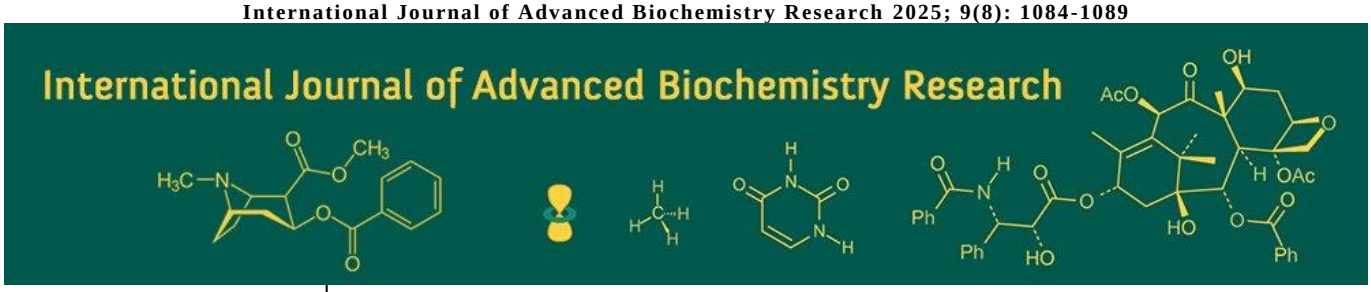

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Anti-ulcerative and biochemical effects of aqueous extract of *Carica papaya* pulp on indomethacin-induced ulcerative rats

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Abstract
Carica papaya is a tropical and subtropical fruit plant recognized for its medicinal properties. Ulcer remains a significant health concern in many developing countries, including Nigeria. In this study, we investigated the effects of aqueous extract of *Carica papaya* pulp on male rats with indomethacin-induced ulcer and the bacteria, *Helicobacter pylori* from human stool. Thirty (30) healthy male wistar rats were randomly assigned into six (6) groups of five rats each as follows; Group A, B, C, D, E, and F. Ulcer was induced using indomethacin in all the groups except Group A; Group B was left untreated; Group C was treated using a standard drug (Omeprazole); and different doses (100 mg/kg, 200 mg/kg, and 400 mg/kg) of the extract was administered orally to Groups D, E, and F respectively. The results of the *in vitro* analysis indicated that the bacteria (*Helicobacter pylori*) did not respond well to the extract showing less inhibition (11.20 mm) compared to the expected response (23.50 mm). From the results obtained, it was revealed that the aqueous extract of *C. papaya* pulp slightly exhibited an antiulcer activity in wistar albino rats although with reduced efficacy and potency. The administration of the extract showed significant increase in values of total bilirubin ($p = 0.027$) while significant decline was observed in levels of AST ($p = 0.16$), ALP ($p = 0.22$), ALT ($p = 0.83$) and direct bilirubin ($p = 0.70$). The results showed no statistically significant difference in both the urea ($p = 0.639$) and creatinine ($p = 0.191$) concentrations which suggests that aqueous extract of *Carica papaya* pulp is safe for consumption in the case of toxicity to the kidney.

Keywords: *Carica papaya*, *Helicobacter pylori*, indomethacin-induced ulcer, liver enzymes

Introduction
Ulcer is one of the most common gastrointestinal disorders which affect the worldwide population. It is estimated that approximately 10% of the world population develops this disease, which represents a serious health problem with a large impact on the quality of life of millions of individuals (Havens *et al.*, 2018) [13]. An ulcer is defined as an open sore or lesion that occurs on the skin or mucous membrane resulting from the gradual disintegration of surface epithelial tissue (Kuna *et al.*, 2019) [19], which fails to heal spontaneously or after appropriate treatment within a reasonable period. Ulcer is developed as a result of an imbalance between endogenous mucosal mechanisms, such as mucus, bicarbonate, prostaglandins, nitric oxide (NO) and sulfhydryl compounds, the presence of endogenous aggressive factors such as hydrochloric acid and pepsin; and exogenous factors such as Helicobacter pylori, use of steroidal anti-inflammatory drugs (corticosteroids) and non-steroids (NSAIDs), alcohol abuse and stress (Saxena, and Singh, 2011; Kangwan *et al.*, 2014) [26, 16]. Several therapeutic approaches have been made in the treatment of ulcer, the current medications include proton pump inhibitors (e.g., omeprazole, lansoprazole) and H2-receptor antagonist (H2RAs) (e.g., ranitidine, cimetidine) but these drugs are focused on pain suppression and exhibit some side effects (Kuna *et al.*, 2019) [19].
Plant materials have been used as sources of medicinal agents for many years and continue to play a dominant role in the maintenance of human health, over 50% of all modern chemical drugs originate from natural plant products (Burton *et al.*, 1983) [7]. Numerous studies have shown that plants, through various methods, can effectively cure ulcers in humans and

animals. *Carica papaya* L, one of the extensively studied plants, belonging to the family *Caricaceae* (Kugo *et al.*, 2018) [18] has been known since ancient time as a nutritious and medicinal plant or herb. It is a perennial horticultural shrub native to southern Mexico and Central America (Yap *et al.*, 2020) and is mainly cultivated in the tropical and subtropical regions of Brazil, Australia, Malaysia, China, India, Thailand, Myanmar, Philippines, and other adjoining (Husin *et al.*, 2019) [14]. *C. papaya* has numerous medicinal activities, as documented, owing to its constituents. *C. papaya* contains an extensive range of secondary metabolites such as alkaloids, tannins, flavonoids, saponins, which have been shown to a marked effect to reduce chronic inflammatory reaction. Proteolytic enzymes that are present in papaya such as papain and chymopapain also showed an anti-inflammatory effect as well as an effect on immunomodulation (Pandey *et al.*, 2016) [24]. Traditionally, it is used mainly to treat several conditions such as stomach disorders, diarrhea, skin diseases, male contraceptives, home remedies for colds, malarial fever, diabetes mellitus, bacterial infections and also used as a de-wormer agent (Lohiya and Goya, 1992; Chinoy *et al.*, 1985) [21, 8]. Good numbers of studies have indicated that papaya possesses significant anticancer activities for colorectal, prostate, cervical and breast cancers (Banu and Catherine, 2018) [4]. Unripe *C. papaya* fruit possesses anti-sickling, laxative, abortifacient, and diuretic qualities, according to reports (Karunamoorthi *et al.*, 2014) [17] and the consumption of the plant's unripe fruit extract has been connected to an anti-ulcer effect (Ezike *et al.*, 2009) [11]. In this study, we investigated the effects of aqueous extract of *Carica papaya* pulp on male rats with indomethacin-induced ulcer

Materials and Methods

Chemicals and reagents

All chemicals and reagents used in this research were of analytical grade. Indomethacin and omeprazole were purchased from Right Health Pharmacy and Stores Ltd, Awka, Anambra State.

Identification and preparation of fruit extracts

Fresh unripe fruits of *C. papaya* were purchased from Ifite, Awka Local Government Area of Anambra State, South-Eastern Nigeria in October, 2023. The fruit samples were identified and authenticated by a taxonomist, Mr. Iroka Finian of the Department of Botany, Nnamdi Azikiwe University, Awka, where a voucher specimen was deposited. *C. papaya* fermentation was carried out with slight modification, referencing the methods of (Akpan *et al.*, 2022) [3]. The unripe fruits were rinsed thoroughly, the seeds and skin were removed and the pulp was cut up into small pieces. It was ground with a grinding machine into a wet paste which was then weighed using a weighing balance. The paste was then allowed to ferment for 3 days in a fermenting jar containing approximately 3 liters of distilled water with intermittent stirring every 2 hours. The aqueous extract of the sample was obtained by straining the fermented paste of *C. papaya* fruits using a chiffon cloth and the filtrate was collected and preserved in the refrigerator for further usage.

In vitro study

H. pylori in vitro Analysis

The sample was aseptically streaked on Columbia agar. The culture plates were incubated at 37 °C micro aerophilically for 24-48 hours for bacteria. Discrete colonies for the bacteria were obtained by sub culturing into Nutrient agar plates and were subsequently identified using standard methods. Identification of the bacterial isolates was accomplished by the observation of colonial characteristics, Gram reaction and biochemical tests. The characterization of the isolates was carried out, by employing Gram staining reaction, Catalase test, Citrate test, Sugar fermentation test, Coagulase test, Motility test, Oxidase test, Urease test, Indole test, Methyl Red and Voges proskauer test as described by Bergey, (1994) [5].

In vivo study

Experimental animals

A total of thirty (43) adult wistar albino rats with average weight of 120-200 g were used for the study. The experimental animals were obtained from Chris Experimental Animal Farm and Research Laboratory, Mgbakwu, Awka. The animals were maintained and housed in cages in the same laboratory freely on standard pellets and water and allowed 2 weeks for acclimatization before commencement of the experiment and all conditions were set to minimize animal sufferings. They were housed and bred under standardized environmental conditions (temperature 23±2 °C and humidity 55±15%) and fed with a standardized diet and water. All rats were employed in the experiment at the same time of the day to avoid variations due to diurnal rhythms as putative regulators of gastric functions (El-Dien *et al.*, 2020) [10]. The principles governing the use of laboratory animals as laid out by the Animals Research Ethics Committee of Nnamdi Azikiwe University, Awka were duly observed and approval was obtained (Reference number **:** NAU/AREC/2023/000116). Acute toxicity tests were carried on adult male Wistar rats to determine the toxicity levels of *Carica papaya* pulp.

Measurement of Ulcerative Index

Ulcerative index was measured briefly as reported by Divyapraba, *et al.*, (2021) [9], the stomach was opened and washed with running tap water, then was placed on a flat glass plate and observed under 10X magnification for ulcers (Brzozowski, 1996) [6]. Scoring of the ulcer will be made as follows:

Normal stomach - (0)
Red colouration - (0.5)
Spot ulcer - (1)
Hemorrhagic streak - (1.5)
Ulcers - (2)

The lesion score for each rat was calculated as the number of lesions in that rat multiplied by their respective severity factor. Mean ulcer sore for each animal will be expressed as ulcer index. The percentage of ulcer protection was determined as follows% Protective = Control mean ulcer index-Test mean ulcer index / Control mean ulcer index × 100 (Inas *et al.*, 2011) [15].

Induction of ulcer

Gastric ulcer was induced orally in the rats, the dose for induction was formulated as 10 mg/kg of indomethacin. The stock was prepared by dissolving 25 mg of indomethacin (1 tablet) in 5 ml of distilled water that is 5 mg/ml (Urishidani *et al.*, 1979) [28]. Induction was done every 2 days over a period of 21 days after which they were fed and treated

according to the experimental design; the animals were fasted for 8 hours before every induction but fasted for 36 hours before the final induction.

Experimental Design
Thirty (30) rats were assigned into 6 groups consisting of five animals each;

Group A (Normal control group): No induction of ulcer, normal feed and water given to the animals.

Group B (Ulcer untreated): Ulcer was induced with 10 mg/kg of Indomethacin and left untreated.

Group C (Ulcer + Standard drug): This group was induced with 10 mg/kg of Indomethacin and treated with 20 mg/kg of standard drug (Omeprazole).

Group D (Ulcer + 100 mg/kg *C. papaya*): This group was induced with 10 mg/kg of Indomethacin and treated with 100 mg/kg of aqueous extract of *C. papaya*.

Group E (Ulcer + 200 mg/kg *C. papaya*): This group was induced with 10 mg/kg of Indomethacin and treated with 200 mg/kg of aqueous extract of *C. papaya*.

Group F (Ulcer + 400 mg/kg *C. papaya*): This group was induced with 10 mg/kg of Indomethacin and treated with 400 mg/kg of aqueous extract of *C. papaya*.

Sacrifice and blood sample collection
The animals were anaesthetized using chloroform vapor and the blood samples were collected through closed cardiac puncture. Five (5) ml of blood was collected from each rat, 3 ml of blood was transferred into plain tubes and were centrifuged for 15 minutes at 3000 revolutions per minute (3000 rpm) to obtain serum for biochemical analysis while 2 ml was transferred into EDTA bottles for hematological analyses. Using surgical blade, scissor, and scalpel, the stomach of the animals was dissected out and an incision was made at the greater curvature in order to collect gastric contents and to observe gastric mucosa for the presence of gastric ulceration.

Determination of Biochemical Parameters
Serum was used for the evaluation of biochemical parameters, including urea, creatinine, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, using commercial kits from Randox Laboratories, UK, according to the manufacturer's protocol.

Data Analysis
Data obtained was analyzed using the SPSS statistical package, version 23 with one-way analysis of variance (ANOVA). Values were presented as Mean ± SEM and were considered significant at $p<0.05$.

Results
Table 1 shows the identification of the bacterial isolates by the observation of colonial characteristics, Gram reaction and biochemical tests. Table 2 indicates that the bacteria (*H. pylori*) being studied was not responding to the treatment, showing less inhibition (11.20 mm) compared to the expected response (22.50 mm). The substance being tested also showed minimal anti-microbial effects. The control tests confirmed that the experimental conditions were appropriate.

Table 1: Morphological and Biochemical Identifications of the Various Bacterial Isolates

Isolate	1
Form	Circular
Surface	Moist
Colour	Cream
Margin	Entire
Elevation	Raised
Opacity	Translucent
Gram	-helix
Cat	+
Mot	+
Ind	-
MR	+
VP	+
Cit	+
Lac	+
Glu	+
Suc	+
Fru	-
Mal	+
Oxi	+
Ure	+
Identity	*Helicobacter pylori*

Key:
Gram: Gram reaction, Cat: Catalase test, Mot: Motility test, Ind: Indole test, MR: Methyl-red test, VP: Voges-Proskauer test, and Cit: Citrate Utilization test
Sugar Fermentation Tests:
Lac: Lactose Fermentation, Glu: Glucose Fermentation, Suc: Sucrose Fermentation, Fru: Fructose Fermentation, Mal: Maltose Fermentation, Oxi: Oxidase and Ure: Urease.

Table 2: Antimicrobial Susceptibility Pattern of the Isolate

Isolates	Positive control	Extract	Negative control
*H. pylor*i	23.50 mm	11.20 mm	negative

Acute toxicity studies
The acute toxicity and lethality of the aqueous extracts of *Carica papaya* pulp were determined using the method described by Lorke (Lorke, 1983) [22]. From the result shownin Table 1, there was no record of mortality within 24 h of treatment withthe extract and the result of this study suggested that the LD_{50} is greaterthan 5000 mg/kg BW.

Table 3: Acute toxicity effects of *Carica papaya*fruit extracts in wistar albino rats.

Experiment	Dose (mg/kg B.W.)	No of Death After 24 h
Phase 1	10	0/3
	100	0/3
	1000	0/3
Phase 2	1600	0/3
	2900	0/3
	5000	0/3

Table 5 revealed that there was no significant difference ($p>0.05$) in ulcer index between the experimental and treatment groups. Although the ulcer index of the rats fed with 100 mg/kg and 400 mg/kg of the extract were lower

when compared with the rats that were untreated and the rats that received 200 mg/kg of the extract. The results of the gastric pH revealed that there was no significant difference (p>0.05) between the experimental and the treatment Groups. However, the rats treated with 100 mg/kg of the extract showed the highest level of gastric pH in comparison with the other groups.

Table 4: Ulcer severity score of Indomethacin-induced ulcer in wistar albino rats.

Groups	Red Coloration	Spot Ulcer	Hemorrhagic Stress	Deep Ulcer	Perforation
Normal control	0	0	0	0	0
Ulcer untreated	2.2±0.96	8.4±2.03	1±0.6	2.6±1.16	1.0±0.6
Ulcer + Std drug	0.4±0.37	2.40±1.0	0.40 + 0.20	0.2±0.10	0
100 mg/kg extract	4.8±0.96	8.0±1.00	0	1.4±0.97	0
200 mg/kg extract	0.4±0.40	6.2±2.26	0.40±0.4	0	0
400 mg/kg extract	0.40±0.4	4.40±1.4	1.20±0.96	0	0

Values are expressed as Mean ± SEM (n = 5)

Table 5: Ulcer parameters (Ulcer index, Gastric pH, Number of ulcer) analysis of Indomethacin-induced ulcer in wistar albino rats.

Groups	Ulcer Index	Gastric PH	% Inhibition
Normal control	0	5.2±0.20	0
Ulcer untreated	11.07±0.64	4.40±0.24	0
Ulcer + Standard drug	3.59±1.80	4.40±0.37	67.57
100 mg/kg extract	10.95±0.26	4.20±0.37	01.00
200 mg/kg extract	11.38±1.80	4.50±0.44	00.00
400 mg/kg extract	7.16±1.79	4.40±0.50	35.00

Values are expressed as Mean ± SEM (n = 5)

Table 6 revealed that there was no statistically significant difference (p>0.05) in the urea and creatinine concentration of the rats treated with the aqueous extract of *C. papaya* pulp when compared with the control groups but the extract had minimal effects on the groups administered. The results showed a decrease in the creatinine concentration upon administration of 200 mg/kg of *C. papaya* (0.81±0.08) when compared to the ulcer untreated group (1.53±0.18). There was also a slight increase in the urea concentration in the group administered 400 mg/kg of *C. papaya* (61.80±10.11) when compared to the normal control group (50.51±12.86) and in the creatinine concentration in this same group administered 400 mg/kg of *C. papaya* (1.25±0.36) when compared to the normal control group (1.189±0.22).

Table 6: Effect of aqueous extract of *Carica papaya* on Kidney function parameters of Indomethacin-induced ulcer in wistar albino rats.

Groups	Creatinine (mg/dl)	Urea (mg/dl)
Normal control	1.189±0.22	50.51±12.86
Ulcer untreated	1.53±0.18	62.01±6.32
Ulcer + Standard drug	1.27±0.09	52.98±8.41
100 mg/kg extract	1.29±0.38	48.87±5.29
200 mg/kg extract	0.81±0.08 b	43.94±6.95
400 mg/kg extract	1.25±0.36	61.80±10.11

Values are expressed as Mean ± SEM (n = 5)

Table 7 revealed that there was a significant increase in the alanine aminotransferase activity of the normal control (22.67±12.72) compared to 200 mg/kg group of *C. papaya* extract (9.33±2.67). The results of the aspartate aminotransferase concentration showed a slight increase in the ulcer untreated group (28.67±5.04) and the 400 mg/kg extract (28.33±2.67) when compared to 200 mg/kg extract (16.00±1.73). The results of the alkaline phosphate activity revealed that the ulcer untreated group (106.72±23.49) showed a significant alkaline phosphate activity compared to 200 mg/kg extract group (56.79±4.63). The results of the direct bilirubin concentration revealed that the continuous administration of the 400 mg/kg body weight for the remaining period of two weeks showed a slight increase on all the direct bilirubin levels compared to the normal 200 mg/kg at (1.87±0.21). Induction of ulcer in the experimental rat group caused a significant (p0.05) increase in the total bilirubin level of the rats. The result of the untreated group (7.85±1.07) showed a significant increase in the total bilirubin level compared to the 200 mg/kg extract (4.48±0.40) and the normal control (4.50±0.51).

Table 7: Effect of aqueous extract of *Carica papaya* on Liver function parameters of Indomethacin-induced ulcer in wistar albino rats.

Groups	ALT(u/l)	AST (u/l)	ALP (u/l)	Direct bilirubin (mg/dl)	Total bilirubin (mg/dl)
Normal control	22.67±12.72	18.67±4.26	58.80±5.60	2.03±0.33	4.50±0.51
Ulcer untreated	12.33±6.44	28.67±5.04	106.72±23.49	2.35±0.27	7.85±1.07
Ulcer+Std drug	15.33±6.12	22.33±5.21	84.06±7.93	2.36±0.34	5.38±0.16
100 mg/kgextract	11.00±3.79	20.33±1.33	82.80±23.80	2.33±0.30	4.97±0.71
200 mg/kg extract	9.33±2.67	16.00±1.73	56.79±4.63	1.87±0.21	4.48±0.40
400 mg/kg extract	15.00±7.37	28.33±2.67	79.12±3.32	2.37±0.10	6.44±0.69

Values are expressed as Mean ± SEM (n = 5)

Discussion

The significance of medicinal plants and their application to the health of mankind has very well been established. A variety of herbal plants are being used in daily life as remedies to treat various diseases worldwide. *C. papaya* has been used since early times for the treatment of diverse disease conditions. In the acute toxicity test carried out, it was observed that the unripe Unripe *Carica papaya* extract administered at lower administration doses of 10 mg/kg, 100 mg/kg and 1000 mg/kg recorded no mortality rate. It depicts that the extract was effective at this doses range and was non-lethal to the animals. This study also depicts the higher dose administration of the Unripe *Carica papaya* at administration dose 1600 mg/kg, 2900 mg/kg and 5000 mg/kg respectively and recorded no mortality rate. However, the *in vitro* analysis revealing the antiulcerative activity of 11.20 mm, falling notably short of the expected 23.50 mm, prompts careful consideration. Several factors could contribute to this disparity, including variations in assay conditions, inherent variability of natural products. It becomes crucial to critically evaluate these aspects to better understand the observed outcome. Several mechanisms are associated with the production of gastric mucosal lesions. Indomethacin causes intense damage to the gastric mucosa in the form of ulcerative lesions. These resulting to the weakening of the gastric mucosa caused by synthesis inhibition of prostaglandins by COX-1. Our research suggests that there was no Significant difference in Gastric pH as observed between the experimental or the treatment Groups. However, the rats treated with 200 mg/kg of the extract showed the highest level of gastric pH in comparison with the other groups. This posits that treatment with unripe pulp of carica papaya extract could promote gastric healing of chronic ulcers in the gastric tissue of rats induced.100 mg/kg, 200 mg/kg, 400 mg/kg of *Carica papaya* pulp extract and cimetidine 30 mg/kg did not have a significant effect on Ulcer Index (p>0:05) and acid secretion. In this finding, antisecretory drugs or acid suppressive therapies may not be necessarily effective on the rate of tissue regeneration, as similar scenario of ranitidine was reported in previous studies (Adane, *et al*, 2021; Reddy *et al.*, 2012) [2, 25] There was also no significant change in pH (p<0:05) on 100 mg/kg, 200 mg/kg and 400 mg/kg treated groups with *Carica papaya* pulp extract. This finding is not in agreement with a previous study. (Abebaw *et al.*, 2017; Adane *et al.*, 2021) [1, 2]

This effect of 400 mg/kg of *Carica papaya* pulp extract suggests slight mucosal tissue regeneration of the plant due to the presence of the active phytochemicals. Might be efficient in high concentration (Adane *et al.*, 2021) [2].

Creatinine and urea levels are used as markers of kidney function, but the test for creatinine is more sensitive than urea. As the excretory function of kidney is impaired, urea and Creatinine excretion is hampered leading to its increased levels in blood. The results of this study showed that the administration of the aqueous extract of *C. papaya* revealed no statistically significant difference (p>0.05) in the urea (p = 0.639) and creatinine (p = 0.191) concentration of the rats treated with the aqueous extract of *C. papaya* when compared with the control group and the groups administered with extracts at different concentration . The results showed no significant decrease in the creatinine concentration upon administration of 200 mg/kg of *C. papaya* (0.81±0.08) when compared to the ulcer untreated group (1.53±0.18). There was also a slight increase in the urea concentration in the group administered 400 mg/kg of *C. papaya* (61.80±10.11) when compared to the normal control group (50.51±12.86) and in the creatinine concentration in this same group administered 400 mg/kg of *C. papaya* (1.25±0.36) when compared to the normal control group (1.189±0.22). Overall, the results imply that administering papaya plant pulp at specified doses did not significantly affect the renal function, with observed values within clinically acceptable ranges. (Ullah *et al.*, 2024; Kwo *et al.*, 2017) [27, 20].

In our research involving rats, liver enzymes such as AST, ALT, and ALP levels among the treatment groups did not demonstrate significant differences when compared to the control group. It may be inferred from the results of this study that the aqueous extract of *C. papaya* is not toxic to the liver function and it was observed to ameliorate liver dysfunctions brought on by the induction of ulcer as noticed in the ulcer untreated group. Elevated serum levels; aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline phosphate (ALP), total bilirubin and direct bilirubin which was observed in this study due to the induction of ulcer (ulcer untreated group). Our findings are in agreement with analysis performed by Ullah *et al.*, 2024 [27]; Furthermore, Kwo*et al*, (2017) [20] has emphasized that abnormalities in AST, ALT, and ALP levels are more strongly associated with indications of liver cell injury.

Our investigation revealed that Carica papaya unripe pulp exhibited a nephrocurative or healing effect, even at high doses, without causing significant changes in healthy rats. Our analysis is in alignment with the research conducted by Ullah *et al.*, 2024 [27]. Similarly, in an investigation conducted by Madinah *et al.* (2015) [23] and Gheith *et al.* (2018) [12] observed that an aqueous extract of *Carica papaya* seeds demonstrated effective nephroprotective activity in albino Wistar rats. This was evidenced by a reduction in biochemical parameters and an improvement in kidney architecture among rats with kidney injury.

Conclusion

According to findings from this study indicated that the extract of Unripe *C. papaya* could not be a potential source for the development of novel antiulcer drug. The obtained results revealed that the aqueous extract of unripe *C. papaya may possess* very slight antiulcer activity even with reduced efficacy and potency. It can be inferred from the observed that an aqueous extract of Carica papaya seeds demonstrated effective nephroprotective activity in albino Wistar rats. This was evidenced by a reduction in biochemical parameters and an improvement in kidney architecture among rats with kidney injury

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