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Effect of Different Rates of Rambutan Peel Extract on Visfatin and Cardiac Troponi N I Response in Type 2 Diabetic Rats Induced with Streptozotocin

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ABSTRACT

Background: The aim of this study was to investigate the effects of STZ (Streptozotocin) and Rambutan peel extract (RPE) on serum visfatin and cardiac response in experimental Type 2 diabetic rats.

Methods: In this study, 64 adult male Wistar albino rats, aged between 8-10 weeks, were used. 8 groups were randomly selected, each containing 8 rats as Control (C), R100 (RPE 100 mg/kg group given with oral gavage route of administration (OGRA), R200 (RPE 200 mg/kg group given with OGRA), R300 (RPE 300 mg/kg group given with OGRA); Diabetes Control (DC): STZ 50 mg/kg i.p administered group, DR100 (D+100 mg/kg JPE), DR200 (D+200 mg/kg JPE), DR300 (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. Visfatin and cTnI levels in the serum samples were measured and evaluated by ELISA method.

Result: While the increase in mean serum visfatin and cTnI levels in diabetic groups was seen mostly in DC groups, the most significant decrease in mean serum visfatin level due to the addition of RPE was determined in DR100 groups ($p<0.01$). As a result, it was concluded that the administration of 100 mg/kg RPE in rats had no adverse effects. It was concluded that RPE, which has a cardioprotective effect by regulating the visfatin response that plays a role in the development of diabetes, may be useful in supporting the impaired cardiovascular system function that occurs in diabetes.

Key words: Cardiac troponin, Rambutan, Rat, Type 2 Diabetes mellitus, Visfatin.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic hyperglycemic metabolic disease that causes disorders in carbohydrate, protein and fat metabolism as a result of absolute or relative deficiency of insulin hormone secretion and/or insulin action (Pleus *et al*., 2024). Type 1 (insulin-dependent) diabetes mellitus is a form of diabetes that occurs as a result of a series of events that lead to progressive beta cell destruction, usually resulting in absolute insulin deficiency. The disease, which usually develops from an autoimmune cause, mostly occurs in childhood and young adulthood (Bielka *et al*., 2024).

Hormones are biomolecules that regulate many physiological processes in the body (Bayraktar, 2020). Visfatin is an adipokine that plays a role in adipogenesis and has hypoglycemic and insulin-mimetic effects by reducing glucose release and promoting glucose utilization in peripheral tissues (Arner, 2006). Visfatin is identified as an antidiabetic adipocytokine (Song *et al*., 2008). Visfatin interacts with insulin receptors at sites other than insulin binding sites, increasing muscle and liver cell glucose utilization and reducing blood glucose levels. Circulating visfatin/ Nicotinamide phosphoribosyltransferase (Nampt) levels are reported to increase in metabolic diseases such as obesity and type 2 diabetes. In cardiovascular diseases, visfatin/Nampt is initially reported as a clinical marker of atherosclerosis, endothelial dysfunction and vascular damage with potential prognostic value (Vanhoutte, 2009). Visfatin is reported to provide cardioprotection through activation of PI3K-Akt and MAP kinase kinases (MEK1/2-Erk1/2, known as MAPKKs) and subsequent inhibition of mitochondrial permeability transition pore (mPTP) opening (Lim *et al*., 2008). DM is considered a primary risk factor for

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cardiovascular diseases. Troponins, together with tropomyosin, are structural proteins that play a role in regulating skeletal and cardiac muscle contraction and are known to be sensitive and specific markers of cardiac muscle damage. Cardiac troponins are sensitive and specific markers of heart muscle damage. Cardiac troponin I (cTnI) is a cardiac biomarker used to evaluate myocardial damage and diseases due to its release into plasma from cardiac myocytes after cardiac damage (Adams *et al*., 1993; Wu *et al*., 1996).

Medicinal and aromatic plants are one of the important alternatives in traditional and complementary medicine treatments used for therapeutic and protective purposes in diseases thanks to their antioxidant, antidiabetic and antimicrobial effects and the valuable phytochemicals they contain. In this context, many medicinal aromatic plants and fruits have been reported to have protective effects against streptozotocin-induced diabetes (Manikandan *et al*., 2017; Song *et al*., 2019; Wang *et al*., 2020). Rambutan fruit has an antidiabetic effect as it has been reported to increase insulin sensitivity and reduce fasting blood sugar levels and insulin resistance (Ma *et al*., 2017).Rambutan is a fruit with nutritional properties and therapeutic potential such as antioxidant (Chingsuwanrote *et al*., 2016), antibacterial, anticancer (Nilmat *et al*., 2024), antidiabetic (Tran *et al*., 2024), antiviral, anti-inflammatory (Chingsuwanrote *et al*., 2016) and antiproliferative activities (Ma *et al*., 2017). There are no studies investigating the changes in mean serum visfatin and cTnI levels in diabetic rats with different amounts of RPE. This study investigated the effects of STZ and RPE on visfatin and cardiac response in type 2 DM rats.

MATERIALS AND METHODS

The study used 64 male Wistar rats, 8-10 weeks old and weighing an average of 195-215 grams, as animal material. Before starting the study, ethics committee approval was obtained from the Veterinary Control Research Institute Ethics Committee (Decision date and number 09.07.2021-2021/11). The study was carried out in accordance with ethical principles and rules, considering animal welfare and rights. The study lasted a total of 31 days, including adaptation (7 days), induction of diabetes (3 days) and trial period (21 days). The nutrient compositions and chemical analysis results of the rat feeds used in the study are presented in Table 1 and the content analysis of the rambutan oil extract used is presented in Table 2. All applications during the study were performed in the same time periods (09:00-10:00).

The experimental protocol was formed as follows:

Control group (C)

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

Ram 100 mg/kg group (R100)

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

Ram 200 mg/kg group (R200)

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

Ram 300 mg/kg group (R300)

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

Diabetic control group (DC)

50 mg/kg of STZ solution prepared in citrate buffer (pH 4.5) was administered to rats *via* i.p.

Diabetic Ram 100 mg/kg group (DR100)

A single dose of 50 mg/kg of STZ citrate buffer (pH 4.5) solution was administered to rats *via* i.p. Rats were given OGRA and RPE at a dose of 100 mg/kg every day for 21 days. Those with fasting blood glucose levels of e”250 mg/dL after 3 days of the application were evaluated as diabetic.

Diabetic Ram 200 mg/kg group (DR200)

A single dose of 50 mg/kg of STZ citrate buffer (pH 4.5) solution was administered to rats *via* i.p. Rats were given

Table 1: Composition of experimental diet.

Ingredient	gm%	kcal%
Protein	20	18
Carbohydrate	68	67
Fat	7	15
Total		100
Casein	180	590
L-cystine	3	12
Corn starch	375.5	1562
Maltodextrin 10	110	440
Dextrose	150	600
Soybean oil	70	630
Mineral mix S10026	10	0
Dicalcium phosphate	13	0
Calcium carbonate	5.5	0
Potassium citrate, 1 H_20	16.5	0
Vitamin mix V10001	10	40
Choline bitartrate	2	0

Table 2: Nutritional composition of rambutan fruit peel.

Components	Rambutan fruit peel
Carbohydrates (g 100 g^{-1})	24.85
Lipids (g 100 g^{-1})	0.23
Moisture (g 100 g^{-1})	69.05
Ash (g 100 g^{-1})	1.18
Fiber (g 100 g^{-1})	0.62
Protein (g 100 g^{-1})	1.87
Vitamins	
Riboflavin (mg 100 g^{-1})	0.05
Niacin (mg 100 g^{-1})	0.30
Thiamine (mg 100 g^{-1})	0.05

OGRA and RPE at a dose of 200 mg/kg every day for 21 days. Then, those with fasting blood glucose levels of ≥250 mg/dL after 3 days were evaluated as diabetic.

Diabetic Ram 300 mg/kg group (DR300)

A single dose of 50 mg/kg of STZ solution prepared in citrate buffer (pH 4.5) was administered to rats *via* i.p. Rats were given OGRA and RPE at a dose of 300 mg/kg every day for 21 days. Those with fasting blood glucose levels ≥250 mg/dL 3 days after the application were evaluated as diabetic.

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 (VACUETTE® TUBE Z Serum Clot Activator) 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.

Measurement of serum visfatin and cTnI level

In measuring serum visfatin and cTnI levels obtained in the study, ELISA kit type-specific for rat visfatin Elisa Kit (SinoGeneclon, Cat. No: SG-20381, CHINA) and cTnI ELISA kit (BT LAB, Cat. No SG-20697, CHINA) an intra-assay coefficient of 8.0% and an inter-assay coefficient of 10.0% was utilized under the manufacturer's protocol. The results were evaluated by reading absorption values at 450 nm under the procedure reported in the kit.

Statistical analysis

Statistical analyses of the data 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 disease characterized by hyperglycemia caused by insulin deficiency or insulin resistance (Mishra *et al*., 2024). STZ is a naturally occurring alkylating antineoplastic agent that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals. The formation of diabetes by STZ is formed as a result of destroying the β-cells of the pancreas. STZ is one of the most commonly used agents to induce experimental diabetes (Cardinal *et al*., 1999). Adipokines are biomolecules secreted from adipose tissue that play a role in many physiological processes in the body (Bayraktar, 2020) such as nutrition (Romacho *et al*., 2015), appetite (Silveira *et al*., 2009), energy balance (Trayhurn *et al*., 2006), insulin and glucose metabolism, lipid metabolism (Rabe *et al*., 2008), blood pressure regulation (Yiannikouris *et al*., 2010), coagulation, inflammation (Romacho *et al*., 2015).

Adipokines have a role in the development of diabetes and diabetes-related complications (Al-Hamodi *et al*., 2014).Visfatin is an adipocytokine with a pro-inflammatory effect that is also secreted from adipose tissue. It is thought that visfatin may be a promising molecule due to its potential role in the pathogenesis of metabolic diseases and related complications, especially DM. Visfatin levels are reported to be increased in T2 DM (Berndt *et al*., 2005). The mean serum visfatin levels on day 0 of the study in the C, R100, R200, R300 control groups were found to be 40.3, 40.75, 40.98 and 41.15 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 53.11, 52.36, 53.84 and 52.59 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 41.51, 42.48, 42.45 and 43.41 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and D300 were determined to be 57.33, 51.14, 50.09 and 48.33 ng/ml, respectively (Table 3). When the current results were examined, a statistical difference was observed between the groups ($p<0.01$). While the increase in mean serum visfatin levels due to diabetes was mostly seen in DC groups, similarly, in DR groups, mean serum visfatin levels decreased in all groups due to the addition of antioxidant-effective RPE, while the most significant decrease was determined in DR300 groups ($p<0.01$). Although the current results of our study are limited in terms of the studies examining the effect of RPE 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). Our data also showed that treating diabetic rats with RPE could lead to a decrease in visfatin levels. We think that this is due to the phytochemicals contained in RPE, which have antioxidant effects.

Cardiovascular diseases are among the leading causes of death worldwide. DM has an active role in the development of cardiovascular diseases. Cardiac troponins (cTn) are cardiospecific markers of ischemic myocardial damage used in diagnosing acute coronary syndrome and myocardial damage with different etiology and pathogenesis. cTnI is a highly specific biomarker for cardiac injury (Adams *et al*., 1993). It is the gold standard for screening for acute coronary syndrome or rapid diagnosis of acute myocardial infarction (Anand and Mills, 2019). The mean serum cTnI levels on day 0 of the study in the C, R100, R200 and R300 control groups were found to be 0.41, 0.43, 0.44 and 0.43 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 0.70, 0.69, 0.70 and 0.74 ng/ml, respectively. The mean serum cTnI levels on day 21 of the study in the C, R100, R200 and R300 control groups were found to be 0.44, 0.45, 0.46 and 0.48 ng/ml. In the same way, diabetic groups DC, DR100, DR200 and DR300 were determined to be 0.78, 0.73, 0.79 and 0.78 ng/ml, respectively (Table 4). When the current results were

Table 3: Mean serum visfatin values (ng/ml) and statistical comparisons (Mean±SH) of the study groups.

Grup		Visfatin (ng/ml)			
		0 day		21 day	
		Mean	Standard deviation	Mean	Standard deviation
C		40.3	0.48	41.51	0.49
R100		40.75	0.78	42.48	0.46
R200		40.98	0.79	42.45	0.71
R300		41.15	0.9	43.41	1.07
DC		53.11	0.83	57.33	0.97
DR100		52.36	1.09	51.14	0.97
DR200		53.84	1.28	50.09	1.02
DR300		52.59	1.19	48.33	0.66
P-value	Diet	<0.01		<0.01	
	Time	0.110			
	Diet × Time	<0.01			

*Means within a column showing different superscripts are significantly different (p<0.05): SEM= Standard error of the mean.

Table 4: Mean serum cTn1 values (ng/ml) and statistical comparisons (Mean±SH) of the study groups.

Grup		cTnI (ng/ml)			
		0 day		21 day	
		Mean	Standard deviation	Mean	Standard deviation
C		0,41	0,14	0,44	0,12
R100		0,43	0,14	0,45	0,13
R200		0,44	0,14	0,46	0,12
R300		0,43	0,13	0,48	0,10
DC		0,70	0,19	0,78	0,19
DR100		0,69	0,17	0,73	0,15
DR200		0,70	0,15	0,79	0,17
DR300		0,74	0,14	0,78	0,10
P-value	Diet	<0.01		<0.01	
	Time	<0.01			
	Diet ×Time	0.168			

*cTnI (Cardiac Troponin I), Means within a column showing different superscripts are significantly different (p<0.05): SEM= Standard error of the mean.

examined, a statistical difference was observed between the groups (p<0.01). The highest mean serum cTnI level was determined in the DC and DR300 groups due to increased cardiac damage due to diabetes. Similarly, the most significant decrease in the mean serum cTnI level on day 21 compared to day 0 was determined in the DR100 groups due to the addition of different amounts of RPE, which has been reported to have a cardioprotective effect in the diabetes groups (p<0.01). The current results of our study are consistent with research results reporting that serum cTnI levels increase in diabetes (Berndt *et al*., 2005; Brouwers *et al*., 2013). On the other hand, although studies examining the effect of RPE, which has been reported to have a cardioprotective effect, on mean serum cTnI levels are limited, they are consistent with similar research results in the literature (Afzaal *et al*., 2023; Miraghaee *et al*., 2024). We think that the reason for this situation is due to the cardioprotective effect of RPE.

CONCLUSION

As a result of cardiac damage caused by diabetes, there is an increase in the level of cTnI, the most cardio-specific cardiac damage marker in the serum. Visfatin, as an inflammatory mediator, is associated with the development of DM and complications. In conclusion, it can be stated that RPE, which is reported to have cardioprotective and anti-inflammatory effects, may be safe and beneficial when administered at a dose of 100 mg/kg in diabetic groups.

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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

The Committee of Experimental Animal Care and Local Ethics Committee approved all animal procedures for experiments Veterinary Control Central Research.

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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