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Chemical Composition and *In vivo* Antioxidant Activity of *Carica papaya* leaves in Female Albino Mice

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ABSTRACT
Carica papaya L., (pawpaw), belongs to the family of Caricaceae. Papaya is not a tree but an herbaceous succulent plant that possess self-supporting stems. In traditional medicine, different parts of C. papaya including its leaves, barks, roots, latex, fruit, flowers, and seeds have a wide range of reputed medicinal application. Crude extraction protocol was done using ethanol. The proximate and phytochemical composition of the fruit was determined using standard methods. Twenty rats were divided into five groups. Rats in group 1 served as control, while rats in group 2, 3 and 4 received 100 mg/kg, 200 mg/kg and 300 mg/kg per body weight of Carica papaya fruits extract orally respectively for 14 days. Glutathione (GSH), Catalase (CAT), Superoxide (SOD) and Malondialdehyde (MDA)levels were determined from the serum using standard kits. Proximate analysis shows the contents of moisture (55.91%), ash (4.02%), fiber (2.18%), protein (17.56%), fat (8.83%) and carbohydrate (11.21%). Phytochemical screening reveals the contents of phenols (134.11 mg/g), flavonoids (56.00 mg/g), tannins (4.03 mg/g), saponins (8.22 mg/g)and alkaloids (1.79 mg/g). There was a significant ($p<0.05$) increase in the GSH, CAT, SOD and MDA levels of the groups that received the extract, while the highest significance was noted with the group that received the highest dose as compared to the control. The results obtained corroborates the antioxidant activity of the leaves which might be due to its high amount of phenols and flavonoids and might be relevant in the prevention and management of oxidative stress-induced diseases.
Keywords: *Carica papaya, Proximate analysis and Antioxidant*

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INTRODUCTION

Carica papaya L. Is commonly known as papaya in English, it belongs to Caricaceae family[1]. It is one of the most cultivated plants in tropical regions [2]. The plant is characterized by usually unbranched weak soft stem which grows up to 20 m, and large long stalked leaves [1].In several Asian Pacific countries, the fruits of papaya are used as commercial produces; however, the leaves are also used in traditional medicine for several complaints and diseases such as fever, asthma, colic, malaria, jaundice, dengue fever and cancer [3].

Leaves are rich in several constituents including flavenoids, phenolic compounds, alkaloids, tannins, saponins, glycosides, steroids and the cyanogenetic compounds [4]. Moreover, the amount and type of Flavenoids in papaya varies based on several factors such as locationof growth, variety, harvesting, storage, and processing conditions [5]. The presence of such compounds and other compounds made the plant having medicinal characteristics such as hepatoprotective, anti-inflammatory, anticancer, antihypertensive, antiviral, antimicrobial, antidiabetic, and free radical scavenging activity [4,6]. The juice, seeds, and leaves of papaya have free radical scavenging activity and antioxidant activity [4]. The leaf extract of papaya was found to have significant antioxidant activity and potent free radical scavenging activity [7]. This study aims to investigate the chemical composition of *Carica papaya* leaves and the in vivo antioxidant activity of the leaves.

MATERIAL AND METHODS

Preparation of *Carica papaya* leave powder

Carica papaya leave were purchased from a papaya farms. The sample was dried in airin shade and then grounded into a fine powder.

Proximate analysis

Proximate analysis of the *Carica papaya* leave powder was carried out to determine the crude protein, crude fibre, total ash, total carbohydrates, crude lipid and moisture content following methods described by AOAC (2000).

Preparation of *Carica papaya* powder extract

200 g of the powder was weighed and soaked in 70% ethanol for seventy-two hours. The soaked samples were then filtered into volumetric flasks and the residue was discarded. The filtrate was placed in a flat container and was allowed to dry at ambient temperature. The resulting dry extract was stored at 4°C until when needed when the extract was mixed with 1 ml of distilled water.

Phytochemical analysis

The preliminary phytochemical analysis was conducted for the presence of bioactive compounds such as alkaloids, glycosides, tannins, saponins, flavonoids in accordance to the guidelines of Harborne [8], Hebert and Kenneth [9] and Kokate[10].

Determination of total phenolic content of the extract: Total phenolic content of the extract was done using Folin-Ciocalteu's phenol reagent reaction as described by Singleton [11]. The calibration curve solutions were prepared by pipetting 0, 0.2, 0.4, 0.6, 0.8, and1.0 mL of gallic acid standard solution (1.0 mg/mL garlic acid) in triplicates into clean dried test tubes. 10 mg of *Carica papaya* leave powder extract was dissolved in 10 mL of distilled water (mg/mL) to make stock sample solution. From the stock, 0.2 mL each of 1 mg/mL was pipetted into clean dry test tubes in triplicates. The test- tubes were made up to 1.0 mL with distilled water. To each of the test tube was added 1.5 mL of diluted (1:4 v/v) Folin Ciocalteu's reagent, incubated at room temperature for 5 minutes followed by the addition of 1.5 mL of 10% (w/v) NaHCO3 solution to give a total volume of4.0 mL. The reaction mixtures were further incubated for an additional one and half hours and the absorbance was read at 725 nm against a blank in a spectrophotometer. The standard curve was obtained by plotting absorbance against the concentration. The concentration of the phenolic extract was determined from the standard curve and expressed in µgGAE/mL. The concentration in mg GAE/g extract was obtained using the equation below:

$$\text{TPC (mg GAE/g)} = \frac{\mu\text{g GAE X1mg Xml of solvent X dilution factor}}{\text{ml X 1000}\mu\text{g X mass of the sample used}}$$

Determination of tannin content: 200 mg of *Carica papaya* leavepowder extract was weighed into a bottle and 10 ml of 70% aqueous acetone was added and properly covered. The bottle was put into an ice bath shaker and shaken for 2 hours at 30°C. Each solution was then centrifuged and the supernatant stored in ice. 0.2 ml was pipetted each into test tubes and 0.8 ml of distilled water was added. Standard tannic acid solutions were prepared from a 0.5 mg/ml stock and the solution was made up to 1 ml with distilled water. About 0.5 ml Folin reagent was then added to both sample and standard followed by the addition of 2.5 ml of 29% Na_2CO^3. The solution was mixed and incubated for 40 minutes at room temperature after which the absorbance was read at 725 nm **[12].**

Determination of saponin content: The saponin content was determined in line with the method of Brunner **[13].** 100 ml of isobutyl alcohol was added to 1 g of *Carica papaya* leave powder extract in a beaker and the mixture was shaken for 2 hours to ensure uniform mixing. Thereafter the mixture was filtered into a 100 ml beaker and 20 ml of 40% saturated solution of Magnesium carbonate was added and the mixture made up to 250 ml. The mixture was again filtered to obtain a clear colorless solution. 1 ml of the colorless solution was then pipetted into a 50 ml volumetric flask and 2 ml of 5% FeCl3 solution was added and made up to mark with distilled water. It was allowed to stand for 30 minutes for blood red color to develop. 0.1–1.0 mg/ml standard saponin solution was prepared from saponin stock solution. The standard solution was treated similarly with 5% of FeCl3 solution as done for 1 ml of sample above. A dilution of 1 to 10 was made from the prepared solution. The absorbance of the samples as well as that of the standard solution was read after colour development in a spectrophotometer at a wavelength of 380 nm.

$$A_{\text{sample}} \text{X dilution factor X gradient of standard graph}$$

$$\text{Saponin} = (\text{mg/g}) \quad \text{Sample weight X } 10{,}000$$

Determination of total flavonoids content: The flavonoid content in the *Carica papaya* leave powder extract was determined spectrophotometrically according to the procedure of Bohm and Koupai Abyazani [14]. 0.01 g of the extract was dissolved in 5mL of methanol and made up to 20 mL to give a final concentration of 0.5 mg/ml. To clean, dry test tubes (in triplicate) were pipetted 0.2mL of working solution of the sample and diluted with 4.8 mL distilled water. To each test tube was then added 0.3 mL of 5% (w/v) NaNO2, 0.3 mL of 10% AlCl3 and 4 mL of 4% (w/v) NaOH. The reaction mixtures were incubated at room temperature for 15 minutes. The absorbance was read at 500 nm against reagent blank containing all reagents except the extract or standard catechin in the case of standard curve solutions. The standard calibration curve was prepared by pipetting 0.0, 0.2, 0.4, 0.6, 0.8, 1.0 ml of 1 mg/mL catechin into clean dry test tubes. The volumes were made up to 5 mL with distilled water. To each of the tubes were added 0.3 mL of 5% (w/v) NaNO2, 0.3 mL of 5% (w/v) AlCl3 and 4 mL of 4% (w/v) NaOH. The reaction mixture was incubated at room temperature for 15 minutes. Absorbance was taken at 500 nm and was plotted against the concentration to give the standard calibration curve. The concentrations of the flavonoids in the extract was extrapolated from standard calibration curve and expressed as milligram catechin (CAT) equivalent per g of extract (mg CAT/g extract).The value extrapolated from the standard curve gave the was obtained using the equation below:

$$\text{TFC (mg CAT/g)} = \frac{\mu\text{g CAT X1mg Xml of solvent X dilution factor}}{\text{ml X 1000}\mu\text{g X mass of the sample used}}$$

Experimental animals

A total of twenty adult female wistar albino rats were allowed to acclimatize under the same condition for two weeks. The animals were kept in clean cages and maintained under the standard laboratory condition for temperature (26 ± 6°C, humidity (60 ± 5%) and controlled environment (5:12 h light/dark cycle). They were given free access to standard pellet and water. All the experimental procedures were carried out in accordance to the guidelines of the Institutional Animal Ethics Committee (IAEC).

Experimental design

At the end of the acclimatization period, the twenty rats were randomly divided into five groups, with four rats in each. The rats in:-

Group I- was the control group fed on pellet and water only;

Group II- received 100 mg/kg per body weight of *Carica papaya* extract orally for 14 days.

Group III- received 200 mg/kg per body weight of *Carica papaya* extract orally for 14 days.

Group IV- received 300 mg/kg per body weight of *Carica papaya* extract orally for 14 days.

Measurement of body weights

The initial and final body weights of the animals were taken before and after the experiment using a weighing balance. The weight gain was then extrapolated from the initial and final weight values.

Assessment of the *in vivo* antioxidant activity of *Carica papaya* extract

At the end of the experiment, the animals were placed on overnight fasting for 12 hours and then sacrificed under light ether anaesthesia by cervical dislocation. Blood samples were collected by direct cardiac puncture. The serum was separated from the blood by centrifuging at 2500 rpm for 15 minutes and the levels of the following antioxidant parameters were determined from the serum:

Determination of catalase (CAT): Catalase activity was determined in the serum using Aebi's method **[15]**. 50 microliter of the sample was added to a cuvette containing 450 µL of phosphate buffer (0.1M, pH 7.4) and 500 µL of 20 mM H2O2. Catalase activity was measured at 240 nm for 1 minute using spectrophotometer. The molar extinction coefficient of H2O2, 43.6 M cm−1 was used to determine the catalase activity. One unit of activity is equal to 1 mmol of H2O2 degraded per minute and was expressed as units per milligram of protein.

Calculation:

$$Units/ml = \frac{\Delta A/\text{min} \times d \times 1}{V} \times 0.0436$$

d = dilution of original sample for Catalase Reaction

V = Sample volume in Catalase Reaction (ml)

0.0436 = ε^{mM} for hydrogen peroxide

1 = Total reaction volume

Determination of Superoxide dismutase: The method used was described by Mccord and Fridovich**[16]**. To 200µl of the lysate, 2.5 ml of 75 mM of Tris–HCl buffer (pH 8.2), 30 mM EDTA and 300µl of 2 mM of pyrogallol was added. An increase in absorbance was recorded at 420 nm for 3 minutes by spectrophotometer. One unit of enzyme activity is 50% inhibition of the rate of auto oxidation of

pyrogallol as determined by change in absorbance/min at 420 nm. The activity of SOD was expressed as units/mg protein.

Calculation:

Increase in absorbance per minute = $A_3 - A_0$ / 2.5 Where A_0 = absorbance after 30 seconds

A_3 = absorbance after 150 seconds

% inhibition = 100 – 100 X (increase in absorbance for substrate/ increase in absorbance for blank)

1unitofSODactivitywasgivenastheamountofSODnecessaryto cause 50% inhibition of the oxidation ofadrenaline.

Determination of glutathione (GSH): The reduced glutathione (GSH) content of blood tissue as non-protein sulphydryl was determined according to the method described by Sedlak and Lindsay **[17].** To the serum, 10% TCA (Trichloro Acetic Acid) was added and centrifuged. 1.0 ml of supernatant was treated with 0.5 ml of Ellman's reagent (19.8 mg of 5, 5-dithiobisnitro benzoic acid (DTNB) in 100 ml of 0.1% sodium nitrate) and 3.0 ml of phosphate buffer (0.2M, pH 8.0). The absorbance was read at 412 nm.

Determination of malondialdehyde (MDA): Serum malondialdehyde (MDA) level was measured asthe end product of lipid peroxidation by the thiobarbituricacid (TBA) reaction method as described previously **[18].**

Statistical analysis: All data were subjected to statistical analysis of variance, and means was separated according to their significant differences using the Duncan multiple Range Test. A value of $p<0.05$ was considered statistically significant when compared to the control group.

Results and discussion:

Proximate composition of*Carica papaya* leave

The proximate composition of the *Carica papaya* leave powder showed presence of 55.91±0.03 moisture, 4.02±0.04 ash, 2.18±0.01fibre, 17.56±0.05 protein, 8.83±0.03 Fat, and 11.21±0.12 carbohydrates (table1). A previous study reported the proximate composition of *Carica papaya* leaves as follow; 57.01% moisture, 2.18% ash, 6.5% protein, 2.01% fat, and 29.2% carbohydrate **[19].**Similar findings to ours were reported by Oche *et al*. who reported that the proximate composition of *Carica papaya* was as follow; 59.5 moisture, 3.65 ash, 2.13 fiber, 18.86 protein, 6.13 fats, and 10.63 carbohydrates **[20].** The previous findings were similar to ours.

Table 1: Proximate composition of *Carica papaya* leaf powder.

Parameter (%)	*Carica papaya* leaves
Moisture	55.91± 0.03
Ash	4.02± 0.04
Fibre	2.18± 0.01
Protein	17.56± 0.05
Fat	8.83± 0.03
Carbohydrate	11.21± 0.12

Effect of *Carica papaya* leaves extract on Body weight

The effect of *Carica papaya* leave extract on body weight is shown in (table2).The mean weight of control group increased from the initial weight to the final weight after 14 days by 18.45 g. Regarding groups administrated *Carica papaya* leave extracts; the weight of group II, III, IV was increased by 29.04g, 35.48g, and 23.89 g, respectively. This reflects that *Carica papaya* leave extract lead to increase in weight compared to control groups; moreover, the weight gained of groups administrated the leave extract was dependent on the concentration of the extract used. Increasing the concentration of *Carica papaya* leave extract lead to more increase in weight gain. It was stated that papaya is an excellent source of vitamin A, E and C, as well as dietary fibers; however, it was reported that there is not enough information about the nutritive value of seeds and leaves of papaya [4]. It was found that *Carica papaya* have beneficial influences on the cardiovascular system such as protection against heart attack and this beneficial effects return to the nutritional constituent of papaya [21]. Another study stated that fruit is an excellent source of beta carotene [22]. However, the impact of leave extract on the body weight hasn't been reported before.

Table 2: Effect of *Carica papaya* leaves extract on Body weight.

Group	Treatment *C. papaya* extract	Mean Initial body weight before treatment(g)	Mean final body weight after 14 days (g)	Weight increase (g)
Group I	Control	120.00 ± 0.01	138.45 ± 0.02	18.45
Group II	(100 mg/kg)	112.08 ± 0.01	141.12 ± 0.01	29.04
Group III	(200 mg/kg)	108.90 ± 0.02	144.38 ± 0.02	35.48
Group IV	(300 mg/kg)	116.33 ± 0.03	140.22 ± 0.03	23.89

Phytochemical analysis of *Carica papaya* leave

The phytochemical analysis of *Carica papaya* leave extract showed presence of phenol, tannin, saponin, flavenoids, and alkaloids, with a mean± SD value of 134.11±0.11, 4.03±0.02, 8.22±0.01, 56±0.09, and 1.79±0.06, respectively (table3). These findings were in agreement with previous reports which demonstrated that the extract of *Carica papaya* leaves contain flavenoids, alkaloids, saponins, tannins, and phenols [23,24]. A study by Nugroho et al. reported that flavenoids were extracted from *Carica papaya* leaves; the authors could isolate seven flavenoids from the leave of the plant and identified a potent antioxidant activity related to such compounds [2].Another study demonstrated that the papaya leaves contain alkaloids [25].Delphin et al.also reported that the seeds of papaya extract contain alkaloids, saponins, tannins, and flavenoids[26]. In contrast to our findings, a study by Oche et al reported that the concentrations of tannin, saponin, alkaloid, and flavenoid of *Carica papaya* leave extract were 0.55, 3.84, 8.09, and 2.89 , respectively [20], and these findings were varied compared to ours, this can be attributed to the material used in the extraction process, where Oche et al used n-hexan and methanol in the extraction process[20].

Table 3: Phytochemical of *Carica papaya* leaves extract.

Phytochemical (mg/g)	***C. papaya leaves* extract**
Phenol	134.11± 0.11
Tannin	4.03 ± 0.02
Saponin	8.22 ± 0.01
Flavonoids	56.00 ± 0.09
Alkaloids	1.79 ± 0.06

Effect of *Carica papaya* leaves extracts on antioxidant parameters of serum in mice

The impact of *Carica papaya* leave extract on antioxidants of serum is shown in (tabel4). The mean ±SD of glutathione, superoxide dismutase, catalase, and malondialdehyde was 44.37±1.05, 312±9.12, 560.13±12.66, and 3.88±0.18, respectively. The concentrations of glutathione were significantly increased over the experimental groups with increasing the concentration of leave extract; the concentrations of glutathione were 50±1.58, 55.08±1.22, and 58.78±1.41 for group I, II, III, respectively. The concentrations of superoxide dismutase were increased significantly in the three groups with increasing the concentration of the leave extract compared to the control group. The concentrations of superoxide dismutase were 325.1±13.73 for group I, 391.2±22.78 for groupII, and 408.11±21.33 for group III. Also, the concentrations of catalase and malondialdehyde were increased in the three groups with increasing the concentration of leave extract compared to the control group. The free radical scavenging and antioxidant activity of *Carica papaya* were reported in several studies. The leave extract of *Carica papaya* was confirmed to have significant free radical scavenging and antioxidant activity [7].Aboobacker et al revealed that the methanolic extract of papaya leave showed antioxidant activity with free radical scavenging properties, which increased with the increase in concentration; however, the study was conducted in vitro conditions and the study estimated the antioxidant activity using IC50 value, not the impact on antioxidant parameters[27]. A study conducted on mice with cyclophosphamide induced oxidative stress showed that the leave extract of *Carica papaya* act against the oxidative stress and prevented the damage of the DNA; however hepatotoxicity was noted with prolonged infusion [28].

Table 4: Effect of *Carica papaya* leaves on the serum levels of antioxidant parameters in mice.

Antioxidant parameter (µmol/ml/min)	**Control group**	**Group I (100 mg/kg)**	**Group II (200 mg/kg)**	**Group III (300 mg/kg)**
Glutathione	44.37 ± 1.05	50.00± 1.58	55.08± 1.22	58.78± 1.41
Superoxide dismutase	312.19 ± 09.12	325.1 ± 13.73	391.2 ± 22.78	408.11 ± 21.33
Catalase	560.13 ± 12.66	688.00± 07.54	702.12± 11.39	712.04± 21.71
Malondialdehyde	3.88 ± 0.18	3.71 ± 0.09	3.84 ± 0.13	3.87 ± 0.04

Values are means ± standard deviation for triplicate determinations. Values statistically significant at ($p<0.05$) when compared to control group

CONCLUSION

The present study showed that the extract of *Carica papaya* leave contained high levels of phenols and flavenoid compounds that lead to potent antioxidant activity increased with increasing the concentration of the extract and represented by increasing the concentration of antioxidant parameters in serum. The study also revealed that the plant leaves contain high content of protein and carbohydrate, and it caused gaining weight in mice which increased with increasing the concentration. There were no previous studies reported the impact of leave extract of *Carica papaya* on the weight gaining.

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