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Original Article

Hypoglycemic and Antioxidants Activities of *Carica Papaya* Leaves

Olumakinde Charles Omiyale [1*], Blessing Ifeoluwa Ogunniran [2], Mercy Ogochukwu Ezeh [3], Mubaraq Damilare Yussuf [4], Confidence Damian Oparah[5], Fawaz Isshak [6]

[1]Department of Pharmacology, Toxicology and Therapeutics, College of Medicine, University of Lagos, 101014, Nigeria
[2]Department of Environmental Science, School of Environment, Northeast Normal University, 130024, China
[3]Department of Plant Breeding, Crop Improvement Unit, Cocoa Research Institute of Nigeria (CRIN), Nigeria
[4]Department of Biochemistry, Faculty of Life Sciences, Lagos State University, Lagos, 102101, Nigeria
[5]Department of Internal Medicine, National Hospital Abuja, Abuja, 900211, Nigeria
[6]Department of Horticulture, Faculty of Agriculture and Natural Resources, Kwame Nkrumah University of Science and Technology, Ghana

*Corresponding Author E-mail: 199096019@live.unilag.edu.ng

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Abstract

The objective of the current study was to assess the ethanolic and methanolic extracts of Carica papaya's hypoglycemic effects. Yeast glucose uptake, muscle glucose uptake, and glucose adsorption capacity were used to measure the extracts' *in vitro* hypoglycemic effects. The antioxidant capacity of the extracts was assessed by investigating how they affect lipid peroxidation brought on by iron (II) sulphate and sodium nitroprusside. The findings showed that glucose was absorbed by both the ethanolic and methanolic extracts of *Carica papaya,* and that this adsorption significantly increased as the concentration of glucose rose. There were no variations in their adsorption capabilities that were statistically significant (p=0.05). The yeast cells were also stimulated to take up glucose by the plant extracts, and this stimulation was influenced by the sample and glucose content. In the study's muscle glucose uptake, the ethanolic extract of *Carica papaya* leaves showed substantially greater (p=0.05) performance than the methanolic of the same leaves with increasing concentration. The study's findings showed that the plant's methanolic extract was substantially more potent than its ethanolic (p=0.05). In addition, the methanolic extract considerably inhibited the generation of MDA (malondialdehyde) in the liver and brain homogenates more than the ethanolic extract did. Both plant extracts also exhibit dose-dependent inhibition of the various pro-oxidant agents (Iron (II) Sulphate and sodium nitroprusside) caused fatty acid oxidation tissues present in the brain and liver.

Keywords: *Carica papaya,* Hypoglycemic, Antioxidant activity, Lipid peroxidation, Malondialdehyde.

Introduction

There has been a growing interest over the years in scientific research related to the pursuit of scientific knowledge of the root cause of diabetes mellitus (DM) and the ultimate development of evident therapeutic and/or preventative options in its care [1-2]. Treating diabetes with drugs without causing side effects is challenging in traditional medicine. As advised by the WHO Expert Committee on DM [3-4], this has required the discovery and evaluation of plants having beneficial properties and establis hed medical benefits in the treatment of diabetes. The dry leaves of *Carica papaya* are among the therapeutic plants with possible oral hypoglycemic effects [5].

Originally from the tropics of the Americas, *Carica papaya* Caricaceae is extensively planted in various tropical areas of the world for its palatable, year-round fruit that resembles a melon [6]. According to the findings, the *Carica papaya* tree is an upright, quickly growing tree that can reach an elevated level of seven to eight metres. It has a 20 cm diameter trunk and produces a lot of latex. According to Solikhah [7], the leafy part of the plant are long-petioled, anywhere from 80 cm in length, pliable, clustered near to the top, and long-petioled. Its fruit is a huge, rectangular to almost globose or pyriform, yellow to greenish-orange berry that can range in size from 7.5 cm in wild varieties to 45 cm in cultivars, having between two and five cm of delicious, juicy, and orange-colored flesh [7]. “Ibepe”, “Gwanda”, and “Okwere” are the regional names for the ripe fruit in Nigeria, at which melon kernels and other seasoning are used to produce a sauce [8]. According to phytochemical investigations, *Carica papaya* contains enzymes such papain and chymopapain as well as alkaloids, carpain, nicotine, flavonoids, tannins, and terpinenes [9-10]. Different parts of the tree are utilized to treat various human and veterinary conditions in a number of different parts of the world. In traditional Asian healthcare, for instance, the waxy plant fluid is used as an abortion inducer, a sterilizer for dressing injuries, in addition a cure for gastrointestinal discomfort [11], whilst in traditional African medicine, decoction produced from a blend of its roots is reported to be beneficial for treating piles, yaws, and venereal diseases [6]. According to Solikhah [7], the waxy plant fluid is useful in Cuba to cure dermatitis and malignant tumors. According to Callixte [12], its fruit and seed extracts possess potent antibacterial properties against *Shigella flexneri, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.* Furthermore, studies have demonstrated that the ground seeds are anti-parasitic against diseases brought on by *Entamoeba histolytica* and *Dirofilaria immitis* [13]. Also, the asserted ones are the laxative effects [14], infertility-reversing [15-16], and sedative [17] properties of plant extracts. Despite its widespread and long-standing use in the conventional therapy of diabetes and obesity, there are few reports on the anti-diabetic effects of the plant seed. This is true even though there are many reports on the beneficial effects against diabetes of the unripe mature fruits of *Carica papaya* [18-20]. According to Edison [6], seeds cooked in milk have potent abortificant properties and can treat diabetes. Although Yoruba herbalists in South-West Nigeria have long used the dry seeds of *Carica papaya* to treat patients who may be diabetic or obese, the use of this method to treat diabetes mellitus, obesity, or dyslipidemia is not yet supported by any findings from science [13].

According to Halliwell *et al.* (1995), any substance that substantially impedes or prevents the oxidation of an oxidizable

material if available in tiny amounts compared to that material, possesses antioxidant properties. According to Dugan *et al*. [21], antioxidant effects are linked to lowered DNA damage, decreased lipid peroxidation, preserved immunological function, and suppressed malignant cell transformation. According to several research, the main bioactive phytochemicals with advantages for human health are phenolic compounds [22]. According to numerous researchers, the entirety of the phenols and antioxidants of most seeds and greens are in fact directly associated [23].

Vitamins and polyphenols, present in nature, in agricultural products have been related to the prevention of degenerative illnesses like malignancy and heart disease [24]. During typical aerobic metabolism, superoxide is continuously produced [25]. Superoxide radicals have an unpaired electron due to the fact that two electrons frequently merge to produce pair-electron bonds, radicals are typically extremely reactive entities. Superoxide is additionally referred to as a "Reactive Oxygen Species" (ROS) due to its radical nature. Proteins, lipids, and DNA are just a few of the biological components that the ROS generated can oxidatively damage. Since antioxidants play crucial roles in an organism's defense mechanism against ROS, there is growing interest in their presence in the diet [26].

According to Rafiei [27], phenolic compounds are a significant class of phytochemicals that have demonstrated strong free radical waste removal properties. They work through an inhibition of the enzymes that produce ROS and a reduction of highly oxidized ROS to exert chemo-preventive effects and protect internal organs of humans from oxidative injury. The current study was done to assess the hypoglycemic and antioxidant properties of *Carica papaya* leaf extract.

The Purpose of the Study

The purpose of this study is to examine the antioxidant and hypoglycemic effects of *Carica papaya* leaf extracts.

Objectives

Ascertain the in-vitro hypoglycemic effectiveness of *Carica papaya* leaf extract. Analyse *Carica papaya* leaf extract's in vitro antioxidant capacity.

How this study fills the knowledge gap: Research examines the hypoglycemic effects of ethanolic and methanolic extracts of *Carica papaya* leaves using assays for the absorption of glucose by yeast, muscle, and adsorption capacity.

Comparative Analysis: This study examines the hypoglycemic effects of the two different extract kinds, shedding light on potential discrepancies and action mechanisms.

Antioxidant Capacity: Studies examine the impact of extracts' antioxidant qualities on the lipid peroxidation caused by iron (II) sulphate and sodium nitroprusside.

Traditional Use Validation: The conventional utilization of *Carica papaya* leaves as part of the management of diabetes and obesity has been supported by scientific studies.

Identification of Bioactive Compounds: This study finds bioactive compounds in extracts, including alkaloids, flavonoids, tannins, and terpinenes, and links them to effects that were seen.

Enhanced Understanding: Overall, research fills in knowledge gaps by clarifying the mechanisms underlying the impacts of glucose metabolism, the possible health advantages of *Carica papaya*, and the control of oxidative stress.

Materials and Methods

Apparatus: An electric blender, a centrifuge, a spectrophotometer, a conical

flask, a weighing scale, a pipette, test tubes, aluminium foil, a refrigerator, and a mortar and pestle for use in the lab.

Reagents: Commercial baker's yeast, ethanol, methanol, ferrous sulphate ($FeSO_4$), phosphate buffer, sodium nitroprusside, glucose reagents, distilled water, metronidazole, hydrochloric acid, acetic acid, and sodium duodecyclsulphate.

Collection of plant samples: Pawpaw (*Carica papaya*) leaves came from the OJO market in Lagos City, Nigeria. The leaves were identified and verified at the botanical unit of Lagos State University. Nigeria.

Plant extracts preparation: The leaves were taken from the plants, dried separately at room temperature, and then processed separately into powder using an electric blender. To get fine powder, the obtained powder was sieved. 500 g of the powdered plant sample was separately steeped in 2 liters of 70% methanol and ethanol for roughly 48 hours while being agitated occasionally to obtain an extract. The extraction was done using the maceration method, which involves cold extraction. The filtrates were concentrated after the extracts had been filtered. To prevent damage, the concentrated extract was then put in a beaker glass, covered with aluminum wrap, and maintained at 4 °C.

The application of diverse In vitro technique in the evaluation of plant extracts' hypoglycemic efficacy

Assessment of glucose adsorption potential: The portions of plants extracted from the different solvents' phases (at a concentration of 1%) were added to a solution of glucose (5, 10, 20, 50, and 100 mM) in a volume of 5 mL. After 20 minutes of centrifugation at 4000 g, 10 mL of the supernatant was collected in each sample test tube and incubated for 10 minutes at 37 °C after adding 1 ml of glucose reagents and mixing.

At 505 nm, the absorbance was measured and recorded as "Go". Approximately 10 litres of the supernatant were taken and placed in each test tube after the extract and glucose solution mixture was left to stand at the following conditions: 37 °C, 6 hours. This was then mixed, and 1ml of glucose reagents were added. It was further left to stand once again at: 7 °C, 10 minutes. At 505 nm, the absorbance was measured and identified as G6.

Standard

To determine the absorbance, 1 ml of the glucose reagents were added to 10 l of the standard (metronidazole) in a reaction mixture. Following is the formula used to determine the amount of bound glucose [28]. Where, G1 represents the initial solution's sugar level, and the G6 represents the solution's sugar level six hours later.

Glucose Uptake by Yeast Cells

Commercial baker's yeast was centrifuged (3,000 g; five minutes) to the point where the supernatant liquids became colorless, and then dissolved in distilled water at a concentration of 10% (v/v). 1 mL of a solution made of glucose (5-25 mM) was mixed with various extract concentrations (1-5 mg), and the combo was left to stand at: 37 °C, 10 min. A 100-litre batch of yeast suspension was added to the process, which was then swirled and kept at 37 °C for 60 minutes. After 60 minutes, the tubes were spun at 3000 g for five minutes, and the total quantity of glucose in the resulting centrifuged liquid was determined. The percentage increase in the uptake of glucose by fungi cells was calculated using the formula below [29].

$$Glucose\ Bound = \frac{G1 - G6}{Weight\ of\ the\ sample}\ x\ Volume\ of\ solution$$

$$Increase\ in\ glucose\ uptake = \frac{[Absorbance\ (control) - Absorbance\ (sample)]}{Absorbance\ (control)}\ x\ 100$$

Where, Abs control is the absorbency of the control mixture, which includes every component besides the test sample, while Abs sample is the absorbency of the tested material.

LIPID Peroxidation

Preparation of Tissue Homogenates

A male cow body organs (muscle, brain, and liver) was obtained from a local abattoir, the cow muscle head was severed, and the liver and cerebral tissue (the entire brain) were quickly separated, chilled, and weighed. This was followed by using a crusher and pestle to break up the tissues in iced saline (1/10 weight/volume). The resulting mixture was then spun for 10 min at 3000 gravity to form a pellet, which was thrown away, and the top liquid from the centrifugation (S1) was kept for the lipid peroxidation test.

Lipid Peroxidation and Thiobarbibutric acid Reactions

Seventy moles of sodium nitroprusside (pro-oxidant) and 10 M freshly made $FeSO_4$ were created. Pro-oxidant (freshly prepared $FeSO_4$ and 70 M sodium nitroprusside) and the extract from *Carica papaya* leaves were added to the reaction mixture at increasing concentrations (50, 100, 200, and 400 g/ml), resulting in a total volume of 100 l, to which 100 l of supernatant was added. Before the 300 l of water was added, the volume left to stand at: 37 °C, one hour.

Following incorporating 100 l of 8.1% sodium dodecyl sulphate (SDS) to the product of the reaction, 600 l of an acetic acid/HCl (pH 3.4) mixture and 600 l of 0.8% thiobarbituric acid were added to the reaction liquid to induce the color reaction. This mixture was heated to 100 °C for an hour. At a wavelength of 532 nm, and thiobarbituric acid reactive species were discovered, and the absorbance was measured in comparison to a standard graph utilizing malondialdehyde.

Muscle Glucose Uptake

Psoas muscle was removed from the animals and washed with Kreb's buffer, then cut into very tiny, same weight sections (500 mg). The weighted muscle was placed in Kreb's buffer, and 1 ml of progressively stronger extract (50, 100, 200, 400, and 800 g/ml) was introduced into test tubes, and then 1ml of the muscle combination was added. This was diluted with three millilitre of scientific-grade water.

A portion of 1 ml was obtained prior to being left to stand and 1 millilitre of the glucose comp ound was thereafter mixed into the result ing solution. The quantity of glucose (mg) absorbed per gramme of muscle tissue, or muscle glucose, was determined:

Assimilation of glucose in muscular tissue = Gc1- Gc2/0.5 muscle tissue

Gc1 = glucose level prior to incubation

Gc2 = glucose concentration after incubation

Statistical Analysis

After considering all factors, the data were analyzed using a two-way ANOVA, and a Sidak's multiple comparison test showed statistically significant differences. The graphs were made using Graph Pad Prism 8.5.2.

Results and Discussion

Yeast Glucose Uptake

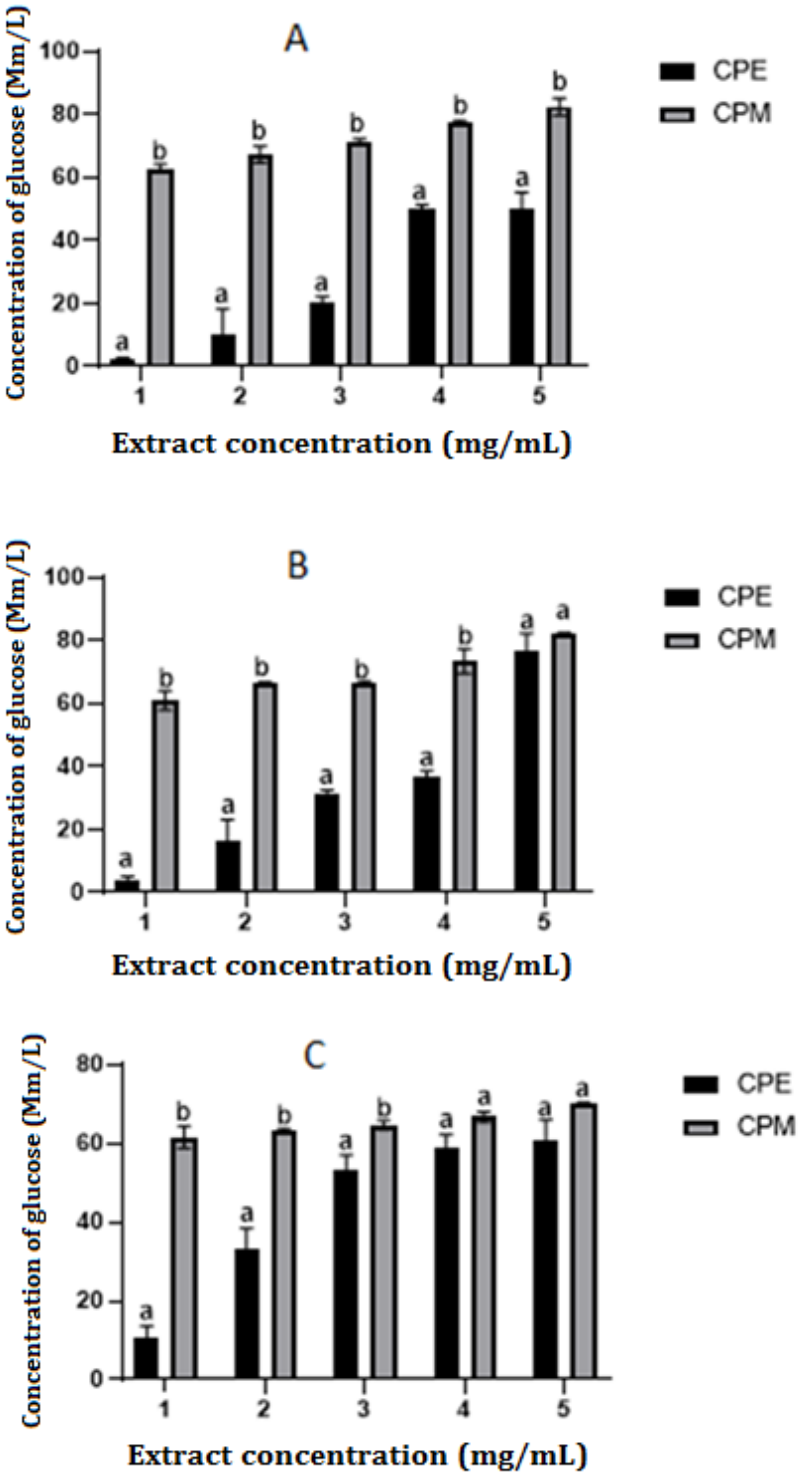

Figure 1 Methanol and Ethanol Papaya extract's effects on the absorption of glucose by yeast in methanol and ethanol. (a) 5 mM, (b) 105 mM, and (c) 25 mM. Different letters on each concentration implies significant difference on the samples, the same letter on each concentration implies no significant difference on the sample. Using two-way ANOVA, and a Sidak's multiple comparison test. CPE: Carica papaya ethanol extract and CPM: Carica papaya methanol extract (Figures are mean + standard deviation for repeated measurements.)

B. Glucose Adsorption

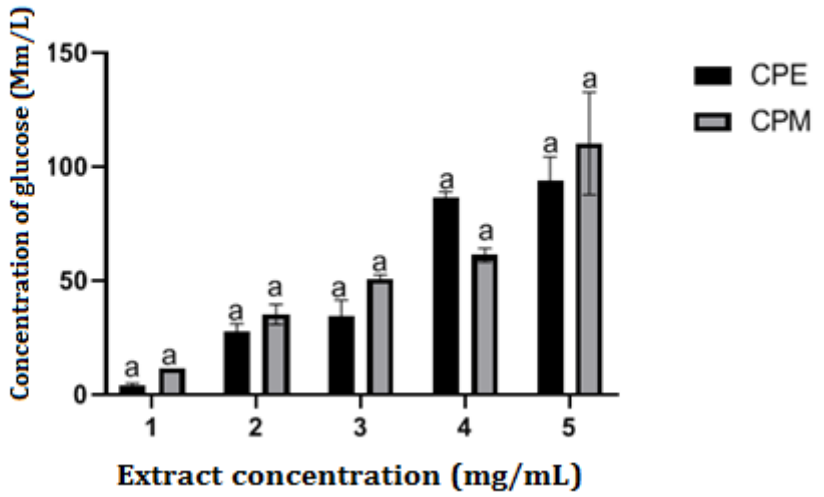

Figure 2 Effect of methanolic and ethanolic extract of *Carica papaya* on the glucose adsorbing capacity. Different letters on each concentration implies significant difference on the samples, the same letter on each concentration implies no significant difference on the sample. Using two-way ANOVA, and a Sidak's multiple comparison test. CPE: *Carica papaya* ethanol extract, CPM: *Carica papaya* methanol extract
(Figures are mean + standard deviation for repeated measurements.)

C. Muscle Glucose Uptake

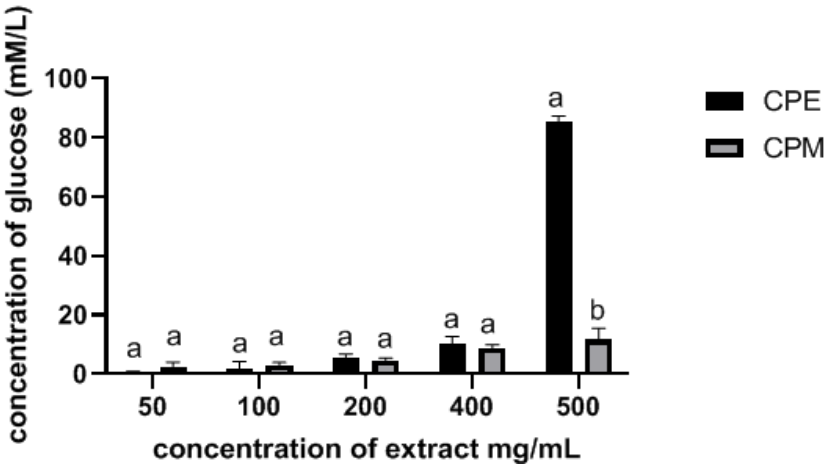

Figure 3 Effect of methanolic and ethanolic extract of *Carica papaya* on the muscle glucose uptake. Different letters on each concentration implies significant difference on the samples, the same letter on each concentration implies no significant difference on the sample. Using two-way ANOVA, and a Sidak's multiple comparison test. CPE: *Carica papaya* ethanol extract, CPM: *Carica papaya* methanol extract
(Values are mean ± SD of duplicate determinations)

D. Iron Sulphate Peroxidation

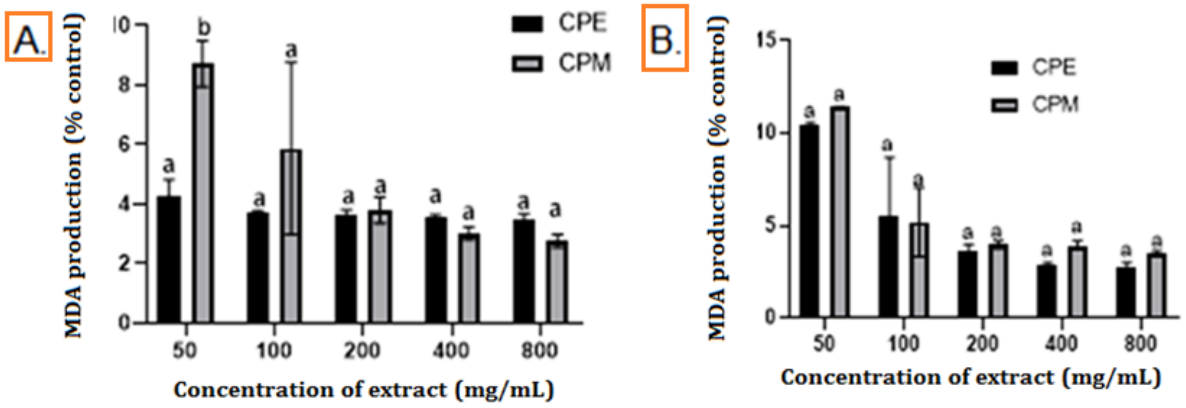

Figure 4 Methanol and ethanol extracts of *Carica papaya* inhibit pro-oxidants induced lipid peroxidation in cow liver. (a) $FeSO_4$ brain and (b) $FeSO_4$ liver. Different letters on each concentration implies significant difference on the samples, the same letter on each concentration implies no significant difference on the sample. Using two-way ANOVA, and a Sidak's multiple comparison test.
CPE: *Carica papaya* ethanol extract, CPM: *Carica papaya* methanol cONCENTRATION extract

E. Sodium Nitroprusside Lipid Peroxidation

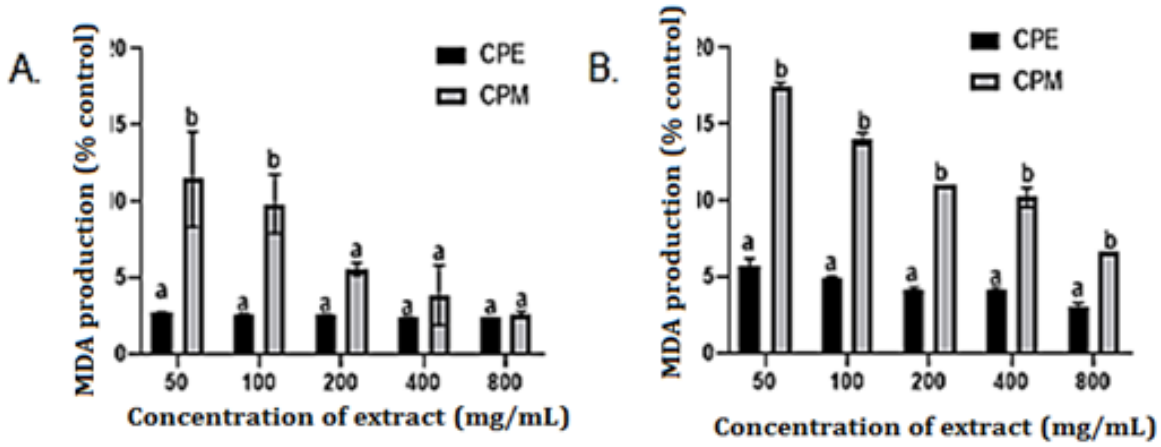

Figure 5 Methanol and ethanol extracts of *Carica papaya* inhibit pro-oxidants induced Lipid peroxidation in cow liver. (a) Sodium nitroprusside brain (b) Sodium nitroprusside liver. Different letters on each concentration implies significant difference on the samples, the same letter on each concentration implies no significant difference on the sample. Using two-way ANOVA, and a Sidak's multiple comparison test. CPE: *Carica papaya* ethanol extract and CPM: *Carica papaya* methanol extract

Discussion

Natural plant remedies are a new trend in modern clinical medicine, but have a long history of use as alternative treatments for diabetes [30], in which they have shown the satisfactory efficacy and few side effects [31]. Since all of the diabetic medications that are now on the market have one or more side effects, for medical professionals, diabetes therapy devoid of any adverse reactions is still a challenge [32]. The quest for novel pharmaceuticals is ongoing because the

diabetes mellitus treatments that are currently available fall short of what we want [33]. Particularly in patients with mild hyperglycemia, food products, and supplements have grown to be appealing solutions to prevent or treat hyperglycemia. As a result of its affordable price, easy accessibility, and lack of negative effects, plant-based foods and products with anti-diabetic activity are becoming more and more popular. Traditional medicine is well aware of the hypoglycemic properties of plants. Papaya leaves from the Carica species are crucial in one of the oldest medical systems, both for treatment and prevention [34-35] helpful for achieving and preserving good health. Figure 2 depicts the findings of the plant extracts' demonstrated capacity to absorb glucose.

The results of research on the ability of *Carica papaya* leaves to bind glucose demonstrated that these leaves' methanolic and ethanolic extracts were capable of doing so. It was discovered that the relationship between the glucose concentration and the glucose adsorption capacity was linear. Both low and high glucose concentrations utilized in the study could be effectively absorbed by the methanolic and ethanolic extracts of *Carica papaya*. An elevated glucose concentration was observed to enhance the amount of glucose that was bound. The adsorption capabilities of the methanolic and ethanolic extracts of *Carica papaya* leaves were not statistically different (P=0.05).

The study also revealed the fact that the flora under examination was capable of effectively binding glucose at minimal glucose levels, which would lower the concentration of glucose and hold back its uptake via the walls of the intestines. The extracts successfully lower postprandial hyperglycemia as a result.

The method by which glucose is carried through the yeast fungi membrane has attracted interest and is now viewed as a crucial technique for evaluating the in vitro hypoglycemic capacity for various chemicals and medicinal plants. According to the study's results, both extracts made it easier for glucose to move between yeast cells, albeit the methanolic extract somewhat increased this ability.

The quantity of glucose remaining in the media following a specific amount of time serves as a gauge for the absorption of sugar by yeast cells. It was found that the speed of the uptake of glucose into yeast cells was continuous for all of the levels of glucose used in this investigation. The portion of *Carica papaya* leaves from the methanol phase exhibited considerably greater potential (P=0.05) over the *Carica papaya* leaves extract made from ethanol in a dose-wise manner. The more concentrated the solution, the less sugar the yeast absorbed, showing an inverse relationship.

As indicated in Figure 3, the ethanolic extract of *Carica papaya* leaves displayed considerably higher (P=0.05) activity than the methanolic extract of *Carica papaya* leaves at all doses utilized in the study.

Lipid Peroxidation

In this study, we examined the protective effects against various oxidation-causing, "$FeSO_4$ and sodium nitroprusside" produced lipid peroxidation in the rat hepatocytes and brain cells (Figure 4 (a and b). According to Figure 5 (a and b), the *Carica papaya's* methanolic and ethanolic extracts may offer defence against sodium nitroprusside. Methanolic and ethanolic extracts inhibited MDA production in grown cow brain and liver tissues. The inhibition happened at all doses.

However, the methanolic extract significantly (P=0.05) raised the level of suppression in the brain cells and

hepatocytes in contrast to the extract from the ethanol phase.

After being treated with 10M $FeSO_4$, MDA levels in the hepatocytes and brain cells both dramatically rose. However, compared to the liver tissues, the brain tissue had more than half increase in tissue Malondialdehyde. There may be fatter oxidation in the neurological system than in the hepatic system due to the fact that neurons in the brain are unable to produce glutathione. Neurons are the initial cell types to be harmed by antioxidant deficiency and are most susceptible to reactive oxygen species since the brain has constrained exposure to the bulk of antioxidant compounds generated by the human system. They rather count on the astrocyte cells in the area to provide useable glutathione molecules predecessors.

The methanolic and ethanolic extracts of the *Carica papaya*; however, led to a dose-associated reduction in the Malondialdehyde concentration of the hepatocytes and neurons.

However, at larger dosages of the extract (800 mg/ml), but not at lower doses (50 mg/ml), the ability of ethanolic and ethanolic extracts to attenuate $FeSO_4$ and sodium nitroprusside pro-oxidant lipid damage in the neurons and hepatocytes differed significantly (P=0.05). However, the ethanolic extract appeared to preserve the liver's function more than the brain, as demonstrated in Figures 4 and 5 (a and b).

Conclusion

To sum up, the study demonstrated the hypoglycemic and antioxidant effects of *Carica papaya* leaf extracts, obtained through methanol and ethanol solvents. *In vitro* techniques revealed that these extracts improve glucose absorption and facilitate glucose migration across cell pores. The study suggests the need for further validation through diverse models and human trials for effective diabetes management. Notably, the ethanol extract exhibited superior hypoglycemic and protective properties in liver and brain tissues compared to the methanol extract. This emphasizes the potential of *Carica papaya* leaf extracts, particularly the ethanol variant, in managing diabetes and mitigating oxidative damage.

Declarations

The authors declare that Ethics Committee approval was not required for this study as no animals were sacrificed in the study as it is *in vitro* research. The work contains plants study with data collection from online resources freely available in the public domain that does not collect or store identifiable data. All related laws, rules, and regulations necessary for the study execution have been followed.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that there is no conflict of interest in this article.

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Author's Contributions

All co-authors were involved in all stages of this study while preparing the final version. All authors read and approved the final manuscript.

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ORCID

Olumakinde Charles Omiyale
https://orcid.org/0000-0002-4951-3881
Blessing Ifeoluwa Ogunniran
https://orcid.org/0009-0008-5671-1836
Mercy Ogochukwu Ezeh
https://orcid.org/0009-0005-0396-8468
Mubaraq Damilare Yussuf
https://orcid.org/0009-0004-3105-7250
Confidence Damian Oparah
https://orcid.org/0009-0003-1265-9718
Fawaz Isshak
https://orcid.org/0000-0001-8640-3465

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