with *S macrocarpon* extracts alleviated these alterations. Our results are consistent with those of Nasution *et al.* (2020). The reno-protective effects *Solanum macrocarpon* leaves extract may be due to phytoconstituents such as polyphenolic compounds, particularly the characteristic flavanone glycosides hesperidin, neohesperidin, naringin, rutin, and narirutin (Bureš *et al.,* 2022 and Mostafa *et al.,* 2020).

Conclusion

This study demonstrated that the ethanol extract of *Solanum macrocarpon* effectively mitigates adenine-induced nephrotoxicity in male Wistar rats, outperforming the diethyl ether extract. Key mechanisms include antioxidant properties effects, prevention of crystal formation, electrolyte balance, acid-base homeostasis, and anti-fibrotic properties. These findings suggest that *Solanum macrocarpon* leaves offer a safe and potent natural remedy for kidney protection,

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