



Effect of Jackfruit Pulp Extract on Serum Nesfatin-1 and Visfatin Levels in Streptozotocin-induced Rats

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ABSTRACT

Background: The aim of this study was to investigate the effects of different amounts of jackfruit pulp extract (JPE) in the diets on serum nesfatin-1 and visfatin levels in Streptozotocin (STZ)-induced Type 1 diabetic rats.

Methods: In this study, 64 adult male Wistar albino rats, aged between 8-10 weeks, were used. 8 groups were created, with 8 rats in each group: Control (C), J100 (JPE 100 mg/kg group given with oral gavage route of administration (OGRA), J200 (JPE 200 mg/kg group given with OGRA), J300 (JPE 300 mg/kg group given with OGRA); STZ 55 mg/kg i.p administered group, DJ100 (D+100 mg/kg JPE), DJ200 (D + 200 mg/kg JPE), DJ300 (D. + 300 mg/kg JPE). The study lasted a total of 31 days, including adaptation (7 days), induction of diabetes (3 days) and trial period (21 days). Blood samples were taken from the tail vein (*Vena caudalis*) of all subjects on days 0 and 21 of the study. Nesfatin-1 and visfatin levels in the serum samples were measured by ELISA method.

Result: As a result, in the diabetes groups of our study, the most significant increase in the mean serum nesfatin-1 level and the most significant decrease in the mean serum visfatin level occurred in the DJ200 groups at the end of the 21st day due to the addition of JPE ($p < 0.05$). As a result, it was concluded that JPE may be safe and beneficial when administered at a dose of 200 mg/kg in diabetic groups.

Key words: Jackfruit, Nesfatin-1, Rat, Type 1 diabetes mellitus, Visfatin.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic hyperglycemic metabolic disease that causes disorders in carbohydrate, protein and fat metabolism along with hyperglycemia, which occurs as a result of absolute or relative deficiency of insulin hormone secretion and/or insulin action (Umpierrez *et al.*, 2024). Type 1 DM is a chronic autoimmune disease involving immune-mediated destruction of insulin-producing pancreatic β -cells, leading to insulin deficiency and hyperglycemia (DiMeglio *et al.*, 2018).

The hormonal physiology of hunger with satiety and the regulation of energy homeostasis processes are regulated by a complex process involving orexigenic and anorexigenic factors. Nesfatin-1 is an adipokine derived from the NUCB2 precursor protein, which is effective in the physiological control of appetite and feeding behavior with its anorexigenic effect that reduces body weight (Oh *et al.*, 2006; Ramanjaneya *et al.*, 2010). It reduces food intake by inhibiting gastrointestinal peristalsis and controls body weight (Oh-I *et al.*, 2006). Nesfatin-1 plays a role in the pathophysiology of diabetic hyperphagia (Li *et al.*, 2010). Visfatin is an adipokine that stimulates the release of glucose in tissues by reducing the release of glucose from hepatocytes, has an insulin-mimetic effect by binding to insulin receptor-1 and has a hypoglycemic effect (Radzicka *et al.*, 2018). Visfatin is reported to be associated with the development of type 1 diabetes and its complications such as nephropathy (El Samahi *et al.*, 2017), retinopathy (Shao, 2020) and neuropathy (Mohammed *et al.*, 2023). Nesfatin-1 and visfatin are adipokines that are promising therapeutic agents, especially for the treatment of obesity and diabetes (Blühler, 2014).

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Medicinal and aromatic plants and immune-boosting foods are important alternatives in traditional and complementary medicine for therapeutic and preventive purposes in diseases due to their antidiabetic, antioxidant and immunomodulatory effects due to the phytochemicals they contain. Jackfruit is reported to have an anti-diabetic effect due to its high proanthocyanidin and flavonoid content, inhibiting lipid peroxide formation and reducing fasting blood sugar levels with its α -amylase inhibitor effect (Omar *et al.*, 2011). Jackfruit is a fruit with nutritional properties and therapeutic potential such as antidiabetic (Biworo *et al.*, 2015), antioxidant (Bossi *et al.*, 2024), anticancer (Mutiyani and Nuriliani, 2024), antiviral, anti-inflammatory (Kumar *et al.*, 2024) and antibacterial activities (Indrianingsih *et al.*, 2024). Streptozotocin (STZ) is a chemical widely used to create an experimental diabetes model, which is particularly toxic to the insulin-producing β -cells of the pancreas,

leading to inadequate insulin secretion and hyperglycemia. In the literature research, no study was found examining the effects of different rates of JPE application on serum nesfatin-1 and visfatin levels in Type 1 diabetic rats. This study investigated the effects of different rates (100, 200 and 300 mg/kg) of JPE application on serum nesfatin-1 and visfatin levels in healthy normal rats with Type 1 diabetes induced by STZ.

MATERIALS AND METHODS

The study used 64 male Wistar rats, 8-10 weeks old and weighing an average of 200-240 grams, as animal material. Before starting the study, ethics committee approval was obtained from the Research Centre Ethics Committee (Decision No: 2022/30). The research was conducted in accordance with ethical principles and rules, while protecting animal welfare and rights. All rats were kept in a controlled room with 50-60% humidity, 22 °C temperature and 12 hours of light (06:00, 18:00) and 12 hours of darkness, with 2 cages in each group and 4 animals in each cage. The study lasted a total of 31 days, including adaptation (7 days), induction of diabetes (3 days) and trial period (21 days). All applications during the study were performed in the same time periods (09:00-10:00). Sample calculation in creating the diabetes model was performed with the G*Power 3.1.9.7 analysis program and power analysis was performed. The power of the study was determined by the power analysis as a sample size that could detect 99% power when the α value was taken as 0.05 and the η^2 value as 0.06 and the experimental groups were determined as 8 rats in each group. To create a DM model, STZ (55 mg/kg) solution prepared in phosphate citrate buffer (0.1 M, pH: 4.5) was injected intraperitoneal (*i.p.*) to rats (DC, DJ100, DJ200 and DJ300) except for control, J100, J200 and J300 groups. Those with fasting blood sugar levels ≥ 250 mg/dL 3 days after STZ injection were considered to have Type 1 diabetes. The composition of the experimental diet used in the study is shown in Table 1 and the chemical composition of jackfruit pulp extract (JPE) is shown in Table 2.

The experimental protocol was formed as follows:

Control group (C)

Only physiological saline was administered to rats *via i.p.*

J100 mg/kg group (J100)

Rats were given OGRA and JPE 100 mg/kg daily for 21 days.

J200 mg/kg group (J200)

Rats were given OGRA and JPE 200 mg/kg daily for 21 days.

J300 mg/kg group (J300)

Rats were given OGRA and JPE 300 mg/kg daily for 21 days.

Diabetic J100 mg/kg group (DJ100)

Rats induced with STZ injection were given OGRA and JPE orally at 100 mg/kg daily for 21 days.

Diabetic J200 mg/kg group (DJ200)

Rats induced with STZ injection were given OGRA and JPE orally at 200 mg/kg daily for 21 days.

Diabetic J300 mg/kg group (DJ300)

Rats induced with STZ injection were given OGRA and JPE orally at 300 mg/kg daily for 21 days.

Collection of serum samples

Blood samples were taken from the tail vein of rats on day 0 of the study and intracardially on day 21. Blood samples were collected in tubes without anticoagulant and centrifuged in a refrigerated centrifuge (NF 1200R, NÜVE, Türkiye) for 10 minutes at 3000 rpm in the laboratory and the resulting sera were separated (Fig 1).

Measurement of serum visfatin and cTnI level

In measuring serum nesfatin-1 and visfatin levels obtained in the study, ELISA kit type-specific for rat nesfatin-1 ELISA kit (BT LAB, Cat. No SG- E0878Ra, CHINA) and visfatin ELISA Kit (SinoGeneclon, Cat. No: SG-20381, CHINA) an intra-assay coefficient of 8.0% and an inter-assay coefficient of 10.0% was utilized under the manufacturer's protocol.

Table 1: Composition of experimental diet (%).

Ingredients	Quantity %
Maize	59.12
Soybean meal	16.03
Groundnut cake	6.00
Wheat offal	5.00
Bonemeal	3.46
Limestone	9.62
Salt	0.22
Methionine	0.18
Lysine	0.12
Premix	0.25
Total	100
ME (kcal/kg)	2683.60
Crude protein (%)	18.00
Crude fibre (%)	3.44
Ether extract (%)	3.01
Calcium (%)	4.72
Phosphorus (%)	0.87

Table 2: Composition of graviola (*Annona muricata* L.) leaf oil extract.

Ingredients	Value
Moisture (%)	95.18
Protein (%)	0.80
Ash (%)	0.77
Fat (%)	0.12
Total carbohydrate (%)	3.25
Dietary fiber (%)	0.80

The results were evaluated by reading absorption values at 450 nm under the procedure reported in the kit.

Statistical analysis

Statistical data analyses were performed with SPSS version 15 (IBM, USA). Normality and homogeneity tests of the data were performed with Kolmogorov-Smirnov, Shapiro-Wilk and Levene's tests. Differences between groups were analyzed with the nonparametric Kruskal Wallis Test. The interaction between groups and time for repeated measurements (0 and 21 days) was analyzed with the general linear model (GLM). The significance level in the analysis results was accepted as $p < 0.05$.

RESULTS AND DISCUSSION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia caused by the pancreas not producing enough insulin or the body's inability to use the insulin it produces effectively (Elkhalifa *et al.*, 2024). Adipokines are hormones secreted from adipose tissue that play a role in many physiological processes (such as energy regulation, glucose, insulin, metabolism and lipid metabolism) (Bayraktar, 2020).

Nesfatin-1 (known as anorexigenic and satiety peptide) is an adipokine that plays a role in appetite, food intake and energy regulation. Nesfatin-1 can inhibit food intake through melatonin system activation, independent of the leptin pathway (Cowley and Grove, 2006). It has been reported that nesfatin-1 has an antihyperglycemic role in glucose homeostasis (Su *et al.*, 2010), a regulating effect on insulin sensitivity in the brain (Yang *et al.*, 2012) and an effect of increasing insulin secretion in beta cells under hyperglycemic conditions (Nakata *et al.*, 2011). The mean

serum nesfatin-1 levels on day 0 of the study in the C, R100, R200 and R300 control groups were found to be 2.06, 2.11, 2.13 and 2.06 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 0.96, 0.97, 1.25 and 1.01 ng/ml, respectively. The mean serum nesfatin-1 levels on day 21 of the study in the C, R100, R200 and R300 control groups were found to be 2.61, 2.82, 3.28 and 2.61 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 0.82, 1.58, 1.92 and 1.62 ng/ml, respectively (Fig 2).

In the diabetes groups, the lowest mean serum nesfatin-1 levels on day 21 compared to day 0 were determined in the DC groups, while the highest were determined in the DJ200 groups ($p < 0.01$). The results of our study are consistent with research results reporting that serum nesfatin-1 levels decrease in diabetes (Li *et al.*, 2010; Eskandari Mehrabadi and Fallah, 2021; İğci *et al.*, 2024) and differ with some research results (Riva *et al.*, 2011). Although studies examining the effects of JPE, which is reported to have antihyperglycemic and antidiabetic effects, on mean serum nesfatin-1 levels are limited, they are consistent with the results of research reporting that mean serum nesfatin levels increase due to the use of extract in rats with STZ diabetes (Eskandari Mehrabadi and Fallah, 2021). We think that the reason for this situation is due to the antihyperglycemic and antidiabetic effects of JPE.

Visfatin, also known as nicotinamide phosphoribosyl transferase (Nampt), is an adipokine with a pro-inflammatory effect that is extensively expressed in adipose tissue (Fukuhara *et al.*, 2005). Visfatin is reported as a biomarker of inflammation in metabolic syndrome (Hognogi and Simiti, 2016). It has been reported that visfatin

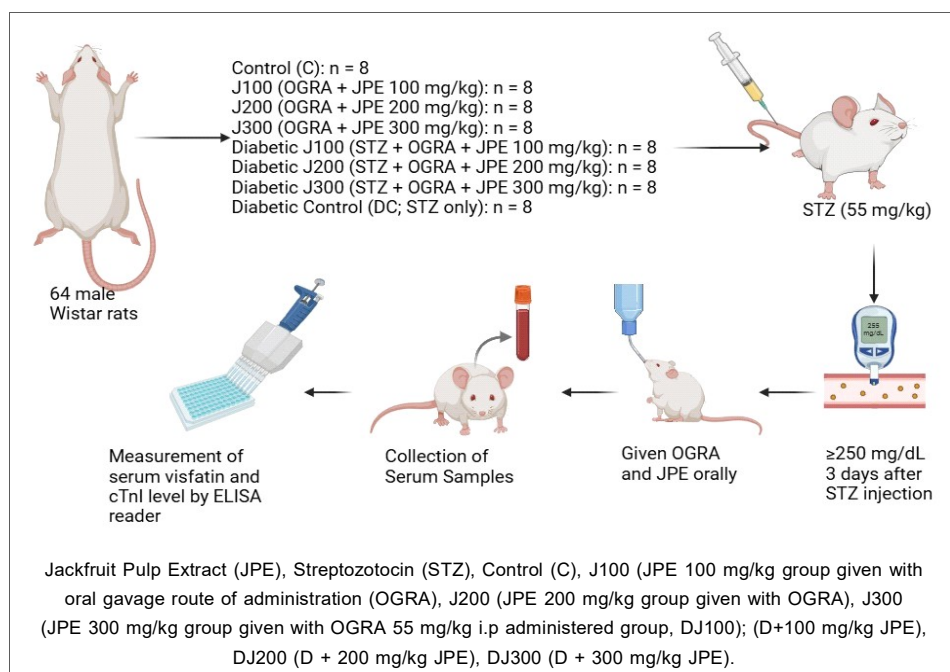


Fig 1: Experimental scheme. Scheme of our experimental groups, number of rats we used, the treatment way and duration.

can be used as a marker for obesity, insulin resistance, diabetes, metabolic syndrome and cardiovascular diseases (Chang *et al.*, 2011).

The mean serum visfatin levels on day 0 of the study in the C, R100, R200, R300 control groups were found to be 37.68, 37.18, 37.21 and 37.20 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 55.01, 54.21, 54.12 and 54.13 ng/ml, respectively. The mean serum visfatin levels on day 21 of the study in the C, R100, R200 and R300 control groups were found to be 39.45, 41.65, 42.31 and 43.76 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and D300 were determined to be 58.45, 51.13, 46.37 and 49.85

ng/ml, respectively (Fig 3). While the increase in mean serum visfatin levels due to diabetes was mostly seen in DC groups, similarly, in DJ groups, mean serum visfatin levels decreased in all groups due to the addition of antioxidant-effective JPE. In contrast, the most significant decrease was determined in DJ200 groups ($p < 0.01$). Although the current results of our study are limited in terms of the studies examining the effect of JPE on serum visfatin levels, they differ from studies reporting that it does not change (Akbarzadeh *et al.*, 2015), which is consistent with similar research literature (Han *et al.*, 2013; Berndt *et al.*, 2005; Tond *et al.*, 2016). According to our findings, we think that the decrease in serum visfatin levels due to the

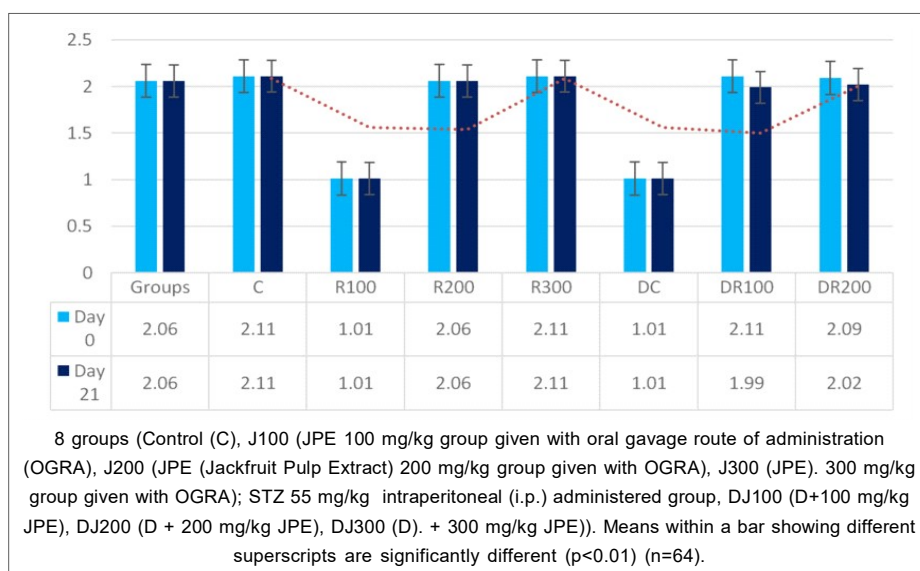


Fig 2: Bar graph showing day 0 and day 21 of serum Nesfatin-1 levels in rats.

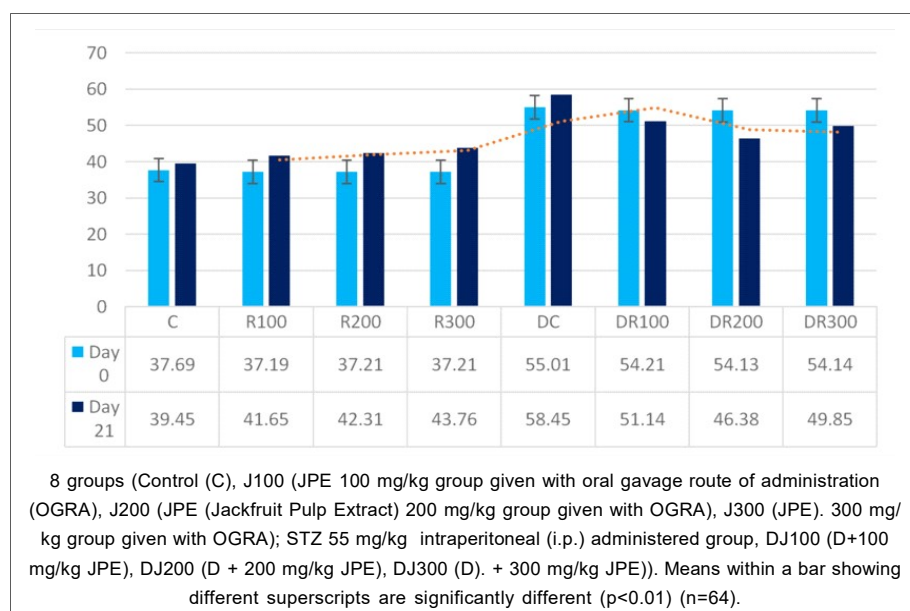


Fig 3: Bar graph showing day 0 and day 21 of serum visfatin levels in rats.

application of different amounts of JPE in diabetic groups due to hyperglycemia in diabetes is due to the antihyperglycemic and antidiabetic effects together with the phytochemicals in the JPE content.

CONCLUSION

In type 1 DM, unintended and excessive weight loss plays a role in the development of diabetes complications. Since nesfatin-1 also reduces body weight gain, is an anorexigenic factor and modulator of energy balance and visfatin has proinflammatory and immunomodulatory properties and plays a role in the development of DM and complications, it is thought that examining their levels in diabetes management would be beneficial. As a result, it was concluded that JPE, which is reported to have antidiabetic effects, may be safe and beneficial when administered at a dose of 200 mg/kg in diabetic groups.

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments Central Research were approved by the Committee of Experimental Animal Care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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