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Anti-Oxidant Activity of *Carica Papaya* Seed Extracts on Indomethacin-Induced Ulcer in Rats

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Abstract: ***The seed of Carica papaya has been traditionally used for the treatment of peptic ulcer disease and other ailments. The Anti-oxidant Activity of Carica papaya seed Extracts on Indomethacin-induced Ulcer in Rat was investigated to validate this claim. The qualitative phytochemical screening of the aqueous Carica papaya seed extract showed the presence of tanins, saponins, flavonoids, alkaloids, phenols, terpenoids, cardiac glycosides, anthraquinones and steroids. Quantitatively, Phenols and flavonoids (20.80% and 20.40%) were found to be the highest in the phytochemicals while anthraquinones and saponins (5.80% and 6.40%) were the least in content. The study was conducted on fifty-five (55) young albino rats weighing between 120-150g were grouped into eleven (11) of five (5) each. Peptic ulcer was induced in all the rats using indomethacin at 50mg/kg/bw single dose and the level of total endogenous anti-oxidants were significantly (p>0.05) reduced when normal groups (73.30 ± 0.92) was compared with the induced group (27.42 ± 0.85). The rats were treated with varied concentrations of both aqueous and ethanolic seed extracts at 100, 150, 300 and 450mg/kg/bw. Oral administration of aqueous extract (100mg/kg/bw) of the seed significantly (p>0.05) increased the total anti-oxidant levels to (86.28 ± 3.82) in the treated animals. Treatment was able to prevent reduction in the levels of anti-oxidant caused by indomethacin. Treatment using the extract also significantly (p>0.05) boosted total protein concentration level (80.08 ± 0.80) when compared to the negative control (56.94 ± 3.29). This study showed anti-ulcer activity of Carica papaya seed extracts by improving the anti-oxidant activity.***

Keywords: Anti-oxidant Activity, Anti-ulcer effect, Carica papaya, Albino rats, Indomethacin. Aqueous Extract (AE), Ethanolic Extract (EE)

1. Introduction

An ulcer is basically an inflammed break in the skin or in the mucus membrane lining the gastrointestinal tract (Fong and Devlin, 2008). Peptic ulcer, also known as peptic ulcer disease (PUD), is defined as a breach in the lining (mucosa) of the digestive tract produced by digestion of the mucosa by pepsin and acid basically as a result of the disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance (Grossman, 2009). The peptic areas of the human body under normal circumstances are the stomach and duodenum. Therefore, a common medical disorder with the peptic areas of the body is peptic ulcer disease. Gastrinomas (Zollinger Ellison syndrome), a rare gastrin-secreting tumours, also cause multiple and difficult-to-heal ulcers (Greenstein and Greenstein, 2007).

The prevalence of PUD is kept at maximum of 40% in developed countries, but it is higher in developing countries being estimated at 70% of the population. Generally, the impressive fall in its incidence is as a result of the development of new effective medication and acid suppresants, as well the discovery of the causative agent, *H. Pylori* (Wolfe *et al*., 1999). Similarly, Peptic ulcer disease (PUD) has a tremendous effect on morbidity and mortality, and the lifetime risk for developing the disease is approximately 10% (Jyotheeswaran *et al*., 1998).

People who regularly take Non-Steroidal Anti-inflammatory Drugs (NSAIDs)—such as those with chronic conditions like arthritis—are five times more likely to develop peptic ulcers than people who do not take those (Huang *et al*., 2002). Similarly, even occasional users of NSAIDs—of any age—can develop a peptic ulcer disease, since they tend to inhibit the formation of prostaglandins thereby leading to gastric bleeding and erosion.

But infection of the stomach mucosa with *Helicobacter pylori* is now generally considered to be a major cause, especially of duodenal ulcer (Huang *et al*., 2002).

Free radicals are capable of attacking the healthy cells of the body which may lead to damage, disease and severe disorders. Free radicals have been implicated in the pathogenesis of many diseases which include peptic ulcer disease. Therefore, free radical formation is controlled naturally by various beneficial compounds known as antioxidants

Carica papaya seeds have recently attracted attention as a potential health food, while much of the evidence supporting this notion is unverified. The *papaya* seeds are nontoxic and might be treated as supplement or eating them whole, or the seeds could be grinded and used as pepper since they taste fairly similar (Aravind, 2013). Several medicinal plants including *Carica papaya* have been reported to possess anti-ulcerogenic activity by virtue of their predominant effect on mucosal defensive factors. These plants are used to treat different gastrointestinal illnesses , including peptic ulcer disease (Aravind, 2013). Here in this study, we present the antioxidant activity of *Carica papaya* seed extract as one of the indices for the treatment of peptic ulcer disease.

2. Materials and Methods

Plant Material

Pawpaw seeds from riped pawpaw (*Carica papaya*) fruits was obtained from Asma'u Farms, along Gombi Road, Jimeta. The seeds were inspected and identified in the

Department of Plant Science, Modibbo Adama University of Technology; Yola, Nigeria. Debris and other pawpaw dirts were washed off the choosen seeds with clean water. And the seeds was allowed to first drain and evenly spread out on clean papers, and put under shade to allow proper drying.

Experimental Animals
Fifty-five albino rats, weighing 150 ± 5kg were procured from National Veterinary Research Institute, Vom-Jos, Plateau State, Nigeria. The animals were fed on standard rat pellet made (by Pfizer feeds, Jos) and clean water ad-libitum for 7days before experiment was done on them.

Drugs
Anti-ulcer agent Omecid (Omeprazole) was obtained in the form of Capsules from Saga Laboratories Survey No. 198/2 & 198/3 ChachrawadiVasna, Ta,: Sanand, Dist,: Ahmedabad-382 210 INDIA.

Methods
Preparation of Ethanolic Extract
The ethanolic extraction of the *carica papaya* seeds was done using 70% ethanol according to the method of Mogana *et al* (2011). About 500g of the pulverised *carica papaya* seed extracts was mixed and shaken well in 70% ethanol at 4^{o}C and kept for 24hrs with intermittent shaking. The mixture was then separated using Whatman filter paper No.1 and finally evaporated to dryness at 50^{0}C in hot air oven. The dried extracts obtained was kept in a clean dried container and appropriately labelled. The extracts was appropriately reconstituted in distilled water in the course of the experiment.

Experimental Design
A total number of Fifty-five albino rats weighing 120-150g were used for the experiment. All animals were fed on normal rat diet and water *ad-libitum*, and were caged under healthy conditions of humidity, temperature (20-25^{o}C) and light (12hr-light: 12hr-dark cycle) for fourteen days to acclimatise before the on-set of the experiment. Rats were divided into eleven groups of equal weights and number (5 rats per each group). Group (1) kept as positve control group, Group (2) kept as negative control group and Group (3) served as Standard Drug control group. These groups were all fed on normal rat diets but Group (2) and (3) had ulcer induced with indomethacin, 50mg/kg/bw (Magistreni *et al.,* 1988). Group (2) had no treatment while Group (3) had treatment with Standard Drug (Omeprazole, 20mg/kg/bw). The first and second groups of (4, 5, 6 and 7) had normal diets, ulcer induced and treated orally with (100, 150, 300 and 450mg/kg/bw) by tubing of both Aqueous and Ethanolic extracts of *Carica papaya* seed. All experiment lasted for fourteen days.

At the end of the experiment, all rats were fasted for 12hrs and their blood were collected into heparinised containers through cardiac puncture.

Ethical Consideration
The experimental protocol was adhered to minimise adverse effects on each experimental animal. The experiments was carried out under supervision and experiments were conformed to the guidelines and ethics on Animal Care and Research.

Statistical Analysis
The data obtained were expressed as the Mean ± Standard Error of Mean (SEM). And the data were also analysed using the Student's t-test and the Analysis of Variance (ANOVA).

3. Results

Table 1. shows qualitative phytochemical components of the aqueous seed extract of the *Carica papaya* plant was determined. The phytochemicals that were qualitatively present in the aqueous extract included: saponins, tannins, phenols, alkaloids, flavonoids, terpenoids, anthraquinones, cardiac glycosides and steroids.

Table 1: Qualitative phytochemical Analysis of Aqueous Extract of *Carica papaya* seed

Phytochemical	*Inference*
Saponins	+
Tannins	+
Phenols	+
Alkaloids	+
Terpenoids	+
Anthraquinones	+
Cardiac Glycosides	+
Steroids	+

Keys: + = Present, – = Absent.

Table 2. indicated the quantitative phytochemicals estimated in the aqueous seed extract of *Carica papaya*. The phytochemicals showed phenols and flavonoids to have the highest percentage of 20.80 and 20.40% respectively, while saponins and anthraquinones have the lowest percent constituent as 6.40 and 5.80%.

Table 2: The Quantitative determination of phytochemical components of Aqueous Extract of *Carica papaya* seed

Constituents	*Concentrations (mg)*	*Percentage (%)*
Saponins	0.31 ± 0.01	6.40
Tannins	0.47± 0.01	9.40
Phenols	1.04 ± 0.01	20.80
Alkaloids	0.63 ±0.01	12.60
Flavonoids	1.02 ±0.01	20.40
Terpenoids	0.46 ±0.01	9.20
Anthraquinones	0.31± 0.00	5.80
Glycosides	0.94 ± 0.01	18.60
Steroids	0.48 ± 0.01	9.60

Results are expressed as mean ± SEM (n = 5) and Percentage (%).

The results of *Table* 3, showed significant difference between Group 2 and Group 1 in both extracts. While aqueous exract has shown more activity ($p>0.05$) than ethanolic extract.

Table 3: Total Antioxidant Activity of Aqueous and Ethanolic Extracts of *Carica papaya* seed using DPPH Assay

Treatment	*Concentration (%) AE*	*Concentration (%) EE*
Group 1: Normal Control	73.30 ± 0.92	73.30 ± 0.92
Group 2: Negative Control	27.42 ± 0.85*	27.42 ± 0.85*
Group 3: Standard Drug (Omeprazole, 20mg/kg/bw)	42.58 ± 0.31[a]	42.58 ± 0.31[a]
Group 4: 100mg/kg/bw	86.28±3.82[ab]	30.52 ± 1.95
Group 5: 150mg/kg/bw	67.48±2.85[ab]	15.94 ± 0.33
Group 6: 300mg/kg/bw	63.94±1.14[ab]	10.54 ±0.20
Group 7: 450mg/kg/bw	43.7± 2.93	35.28 ± 0.34

Results are expressed as mean ± SEM (n = 5). *significant decrease than group 1; [a]significant increase than group 2; [ab]significant increase than group 3; AE = Aqueous Extract of *Carica papaya* seed; EE = Ethanolic Extract of *Carica papaya* seed; SEM = Standard Error of Mean; mg/kg/bw = Milligram/Kilogram/Body weight; DPPH = (2,2-diphenyl-1-picryl hydrazyl).

In *Table* 4, there is generally no significant difference in effect between the extracts and the Standard drug.

Table 4: The Total Antioxidant Activity of Aqueous and Ethanolic Extracts of *Carica papaya* Seed using TBARS Assay

Treatment	*Concentration (%) AE*	*Concentration (%) EE*
Group 1: Normal Control	91.35 ± 0.95	91.35 ± 0.95
Group 2: Negative Control	67.84 ± 0.74*	67.84 ± 0.74*
Group 3: Drug Control	77.54 ± 0.52	77.54 ± 0.52
Group 4: 100mg/kg/bw	73.82 ± 0.44	71.12 ± 0.60
Group 5: 150mg/kg/bw	64.10 ± 6.89	79.40 ± 1.38
Group 6: 300mg/kg/bw	70.10 ± 1.40	64.86 ± 1.40
Group 7: 450mg/kg/bw	70.40 ± 0.72	65.74 ± 0.94

Results are expressed as mean ± SEM (n = 5). *significant decrease than group 1; AE = Aqueous Extract of *Carica papaya* seed; EE = Ethanolic Extract of *Carica papaya* seed, SEM = Standard Error of Mean; mg/kg/bw = Milligram/Kilogram/Body weight; % = Percent; TBARS = Thiobarbaric Acid Reactive Substances.

In *Table* 5, ethanolic extract showed higher activity (p>0.05) when compared with Aqueous extract.

Table 5: Total Antioxidant Activity of Aqueous and Ethanolic Extracts of *Carica papaya* Seed using FRAP Assay

Treatment	Concentration (%) AE	Concentration (%) EE
Group 1: Normal Control	51.64 ± 0.41	51.64 ± 0.41
Group 2: Negative Control	29.90 ± 6.92*	29.90 ± 6.92*
Group 3: Drug Control	45.28 ± 1.60[a]	45.28 ± 1.60[a]
Group 4: 100mg/kg/bw	24.34 ± 7.10	41.14 ± 1.62[b]
Group 5: 150mg/kg/bw	21.90 ± 5.13	38.14 ± 3.19[b]
Group 6: 300mg/kg/bw	16.44 ± 4.49	24.18 ± 1.85
Group 7: 450mg/kg/bw	16.56 ± 3.85	6.56 ± 0.21

Results are expressed as mean ± SEM (n = 5). *significant decrease than group 1; [a]significant increase than group 2; [b]significant increase than same groups of AE; AE = Aqueous Extract of *Carica papaya* seed; EE = Ethanolic Extract of *Carica papaya* seed; SEM = Standard Error of Mean; FRAP = Ferric reducing antioxidant power; mg/kg/bw = Milligram/Kilogram/Body weight.

The results of *Table* 6, showed group 2 (56.94 ± 3.29) were significant (p>0.05) compared with group 1 (80.08±0.80).

Table 7: The Total Antioxidant Activity of Aqueous and Ethanolic Extracts of *Carica papaya* Seed using Total Proteins as an index

Treatment	*Concentration (g/dl)AE*	*Concentration (g/dl)EE*
Group 1: Normal Control	80.08 ± 0.80	80.08 ± 0.80
Group 2: Negative Control	56.94 ± 3.29*	56.94 ± 3.29*
Group 3: Drug Control	72.12 ± 1.02[a]	72.12 ± 1.02[a]
Group 4: Conc 100mg/kg/bw	70.12 ± 2.09	58.20 ± 2.65
Group 5: Conc 150mg/kg/bw	65.20 ± 2.27	71.56 ± 4.44[a]
Group 6: Conc 300mg/kg/bw	63.40 ± 1.21	51.88 ± 2.56
Group 7: Conc 450mg/kg/bw	81.00 ± 2.92[ab]	60.36 ± 0.75

Results are expressed as mean ± SEM (n = 5). *significant decrease than group 1; [a]significant increase than group 2; [ab]significant increase than group 7 of EE; AE = Aqueous Extract of *Carica papaya* seed; EE = Ethanolic Extract of *Carica papaya* seed; SEM = Standard Error of Mean; mg/kg/bw = Milligram/Kilogram/Body weight; g/dl = Gram/Decillitre.

4. Discussion

The phytochemicals components present in the aqueous *Carica papaya* seed included: saponins, tanins, phenols, alkaloids, flavonoids, terpenoids, anthraquinones, cardiac glycosides and steroids which is in agreement with the findings of Adebiyi *et al* (2002); Udoh and Udoh, (2005). However, the presence of Carotenoids and the absence of Cardiac glycosides, and Terpenoids were in contrast with the work of Delphin *et al* (2014), who reported Carotenoids was present, while Cardiac glycosides and Terpenoids were absent in the *Carica papaya* seed extract. This observed difference may be due to geographical location of the plant, storage or solvent used. The quantitative phytochemicals carried out revealed that phenols 20.80%, flavonoids 20.40%, akaloids 12.60%, cardiac glycosides 18.60%, tanins 9.40%, steroids 9.60%, terpenoids 9.20% and anthraquinones 5.80%. This result has shown phenols and flavonoids (20.80% and 20.40%) had the highest contents which agreed with the views of Delphin *et al* (2014). Anthraquinones and saponins (6.40% and 5.80%) had the least compositions.

Most phytochemicals have antioxidant activity and which protect the body cells against oxidative damage and reduce the risk of developing some biochemical disorders (Amorati and Valgimigli, 2012). The *Carica papaya* seed decoction which contains these phytochemicals are responsible for the treatment of different ailments in many countries and also in western Nigeria (Gill, 1992). It is also used for the treatment of sickle cell anaemia (Ogunyemi *et al*., 2008). Flavonoids have proven ability to inhibit specific enzymes, some hormones and to scavenge free radicals (Moltiva *et al*., 1994). It has anti-inflammatory activity and protects gastric mucosa against a variety of ulcerogenic agents in different

animal species (Harbone and Williams, 2000). Plants containing flavonoids were found to be effective in preventing ulcer diseases because of their anti-oxidant properties (Delphin *et al*., 2014). The antioxidant activity of flavonoids has attracted interest because of the strong evidence that oxidation processess are involved in the mechanisms of ulcerogenesis and several other gastric disorders (La Casa *et al*., 2000).

The results of antioxidant activity of the *Carica papaya* seed extracts on indomethacin-induced peptic ulcer disease presented in Table 3 provided scientific evidence that the *papaya* seed extract may contain biologically active antioxidant substances. Such components like flavonoids and phenols had revealed potential anti-ulcer properties which agreed with the findings of Amorati and Valgimigli, (2012) and also with the work of Delphins *et al* (2014). The aqueous extract at concentration of 100mg/kg/bw produced increased effects ($p>0.05$) when compared with the induced group. This could be mediated by any of the phytoconstituent present in the seed via anti-oxidant and free radical scavenging mechanism which agrees with the views of Amorati *et al* (2012). The 100mg/kg/bw of AE has increased ($p>0.05$) effect when compared with the standard drug control (Omeprazole). However, the standard control group has significantly increased activity ($p>0.05$) when compared with the induced group. And when compared with 150, 300 and 450mg/kg/bw of EE. The result has also shown that the 100mg/kg/bw of AE has significantly increased activity ($p>0.05$) when compared with the same concentrations of EE. This could probably be attributed to the fact that ethanol is one of the noxious agent that can cause peptic ulcer disease (Falalyeyeva *et al*., 2010). The extract is not dose-dependent as the effect of 100mg/kg/bw of AE gave the highest activity.

Similar treatment as presented in Table 4 has shown the Normal group has increased activity ($p>0.05$) when compared to the treated. However, there was no statistical difference ($p>0.05$) when the activity of the standard drug was compared with the activities of both aqueous and ethanolic extracts at all concentrations. This could probably mean that the extracts have equipotent effect as that of Omeprazole in protecting the mucosal lining against peroxidation. This agrees with the findings of Preeth *et al* (2010) in which the ethanolic extract of *Coccinia grandis* exhibited significant anti-ulcer activity with almost equipotent effect as Omeprazole.

The results presented in Table 5 has shown the standard drug has more potent effect ($p>0.05$) when compared with the induced group and when compared with all the concentrations of AE. Standard drug has shown equipotent effect with 100mg/kg/bw of EE. This may probably be due to the mediation via antioxidant due to high concentration of phenols and flavonoids components of the extract as observed by Miller and Rice-Evans (1997); Adeneye and Benebo (2008) and also by Amorati and Valgimigli (2012).

Similarly, the total protein results presented in Table 6 showed significant increase ($p>0.05$) when the Normal control was compared to the Negative. There was significant increase in activity ($p>0.05$) when the Standard Drug control was compared with the Negative. All concentrations of both extracts have shown equipotent effect with the standard drug. This indicate their ulcer-healing property. The 450mg/kg/bw of AE has shown a significant increase when compared to 450mg/kg/bw of EE. This may probably be as a result of the effect of ethanol on the mucosal tissue protein which can affect it in a negative way, this is in line with the views of Aravind, (2012).

5. Conclusion

This study has shown that both aqueous and ethanolic extracts of *Carica papaya* seed has flavonoids and phenols as its more abundant antioxidant and has thus possessed anti-ulcerogenic effect. The results suggest statistically improved anti-oxidant activity of aqueous extract of *Carica papaya* seeds of AE at 100mg/kg/bw when compared with the same concentration of EE. The findings also showed that the aqueous extract of the seed has increased the total anti-oxidant activity when compared with that of ethanolic extract. Although the molecular mechanism of action of the bioactive components are not yet understood, but based on this study, it suggested this seed is a potential source of natural anti-oxidant that could in the near future serves as an important therapeutic agent in not only healing ulcer, but preventing its occurence.

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