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ORIGINAL RESEARCH ARTICLE

Gastro-protective Effect of *Carica papaya* Leaf Extracts on Ethanol-Induced Gastric Ulcer in Rats

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ABSTRACT

Carica papaya leaves are commonly used traditionally to treat many diseases, including peptic ulcers; however, these pharmacological claims and safety issues of the leaves have not been adequately resolved. The present study aims to evaluate the possible gastro-protective potential of *Carica papaya* aqueous and methanol leaf extracts on ethanol-induced ulcers. Aqueous and Methanol extracts of *C. papaya* were prepared by percolation method and screened for phytochemicals using conventional method and Gas Chromatography-Mass spectrometric methods. The gastro-protective effects of the extracts were determined using thirty (30) rats weighing 180 and 250 g were randomly divided into five groups. Group 1 served as the normal control (distilled water), groups 2 served as the (negative control), group 3 received 25mg/kg Omeprazole (standard drug) group 4 and 5 received 300 mg/kg and 600 mg/kg of aqueous and methanol extracts of *Carica papaya*. Two weeks after the oral administration, gastric ulcer was induced in all rats with 95% ethanol (2 mL). The aqueous and methanol leaf extract of *C. papaya* showed a significant ($p < 0.05$) dose-dependent protection against peptic ulcer. The effects produced by the methanol leaf extract of *C. papaya* were comparable to those of the standard drugs (Omeprazole). Phytochemical analysis of the aqueous and methanol leaves extracts of *C. papaya* revealed the presence of flavonoids, tannins, alkaloids, terpenoids, cardiac glycosides, reducing sugar and saponins, some of which have been reported to elicit cytoprotective effect. Gas chromatographic analysis showed the presence of cytoprotective agents. These findings show that aqueous and methanol extracts of the leaves of *C. papaya* possess potent antiulcer properties; hence justifies the traditional usage of this plant for ulcer treatment.

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INTRODUCTION

A Peptic ulcer is considered one of the significant ailments affecting about 60% of adults and nearly 80% of the child population in tropical countries (Krishna *et al*., 2014; Yau *et al*., 2017). Peptic ulcer is a gastrointestinal disorder, characterized by disruption in gastric mucosal infiltration through the muscularis mucosa (Garg *et al*., 2022). The pathophysiology of peptic ulcers caused by multiple etiologies involving unbalance between invasive factors (pepsin, bile salt H. pylori and acid,) and protective factors (prostaglandin, nitric oxide, bicarbonate, growth factors and mucin,) (Michael *et al*., 2013).

Many factors predispose an individual to peptic ulcer disease include Helicobacter pylori infections, excessive use of anti-inflammatory drugs like NSAIDs, smoking, stress, family history, alcohol consumption and lower socio-economic status (Yau *et al*., 2017). It is should be noted that ulcerative disease is not fatal but could lead to serious complications, such as perforations, gastric outlet obstruction, gastrointestinal bleeding and ulceration that invades adjacent organs (Yau *et al*., 2017: Garg *et al*., 2022).

To achieve steady state, different therapeutic agents including plant extract have been employed to inhibit the secretion of excess gastric acid secretion or stimulate mucosal protective mechanisms by enhancing mucus secretion, interferes with the synthesis prostaglandins or stabilising surface epithelial cells (Ani *et al*., 2021). Synthetic drug currently used to treat ulcers include proton pump inhibitors, prostaglandin analogues, antacids, and H2 receptor blockers. Despite the fact that these drugs are

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very effective, numerous negative effects have been noted. Therefore, scientific screening plants to develop safer, effective anti-secretory and anti-ulcer drugs is essential (Garg *et al*., 2022).

Carica papaya Linn (family: Caricaceae) is a herbaceous and tropical succulent plants that possess self-supporting stems which grows in all tropical countries and many subtropical regions of the world, and it is largely used in tropical folk medicines (Okewumi, and Oyeyemi, 2013). It is called by names, such as pawpaw in English and Gwanda in Hausa. The ripe fruit is edible and unripe (which is a rich source of vitamin A) can be eaten cooked (Lohiya *et al*., 2012). More so, the unripe fruit is preferred due to it large amount of latex which have abundant enzymes required for many industrial, nutritional, and therapeutic applications (Krishna *et al*., 2014). It contains bioactive compounds, namely, papain, chymopapain, alkaloids, flavonoids, benzylisothiocyanate and phenolic (Anaga and Onehi, 2010). *C. papaya* fruits consist mostly of water and carbohydrate, low in calories and rich in natural vitamins and minerals, particularly vitamins A and C, ascorbic acid and potassium (Dibyajyoti *et al*., 2021).

Numerous scientific studies have demostrated that C. papaya possessed anti-inflammatory, anti-diabetes, anti-hyperlipidemic, diuretic, anti-helminthic, hypoglycemic, anti-amoebic, nephroprotective, wound and burn healing, antioxidant, bactericidal anti-nociceptive, and anti-ulcer (Okewumi, and Oyeyemi, 2013). Papain and chymopapain which are part of the plant constituents are being useful for digestive disorders and disturbances of the gastrointestinal tract (Mohamed *et al*., 2022).

Traditional healers have utilised Nigerian plants leaves, including *C. papaya* to treat ulcer in the Northwestern region of Nigeria . For instance, the decoction of *C. papaya* is taken as daily tea to treat ulcer (Basal and Grel, 2012).

Several medicinal plants including *Carica papaya* seed have been reported to possess anti-ulcerogenic activity by virtue of their predominant effect on mucosal defensive factors (Gadzama *et al*., 2014). Anti-ulcer potential aqueous extract of *C. papaya* seed against indomethacin-induced ulcer and aspirin-induced ulcers was reported (Okewumi, and Oyeyemi, 2013). Krishna *et al*., 2014 also gastro-protective activity of aqueous extract of *C. papaya* seed against ulcer models by pylorus ligation.

Considering these preliminary results with *C. papaya* seed extract in acute gastric lesions induced by indomethacin, aspirin and pylorus ligation and the relevant protective potential of this plant, this work has the objective to evaluate gastro-protective properties of both the aqueous and methanol extracts of *C. papaya* leaf against ethanol–induced ulcer in rats and identify the bioactive compounds responsible for the gastro-protective activity by conventional method and Gas Chromatography- Mass Spectrometric methods.

MATERIALS AND METHODS

Ethical Approval

The following research methodology and its ethics have been fully reviewed and approved, in the 2021/2022 academic session, by the Departmental academic board, Department of Biochemistry and Molecular Biology, Federal University Dutsin-Ma, Katsina State, Nigeria.

Collection and authentication of plant material

Carica papaya leaves were obtained from the surroundings of the Badole community of Dutsinma Local Government in February, 2021 and authenticated by the Taxonomist at Department of Biological Science; Federal University Dutsinma. The voucher specimen was deposited at their herbarium with voucher accession numbers MA004.

Preparation of Plant Extracts

Aqueous extraction: 1000g of dried fresh leaves were macerated using a mechanical grinder. 250ml of clean water was added to the macerated leaves and homogenised using a wooden rod as a stirrer. The homogenate was strained through muslin. The filtrate was further concentrated by allowing it to stand overnight in an oven at 30°C and stored at 4°±2°C until required (Michael *et al*., 2013). The aqueous extract gave a percentage yield of 27.6%.

Methanol extraction: 100g of powdered leaves of *C. papaya* was macerated in 2 litres of 80% methanol for 48hrs. The extract was filtered through a Whatman no. 1 filter paper. The filtrate was then evaporated to dryness on a rotary evaporator (Model type 349/2 Corning Ltd). The dried residue was stored at 4°±2°C. A yield of 20.8 % of the methanol extract was obtained. A known quantity of the methanol extract was dissolved in 3% aqueous suspension of Tween 80 to obtain the desired concentration for the study (Ajaib, *et al*., 2022).

Animals

Wistar rats of either sex (120 to 150 g) were obtained from Veterinary Institute Vom, Jos and kept in the

animal house of the Department of Biochemistry and Molecular Biology, Federal University Dutsin-Ma. The animals were kept in well-constructed cages under standard conditions (25 ± 2°C, 12 h light and dark cycle) that allowed freedom of movement for two weeks for acclimatisation to the laboratory conditions before the commencement of the study. Water and standard rat chow were provided ad libitum throughout the study.

Acute toxicity study

Acute oral toxicity study of aqueous and methanolic leaf extract of the *C. papaya* was carried out to determine LD50 by adopting dosing schedule as per OECD guideline no. 425. Female albino rats weighing 20-30 g were used for the study. The animals were continuously observed for 12 h to detect changes in autonomic or behavioral responses. Mortality was observed for 24h. The doses of 300 and 600mg/Kg, p.o. were selected.

Animal grouping and treatments

Wister albino rats weighing 180-250g were used for the study. The rats were divided into five groups. Groups 1, 2 and 3 composed of ten rats. The rats in groups 4 and 5 were divided into two subgroups of five rats each: one subgroup given the extract at 300mg/kg, and the other at 600mg/kg.

Group 1 (normal control) was given normal rat chow and water with no treatment. Group 2 (negative control) was received ulcer-induced without pretreatment. Group 3 (standard control) was ulcer-induced and pretreated with 25mg/kg omeprazole. Group 4 was ulcer-induced and pre-treated with 300 and 600 mg/kg aqueous extract of *C. papaya*. Rats in group 5 were ulcer-induced and pre-treated with 300 and 600 mg/kg methanol extract of *C. papaya*. The treatment in all the groups was single dose for fourteen consecutive days through gavages.

Induction of gastric ulcer

After two weeks of treatment, all the rats fasted for 24 h with free access to water, water was withdrawn two hours prior to ulcer induction. Gastric ulcer was induced with 1 ml of 95% ethanol which was administered orally to each animal after 24 h fasting (Jalilzadeh-Amin *et al*., 2015).

Determination of Ulcer lesion and Ulcer index

Two hours after gastric ulcer induction, the rats were killed by cervical dislocation; the abdomen was opened to remove the stomach. After removing gastric content from the stomach, the stomach was rinsed with 0.9% saline and then pinned onto a soft board and ulcer lesion were measured using a hand lens 10x and a rule. Scoring of ulcer was carried out as reported by (Yau *et al*., 2017). Following method: 1 = erosions 1 mm or less, 2 = 1 to 2 mm, 3 = >2 mm. The overall score was divided by a factor of 10 which was designated as the ulcer index (Panda and Khambat, 2014).

Ulcer Index = (Ulcerated Area)/(Total Stomach Area) ×100

The percentage of ulcer inhibition was calculated as follows (Gupta *et al*., (2012):

Ulcer Inhibition (%) = (Mean Ulcer Index of Control-Mean Ulcer Index of Test)/(Mean Ulcer Index of Control) ×100

Phytochemical testing

The qualitative analyses of the plants' constituents were carried out using the methods described by Sonam *et al*., (2017). The presence of alkaloids, tannins, saponins, flavonoids, glycosides, anthraquinones, volatile oil and steroids were tested.

Gas Chromatography Mass Spectrometry analysis (GC-MS) of aqueous and Methanolic leaves extract of *Carica papaya*.

The Gas chromatography-mass spectrometry Analysis was conducted using an Agilent – 7890B GC-MS (company name). The GC-MS was equipped with a split injector, an ion – trap mass spectrometer detector, and a fused capillary column (Agilent Hp.5ms ultra inert) with a thickness of 3µm, 250µm, x 0.25µm and temperature limits of 60oC to 325oC. The column temperature was programmed between 60oC and 250oC and flow rate at a rate of 3.0ml/min, pressure; 4.4867psi. The temperature of the injector and detector were at 250oC and 200oC respectively. The split ratio was 20:1 Split flow at 14ml/min. Helium gas was used as a carrier gas, methanol was used as the solvents used to dissolve the sample (Aliyu *et al*., 2017)

Real-time and post-run analyses were evaluated using MSD (Masshunter) matching the unknown spectra with spectras of known compounds from the Library of Spectra, from the National Institute of Standards (NIST14.L), respectively Washington, USA. The fragmentation patterns of the identified compounds were examined for consistency with known data from literature (De Araújo *et al*., 2021). In addition, the hit quality which indicates how closely matched the compound is with the Library data) was used further

to verify the identity of the compounds in the sample. The name, molecular weight, mass to charge ratio, retention time, relative percentage composition and the structure of the components of the test materials were determined.

RESULTS AND DISCUSSION

Acute toxicity study

The acute toxicity test result showed that all the rats in each of the plants' groups survived, indicating that the LD50 is greater than 6000 mg/kg (OECD, 2001), and absence of acute toxicity in rats ensured a good margin of safety for the doses of this extract in the experimental protocols of gastric lesions, as no mortality recorded for each animal (Rtibi *et al*., 2015).

Gastro-protective Activity of Aqueous and Methanol Extracts of *C. papaya* leaves

In this experiment, the gastro-protective effect of aqueous and methanol extracts of *C. papaya* leaves is presented in Table 1. It was observed that the rats pretreated with different doses of aqueous and methanol extracts of *C. papaya* leaves and Omeprazole significantly ($p < 0.05$) reduced the gastric lesions as compared to the normal negative control in a dose dependent manner. Aqueous extract at all doses (200and 400 mg/kg) produced gastro-protective effects by as much as 58.00 and 68.90% respectively comparable to the standard drug, Omeprazole (91.20%). The methanol extract (400 mg/kg) produced the most potent inhibition of gastric lesions at 78.50% when compared to Omeprazole (20 mg/kg).

Table 1: Effect of *C. papaya* leaf extracts on ethanol-induced gastric ulcer.

Groups	Dose (mg/kg)	Ulcer index	%Ulcer protection
I (Control)	0	0	
II (Ulcer control)	0	3.85±0.08	-
III (Standard control)	25	0.34±0.02[a]	91.20
IV (Aqueous extract)	300	1.62±0.06[a]	58.00
	600	1.20±0.04[a]	68.90
V (Methanol extract)	300	1.05±0.04[a]	72.80
	600	0.83±0.02[a]	78.50

Results were expressed as mean ± SEM. Different subscripts in the same column are significantly different from ulcer control ($P < 0.05$) at 95% confidence level.

The gastro-protective activity aqueous and methanol extracts of *C. papaya* leaves was studied in ethanol-induced ulcer in rats. This model is one of the common causes of gastric ulcer in human (Sharma *et al*., 2014). Ethanol induced gastric injury is associated with significant production of oxygen free radicals leading to increased lipid peroxidation, which causes damage to cell and cell membrane (Okewumi and Oyeyemi, 2013).

Ethanol induced gastric lesions are thought to arise due to of direct damage of gastric mucosal cells, resulting in the development of free radicals and hyperoxidation of lipids in the body system (De Araújo *et al*., 2021). Ethanol is noxious to the stomach. Oral administration of 95% ethanol antagonises the cytoprotective mechanism in the body and produces lesions in the gastric mucosa by making the mucus membrane more susceptible to the attack of hydrochloric acid (HCl) (Sharma *et al*., 2014).

Oral administration of ethanol in the control group of rats promoted necrotic lesions and bleeding characteristics however aqueous and methanol extracts were found to reduced lesion areas. The methanol leaf extract of *C. papaya* has significantly protected the gastric mucosa against ethanol challenge as shown by reduced values of ulcer index as compared to control group, suggesting its potent cytoprotective and free radical scavenging effect.

This result is comparable with the report of Okewumi and Oyeyemi (2013), which demonstrated gastro-

protective activity of aqueous *C. papaya* seed extract on ethanol-induced gastric ulcer in male rats. Another finding showed more than 75% protective effect of aqueous extract of *C. papaya* seed against gastric ulcer model induced by pylorus ligation (Krishna *et al*., 2014).

The observed effect of both the aqueous and methanol extracts is dose dependent, the high dose of the extracts significantly produced more potent effect in reducing gastric secretion and protecting the gastric mucosa from noxious effect of ethanol (Ajaib *et al*., 2022), although the effect observed in rats treated with the aqueous extract was low as compared to that of omeprazole (standard drug) which is a well-known drug for the treatment of gastric ulcer, there is tendency that further increase in the extract dose might produce the same effect as that of omeprozole.

Phytochemical Analysis

Phytochemical screening revealed the presence of carbohydrates, reducing sugars, alkaloids, tannins, and moderate amounts of flavonoids, terpenoids, saponins and cardiac glycosides and is presented in (Table 2).

Table 2: Qualitative phytochemical analysis of aqueous and methanolic extract of *Carica papaya*

Phytochemicals	Inference	
	Aqueous extract	Methanolic extract
Alkaloids	+	+
Saponins	-	-
Tannins	+	+
Cardiac glycoside	+	+
Flavonoids	+	+
Terpenoids	+	+
Reducing sugar	+	+

+ indicates present and - indicates absent

These chemicals are reported to possess antiulcer effect (De Araújo *et al*., 2021). Flavonoids have antiulcer and gastroprotective activities. Several gastroprotective mechanism have been proposed to explain the biological effects of flavonoids including free radical scavenging during hyperoxidation of lipid memebrane, increases mucosal PGE2, increases mucosal blood flow, decreases histamine secretion from mast cells by inhibition of histidine carboxylase, inhibit H. pylori growth, act as free radical scavengers and inhibit H+/K+-ATPase (Sharath *et al*., 2015). On the other hand, tannins may prevent ulcer development due to their protein precipitating and vasoconstricting effects. Their astringent action can help precipitating microproteins on ulcer site thereby forming an impervious layer over the linning that hinders gut secretions and protects underlying mucosa from toxins and other irritants and stimulate PGE2 formation. Terpenes are known to possess antiulcer activity and their action has been suggested to be due to the activation of cellular protection, reduction of mucosal prostaglandins metabolism-cytoprotective action and reduction of gastric vascular permeability. Saponins may activate mucous membrane protective factors (Gadzama *et al*., 2016). Furthermore, alkaloids were abundant in the extracts and alkaloids are substances known to affect the integrity of the mucous membrane. Alkaloids such as hyoscine-N-methyl bromide have been shown to suppress acid secretion (Neelam *et al*., 2012).

The Gas-chromatography coupled with mass spectrometry analysis of compounds obtained in aqueous and methanol extracts of *C. papaya* leaves were recorded in table 3 and 4 respectively.

About 11 compounds were revealed in aqueous extract of *C. papaya* leaves and out of these compounds, Resorcinol, 2-Methoxy-4-vinylphenol tans-cinnamic,

Procaine, Methyl stearate and n-Hexadecanoic acid (Palmitic Acid) have been shown to possess both antioxidant and anti-inflammatory properties. (Sermakkani and Thangapandia, 2012; Jaemin *et al*., 2015; Cheriet *et al*., 2015; Salisu *et al*., 2017). On the other hand, Phenol l, 2, 3, 6-trimethyl, 1, 2, 3, 4-Cyclohexanetetrol, Hexadecanoic acid, methyl ester, Hexadecanoic acid, butyl ester and α-cardinol possess antioxidant properties (Abolfail *et al*., 2014; Uloma *et al*., 2016; Belakhdar *et al*., 2015; Radhakrishnan *et al*., 2016). Octadecanoic acid and 9,12-Octadecadienoic acid (Z, Z)-methyl ester are reported to possessed anti-inflammatory properties (Sermakkani and Thangapandia, 2012; Salisu and Shema, 2020).

Table 3: Phytocontituents having anti-ulcer activity in aqueous extract of *C. papaya* leaves identified by GC-MS analysis

Compound	Retention Time	Molecular Formula	Mol. Weight	Area % (Relative abundance)
Resorcinol	17.834	$C_6H_6O_2$	110.1	0.19
2-Methoxy-4-Vinyl phenol	18.616	$C_9H_{10}O_2$	150.177	1.48
Trans-cinnamic acid	21.639	$C_9H_8O_2$	148.161	0.12
Phenol,2,3,6-trimethyl	22.144	$C_9H_{12}O$	136.19	0.14
Procaine	25.818	$C_{13}H_{20}N_2O_2$	236.315	2.16
Alpha-Cardinol	31.640	$C_{15}H_{26}O$	222.372	0.19
Hexadecanoic acid	33.468	$C_{17}H_{34}O_2$	270.45	1.35
Octadecanoic acid	35.506	$C_{18}H_{36}O_2$	284.482	0.04
9,12-Octadecanoic acid	37.003	$C_{19}H_{34}O_2$	294.479	2.43
Quercetin 3[1]-methyl ether	43.075	$C_{16}H_{12}O_7$	316.234	1.75
Alpha-Tocophero	48.644	$C_{29}H_{50}O_2$	340.521	1.35

9 compounds were detected in methanol extract of *C. papaya* leaves. 3-Hexanol, 2-methyl-1-Octadecene, Oleyl alcohol and trifluoroacetate were reported to have antioxidant activity (Ravikumar *et al*., 2012; Belakhdar *et al*., 2015), while; Benzoic acid, 2-Methoxy-4-vinylphenol trans-Cinnamic acid, Quercetin 3'-methyl ether, alpha-Tocopherol and Myo-Inositol, 4-C-methyl- (Laminitol) possessed both anti-oxidant and anti-inflammatory properties (Ravikumar *et al*., 2012; Cheriet *et al*., 2015).

Table 4: Phytocontituents having anti-ulcer activity in methanolic extract of *C. papaya* leaves identified by GC-MS analysis

Compound	Retention Time	Molecular Formula	Mol. Weight	Area% (Relative abundance)
Hexanol, 2-methyl	3.296	$C_7H_{16}O$	55	0.59
Benzoic acid	14.095	$C_7H_6O_2$	124.0	0.69
2-Methyl-4-vinylphenol	17.087	$C_9H_{10}O_2$	151.200	2.29
Trans-cinnamic acid	21.657	$C_9H_8O_2$	147.1	0.29
Myo-Inositol, 4-C-methyl	30.84`	$C_7H_{14}O_6$	73.0	0.38
Quercetin 3[1]-methyl ether	43.075	$C_{16}H_{12}O_7$	316.234	2.12
Oley alcohol, Trifluoroacetate	46.608	$C_{20}H_{33}F_3O_2$	37.100	0.51
1-Octadecene	46.642	$C_{18}H_{36}$	252.486	1.01
Alpha-tocopherol	48.644	$C_{29}H_{50}O_2$	430.71	0.61

It is possible that these compounds act synergistically to protect the stomach lining from damage during oxidative stress (Radhakrishnan *et al*., 2016), by either scavenging these free radicals such as superoxides anion radical (O2•−), hydroperoxyl radical (HOO•), hydrogen peroxide (H2O2), hydroxyl radical (OH•), Lipid peroxide radical (ROO•) e.t.c or inhibiting the production of these radicals. Most of these compounds do this by donating their electrons, and their ability to donate their electrons lies in their structural orientations and their functional groups. Compounds like Myo-Inositol, 4-C-methyl-, alpha-Tocopherol, Quercetin 3'-methyl ether, 2-Methoxy-4-vinylphenol, Oleyl alcohol and Resorcinol have hydroxyl groups (-OH) as part of their functional groups and helps in quenching the free radicals by donating it electron as

hydrogen atom. Compounds like 1, 2-Cyclopentanedione and Procaine have carbonyl group (C=O) as part of their functional groups (Belakhdar *et al*., 2015). It's donates electrons from the lone pair electron on the oxygen atom. Compounds like Octadecanoic acid, n-Hexadecanoic acid, 9, 12-Octadecadienoic acid (Z, Z)-methyl ester, Hexadecanoic acid, butyl ester, Benzoic acid, trans-Cinnamic acid, Quercetin 3'-methyl ether have both hydroxyl groups (-OH) and carbonyl group (C=O) as part of their functional groups. Procaine is an analgesics and anti-aging drugs (Daniela *et al*., 2019).

CONCLUSION

The aqueous and methanol extracts of C. papaya leaves possessed gastro-protective activity against ethanol-induced ulcer rats and methanol extract displayed the highest gastro-protective potential. Therefore, the traditional use of this plant to treat ulcer could be justified by the result of the study.

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