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Research Article

Aqueous Extract of *Carica papaya* Leaves Improves Hyperglycemia, Hyperalgesia, and Oxidative Stress in Streptozocin-induced Diabetic Peripheral Neuropathy in Male Wistar Rats

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ABSTRACT

Aqueous extract of *Carica papaya* leaves was investigated for its acclaimed neuroprotective activity in streptozotocin-induced diabetic peripheral neuropathy in rats. Twenty male, Wistar rats weighing between 120 & 170g were randomly assigned into four groups of five animals each. Rats in group 1 were normal, healthy rats that received normal saline 1.0ml/kg b. w. Those in group 2 (diabetic untreated) received normal saline 1.0ml/kg b. w., group 3 was treated with pregabalin 0.71mg/kg b. w. and group 4 received the aqueous leaf extract of *Carica papaya* 200mg/kg b. w. Plasma glucose concentration, thermal and mechanical allodynia, and biochemical biomarkers in the brain [malondialdehyde (MDA) and nitric oxide (NO)]; nerve [brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)]; and serum [superoxide dismutase (SOD) and glutathione (GSH)] were assessed. The results showed that the C*arica papaya* leaf-treated (group 4) rats had a significant fall in the plasma glucose level ($p<0.0001$); higher pain threshold on ice cold and von Frey tests ($p<0.0001$); lower MDA and higher NO, BDNF, NGF, SOD and GSH levels compared to diabetic untreated ($p<0.0001$) and pregabalin-treated ($p<0.0001$) rats. *Carica papaya* leaf extract reduces plasma glucose, mechanical and thermal hyperalgesia, oxidative stress, and nerve damage in streptozocin-induced diabetic peripheral neuropathy in male Wistar rats..

Keywords: *Carica papaya*, Diabetes mellitus, Peripheral neuropathy, Rat, Streptozotocin

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INTRODUCTION

Diabetes mellitus is a disease marked with hyperglycemia (unusually high levels of blood glucose) and dysregulation in the metabolism of lipids and proteins that result from abnormalities in both the secretion and action of insulin. It is termed a 'modern-day epidemic' with an incidence of 45 percent all over the world and a projected 366 million sufferers by the year 2030, as against 191 million expected in the year 2000 (Koyuturk, *et al*., 2005). In Nigeria, the incidence of diabetes mellitus was put at about 2.8 million (2,819,000) in the year 2010 and is projected to rise to over 5.3 million (5,316,000) in 2030 (Shaw *et al*., 2010). Diabetes mellitus is a public health concern not only because of the disease itself but, also the management of the complications that are the sequel to it. These complications are not only very expensive to manage but, incur a substantial economic burden on the healthcare delivery system (Bahia *et al.*, 2019). Underpinning these complications are hyperglycemia-induced oxidative stress and inflammation which destroys micro-vascular and macro-vascular blood vessels (diabetic nephropathy and diabetic retinopathy) and the nervous system (diabetic neuropathy) (Charlton *et al.*, 2020). Diabetic neuropathy is a peripheral nerve system neuro-degenerative condition that disproportionately impacts sensory axons, autonomic axons, and, to a lesser degree, motor axons. The most common type of neuropathy in diabetes mellitus is diabetic polyneuropathy (DPN), with up to 50% of patients experiencing some degree of painful symptoms and 10% to 20% having symptoms severe enough to warrant treatment (Malik *et al* ., 2005). A study found some degree of neuropathy in 66% of patients with diabetes mellitus (Vinik, 2005). Among those with type 1 and type 2 diabetes mellitus, 54% and 45%, respectively,

had DPN and 15% and 13%, respectively, were symptomatic (Dyck *et al.,* 1993). Regular medications for diabetic neuropathy haven't been perfect. For example, the efficacy of pregabalin was not positive in many cases of advanced refractory patients asides from side effects such as confusion and dizziness, and insomnia (Feldman *et al.,* 2019). It would be necessary to look for drugs with fewer side effects and possibly address the hyperglycemia predisposing patients to the neuro-degenerative condition of diabetic neuropathy. Therefore, the discovery and development of novel drugs from botanicals will not be out of place (Katiyar *et al.,* 2012). *Carica papaya* is a member of the small family *Caricaceae*. Different parts of *C. papaya* are used in Mexican folk medicine to treat various diseases such as diarrhea, inflammation, and diabetes (Heena, 2019; Nafiu *et al*., 2019). The aqueous leaf extract is also known to accelerate wound healing (Mahmood *et al.,* 2005).

MATERIALS AND METHODS

Ethical consideration: This study was carried out based on the institutional guidelines on animal use and care of the University of Ilorin and ethical approval was obtained from the University's ethical review committee.

Plant preparation: Fresh leaves of C*arica papaya* were obtained from a local market in Ilorin, Kwara State, Nigeria. The leaves were identified and authenticated at the Herbarium of the Department of Plant Biology, the University of Ilorin with voucher number UIL/001/1296. The leaves were air-dried at room temperature for five days and ground in powdery form using a ceramic mortar and pestle. 210g of the powdered leaves were boiled in 3 liters of distilled water for fifteen minutes and the extract was decanted. The extract was then filtered using a fine mesh cloth and the filtrate was centrifuged and evaporated to dryness in a water bath at 60°C for 24 hours. The evaporated extract was allowed to cool down to room temperature and then stored at 4^0C until administered to the animals.

Experimental Animals: Twenty (20) male Wistar rats weighing between 120 & 170g were purchased from a private breeder in Ogbomosho and housed in the animal house of the College of Health Sciences, University of Ilorin, Ilorin, Nigeria, under natural, normal light and dark cycles at room temperature with the appropriate ventilation and spacing. The rats were acclimatized for two (2) weeks and fed rat pellets and distilled water *ad libitum*. After acclimatization, the baseline plasma glucose concentration of the rats was determined before induction of type 2 diabetes mellitus and subsequent treatment with pregabalin (0.71m/kg b. w.) and *Carica papaya* leaf extract (200mg/kg b. w.) for four (4) weeks.

Animal grouping: Animals were randomly divided into four (4) groups of five (5) animals each and treated as follows: Group 1 (healthy rats); Group 2 (diabetic rats): treated with normal saline 1ml/kg b.w; Group 3 (diabetic rats): treated with pregabalin 0.71mg/kg b.w; Group 4 (diabetic rats): treated with *Carica papaya* 200mg/kg b.w.

Estimation of plasma blood glucose: After acclimatization, the rats fasted for 10-12 hours, and the baseline plasma glucose concentration of all the rats was determined by putting a tail vein blood sample on a glucometer (On Call, ACON Laboratories). This was repeated after successful induction of diabetes mellitus (fasting plasma glucose ≥13.9mmol/L) and after treatment.

Induction of diabetes: Diabetes mellitus was induced via intraperitoneal injection of streptozocin (50mg/kg b. w.), dissolved in 10ml of citrate buffer (0.1M at 4.5 PH)]. A waiting period of 3 days was allowed for successful induction of diabetes mellitus which was taken at fasting plasma glucose ≥13.9mmol/L. A period of 10 days was allowed for neuropathy to set in.

Assessment of thermal nociception

Ice cold test: The surface of the hind paw of each rat was placed on ice and a timer was started. The timer was stopped immediately after the rat withdrew its hind paw and the duration was recorded. The test was carried out after the successful induction of diabetes mellitus and weekly until the end of treatment.

Assessment of tactile allodynia

von Frey test: The mechanical withdrawal threshold of the hind paw was tested using the ascending method of force application of von Frey hair (VFH) monofilament. VFHs with bending forces of 4-300g were applied to the center of the plantar region of the ipsilateral hind paw for 5 seconds, beginning with the lowest force, and hind paw withdrawal threshold (time taken for each rat to withdraw hind paw) was determined. If the animal did not respond to a particular force of the VFH, the next higher force was applied until recoil is observed.

Brain sample collection: At the end of treatment, the animals were sacrificed under a mild dose of ketamine (87.5 mg/kg b.w.) and xylazine (12.5mg/kg b.w.). The brain was excised on ice and the hippocampus was isolated. The hippocampus was homogenized using 0.1M phosphate buffer saline at pH 7.4 (100mg/ml of PBS buffer). Homogenates were then assayed for malondialdehyde (MDA) and nitric oxide (NO).

Nerve sample collection: The sciatic nerve was excised on ice and homogenized using 0.1M phosphate buffer saline at pH 7.4 (100mg/ml of PBS buffer). Homogenates were then assayed for nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF).

Blood sample collection: Blood was collected through a cardiac puncture in a plain bottle. The blood collected was kept on ice, then centrifuged at 3, 000rpm for 10 minutes. Serum was collected in another plain bottle using a micro-pipette and assayed for superoxide dismutase (SOD) and glutathione (GSH).

Statistical analysis: All data were expressed as Mean ± S. E. M. The effects of the varied intervention of each group were tested for homogeneity using one-way analysis of variance (ANOVA) through GraphPad prism version 5.01software. The *posthoc* test used was Tukey. The level of significance was set at $p < .05$.

RESULTS

Plasma glucose: The hyperglycemic condition was established in all the rats after the successful induction of diabetes as shown in table 1. The post-induction plasma glucose levels were significantly higher than that at baseline in diabetic untreated, pregabalin-treated, and *Carica papaya*-treated (groups 2, 3, and 4) rats ($p<0.001$). The value remained the same after treatment in pregabalin-treated (group 3) rats. In contrast, the C*arica papaya* leaf-treated (group 4) rats showed a significant fall in the plasma glucose level ($p<0.0001$) after treatment.

Table 1:
Effect of aqueous extract of *Carica papaya* leaf on plasma glucose concentration (mmol/L) of diabetic peripheral neuropathic rats.

	Baseline	Post-induction	After Treatment
Group 1	3.9±0.27	-	-
Group 2	3.84±0.37	19.72±0.98^{a}	22.46±1.55^{a}
Group 3	4.41±0.31	19.74±1.34^{a}	13.68±0.84^{ab}
Group 4	4.04±0.57	19.02±1.07^{a}	5.4±0.85^{b}

Data are expressed as mean±SEM, n = 5. Data were analyzed by one-way ANOVA followed by Tukey's multiple posthoc tests. a,b p < 0.05 vs, baseline and post-induction group respectively.

Pain threshold

Ice cold test: Table 2 shows the pain threshold on days 7, 14, 21, and 28 post-induction of diabetes mellitus in the rats using the ice-cold method. On day 7, pregabalin-treated (group 3) rats showed a significant increase in pain threshold compared to diabetic, untreated (group 2) and *Carica papaya*-treated (group 4) rats ($p<0.01$, $p<0.03$ respectively). On day 14, diabetic, untreated (group 2) rats showed significantly lower pain threshold compared to the control (group 1) rats ($p<0.0001$), while pregabalin- and *Carica papaya*-treated (groups 3 and 4) rats showed significantly higher pain thresholds ($p<0.001$, $p<0.001$ respectively) when compared to diabetic untreated (group 2) rats. On day 21, the pain threshold of diabetic, untreated (group 2) rats was significantly lower than rats in the control (group 1) rats ($p<0.0001$), while the pain thresholds in the pregabalin- and *Carica papaya*-treated (groups 3 and 4) rats were significantly higher than that of diabetic, untreated (group 2) rats ($p<0.01$, $p<0.0001$ respectively). The pain threshold results on days 21 and 28 showed a similar trend compared to that of day 14 result.

von Frey test: Figure 1 shows the pain threshold on day 7 post-induction of diabetic peripheral neuropathy across all four groups using the von Frey filament. Healthy (group 1) and pregabalin-treated (group 3) rats showed a significantly higher pain threshold compared to diabetic untreated (group 2) and *Carica papaya*-treated (group 4) rats ($p<0.003$, $p<0.0001$ respectively). It also shows that pregabalin-treated (group 3) have higher pain threshold compared to *Carica papaya*-treated (group 4) rats ($p< 0.005$).

Table 2:
Analgesic effect of aqueous extract of C*arica papaya* leaf on the pain threshold of the diabetic peripheral neuropathic rat using an ice-cold test (seconds)

	Group 1	Group 2	Group 3	Group 4
Day 7	9.6±0.90	6.8±0.66	12.8±0.73^{b}	9.0±0.71^{c}
Day 14	9.0±0.71	4.04±0.53^{a}	8.98±0.36^{b}	7.58±0.35^{b}
Day 21	7.4±0.45	2.94±0.39^{a}	8.32±0.39^{b}	7.6±0.46^{b}
Day 28	6.7±0.43	1.84±0.22^{a}	6.08±0.38^{b}	6.26±0.44^{b}

Data are expressed as mean±SEM, n = 5. Data were analyzed by one-way ANOVA followed by Tukey's multiple posthoc tests. A b,c p < 0.05 vs group 1, 2, and 3 respectively.

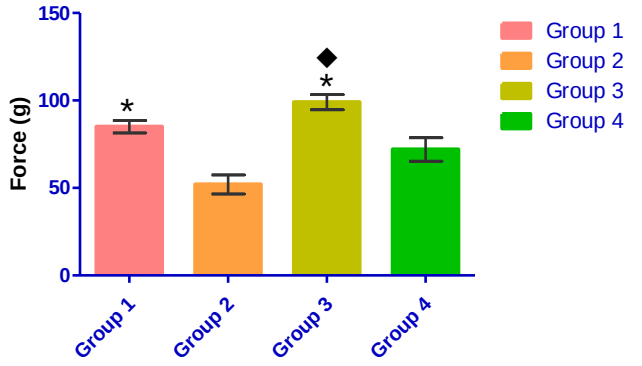

Figure 1:
Effect of *Carica papaya* leaves aqueous extract on pain threshold on day 7 post-induction of diabetic peripheral neuropathy across all four groups. Values are expressed as mean±SEM with n=5. Data were analyzed by one-way ANOVA followed by Tukey's multiple *posthoc* tests. *,♦ $p < 0.05$ vs group 2, and 4 respectively.

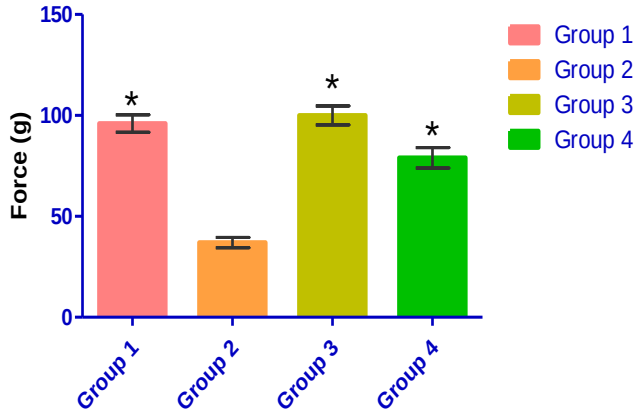

Figure 2:
Effect of *Carica papaya* leaves aqueous extract on pain threshold on day 21 post-induction of diabetic peripheral neuropathy across all four groups. Values are expressed as mean±SEM with n=5. Data

were analyzed by one-way ANOVA followed by Tukey's multiple *posthoc* test. * p < 0.05 vs group 2.

Figure 2 shows the pain threshold of diabetic peripheral neuropathic rats on day 21 using von Frey filament. Healthy, pregabalin-treated, and *Carica papaya*-treated (groups 1, 3, and 4) rats showed a significantly higher threshold compared to diabetic untreated (group 2) rats (p<0.001, p<0.00001, p< 0.0001 respectively).

Figure 3 shows the pain threshold on day 35 post-induction of diabetes mellitus across all four groups using the von Frey filament. Healthy, pregabalin-treated, and *Carica papaya*-treated (groups 1, 3, and 4) rats showed a significantly higher threshold compared to diabetic untreated (group 2) rats (p<0.001, p<0.00001, p< 0.0001 respectively).

Figure 4 is a line graph showing a comparison of pain threshold between *Carica papaya*-treated and pregabalin-treated diabetic peripheral neuropathic rats on days 7, 21, and 35 using the von Frey test. Pregabalin-treated rats had a higher pain threshold which declined over time while *Carica papaya* had a lower threshold which gradually improved over the weeks.

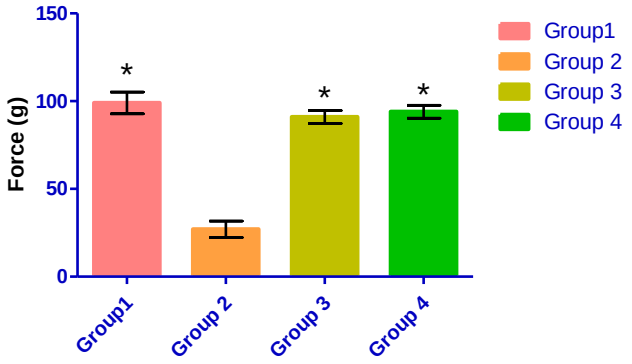

Figure 3:
Effect of *Carica papaya* leaves aqueous extract on pain threshold on day 35 post-induction of diabetic peripheral neuropathy across all four groups. Values are expressed as mean±SEM with n = 5. Data were analyzed by one-way ANOVA followed by Tukey's multiple *posthoc* test. *p < 0.05 vs group 2.

Biochemical parameters

Brain Malondialdehyde (MDA) and Nitric oxide (NO); Nerve Brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF): Table 3 shows that the concentration of brain MDA in diabetic untreated, pregabalin-treated, and *Carica papaya*-treated (groups 2, 3, and 4) rats is significantly higher than in healthy (group 1) rats (p<0.0001, p<0.0001, p<0.01 respectively). Brain NO concentration was significantly lower in diabetic untreated rats compared to the healthy group (p<0.00001). The same trend was observed when compared to pregabalin-treated and C*arica papaya*-treated groups (p<0.00001, p<0.0001 respectively). The result also showed that the concentration of nerve BDNF was significantly higher in group 1 compared to all the other groups (p<0.00001, p<0.0001, p<0.03), likewise, group 4 rats had a significantly higher value compared to group 2 (p<0.001). Also, the result demonstrated that the concentration of NGF in diabetic untreated and pregabalin-treated (groups 2 and 3) rats were significantly lower compared to healthy (group 1) rats (p<0.0001, p<0.0001 respectively), while the *Carica papaya*-treated (group 4) rats demonstrated higher significant concentration of NGF compared to both the diabetic untreated and pregabalin (groups 2 and 3) rats (p<0.0001, p<0.0001 respectively).

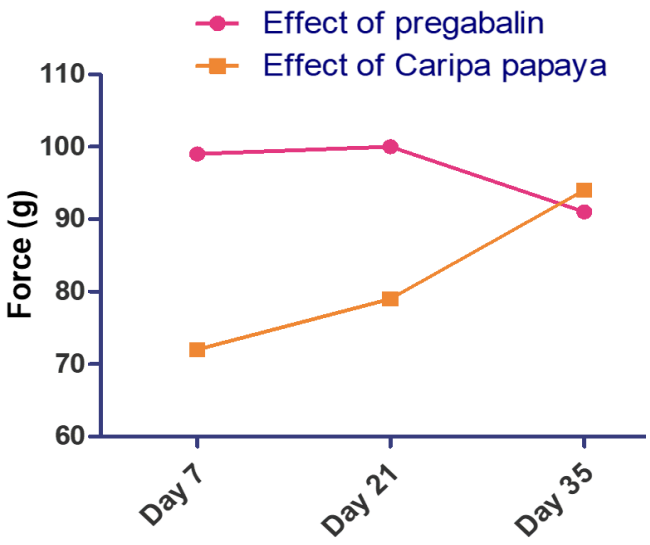

Figure 4:
Comparative effect of pregabalin and *Carica papaya* leaves aqueous extract on pain threshold on days 7, 21 & 35 post-induction of diabetic peripheral neuropathy. Values are expressed as mean±SEM with n=5.

Table 3:
Effect of aqueous extract of *Carica papaya* leaf on brain and nerve biochemical parameters of diabetic peripheral neuropathic rats.

	Group 1	Group 2	Group 3	Group 4
Brain MDA (nmol/mg)	3.31 ±0.37	7.33 ±0.66**a**	7.16 ±0.12**a**	5.98 ±0.31**a**
Brain NO (µM)	10.45 ±0.23	4.20 ±0.70**a**	10.36 ±0.88**b**	14.91 ±2.30**b**
Nerve BDNF (ng/g)	6.39 ±0.19	1.93 ±0.14**a**	3.07 ±0.56**a**	4.09 ±0.65a**b**
Nerve NGF (ng/g)	64.85 ±6.35	29.37 ±3.88**a**	32.6 ±5.18**a**	61.99 ±4.84**bc**

Data are expressed as mean±SEM, n=5. Data were analyzed by one-way ANOVA followed by Tukey's multiple posthoc tests. a,b,c p < 0.05 vs groups 1, 2, and 3 respectively.

Serum superoxide dismutase (SOD): Figure 5 shows the effect of C*arica papaya* leaf aqueous extract on serum SOD concentration of diabetic peripheral neuropathic rats. There was a significantly higher level of SOD in the control group compared to the diabetic untreated and pregabalin-treated groups (p<0.00001, p<0.001 respectively). The C*arica papaya*-treated group also showed significantly higher concentration compared to the diabetic untreated and pregabalin-treated groups (p<0.0001, p<0.001 respectively).

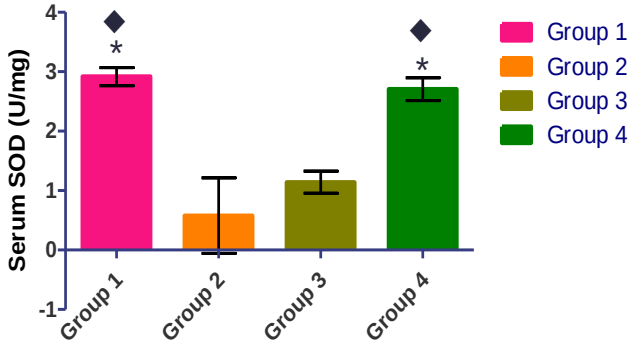

Figure 5:
Effect of C*arica papaya* leaf aqueous extract on serum SOD concentration of diabetic peripheral neuropathic rats. Values are expressed as mean±SEM with n = 5. Data were analyzed by one-way ANOVA followed by Tukey's multiple *posthoc* test. *,♦ p < 0.05 vs group 2, and 3 respectively.

Serum glutathione (GSH): Figure 6 shows the effect of C*arica papaya* leaf aqueous extract on serum GSH concentration of diabetic peripheral neuropathic rats. There was a significantly higher level of GSH in the control group compared to the diabetic and pregabalin-treated groups (p<0.00001, p<0.001 respectively). The C*arica papaya*-treated group showed a significantly higher concentration of GSH compared to the diabetic and pregabalin-treated groups (p<0.0001, p<0.001 respectively).

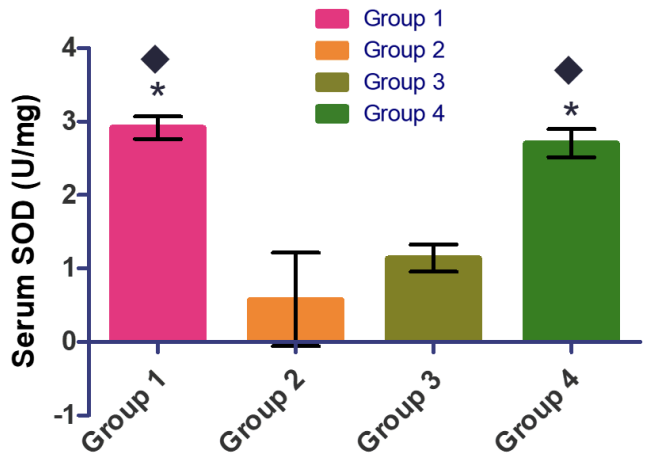

Figure 6:
Effect of C*arica papaya* leaf aqueous extract on serum GSH concentration of diabetic peripheral neuropathic rats. Values are expressed as mean±SEM with n = 5. Data were analyzed by one-way ANOVA followed by Tukey's multiple *posthoc* test. *,♦ p < 0.05 vs group 2, and 3 respectively.

DISCUSSION

The pathogenesis of diabetic peripheral neuropathy has many pathways which include but, are not limited to increased reactive oxygen species (ROS) (Vats *et al.*, 2004), polyol pathway (Gabbay, 2004), formation of advanced glycation end-products (AGEs), the elevation of pro-inflammatory cytokines such as interleukin (Il-6), and tumor necrosis factor-α (TNF-α), down-regulation of anti-inflammatory cytokines such as Il-10 (Akintoye *et al.*, 2018; Bishnoi *et al.*, 2011), and increased insulin resistance (Akintoye *et al.*, 2020; Alzamil, 2020). This research was aimed at investigating and evaluating the anti-hyperglycemic, analgesic, antioxidant, and neuroprotective activities of the aqueous extract of *Carica papaya* leaves in male Wistar rats.

The exact mechanism through which *Carica papaya* exerts its hypoglycemic effect remains elusive. However, decreased rate of intestinal glucose absorption (Hamden *et al.*, 2011; Porchezhian *et al.*, 2000; Gupta *et al.*, 2012), increased peripheral glucose utilization (Porchezhian *et al.*, 2000; Gupta *et al.*, 2012), and increased glucose catabolism due to GLUT4 translocation ()Adisa *et al.*, 2011; Shen *et al.*, 2010), are some of the mechanisms that have been proposed. *C. papaya* extract has been reported to cause hypoglycemia in diabetic rats but not in healthy rats (Juarez-Rojop *et al.*, 2012). This is consistent with the findings of this study which showed that there was a significant increase in blood glucose levels in the untreated animals; pregabalin-treated animals showed a significant reduction in blood glucose levels at the end of treatment, while *Carica papaya*-treated animals showed a slight decrease in blood glucose levels at the end of treatment. Hyperglycemia is associated with the inhibition of endothelial nitric oxide synthase (eNOS), leading to diminished NO production, increased formation of reactive oxygen species (ROS), impaired endothelial-dependent relaxation, increased formation of free radicals that leads to oxidative stress in the brain (Bakker *et al.*, 2009). Nitric oxide (NO), which is a vasodilation is secreted by endothelial cells, particularly in the brain, and is used as a biomarker of hyperglycemia. This study showed a slight increase (p<0.05) in the levels of NO in both the pregabalin- and *Carica papaya*-treated groups, compared to the untreated group as shown in table 3. This is in tandem with the findings of Juárez-Rojop, *et al.*, 2012.

Cells possess a variety of primary and secondary defenses against oxidative stress and other deleterious effects of oxidative damage (Bakker *et al.*, 2009). Biomarkers of nerve damage act to diagnose diseases as well as to monitor the progression of treatment. Primary afferent neurons and sympathetic neuron sprouting are the most important peripheral modifications (Stein & Lang, 2009). Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and several cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) can be responsible for the sprouting formation (Siniscalo *et al.*, 2007). It has been demonstrated that BDNF can regulate the pattern of expression and the level of activity of the transducer channel TRPV1. A well-known receptor that has been implicated in mechanical, chemical, and thermal nociceptive stimuli transmission (Ciobanu *et al.*, 2009). There was a slight increase (p<0.05) in the levels of BDNF in both the pregabalin and *Carica papaya*-treated groups, compared to the untreated group. One of the proposed mechanisms of action of NGF might be through up-regulated several pain-related genes in the primary sensory neurons of DRG. Indeed, genes codifying for substance P, calcitonin gene-related peptide, TRPV1, Na(v)1.8 and Na(v)1.9 sodium channels and mu-opioid receptor (MOR) are up-regulated by

NGF (Mousa *et al*., 2007). There was a slight increase ($p<0.05$) in the levels of NGF in both the pregabalin- and *Carica papaya-t*reated groups, compared to the untreated group. Superoxide dismutase (SOD) is a group of metalloenzymes that elicits primary antioxidant defense against oxidative stress in the body. Its primary functions are mainly preventive and it acts by scavenging/inactivation of Reactive Oxygen Species (ROS) or redox metal ions before lipid peroxidation takes place (Girotti, 1990). There was a slight increase ($p<0.05$) in the levels of SOD in both the pregabalin and *Carica papaya-t*reated groups, compared to the untreated group. There was a slight increase ($p<0.05$) in the levels of GSH in both the pregabalin- and *Carica papaya-t*reated groups, compared to the untreated group. Glutathione is an abundant and important antioxidant tripeptide and an essential bio-factor synthesized in all living cells. It functions mainly as an effective intracellular reductant. It protects cells from free radicals-mediated damage caused by drugs and ionizing radiation (Rahman & Macnee, 1999). Brain Malondialdehyde (MDA) has been documented as a primary biomarker of free radical-mediated lipid damage and oxidative stress. It is a highly toxic by-product formed in part by lipid oxidation-derived free radicals. It is increased considerably in the brain in diabetes mellitus. MDA mediates inter-molecular cross-links which results in the n stiffening of collagen tissues. MDA modification of basic amino acid side chains also results in a change in the charge profile of a molecule resulting in modified cell-matrix interactions (Shodeinde & Oboh, 2013). In this study, there was a significant decrease ($p<0.05$) in the levels of MDA in both the pregabalin- and *Carica papaya-t*reated groups, compared to the untreated group. There was a significant increase in the latency period in the untreated animals, thus exhibiting thermal hypoalgesia, which is consistent with the study carried out by Fox, *et al.,* in 1999 (Fox, *et al.,* 1999). However, pregabalin-treated animals and *Carica papaya*-treated animals showed a significant reduction ($p<0.05$) in the latency period at the end of treatment. The pregabalin- and papaya-treated treated groups showed a significant reduction ($p<0.05$) in sensitivity to mechanical tactile stimulation; however, the untreated rats had an increased sensitivity to mechanical tactile stimulation. The mechanical hyperalgesia shown by the STZ-induced group is consistent with the result of the study carried out by Fox, *et al.,* 1999.

In conclusion, the results of this study suggest that *Carica papaya* leaves extract helps to reduce plasma glucose, mechanical and thermal hyperalgesia, oxidative stress, and nerve damage in streptozocin-induced diabetic peripheral neuropathy in male Wistar rats. Further studies are required in humans to complement these findings for translation to clinical practice.

Authors' contributions

All authors contributed to various extents to the conception and design of the work; acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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