SHORT COMMUNICATION

Effect of Heparin and Carica Papaya Leaf Extract on Blood Glucose Levels in Wistar Rats: A Pilot Study

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Abstract

Diabetes is a chronic metabolic disorder identified by raised blood glucose levels due to suppressed insulin production. Heparin, a familiar anticoagulant, has been shown to hinder the insulin channeling and increase blood glucose levels. Carica papaya Leaf Extract (CPLE) is attracting attention as a potential natural therapeutic agent for managing high blood glucose levels in patients with diabetes. This study investigates the effects of CPLE and Heparin on body weight, diet consumption, and blood glucose levels in experimental Wistar rats. This preliminary pilot study was conducted for 1 month, from November 2023 to December 2023, at the Animal House Facility of the Department of Physiology at the University of Karachi. A total of 20 male Wistar rats were taken and randomly divided into four groups (n=5). Control, Heparin-induced, CPLE-induced, and a combination Heparin and CPLE-induced group. Heparin was administered intravenously at 0.1 ml/100 g body weight, whereas CPLE was administered orally at 2000 mg/kg body weight. Diet intake and body weight were observed during the trial. Blood glucose levels were estimated at the end of the study. The Kruskal-Wallis test was used to compare the medians across groups. P-value <0.05 was considered significant. The study found a notable decline in dietary intake ($p<0.001$) and body weight ($p<0.001$) in all treatment groups. Blood glucose levels were elevated in all treatment groups except the CPLE-treated group, where they decreased from baseline ($p<0.001$). In conclusion, CPLE and Heparin may affect blood glucose levels in Wistar rats. CPLE may lower blood glucose levels, while Heparin raises them.

Keywords: *Diabetes mellitus, heparin, Carica papaya leaf extract, blood glucose levels, Wistar rats.*

INTRODUCTION

Diabetes mellitus is a long-standing medical condition characterized by elevated blood glucose levels due to reduced or absent insulin production [1]. It is commonly known as a "silent disease," because it develops gradually and usually without symptoms [2]. Diabetes mellitus leads to uncontrolled hyperglycaemia which may result in serious health problems such as renal failure, neuropathies, and cardiovascular diseases [3]. These concerning figures highlight the importance of investigating efficient and inexpensive therapies. Heparin is a natural anticoagulant and antithrombotic glycoprotein, found in mast cells [4]. Apart from its well-established role as an anticoagulant, it has been explored for various physiological properties [5], including increased lipid metabolism and appetite stimulation [6]. However, research shows that Heparin's effect on diabetes is complex. It will reduce the glucose oxidation and inhibit insulin binding in hepatocytes [7]. Few studies report that Heparin disrupts insulin signaling by decreasing insulin receptor binding and also inhibits the activation of the PI3K/Akt pathway in skeletal muscle, leading to impaired glucose uptake and elevated blood sugar levels [8]. Hence, Heparin as an anticoagulant also has some potential to develop hyperglycaemia in those patients who are receiving heparin therapy.

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In traditional healthcare systems, herbal medicines have been utilized for a long time, and recent pharmacological research has confirmed many of their reported advantages [9]. *Carica papaya* Leaf Extract (CPLE) is a well-known herbal treatment for managing hyperglycemia, with significant hypoglycemic and hypolipidemic properties, particularly in diabetic rat models [10]. The CPLE stimulates insulin secretion from pancreatic β-cells, leading to reduced plasma glucose and triacylglycerol levels [11]. The hypoglycaemic property of CPLE is due to its antibacterial effect of benzyl isothiocyanate (BTC) and enzyme-like papain [12]. The bioactive compounds present in CPLE make it an effective natural remedy for blood glucose management [13]. This study aimed to investigate the potential of CPLE and Heparin on body weight, diet consumption, and blood glucose levels in experimental Wistar rats.

METHODOLOGY

This preliminary pilot study was conducted for a month, from November 2023 to December 2023, at the Animal House Facility of the Department of Physiology, University of Karachi. The study was reviewed and approved by the National Institute of Health and the local ethical committee of the Department of Physiology at the University of Karachi (IRB No.: 2277388882).

The study included 2 weeks of acclimatization, 1 week for dosing, and the experimental period. Twenty male Wistar rats, each weighing between 170 and 200 grams, were housed in a controlled environment. Rats were

distributed into four groups (n=5 per group): Group 1: Control, Group 2: Heparin-induced, Group 3: *Carica papaya* Leaf Extract (CPLE)-induced, and Group 4: combined Heparin and CPLE-induced, presented in **Fig. (1)**. The rats had unrestricted access to a standard diet and water throughout the study period.

The sample size was determined using the Resource Equation Method as described by Arifin and Zahiruddin and endorsed by NIH guidelines for animal experimental studies [14]. According to this method, the value of E (the total number of animals minus the total number of groups) should fall between 10 and 20 to ensure adequate statistical power. In the present study, E = 20 – 4 = 16, which lies within the acceptable range, thereby justifying the selected sample size for this pilot experiment.

Fresh leaves of *Carica papaya* were collected from a household plant. The leaves were washed thoroughly with tap water, then with distilled water, to remove dirt and impurities. The cleaned leaves were weighed using an electronic balance. Approximately 40 g of fresh leaves were ground into a fine paste and mixed with 100 mL of distilled water to prepare an aqueous extract. The mixture was filtered through sterile filter paper to obtain *Carica papaya* leaf extract (CPLE). The extract was freshly prepared and stored at 4°C until administration to the experimental animals. *Carica papaya* Leaf Extract (CPLE) was administered orally at a concentration of 2000 mg/kg body weight, as outlined in the study by Halim *et al*. (2011) [15]. Each rat, weighing approximately 200 grams, received about 400 mg of CPLE daily *via* a 20-gauge oral gavage needle. Heparin was given intravenously through the tail vein at a dose of 0.1 ml per 100 grams of body weight to the Heparin-induced and combined (Heparin and CPLE-induced) groups, following the protocol established by Cahyati *et al.* (2021) [16]. Body weight was recorded on the first and last days of the study. The Bonso Model-322 weighing scale was used to calculate dietary intake by weighing their diet regularly. Diet was given as biscuits and measured in grams. The diet consumption was measured through the given formula:

Total amount of diet - **Remaining amount of diet** = **Diet consumed in a day**

Blood glucose levels were measured at the end of the study by using a glucometer (On Call EZ II). Blood glucose level was recorded by applying a drop of blood to the test strip obtained *via* sterile tail-tip pricking.

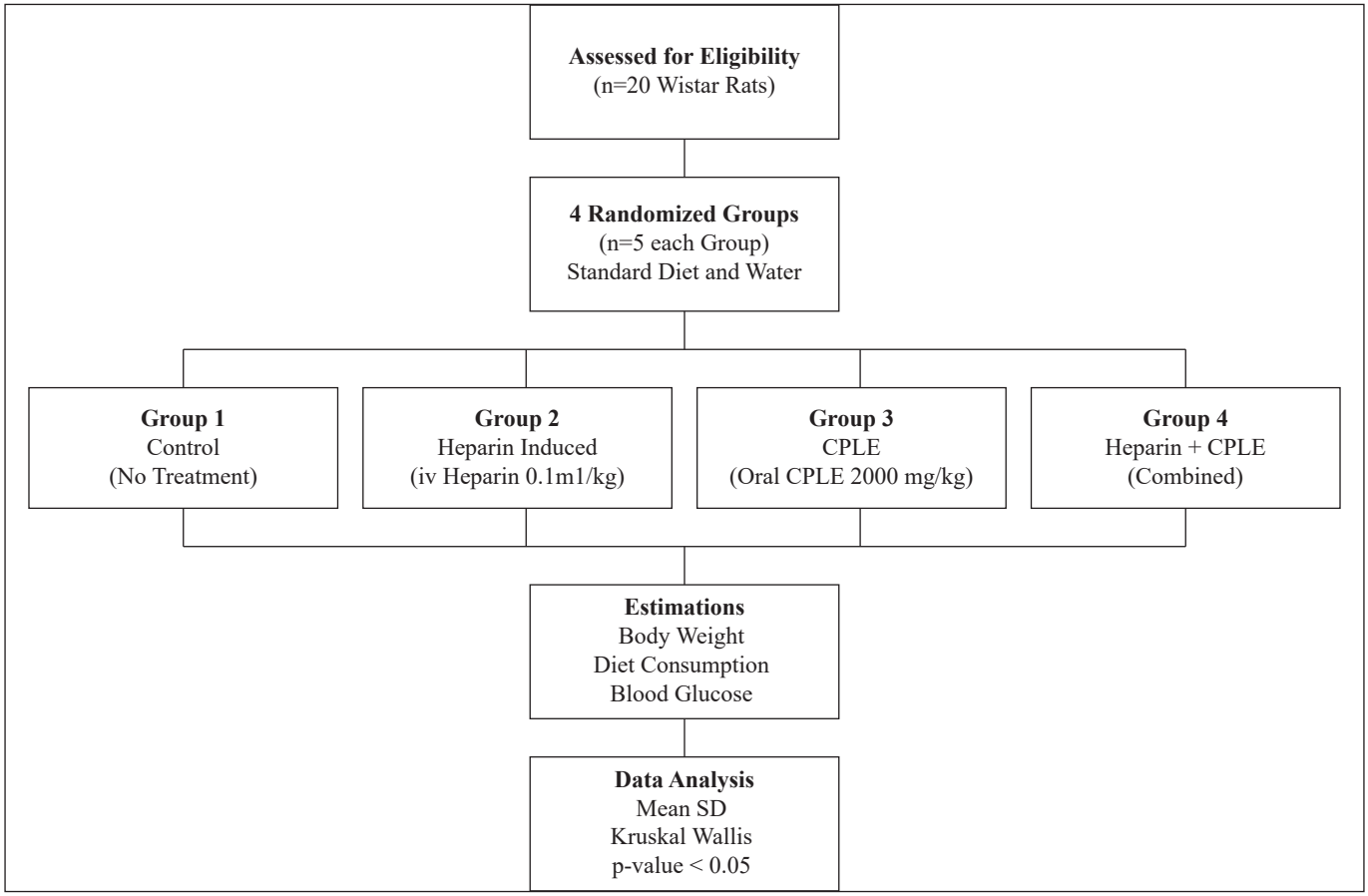

Fig. (1): Methodology Outline.

Statistical analysis was performed using GraphPad Prism 10. Numerical variables were presented as the median ± interquartile range (IQR). Intergroup comparisons were performed using the Kruskal-Wallis test, as the data were non-normally distributed and the sample size per group was small. P-values < 0.05 were considered statistically significant.

RESULTS

A total of 20 rats were studied, with 5 in each group. Initially, diet intake was within normal limits across all groups before the administration of Heparin and the oral dosage of *Carica papaya* Leaf Extract CPLE. However, a significant reduction in dietary intake was observed across all experimental groups compared with the control group. This reduction in diet consumption was statistically significant ($p<0.001$).

Gradually, the body weight of the animals in all treatment groups declined after the administration of Heparin and CPLE. On the last day, a significant reduction in body weight was observed in the treatment groups compared with the control group, suggesting that Heparin and CPLE influenced body weight and dietary intake. Body weight alterations were also statistically significant ($p<0.001$).

Regarding blood glucose levels, a notable increase was observed in all experimental groups by the end of the study, except in group 3, which received only CPLE. In fact, group 3 showed a minute decrease in blood glucose levels from the baseline. Table **1** represents the final measured values of diet intake, body weight, and blood glucose levels at the end of the experimental period. These values were compared between groups to assess treatment effects.

DISCUSSION

Heparin is a glycosaminoglycan with anticoagulant properties. It can influence insulin signaling and glucose homeostasis by altering Heparin's ability to inhibit insulin. Stimulated activation of the P13K/AKt pathway and reduced glucose oxidation [7]. At the same time, it can intensify hyperglycemia. In this study, we found that Heparin elevates glucose levels and may cause hyperglycemia. At the same time, Heparin's anti-inflammatory effects can augment lipid metabolism and potentially stimulate appetite [6].

In contrast, *Carica papaya* Leaf Extract CPLE is commonly considered a natural remedy for the management of diabetes. CPLE has a great ability to cure hyperglycemia. This effect is exhibited by CPLE's rich phytochemical profile, which causes release of insulin from the β cells of pancreas and, in return plasma glucose and triacylglycerol levels are minimized [12] The abundance of bioactive compounds such as benzyl isothiocyanate (BITC) and papain in CPLE, shows its strong antioxidative strength [17], that contributes to its diverse therapeutic potential. These characteristics of CPLE are the root of its beneficial effects on glucose metabolism and lipid profiles, and align with CPLE as a worthwhile complementary treatment for diabetes. CPLE also has an anti-obesity effect due to its alkaloid and flavonoid content [18]. Similar to these findings, our study observed a significant reduction in dietary intake across all experimental groups, including those receiving Heparin and CPLE.

Heparin elevates blood glucose levels by disrupting insulin binding and inhibiting glucose uptake [19]. It was observed that weight and diet decreased after heparin administration, contradicting previous results. The reduction in body weight observed in the heparin-treated groups may be attributed to altered glucose metabolism and impaired insulin signaling. Heparin has been reported to interfere with insulin receptor binding and PI3K/Akt pathway activation, leading to decreased glucose uptake and metabolic imbalance [6]. In contrast, CPLE exhibits antidiabetic properties and hypoglycemic effects due to its rich content of polyphenols, alkaloids, glycosides, and flavonoids, which enhance insulin sensitivity and regulate blood glucose levels [20]. Moreover, a recent study reported a significant reduction in blood glucose levels in

Table 1: Post-intervention comparison of diet intake, body weight, and blood glucose levels among experimental groups.

Parameters	Group 1	Group 2	Group 3	Group 4	p-value
Diet (gm/day)	4.75(4.35-5.15)	2.6(2.45–2.75)	2.65(2.5–2.8)	3.2(3.05–3.35)	<0.001
Weight (/gm)	203(199–207)	173(165–181)	178(165–183)	177(171.5–183)	<0.001
Blood Glucose Level (mg/dl)	85 (78–91.5)	127(116.5–138)	66 (62.5–70)	118 (106–130)	<0.001

Data is expressed as median (interquartile range).

streptozotocin-induced diabetic rats following administration of papaya leaf extract [21].

Additionally, *Carica papaya* leaf extract is rich in phenolic and flavonoid compounds and exhibits strong free radical scavenging activity, contributing to its antioxidant capacity and potential therapeutic benefits [22]. Consistent with previous research, our study found that blood glucose levels increased with Heparin alone and with Heparin combined with CPLE, whereas CPLE alone decreased blood glucose levels. Similar to our findings, the papaya leaf extract from *the Carica papaya* group showed a definite reduction in glucose levels [23]. The inclusion of polyphenols, flavonoids, and alkaloids that enhance insulin sensitivity and release may account for its activity [23, 24]. Papaya leaf extract's antioxidant qualities may potentially maintain pancreatic cells and support healthy glucose metabolism. Many studies have shown similar outcomes: papaya leaf extract lowers blood glucose levels and reduces oxidative stress in diabetic rats [23, 24].

Overall, our findings showed that papaya leaf extract lowers blood glucose levels, whereas Heparin raises them [8, 23]. Heparin is known to affect glucose metabolism and may increase blood glucose levels. Consequently, its use in hyperglycemic patients may be potentially harmful due to the risk of worsening glycemic control. In contrast, *Carica papaya* leaf extract does not appear to affect blood glucose levels. Even in the absence of a significant therapeutic benefit, the lack of a negative impact on glycemic status is clinically relevant. It supports its favorable safety profile, particularly in patients with diabetes or impaired glucose tolerance. The adverse effects of Heparin were not fully eliminated by combining the two therapies, indicating the need for additional research to examine various dosages and treatment durations [24].

Future studies should be conducted with a larger sample size and a longer duration to evaluate better the efficacy and safety of *Carica papaya* leaf extract. Well-designed randomized controlled trials are recommended to validate these findings and to explore dose optimization, long-term outcomes, and potential benefits in specific patient subgroups, including those with coexisting metabolic disorders.

The present study contributes to the limited information on the cumulative effect of *Carica papaya* leaf extract and Heparin, highlighting the need for further, more advanced investigation to determine the full potential of CPLE as a supportive treatment for diabetes. This study was primarily designed to evaluate the effects of papaya leaf extract and Heparin on glycemic profile, body weight, and dietary intake in rats. The combined effects of *Carica papaya* leaf extract and Heparin on blood glucose regulation have not been extensively studied. However, this study has certain limitations. It was conducted as a pilot study with a small sample size, which may affect the reliability of the findings. Additionally, the short duration of the study limits conclusions regarding long-term effects on blood glucose regulation and metabolic outcomes. Therefore, further studies with larger sample sizes and longer durations are required.

CONCLUSION

This pilot study demonstrates that heparin administration significantly increases blood glucose levels, whereas *Carica papaya* leaf extract (CPLE) exhibits hypoglycemic potential in Wistar rats. The combined administration did not fully neutralize Heparin's hyperglycemic effect. Although CPLE appears promising as a complementary therapy for glycemic control, larger-scale, long-term studies are needed to confirm its efficacy and safety.

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Review Committee of Department of Physiology at the University of Karachi, Karachi (IRB No.: 2277388882). All the procedures have been performed in accordance with Guidelines for Animal Experiments established by University of Karachi, Karachi, Pakistan.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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AUTHORS' CONTRIBUTION

MA: Conceptualization, methodology, data collection, and manuscript writing.

FS: Statistical analysis, manuscript writing, and data interpretation.

HMU: Supervision and manuscript review.

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