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Role of ginger in ameliorating streptozotocin-induced diabetic rats

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Abstract
Diabetes is the most important growing health risk throughout the World. In this study, antidiabetic effects of ginger extract were investigated through measurements of metabolic hormones irisin and hepcidin, liver function enzymes and hematological analysis. Forty female, healthy Wistar albino rats were divided into 5 groups: Control, Sham, Diabetic, Ginger (200 mg/kgbw) and Ginger+Diabetes group (200 mg/kgbw). While the plasma irisin level decreased in diabetic group, it increased in the Ginger group. However, hepcidin level increased in the diabetic group, but decreased in the Ginger group. Also, a positive and significant correlation was found between hematocrit and hepcidin in Ginger+Diabetes group rats. In addition, increased total cholesterol level was improved in Ginger+Diabetes group. Based on the findings, it can be suggested that ginger may have an important role on glucose intolerance in diabetes though irisin and hepcidin metabolism. Also, irisin may be used as a marker of diabetes.

Keywords: Diabetes, ginger, hepcidin, insulin, irisin

1. Introduction
Diabetes is a chronic metabolic disease which has disruptive effects on health and life quality. It progresses with high blood sugar along with impaired carbohydrate, fat and protein metabolism which is caused by inadequate insulin production combined with either insufficient insulin production or insulin resistance. Diabetes is associated with increased oxidative stress and chronic complications, especially in heart, blood, liver, brain, nerves, and kidneys. Nevertheless, Diabetes mellitus (DM) is the widest form of diabetes which has important impacts on several organs, hormones, and enzymes, and has a role in regulating the energy metabolism and homeostasis. Degeneration of insulin secretion in DM causes alterations in carbohydrate, protein, and lipid metabolisms [1]. Structural and functional changes occur, and membrane integrity is lost due to lipids, proteins and nucleic acids interacting with increased free radicals [2].

Many important metabolic biomarkers have roles on the metabolic process of DM. A new potential target named irisin was identified in 2012 which is associated with insulin resistance. Irisin is an important myokine which can improve the insulin resistance due to its efficiency on energy metabolism and participating in normal physiological functions [3, 4]. Researchers observed that irisin has a protective effect on endoplasmic reticulum and can inhibit oxidative stress [5]. It was also reported that irisin makes white adipose tissues act as brown [6]. Irisin is secreted from fibronectin type III domain containing FNDC5 [7]. FNDC5/irisin overexpression diminishes hyperglycemia, hyperlipidemia, and insulin resistance [3]. Also, it has a potential role in mediating antidepressant-like effects by regulating the insulin impairment in DM and cholesterol homeostasis [8]. Besides irisin, there has been an attention of hepcidin on DM. Hepcidin is a peptide hormone secreted from liver which is linked to iron metabolism and homeostasis [9]. This hormone can be controlled and released by iron stores and erythropoietic activity [10]. It stimulates the inflammatory process. Also, it was reported that body iron elevation may be a risk factor for Type 2 diabetes [11]. It was noticed that hepcidin can improve the paracrine function and thereby increase the insulin secretion. In addition, studies indicated that hepcidin has a role on immune response and general defense mechanism [12].

In recent years, it was accepted that a balanced diet including natural antioxidants is important to regulate the insulin secretion in blood circulation. Ginger is one of the antioxidant herb used in medicine due to its ingredients. It has rich phytochemical components and several beneficial effects as a hepatoprotective [13-15]. Researchers have been making efforts to identify the antidiabetic effects of ginger in some rat models, either streptozotocin-(STZ) or alloxan-induced [16].

Therefore, studies reported that ginger has an antihyperglycemic role on reducing glucose level that explained by increasing phosphorylation of insulin receptor [17].

In the present study, it was aimed to identify the roles of the metabolic hormones of hepcidin and irisin in streptozotocin induced diabetic rats, and to evaluate the effects of ginger on these metabolic hormones, lipid profile, and hematological parameters.

2. Materials and Methods

The experimental protocols were approved by the National Institute of Health Guide for the Care and Use of Laboratory Animals and the Animal Care and Use Committee of the University (Approval No: T2019-232).

2.1 Sampling

Forty female, healthy Wistar albino rats aged about 4 months old with an average body weight (150-250g) were used in this study. The animals were housed under standard laboratory conditions (22 ± 10 ^{0}C; 55 ± 10% humidity) in clear, standard cages, with stainless steel feed hoppers. Rats were given ad libitum access to a standard rat pellet diet and tap water.

2.2 Plant supplementation

Fresh ginger rhizomes were purchased from a local store, and authenticated at department of Botany of the University. The rhizomes were washed and air-dried. The air-dried rhizomes were transformed into powder mechanically and extract was prepared with 95% ethanol for 24 h. The extract was filtered and 95% ethanol was added. This process was repeated three times.The three extracts were pooled together, then filtered and evaporated to dry. This process resulted in procured dark brown and gelatinous extract. A dose of 200 mg/kg gelatinous extract was dissolved in 2% Tween 80 solution before commencement of the experiment. This ethanolic extract of ginger and experimental design were prepared using the method described by Shanmugam *et al*, [18].

2.3 Experimental design and treatment process (Protocol)

The experiment rats were divided into five groups and each group included eight animals according to literatures [19, 20]. The total experiment protocol was maintained for 30 days. The experimental groups were as follows: Control (C), sham (S) (2% Tween 80 was applied), ginger (G) (oral gavage 200 mg/kg ginger extract), diabetic group (D) (50 mg/kg STZ i.p.), and diabetic + ginger group (DG) (oral gavage 200 mg/kg ginger extract).

Diabetes mellitus was induced by a single intraperitoneal injection (i.p.) of 50 mg/kg streptozotocin (STZ) (Sigma, st. Louis, MO, USA) dissolved in 50 of mL citric acid + 40 mL of disodium hydrogen phosphate buffer (pH 4.5) which was administered after an overnight fasting. Three days after the STZ administration, fasting blood glucose levels of tail vein blood of rats were measured with glucometer (Accu-Chek Instant, Roche), and animals with fasting blood glucose of 250 mg/dL and above were labeled diabetic.

2.4 Blood analysis

Blood samples were obtained by puncturing the heart under short (2-3 min) isoflurane anesthesia at the end of the study and taken to EDTA tubes. Blood samples were centrifuged in the same day at 3000 rpm for 10 minutes to separate the plasma, and then the plasma was transferred to micro tubes, and samples were stored at -80 °C until the analysis day.

Hematologic profile: The blood taken was counted using the haemogram device available in the Experimental Animal Center of the University. In addition, fresh blood smears were prepared after the blood sample collection. The differential leukocyte count was performed on a May-Grunwald Giemsa-stained blood smear, and the percentage and numbers of neutrophils, eosinophils, basophils, lymphocytes and monocytes were determined manually.

Biochemical and hormone profile: The changes of metabolic hormones, Irisin (Catalog no: 201-11-0598, Shanghai Sunred Biological Technology Co., Ltd, China) and Hepcidin (Catalog no: 201-11-1713, Shanghai Sunred Biological Technology Co., Ltd, China), were measured with commercial rat specific kits using the ELISA method. Total Protein (Ref No: ALBG045, BEN Biochemical Enterprise, Italy), Albumin (Ref No: PT371, BEN Biochemical Enterprise, Italy), Total cholesterol (Ref No: C20T5, BEN Biochemical Enterprise, Italy), Triglyceride (Ref No: TG381, BEN Biochemical Enterprise, Italy), AST and ALT (Ref No: A2211N-909, A2211N- 813 Archem Diagnostics, Turkey) levels were measured by using spectrophotometric and colorimetric methods. All biochemical parameters were determined using a microplate reader (Biotek, Epoch, USA).

2.5 Statistical analysis

Statistical analyses were performed with SPSS (Version 20.0; Chicago, IL). Data were examined for normality distribution and variance homogeneity assumptions (Shapiro-wilk test). If normally distributed, a One-way ANOVA test was applied, and the differences between groups were analyzed with the post-hoc Tukey's test. The differences were considered significant at $p<0.05$, and the means and standard errors were calculated. In the study, nonparametric tests were used as the data did not provide normal assumptions. Therefore, the differences between the groups were analyzed with Kruskal Wallis and Mann Whitney U tests. Additionally, the differences were considered significant at $p<0.05$, and the median values (minimum - maximum) were calculated.

3. Results and Discussion

In this study, we assessed the effects of ginger on streptozotocin-induced diabetic rats through antidiabetic, hepatoprotective, and hematopoietic efficiency. We observed the protective effect of ginger on blood glucose, hematological parameters, plasma metabolic hormones (irisin and hepcidin) and plasma liver enzymes of STZ induced diabetic rats.

Diabetes mellitus is a complex disorder described by the changes of homeostasis. The assessment of homeostasis parameters could be used to evaluate the possible changes of metabolic hormones, blood hematological and biochemical products in the metabolism, especially increase in blood glucose levels. Our result in Figure-1A showed that the percentage change of blood glucose was significantly increased in the Diabetes group when compared to Control group (p:0.001; 82.50±4.33and 438.63±21.25, Control and Diabetes group respectively). This means diabetes was occurred successfully. On the other hand, treatment with ginger was recorded a significant decrease in the blood glucose level compared to diabetic rats (p:0.001; 438.63±21.25and 262.00±22.25, group Diabetes and Ginger+Diabetes respectively). Similar results were observed by Al-Amin *et al*. [19] that blood glucose increased when rats subjected to STZ for diabetes, and dose of 500 mg/kg ginger significantly decreased the serum glucose. In another study,

the feeding dietary ginger orally resulted in a significant decrease of glucose levels in diabetic rats [21].

Irisin has been observed as a new marker for diabetes diagnosis. There are some studies on irisin levels reporting important insights into the diabetes and insulin resistance [4, 6]. Boström *et al*. [4] reported that irisin level decreased the high blood glucose in animal models due to the increase of total energy expenditure. Also, it was determined that breaking of irisin signaling in adipose tissue may be related to the development of diabetes [6]. The alteration of metabolic hormones irisin and hepcidin levels and their percentage differences are presented in Figure 1. As expected, the plasma irisin level decreased in Diabetes group compared to the control group (p: 0.008; respectively group Control and Diabetes, 19.90±1.48 and 10.51±1.40). However, ginger improved the decreasing irisin value significantly in ginger treated diabetic rats compared to group diabetes. (P:0.008; 10.51±1.40 and 22.76±2.05, respectively groups Diabetes and Diabetes+Ginger). Ginger is an important herb with notable medicinal property, especially the base ingredient of ginger named 6-gingerol. Excess of hepatoprotective, anti-oxidant and anti-inflammatory markers may be induced by ginger and its ingredient 6-gingerol in diabetes. It can be suggested that irisin may play a crucial role in glucose intolerance in diabetes. Also, ginger may have positive effects on irisin expression.

Nevertheless, plasma hepcidin levels were found statistically higher in group Diabetes (p:0.008; 716.26±42.44 and 450.91±38.73, group Diabetes and Control, respectively) than Control. Also, feeding ginger improved the hepcidin value compared than the Control group (p:0.032; 654.76±63.60 and 450.91±38.73, group Ginger and Control). However, ginger treatment decreased the plasma hepcidin value significantly in group Diabetes+Ginger compared to the group Diabetes. (p:0.036; 324.78±46.49 and 716.26±42.44, Diabetes+Ginger and Diabetes groups, respectively). The mechanism of high hepcidin may be related to evoke the paracrine function by releasing insulin and hepcidin which localize in beta cells of pancreas. Thereby, concomitant production of hepcidin and insulin are stimulated by glucose [22]. Studies suggested that hepcidin is an important hormone that can generate the liver against iron overload and upregulation of proinflammatories [23].

Diabetes has several hematological alterations. Studies have showed that Hematocrit, Hemoglobin, Erythrocytes (RBC) and Platelet (PLT) counts decrease in diabetes-induced STZ rats. On the other hand, an increase of leukocyte count (WBC), percentages of neutrophil, lymphocyte, and monocyte have been reported whereas a decrease in eosinophils has been reported. Especially, decreasing of hematocrit and RBC is related to the increase of red blood cells' membrane proteins. The membrane proteins of red blood cells increase in diabetes, and therefore hemolysis occurs due to the increase of lipid peroxidase production [24]. In the present study, the blood hematocrit and platelet counts (PLT) decreased, while Leucocyte (WBC), Lymphocyte counts, and N/L ratio statistically increased in the Diabetes group compared to the Control (Table 1, $p<0.05$). However, hematocrit value increased in the group Diabetes+Ginger as to group Diabetes statistically (p:0.05; 32.34±2.03 and 27.36±0.94, groups Diabetes+Ginger and Diabetes, respectively). This high hematocrit level may be due to the decreased lipid peroxidase levels in erythrocyte membrane because of hemolysis decreasing. Similar to our results, Olayaki *et al*. [25] found an increase in the RBC and hematocrit counts in ginger-treated diabetic rats compared to the alloxane-induced diabetic rats. Also, WBC, percentage of lymphocyte and Neutrophil/Lymphocyte ratio increased significantly in the group Diabetes compared to the Control. The lymphocyte count decreased significantly in group Diabetes+Ginger in comparison to diabetic rats (p:0.03; 63.00 (53.00-64.00) and 71.50 (67.00-75.00), groups Diabetes+Ginger and Diabetes, respectively).

Nevertheless, there was no significant difference between the Diabetes and Diabetes+Ginger groups in hematological parameters. However, N/L ratio and WBC counts decreased in group Diabetes+Ginger compared to the group Diabetes non-significantly. These results may be due to the ginger treatment which has a defense role against infections in diabetes. The evaluation of hematological values could identify the efficiency of plant extracts on blood constituents. Consequently, it can be suggested that ginger treatment in diabetes may ameliorate important hematological parameters in diabetic rats. Besides these results, in the present study, a negatively and non-significant correlation was found between hepcidin and hematocrit (r:-0.041; p: 0.959) in group Diabetes. This confirms the statement the plasma hepcidin value increases while hematocrit decreases due to the regulatory activity of hepcidin on iron overload in diabetes. Plasma iron concentration increases by upregulation of hepcidin in hepatocytes, and thereby erythropoietin reduces [26]. However, a positive and significant correlation was found between hepcidin and hematocrit in group Diabetes+Ginger (r:1.000; p: 0.01). Plasma hepcidin decreased while blood hematocrit increased in group Diabetes+Ginger. This may be due to the improvement of absorption and production of iron by ginger. It was reported that ginger can improve absorption and production of iron which regulates the activity of hepcidin in iron overload [27]. Also, it was determined that ginger has a haematopoietic effect which promotes the protein expressions of erythropoietin [28].

Researchers reported that ginger showed a lipid-lowering effect due to its phytochemical ingredients, and can also interfere with cholesterol biosynthesis in liver damage [19, 29]. Ginger has an antagonistic role on streptozotocin receptors which can increase the insulin level [15, 30]. In Table 2, some plasma biochemical parameters and liver weight are presented for evaluating the effects of ginger on diabetes. The total cholesterol concentration was found higher in the Diabetes group when it was compared to the Control (p:0.05; 101.42±4.49 and 126.07±3.66, Control and Diabetes, respectively). However, it was diminished in the Diabetes+Ginger rats group compared to the Diabetes (p:0.03; 126.07±3.66 and 83.55±5.41, groups Diabetes and Diabetes+Ginger). Additionally, plasma triglyceride, which is an important hepatic marker for normal liver structure, slightly increased in Diabetes group than the Control ($p>0,05$; 83.19±2.20 and 93.58±6.14, groups Control and Diabetes). Also, plasma triglyceride value tended to decrease in group Diabetes+Ginger compared to the Diabetes group ($p>0,05$; 93.58±6.14 and 83.85±3.33, groups Diabetes and Diabetes+Ginger). Nevertheless, it was reported that increased triglyceride accumulation is resulted with liver enlargement due to the increase of fatty acids in the liver [31]. Nevertheless, liver enzymes ALT increased in group Diabetes than Control group (p:0.05; 24.30±3.19 and 55.22±11.00, Control and Diabetes groups, respectively). Also, ALT/AST ratio increased in the Diabetes group compared to the Control (p:0.05; 0.33±0.06 and 1.16±0.21, Control and Diabetes groups). Furthermore, the liver weight increased in the

Diabetes group than Control (p:0.01; 6.43 and 9.80, Control and Diabetes groups, respectively). It was observed that the liver weight decreased in group Diabetes+Ginger compared to the group Diabetes (p>0,05; 9.80 and 8.40, groups Diabetes and Diabetes+Ginger). In addition, there was no significant difference in other biochemical parameters among all groups.

Liver has important several functions such as protein synthesis, glycogen storage, and hormone production. According to our results, it was determined that the total protein and albumin values decreased in diabetic rats compared to control group. However, ginger treatment increased protein and albumin values which meant improvement of the liver functions, although non significant (Table 2, p>0,05). These result may be due to the hepatoprotective effect of ginger as well as the mitigate efficiency on liver damage in diabetes. Our results are in agreement with some studies reporting decreased enzyme levels and higher protein levels in ginger treated with diabetic rats in group DG [32, 33]. These results may be due to the amount of dose or experiment day and time of ginger. However, it was suggested that ginger has hepatoprotective effects on liver metabolism in diabetes.

Table 1: Effect of feeding with ginger for 30 days on haematological parameters of rats (n=40).

Parameters	**Groups**				
	Control	**Sham**	**Diabetes**	**Ginger**	**Diabetes+Ginger**
Haematocrit	31.86±0.54	29.08±1.32	27.36±0.94[a]	32.15±0.50	32.34±2.03[c]
Haemoglobin	13.64±0.15	12.36±0.51	12.04±0.37	13.58±0.33	13.32±0.80
RBC	6.68±0.08	5.95±0.29	5.89±0.16	6.46±0.21	6.60±0.39
WBC	2.10 (2.00-2.60)	2.00 (1.80-3.80)	4.35[a] (3.40-7.40)	3.40 (2.00-4.00)	3.50 (2.50-5.10)
Neutrophile	25.00 (24.00-29.00)	27.00 (21.00-34.00)	32.50 (29.00-34.00)	29.00 (25.00-35.00)	27.50 (26.00-32.00)
Lympocyte	64.50 (60.00-68.00)	68.00 (64.00-74.00)	71.50[a] (67.00-75.00)	66.00 (61.00-73.00)	63.00[c] (53.00-64.00)
Eosinophile	2.00 (1.00-3.00)	3.00 (1.00-4.00)	1.67 (1.00-2.00)	1.75 (1.00-3.00)	1.00 (1.00-1.00)
Monocyte	2.50 (1.00-4.00)	2.00 (1.00-4.00)	3.75 (1.00-7.00)	3.00 (1.00-7.00)	4.00 (1.00-7.00)
Basophile	1.00 (1.00-1.00)	none	none	1.00 (1.00-1.00)	2.00 (1.00-3.00)
N/L Ratio	0.32 (0.32-0.38)	0.32 (0.28-0.48)	0.49[a] (0.43-0.55)	0.34 (0.20-0.44)	0.42 (0.39-0.44)
MCV	47.52±0.53	49.37±0.68	47.81±0.73	49.16±0.74	48.60±0.71
MCH	20.50 (20.00-21.10)	20.80 (20.50-21.70)	20.75 (19.70-21.60)	20.70 (20.10-21.80)	20.71 (19.70-21.80)
MCHC	43.27±0.42	42.57±0.26	43.44±0.38	42.39±0.23	42.73±0.42
PLT	988.0 (863.0-1159.0)	896.0 (807.0-1229.0)	366.0[a] (190.0-552.0)	849.5 (608.0-1015.0)	499.0 (313.0-765.0)
RDW	17.78±0.07	15.68±0.20	15.54±0.31	15.04±0.34	16.20±0.47
MPV	4.32±0.09	4.38±0.07	4.39±0.17	4.53±0.12	4.49±0.23

RBC= Red blood cells-Erytrocytes; WBC= White blood cells-Leukocytes; N/L= Neutrophile/Lympocyte Ratio; MCV= Mean corpuscular volume; MCH= Mean corpuscular haemoglobin; MCHC= Mean corpuscular hemoglobin concentration; PLT= Platelet count; RDW= Red blood cell distribution width; MPV= Mean platelet volume.

[a,b,c] Values within a row with different superscripts differ significantly at p<0.05

a: Diabetes induced rats (D) versus Control group (C)

b: Diabet induced rats (D) versus Sham group (S)

c: Ginger treated diabetes (DG) versus Diabetes induced rats (D)

Table 2 Effect of feeding with Ginger for 30 days on plasma biochemical parameters and liver weight of rats (n=40).

Parameters	**Groups**				
	Control	**Sham**	**Diabetes**	**Ginger**	**Diabetes+Ginger**
Total Cholesterol (mg/dl)	101.42±4.49	96.71±5.19	126.07±3.66[a]	103.78±3.75	83.55±5.41[c]
Trigliseride (mg/dl)	83.19±2.20	82.06±1.85	93.58±6.14	81.30±2.48	83.85±3.33
AST (U/l)	51.94±6.96	47.00±0.58	55.44±5.94	52.38±9.25	47.32±4.32
ALT (U/l)	24.30±3.19	18.05±2.59	55.22±11.00[a,b]	46.56±8.01	45.40±5.21
ALT/AST ratio	0.33±0.06	0.46±0.010	1.16±0.21[a,b]	0.69±0.06	0.80±0.05
Total protein (g/dl)	6.83±0.61	5.86±0.33	5.41±0.12	6.60±0.35	6.90±0.61
Albumin (g/dl)	3.81±0.62	3.90±0.21	3.00±0.17	3.25±0.06	3.63±0.37
Globulin (g/dl)	2.86±0.46	2.62±0.08	1.92±0.34	3.07±0.31	3.59±0.67
Albumin/Globulin ratio	2.46±0.49	3.00±0.66	0.99±0.01	2.07±0.65	1.78±0.14
Liver weight (g)	6.43 (6.08-8.09)	7.03 (6.66-7.78)	9.80[a,b] (8.10-11.10)	7.60 (7.28-9.60)	8.40 (7.20-8.84)

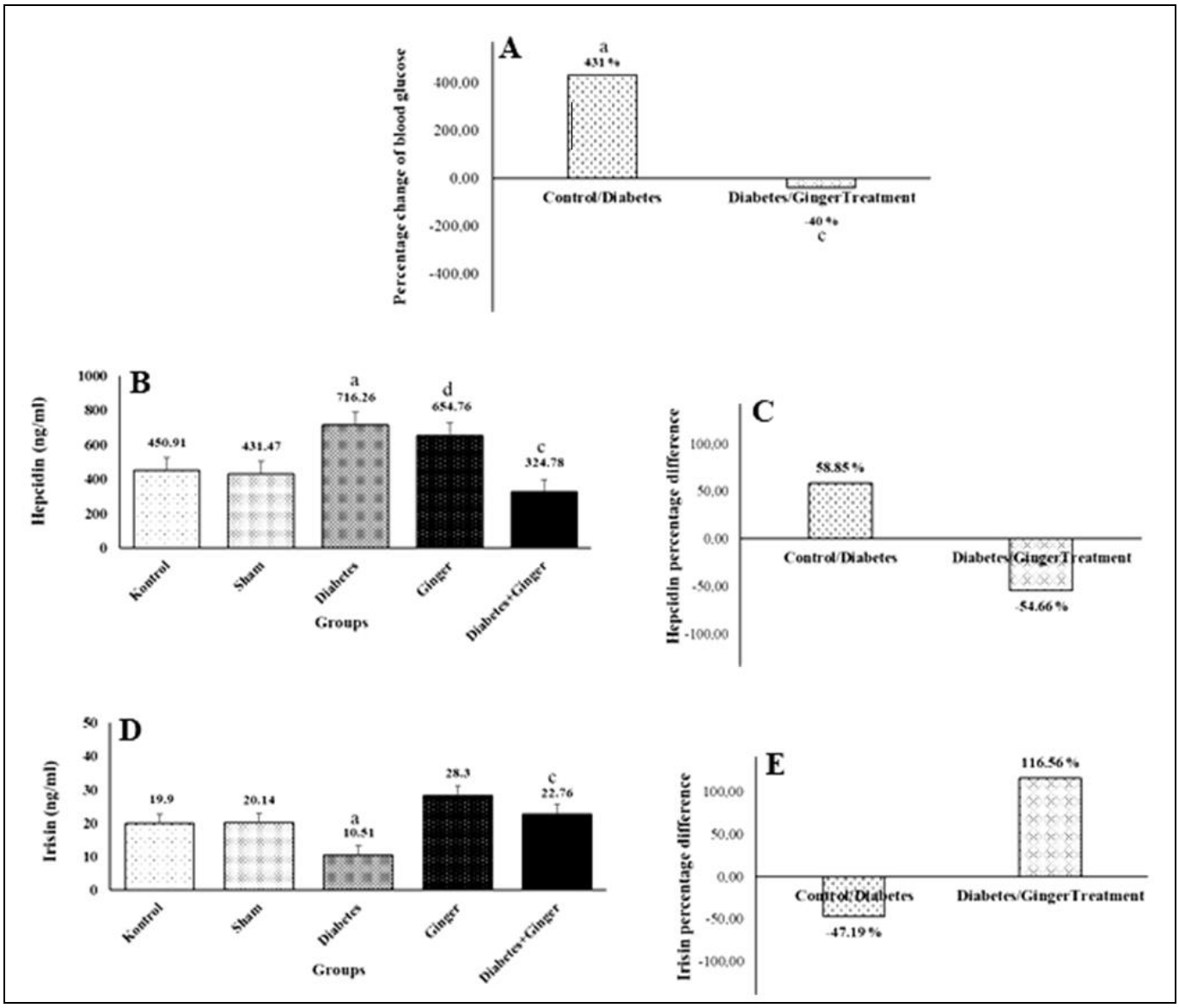
AST= Aspartate Aminotransferase; ALT= Alanine aminotransferase.

a,b,c Values within a row with different superscripts differ significantly at p<0.05

a: Diabetes induced rats (D) versus Control group (C)

b: Diabet induced rats (D) versus Sham group (S)

c: Ginger treated diabetes (DG) versus Diabetes induced rats (D)



a: Diabetes induced rats (D) versus Control group (C)
c: Ginger treated diabetes (DG) versus Diabetes induced rats (D)
d: Ginger group (G) versus Control group (C)

Fig 1: Effects of ginger extract for 30 days of the percentage change of the blood glucose (A), and the plasma concentrations and percentage change in mean the plasma Hepcidin and Irisin of rats. B) Hepcidin concentration; C) Hepcidin percentage difference; D) Irisin concentration; E) Irisin percentage difference; All data are presented as the mean ± SE (n=40). a, c, d Values within a row with different superscripts differ significantly at $p<0.05$

4. Conclusions

The findings of the study showed that ginger treatment in diabetes reduces diabetic results, and prevents the liver damage, and enhances the organism well. The varying results of studies may be related to the different preparations of ginger. However, it was suggested that ginger is the most important anti-hyperglycaemic, antidiabetic, and hepatoprotective agent for diabetes. We discuss the effects of ginger on diabetes with plasma metabolic hormones, irisin and hepcidin. Ginger efficiency on diabetes was demonstrated by increased irisin expression and improved iron regulatory activity by hepcidin. Furthermore, our results confirm that irisin may be used as a marker for diabetes due to its efficiency on energy metabolism.

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