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Research Article

Ameliorative effects of *Psidium guajava* leaf extract on ibuprofen-induced renal toxicity

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Abstract

Ibuprofen is an effective, cheap, and frequently used non-steroidal anti-inflammatory drug. Due to its availability as an over-the-counter (OTC) drug, there has been a prevalent increase in its abuse and overuse which poise high level risk of toxicity. *Psidium guajava* has been shown to be organoprotective. This present research study probed the efficacy of *Psidium guajava* (guava) leaf extract in mitigating ibuprofen-induced toxicity using renal parameters, haematological parameters in male albino Wistar rats. Adult male albino Wistar rats were weighed and separated into six groups of six rats each. Groups 1 & 2 served as normal and toxic controls receiving deionized water rand ibuprofen (20mg/kg) respectively. Groups 3, 4 and 5 were given 1250, 2500 and 3750mg/kg of *Psidium guajava* orally, respectively concomitantly with ibuprofen 20mg/kg for 28 days. Renal and haematological parameters obtained from the results served as scientific evidence in the study. *Psidium guajava* treatment significantly ($P < 0.05$) reversed the decrease in the levels of haematological parameters (PCV, Hb, RBC, WBC, PLT, MCHC, MCV, N, L, E, and M) as produced by ibuprofen. This decrease was significant ($P<0.05$) for RBC and platelet count. Similarly, alterations in the renal parameters produced by ibuprofen were mitigated by *Psidium guajava* administration. There were significant ($P < 0.05$) decrease in serum levels of sodium (126.0 ± 5.7 to 118.0 ± 1.0), potassium (3.8 ± 0.3 to 3.4 ± 0.3 mmol/L), creatinine (184 ± 6.6 to 83.5 ± 6.4 mg/dL) and urea (11.0 ± 1.0 to 4.3 ± 0.9 mg/dL) in the ibuprofen (20mg/kg) plus 2500 mg/kg *Psidium guajava*-treated groups. Ibuprofen produced a significant ($P < 0.05$) decrease in serum albumin (45.0 ± 4.2 to 39.4 ± 3.6 g/dL) which was reversed in the *Psidium guajava*-treated groups. Histoarchitecture of the kidney tissues obtained from rats treated with ibuprofen with *Psidium guajava* extract (2500mg/kg and 3750 mg/kg) extract showed normal glomerulus, renal vessel, proximal and distal convoluted tubules with no obvious distortions. The collated evidence in this study indicates that *Psidium guajava* leaf extract may possess ameliorative effects against ibuprofen-induced toxicity in albino Wistar rats.

Keywords: *Psidium guajava, nephroprotection, ibuprofen toxicity, renal function, heamatology*

INTRODUCTION

Ibuprofen is one of the widely used NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) that has various health-related benefits due to its analgesic, Inflammation-modulating characteristics and antipyretic. Their adverse effect is marked by oxidative stress inflammation and destruction of renal architecture.[1,2] The mechanism of action involves inhibition of synthesis of prostaglandin formation through cyclooxygenase (COX) is a key enzyme that is an important process by which non-steroidal anti-inflammatory drugs (NSAIDs) can cause severe renal damage.[3] This disruption in renal perfusion could lead to various kidney dysfunction and damage in the susceptible group.[3,4] The nephrotoxicity of ibuprofen requires investigating protective agents against these effects.[5] *Psidium guajava* (guava) has always been an important part of traditional medicine and are used for various therapeutic properties owing to their antimicrobial and anti-inflammatory properties. [6,7] These therapeutic properties are associated with both ameliorative [6,7] curative[8,9] potentials.

The pharmacological and medicinal uses of the aqueous leaf extract of *Psidium guajava* (guava) include various disturbances such as; diarrhoea, vomiting, gastric pain, and dysentery.[10] Aqueous extracts from *P. guajava* have shown anti- oxidant or radical-scavenging properties.[11] Most of these activities are associated with the polyphenol constituents in the plant; however, as well as antioxidants, such as ascorbic acid and carotenoids.[12] The aim of this study was to investigate the ameliorative

potential of guava leaf extract against ibuprofen-induced renal toxicity.

MATERIALS AND METHODS

Plant identification

Fresh leaves (5.50Kg) of *Psidium guajava* (Guava) was identified and authenticated by Dr M. Suleiman of the department of Pharmacognosy, Faculty of Pharmacy, University of Port Harcourt. A voucher specimen (Ref. No UPHM0588) was deposited at the university herbarium.

Sample processing and extraction

Psidium guajava leaves were rinsed with distilled water and air-dried for two weeks at room temperature. The dried leaves were reduced to powdered form using a grinding machine. A total of 400g of the powdered leaves was extracted by cold extraction using 2 L of 96% ethanol solvent for 72 hours, applying the "intermittent shaking" method. The macerated mixture was filtered (through a Whatman no. 1 filter paper) and evaporated in a carefully regulated water bath (maintained at 50 °C). The quantity of the dried extract was determined. It was transferred into a glass beaker, enclosed with an aluminum foil and stored in a refrigerator at 4 °C.

Animal husbandry

Thirty-six (36) male albino Wistar rats weighing between 190 - 238g were purchased from the Department of Experimental Pharmacology & Toxicology Animal house Abuja campus, Faculty of Pharmaceutical Science, University of Port-Harcourt, Rivers State. The rats were kept in polypropylene cages and maintained under standard and ethical conditions. They were weight matched into six groups of six animals each and allowed to acclimatize for two weeks. They were housed in a standard cage and maintained in standard laboratory condition at ambient temperature (25 ± 2°C) with relative humidity (55-64%) and light and dark conditions. They were fed with Top Feeds (Flour Mills Lagos, Nigeria.) and water *ad libitum.*

Animal ethics and proper handling method were strictly adhered to. The bedding of the cage was changed daily, and the cage was also washed and disinfected weekly.

Experimental design

Six groups of six male albino wistar rats were used in the experiment. Each group was treated and fed as follows for 28 days:

Group 1: served as the normal control and received deionized water; **Group 2:** served as toxic control and received ibuprofen 20mg/kg daily; **Group 3** received ibuprofen 20mg/kg daily plus 1250mg/Kg (25% LD50) of *Psidium guajava* extract; G**roup** 4 received ibuprofen 20mg/Kg plus 2500mg/kg (50% LD50) of *Psidium guajava* extract daily*;* **Group 5** received ibuprofen 20mg/kg plus 3750mg/kg (75% LD50) of *Psidium guajava* daily; **Group 6** served as the reference group and received only *Psidium guajava* extract 2500mg/Kg (50% LD50) daily. The dose of the *Psidium guajava* extract and experimental design used was based on previous studies by Seo et al.[13] The dose for Ibuprofen used was based on the previous studies by.[14] The body weights were monitored weekly for 28 days.

Necropsy

On the 28th day, the rats were fasted overnight, weighed, and sacrificed under ether anesthesia on the 29th day. The blood samples were collected by cardiac puncture and kept at temperature of 4°C for 6 hours. The clotted blood samples were then centrifuged at 3000 rpm for 15 minutes and stored in well-labelled anticoagulant bottles, at temperature of 4 °C for further analysis

Renal-biochemical parameters analysis

Haematological analysis

Five mL of blood was collected from the animals in each group in anticoagulant bottles for hematological analysis. Serum obtained from blood samples following centrifugation were assayed for the following hematologic parameters: Red Blood Cell (RBC); Total White Blood Cells (TWBC) and Differentials; Total White Blood Cell (TWBC) Count; Packed Cell Volume (PCV); Red Blood Cell (RBC) Count; Lymphocytes (L%); Neutrophils (N%); Eosinophils (E%); Monocyte (M%) using the Hemocytometer method .[15]

Serum potassium concentration (K) (mmol/L)

A total of 1 mL of the reagent was transferred into a tube and 0.01mL of the sample was added into the tube. It was mixed and allowed for 3 minutes at 25°C, after which the absorbance was measured using a spectrophotometer at 500nm.

Serum sodium concentration (Na) (mmol/L)

A total of 1.0 mL of the reagent was transferred into a test tube and 0.01mL of the sample was added into it. The tube was incubated for 5 minutes at 25°C, after which the absorbance was measured at 630 nm.

Serum total protein (TP) (g/L)

A total of 0.02 mL of plasma was added to 1 mL of Biuret reagent in a well labelled test tube. The contents were mixed, incubated for 30 minutes at 25^{0}C and the concentration was read using a spectrophotometer at 630 nm.

Serum albumin concentration (ALB) (g/L)

Plasma albumin concentration was determined using spectrum test kit. 0.01mL of sample was added to 1ml of reagent, mixed, incubated for 5minutes at 20 - 25°C and the absorbance measured using a spectrophotometer at 623nm.

Serum urea concentration (UR) (mmol/L)

A total of 0.01mL of plasma was added to 0.1mL of Randox reagent in a well labeled test tube. The contents were mixed and allowed at 37^{0}C for 10 minutes. 2.5mL of Randox phenol concentrate and 2.5mL of Randox hypochlorite concentrate were added to the test tube. The contents were mixed and incubated at 37^{o}C for 15 minutes; the concentration was read at 546 nm.

Serum creatinine concentration (Cr) (micromol/L)

A total of 1 mL of Randox alkaline picrate reagent was added to 0.1mL Randox standard creatinine solution. The content was mixed and read at 30 seconds intervals for concentration (A_1) and at exactly 2 minutes later for concentration (A_2) at 492nm. $A_1 - A_2 = A$.

Serum globulin (g/L)

This was obtained by subtracting the Total Serum Protein from the corresponding Serum Albumins (i.e ALB - TP).

Histology

For the histology examination, formalin fixed tissues (kidney) were dehydrated via ascending grades of alcohol, cleared in three changes of xylene, and were embedded in paraffin. Serial sections, each of 4-micron thickness, were cut and stained with H and E as per standard protocol. Stained sections were morphologically evaluated, and the pictures of the slides were taken for comparison.

RESULTS

Effect of *Psidium guajava* extract on the body and organ weights

Ibuprofen-only or in combination with *Psidium guajava* did not cause any significant change in the body and organ weight of the rats for the 28 days of observation. The percent gain in body weight ranged from 10.0 % in the normal control (untreated) to 9.3 % in ibuprofen-only treated group to 2.9, 4.5 and 13.8 % in the *Psidium guajava* extract treated animals respectively. However, the body weight increases in all treated groups were not significantly different in all the groups Furthermore, both the absolute and relative weights of the kidneys did not change significantly at the end of the experiment (Table 1).

Table 1: Effect of ethanol leaf extract of *Psidium guajava* on the body weights, absolute and relative weights of kidney of Ibuprofen-treated rats

Group	Mean initial weight (g)	Mean final weight (g)	Weight gain/ % weight gain	Mean organ weight (g)	Relative organ weight (%)
Deionized water	189.5 ± 4.7	208.5 ± 7.5	19.0/10.0	0.55 ± 0.05	0.26
Ibuprofen alone (20mg/kg)	185.8±2.41	203.0±9.87	17.2/9.3	0.54 ± 0.05	0.27
Ibuprofen (20mg/kg)) + (*Psidium guajava* (1250mg.kg)	194.3 ± 3.1	200.0 ± 0.1	5.7/2.9	0.55 ± 0.01	0.28
Ibuprofen (20mg/kg) + (*Psidium guajava* (2500 mg.kg)	201.5 ± 0.7	210.5 ± 4.9	9.0/4.5	0.56 ± 0.09	0.27
Ibuprofen (20mg/kg) +) + (*Psidium guajava* (3750mg.kg)	202.0 ± 1.3	229.0 ± 11.1	27/13.4	0.64 ± 0.11	0.28
(*Psidium guajava* (2500 mg.kg)	217.0 ± 1.4	227.5 ± 10.6	10.5/4.8	0.72 ± 0.18	0.32

Effects on renal parameters

Table 2 shows the effects of *Psidium guajava* on renal parameters. Treatment of rats with ibuprofen(20mg/kg) caused a significant ($P < 0.05$) increase in serum sodium, potassium, total protein, albumin, and urea when compared with normal control. However, this effect was reversed in the *Psidium guajava*-treated groups which showed significant ($P < 0.05$) decrease in serum levels of sodium (126.0 ± 5.7 to 118.0 ± 1.0), potassium (3.8 ± 0.3 to 3.4 ± 0.3 mmol/L), creatinine (184.0 ± 6.6 to 83.5 ± 6.4 mg/dL) and urea (11.0 ± 1.0 to 4.3 ± 0.9 mg/dL) in the ibuprofen (20mg/kg) plus 2500 mg/kg *Psidium guajava*-treated groups. Ibuprofen also produced a significant ($P < 0.05$) decrease in serum albumin (45.0 ± 4.2 to 39.4 ± 3.6 g/dL) which was reversed in the *Psidium guajava*-treated groups.

Table 2: Effect of *Psidium guajava* leaf extract on the renal parameters of Ibuprofen treated rats

Treatment groups	K (mmol/L)	Na (mmol/L)	Total Protein (g/dL)	Albumin (g/dL)	Urea (mg/dL)	Creatinine (mg/dL)
Deionized water (Normal control)	3.5 ± 0.0	119.0 ± 9.0	77.3 ± 5.5	45.0 ± 4.2	10.0±0.5	171.0 ± 6.7
Ibuprofen alone (20mg/kg) alone	3.8 ± 0.3**	126.0 ± 5.7**	67.2± 2.2**	39.4 ± 3.6**	11.0±1.0	184.0±6.6**
Ibuprofen (20mg/kg) + *Psidium guajava* (1250mg/kg)	3.7 ± 0.5	122.0 ± 1.4	61.0 ± 2.8	41.0 ± 1.4	5.0 ± 0.3*	99.0 ± 8.0*
Ibuprofen (20mg/kg) + *Psidium guajava* (2500mg/kg)	3.4 ± 0.3*	118.0 ± 1.0*	60.0 ± 1.5	40.5 ± 2.1	4.3 ± 0.9*	88.3 ±16.5*
Ibuprofen (20mg/kg) + *Psidium guajava* (3750mg/kg)	3.4 ± 0.2*	126.0 ± 7.4	61.0 ± 1.4	41.0 ± 2.8	4.6 ± 0.5*	87.8 ± 7.3*
Psidium guajava alone (2500mg/kg)	3.3 ± 0.4*	124 ± 10.1	60.7 ± 2.1	41.0 ± 1.0	4.5 ± 1.1*	± 6.4*

Data expressed as mean ± S.D. **values differ significantly from normal control ($P < 0.05$). *values differ significantly from ibuprofen-only group ($P < 0.05$)

Effect of *Psidium guajava* extract on the haematological parameters

Table 3 shows the effects of *Psidium guajava* on haematological parameters. Treatment of rats with ibuprofen(20mg/kg) caused a decrease in PCV, Hb, RBC, WBC, PLT, MCHC, MCV, N, L, E, and M concentrations compared with normal control. This decrease was significant (P<0.05) for RBC and platelet count. There was a significant (P < 0.05) dose-dependent reversal of the effects produced by ibuprofen administration on the haematological parameters following ethanol leaf extract of *Psidium guajava* administration except for eosinophils and monocytes which were not dose-dependent. This reversal was significant for RBC count (Groups 4 and 5); platelet (Group 5); Neutrophils (groups 4 and 5); lymphocytes; eosinophils (Group 3) and monocytes (Group 2).

Table 3: Effect of *Psidium guajava* leaf extract on the haematological profile of ibuprofen-treated rat

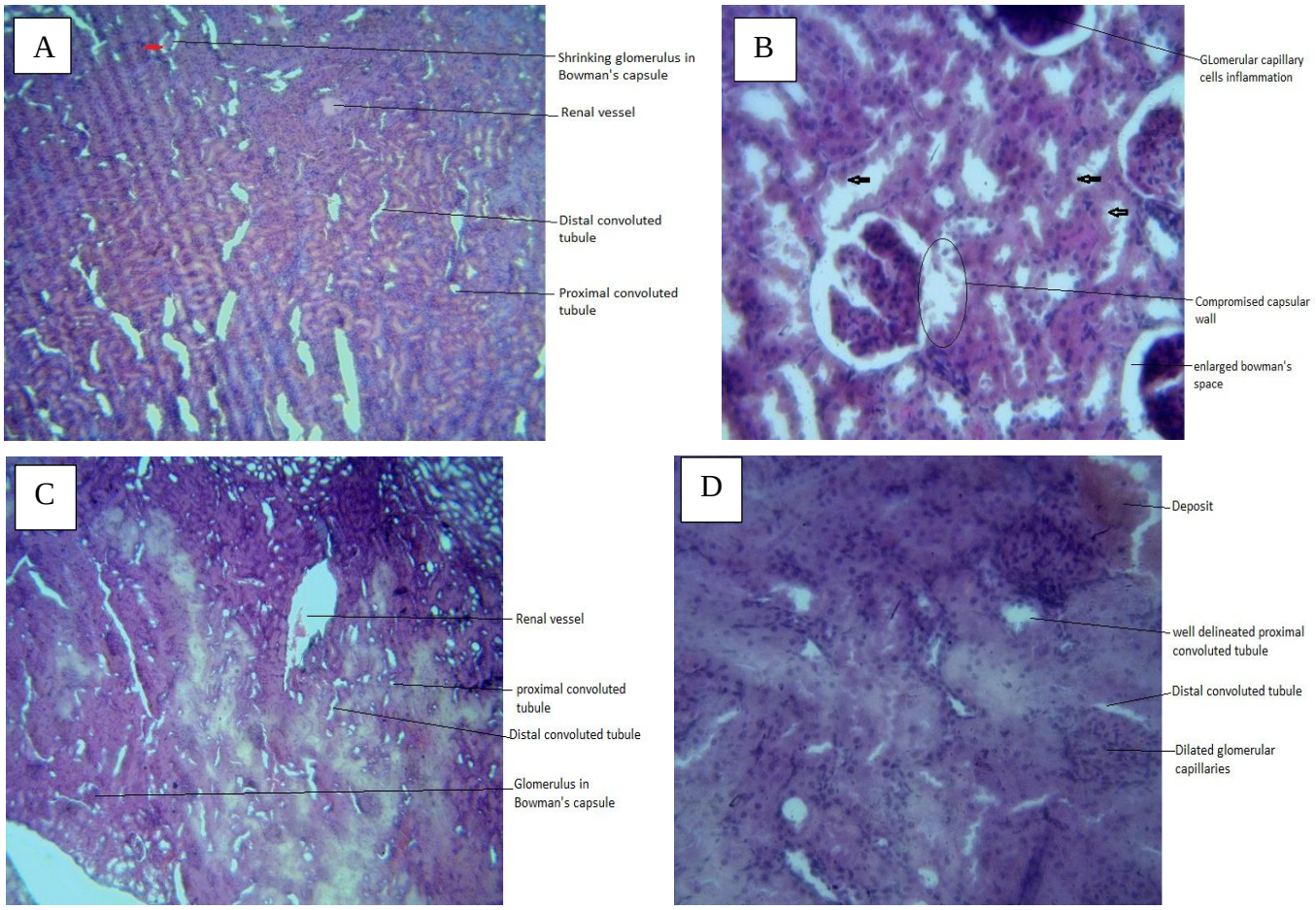
Treatment Group	PCV(%)	HB (g/dL)	RBC (10^6/uL)	WBC (10^3/uL)	PLT (10^3/uL)	MCHC (g/dL)	MCH (pg)	MCV (fl/um^3)	N (%)	L (%)	E (%)	M (%)
Deionized water (Normal control)	44.3 ± 0.6	14.9 ± 0.3	7.4 ± 0.4	6.9 ± 0.7	734.8 ± 126.1	33.3 ± 0.2	19.0 ± 0.6	58.0 ± 0.1	16.5 ± 0.7	83.3 ± 1.1	2.0 ± 0.9	4.3 ± 1.3
Ibuprofen alone (20mg/kg)	43.5 ± .0	13.9 ± 0.1	6.2 ± 0.7**	6.7 ± 1.6	663.6 ± 104.6**	31.9 ± 0.5	17.3 ± 0.5	56.4 ± 0.3	13.8 ± 0.4**	76.0 ± 0.5	1.8 ± 0.4	3.8 ± 1.3
Ibuprofen (20mg/kg) + *Psidium guajava* (1250mg/kg)	42.0 ± 0.1	14.4 ± 0.1	6.4 ± 0.6	7.4 ± 3.2	656.0 ± 51.1	34.1 ± 0.9	19.7 ± 0.2	57.7 ± 0.8	15.3 ± 0.6	80.3 ± 1.0*	2.0 ± 0.8	4.5 ± 1.0*
Ibuprofen (20mg/kg) + *Psidium guajava* (2500mg/kg)	44.5 ± 4.0	14.9 ± 0.2	7.5 ± 0.7	9.7 ± 1.3*	687.0 ± 6.9	33.6 ± 0.2	19.0 ± 0.3	58.8 ± 0.9	16.6 ± 1.2*	77.7 ± 0.5	2.3 ± 0.6*	4.3 ± 0.8
Ibuprofen (20mg/kg) + *Psidium guajava* (3750mg/kg)	43.0 ± 0.1	14.0 ± 0.1	7.4 ± 0.2	11.6 ± 0.7*	712.3 ± 19.1*	33.4 ± 0.5	19.1 ± 0.4	58.2 ± 0.3	16.5 ± 1.5*	80.3 ± 1.2*	2.0 ± 0.4	4.3 ± 0.6
Psidium guajava alone (2500mg/kg)	46.0 ± 1.0*	15.2 ± 0.1*	7.8 ± 0.2	10.0 ± 0.5*	676.5 ± 37.5	33.6 ± 0.5	19.2 ± 0.6	58.3 ± 0.5	17.0 ± 1.4*	77.8 ± 1.3	2.0 ± 0.6	± 1.2*

The rats who received Ibuprofen demonstrated extensive modifications which contrasted with regular control subjects when testing their blood components. A single dose of ibuprofen (20 mg/kg) caused decreased packed cell volume (PCV) levels and decreased variables like haemoglobin (HB), red blood cells (RBCs) and platelets (PLT) while increasing neutrophil N% in rats but addition of *Psidium guajava* leaf extract to ibuprofen treatment provided haematological protection at different dose levels. The combination treatment of *Psidium guajava* leaf extract with ibuprofen showed gradual healing effects on PCV, HB, RBC, and PLT levels in rats receiving three different extract doses (1250, 2500, and 3750 mg/kg). Results from *Psidium guajava*

administration at 2500 mg/kg showed equal protective ability to the highest dose combination which confirmed its haematological system protection capacities. The scientific findings indicate *Psidium guajava* leaf extract works as a therapeutic agent which decreases haemoglobin and platelet counts after ibuprofen medication alters these values.

Histology Results

Figure A shows photomicrograph of the kidney tissue obtained from rats treated with deionized water showing medullary area with several convoluted tubules (distal and proximal convoluted tubules). The cytoarchitecture of the tissue appear normal. Figure B shows photomicrograph of kidney tissue obtained from rats treated with ibuprofen 20mg/kg daily for 28 days. Picture showing dilated glomerular with cellular hypertrophy and haemorrhage. The capsular wall was destroyed as indicated in the circle area. Severe case of renal nephritis. Figure C shows photomicrographs for the kidney tissues obtained from rats treated with ibuprofen with *Psidium guajava* (2500mg/kg) extract showing glomerulus, renal vessel, proximal and distal convoluted tubules with no obvious distortion. The tissue has normal cytoarchitectural appearance. Figure D shows photomicrograph of kidney tissue from rats administered with (3750mg/kg) *Psidium guajava* leaf extract alone. Picture shows the convoluted tubules which appears normal.



A) Photomicrograph of kidney sections of positive control treated with deionized water showing medullary area with several convoluted tubules (distal and proximal convoluted tubules); **B)** negative control treated with ibuprofen only, showing dilated glomerular with several cellular hypertrophy, haemorrhage and hyperplasia. **(C and D)** Photomicrographs (for the kidney sections treated with ibuprofen plus Psidium guajava extract (2500mg/kg and 3750mg/kg respectively) showing glomerulus, renal vessel, proximal and distal convoluted tubules with no obvious distortion. The tissue has normal cytoarchitectural appearance

DISCUSSION

Ibuprofen overdose is known to cause renotoxicity effects by eliciting an inhibition of the COX-enzyme which leads to a reduced production of prostaglandin (PG) so that the renal tubules contract, resulting in a decrease in renal blood flow (RBF), a decrease in glomerular filtration rate (GFR), and finally renal tubular toxicity.[16] Previous research studies done on *Psidium guajava* leaves for its renoprotective effects, suggest that the presence of certain phenolic compounds is responsible for its renoprotective effects.[17]

Inhibition of the COX enzyme reduces the production of prostaglandins and thromboxane A2 which is vital for platelet aggregation and hence coagulation which results in inhibition of platelet aggregation, blood thinning and excessive bleeding.[18] In this study, daily administration of ibuprofen for a period of 28 days in male albino Wistar rats caused a decrease in the measured hematological parameters compared with normal control. However, there was a significant ($P < 0.05$) dose-dependent reversal of the effect of ibuprofen administration on the haematological parameters following ethanol leaf extract of *Psidium guajava* administration except for eosinophils and monocytes which were not dose-dependent. Ibuprofen is a non-steroidal anti-inflammatory agent. It also possesses anti-platelet property.[14] This explains the decrease in the level of platelets, monocytes, lymphocytes and neutrophils over the period of 28 days. However, this effect was mitigated by *Psidium guajava* in a dose-dependent manner. Alterations in haematological parameters over long period of time could consequently reduce renal perfusion resulting in acute kidney injury and dysfunction.[19]

Alterations in renal function or kidney damage is associated with distortions in the serum levels of various renal parameters such as Potassium (K), Sodium (Na), Total Protein (TP), Albumin (ALB), Urea and Creatinine. The kidney functions to regulate, balance water and electrolyte levels.

Kidney damage is associated with distortions in various renal functions like albuminuria, reduced glomerular filtration rate, and decreased creatinine.[20,21]

Urea and creatinine are metabolic waste products that are freely filtered by the glomeruli of the kidneys,[22] and their serum concentrations are commonly used as surrogate markers of renal toxicity.[23] From our results, ibuprofen would affect renal function as it increased urea and creatinine levels, this was mitigated by *Psidium guajava* in a non-dose-dependent manner. The increased level of blood urea and creatinine concentration in ibuprofen-treated rats suggests the inability of the kidney to excrete these products causing their increase in blood and decrease their excretion in urine. Sub-chronic exposure to ibuprofen resulted in electrolyte retention evidenced by elevation of sodium and potassium suggestive of impaired renal tubular transport mechanisms by ibuprofen. This data shows that prolonged use of standard dose levels of ibuprofen may alter renal function.

Studies have demonstrated a strong association between hypoalbuminemia and lower glomerular filtration rate (GFR) among patients with moderate to advanced kidney dysfunction.[24] In patients with renal failure, serum total protein and albumin levels are often but not always elevated .[25] From this work, ibuprofen caused a decrease in serum total protein and albumin, indicative of impaired glomerular filtration resulting in increased excretion of albumin. Administration of *Psidium guajava* produced a dose-dependent elevation of serum albumin.

For *Psidium guajava*, histoarchitecture of the kidney tissues obtained from rats treated with ibuprofen with *Psidium guajava* extract (2500mg/kg and 3750 mg/kg) extract showed normal glomerulus, renal vessel, proximal and distal convoluted tubules with no obvious distortions. The tissues showed normal cytoarchitectural appearance. Similarly, the data from *Psidium guajava* administration indicated mitigative/ameliorative effects. However, while there seemed to be complete amelioration with *Psidium guajava*, data obtained from *Mangifera indica* showed minimal distortions in the tissue architecture indicating that *Psidium guajava* may possess more potent mitigative potential. The ameliorative potentials of *Mangifera indica* and *Psidium guajava* leaf extracts (2500–3750 mg/kg) as shown in this study may affirm their use in kidney diseases in folk medicine. The speculated mechanism of kidney damage by ibuprofen may occur via oxidative stress and lipid peroxidation. [14]

CONCLUSION

The findings from this research showed a dose-dependent ameliorative potential of P. guajava leaf extract against ibuprofen-induced renal toxicity.

Author Contributions: C.N.O Conceptualization, Supervision, writing, review and editing. U.G Data collection, review and editing. P.A.T, U.F.P, N.E.C and C.N.O: Methodology, data collection; visualization, investigation, writing original draft preparation.

D.Z and VA: Review and editing.

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