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# The Potential Protective Effects of Ethanolic Extracts of Plantain Root on Diclofenac-Induced Nephrotoxicity and Hepatotoxicity Through Biochemical Analysis

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## Abstract

The toxicity of non-steroidal anti-inflammatory medicines has been linked to liver and kidney damage. This study assessed the degree of hepatotoxicity and nephrotoxicity caused by diclofenc as well as the protective effects of Musa paradiasca roots. Nine groups of six albino wistar rats each were used in this study: group 1 was the negative control, group 2 was the positive control, group 3 was the high dose of diclofenac and plantain root, group 4 was the low dose of diclofenac and plantain root, group 5 was the low dose of diclofenac and plantain root, and group 6 was the combination of diclofenac and vitamin C.Toxicity of group 2-9 was induced by oral administrative of diclofenac for 7 days. After which they were treated with *Musa paradiasca* roots for 3 weeks. On the 29$^{th}$ day after an overnight fast, the rats were anaethesied with chloroform, five mililitres of blood samples were put into plain bottles for the analysis of biochemical parameters. The liver and kidney of the rats were harvested for histological analysis. The inflammatory makers, S0D, MDA were analyzed using ELISA technique. Liver enzymes (AST, ALP and ALT) were assayed using Mindray biochemistry autoanalyser. There were significant reduction in the weights of the rats of the positive control group while the treated groups had some recovery in their weights. There were significant reduction liver function (AST, ALP, ALT) of the positive control groups ($p<0.001$) and kidney function (creatinine and urea) at ($p<0.5$). there were no significant difference between the groups treated with *Musa paradisca* roots and Vitamin C treated group. Histochemical study of the kidney and liver revealed that the kidney's glomeruli and basement membrane were deformed in the positive control groups, whereas the groups that received the plant extract showed some degree of healing. The appearance of the magenta color in the Periodic Acid Schiff stain suggested histomorphological distortion in the liver's gylogen storage capacity. The plant extracts utilized in this investigation had a mitigating effect on the harm caused by the medication. It can be taken as a stand-alone medication to treat diclofenac-induced toxic situations, reduce inflammation, and enhance liver and kidney indices.

**Keywords:** Plantain Root, Diclofenac, Nephrotoxicity, Hepatotoxicity.

## INTRODUCTION

Nonsteroidal anti-inflammatory medications (NSAIDs) are frequently utilized because of their analgesic and anti-inflammatory qualities, Diclofenac, an NSAID that is frequently prescribed, works well to reduce pain and inflammation brought on by a variety of illnesses. [1] On the other hand, diclofenac overuse or large dosages may have negative effects on important organs, especially the liver and kidneys [2]. When using diclofenac, nephrotoxicity and hepatotoxicity are serious risks [3].

Plant-based extracts are recognized to have anti-inflammatory and antioxidant qualities, and they have long been utilized for medical purposes [4]. Extracts from plantain roots (Musa paradisiaca) have drawn interest due to possible medical advantages [5]. It has been observed that plantain root contains nephroprotective, anti-inflammatory, and antioxidant qualities [6]. Therefore, examining these extracts' histopathological effects on diclofenac-induced hepatotoxicity and nephrotoxicity could give valuable insights into their protective potential.

Histological studies entail the microscopic analysis of tissues to detect pathological states, cellular changes, and structural changes [7]. Histological investigation enables the evaluation of tissue integrity, inflammation, necrosis, and other pathological changes in the context of drug-induced organ damage. This method offers a thorough grasp of how interventions work and can direct the creation of new therapeutic approaches.

One popular nonsteroidal anti-inflammatory medicine (NSAID) that can have negative side effects is diclofenac; these include nephrotoxicity and hepatotoxicity [8]. For patients who need high-dose or long-term diclofenac therapy, these toxicities are a serious issue [9]. Therefore, research into possible protective medicines that can lessen the harmful effects of diclofenac on the liver and kidneys is necessary.

The medicinal qualities of plant-based therapies have been thoroughly investigated, and they have demonstrated promise in preventing drug-induced organ damage [10]. Extracts from the plantain root (Musa paradisiaca) have been shown to have anti-inflammatory and antioxidant qualities, which may make them useful for lowering the nephrotoxicity and hepatotoxicity caused by diclofenac [11].

Nevertheless, nothing is known about the histological effects of these plant extracts on organ damage caused by diclofenac, despite the potential advantages of these extracts [12]. Important information about the morphological modifications, cellular changes, and pathological states that occur in organs can be gained via histological investigations [13]. To evaluate their protective potential and clarify the underlying mechanisms, it is crucial to comprehend the histological effects of plantain root on diclofenac-induced nephrotoxicity and hepatotoxicity [14].

Because of their well-established anti-inflammatory and antioxidant qualities, root extracts from Musa paradisiaca have considerable therapeutic potential [15]. One important factor in drug-induced organ damage is oxidative stress, which antioxidants can lower and neutralize [16]. Furthermore, these extracts' anti-inflammatory qualities may aid in reducing the inflammatory reaction brought on by diclofenac toxicity.

An effective and trustworthy technique for assessing tissue morphology and pathological alterations is histological examination. A thorough understanding of how interventions affect organ health is provided by histological examination, which evaluates structural integrity, cellular changes, and inflammatory responses. Histological examination of the kidney and liver tissues used in this investigation will make it possible to identify certain alterations brought on by diclofenac as well as any potential safeguarding effects of extracts from the roots of Musa paradisiaca. [17].

The results of this investigation will further our knowledge of the possible defense mechanisms of Musa paradisiaca root extracts against hepatotoxicity and nephrotoxicity brought on by diclofenac. If the results show a positive impact, these extracts may be used as safer, natural alternatives to diclofenac in order to prevent or lessen the negative side effects. This work intends to shed important light on the potential of Musa paradisiaca root extracts as protective agents against drug-induced organ damage by clarifying their histological effects.

## MATERIALS AND METHODS

### Experimental Animals

Sixty-Six (66) Albino Wistar rats, weighing 130 -170g was used for this study. The rats were purchased from the Department of Medical Laboratory Science, Rivers State University, Port Harcourt, Nigeria. The rats were fed with rat pre-mix rat feed and water *ad libitum*. The animals were placed in a well-ventilated rat cage with water cans and feed containers in place.

### The Drug and Herbal Formulations

The standard drug used to induce toxicity in this study was Diclofenac Sodium, purchased from a pharmacy store in Port Harcourt.

The plants extracts used in this study, was plantain root (*Musa paradisiaca*)

### Preparation of Extract

The raw herbs were given to the Food Science Department in Rivers State University to produce alcoholic extracts of the herbs using Soxhlet method.

## Phytochemical Analysis of the Extract

The phytochemicals in the plant extracts were determined qualitatively using classical methods and quantitatively using spectrophotometric methods (Spectro UV-Vis UV-2500, manufactured by LaboMed Inc., USA).

## Induction of Toxicity in Rats

Toxicity in the rats was induced by intraperitoneal injection of 240mg/kg of diclofenac

## Acute Toxicity Testing of the Herbal Extracts

## Plantain Root Extract

This was done using the Up-and -Down Method with the aim of determining the LD 50 of the plant extracts. Briefly, two groups of 3 rats were given 3000mg/kg of the extracts and observed for 24 hours. There was no death, then 5000mg/kg was administered. After 24 hours there was no death. Therefore, the extract was safe and non-toxic at 5000mg/kg.

## Determination of Therapeutic Dose Vitamin C

The rat doses of orthodox drug (vitamin C) were extrapolated from the human therapeutic doses using the method of [18]

## Experimental Design

Fifty-four (54) albino rats will be distributed into seven (9) groups of six (6) rats each as follows:
Group 1(negative control): Distilled water and feed only

Group 2 (positive control): Diclofenac + water + feed

Group 3 (high dose Plantain Root Extract): Diclofenac + plantain root

Group 4 (high dose Plantain Root Extract): Diclofenac + Plantain root

Group 6 (Vitamin C): Diclofenac + Vitamin C

## Sample Collection

The rats were sacrificed after an overnight fast. They were anaesthetized using chloroform. Blood samples were collected by cardiac puncture and put into plain bottles for Biochemical analysis. The blood samples were kept for at least 20 minutes to allow for clot retraction. Afterwards, tubes will be centrifuged at 3000 rpm for 10 min, at 20 °C. The serum was used to analyze liver functions, kidney functions, markers of oxidative stress and intracellular antioxidants.

## Biochemical Investigations

## Liver Function Test

Determination of Plasma Alkaline Phosphatase by Roy Method
Determination of Plasma Alanine Aminotransferase (ALT) by Reitman and Frankel Method
Determination of Plasma Aspartate Aminotransferase (AST) by Reitman and Frankel

## Renal Function Test

Determination of Plasma Urea by Berthelot's Enzymatic Method
Determination of Plasma Creatinine by Jeffe Colorimetric-Kinetic Method

**Determination of Markers of Oxidative Stress.** This was by measuring Malondialdehyde (MDA) and Superoxide Dismutase (SOD) **as well as** Glutathione Peroxidase (GPx) [19]

## Statistical Analysis

Data obtained were analyzed with Graph pad prism (version 5.03). Results of biochemical parameters were presented as Mean± Standard Deviation. Inferential statistics was done using the One – Way ANOVA (Post Hoc: Tukey's Multiple Comparative Test). Statistical significance was set at $p \leq 0.05$.

# RESULTS

## 4.1 Comparison of Hepatic and Renal Parameters of the Rats according to Treatment Groups

The results of the hepatic parameters indicate that the levels of parameters in the treated groups were significantly lower than the levels of the parameters in the positive control group. The results indicate that there was therapeutic effect from the administration of the extracts. The therapeutic effects of the extracts were not significantly different from that obtained by vitamin C administration. The results are as shown in table 4.1.

**Table 4.1: Comparison of Hepatic and Renal Parameters of the Rats according to Treatment Groups**

| | AST | ALT | ALP | TP | ALB | TB | CB |
|---|---|---|---|---|---|---|---|
| Group 1 (NC) | 31.60 ± 3.05a | 30.40 ± 3.51a | 33.80 ± 5.85a | 58.60 ± 2.41a | 39.20 ± 1.92a | 5.62 ± 0.28a | 3.30 ± 0.32a |
| Group 2 (PC) | 43.00 ± 6.28a | 41.20 ± 7.52b | 45.80 ± 5.02b | 62.00 ± 3.16b | 42.20 ± 1.92b | 7.94 ± 0.96b | 6.92 ± 0.60b |
| Group3 High Dose PRE) | 37.60 ± 5.41a | 31.20 ± 2.59a | 38.20 ± 4.21c | 51.40 ± 4.33c | 31.00 ± 2.55c | 7.06 ± 0.86c | 5.26 ± 0.30c |
| Group4 (Low Dose PRE) | 35.20 ± 3.63a | 28.80 ± 2.35c | 38.80 ± 2.39c | 57.60 ± 4.77c | 39.00 ± 2.92a | 7.16 ± 0.72c | 5.32 ± 0.40c |
| Group 5 (High Dose Combo) | 31.80 ± 6.57a | 38.00 ± 2.35a | 39.20 ± 3.19c | 57.60 ± 3.05c | 31.00 ± 2.55c | 7.01 ± 0.65c | 4.92 ± 0.48c |
| Group 6 (Vit C) | 29.40 ± 5.55c | 25.00 ± 4.36c | 39.80 ± 2.49c | 58.40 ± 4.28c | 36.40 ± 2.70a | 7.10 ± 0.65c | 4.98 ± 0.36c |
| p-value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| F-value | 6.761 | 4.988 | 9.332 | 14.739 | 5.189 | 6.410 | 31.145 |

Values with different superscripts are significantly different from each other ($p \leq 0.05$)
Keys: NC- Negative control, PC- Positive Control, PRE- Plantain Root Extract, Vit C- Vitamin C

## 4.2: Comparison of Renal Parameters

The results of the renal parameters indicate that the levels of parameters in the treated groups were significantly lower than the levels of the parameters in the positive control group. The results indicate that there was therapeutic effect from the administration of the extracts. The therapeutic effects of the extracts were not significantly different from that obtained by vitamin C administration. The results are as shown in table 4.2.

**Table 4.2: Comparison of Renal Parameters**

| | Urea | Creatinine |
|---|---|---|
| Group 1 (NC) | 5.10 ± 0.73a | 118.20 ± 4.82a |
| Group 2 (PC) | 6.72 ± 0.73b | 136.60 ± 7.06b |
| Group 3 High Dose PRE) | 4.64 ± 0.38c | 113.00 ± 4.00d |
| Group 4 (Low Dose PRE) | 5.98 ± 0.47a | 101.40 ± 1.34e |
| Group5 (High Dose Combo) | 4.58 ± 0.19c | 121.60 ± 7.76f |
| Group 6 Low Dose Combo | 5.88 ± 0.76a | 95.00 ± 1.87c |
| Group 7 (Vit C) | 5.10 ± 0.73a | 117.00 ± 3.74d |
| p-value | <0.001 | <0.001 |
| F-value | 12.374 | 51.431 |

Values with different superscripts are significantly different from each other ($p \leq 0.05$)
Keys: NC- Negative control, PC- Positive Control, GE- Guava Extract, PRE- Plantain Root Extract, Vit C- Vitamin C

## 4.3 Comparison of Antioxidant Parameters

The results of the glutathione indicate that the levels of parameters in the treated groups were significantly higher than the levels in the positive control group. The results of the superoxide dismutase indicate that the levels were significantly lower in the treated groups compared to the positive control. The results show that there was therapeutic effect from the administration of the extracts on glutathione peroxidase and superoxide dismutase. The therapeutic effects of the extracts were not significantly different from that obtained by vitamin C administration. There was no significant difference in the levels of malondialdehyde. The results are as shown in table 4.3.

### Table 4.3: Comparison of Antioxidant Parameters

| | Glutathione Peroxidase | Superoxide Dismutase | Malondialdehyde |
|---|---|---|---|
| Group 1 (NC) | 0.06 ± 0.01a | 0.18 ± 0.02a | 0.54 ± 0.02 |
| Group 2 (PC) | 0.04 ± 0.02b | 0.35 ± 0.09b | 0.51 ± 0.14 |
| Group 3 High Dose PRE) | 0.06 ± 0.03a | 0.28 ± 0.09c | 0.53 ± 0.10 |
| Group 4 (Low Dose PRE) | 0.06 ± 0.01a | 0.23 ± 0.06b | 0.51 ± 0.10 |
| Group5 (Vit C) | 0.05 ± 0.01a | 0.28 ± 0.08c | 0.46 ± 0.13 |
| p-value | 0.008 | <0.001 | 0.135 |
| F-value | 1.921 | 5.345 | 1.696 |

Values with different superscripts are significantly different from each other ($p \leq 0.05$)
Keys: NC- Negative control, PC- Positive Control, GE- Guava Extract, PRE- Plantain Root Extract, Vit C- Vitamin C

### 4.4: Comparison of Weights of Liver and Kidney of Rats after Sacrifice

The results of the weights of the liver and kidney of the treated groups were significantly higher than the weights of the liver and kidney in the positive control group. The results indicate that there was therapeutic effect from the administration of the extracts, as indicated by the increase in the weights of the organs. The therapeutic effects of the extracts were not significantly different from that obtained by vitamin C administration. The results are as shown in table 4.4.

### Table 4.4: Comparison of Weights of Liver and Kidney of Rats after Sacrifice

| | Weights of Liver (g) | Weights of Kidneys (g) |
|---|---|---|
| Group 1 (NC) | 2.94±0.36a | 0.84±0.09a |
| Group 2 (PC) | 2.16±0.11b | 0.52±0.08b |
| Group 3 High Dose PRE) | 3.82±0.19c | 1.00±0.10c |
| Group4 (Low Dose PRE) | 5.06±0.62d | 1.06±0.15c |
| Group 5 (High Dose Combo) | 3.92±0.88c | 1.24±0.18d |
| Group 6 (Vit C) | 4.34±0.52d | 1.22±0.08d |
| p-value | <0.001 | <0.001 |
| F-value | 16.075 | 6.626 |

Values with different superscripts are significantly different from each other ($p \leq 0.05$)
Keys: NC- Negative control, PC- Positive Control, , PRE- Plantain Root Extract, Vit C- Vitamin C

## DISCUSSION

Examining the anti-inflammatory and antioxidative properties of two plant extracts used to lessen the toxicity caused by diclofenac was the focus of this study. Alkaloids, flavonoids, and saponins have been found in the plant extracts utilized in the study according to phytochemical analysis. The phytochemicals included in plant extracts are thought to be responsible for their restorative and therapeutic properties. [20]

According to the diclofenac toxicity study, taking an excessive amount or taking it regularly over an extended length of time can result in nephrotoxicity and hepatotoxicity. This work aligns with the findings of [21].

The research on Musa paradiasca's therapeutic and ameliorative properties is synonymous with the findings of [22], which suggests that the extracts contain these properties.

According to the study, the rats' weights significantly decreased after receiving diclofenac. The main cause of this is the poisonous compounds that the rats' diclofenac injection released.

According to the study's findings, the positive control group's inflammatory marker levels were noticeably greater than those of the other groups. Inflammation frequently results in the production of toxins and free radicals [23]. In comparison to the diclofenac control group, the groups treated with plant extracts showed a significant decrease in the levels of inflammatory markers. This result is most likely the result of the inhibitory actions of. According to this study, there was a notable variation in the Guava leaves are the ideal plant to utilize since they contain flavonoids or polyphenols. Therefore, the phytochemicals present in these extracts may be responsible for their pharmacological actions. Flavonoids' molecular structure contains a 2,3-double bond, which gives them anti-inflammatory characteristics. Similarly, flavonoids can block lipoxygenase due to their molecular makeup. Adjust the factors related to lipid metabolism and other aspects linked to metabolic syndrome. Additionally, flavonoids have a strong affinity for the body's hydrophilic amino acids. They prevent neutrophil degranulation and limit leucocyte adhesion to blood vessel endothelium, but they have no effect on the body's synthesis of superoxide dismutase [25].

In general, flavonoids and nonsteroidal anti-inflammatory medications (NSAIDs) have comparable mechanisms of action [26].

Similar to this, polyphenols have been shown to be able to stop transcription factors and inflammatory mediators from being expressed and eventually released.

In this study, various groups of rats were given a combination of both plant extracts. Since none of the characteristics derived from the rats receiving monotherapies of either plant extract or conventional medication differed significantly from the data collected, the results did not point to a significant favorable effect of plantain therapy.

# CONCLUSION

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