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Effect of *Moringa oleifera* Oil Extract on Adipokine (Apelin, Visfatin and Nesfatin-1) and Cardiac (cTnI) Response in Streptozotocin-induced Rats

Tuğçe ORKUN ERKILIÇ[1], Bülent BAYRAKTAR[2]

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ABSTRACT

Background: The aim of this study was to investigate the effects of Moringa *oleifera* extract (MOE) added to the diets at different amounts on Adipokine (apelin, visfatin and nesfatin-1) and Cardiac (cardiac troponin I (cTnI)) Response 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. Eight (8) groups were created, with 8 rats in each group: Control (C), M100 (MOE 100 mg/kg group given with oral gavage route of administration (OGRA), M200 (MOE 200 mg/kg group given with OGRA), M300 (MOE 300 mg/kg group given with OGRA); STZ 55 mg/kg i.p administered group, Diabetic control group (DC), DM100 (D+100 mg/kg MOE), DM200 (D+200 mg/kg MOE), DM300 (D)+300 mg/kg MOE). 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 subMects on days 0 and 21 of the study. Apelin, visfatin, nesfatin-1 and cTnI levels in the serum samples were measured by ELISA method.

Result: In the present study, the most significant increase in mean serum apelin, visfatin, nesfatin-1 and cTnI levels in diabetes groups was observed in DC groups, while the most significant decrease due to MOE addition was observed in DM200 groups ($p<0.01$). As a result, it was concluded that MOE may be safe and beneficial when administered at a dose of 200 mg/kg in rats with STZ-induced diabetes.

Key words: Apelin, cTnI, *Moringa oleifera*, 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). Mitochondria serve as the energy powerhouses of cells and produce ATP (adenosine triphosphate). Mitochondria play a critical role in the conversion of glucose into energy (Bayraktar *et al*., 2024). DM, especially type 2 DM, can lead to mitochondrial dysfunction. This prevents cells from using glucose effectively. 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).

Hormones are biomolecules that take part in many physiological processes in the organism (Bayraktar, 2020). Apelin is the endogenous ligand of the G protein-coupled orphan apelin receptor (APJ) and is an important adipokine that plays a role in the cardiovascular and immune systems and in energy, nutrient and fluid metabolism (Tatemoto *et al*., 2001). Visfatin is reported to be associated with the development of type 1 DM and its complications such as nephropathy (El Samahi *et al*., 2017), retinopathy and neuropathy (Mohammed *et al*., 2023). Nesfatin-1 and visfatin are adipokines that are promising therapeutic agents, especially for treating obesity and diabetes (Blühler, 2014). Nesfatin-1 is an adipokine derived from the NUCB2 precursor protein, which effectively controls appetite and feeding behavior with its anorexigenic effect that reduces body weight (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

[1]Department of Nutrition and Dietetics, Bayburt University, Faculty of Health Sciences, Bayburt, Türkiye.
[2]Department of Physiotherapy and Rehabilitation, Bayburt University, Faculty of Health Sciences, Bayburt, Türkiye.

Corresponding Author: Bülent BAYRAKTAR, Department of Physiotherapy and Rehabilitation, Bayburt University, Faculty of Health Sciences, Bayburt, Türkiye.
Email: bulenttbayraktar@gmail.com
Orcids: 0000-0001-6578-9805, 0000-0002-2335-9089

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to insulin receptor-1 and has a hypoglycemic effect (Radzicka *et al*., 2018). Cardiac troponin I (cTnI) is a highly specific cardiac biomarker used to evaluate myocardial damage and diseases due to its release into plasma from cardiac myocytes in cases of heart attack and cardiac damage (Wu *et al*., 1996).

Medicinal and aromatic plants are used in traditional and complementary medicine for therapeutic and preventive purposes as they contain valuable phytochemicals (Sansri vd., 2022). Moringa *oleifera* (MO), is reported to have a protective effect against STZ-induced diabetes due to its antidiabetic and antioxidant effects and hypoglycemic effects (Gupta *et al*., 2012). It is also reported to have cardioprotective effects (Alia *et al*., 2022). 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 search, no study was found examining the effects of different doses of Moringa oleifera extract (MOE) application on serum apelin, visfatin, nesfatin-1 and cTnI levels in Type 1 diabetic rats. This study investigated the effects of different doses (100, 200 and 300 mg/kg) of MOE application on serum visfatin, nesfatin-1 and cTnI levels in healthy normal rats with Type 1 DM 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. Before starting the study, the Ethics Committee's approval was obtained from the Research Centre Ethics Committee (Decision No: 2024-86-1). The research was conducted in accordance with ethical principles and rules while protecting 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). To create a DM model, STZ (55 mg/kg) solution prepared in phosphate citrate buffer (0.1 M. Ph: 4.5) was injected intraperitoneally (*i.p.*) to rats (DC, DM100, DM200 and DM300) except for control, M100, M200 and M300 groups. Those with fasting blood sugar levels ≥250 mg/dL 3 days after STZ injection were considered to have Type 1 DM. The composition of the experimental diet used in the study is shown in Table 1 and the chemical composition of *Moringa oleifera* essential oil is shown in Table 2.

The experimental protocol was designed as follows

Control group (C): Only normal saline was administered to rats *via* i.p.

M100 mg/kg group (M100): Rats were given OGRA and MOE 100 mg/kg daily for 21 days

M**200 mg/kg group (M200):** Rats were given OGRA and MOE 200 mg/kg daily for 21 days.

M300 mg/kg group (M300): Rats were given OGRA and MOE 300 mg/kg daily for 21 days.

Diabetic control group (DC): Only STZ (55 mg/kg) was administered to rats *via* i.p.

Diabetic M100 mg/kg group (DM100): STZ-induced diabetic rats were given OGRA and MOE orally at 100 mg/kg daily for 21 days.

Diabetic M200 mg/kg group (DM200): STZ-induced diabetic rats were given OGRA and MOE orally at 200 mg/kg daily for 21 days.

Diabetic M300 mg/kg group (DM300): STZ-induced diabetic rats were given OGRA and MOE 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 laboratoryand the resulting sera were separated.

Measurement of serum apelin, visfatin and cTnI level

In measuring serum apelin, nesfatin-1 and visfatin levels obtained in the study, ELISA kit type-specific for rat apelin ELISA kit (BT LAB, Cat. No SG- E1026Ra, CHINA), ELISA kit type-specific for rat visfatin Elisa Kit (SinoGeneclon, Cat. No: SG-20381, CHINA), ELISA kit type-specific for rat nesfatin-1 ELISA kit (BT LAB, Cat. No SG- E0878Ra, 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.

Statistical analysis

Statistical data analyses were performed with SPSS version 15 (IBM, USA). Normality and homogeneity tests of the data

Table 1: Composition of experimental diet.

Ingredients	g/kg
Maize	325.0
Wheat bran	202.0
Soybean meal (% 46 protein)	170.0
Sunflower meal	110.0
Alfafa flour (% 17-19)	100.0
Soybean whole	45.0
Premix[1]	25.0
Limestone	13.0
Calcium propionate	6.0
NaCl	4.0
Total	1000
Analysed composition (% dry matter, DM) (per kg)	
ME, kcal/kg*	3213.2
Dry matter	886.9
Crude protein	200.0
Ether extsract	46.58
Crude ash	90.40
Crude fiber	97.89

Table 2: Composition of *Moringa oleifera* seed essential oil.

Constituents	%
Crude ash	3.94
Crude fiber	6.85
Crude protein	31.39
Carbohydrates	18.21
Crude fat	37.30
Ether extract	1.71
Moisture content	0.60
ME, kcal/kg*	1.42

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 an important public health problem with an increasing prevalence. 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). Apelin has a regulatory role by regulating insulin sensitivity and stimulating glucose utilization in different tissues associated with diabetes (Hu *et al*., 2016). 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). It has been reported that visfatin can be used as a marker for obesity, insulin resistance, diabetes, metabolic syndrome and cardiovascular diseases (Chang *et al*., 2011). While the increase in mean serum apelin and visfatin levels due to diabetes was mostly seen in DC groups, similarly, in DM groups, mean serum apelin and visfatin levels decreased in all groups due to the addition of antioxidant-effective MOE. The most significant decrease in serum apelin and visfatin levels due to MOE supplementation in diabetes groups was determined in DM200 groups (Table 3), ($p<0.01$). Although there are limited studies examining the effect of MOE on serum apelin levels in STZ-induced diabetes rats, our results are consistent with similar research findings in literature (Shehata *et al*., 2015; Hegab, 2018). Similarly, our results regarding serum visfatin levels of MOE in STZ-induced diabetes rats are consistent with similar research results in the literature (Berndt *et al*., 2005; Tond *et al*., 2016) and differ from some studies (Akbarzadeh *et al*., 2015). We think that the decrease in serum apelin and visfatin levels due to the application of different amounts of MOE in diabetic groups due to hyperglycemia in diabetes is due to the antihyperglycemic and antidiabetic effects together with the phytochemicals in the MOE content.

Table 3: Mean serum apelin, visfatin, nesfatin-1 and cTnI values (ng/ml) and statistical comparisons (Mean±SD) of the study groups.

Diet	Apelin (ng/ml)				Visfatin (ng/ml)				Nesfatin-1 (ng/ml)				cTnI (ng/ml)			
	0 day		21 day		0 day		21 day		0 day		21 day		0 day		21 day	
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
K	0.71	0.12	0.74	0.13	37.69	0.93	39.45	1.38	2,06	0.2	2,61	,20	0.41	0.11	0.44	0.12
M100	0.73	0.11	0.77	0.7	37.19	1.31	41.65	1.03	2,11	0.31	2,83	,26	0.43	0.13	0.46	0,13
M200	0.74	0.94	0.84	0.88	37.21	0.92	42.31	2.56	2,14	0.28	3,29	,32	0.44	0,14	0.48	0,12
M300	0.74	0.13	0.80	0.14	37.20	1.61	43.76	2.63	2,06	0.22	2,61	,20	0.45	0,13	0.44	0,1
D	0.85	0.11	0.88	0.12	55.01	1.67	58.45	0.37	,96	0.20	,83	,17	0.71	0,19	0,78	0,19
DM100	0.90	0.96	0.86	0.92	54.21	1.80	51.14	0.97	,98	0.22	1,59	,27	0.7	0,17	0.66	0,15
DM200	1.01	0.93	0.91	0.11	54.13	0.84	46.38	1.48	1,25	0.12	1,93	,18	0.68	0,15	0.62	0,17
DM300	0.95	0.11	0.88	0.13	54.14	2.53	49.85	2.69	1,01	0.19	1,63	,18	0.69	0,14	0.65	0,1
Diet	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01		<0.01		<0.01	
Time	0.01				0.110				0.01				0.01			
Diet×Time	<0.01				<0.01				<0.01				<0.01			

*cTnI: Cardiac Troponin I, Control (C), M100 (MOE 100 mg/kg group given with oral gavage route of administration (OGRA), J200 (MOE (Jackfruit Pulp Extract) 200 mg/kg group given with OGRA), M300 (MOE). 300 mg/kg group given with OGRA); STZ 55 mg/kg intraperitoneal (i.p.) administered group, DM100 (D+100 mg/kg MOE), DM200 (D + 200 mg/kg MOE), DM300 (D). + 300 mg/kg MOE). The mean difference was considered significant at the 0.05 level.

Nesfatin-1 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). 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 DM200 groups (Table 3), ($p<0.01$). 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 MOE, 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; Algül *et al*., 2023). We think that the reason for this situation is due to the antihyperglycemic and antidiabetic effects of MOE.

DM has an active role in the development of cardiovascular diseases. The highest mean serum cTnI level was determined in the DC 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 DR200 groups due to the addition of different amounts of MOE, 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; Al-Rasheed *et al*., 2017; Taşci Çelikel vd., 2024). Although studies examining the effect of MOE, which is 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 MOE.

CONCLUSION

Apelin, because of its role in insulin sensitivity and glucose homeostasis, visfatin, because of its proinflammatory and immunomodulatory properties and its role in the development of DM and its complications and nesfatin-1, because of its role in regulating food intake control and being a specific cardiac damage marker, cTnI, are thought to be useful in examining their levels in diabetes management. As a result, it was concluded that MOE, which has been reported to have antidiabetic and antihyperglycemic effects, may be safe and beneficial when applied 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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