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GINGER OIL ALLEVIATES SERO-BIOCHEMICAL AND HISTOPATHOLOGICAL CHANGES IN PANCREATIC AND LIVER TISSUES OF DIABETIC-INDUCED RATS

NERMEEN YOUSSEF M. MOHAMED [1]; MAHMOUD, A.Z.;
SARY KH.ABD-ELGHAFFAR [2] and FATMA ABO ZAKAIB ALI [1]

[1] Department of Pathology and Clinical Pathology, Faculty of Veterinary Medicine, Sohag University, Sohag 82524, Egypt.

[2] Department of Pathology and Clinical Pathology, Faculty of Veterinary Medicine, Assiut University, Assiut, Egypt.

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ABSTRACT

There is no satisfactory therapy for diabetes. Therefore, there is a need to develop recent co-treatment strategies of plant origin which might have no side effects and are cost-effective. Ginger (*Zingiber officinale*) has anti-diabetic, antioxidant, and anti-inflammatory effects as documented previously. This study aims to investigate the histopathological alterations which occur in the pancreas and liver associated with experimentally diabetic-induced animals, in addition to evaluating the effect of Ginger in modulating the histopathology and the level of blood sugar and insulin in diabetic-induced animals. Fifty-one mature male and female Wister albino rats weighing between 200 and 280 grams were used in this study. Animals were split into three groups, each of 17 rats. The negative control group is referred to as Group I, Group II: Diabetes positive control group injected with (45mg/kg body weight) Streptozotocin intraperitoneally and Group III: Diabetic rats; received Ginger oil (dose of 1.5 mL/kg b.wt) approximately about 460 mg/kg b.wt day after day for 7 weeks. The fasting blood sugar levels were determined during the treatment. Blood was collected after scarification for an additional examination of insulin levels, cumulative blood sugar and liver enzymes. Pancreas and liver tissue specimens were dissected and processed for histological examination. Our results showed that diabetic animals treated with Ginger showed significant ($P \leq 0.05$) improvements in fasting blood sugar, insulin, cumulative blood sugar and liver enzymes when compared with the diabetic untreated group. Histopathological examination of diabetic rats' liver and pancreatic tissues revealed vascular changes including congestion and perivascular edema and atrophy in pancreatic cells of Islets of Langerhans associated with necrobiosis. On the other hand, hepatic tissue from diabetic rats showed also severe vascular changes, vacuolar hepatocellular degeneration and focal nodular leucocytic aggregations. However, treatment with Ginger reversed these changes in both pancreatic and hepatic diabetic tissues, and the majority of the cells returned to a more or less normal state. This improvement in the cells may explain Ginger's anti-diabetic action. Ginger oil exhibited an antidiabetic effect as it improved both pathophysiological and pathomorphological alterations associated with hyperglycemia. As a result, we advised diabetic patients to use Ginger as a daily co-treatment for the control of Diabetes mellitus.

Keywords: Diabetes mellitus. Streptozotocin, Ginger, hypoglycemic, pancreas, liver

Corresponding author: Nermeen Youssef M. Mohamed
E-mail address: nermeenyoussef96@gmail.com
Present address: Department of Pathology and Clinical Pathology, Faculty of Veterinary Medicine, Sohag University, Sohag 82524, Egypt.

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disease correlated with a series of metabolic diseases characterized by hyperglycemia caused by insulin insufficiency, insulin resistance, or both (Al-Saeedi *et al.,* 2021). Long-term blood glucose increase is linked to macro-and microvascular complications, which can result in heart disease, stroke, blindness and renal disease. Other factors such as hyperlipidemia and oxidative stress, in addition to hyperglycemia, play a key part in diabetic pathogenesis, raising the risk of complications (Kangralkar *et al.,* 2010).

Diabetes mellitus has been studied using a variety of animal models which test anti-diabetic drugs, through the usage of drugs to cause both forms of diabetes in numerous animal species (King, 2012). Streptozotocin (STZ) is a naturally occurring antibacterial compound produced by the soil bacterium Streptomyces chromogens. It is also known as 2-deoxy-2-(3-methyl-3-nitrosourea)-1-D-glucopyranose (Qinna *et al.,* 2015). STZ's toxicity is due to its uptake into cells (Eleazu *et al.,* 2013). STZ was shown to be capable of generating peripheral insulin resistance or reducing insulin release from these cells, in addition to its capacity to produce insulin-dependent Diabetes mellitus (type 1) by total loss or destruction of pancreatic β cells. STZ can cause mild to severe hyperglycemia in animals, depending on the dose, strain and age of the animals, nutritional state, and route of administration, among other conditions (Hayashi *et al.,* 2006).

The ability of STZ to generate reactive oxygen species (ROS) contributes to Streptozotocin's diabetogenic effects. However, in this model of experimental diabetes, the pathological pathway of ROS generation does not play a prominent role (Radenković *et al.,* 2016).

Many synthetic oral hypoglycemic agents currently are available, but they all have several side effects. This necessitates the utilization of therapeutic plants as a source for the development of novel medications because they are effective, inexpensive and have fewer adverse effects (Bailey & Day, 1989). Many species utilized as culinary herbs and spices belong to the Zingiberaceae plant family, which is known for its anti-diabetic and hypoglycemic effects. This family includes Ginger (*Zingiber officinale*), which has a long and varied history of use as a culinary spice and in traditional and alternative medicine (Otunola *et al.,* 2019). Non-volatile pungent compounds such as Gingerols, paradols, shogaols, and zingerones, as well as other bioactive phenolics, are abundant in Ginger (Srinivasan, 2017).

Previous studies had shown Ginger's protective role on islet β-cells in several animal models with diabetes (Madkor *et al.,* 2011). Ginger can affect insulin sensitivity with the improvement of the liver, kidneys, nerves and eyes complications associated with diabetes (Li *et al.,* 2012).

Some studies relate Ginger's anti-diabetic properties to bioactive compounds such as Gingerol and shogaol, which can augment glucose uptake in rat skeletal muscle cells and encourage elevated expression and translocation of the GLUT-4 glucose transporter to the cell plasma membrane, as a consequence, excess glucose in the serum is removed (Otunola et al., 2019). Another mechanism hypothesized was the suppression of important glucose metabolism enzymes glucosidase and amylase by phenolic chemicals found in Ginger (Gingerols and shogaols) (Sattar *et al.,* 2012). Other authors noted that Ginger enhances muscle and liver glycogen stores through increasing peripheral glucose utilization, thus inhibiting gluconeogenesis in the liver and kidney in a way that insulin did (Iranloye *et al.,* 2011). There is no seemly therapy for diabetes. Therefore, there is a need to develop recent treatment strategies of plant origin which might have no side effects and are cost-effective. Anti-

diabetic, antioxidant and anti-inflammatory effects have been reported in Ginger (*Zingiber officinale*). The current study aims to investigate the histopathological alterations which occur in the pancreas and liver associated with experimentally diabetic-induced animals, in addition to evaluating the effect of Ginger in modulating the histopathology and the level of blood sugar and insulin in diabetic-induced animals.

MATERIALS AND METHODS

Ethical Considerations

Animal handling and rights were kept in agreement with the Ethical Committee guidelines of the Faculty of Veterinary Medicine, Sohag University.

Materials

1-Drugs, chemicals and oils

Streptozotocin powder was purchased from MP Biomedicals, LLC Company (France). Trisodium citrate dihydrate was obtained from Sigma-Aldrich Company (St. Louis, MO, USA). Citric acid monohydrate was purchased from Sigma-Aldrich Company (St. Louis, MO, USA). Ginger oil was obtained from EL Captain Company (Al Obour City, Cairo, Egypt).

2-Kits and Reagents:

Kits for determination of Liver transaminases AST (SGOT), ALT (SGPT).

3-Animals

Fifty-one mature male and female Wister albino rats with an average body weight of 200-280 g. Animals were purchased from the Experimental Animal House of the Faculty of Medicine, Sohag University. Animals were housed in specific clean and pathogen-free stainless-steel cages (five rats in each cage) with a 12 h light/12 h dark cycle, at a temperature of 23 ± 2 °C, humidity 50:55%. Throughout the trial, rats were given a regular pellet meal and free access to water. To maintain a clean environment, the bedding was changed regularly. Before beginning the experiment, they were given a week to acclimate.

4-Experimental design:

Rats were put under observation for one week before the experiment. During this week, fecal samples from each group were examined by concentration floatation sedimentation test, and samples from sediment and supernatant fluid after centrifugation were examined separately for detection of parasitic eggs and/or larvae to avoid parasitic infected animals before the experiment. After acclimation, rats were randomly assigned to three different isolated groups (seventeen animals each).

Group I: Normal control (n=17): this group of rats received standard rat chow and drinking water. **Group II:** (Diabetes positive control group) (n=17): Animals were fasted overnight (12 h before induction of diabetes).

Diabetes was induced by a single intraperitoneal injection of freshly prepared Streptozotocin (45 mg/kg body weight) (Singh *et al.*, 2007) in a 0.1 M cold citrate buffer (pH 4.5).

Diabetes was identified by polydipsia, polyuria, and by measuring blood glucose levels 48 h after injection of STZ in a blood sample obtained by tail prick, using a glucometer (On Call Plus, ACON Laboratories, Germany). Only STZ-injected rats with blood glucose levels of 250 mg/dl or more will consider diabetic. Rats were given free access to standard ration and water after receiving STZ, as well as a 15% glucose solution added to the drinking water to prevent hypoglycemic shock.

Group III: Diabetic-induced animals treated with Ginger oil (n=17). Diabetic-induced rats (as described in group II), were orally administered with Ginger oil at a dose of 1.5 (0.5 Ginger + 1 corn oil) mL/kg b.w approximately about 460 mg/kg b.w (Al-Qudah *et al.*, 2016) day after day for 7 weeks.

Methods

Samples collection:

A. Blood samples used for determination of fasting blood sugar: During the experiment, the animals' fasting blood glucose levels were measured by sterilizing their tails with 10% alcohol, taking a blood sample via tail prick, and allowing the blood to touch a test strip that was inserted into a calibrated glucose meter (On-Call Plus Glucometer, ACON Laboratories, Germany). After 5 seconds, a direct reading in mg/dL was obtained (Airaodion *et al.*, 2019).

B. Whole blood samples: Rats were sacrificed at the end of the experiment, and individual blood samples from each group were collected in dry and clean tubes containing EDTA as an anticoagulant for assessment of glycosylated hemoglobin.

C. Blood samples used for serum separation: Rats were sacrificed at the end of the experiment, and individual blood samples from each group were collected in dry plain vacuum centrifuge tubes for separation of serum for biochemical analysis and hormonal assay. The samples were centrifuged at 3000 rpm for 10 minutes. The collected sera were kept and coded in Eppendorf tubes and froze at - 20°C until the time of analysis.

Biochemical analysis:

1. Determination of fasting blood glucose level:

Fasting blood glucose level was measured continuously during the experiment as described previously in the experimental design (Airaodion *et al.*, 2019).

2. Estimation of serum insulin:

By I flash 1800 chemiluminescence immunoassay analyzer, SHENZHEN YHLO BIOTECH CO. CHINA (Goodman, 1996) (Chevenne *et al.*, 1999).

3. Determination of cumulative blood sugar:

By Arkary Automatic Glycohemoglobin Analyzer (ADAMS A1c HA-8190V, ADAMS A1c, HA-8190V) is a fully automated Glycohemoglobin. (HbA1c) analyzer based on HPLC (High-Performance Liquid Chromatography). HA-8190V detects and separates variant hemoglobin automatically (Weykamp *et al.*, 2011).

4. Estimation of liver function:

The activities of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by kits obtained from Bio Diagnostic (Egypt) according to the method of (Reitman & Frankel, 1957).

Histopathological examination:

Animals were sacrificed at the end of the experiment and tissue specimens from the pancreas and liver were taken and fixed in 10% formalin for 24 hours before being dehydrated in a graded alcohol series, cleared in xylene, and embedded in paraffin. Tissue sections were cut at 5mm thickness and stained with hematoxylin and eosin (H&E) for histopathological examination (Bancroft & Stevens, 1982).

***Morphometric study*:**

Organ histomorphometric analysis was carried out by giving a score based on the level of damage seen in each group severity in the examined pancreatic and liver tissue: 0 = no lesions; 1 = mild (1 to 25%); 2 = moderate, (26 to 45%); 3 = severe (> 45%) as described previously (Gibson-Corley *et al.*, 2013; Hamdin *et al.*, 2019).

Statistical analysis:

SPSS 16 software was used to perform the statistical analysis. One-way analysis of variance (ANOVA) was used to analyze the experimental data. The significant differences between means were calculated using Duncan's multiple range tests. The significance level was set at $P \leq 0.05$ and all values were expressed as mean ± SE. Regarding histomorphometric measurements get from experimental groups were statistically estimated by the use of

GraphPad Prism, version 5 (San Diego, California, USA) using one-way ANOVA with Tukey's post hoc multiple comparison tests; P< 0.05 to an analysis of data comparing, to define statistical significance between groups.

RESULTS

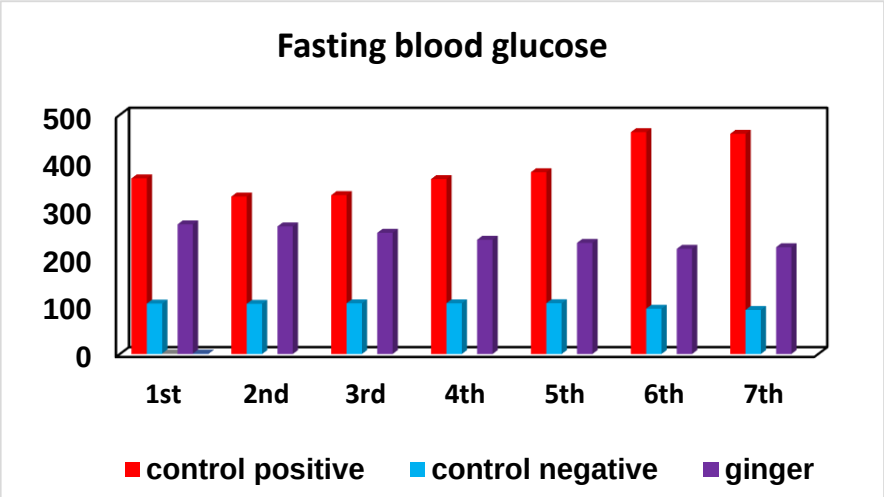
1-Biochemical assessments:

A-Fasting blood glucose:

Table 1: Fasting blood glucose level between experimental groups during the experimental duration.

weeks	Control positive	Control negative	Ginger
1st week	367.1±68.1 A	105.3±6.4 B	271.0±26.0 A
2nd week	329.0±71.9 A	104.8±6.9 B	266.6±45.9 A
3rd week	332.0±69.5 A	105.9±6.7 B	253.2±41.6 A
4th week	365.6±76.6 A	106.0±6.0 C	238.8±49.2 B
5th week	380.0±22.9 A	106.1±4.3 E	232.2±5.8 D
6th week	463.7±8.0 A	94.5±4.7 D	219.8±8.3 C
7th week	460.2±21.8 A	92.0±8.0 D	223.2±53.1 C

Values are expressed in Means ± SD. Values superscripted by different letters within the same column are significantly ($P \leq 0.05$) different.



(Fig.1): Graph showing fasting blood glucose level between experimental groups during the experimental duration, Values were expressed in Means ± SD. significantly ($P \leq 0.05$) different.

Statistical analysis of fasting blood sugar during the 1st, 2nd, and 3rd weeks of the experiment revealed that both groups including the control positive group and the Ginger-treated group were significantly ($P \leq 0.05$) increased in comparison to those of the control negative group. During the 4th week, the mean value of the Ginger-treated group was significantly ($P \leq 0.05$) decreased in comparison to the control positive group (Table 1) and (Fig.1).

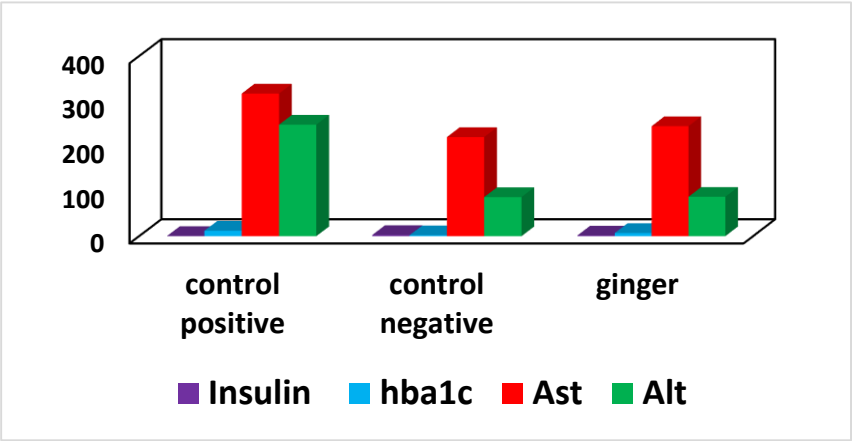
During the 5th, 6th, and 7th weeks, the fasting blood sugar level of the control positive group was significantly ($P \leq 0.05$) higher than the control negative group but, in the Ginger-treated group, it was significantly lowered than the control positive group (Table 1) and (Fig.1).

B-Insulin, cumulative blood sugar (Hba1c), AST, and ALT measurements:

Table 2: Insulin, Hba1c, AST, and ALT measurements of the experimental animal groups.

Group	Insulin	Hba1c	AST	ALT
Control positive	0.47±0.1 ^{D}	12.06±0.6 ^{A}	316.75±25.2 ^{A}	247.67±8.4 ^{A}
Control negative	2.67±0.2 ^{B}	2.11±0.1 ^{C}	220.12±7.9 ^{B}	86.8±7.4 ^{B}
Ginger	1.56±0.1 ^{C}	6.97±1.1 ^{B}	244.4±17.6 ^{B}	87.5±4.7 ^{B}

Values were expressed in Means ± SD. Values superscripted by different letters within the same column are significantly ($P \leq 0.05$) different.

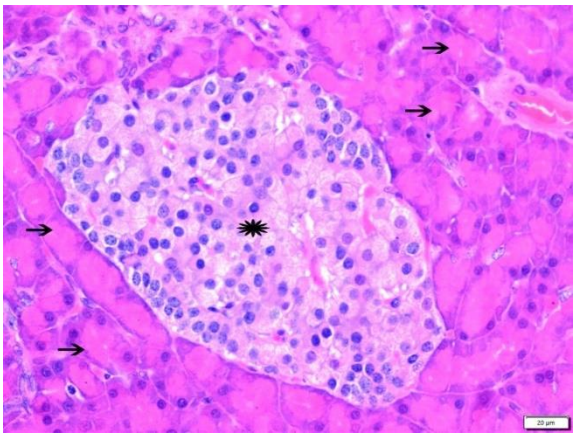


(Fig.2): Graph showing Insulin, hba1c, AST, and ALT measurements of the experimental animal groups, Values were expressed in Means ± SD. significantly ($P \leq 0.05$) different.

The lowest mean value of blood insulin level was seen in the control positive group which was significantly ($P \leq 0.05$) lowered in comparison to the control negative group. The mean value of blood insulin level in the Ginger-treated group was significantly ($P \leq 0.05$) decreased in comparison to the control negative group and significantly ($P \leq 0.05$) increased in comparison to the control positive group (Table 2) and (Fig.2). Whole blood samples from each group were collected in tubes containing EDTA as an anticoagulant for assessment of glycosylated hemoglobin (HbA1c). The highest level of cumulative blood sugar was observed in the control positive group which was significantly ($P \leq 0.05$) higher in comparison to the control negative group, it also reflected the diabetic status of rats in this group. The lowest level was observed in the control negative group which was significantly ($P \leq 0.05$) lowered from those of other groups. In the Ginger-treated group, the mean value of the level of cumulative blood sugar was significantly ($P \leq 0.05$) higher in comparison to the control negative group and it was also significantly lowered in comparison to the control positive group (Table 2) and (Fig.2). The highest mean value of AST and ALT was reported in the control positive group which correlated well with the severe damage occurring in the liver in this group. The mean value of AST and ALT in the control negative and Ginger-treated groups were nearly similar and no significant change was reported between both groups. Only a significant change (decreased) occurred between both groups and the control positive group (Table 2) and (Fig.2).

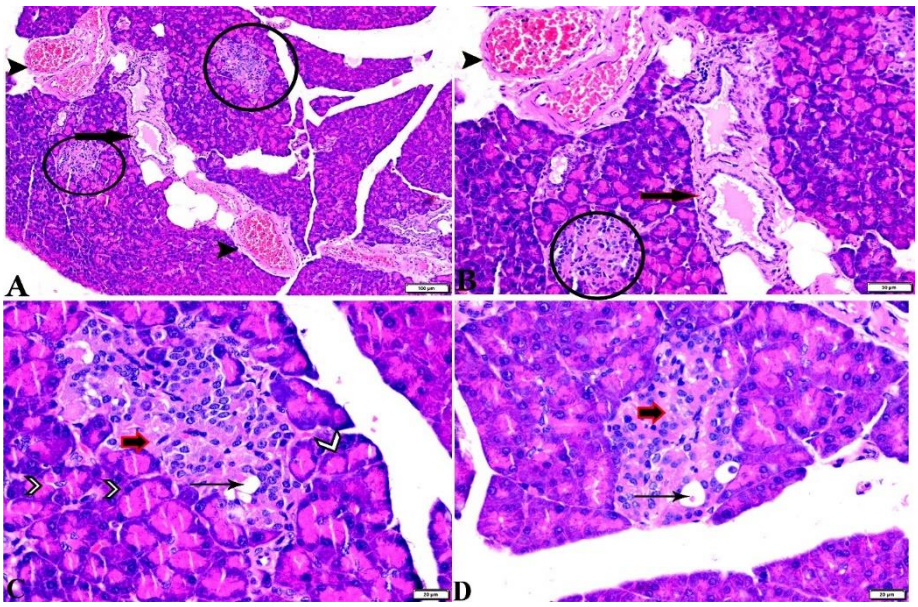
Pancreas

The pancreatic tissue from the control negative group rays revealed normal structure and architecture. The islets of Langerhans showed normal size and normal density of islet cells, and normal structure of the exocrine acinar cells (Fig.3).



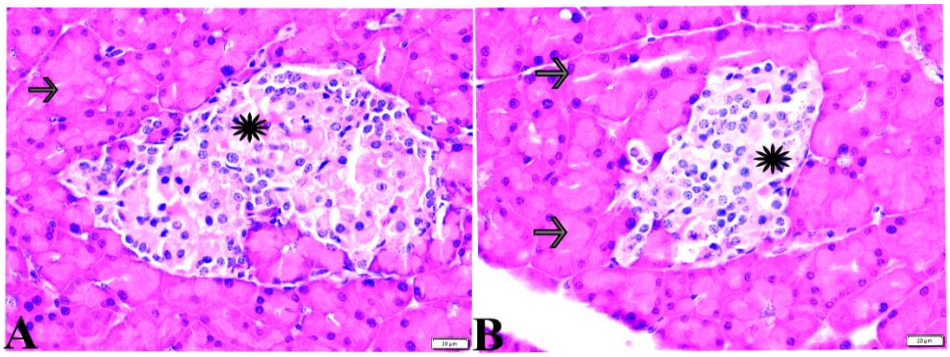
(Fig.3): Photomicrograph of rat pancreas sections from control negative group demonstrating: Normal pancreatic structure and architecture in the form of Normal-sized islets of Langerhans showing the normal density of islet cells (star), normal exocrine acinar cell (arrows). Hx&E stain, Bar =20 µm.

On the other hand, pancreatic tissue from the diabetic-induced animal untreated group (Group II) showed necrobiotic changes in some cells of the islets of Langerhans in which the cytoplasm is homogenous and coagulated sometimes vacuolated and showed cytoplasmolysis, the nucleus sometimes pyknotic other time were lysed and disappeared. Degenerative changes and dissociation of some exocrine acini (Fig.4). Leucocytic infiltration was observed here and there in the islets of Langerhans. Generally, the vascular system of the pancreatic tissue from this group revealed severe congestion and perivascular edema and the blood content of the large blood vessels showed an increased population of leucocytes. The pancreatic duct especially the small one showed dilatation and increased exocrine secretions (Fig.4).



(Fig.4): Photomicrograph of pancreas sections from control positive group showing: (A maximized in B): Atrophy on the Islets of Langerhans (circles), severely congested blood vessels with perivascular edema and infiltration by leucocytes (arrowhead). Dilatation in the small pancreatic duct with an increase in exocrine secretions (arrow). (C-D): Islets of Langerhans showed necrobiotic changes of some cells (red arrows), and surrounding exocrine tissue showed degenerative changes (white arrowheads). Hx&E stain, Bar =100(A), 50(B) and 20(C-D) µm.

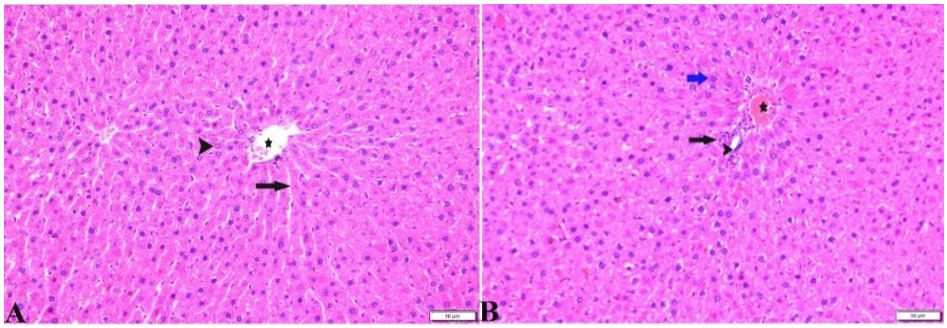
Histological structure of Pancreatic tissue from the diabetic animals treated with Ginger oil (Group III) demonstrated normal cellular density of islets of Langerhans and cells had improved morphological appearance but few leucocytes were infiltrating the islets (Fig.5).



(Fig.5): Photomicrograph of pancreas sections from diabetic + Ginger-treated group showing: Normal cellular density of islets of Langerhans with few leucocytes infiltrated the islets (stars). Hx&E stain, Bar =20 µm.

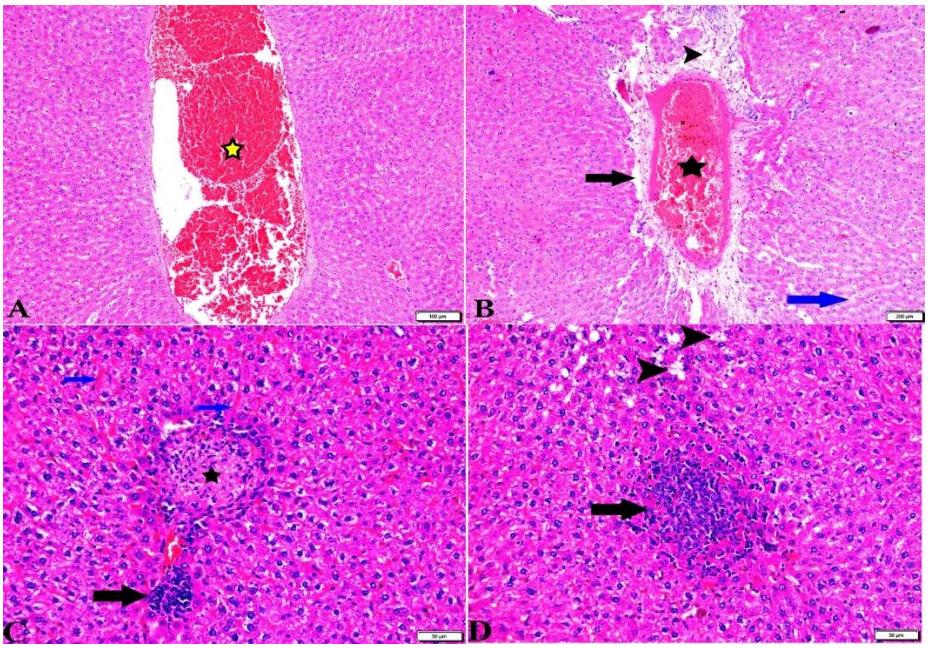
Liver

The liver of the control negative group showed normal hepatic architecture and structure (Fig.6): Normal hepatic vasculature as a normal central vein with normal lining endothelium, normal portal vein with intact lining endothelium, normal hepatic artery, and normal sinusoids. parenchymal hepatic cells present normal histological structure and arrangement with pink cytoplasm and vesicular central vesicular nucleus.



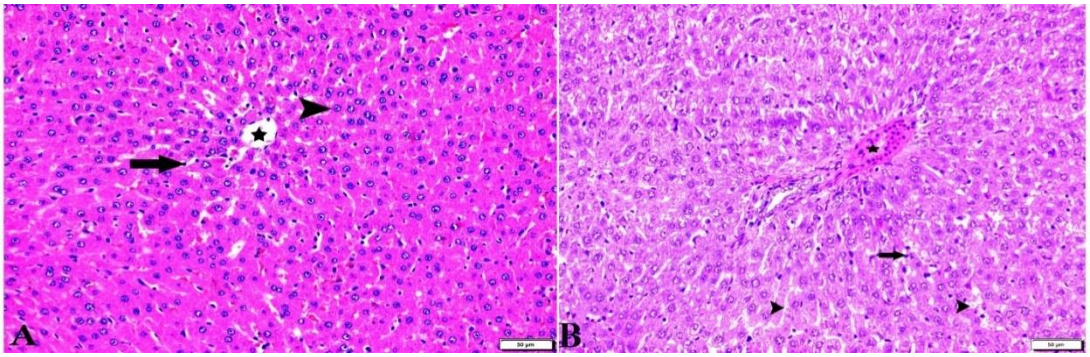
(Fig.6): Photomicrograph of rat liver sections from control negative group demonstrating: (A): Normal hepatic architecture compromising in a normal central vein (star), sinusoids (arrow), and hepatocytes (arrowhead). (B): Normal portal triad structures: hepatic artery (black arrow), portal vein (star), and bile duct (arrowhead). Normal hepatocellular structure (blue arrow). Hx&E stain, Bar =50 µm.

The Hepatic tissue from group II rats revealed a series of histopathological changes, these changes involved hepatic vasculature, parenchymal cells, and interstitial tissue. Central vein and sinusoids were congested in which the blood vessels of the portal tract were prominently dilated and filled with blood. Vessels of the portal tract showed prominent perivascular edema. In addition, edema of the Disse space was observed in the sinusoids with focal distribution (Fig.7). Some of the parenchymal tissue of the liver (hepatocytes) showed coagulative necrosis in which the cytoplasm was homogenous and the nucleus was pyknotic. Other hepatocytes showed lysis of the cytoplasm and nucleus. Some hepatocytes showed granular vacuolated cytoplasm. In the parenchymal tissue leucocytic infiltration was prominent, sometimes the leucocytes forming nodules here and there (Fig.7). Changes in the parenchyma were focal and multiple observed involving a massive area of the liver. The interstitial tissue of the liver especially those arising from the portal tract was thickened with edema and a slight fibroblastic reaction (Fig.7).



(Fig.7): Photomicrograph of liver sections from control positive group showing: (A-B): Congestion of central vein (yellow star) and portal vein (black star), perivascular edema (black arrow), thickening of portal interstitial tissue with edema, and slight fibroblastic reaction (arrowhead), edema of the Disse space (blue arrow). (B-C): Coagulative necrosis of hepatocytes (star), leucocytic nodular aggregation (arrow), hyperemia of sinusoids (blue arrow), vacuolated cytoplasm of hepatocytes (arrowhead). Hx&E stain, the bar size was indicated under each picture.

Microscopical examination of tissue sections from diabetic rats treated with Ginger oil showed minimal micromorphological changes in comparison with the control group, it consists of a minute focal single area of coagulative necrosis, necrobiotic changes, and vacuolation. The most prominent changes were the pavementation of leucocytes through the wall of the blood vessels especially those in the portal areas together with the diffuse presence of single leucocytes in the lumen of the sinusoids (Fig.8).



(Fig.8): Photomicrograph of liver sections from diabetic + Ginger-treated group showing: (A): Marked improvement in the histologic hepatic architecture and structure: Normal central vein, hepatocytes restored its normal structure and arrangement with visible vesicular nucleus (arrowhead), presence of single leucocytes in sinusoids lumen (arrow). Hx&E stain, the bar size was indicated under each picture. (B): Pavementation of leucocytes through the wall of the portal vein (star), presence of single leucocytes in the lumen of the sinusoids (arrow), edema in the Disse space (arrowhead). Hx&E stain, the bar size was indicated under each picture.

semiquantitative histomorphometry studies

1- Pancreatic tissue lesion scoring

Pancreatic histomorphometric results indicated significant (P<0.05) different types of cell damage in pancreatic tissue from the diabetic group which was characterized by atrophy in Islets of Langerhans, Vacuolar degeneration in the islets cells, and Vascular congestion, compared with other groups. on the other hand, diabetic rats treated with Ginger oil showed marked significant (P<0.05) improvement compared with the diabetic group (Table 3).

2- Hepatic tissue lesion scoring

Hepatic histomorphometric results indicated significant (P<0.05) different types of cell damage in diabetic untreated rats which was characterized by vascular congestion with perivascular edema, coagulative areas of coagulative necrosis, and leucocytic nodular aggregation, compared with other groups. on the other hand, diabetic rats treated with Ginger oil showed marked significant (P<0.05) improvement compared with the diabetic group (Table 4).

Table 3: Comparisons in lesion scores recorded in Pancreatic tissue sections among the experimental groups.

Groups / Lesions	Control group	Diabetic untreated group	Diabetic + Ginger treater group
Atrophy in Islets of Langerhans	0.0±0.0	3.000±0.0 ***	0.8000±0.4472 **
Vacuolation in Islets cells	0.0±0.0	3.000±0.0 ***	0.4000± 0.5477 ns
Vascular dilatation and congestion	0.0±0.0	2.400±0.5477 ***	0.6000± 0.5477 ns

Values are expressed in Means ± SD. Significant differences vs. the control group are marked by different asterisks through one-way ANOVA with Tukey's post hoc test: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

Table 4: Comparisons in lesion scores recorded in hepatic tissue sections among the experimental groups.

Groups / Lesions	Control group	Diabetic untreated group	Diabetic + Ginger treater group
Vascular congestion +/- perivascular edema	0.0±0.0	3.000±0.0 ***	0.6000± 0.5477 ns
Focal areas of coagulative necrosis	0.0±0.0	3.000± 0.0 ***	0.7000±0.4472 *
Leucocytic nodular aggregation	0.0±0.0	2.400±0.5477 ***	0.6000±0.5477 ns

Values are expressed in Means ± SD. Significant differences vs. the control group are marked by different asterisks through one-way ANOVA with Tukey's post hoc test: * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

DISCUSSION

The principal cause of diabetes is a deficiency in insulin production, insulin action, or both. Diabetes mellitus is a metabolic condition caused by a variety of aetiologies, including changes in carbohydrate, lipid, and protein metabolism (Fowler, 2010). DM caused dysfunction, long-term damage, and failure of different organs, particularly in the eyes, nerves, kidneys, heart, and blood vessels (ADA, 2010). Because existing oral hypoglycemic medicines and insulin have serious adverse effects, alternative safer anti-diabetic traditional medicine is needed (Bailey & Day, 1989).

In this study, statistical analysis of fasting blood sugar during the 1st, 2nd, and 3rd weeks of the experiment revealed that both groups including the control positive group and the Ginger-treated group were significantly ($P \leq 0.05$) increased in comparison to those of the control negative group. During the 4th week, the mean value of the Ginger-treated group was significantly ($P \leq 0.05$) decreased in comparison to the control positive group. During the 5th, 6th, and 7th weeks and the fasting blood sugar level of the control positive group was significantly ($P \leq 0.05$) higher than the control negative group but, in the Ginger-treated group was significantly ($P \leq 0.05$) lowered than the control positive group. This result agreement with (Wi *et al.*, 1998) and (Shanmugam *et al.*, 2011b). In STZ diabetic rats, hyperglycemia was caused mostly by decreased glucose clearance rather than increased hepatic glucose production, both of which were linked to kidney and liver damage, respectively (Wi *et al.*, 1998). This could be attributed to STZ's damage to pancreatic beta cells, through the production of oxygen free radicals (Gupta *et al.*, 2004).

For the trial drug, the Ginger-treated group showed a significant decrease in blood glucose levels in streptozotocin-induced diabetic rats in comparison to the diabetic control group. Our results are similar to those (Abdulrazaq *et al.*, 2012) and (Ebifa *et al.*, 2021). This might be due to Ginger's capacity to stimulate glucose absorption, glycogen synthesis, and insulin receptor phosphorylation (Ebifa *et al.*, 2021). Furthermore, (Li *et al.*, 2012) indicated that Ginger increased glucose clearances in insulin-responsive peripheral tissues and increased insulin release, which maintained blood glucose homeostasis. Ginger therapy prevented STZ-induced oxidative stress due to its capacity to suppress lipid peroxidation and so protect β-cells from the detrimental effects of diabetic free radicals (Mashhadi *et al.*, 2013).

In this study, the lowest mean value of blood insulin level was reported in the control positive group which was significantly lowered in comparison to the control negative group. A similar result was reported by (Yaghmoor & Khoja, 2010). The lowered value of blood insulin level in the control positive group correlated well with the severe histopathological changes occurring in the islets of Langerhans when the pancreas of this group was examined histopathologically and it pointed to the successful establishment of the diabetic model using streptozotocin (Zhang *et al.*, 2000). It could be understood by STZ-induced damage of β-cells in Langerhans islets, resulting in degranulation and insulin secretion reduction, as described by (Zhang *et al.*, 2000).

Similar to (Abdulrazaq *et al.*, 2012) and (Iranloye *et al.*, 2011), ginger's hypoglycemic effect in diabetes may be due to its bioactive and pharmacological components, which may aid in the reduction of free radicals (Ramudu *et al.*, 2011). Ginger has been demonstrated to stimulate insulin release in rat pancreatic β-cells, resulting in higher plasma insulin levels and lowered blood glucose. This could be due to 6-Gingerol, an active component in Ginger that had been shown to protect pancreatic β-cells and restored plasma insulin levels (Chakraborty *et al.*, 2012).

In this study, the highest level of cumulative blood sugar was observed in the control positive group which was significantly higher in comparison to the control negative group, it also reflected the diabetic status of rats in this group. The lowest level was seen in the control negative group which was significantly lowered from those of other groups. Our results were as seen in (Abd-elnoor, 2019; Ojo *et al.,* 2013). Administration of Ginger significantly reduced HbAlc levels in diabetic rats. These findings are corroborated by (Al Hroob *et al.,* 2018) and (Al Syaad *et al.,* 2019). Hepatic glycolytic enzymes such as glucokinase, phosphofructokinase, and pyruvate kinase were activated by *Z. officinale*. These data show that *Z. officinale*'s hypoglycemic effect is due in part to its insulin mimic activity, which results in greater peripheral glucose consumption and diminished gluconeogenesis in the liver (Abdulrazaq *et al.,* 2012).

In our study, the highest mean value of AST and ALT was observed in the control positive group and it was significantly higher than those of all other groups, similar to that (Al Syaad *et al.,* 2019). The highest value of AST and ALT reflect the severe histopathological changes occurring in the liver in this group. The damage in hepatocytes may be due to the increase of oxidative stress and disturbance of enzyme biosynthesis (Xie *et al.,* 2014) and (You *et al.,* 2015). The activities of AST and ALT in the Ginger-treated group were significantly decreased compared to the control positive group. These results are compatible with the findings obtained by (El-Kott *et al.,* 2010) who reported the effects of Ginger on liver damage. Reduced oxidative stress was related to Ginger's protective effect (Shanmugam *et al.,* 2011). In rat liver microsomes, zingerone, a Ginger compound, prevented lipid peroxidation at large levels, according to an in vitro study (Reddy *et al.,* 1992).

In this study, some islets cells undergo necrobiotic changes, and the destroyed cells sometimes were replaced by fat tissue, leucocytic infiltration was observed in the islets, the pancreas vascular system showed severe congestion, perivascular edema and the pancreatic duct especially the small one showed dilatation and increased exocrine secretions. A similar result was obtained by (Atta *et al.,* 2020; Kazeem *et al.,* 2015; Khattab *et al.,* 2013). These results perhaps were due to streptozotocin caused DNA damage and ROS generation in a small amount with a decrease of antioxidant enzymes (Eleazu *et al.,* 2013).

Our study demonstrated that the pancreas of the Ginger-treated group showed the normal cellular density of islets of Langerhans and cells had a good morphological appearance but there were few leucocytes infiltrated the islets. These findings are corroborated by (Al-Qudah *et al.,* 2016) and (Kazeem *et al.,* 2015). These findings could be attributable to Ginger supplementation preventing STZ-induced oxidative stress due to its capacity to prevent lipid peroxidation and hence protect β-cells from the detrimental effects of diabetic free radicals (Mashhadi *et al.,* 2013).

In our study, diabetic rats showed congested blood vessels and perivascular edema, edema of the Disse spaces in sinusoids, and hepatocytes showed coagulative necrosis. Leucocytic infiltration was prominent in the parenchymal tissue, sometimes the leucocytes formed nodules. The portal tract and interstitial tissue were thickened with edema and a slight fibroblastic reaction. These results are compatible with the findings obtained by Alshathly (2019) and Khattab *et al.* (2013). STZ causes renal, hepatic, cardiac, and adipose tissue damage, as well as increased oxidative stress, inflammation and endothelial dysfunction, with STZ or its metabolites concentrations in the liver, kidney, intestine and pancreas being greater than those in the plasma (Gromotowicz-Poplawska *et al.,* 2019).

Our study demonstrated that the liver of the Ginger-treated group showed the very minimum amount of micromorphological changes, it consists of a minute focal single area of coagulative necrosis, necrobiotic changes, vacuolation, small focal areas of edema in the Disse space were infrequently observed and pavementation of leucocytes through the wall of the blood vessels especially those in the portal areas together with the diffuse presence of single leucocytes in the lumen of the sinusoids. Our findings are in accordance with Khattab *et al.* (2013) and Alshathly (2019). Ginger's antioxidant activity appeared to be the underlying potential mechanism for Ginger's hepatoprotective action (Anwar *et al.*, 2003). Ginger's antioxidant action may help to reduce membranous lipid peroxidation, which causes cell damage and necrosis (Reddy *et al.*, 1992).

CONCLUSION

Ginger oil exhibited an antidiabetic effect as it improved both pathophysiological and pathomorphological alterations associated with hyperglycemia. As a result, we advised diabetic patients to use ginger as a daily cotreatment for the control of Diabetes mellitus.

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زيت الزنجبيل كمخفف للتغيرات الكيميائية الحيوية المصلية والتغيرات النسيجية في أنسجة البنكرياس والكبد التي يسببها مرض السكري في الجرذان

نرمين يوسف محمد محمد ، محمود عبد الظاهر عبد السميع ، سارى خليل عبد الغفار ، فاطمة أبو زكايب احمد

E-mail:nermeenyoussef96@gmail.com Assiut University web-site: www.aun.edu.eg

لا يوجد علاج مرضي لمرض السكري. لذلك ، هناك حاجة لتطوير استراتيجيات مساعدة حديثة من أصل نباتي والتي قد لا يكون لها آثار جانبية وفعالة من حيث التكلفة. الزنجبيل *Zingiber officinale* له تأثيرات مضادة لمرض السكر ومضادات الأكسدة ومضادة للالتهابات كما هو موثق سابقًا. تهدف هذه الدراسة إلى التحقق من المضاعفات النسيجية المرضية التي تحدث في البنكرياس والكبد المصاحبة للحيوانات المصابة بداء السكري تجريبياً بالإضافة إلى تقييم تأثير الزنجبيل في تعديل التشريح المرضي ومستوى السكر في الدم والأنسولين في الحيوانات المصابة بداء السكري. تم استخدام واحد وخمسين من ذكور وإناث الجرذان البيضاء الوستر بأوزان تتراوح من ٢٠٠-٢٨٠ جم في هذه الدراسة. تم تقسيمهم إلى ثلاث مجموعات من ١٧ جرذًا لكل مجموعة. المجموعة الأولى: المجموعة الضابطة السلبية. المجموعة الثانية: مجموعة الضابطة الإيجابية لمرض السكري تحقن بـ (٤٥ مجم / كجم من وزن الجسم) الستربتوزوتوسين داخل الغشاء البروتوني. المجموعة الثالثة: الجرذان المصابة بمرض السكر ؛ تناول زيت الزنجبيل (جرعة ١,٥ مل / كجم من وزن الجسم) حوالي ٤٦٠ مجم / كجم من وزن الجسم يومًا بعد يوم لمدة ٧ أسابيع. تم تحديد مستويات السكر في الدم أثناء الصيام أثناء العلاج. بعد الذبح ، تم جمع الدم لمزيد من التحليل لمستوى الأنسولين وسكر الدم التراكمي وأنزيمات الكبد. تم تشريح البنكرياس وأنسجة الكبد وتمرير العينات من أجل دراسة الأنسجة.

أظهرت نتائجنا أن الحيوانات المصابة بمرض السكر التي عولجت بالزنجبيل قد أظهرت تحسنًا معنويًا ($P \leq 0.05$) في سكر الدم الصائم والأنسولين وسكر الدم التراكمي وإنزيمات الكبد عند مقارنتها مع مجموعة مرضى السكر غير المعالجة. أظهر الفحص التشريحي المرضي لأنسجة الكبد والبنكرياس في الجرذان المصابة بداء السكري تغيرات في الأوعية الدموية بما في ذلك الاحتقان والوذمة حول الأوعية الدموية وضمور خلايا البنكرياس في جزر لانجرهانز المرتبطة بالنخر. من ناحية أخرى ، أظهرت الأنسجة الكبدية من الجرذان المصابة بداء السكري تغيرات شديدة في الأوعية الدموية ، وتنكس الخلايا الكبدية الفراغية وتجمعات الكريات البيض العقيدية البؤرية. ومع ذلك ، فإن العلاج بالزنجبيل عكس هذه التغييرات في كل من أنسجة البنكرياس والكبد السكري، وعادت غالبية الخلايا إلى حالتها الطبيعية إلى حد ما. قد يفسر هذا التحسن في الخلايا عمل الزنجبيل المضاد للسكري. أظهر زيت الزنجبيل تأثيرًا مضادًا لمرض السكر لأنه يحسن التغيرات الفسيولوجية المرضية والمرضية المرتبطة بارتفاع السكر في الدم. نتيجة لذلك، ننصح مرضى السكري باستخدام الزنجبيل كعلاج مساعد يومي للسيطرة على مرض السكري.