

RESEARCH ARTICLE

Effect of *Zingiber officinale* and *Nigella sativa* on Streptozotocin-Diabetic Rats with Reference to Biochemical and Hematological Studies

Hosny A. E. Ibrahim¹, Mohamed A. Hashem^{2*}, Nagah E. Mohamed¹ and Aliaa A. Abd El-Rahman³

¹Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt

²Clinical Pathology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt

³Veterinary Directorate, Zagazig, Sharkia Province, Egypt.

Article History: Received: 04/06/2020 Received in revised form: 06/07/2020 Accepted: 27/07/2020

Abstract

This study was aimed to assess the potential ameliorative effect of the ethanolic extract of *Zingiber officinale* (*Z. officinale*; ginger) and *Nigella sativa* (*N. sativa*; black seed) on streptozotocin (STZ)-diabetic rats. Fifty albino rats of Wistar strain were randomly divided into five equal groups. Group 1 received saline orally (a control group). Groups 2 -5 were experimentally exposed to diabetes via intraperitoneal (i.p.) injection of STZ (55 mg/kg BW.). The 2nd group was left without treatment as diabetic non-treated control, while the 3rd to 5th groups were orally treated with metformin (100mg/kg BW), ethanolic extract of ginger (200mg/kg BW.) and *N. sativa* (300mg/kg BW.), respectively for 21 consecutive days. Blood and pancreatic tissue samples were collected at the end of the experiment for biochemical analysis. The results revealed that blood glucose, fructosamine and insulin levels were improved following treatment by metformin (99.00±4.76, 198.69±5.25 and 29.82±2.35, respectively), and ethanol extract of ginger (105.20±4.87, 317.48±17.79 and 13.64±0.72, respectively). Meanwhile, *N. sativa* extract produced insignificant decrease in glucose level (201.60±14.91) and significant improvement in serum fructosamine and insulin levels (273.20±6.39 and 21.65±1.78) if matched with the diabetic control group on the 3rd week of the experiment. Treating of diabetic rats with metformin and *N. sativa* extract elicited a significant increase in blood RBCs count (6.21±0.170 and 5.63±0.135), Hb concentration (12.96±0.229 and 12.00±0.141), PCV% (46.40±1.077 and 74.72±1.085), tissue catalase (0.32 ±0.012 and 0.25±0.009) and superoxide dismutase activities (19.44±2.16 and 12.77±0.914), respectively when compared with the diabetic group. However, administration with ginger extract produced variable changes in the erythrogram and leukogram. This study provided that *Z. officinale* and *N. sativa* extracts have significant effects on some biochemical and hematological assays, as compared with metformin known as standard antidiabetic drug. Consequently, the herbal extracts under current inquiry could have a role in alleviating the risk of some chronic complications of diabetes.

Key words: Metformin, Ginger, *Nigella sativa*, Nicotinamide, Diabetes.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders due to defect in insulin secretion, action or both which leading to a chronic hyperglycemia. The prevalence of DM is raising worldwide [1]. It is commonly associated with elevated oxidative damage [2]. In addition, DM is considered a significant risk factor for cardiovascular diseases, including

ischaemic heart disease, cerebral stroke and peripheral artery disease, resulting in increased mortality rates for diabetes patients [3]. Recently, administration of nicotinamide (NA) in a suitable dose before streptozotocin (STZ) was used for experimental induction of type 2 diabetes in rats. Nicotinamide administration resulted in partial protection of pancreatic β -

*Corresponding author e-mail: (mhashem.vet@gmail.com), Clinical Pathology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Zagazig, Egypt

cells from necrosis resulted from STZ injection [4].

One of the anti-diabetic medicines belonging to the oral antihyperglycemic biguanide class is metformin [5]. However, other studies stated some side effects of metformin therapy such as lactic acidosis [6], diabetic cases [7], high incidence of gastrointestinal side effects [8], and higher homocysteine levels [9].

Hundreds of conventional folk medicines have shown potential for diabetes care with less tolerability and side effects. *Zingiber officinale* (*Z. officinale*; ginger) has been reported to produce various pharmacological effects such as anti-emetic, antiulcer, antioxidant, anxiolytic, anti-inflammatory and antipyretic activities [10]. It has also reported to reduce cholesterol levels and atherogenesis in rabbits fed with high cholesterol diets [11]. *Nigella sativa* (*N. sativa*; black seed) is a medical plant used for treating many diseases such as rheumatism. It has anti-inflammatory, immunomodulatory, antidiabetic and anti-tumor activities [12,13]. The essential oil of *N. sativa* exhibits hypoglycemic and bronchodilator properties [14].

Our work was designed to explore the possibility of ameliorating diabetic negative impacts after administration of *Z. officinale* (ginger) and *N. sativa* (black seed) extracts as compared with metformin, a reference drug, in STZ diabetic rats via biochemical and hematological investigations.

Materials and Methods

Chemicals

Streptozotocin (STZ) and nicotinamide (NA) were obtained from Sigma Company (USA) and was used for induction of the diabetes.

Metformin preparation

Metformin hydrochloride (Glucophage®) hydrochloride, a product of Minapharma Co., Ltd., Egypt). It was administrated orally to diabetic rats at a dose of 100 mg/kg body weight (BW.)/day [15] by gastric tube after dissolving in saline or sodium chloride (0.9%) for 3 weeks.

Plants and extract preparation

Fresh ginger roots and black seeds were obtained from a local herbal medicine shop in Zagazig city, Egypt. The air-dried plants were finely powdered in an electrical grinder and stored at 5°C until further use. Ethanol extracts were prepared by soaking one kilogram of

ginger, or black seed powder in 2 liters of 95% ethyl alcohol under shaking for 5 days and then kept in a refrigerator [13]. The mixture was filtered by Whatman filter paper no.1 (El-Gomhouria Co., Zagazig, Sharkia Governorate, Egypt). The filtrate was evaporated to dryness under reduced pressure using a Soxhlet evaporator at 40°C for removal of alcohol. The yielding residue (about 20-25 g) was kept in tightly closed glass containers and stored at -20 °C before use.

Experimental animals

Fifty healthy adult male Wistar rats, weighing 200–250g, were obtained from Laboratory Animal Unit, Faculty of Veterinary Medicine, Zagazig University, Egypt. These rats were resided in the prepared metal cages under perfect hygienic environment, given balanced feed with water *ad-libitum* and observed for 7 days before starting the experimental procedures. The protocol of our study was in synchronization with the ethical regulations care and use of laboratory animals according to the guidelines of the Animal Welfare and Research Ethics Committee at Faculty of Veterinary Medicine, Zagazig University, Egypt.

Experimental design

A total of 50 rats were haphazardly billed into 5 equal groups. Ten apparently healthy rats were treated with normal saline, used as a negative control (G1). The other 40 rats (G 2-5) were subjected to fasting for 12 h, and diabetes mellitus type II was induced through a single intraperitoneal (i.p.) injection of STZ (55 mg/kg BW.) 15 minutes after nicotinamide (NA; 110 mg/kg $\frac{1}{2}$, i.p.) administration dissolved in normal saline [16,17]. The animals were orally given glucose solution (5%, w/v) on the 1st day after STZ administration to starve off hypoglycemic shock. Two days after STZ injection, the fasting blood glucose level was determined in all the experimental rats and the rats with blood glucose \geq 250 mg/dL were intended as diabetic animals [18,19] and incorporated in the experiment. All STZ-NA injected rats were diabetic and then randomly divided into 4 groups, each of 10 rats: G2 was left as diabetic non treated, G3 was treated with metformin at a dose of 100 mg/kg b.wt., G4 and G5 were treated with ethanol extract of ginger (200mg/kg BW.) [11] and *N. sativa* (300mg/kg BW.) [20], respectively.

The animals were treated orally with stomach tube on day 3 after injection of STZ, and that was considered as day 1 for treatment and continued for 21 days. The mortality rates were then recorded.

Sampling

During the experiment, blood samples (one drop) were obtained from retro-orbital venous plexus of each rat to estimate the fasting blood glucose level on 2nd day, 4th day, 1st week, 2nd weeks and 3rd week during the experimental period, using a portable glucometer (Accu – sure, Roche Diagnostics, USA). On completion of the experiment (21 days), rats were starved overnight for 12h and sacrificed under light ether anesthesia [21]. Two separate blood samples were collected from each rat. The first blood sample (0.5mL) was collected in EDTA tube as anticoagulant for hematological studies. The second blood sample (2mL) was taken in a test tube without EDTA which placed in a slant position and left to clot at room temperature for serum collection after centrifugation at 3000 r.p.m. for 10 minutes. The serum sample was kept frozen at -20°C until biochemical analysis [22].

Tissue samples from pancreas of each rat were quickly excised and trimmed from surrounding tissue, washed and diluted with 0.9 % NaCl solution. They were then blotted over a piece of filter paper. Half gram of each tissue was perfused with a 50 mM sodium phosphate buffer saline (100 mM Na₂HPO₄/ NaH₂PO₄) (pH 7.4) in an ice-containing medium, containing 0.1 mM EDTA to remove any red blood cells and clots. Then tissues homogenates were prepared by homogenizing pancreatic tissue in 5–10 mL cold buffer per gram tissue and centrifuged at 3000 r.p.m. for 30 min. The resulting supernatant was transferred into Eppendorf tubes, and preserved at -80°C in liquid nitrogen until used for antioxidant /oxidant assays [23].

Biochemical Studies

The serum samples were assayed for the diabetic markers, glucose, fructosamine and insulin. Antioxidants/ oxidant assays [catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA)] were determined in the pancreatic tissues according to the instructions of the diagnostic kits purchased from Biodiagnostic Co., Cairo, Egypt.

Hematological Studies

Erythrogram including RBCs count, concentration of hemoglobin (Hb), packed cell volume (PCV), and blood indices (MCV and MCHC) as well as the leukogram including the total and differential leukocytic counts were determined [24] via an automatic cell counter (hematology analyzer, Sysmex IV2000, UK).

Statistical analysis

The obtained results from this study were articulated as mean values ± standard error (SE). The statistical significance between different groups was done by one-way ANOVA, followed by Dunnett's comparison test, with $P \leq 0.05$ being regarded as significant [25]. The highest value was represented with the letter (a) using the computer program (SPSS 16.0 for Windows).

Results

Effects on mortality rate and diabetic markers

Mortality rate was 30% (N=3) rats in STZ-injected group (G2), while administration of metformin or plants extract caused a decrease in mortality rate to 10% (one rat from each group) throughout the experimental periods.

As shown in Table 1, the blood glucose levels were statistically elevated in STZ- non treated rats (451.00±54.98, 451.00±14.65, 264.40±28.38, 350.00±35.59 and 232.40±22.89) when compared to control ones (122.40±9.07, 117.40±9.79, 112.40±9.45, 104.60±1.86 and 105.20 ± 2.96) at 2nd day, 4th day, 1st, 2nd and 3rd week post- injection. Supplement of STZ-injected rats with metformin by a single daily dose (100 mg/kg BW.) for 21days showed a significant decrease in the blood glucose levels (278.80±20.30, 181.00±19.44 and 99.00±4.76) on 4th day, 2nd and 3rd week post-induction of diabetes, in comparison with diabetic group. However, the blood glucose level (389.20±16.67 and 196.60±12.49) was insignificantly decrease on 2nd day and 1st week after induction of diabetes. In addition, ethanolic extract-treated rats (G4) illustrated a diminution in the blood glucose concentrations (309.00±11.98, 131.00 ±3.11, 118.20 ±8.73 and 105.20±4.87) on 2nd day, 1st, 2nd and 3rd week post administration, matched with the second group. However, blood glucose level (418.20±26.06, 383.40±25.37, 326.40±29.45, 309.00±28.62 and 201.60±14.91) on 2nd day, 4th day, 1st, 2nd and 3rd week post-administration was insignificantly decreased in *N. sativa*- treated group, in comparison with diabetic control.

Table 1: Effect of oral administration of metformin (100mg/kg b.wt.), ginger (200mg/kg BW.) or *N. sativa* (300mg/kg b.wt.) on blood glucose levels in STZ- induced diabetic rats. (Mean ± SE) (n=5)

Groups	Blood glucose level (mg/dL)				
	2 nd day	4 th day	1 week	2 weeks	3 weeks
1 (Normal control)	122.40 ± 9.07 ^c	117.40 ± 9.79 ^c	112.40 ± 9.45 ^c	104.60 ± 1.86 ^b	105.20 ± 2.96 ^b
2 (Diabetic control)	451.00 ± 54.98 ^a	451.00 ± 14.65 ^a	264.40 ± 28.38 ^{ab}	350.00 ± 35.59 ^a	232.40 ± 22.89 ^a
3 (Diabetic + metformin)	389.20 ± 16.67 ^{ab}	278.80 ± 20.30 ^b	196.60 ± 12.49 ^{bc}	181.00 ± 19.44 ^b	99.00 ± 4.76 ^b
4 (Diabetic + ginger)	309.00 ± 11.98 ^b	344.40 ± 18.25 ^{ab}	131.00 ± 3.11 ^c	118.20 ± 8.73 ^b	105.20 ± 4.87 ^b
5 (Diabetic + <i>N. sativa</i>)	418.20 ± 26.06 ^a	383.40 ± 25.37 ^{ab}	326.40 ± 29.45 ^a	309.00 ± 28.62 ^a	201.60 ± 14.91 ^a

Mean within the same column in each category carrying different superscripts are significant at $P < 0.05$.

Effects of treatments by metformin, and ethanolic extract of ginger or *N. sativa* on serum fructosamine and insulin levels in the diabetic animals (Table 2). A significant increase and decrease in the serum levels of fructosamine and insulin (370.24 ± 1.44, and 5.63 ± 0.46) were observed in diabetic rats (G2) compared with control group (G1; 101.37 ± 1.82 and 47.61 ± 0.79), respectively. Medication of diabetic rats with metformin, ginger or *N. sativa* ethanolic extract exhibited a significant decrease in fructosamine level when compared with diabetic group. The improvement in fructosamine level was better in the metformin- treated group than those treated with either ginger or *N. sativa*. However, the level of serum insulin was statistically increased after 21 days in rats of groups (G3-5).

Effect on pancreatic antioxidant and oxidant parameters

The levels of antioxidant enzymes activity (CAT and SOD) and lipid peroxidation marker

(MDA) in the pancreatic tissue were summarized in Table 3. Streptozotocin-induced diabetes (G2) significantly decreased tissue CAT (0.09 ± 0.010) and SOD (2.02 ± 0.295) levels and significantly ($P < 0.05$) increased MDA (193.80 ± 1.39) levels compared with those of control group (0.49 ± 0.023, 36.04 ± 0.317 and 84.80 ± 1.41 for CAT, SOD, and MDA, respectively) on 21st day after STZ injection. Tissue CAT and SOD levels were significantly increased and restored towards normal after 21 days supplementation of diabetic rats with metformin, ethanolic extract of ginger or *N. sativa*. However, tissue MDA was significantly decreased compared with that in untreated diabetic group. Treatment results with metformin were better than those with plants extract.

Table 2: Effect of oral administration of metformin (100mg/kg BW.), ginger (200mg/kg BW) or *N. sativa* (300mg/kg b.wt.) on serum fructosamine and insulin levels in STZ- induced diabetic rats. (Mean ± SE) (n=5)

Groups	Parameters	Fructosamine (µmol/L)	Insulin (µU/mL)
1 (Normal control)		101.37 ± 1.82 ^e	47.61 ± 0.79 ^a
2 (Diabetic control)		370.24 ± 1.44 ^a	5.63 ± 0.46 ^e
3 (Diabetic + metformin)		198.69 ± 5.25 ^d	29.82 ± 2.35 ^b
4 (Diabetic + ginger)		317.48 ± 17.79 ^b	13.64 ± 0.72 ^d
5 (Diabetic + <i>N. sativa</i>)		273.20 ± 6.39 ^c	21.65 ± 1.78 ^c

Mean within the same column in each category carrying different superscripts are significant at $P < 0.05$.

Table 3. Effect of oral administration of metformin (100mg/kg BW.), ginger (200mg/kg BW.) or *N. sativa* (300mg/kg b.wt.) on pancreatic CAT, SOD and MDA tissue levels in STZ- induced diabetic rats. (Mean \pm SE) (n=5)

Groups	Parameters	Antioxidants / Oxidative Status		
		CAT (Umol/mg protein)	SOD (U/mg protein)	MDA (nmol/mg protein)
1 (Normal control)		0.49 \pm 0.023 ^a	36.04 \pm 0.317 ^a	84.80 \pm 1.41 ^d
2 (Diabetic control)		0.09 \pm 0.010 ^e	2.02 \pm 0.295 ^e	193.80 \pm 1.39 ^a
3 (Diabetic + metformin)		0.32 \pm 0.012 ^b	19.44 \pm 2.16 ^b	132.20 \pm 1.98 ^c
4 (Diabetic + ginger)		0.16 \pm 0.008 ^d	7.55 \pm 0.531 ^d	171.20 \pm 2.07 ^b
5 (Diabetic + <i>N. sativa</i>)		0.25 \pm 0.009 ^c	12.77 \pm 0.914 ^c	171.20 \pm 2.08 ^b

Mean within the same column in each category carrying different superscripts are significant at $P < 0.05$.

Effect on hematological parameters

The present study revealed that animals with DM induced by i.p. injection of STZ revealed a significant decline in RBCs count, Hb concentration, PCV% and MCHC% when compared with the control group (G1), with a significant augment in the MCV values indicating macrocytic hypochromic anemia (Table 4). Diabetic rats treated with metformin (G3) and *N. sativa* extract (G5) elicited a significant improvement in the erythrocyte parameters compared with diabetic group (G2).

Concerning the leukogram (Table 5), rats with DM displayed a significant raise in total leukocyte count (TLC, 11.83 \pm 0.287), neutrophil (8.35 \pm 0.118) and monocyte (2.23 \pm 0.032) counts as well as a significant decrease in lymphocyte (1.12 \pm 0.189) and eosinophil (0.13 \pm 0.144) counts compared with that of the control group (8.69 \pm 0.218,

5.14 \pm 0.230, 2.26 \pm 0.049, 1.08 \pm 0.020 and 0.21 \pm 0.010, respectively). Diabetic rats treated with metformin and *N. sativa* demonstrated a significant decrease in TLC (9.76 \pm 0.23 and 9.76 \pm 0.43), neutrophil (4.50 \pm 0.11 and 4.97 \pm 0.236) and monocyte (0.88 \pm 0.205 and 1.17 \pm 0.101) counts, respectively, while lymphocyte (3.72 \pm 0.099 and 3.14 \pm 0.262) and eosinophil (0.66 \pm 0.021 and 0.48 \pm 0.032) counts exhibited a raise when compared with diabetic group (G2). Administration of ginger extract produced non-significant change in TLC (10.73 \pm 0.223), whereas neutrophil (6.44 \pm 0.099) and monocyte (1.80 \pm 0.034) counts were significantly decreased, with a significant increase in lymphocyte count (2.20 \pm 0.131) and non-significant increase in eosinophil count (0.29 \pm 0.017) when compared with G2.

Table 4. Effect of oral administration of metformin (100 mg/kg BW), ginger (200mg/kg BW) or *N. sativa* (300mg/kg b.wt) on erythrogram in STZ- induced diabetic rats. (Mean \pm SE) (n=5)

Groups	Parameters	RBCs ($\times 10^6/\text{mm}^3$)	Hb (g/dL)	PCV (%)	MCV (fl)	MCHC (%)
1 (Normal control)		8.38 \pm 0.056 ^a	17.10 \pm 0.100 ^a	53.00 \pm 0.707 ^a	63.25 \pm 0.487 ^c	32.26 \pm 0.422 ^a
2 (Diabetic control)		4.20 \pm 0.215 ^e	8.46 \pm 0.172 ^d	34.80 \pm 1.985 ^d	82.86 \pm 1.154 ^a	24.31 \pm 1.302 ^c
3 (Diabetic + metformin)		6.21 \pm 0.170 ^b	12.96 \pm 0.229 ^c	46.40 \pm 1.077 ^b	74.72 \pm 1.085 ^b	27.93 \pm 0.653 ^b
4 (Diabetic + ginger)		4.78 \pm 0.077 ^{de}	10.38 \pm 0.106 ^d	39.00 \pm 1.516 ^c	81.59 \pm 4.400 ^a	26.62 \pm 1.098 ^{bc}
5 (Diabetic + <i>N. sativa</i>)		5.63 \pm 0.135 ^c	12.00 \pm 0.141 ^c	41.00 \pm 0.707 ^c	72.82 \pm 2.462 ^b	29.27 \pm 0.349 ^b

Mean within the same column in each category carrying different superscripts are significant at $P < 0.05$.

Table 5. Effect of oral administration of metformin (100 mg/kg b.wt), ginger (200mg/kg BW) or *N. sativa* (300mg/kg BW) on leukogram in STZ- induced diabetic rats. (Mean \pm SE) (n=5)

Groups	Parameters	Total leukocyte count	Leukogram ($\times 10^3/\mu\text{L}$)			
			Lymphocyte	Neutrophil	Eosinophil	Monocyte
1 (Normal control)		8.69 \pm 0.218 ^c	5.14 \pm 0.230 ^a	2.26 \pm 0.049 ^d	1.08 \pm 0.020 ^a	0.21 \pm 0.010 ^e
2 (Diabetic control)		11.83 \pm 0.287 ^a	1.12 \pm 0.189 ^c	8.35 \pm 0.118 ^a	0.13 \pm 0.144 ^d	2.23 \pm 0.032 ^a
3 (Diabetic + metformin)		9.76 \pm 0.230 ^b	3.72 \pm 0.099 ^b	4.50 \pm 0.110 ^c	0.66 \pm 0.021 ^b	0.88 \pm 0.205 ^d
4 (Diabetic + ginger)		10.73 \pm 0.223 ^a	2.20 \pm 0.131 ^b	6.44 \pm 0.099 ^b	0.29 \pm 0.017 ^d	1.80 \pm 0.034 ^b
5 (Diabetic + <i>N. sativa</i>)		9.76 \pm 0.430 ^b	3.14 \pm 0.262 ^b	4.97 \pm 0.236 ^c	0.48 \pm 0.032 ^c	1.17 \pm 0.101 ^c

Mean within the same column in each category carrying different superscripts are significant at $P < 0.05$.

Discussion

Diabetes mellitus is one of the world's most common neurological, endocrine and metabolic illnesses. It is caused by a defect in insulin secretion, action or both and characterized by hyperglycemia and metabolic disturbances [26,27].

In this study, type 2 diabetes was induced experimentally by intraperitoneal injections of STZ at 55 mg / kg and nicotinamide (NA) at 110 mg/kg. The diabetogenic effect of STZ-NA was previously reported [4].

Although a wide range of glucose lowering drugs are currently on the market, due to drug resistance, side effects and toxicity, they have not gained much importance. The use of plant-based drugs is now gaining an importance due to its safe to use and non-toxic nature.

In the present research, STZ injection was found to be capable of rising blood glucose levels on the 2nd day post- administration with a mortality rate of 30%, which could be due to pancreatic islet destruction and β -cell death. The deaths may be associated with toxicity of STZ, infection, malnutrition, suffocation of lymphatic circulation, and changes in environmental and climate conditions [28]. In addition, a significant elevation in serum fructosamine and declined insulin values were observed in rats of G2. Streptozotocin toxin causes pancreatic cells to die from alkylation of DNA, resulting in decreased DNA synthesis and insulin release. Moreover, STZ enters the pancreatic β -cells by glucose protein-2 transporter and disrupts the balance between antioxidant and oxidant systems damaging the insulin-producing islet β -cells and inducing the progression of diabetes [3]. A different

literature confirmed STZ caused β -cell islet damage, which in turn elevated the glucose levels and reduced the insulin levels [29]. The serum fructosamine was significantly higher in STZ- induced diabetic rats (370.24 \pm 1.44) than in normal rats (101.37 \pm 1.82). Fructosamine is a stable product, determined after three weeks of DM induction, formed as result of protein modification by glucose and its serum level is reported to increase in diabetes [30]. The observed significantly elevated fructosamine in the serum of the diabetic rats was similar to what was previously reported [31,32]. Many literatures has followed the results of this study [17, 33-35].

Metformin, ethanolic extracts of ginger or *N. sativa* supplementation displayed a decrease in blood glucose and serum fructosamine levels, with a significant augment in serum insulin level matching with STZ- diabetic rats. However, blood glucose did not decrease to normal level as in diabetic rats treated with metformin or ginger. Therefore, this suggests that these hypoglycemic drug in combination with herbal plants produced better glycemic control. A broadly antihyperglycemic drug recommended for type 2 diabetes is metformin, as it reduces blood glucose without raising insulin secretion, but it is considered an insulin sensitizer [9]. Ginger's hypoglycemic activity may be due to actions involving serotonin receptors, an increase in pancreatic insulin secretion from β -cells or the release of bound insulin [36], or promotion of glucose clearances in insulin-responsive peripheral tissues [37]. Finally, the significantly increased serum insulin, and decreased glucose or fructosamine levels in diabetic rats

supplemented with ginger and *N. sativa* extract indicating their antidiabetic and hypoglycemic effects. The data was also supported by the previous reports [20,38,39]. *N. sativa* extract administration insignificantly decrease the blood glucose levels, however other study showed that oral treatment with *N. sativa* ethanolic extract produced a significant decline in the elevated sugar concentration; with an enhanced the antioxidant status of STZ- induced diabetes in rats [40]. The anti-diabetic effect of *N. sativa* possibly clarified by insulin-like stimulation of glucose uptake by adipose tissue or could be due to amelioration of β -cell ultrastructure, thus leading to increased insulin levels [20].

Oxidative stress plays a part in causing diabetes, and it has been shown that antioxidants play a role in alleviating diabetes [21]

In this study, a reduction in the activities of CAT (0.09 ± 0.010) and SOD (2.02 ± 0.295) enzymes with a significant increase in MDA (193.80 ± 1.39) levels were seen in the pancreatic tissue of STZ-induced diabetic rats, in comparison with those of control group (0.49 ± 0.023 , 36.04 ± 0.317 and 84.80 ± 1.41), respectively. Hyperglycaemia in diabetes results in free radicals generation. It weakens the body's defense mechanisms, leading to cellular disruption, oxidative damage to the membranes and increased lipid peroxidation susceptibility [41]. The decreased antioxidants activities in pancreas during diabetes may be due to production of ROS or suggest their excessive utilization in attenuating free radicals generated during the metabolism of STZ [42,43]. The present findings are in consistent with earlier observations [3,17, 44-46]. Similarly, the rates of oxidative stress in the pancreas expressed by rates of the lipid peroxidation product (MDA) increased while the levels of anti-oxidant enzymes (SOD, CAT and GPx) in the pancreas decreased in streptozotocin-nicotinamide induced male diabetic rats [16].

Treatment of rats with metformin, ethanolic extracts of ginger or *N. sativa* declined the diabetes-induced increases in pancreatic MDA and increased tissue SOD and CAT. The same

findings were obtained in STZ-diabetic rats treated with metformin [17]. The antioxidant potency of ginger has been attributed to gingerols preventing ROS production [47]. The increase in antioxidants activities and diminution of MDA level were observed in ginger supplemented rats [48-50]. The antioxidant effect of *N. sativa* extract may be due to counteracting the injury generated during diabetes via the free radicals [41], or due to their contents of phenolics and flavonoids that have scavenging effect on the free radicals [13, 43, 49]. In addition, *N. Sativa* therapy exerts a protective therapeutic impact in diabetes by decreasing morphological changes and maintaining the integrity of pancreatic beta-cells, thereby indicating that it could be clinically useful to defend beta-cells against oxidative stress [50].

Hematological parameters usually reflect the animal physiological responsiveness to its internal and external surroundings, and these parameters being an actual tool for monitoring the animal physiological or pathophysiological status [51].

Erythrogram assessed in the present work following streptozotocin-nicotinamide (STZ-NA) administration in rats revealed a significant decrease in the count of RBCs, Hb concentration and PCV%, in association with a significant high and low values of MCV and MCHC, respectively indicating a macrocytic hypochromic anemia. This type of anemia may be attributed to hemolysis of RBCs as a result of STZ toxin and is a common pathophysiology associated with diabetes mellitus [52-56]. This agrees with existing literature showed a significant decrease in RBCs count, hematocrit and hemoglobin levels following STZ administration [57-59]. Numerous studies documented this anemia to increase in lipid peroxidation of the cell membrane of RBCs, which could elevate the rigidity of plasma membrane, impair RBCs deformability, and reduce erythrocytic survival [60]. Other reports declared that the diabetic anemia was due to increased non-enzymatic glycosylation of RBC membrane proteins, associated with hyperglycemia [61], and this caused increased development of lipid

peroxides that could cause damage to the membrane of RBCs, hemolysis of RBCs and subsequently decrease in the count of RBCs and hemoglobin levels [59,62].

Treatment with either metformin or the ginger and *N. sativa* or extracts resulted in the amelioration of the above-mentioned features induced by streptozotocin/nicotinamide. The plant extracts may contain some phytochemicals which may promote the formation or secretion of erythropoietin in the animals' stem cells to produce RBCs, and this enhancement in RBCs synthesis leading to an improvement in the MCH and MCHC levels [63]. The improving effect of ginger, *N. sativa*, and metformin administrations were parallel with reported results [53- 56]. This positive effect of extract administration of ginger and *N. sativa* may be related to their anti-oxidant activities in scavenging free radicals [64]. The increase in RBC count of ginger – treated diabetic rats in comparison with untreated diabetic group can be attributed to lower lipid peroxide levels in the RBC membrane resulting in reduced RBC susceptibility to hemolysis [65]. It was stated that Zingerone (*Zingiber officinale*) produced their effect by decreasing the high concentration of glucose in treated diabetic rats and this suggest that Zingerone stimulates RBC erythrocyte synthesis (erythropoiesis) and concentration in anemic diabetic rats [66]. Moreover, ginger possesses antioxidant properties and help to stabilize the RBC membrane by binding to RBC membrane-component proteins and carbohydrates, thereby preventing the breakdown of the RBC membrane and antagonizing the anemic impact of STZ. On other hand, the hematological findings in treated animals with aqueous extract of *N. sativa*, garlic, fenugreek individual and its combination at different doses in STZ-NA-induced diabetic rats revealed non-significant change in erythrocyte parameters [67].

Regarding the leukogram results in the present work, diabetic rats showed a significant leukocytosis, neutrophilia and monocytosis with lymphopenia and eosinopenia when compared with control group (G1). This demonstrates weakness of

hematological functions in the diabetic rats and can be due to protective response against STZ-induced diabetes or may be related to stress conditions due to intraperitoneal injection of chemicals (STZ-NA). The leukocytosis may be due to the increased hemopoietic activity as a result of the hemolysis of RBCs in diabetic rats [57]. Stress leukocytosis associated with diabetic animals was confirmed by previous studies [55, 56, 68]. Also, leukocytosis in both of the polymorphonuclears and mononuclears count reported in diabetic rats group could be induced by glycation end products [60]. Glucose interaction with amino protein groups, derivatives called "Advanced Glycation End Products (AGE)" has been shown to enhance some angiogenic and inflammatory cytokine expression including vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF- α) and interleukin-8 (IL-8), and this process could be the reason for leukocyte activation and growth. Our results were in partial agreement with published reports [52,53]. The latter authors [53] stated that diabetes in rats caused by alloxan had a substantially increased WBC count and their differentials compared to normal rats, that may be ascribed to a defense reaction against alloxan-induced diabetes. The neutrophilia and monocytosis may be due to the presence of these cells in the phagocytic cycle against various antigens. Neutrophils have been called the body's first line of defense against infections. This body's defense mechanism was disturbed by the disturbed neutrophil function in diabetes [69]. Lymphopenia and eosinopenia in the DM group may be as a response to stressful condition after antigen (STZ) injection [57]. Moreover, lymphopenia may be attributable to the development of specific or non-specific antibodies to various antigens, as lymphocytes are responsible for achieving the body's defense mechanism [22,24, 57].

Medication of diabetic rats with metformin and *N. sativa* displayed a significant improvement in the total and differential leukocyte counts when compared with diabetic group. The metformin significantly improved

the total WBCs count and their differentials as compared with plant extracts- treated groups. On other hand, the total WBCs count change in type 2 DM patients after *N. sativa* oil treatment was not significant [70]. The difference may be related to different treatment and diabetes model. Ginger extract administration produced no statistical variation in TLC, with a significant neutropenia, monopenia and lymphocytosis when compared with diabetic rats (G2). Other studies showed that treatment with *Zingiber officinale* (400 mg/kg b.wt.) increased WBC to control levels in diabetic rats [66], this indicates that *Zingiber officinale* could also strengthen the body's defense mechanism against diabetic rat infections.

Conclusion

The results of the current study can provide a further proof for the ameliorating the effect of ginger or *N. sativa* extract on diabetic markers, with augmentation of pancreatic antioxidants and decrease of lipid peroxidation in case of diabetes, with some variations between the two plants. Therefore, we can provide a plan to utilize ginger or *N. sativa* as an adjuvant and/or complementary support in therapy of T2DM.

Conflict of interest

The author declares that there is no conflict of interest.

References

- [1] Njolstad, P.R.; Sagen, J.V.; Bjorkhaug, L.; Odili, S.; Shehadeh, N.; Bakry, D.; Sarici, S.U.; Alpay, F.; Molnes, J.; Molven, A.; Sovik, O. and Matschinsky, F.M. (2003): Permanent neonatal diabetes caused by glucokinase deficiency: inborn error of the glucose-insulin signaling pathway. *Diabetes*, 52(11):2854-2860.
- [2] [2] Seet, R.C.S.; Lee, C.J.; Lim, E.C.H.; Quek, A.M.L.; Huang, H.; Huang, S.H.; Looi, W.F.; Long, L.H. and Halliwell, B. (2011): Oral zinc supplementation does not improve oxidative stress or vascular function in patients with type 2 diabetes with normal zinc levels. *Atherosclerosis*, 219(1): 231–239.
- [3] Seedeve, P.; Ganesan, A. R.; Moovendhan, M.; Mohan, K.; Sivasankar, G.P.; Loganathan, S.; Vairamani, S. and Shanmugam, A. (2020): Anti-diabetic activity of crude polysaccharide and rhamnase enriched polysaccharide from *G. lithophila* on Streptozotocin (STZ)-induced in Wistar rats. *Sci Rep*, 10(1):556.
- [4] Lee, J.; Yee, S.T.; Kim, J.J.; Choi, M.S.; Kwon, E.Y.; Seo, K.I. and Lee, M.K. (2010): Ursolic acid ameliorates thymic atrophy and hyperglycemia in streptozotocin-nicotinamide-induced diabetic mice. *Chem Biol Interact*, 188 (3):635-642.
- [5] Bell, P.M. and Hadden, D.R. (1997): Metformin. *Endocrin Metab Clin North Am*, 26 (3):523-537.
- [6] Brassoe, R.; Elkmann, T.; Hempel, M.; and Gravholt, C.H. (2005): Fulminant lactic acidosis in two patients with type 2 diabetes treated with metformin. *Diabet Med*, 22 (10) : 1451-1453.
- [7] Ting, R.; Szeto, C.; Szeto, C.C.; Chan, M.; Ma, K. and Chow, K. (2006): Risk factors of vitamin B(12) deficiency in patients receiving metformin. *Arch Intern Med*, 66(18):1975-1979.
- [8] Hoffmann, I.S.; Roa, M.; Torrico, F. and Cubedide, L.X. (2003): Ondansetron and metformin induced gastrointestinal side effects. *Am J Ther*, 10(6):447-451.
- [9] Wulffel , M.G.; Kooy, A.; Lehert, P.; Bets, D.; Ogterop, J.C.; Borgerder, B.B.; Donker, M.A.J. and Stehouwer, C.D. (2003): Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: A Randomized, Placebo-Controlled Trial. *J Intern Med*, 254(5) :455 - 463 .
- [10] Vishwakarma, S.L.; Pal, S.C.; Kasture, V.S. and Kasture, S.B. (2002): Anxiolytic and antiemetic activity of *Zingiber officinale*. *Phytother Res*, 16(7): 621-626.
- [11] Bhandari, U.; Sharma, J.N. and Zafar, R. (1998): The protective action of ethanolic *Z. officinale* (*Zingiber officinale*) extract in cholesterol fed rabbits. *J Ethnopharmacol*, 61(2): 167-171.
- [12] Houghton, P.J.; Zarka, R.; De lass Herus, B. and Howlt, J.R. (1995): Fixed oil of *Nigella sativa* and derived thymoquinone inhibit

- eicosanoid generation in leukocytes and membrane lipid peroxidation. *Planta Med*, 61(1): 33-36.
- [13] El Rabey, H.A.; Al-Seeni, M. N. and Bakhshwain, A.S. (2017): The antidiabetic Activity of *Nigella sativa* and propolis on streptozotocin-induced diabetes and diabetic nephropathy in male rats. *Evid Based Complement Alternat Med*, Article ID 5439645, 1-14
- [14] AL-Hader, A.; Agel, M. and Hasan, Z. (1993): Hypoglycemic effects of the volatile oil of *Nigella sativa* seeds. *Intern J Pharmacol*, 31(2): 96-100.
- [15] Choudhari, V.P.; Gore, K.P. and Pawar, A.T. (2017): Antidiabetic, antihyperlipidemic activities and herb-drug interaction of a polyherbal formulation in streptozotocin induced diabetic rats. *J Ayurveda Integr Med*, 8(4): 218-225.
- [16] Adam, S.H.; Giribabu, N.; Bakar, N.M.A. and Salleh, N. (2017): *Marantodes pumilum* (Kacip fatimah) enhances in-vitro glucose uptake in 3T3-L1 adipocyte cells and reduces pancreatic complications in streptozotocin-nicotinamide induced male diabetic rats. *Biomed Pharmacother*, 96: 716–726.
- [17] Wen, W.; Lin, Y. and Ti, Z. (2019): Antidiabetic, Antihyperlipidemic, Antioxidant, Anti-inflammatory Activities of Ethanolic Seed Extract of *Annona reticulata* L. in Streptozotocin Induced Diabetic Rats. *Front Endocrinol (Lausanne)*, 10:716.
- [18] Gotama, T.L.; Husni, A. and Ustadi, A.M. (2018): Antidiabetic Activity of *Sargassum hystrix* Extracts in Streptozotocin-Induced Diabetic Rats. *Prev Nutr Food Sci*, 23(3):189-195.
- [19] Francis, B.T. and Sudha, S. (2016): Histopathological changes on streptozotocin induced diabetic rats following administration of polyherbal extract: A study on pancreas and kidney. *World J Pharm Pharm Sci*, 5:1188-1200.
- [20] Asaduzzaman, M.; Nahar, L.; Rahman, S.M.; Hasan, M.; Khatun, A.; Tamanna, Z.; Huda N.; Rabbi, F.M.; Ray, M.N.; Nur Islam M.; Mobassirul I.M.; Maniruzzaman, M. and Alam, M. (2015): Hypoglycemic and Hypolipidemic Potential of *Nigella sativa* L. Seed Extract in Streptozotocin (STZ)-Induced Diabetic Rats. *J Plant Biochem Physiol*, 3(4): 1-5.
- [21] Kanter, M.; Coskun, O.; Korkmaz, A. and Oter, S. (2004): Effects of *Nigella sativa* on oxidative stress and beta cell damage in streptozotocin-induced diabetic rats. *Anat Rec A Discov Mol Cell Evol Biol*, 279(1): 685-91.
- [22] Coles, E.H. (1986): *Veterinary Clinical Pathology*, 4th ed. W.B. Saunders Company, Philadelphia, London.
- [23] Abdulrazaq NB, Cho MM, Win NN, Zaman R, and Rahman MT (2012): Beneficial effects of ginger (*Zingiber officinale*) on carbohydrate metabolism in streptozotocin- induced diabetic rats. *British Journal of Nutrition*, 108 (7): 1194-201.
- [24] Feldman, B.F.; Zinkl, J.G. and Jain, N.C. (2000): *Schalm's veterinary hematology*, 5th edn. Lippincott Williams and Wilkins A Wolters Company Philadelphia, Baltimore, New York, London.
- [25] Tamhane, A.C and Dunlop, D.D. (2000): Multiple comparisons of means. In *Statistics and data analysis from elementary to intermediate*, 475– 476.
- [26] Ali Sangi, S.M. and Al Jalaud, N.A. (2019): Prevention and treatment of brain damage in streptozotocin induced diabetic rats with Metformin, *Nigella sativa*, *Zingiber officinale*, and *Punica granatum*. *Biomed. Res. Ther.*; 6(7):3274-3285.
- [27] Karim, R., Rahman, F., Rahman, R., Tamannaa, Z., Ghose, D.K., Islam, N., Hossain T., Islam, R. and Rahman, A. (2020): Hypoglycemic and antidyslipidemic potential of *Pleurotus ostreatus* in streptozotocin-induced diabetic rats. *J Adv Biotechnol Exp Ther*, 3(1): 49-55.
- [28] Wang, Y.J.; Xie, X.S.; Feng, S.G.; Long, Q.X.; Ai, N. and Wang, B.F. (2014): Causes of Death in STZ-induced Rat Models of Diabetes Mellitus. *Sichuan Da Xue Xue Bao Yi Xue Ban*, 45(4):691-695.
- [29] El-Baz, F.K.; Salama, A. and Salama, R.A.A. (2020): *Dunaliella salina* Attenuates Diabetic Neuropathy Induced by STZ in Rats: Involvement of Thioredoxin. *BioMed*

- Research International, Article ID 1295492, 1-11.
- [30] Kennedy, L. and Baynes, J.W. (1984): Non-enzymatic glycosylation and the chronic complications of diabetes: an overview. *Diabetologia*, 26(2):93-8.
- [31] Ashok, P.; Kyada, A.; Subbarao, P.; Suthar, S.; Singh, D. and Vadaliya, K. (2010): Antioxidant status of a polyherbomineral formulation (Gly-13-C) in STZ-diabetic rats. *Intern J Pharmacol*, 6(3):157-172.
- [32] Erejuwa, O. O.; Sulaiman, S. A.; Ab Wahab, M. S.; Sirajudeen, K.N.S.; Salleh, M. and Gurtu S. (2011): Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. *Intern J Biol Sci*, 7(2): 244-252.
- [33] Kamel, R.; Hashim, A.A. and Ali, S.A. (2014): Palliative effect of curcumin on STZ-induced diabetes in rats. *Intern J Pharm Pharm Sci*, 6(2): 558-563.
- [34] Citro, A.; Valle, A.; Cantarelli, E.; Mercalli, A.; Pellegrini, S.; Liberati, D.; Daffonchio, L.; Kast-siuchenka, O.; Ruffini, P.A.; Battaglia, M.; Allegretti, M. and Piemonti, L. (2015): CXCR1/2 inhibition blocks and reverses type 1 diabetes in mice. *Diabetes*, 64(4):1329-1340.
- [35] Al-Attar, A.M. and Alsalmi, F.A. (2019): Effect of *Olea europaea* leaves extract on streptozotocin induced diabetes in male albino rats. *Saudi J Biol Sci*, 26(1):118-128.
- [36] Al-Amin, Z.M.; Thomson, M.; Al-Qattan, K.K.; Peltonen-Shalaby, R. and Ali, M. (2006): Antidiabetic and hypolipidaemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats. *Br J Nutr*, 96(4): 660–666.
- [37] Li, Y.; Tran, V.H.; Duke, C.C. and Roufogalis, B.D. (2012): Preventive and protective properties of *Zingiber officinale* (ginger) in diabetes mellitus, diabetic complications, and associated lipid and other metabolic disorders: A Brief Review. *Evid Based Complement Alternat Med*, Article No. 516870.
- [38] Kaleem, M.; Kirmani, D.; Asif, M.; Ahmed, Q. and Bano, B. (2006): Biochemical effects of *Nigella sativa* L seeds in diabetic rats. *Indian J Exp Biol*, 44(9):745-8.
- [39] Ramakrishna, C.; Shanmugam, K.R.; Subbaiah, G.V. and Reddy, K.S. (2015): Hepato-protective and antioxidant effect of ginger on hepatic tissue in experimental diabetic rats. *Res J Pharm Biol Chem Sci*, 6(5): 961–967.
- [40] Prasad, K.; Mantha, S.; Muir, A. and Westcott, N. (2000): Protective effect of *Secoisolarici resinoldiglucoside* against streptozotocin- induced diabetes and its mechanism. *Mol Cell Biochem*, 206(1-2):141-149.
- [41] Onyeka, C.A.; Nwakanma, A.A.; Adeola, B.A.; Okoko, I.I.; Ofoego, U.C.; Wali, C.C. and Abengowe, F.C. (2013): Hypoglycemic, antioxidant and hepatoprotective activities of ethanolic root bark extract of *Chrysophyllum albidum* in alloxaninduced diabetic rats. *Bangladesh J Med Sci*, 12(3): 298–304.
- [42] Althnaian, T.; Albokhadaim, I. and El-Bahr, S.M. (2019): Hepatic Gene Expression, Antioxidant Enzymes and Anti-diabetic Effect of *Nigella sativa* in Diabetic Rats. *Intern J Pharmacol*, 15(2): 265-273.
- [43] Abdelmeguid, N.E.; Fakhoury, R.; Kamal, S.M. and Al Wafai, R.J. (2010): Effects of *Nigella sativa* and thymoquinone on biochemical and subcellular changes in pancreatic β -cells of streptozotocin-induced diabetic rats. *J Diabetes*, 2(4): 256- 266.
- [44] Rondi, S.; Peddolla, R. and Venisetty, R.K. (2014): Neuro, cardio, and reno protective activities of rosuvastatin in streptozotocin-induced type 2 diabetic rats undergoing treatment with metformin and glimepiride. *J Adv Pharm Technol Res*, 5(2):78–83.
- [45] Madkor, H.R.; Mansour, S.W. and Ramadan, G. (2011): Modulatory effects of garlic, ginger, turmeric and their mixture on hyperglycaemia, dyslipidaemia and oxidative stress in streptozotocin-nicotinamide diabetic rats. *Br J Nutr*, 105(8):1210-1217.
- [46] Mashhadi, N.S.; Ghiasvand, R.; Askari, G.; Hariri, M.; Darvishi, L. and Mofid, M.R. (2013): Anti-oxidative and anti-inflammatory effects of ginger in health and

- physical activity: Review of current evidence. *Intern J Prev Med*, 4(1): S36-S42.
- [47] Khandouzi, N.; Shidfar, F.; Rajab, A.; Rahideh, T.; Hosseini, P. and Taheri, M. (2015): The Effects of ginger on fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein A-I and aalondialdehyde in type 2 diabetic patients. *Iran J Pharm Res*, 14 (1): 131-140.
- [48] Alshathly, M.R. (2019): Efficacy of Ginger (*Zingiber officinale*) in ameliorating streptozotocin-induced diabetic liver injury in rats: Histological and biochemical studies. *J Microsc Ultrastruct*, 7(2):91-101.
- [49] Toma, C. C.; Olah, N. K.; Vlase, L.; Mogos, C. and Mocan, A. (2015): Comparative studies on polyphenolic composition, antioxidant and diuretic effects of *nigella sativa* L. (black cumin) and *nigella damascena* L. (Lady-in-a-Mist) seeds. *Molecules*, 20(6): 9560–9574.
- [50] Kanter, M.; Akpolat, M. and Aktas, C. (2009): Protective effects of the volatile oil of *Nigella sativa* seeds on beta-cell damage in streptozotocin induced diabetic rats: a light and electron microscopic study. *J Mol Histol*, 40(5-6): 379-385.
- [51] Abeer, A.A.; Shaymaa, I.S. and Faten, F.M. (2017): Potential renoprotective effect of silymarin against amikacin-induced acute nephrotoxicity in rats. *Biosci Res*, 14(4): 993-1004.
- [52] Mahmoud, A. M. (2013): Hematological alterations in diabetic rats - role of adipocytokines and effect of citrus flavonoids. *EXCLI Journal*, 12:647-657.
- [53] Otunola, G.A. and Afolayan, A. J. (2015): Antidiabetic effect of combined spices of *Allium sativum*, *Zingiber officinale* and *Capsicum frutescens* in alloxan-induced diabetic rats. *Frontiers in Life Science*, 8(4) 314-323.
- [54] Nasirian, F.; Mesbahzadeh, B.; Maleki, S.A.; Mogharnasi, M. and Kor, N.M. (2017): The effects of oral supplementation of *Spirulina platensis* microalgae on hematological parameters in streptozotocin-induced diabetic rats. *Am J Transl Res*, 9(12):5238-5244.
- [55] Ali, A.; Shaheen, S.; Memon, Z.; Agha, F.; Shahid, M.A. and Zahid, N. (2019): Effects of Diabetogenic Agent Streptozotocin on Hematological Parameters of Wistar Albino Rats “An Experimental Study”. *J Adv Med Res*, 30(5): 1-8.
- [56] Yassin, S., Mahran, K.M.A., Abd El-Baky, A.A., Soliman, A.M. and Sharaf, E. (2019): Modulatory effects (anti-diabetic and anti-oxidant) of ginger, garlic, and their mix on streptozotocin-nicotinamide induced diabetic rats. *Biosci Res*, 16(3): 3163-3179.
- [57] Helal, E.G.E.; Gawish, A.S.M. and Kahwash, A. (2005): Some hematological Studies on diabetic rats treated with certain hypoglycemic plants. *Egypt J Hos Med*, 19(1): 179–188.
- [58] Gamede, M.; Mabuza, L.; Ngubane, P. and Khathi, A. (2018): The effects of plant-derived oleanolic acid on selected parameters of glucose homeostasis in a diet-induced pre-diabetic rat model. *Molecules*, 23(4):794.
- [59] Abdel-Moneim, A.; Abdel-Reheim, E.S.; Semmler, M. and Addaleel, W. (2019): The Impact of Glycemic Status and Metformin Administration on Red Blood Cell Indices and Oxidative Stress in Type 2 Diabetic Patients. *Malays J Med Sci.*, 26(4):47-60.
- [60] Yakhchalian, N.; Mohammadian, N.; Hatami, K.; Nosrati, H. and Yousofvand, N. (2018): Hematological and Serum Biochemical Analysis of Streptozotocin-Induced Insulin Dependent Diabetes Mellitus in Male Adult Wistar Rats. *bioRxiv preprint first posted online Jun. 30; doi:10.1101-359844*.
- [61] Odoh, U.E.; Onugha, V.O. and Chukwube, V. (2016): Evaluation of antidiabetic effect and hematological profile of methanol extract of *Ceiba pentandra G (Malvaceae)* stem bark on alloxan-induced diabetic rats. *Afr J Pharm Pharmacol*, 10(28): 584–590.
- [62] Kolanjiappan, K.; Manoharan, S. and Kayalvizhi, M. (2002): Measurement of erythrocyte lipids, lipid peroxidation, antioxidants and osmotic fragility in cervical cancer patients. *Clin Chim Acta*, 326(1-2): 143–149.
- [63] Yeom, E.; Byeon, H. and Lee, S.J. (2016): Effect of diabetic duration on hemorheological properties and platelet aggregation in streptozotocin-induced diabetic rats. *Sci Rep*, 6: 21913.
- [64] Bairwa, M.K.; Jakhar, J.K.; Satyanarayana, Y. and Reddy, A.D. (2012): Animal and plant originated immunostimulants used in aquaculture. *J Nat Prod Plant Resour*, 2(3): 397-400.

- [65] Jothi, M.A.; Parameswari, C.S. and Vincent, S. (2016): Hematological studies on the effect of *zingiberone* on streptozotocin induced diabetic rats. Intern J Pharm Res Bio-Sci, 5(2): 21-26.
- [66] Olayaki, L. A.; Ajibade, K. S.; Gesua, S. S. and Soladoye, A. O. (2007): Effect of *Zingiber officinale* on some hematologic values in alloxan-induced diabetic rats. Pharm Biol, 45(7): 556–559.
- [67] Sheikh, T.J.; Joshi, D.V.; Patel, B. J. and Ranjan, R. (2019): Antioxidative potential of spices in experimentally induced type-II diabetes in rats. Intern J Curr Microbiol App Sci; 8(3): 1219-1227.
- [68] Ekind, M.S.; Cheng, J.; Boden-Albala, B.; Paik, N.C. and Sacco, R.L. (2001): Elevated white blood cell count and carotid plaque thickness: the northern manhattan stroke study. Stroke, 32(4): 842-849.
- [69] Ganong, W. F. (2003): Review of medical physiology 23rd ed., Lange med. Public, 19:306-326.
- [70] Bilal, A.; Masud, T.; Uppal, A.M. and Naveed, A.K. (2009): Effects of *Nigella sativa Oil* on Some Blood Parameters in Type 2 Diabetes Mellitus Patients. Asian J Chem, 21(7): 5373-5381.

الملخص العربي

تأثير الزنجبيل وحبّة البركة على الفئران المصابة بداء السكري المستحدث بالستربتوزوتوسين، مع الإشارة إلى الدراسات البيوكيميائية والدموية

حسنى عبدالفضيل ابراهيم¹, محمد عبدالعظيم هاشم², نجاح السيد عمر¹, علياء عبدالمنعم عبدالرحمن³
¹ قسم الفارماكولوجيا - كلية الطب البيطري - جامعة الزقازيق
² قسم الباثولوجيا الاكلينيكية - كلية الطب البيطري - جامعة الزقازيق
³ مديرية الطب البيطري - الزقازيق - محافظة الشرقية.

تهدف هذه الدراسة إلى تقييم التأثير المحسّن المحتمل لمستخلص الإيثانول من مستخلص الزنجبيل وحبّة السودان على الجرذان المصابة بداء السكري والمحدث بالستربتوزوتوسين. تم تقسيم خمسين جرذ بشكل عشوائي إلى خمس مجموعات متساوية. المجموعة الاولى تم إعطائها محلول ملحي بالفم وتعتبر مجموعة ضابطة. تعرضت المجموعات 2-5 تجريبياً لمرض الداء السكري عن طريق الحقن داخل الغشاء البريتوني بالستربتوزوتوسين (55مجم / كجم من وزن الجسم) بعد 15 دقيقة من حقن النيكوتين أميد (110مجم / كجم من وزن الجسم). تم التأكد من إستحداث السكر بقياس مستوى السكر بالدم في الجرذان بعد يومين من الحقن. الحيوانات التي بها مستوى السكر أعلى من 250مجم/100ملى دم تأكد أنها مصابة بداء السكري واستخدمت في التجربة. المجموعة الثانية تركت دون علاج ، بينما تم علاج المجموعات الثالثة إلى الخامسة عن طريق الفم بالميتفورمين (100مجم / كجم من وزن الجسم) ، ومستخلص الإيثانول من الزنجبيل (200مجم / كجم من وزن الجسم) و حبّة السودان (300مجم / كجم بالوزن) على التوالي لمدة 21 يوماً متتالية. تم جمع عينات الدم والأنسجة البنكرياسية في نهاية الفترة التجريبية وخضعت للتحليل البيوكيميائي كما تم تسجيل معدل الوفيات. أظهرت النتائج أن مستويات الجلوكوز في الدم والفركتوز أمين والأنسولين تم تحسينها بعد العلاج بالميتفورمين (4.76 ± 99.00 و 5.25 ± 198.69 و 2.35 ± 29.82) ومستخلصات الإيثانول من الزنجبيل (4.87 ± 105.20 و 17.79 ± 317.48 و 0.72 ± 13.64) و حبّة السودان مع بعض الاختلافات حيث ان مستخلص حبّة السودان أنتج انخفاضاً طفيفاً في مستوى الجلوكوز (14.91 ± 201.60) وتحسناً في مستوى الفركتوز أمين والأنسولين (6.39 ± 273.20 و 1.78 ± 21.65) مقارنة بالمجموعة الثانية المصابة بالداء السكري. وبفحص صورة الدم أدى علاج الفئران المصابة بداء السكري باستخدام الميتفورمين و حبّة السودان إلى زيادة كبيرة في عدد كرات الدم الحمراء (0.170 ± 6.21 ، 0.135 ± 5.63) ، تركيز الهيموجلوبين (0.229 ± 12.96 ، 0.141 ± 12.00) ، ونسبة تكس كرات الدم الحمراء، وكذلك الكتاليز (0.012 ± 0.32 ، 0.009 ± 0.25) والسوبر أكسيد ديسموتيز (2.16 ± 19.44 ، 0.914 ± 12.77) في أنسجة البنكرياس عند مقارنتها بالمجموعة المصابة بالسكري والغير معالجة. ومع ذلك ، أظهرت النتائج أن خلاصة الزنجبيل أدت إلى تغييرات في خلايا الدم. أثبتت هذه الدراسة أن مستخلصات الزنجبيل و حبّة السودان لها تأثير معنوي على بعض القياسات البيوكيميائية والدموية ، مقارنة مع الميتفورمين المعروف باسم الدواء القياسي لمرض السكر. لذا قد يكون لهذه النباتات دور في التخفيف من مخاطر بعض المضاعفات المزمنة لمرض السكري.