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Antioxidant and anti-inflammatory effects of *Ipomoea cairica* leaf extract against acetaminophen nephrotoxicity

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Abstract

Background: Acetaminophen is one of the over-the-counter drugs commonly used by humans as a pain reliever, while it is generally safe at a prescribed dose, abuse of the drug and overdose make it one of those drugs linked to kidney damage. Ipomoea cairica is one of the medicinal plants which has been reported to be an alternative source of treatment and prevention of toxic effect of chemicals against organ function. The aim of this study was to evaluate the nephroprotective effect of I. cairica leaf extract against the nephrotoxic effect of acetaminophen in rats. Methods: Thirty-five rats were randomly divided into five groups (A, B, C, D, and E) of seven rats each. A: normal control; B: orally administered 2000 mg/kg of acetaminophen (ACET); C: orally administered 100 m/kg Methanolic extract of *Ipomoea cairica* (MEIC) for 14 days before single dose administration of ACET; D: orally administered 250 mg/kg of MEIC for 1 consecutive days before single dose administration of ACER; E: orally administered 250 mg/kg of MEIC for 14 consecutive days. Animals were sacrificed 24 h after last administration. Blood was collected and processed for markers of renal function and electrolytes, the kidney was excised and processed for antioxidant, oxidative stress, and anti-inflammatory level. Results: The results showed that MEIC at the two administered doses (100 and 250 mg/kg) caused a significant decrease ($P<0.05$) in the concentration of creatinine, urea, and uric acid when compared to the untreated group. Treatment with MEIC caused an insignificant increase ($P>0.05$) in sodium, potassium, and chloride ions and an increase in potassium ion. The concentration of glutathione (GSH) and the activities of MPO, NOR, XO, and MPO in the renal tissue of rats in the control group were also evaluated. MEIC was able to improve the ability of the kidney to clear creatinine from the blood. Conclusion: The study showed that the MEIC significantly improved the renal function to clear uraemia, implicated in kidney stones and cancer.

Key words: *Acetaminophen, Nephrotoxicity, Ipomoea cairica, Oxidative stress, Inflammation*

1. Introduction

The kidney is one of the most important organs in the body as it functions in excretion, homeostasis balance, blood pressure regulation, hormone regulation, production of erythrocytes, and bone density (Tienda-Vázquez

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et al., 2022). Its multiple function makes it an organ that is prone to the toxic effects of chemical substances. Kidney injury can be due to a progressive loss of function which is termed chronic kidney disease (CKD) or a sudden loss of function called acute kidney injury (AKI). The number of people suffering from either or both CKD or AKI has increased worldwide (Chawla *et al*., 2017; KDIGO, 2012). This can be due to several factors, such as smoking, drug abuse, alcohol intake, herbal concoctions that are not well prepared, etc. (Ilesanmi and Odewale, 2020). Apart from these, the prevalence of kidney disease is also attributed to an increase in the number of people suffering from diabetes, severe forms of COVID-19, and hypertension. One of the major classes of drugs implicated in kidney damage is non-steroidal anti-inflammatory drugs (NSAID). N-acetyl-p-aminophenol, commonly called acetaminophen with the brand name paracetamol (Yousuf *et al*., 2023) in Nigeria is one of the most abused NSAIDs. It is often used as an antipyretic or analgesic drug and can be obtained at any pharmaceutical shop in the country. The drug is non-toxic at the therapeutic dose; however, toxicity develops when the drug is abused or ingestion at a high dose. The drug is metabolized to N-acetyl-p-benzoquinonimine by the phase I metabolizing enzyme, cytochrome P-450, and conjugated to glutathione (GSH) by the enzyme glutathione-S-transferase (GST), a phase II drug-metabolizing enzyme. At a therapeutic dose, this metabolite can be eliminated from the body, thereby causing no harm, however, at a high dose, the concentration of GSH is not enough to conjugate it, thereby attacking other molecules such as lipid, protein, and DNA. This oxidative process is regarded as the origin of nephrotoxicity due to acetaminophen poison. Some of the clinical features of acetaminophen nephrotoxicity include an increase in creatinine level, a decrease in glomerular filtration rate, nephron necrosis, etc. The wide acceptance of medicinal plants as an alternative source to conventional drugs has increased globally. This has led to various aspect in the study of medicinal plants. Medicinal plants are an aspect of science that deals with the investigation of plants with therapeutic properties (Ilesanmi *et al*., 2022). This is generally known as phytomedicine or phytotherapy. One of the major advantages of phytomedicine is the discovery of bioactive natural compounds that can be synthesized in the laboratory and produced at commercial quantity (Chaachouay and Zidane, 2024; Najmi *et al*., 2022). The evolution of medicinal plants started with their being used as an antibiotics and analgesic agents, however the development of synthetic drugs that offer fast relief discouraged the uses of medicinal plants (Li, 2016). *Ipomoea cairica* is one of the underutilized medicinal plants in Africa. It is of the Convolvulaceae family with more than 500 species identified at different part of the world it is commonly called morning glory. Various part of the plant is used for both medicine and ornamental purpose. The plant can be found in various part of the world, where its different parts are used for various purposes. While the leaves and the roots are edible, the flower is used for beautification purpose. Various parts of the plant are ethnomedicinally used for the treatment of malaria, virus and bacterial infection, in addition, it is also applied therapeutically in the management of disease related to inflammation and oxidative stress

2. Materials and methods

2.1. Collection and identification of plant

Fresh leaves of Ipomoea cairica were harvested from a community in Nambe Local Government, Bayelsa State, Nigeria on the 8th of October, 2021. A section of the plant was taken to the department of Botany, University of Benin for identification and authentication by a plant Taxonomist. A voucher number-UBH-1561 was allotted to it.

2.2. Animal handlings and experimental design

Thirty-five rats were randomly divided into five groups (A, B, C, D, and E) of seven rats each. The rats were allowed to acclimatize for two weeks in clean cages under laboratory conditions. They were fed with commercially formulated pelletized feed and clean water, *ad libitum*.

Group A: served as the normal control group.

Group B: were orally administered mg/kg acetaminophen (ACET). ACET dissolved in distilled water and the volume was given according to the weight of each rat

Group C: administered 100 mg/kg of methanolic extract of *Ipomoea cairica* leaf (MEIC) for 14 consecutive days before exposure to ACET. Calculated volume of MEIC in ml according to the weight of each rat were orally administered daily for 14 days before a single dose administration of ACET

Group D: administered 250 mg/kg of methanolic extract of *Ipomoea cairica* leaf (MEIC) for 14 consecutive days before exposure to ACET. Calculated volume of MEIC in ml according to the weight of each rat were orally administered daily for 14 days before a single dose administration of ACET.

Group E; administered 250 mg/kg of methanolic extract of *Ipomoea cairica* leaf (MEIC) for 14 consecutives. This group was only administered MEIC for the duration of the experiment.

2.3. Sacrifice

Animals were observed daily for any physiological changes (such as skin color, mobility, appetite, aggression, salivation, activeness, etc.). In addition, the amount of food consumed daily and weight were measured every three days. Food was withdrawn overnight on the last day of administration prior to sacrifice. Animals were sacrificed via mild anesthesia and the blood collected through cardiac puncture. The blood was processed for markers of renal functions and electrolyte. The kidney was excised and processed for markers of oxidative stress and other biochemical parameters.

2.4. Serum samples were analyzed for determination the following Parameters

Biochemical examination of urea was analyzed according to the method described by Tietz (1976), uric acid analyzed according to the method described by Zhao *et al.*, 2006, creatinine analyzed according to the method described by Henry (1974), Sodium ion analyzed according to the method described by Natelson (1975), Potassium ion analyzed according to the method described by Terri and Sesin (1958).

2.5. Oxidative stress parameters

Malondialdehyde (MDA), the product of lipid peroxidation (LPO) was estimated according to Ohkawa *et al.* (1979). GSH content was determined according to Beutler *et al.* (1963). The activity of SOD was determined according to its ability to inhibit the autoxidation of epinephrine at alkaline medium according to the method of Misra and Fridovich (1972). The activity of CAT was determined based on its ability to decompose H_2O_2 according to Luck (1963). The activity of glutathione-peroxidase was measured according to the method described by Montgomery and Dymock (1961).

2.6. Anti-inflammatory enzymes parameters

NAD(P)H oxidase was determined according to the method of Hernández-Espinosa *et al.* (2019). XO was measured according to the method of Della Corte and Stripe (1972) and described by Battelli *et al.* (1996), and the activity of MPO measured according to the method described by Nishikimi *et al.* (1972).

3. Results

3.1. Serum biochemical analysis of renal function

Table 1 shows the effect of I. cairica on markers of renal function. The results showed a significant increase ($p < 0.05$) in the concentration of creatinine and uric acid due to acetaminophen induction as compared to the rats in the control group. MEIC at the two administered doses (100 and 250 mg/kg) caused a significant decrease in the concentration of CRT, urea, and uric acid when compared to the untreated group (acetaminophen). In addition, administration of 250 mg/kg of MEIC alone had no significant effect on all the renal function tests analyzed.

Table 1: Effect of methanolic extract of *Ipomoea cairica* (MEIC) leaf on the serum concentration of creatinine (CRT), urea, and uric acid in male Wistar rats exposed to acetaminophen

	CRT(µmol/l)	UREA(mmol/l)	URIC ACID (mmol/l)
Control	1.79±0.08	6.02±0.40	0.13±0.02
Acetaminophen	6.01±0.04***	16.01±0.04***	0.19±0.02***
100 mg/kg MEIC+ Acetaminophen	4.41±0.06###	6.4±0.05###	0.17±0.02
250 mg/kg MEIC + Acetaminophen	3.18±0.45###	6.1±0.69###	0.11±0.01###
250 mg/kg MEIC	2.86±0.24	6.28±0.40	0.13±0.01

Note: Values are expressed as mean±SD (n=7); Statistically significant differences: *** $p < 0.0001$ = Control group vs acetaminophen; ## $p < 0.05$ = acetaminophen vs treatment groups.

3.2. Effect of MEIC on electrolyte homeostasis

Table 2 shows the effect of I. cairica on electrolyte. It was observed from the result that acetaminophen intoxication induced a significant decrease ($p < 0.05$) in the concentration of sodium, potassium, and chloride ions in the serum as compared to the rats in the control group. Treatment with 100 and 250 mg/kg of MEIC reflects varying effects on the electrolyte status, treatment with a lower dose (100 mg/kg) causes a further decrease in the concentration of sodium ions, increase in the concentration of potassium and chloride ions when compared with the untreated group (acetaminophen), while treatment with 250 mg/kg of MEIC caused a significant increase in sodium and chloride ions and an insignificant increase ($p > 0.05$) in the concentration of potassium ion when compared to the untreated group. Administration of 250 mg/kg of MEIC alone caused a significant increase in sodium and potassium ions and a decrease in chloride ions when compared to the rats in the control group.

Table 2: Effect of Methanolic extract of Ipomoea cairica (MEIC) leaf on the serum concentration of electrolyte (sodium, potassium, chloride in male Wistar rats exposed to acetaminophen

	Na mmol/l	K mmol/l	Cl2 mmol/l
Control	290.33±40.9	7.10±0.84	134.18±16.16
Acetaminophen	241.09±30.05***	5.47±0.43	87.64±9.59***
100 mg/kg MEIC+ Acetaminophen	224.02±61.65###	6.06±1.58	134.83±30.94###
250 mg/kg MEIC + Acetaminophen	263.98±53.42	5.62±2.11	108.95±6.77###
250 mg/kg MEIC	383.49±49.54	12.58±1.82	120.52±20.98

Note: Values are expressed as mean±SD (n=7). Statistically significant differences; *** $p < 0.0001$=Control group vs acetaminophen; ## $p < 0.05$= acetaminophen vs treatment groups.

3.3. Antioxidant activity of MEIC against acetaminophen-induced renal damage

Figures 1, 2, 3, and 4 shows the effect of I. cairica on superoxide dismutase, catalase, glutathione-s-transferase, and glutathione peroxidase activities respectively in the liver of male wistar rats. Intoxication with acetaminophen caused a significant decrease ($p < 0.001$) in the activities of superoxide dismutase (SOD) (Figure 1), catalase (CAT) (Figure 2), glutathione-S-transferase (GST) (Figure 3), and glutathione peroxidase (GPx) (Figure 4) when compared with the activities of the enzymes in the renal tissue of rats in the control group. In addition, acetaminophen caused a significant increase ($p < 0.01$) in the concentration of

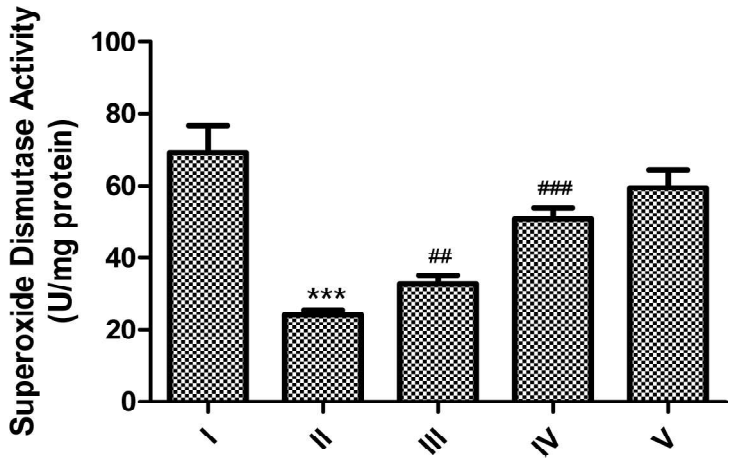

Figure 1: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on superoxide dismutase activity in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols *** indicates significantly different $p < 0.01$ (I vs II), ## indicates significantly different $p < 0.01$ (II vs III), and ### indicates significantly different $p < 0.001$ (II vs IV) using ANOVA and post hoc Tukey test.

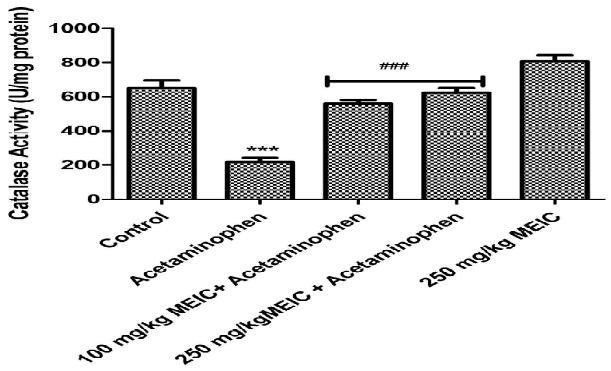

Figure 2: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on catalase activity in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols *** indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ### indicates significantly different $p < 0.001$ (acetaminophen vs treatment) using ANOVA and post hoc Tukey test.

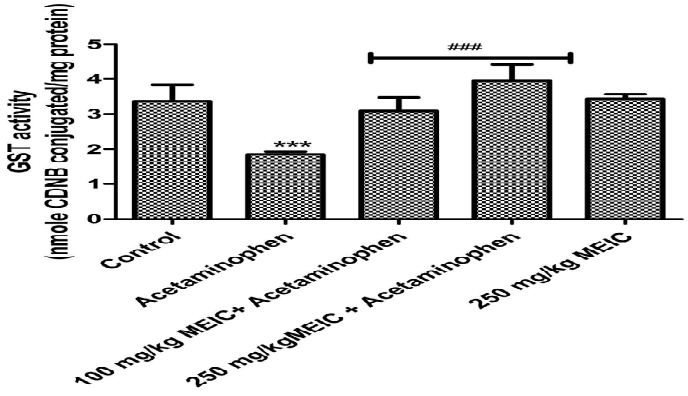

Figure 3: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on glutathione transferase activity in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols ***indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ###indicates significantly different $p < 0.001$ (acetaminophen vs treatment) using ANOVA and post hoc Tukey test.

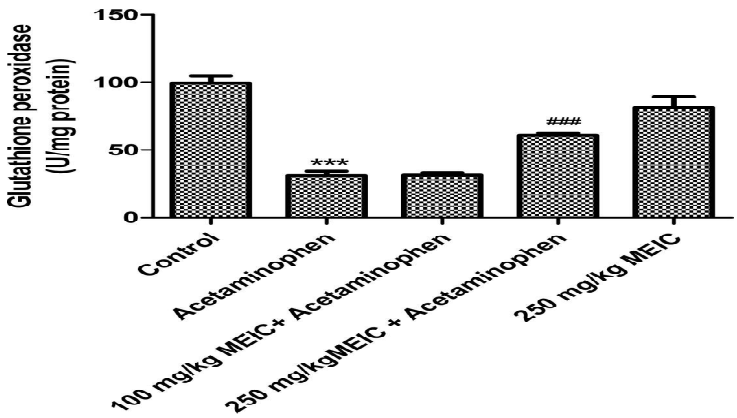

Figure 4: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on glutathione peroxidase activity in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols ***indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ###indicates significantly different $p < 0.001$ (acetaminophen vs 250 mg/kg MEIC + acetaminophen) using ANOVA and post-hoc Tukey test.

malondialdehyde (MDA) (Figure 5) and no significant effect ($p < 0.05$) on glutathione (GSH) (Figure 6) concentration when compared with the rats in the control group. Treatment with 100 and 250 mg/kg significantly increased ($p < 0.05$) the activities of all the enzymes in a dose-dependent manner when compared to the untreated group, except for GPx, where 100 mg/kg of MEIC had no significant effect on its activity. Administration of 250 mg/kg of MEIC had no significant effect on all the parameters in the renal tissue when compared with the rats in the control group. Also, observed is the insignificant effect of the two administered doses on the concentration of GSH when compared with the rats in the untreated group. MEIC at 100 mg/kg caused an insignificant decrease ($p < 0.05$) and 250 mg/kg caused a significant decrease ($p < 0.05$) in MDA concentration when compared to the untreated group. Administration of 250 mg/kg of MEIC had no significant effect on MDA and GSH concentration when compared with the rats in the control group.

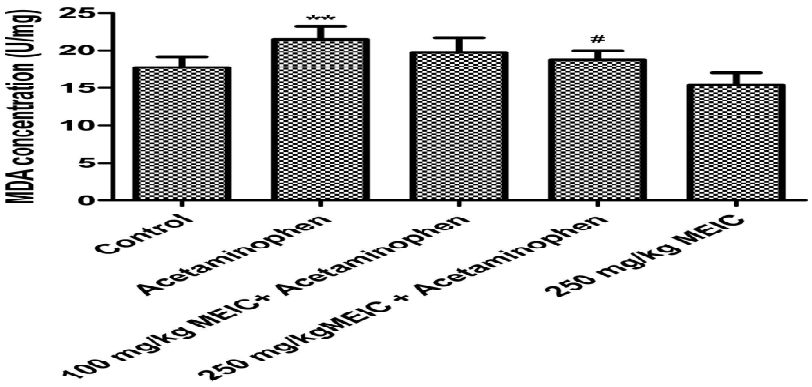

Figure 5: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on concentration of malondialdehyde (MDA) in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols ** indicates significantly different $p < 0.05$ (Control vs Acetaminophen), and # indicates significantly different $p < 0.05$ (acetaminophen vs 250 mg/kg MEIC + Acetaminophen) using ANOVA and post hoc Tukey test.

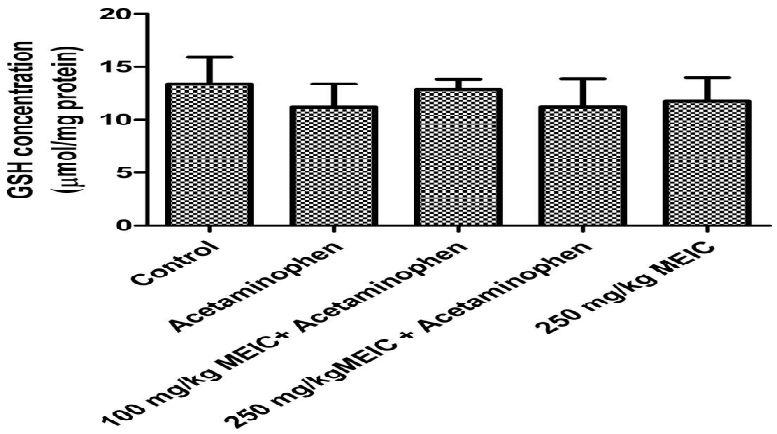

Figure 6: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on concentration of glutathione in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5).

3.4. Effect of MEIC on myeloperoxidase (MPO), NADPH oxidoreductase (NOR), and xanthine oxidase (XO) in the renal tissue of rats intoxicated with acetaminophen

Figure 7, 8, and 9, shows the effect of I. cairica on the activities of myeloperoxidase, NADPH oxidoreductase, and xanthine oxidase respectively. Acetaminophen intoxication induce a significant increase ($p < 0.001$) in the activities of MPO, NOR, and XO in the renal tissue when compared to the rats in the control group. Treatment of rats with 100 and 250 mg/kg of MEIC caused a significant decrease ($p < 0.001$) in the activities of the enzymes when compared to the rats in the untreated group (acetaminophen). In addition, the result shows

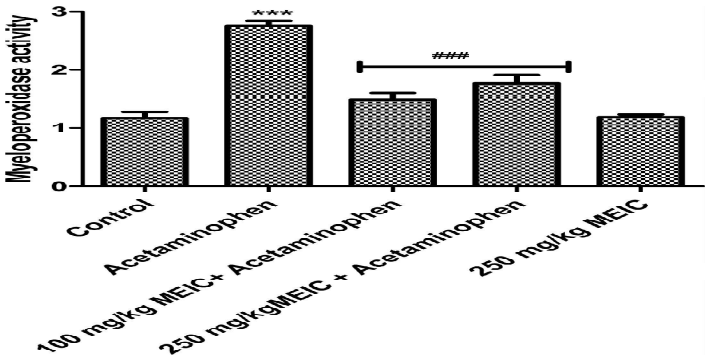

Figure 7: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on activity of myeloperoxidase in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols *** indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ### indicates significantly different $p < 0.001$ (acetaminophen vs treatment) using ANOVA and post hoc Tukey test.

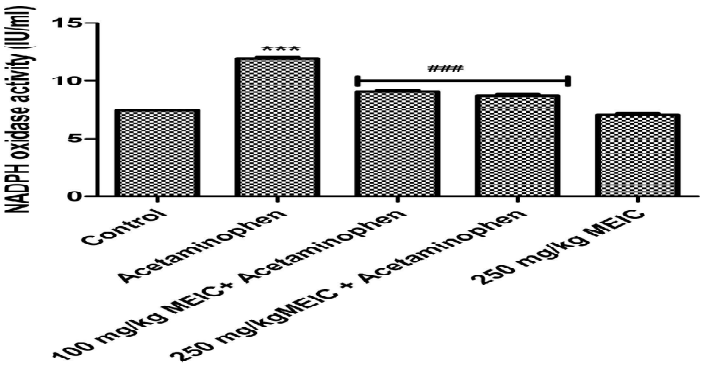

Figure 8: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on activity of NADPH oxidase in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols *** indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ### indicates significantly different $p < 0.001$ (acetaminophen vs treatment) using ANOVA and post hoc Tukey test.

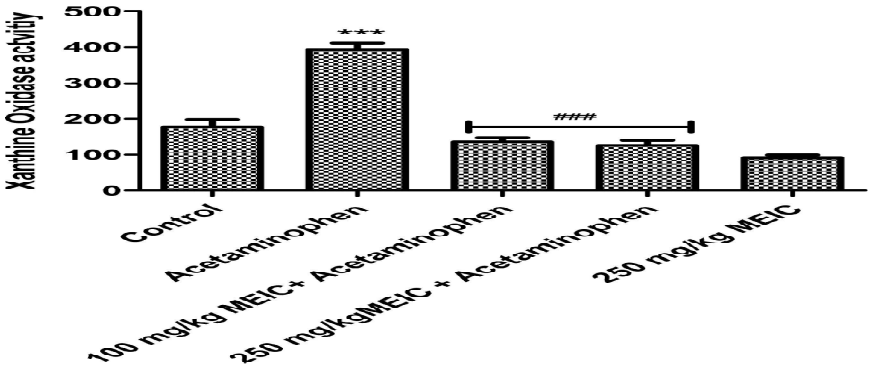

Figure 9: The effect of *I. cairica* leaf extract (MEIC) and acetaminophen on activity of xanthine oxidase in the kidney of male Wistar rats

Note: Each bar represents mean value ± standard deviation (SD) (n=5) and the symbols *** indicates significantly different $p < 0.001$ (Control vs Acetaminophen), and ### indicates significantly different $p < 0.001$ (acetaminophen vs treatment) using ANOVA and post hoc Tukey test.

that administration of 250 mg/kg of MEIC alone had no significant effect on the activities of the enzymes when compared to the rats in the control group

4. Discussion

Acetaminophen is one of the over-the-counter drugs commonly used by humans as a pain reliever, while it is generally safe at a prescribed dose, abuse of the drug and overdose make it one of the drugs linked to kidney and liver damage (Yapar *et al*., 2007; Chinnappan *et al*., 2019). However, the toxicity of acetaminophen against kidney injury is not as reported as the liver. It was reported that more than 2% of patients with acetaminophen overdose suffer renal impairment (Ghosh *et al*., 2010). It can be stated that acetaminophen overdose can trigger renal damage. The toxicity of acetaminophen is dependent on the formation of NADPQ1. There is a strong correlation between oxidative stress and nephrotoxicity (Wu *et al*., 2021). NAPQ1 is the radical form of acetaminophen and is reported to trigger oxidative stress in the kidney by reacting and forming conjugate with glutathione (GSH) and other important biomolecules, causing renal impairment and kidney apoptosis. Acetaminophen-nephrotoxicity is often marked by high serum levels of creatinine, urea, and uric acid (Chinnappan *et al*., 2019). The nephrotoxic effect of acetaminophen was visible in the results of the experiment as administration of acetaminophen elevated the serum level of creatinine, urea, and uric acid. Pretreatment with MEIC was able to prevent the nephrotoxic effect of acetaminophen. It was able to bring down the level of the renal injury markers. Creatinine is a metabolic product of muscle protein, while the kidney filters it from the blood for excretion out of the body through urination (Ali and Ismail, 2012; Ali *et al*., 2001). The significant decrease in the creatinine level in the group administered MEIC is proof that MEIC improves renal function to clear creatinine from the blood. In kidney disease, uremia is one of the key indicators, as a defect in the clearance of urea from the blood. The study showed that MEIC was able to improve the ability of the kidney to clear urea from the blood following acetaminophen intoxication. Uric acid is the metabolic product of purine catabolism. Uricemia is also one of the indicators of renal impairment, implicated in kidney stones and cancer. The elevated level of uric acid due to acetaminophen intoxication was prevented by MEIC pretreatment.

Another toxic effect of acetaminophen is the impairment of the kidney in the retention and homeostasis of electrolytes. Acetaminophen has been reported to cause nephrotoxicity by distorting the electrolyte homeostasis, this includes triggering hypokalaemia, hyponatrium, and a decrease in chloride ions by increasing their excretion from the body (Pakravan *et al*., 2007).

The result also corroborated this report as acetaminophen caused a significant depletion of the electrolyte in the blood. Pretreatment with MEIC was able to prevent the depletion of electrolytes due to acetaminophen intoxication.

Malondialdehyde and protein carbonyl are oxidative products that increase significantly when cells undergo oxidative stress (Ghosh and Sil, 2007). Oxidative stress is a condition whereby the concentration of ROS exceeds the antioxidant systems in the cell. They are produced when free radicals with lipids and proteins, and in the process, they disrupt the integrity of the cells, causing cell injury and death. Intoxication of the rats with acetaminophen triggers the generation of MDA and PC in the renal tissue. This is similar to the report which reveals that acetaminophen overdose causes oxidative stress signified by high concentration of MDA and PC (Qyamuddin *et al*., 2020).

Antioxidant enzymes and non-enzymatic molecules are the body's natural defense system against toxicants and pathogens. Their activities are inversely proportional to oxidative stress. Superoxide dismutase (SOD) and catalase (CAT) work systematically to remove free radicals and prevent them from attacking functional biomolecules and damaging cells. SOD removes superoxide by converting it to hydrogen peroxide which if not converted, produces hydroxyl radicals and hypochlorous that are stronger radicals. Elimination of hydrogen peroxide is done by CAT, converting it to water and oxygen. Low activity of these enzymes exacerbates oxidative stress and makes cells prone to oxidative damage. Acetaminophen overdose is widely reported to deplete tissues and cells of antioxidants (Teofilovi´c *et al*., 2021). This was replicated in the results of the experiment, where the activities of SOD and CAT were significantly depleted following acetaminophen intoxication. In addition, the activities of glutathione-S-transferase (GST) glutathione peroxidase (GPx), and concentration of glutathione (GSH) were evaluated. It reveals the oxidative effect of acetaminophen. GST plays an important role in the conjugation of toxic chemicals or metabolites, thereby enhancing their excretion from the body. The decreased activity of the enzymes implies the burden of acetaminophen overdose and its toxic metabolites (NAPQ1) on the enzyme. GSH homeostasis plays an important role in redox status and defense

system against oxidative stress. GSH can act as a reducing agent in converting radicals to no-radicals and act as a conjugant in removing toxic metabolites and making them water-soluble (Ingawale *et al*., 2014). The decreased in concentration of GSH due to acetaminophen exposure can be linked to the overburden of the toxic metabolites on the antioxidant system, which has been reported by other investigators. An interesting observation about the mechanism of acetaminophen toxicity is inflammation. Though acetaminophen is an NSAID, overdose of acetaminophen has been reported to cause cellular inflammation (Liu *et al*., 2020; Ale *et al*., 2006; Tang *et al*., 2024; Chiew and Isbister, 2023; Liu *et al*., 2023; Ramachandran and Jaeschke, 2021). To investigate the inflammatory effect of acetaminophen, the activities of anti-inflammatory enzymes were investigated. Myeloperoxidase, xanthine oxidase, and NAD(P)H oxidoreductase are inflammatory enzymes that are overly expressed during cellular assault. It was discovered that all the enzymes were significantly expressed in the kidney of rats exposed to the toxic dose of acetaminophen. Treatment with MEIC was able to prevent the inflammatory effect of acetaminophen, reflecting the anti-inflammatory effect of the plants.

5. Conclusion

The investigation shows that toxicity of acetaminophen in the renal tissue can involve oxidative stress and inflammation. Treatment with methanolic extract of *Ipomea cairica* leaves reveals that the plant possesses natural compounds that can act as prophylactic in preventing nephrotoxic effect of acetaminophen.

Conflicts of Interest

Author declares no conflicts of interest in conducting this study.

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Ethical Considerations

Compliance with ethical guidelines: All of the rats used in this study were healthy and treated according to the guidelines of the Helsinki Declaration of 1975 for the care and use of laboratory animals. The experimental design was approved by the Ethics Committee on Animal Research and Treatment (ART) of the Federal University Otuoke, Nigeria (Approval code: ART2023008).

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