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ANTIDIABETIC, HYPOLIPIDEMIC AND HISTOPATHOLOGICAL ANALYSIS OF ZINGERONE IN STREPTOZOTOCIN INDUCED DIABETIC RATS

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Key words:

Diabetes, Streptozotocin, Ginger, Zingerone, Antidiabetic, Hypolipidaemic

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ABSTRACT: The effects of zingerone, on antidiabetic and hypolipidemic potential in streptozotocin-induced diabetic rats were investigated in the present study. Diabetes mellitus was induced by a single intraperitoneal administration of streptozotocin (40 mg/kg bwt). Five days after STZ administration, diabetic rats received zingerone (10 mg/kg bwt) orally for 30 days. Metformin (Met) was used as reference drug. Zingerone treatment significantly reduced blood glucose level, Lipid profiles of serum, liver and kidney showed higher reduction in the levels of phospholipids, triglycerides and free fatty acids of zingerone treated diabetic rats than STZ-induced diabetic rats and Met-treated diabetic rats. In addition, zingerone treatment of STZ-rats was found to be effective in preserving the normal histological appearance of pancreatic islets, liver, and kidney, whereas the untreated diabetic rats exhibited pathological features. Thus, zingerone may have the potential in managing the effects of diabetic complications in human subjects.

INTRODUCTION: Diabetes mellitus (DM) is a group of syndrome characterized by dietary intake, changing in the lifestyle, excessive use of lipid, carbohydrate and protein. Poorly controlled blood glucose level is the major factor in the development of both diabetic complication such as type 1diabetes and type 2 diabetes [1]. STZ is mainly used for induction of experimental autoimmune diabetes. Low dose administration of STZ in the peritoneal cavity of an animal is the best model for type I diabetes.

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Oral hypoglycaemic agents (insulin, sulphonylureas, thiazolidiones and bioguanides) and different plant based drugs were used for the treatment of diabetes, but oral hypoglycaemic drug having some limitation in the treatment of diabetes [2]. Experimental diabetes in animals has provided considerable insight into the physiologic and biochemical derangements of the diabetic state. Many of the derangements have been characterized in hyperglycemic animals. Significant changes in lipid metabolism and structure also occur in diabetes [3]. In these cases, the structural changes are clearly oxidative in nature and are associated with development of vascular disease in diabetes [4].

In diabetic rats, increased lipid peroxidation was also associated with the hyperlipidemia [5]. Liver, an insulin-dependent tissue that plays a pivotal role in glucose and lipid homeostasis, is severely affected during diabetes [6]. Liver participates in the uptake,

oxidation, and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids, and triglycerides. During diabetes, a profound alteration in the concentration and composition of lipid occurs. Decreased glycolysis, impeded glycogenesis, and increased gluconeogenesis are some of the changes of glucose metabolism in the diabetic liver [7]. For various reasons, in recent years the popularity of complementary medicine has increased. Dietary measures and traditional plant therapies as prescribed by ayurvedic and other indigenous systems of medicine are used commonly in India [8].

In recent times, many traditionally used medicinally important plants were tested for their antidiabetic potential by various investigations in experimental animals [9]. World Health Organization (WHO) is recommending the use of complementary and alternative approaches in combating diabetes through the utilization of herbal remedies due to their natural origin and non-toxicity [10, 11]. Ginger, the rhizome of the plant *Zingiber officinale*, is a herbal dietary spice indigenous to India and its use has spread to most of the inhabited world due to the potent anti-inflammatory, antioxidative, antiarthritic, antithrombotic, anticancer, hypolipidaemicand antidiabetic properties [12-14]. The herbal properties of ginger are similar to non-steroid anti-inflammatory drugs (NSAIDs), and hence, it can regulate biochemical pathways which are activated with chronic inflammation such as diabetes [15]. Ginger phytochemicals, upon oral consumption, are readily absorbed into the body where they can exert various activities and excreted after 48 to 60 h [16].

Various reports are available on the use of different preparations of ginger for antidiabetic property. A systematic review reported the analysis of randomized clinical trials (RCTs) conducted on type-2 diabetic human patients for examining the efficacy of ginger preparations against diabetes [17]. However, these studies ascribe the antidiabetic efficacy of ginger to the synergistic effects of phenolic phytochemicals mainly gingerols and their related dehydrated products, the shogaols and zingerone and it is not known that which bioactive compound of ginger is predominantly responsible for antidiabetic activity. Besides, histopathological studies of multiple organs such as pancreas, liver, kidney, adipose, aorta and testis for substantiating the normal functioning of organs as well as non-toxicity of ginger or its phytochemicals while treating the diabetes induced animal models are scarce. Further, there is no report on the antidiabetic and hypolipidaemic effects of zingerone (4-(4-hydroxy-3-methoxy phenyl) butan-2-one), which is a stable active component of dry ginger rhizome and is known to have wide ranging pharmacological activities such as hepatoprotective [13], anti-oxidant [18] anti-inflammatory [19], antidiarrheal [20], antimicrobial [21], immunostimulant [22] and anticancer [23].

The present study is aimed to investigate the efficacy of zingerone for the antidiabetic and hypolipidaemic properties in STZ-induced diabetic rats treated through oral administration for 30 days. Antidiabetic and hypolipidaemic properties were validated by analyzing blood glucose, serum & tissue (liver, kidney) lipid profile (PL,TG,FFA) histological studies on organs such as such as pancreas, liver & kidney.

MATERIALS AND METHODS:

Chemicals:

Zingerone and streptozotocin were purchased from Sigma-Aldrich, St Louis, MO. Glucose kits were purchased from Agappe Diagnostics Ltd., India. All other chemicals were obtained from Hi Media (Mumbai, India) and SD Fine Chemicals Limited (Mumbai, India).

Animals and Diet:

Wistar albino male rats, weighing about 150-250 g, were obtained from King Institute of Preventive Medicine and Research, Chennai and maintained at animal house of Entomology Research Institute (ERI), Loyola College, Chennai. They were maintained under a constant 12 h light and dark cycle at 22–24^{o}C and at 45%-55% relative humidity in accordance with the guidelines of the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India. The study was approved by the Institutional Animal Ethical Committee (833/a/04/CPCSEA), Loyola College. Throughout the experimental period, the animals were fed with a balanced commercial pellet diet (protein, 21%; fat, 5%; nitrogen-free extract, 55%; fiber, 4%; adequate mineral and vitamin contents,

15%; Hindustan Lever Ltd., Mumbai, India) and water *ad libitum*.

Experimental Induction of Diabetes:

Rats were induced diabetes with an intraperitoneal injection of STZ ((40 mg/kg bw) freshly prepared in 0.1 M sodium citrate buffer) after overnight fasting [24]. The rats exhibited diabetes after 5 days (*i.e.*, fasting blood glucose concentration, >300 mg/dL) and were selected for the treatment with zingerone along with reference drug, metformin.

Experimental Procedure:

A total of 30 animals (6 normal and 24 diabetic rats) were used in the experiment. The rats were divided into the following 5 groups of 6 rats each: Normal untreated control (Group I); Diabetic control (rats induced with STZ) (Group II); STZ-induced diabetic rats treated with zingerone (10 mg/kg body weight) orally for 30 days (Group III); and STZ-induced diabetic rats treated with metformin (50 mg/body weight) orally for 30 days (Group IV). Normal rats were treated with Zingerone (10 mg/kg body weight) orally for 30 days (Group V).

Animals were monitored for general health during the treatment period. No death of the animals was observed till the end of the study. At the end of the experimental period and after one day of last zingerone administration, the animals were deprived of food overnight and sacrificed by decapitation. Blood was collected and serum was separated for the estimation of insulin and other biochemical parameters. Tissues such as pancreas, liver, kidney, adipose, aorta and testes were dissected out, washed in ice-cold saline, patted dry, weighed snap-frozen in liquid nitrogen, and finally preserved at -80°C until further analysis.

Analytical Assays:

Lipids were extracted from serum and tissues by the method of Folch et al. [25]. Total cholesterol was estimated using by Parekh and Jung (1970) [26]. Estimation TG [27] PL [28] and FFA [29] were performed using the fresh homogenates of liver and kidney tissues. For serum samples, the parameters such as cholesterol [30], TG [31], PL [32], FFA [29], HDL [33], LDL, and VLDL [34], were measured.

Statistical analysis:

All data are given as mean ± SD (standard deviation). Statistical analysis was performed with past (version 3) several sample tests (ANOVA, kru - wal) followed by Tukey's pairwise test for multiple comparisons. Values of $p<0.05$ were considered significant.

RESULT:

Effect of Zingerone on blood glucose level:

The experimental rats showed a normal basal blood glucose level before the administration of STZ. After 5 days of STZ administration, the rats showed a significant increase (p <0.05) in the blood glucose level. Oral administration of Zio (10 mg/kg bwt) reduced blood glucose levels in diabetic rats to almost the same degree as metformin (50mg/kg bwt) (**Fig.1**). The control rats showed a stable blood glucose level throughout the course of the study and there is no significant modulation in blood glucose level of Zio treated control rats (10 mg/kg bwt).

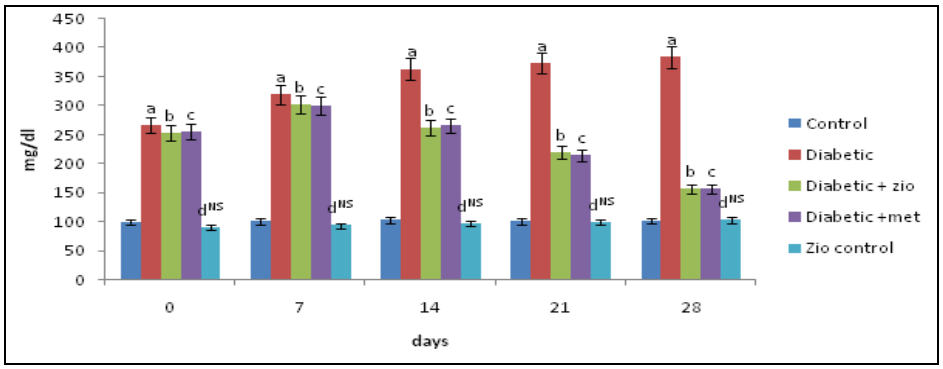


FIG.1: BLOOD GLUCOSE WAS CALCULATED 0, 7, 14, 21, 28 DAYS INTRAVEL IN NORMAL CONTROL AND EXPERIMENTAL GROUPS

Data are expressed as mean ± SD for six rats in each group. Values not sharing a common superscript letter (a-c) differ significantly at P <0.05 (Tukey's pairwise test) NS- not significant. a-group I& II, b-group II& III, c-group II & IV ,d-group I & v.

Effect of Zingerone on cholesterol level:

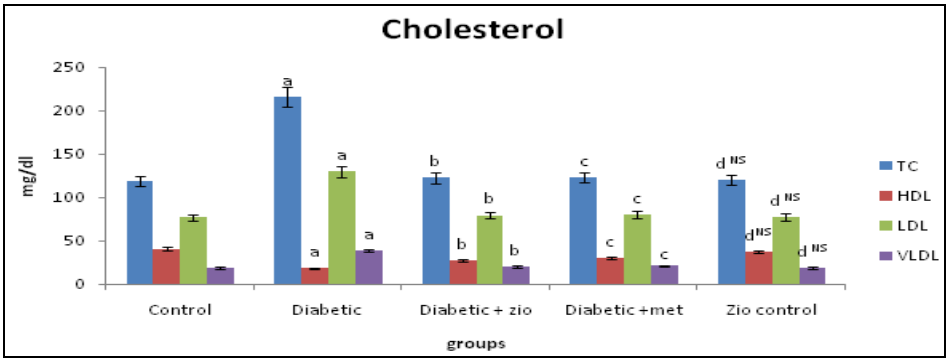


FIG.2: EFFECT OF SERUM CHOLESTEROL LEVEL WAS CALCULATED IN NORMAL CONTROL AND EXPERIMENTAL GROUPS

Data are expressed as mean ± SD for six rats in each group. Values not sharing a common superscript letter (a-c) differ significantly at *P* <0.05 (Tukey's pairwise test) NS- not significant. a-group I& II, b-group II& III, c-group II & IV ,d-group I & v.

Effect of Zingerone on liver and kidney tissue lipid level:

The lipid parameters such as PL, TG and FFA of serum were increased in STZ-induced diabetic rats when compared to normal untreated rats and the increase in the levels of PL, TG and FFA. However, the levels of the that there was no significant variation among the two treated groups. Similarly, data on PL, TG parameters were significant reduced in zingerone and metformin treatments and it was observed and FFA contents in tissues such as liver and kidney showed increase in their levels in diabetic rats against control group whereas the levels of these parameters of treated groups were reduced and were on par with control group.

TABLE 1: THE LIVER, KIDNEY TISSUE LIPID LEVEL WAS MEASURED IN NORMAL CONTROL AND EXPERIMENTAL GROUPS

	TG (mg/100g of tissue)		PL (g/100g of tissue)		FFA (mg/100g of tissue)	
Tissue	**Liver**	**Kidney**	**Liver**	**Kidney**	**Liver**	**Kidney**
Control	307.68±16.01	251.53±13.65	1.58±0.84	0.75±0.46	550.32±21.83	396.33±19.19
Diabetic	569.52±17.17 ^{a}	421.65±10.74 ^{a}	2.80±0.18 ^{a}	1.97±0.71 ^{a}	850.00±19.03 ^{a}	659.22±17.08 ^{a}
Diabetic + zio	332.87±14.94 ^{b}	270.76±16.64 ^{b}	1.61±0.55 ^{b}	0.95±0.44 ^{b}	563.31±21.96 ^{b}	424.43±32.10 ^{b}
Diabetic +met	356.59±12.35 ^{c}	271.84±10.08 ^{c}	1.8±0.70 ^{c}	1.05±0.46 ^{c}	564.60±34.43 ^{c}	428.37±35.07 ^{c}
Zio control	311.01±16.79 ^{d} NS	257.86±22.62 ^{d} NS	1.66±0.90d ^{NS}	0.81±0.38 $^{d\ NS}$	559.06±23.06 ^{d} NS	402.39±16.78 ^{d} NS

Data are expressed as mean ± SD for six rats in each group. Values not sharing a common superscript letter (a-c) differ significantly at *P* <0.05 (Tukey's pairwise test) NS- not significant. a-group I& II, b-group II& III, c-group II & IV ,d-group I & v

Histopathological studies:

The tissues such as pancreas, liver, kidney, adipose, aorta and testes obtained from all the experimental groups were washed immediately with saline and then fixed in 10% buffered neutral formalin solution for 24 h. The organs were dehydrated with a graded series of ethanol and embedded in paraffin wax. Sections of 5 µm were cut using a microtome (Leica RM2255 Rotary Microtome, USA), mounted on glass slides, stained with hematoxylin and eosin (HE) and photographed by microscope (Carl Zeiss, USA). The number and size of islets of Langerhans in pancreas were measured in 10 low-power fields.

Histopathological examination of various organs

Fig.3 Histology of Pancreas:

Histopathological observations of Zio and metformin treated pancreas in STZ-induced diabetic rats after 30 days of treatment (H&E staining, 400×). (A) Normal control – presence of normal pancreatic islet cells; (B) Diabetic control – reduction in the size of islets, damaged β-cell population and extensive necrotic changes followed by fibrosis and atrophy; (C) Diabetic + Zio 10mg/kg bwt- restored necrotic and fibrotic changes and increased number and size of the islets; (D) Diabetic + Metformin 50 mg/kg bw) – absence of necrosis and fibrotic changes, increased

number and size of the islets. (E) Zio control – presence of normal pancreatic islet cells;

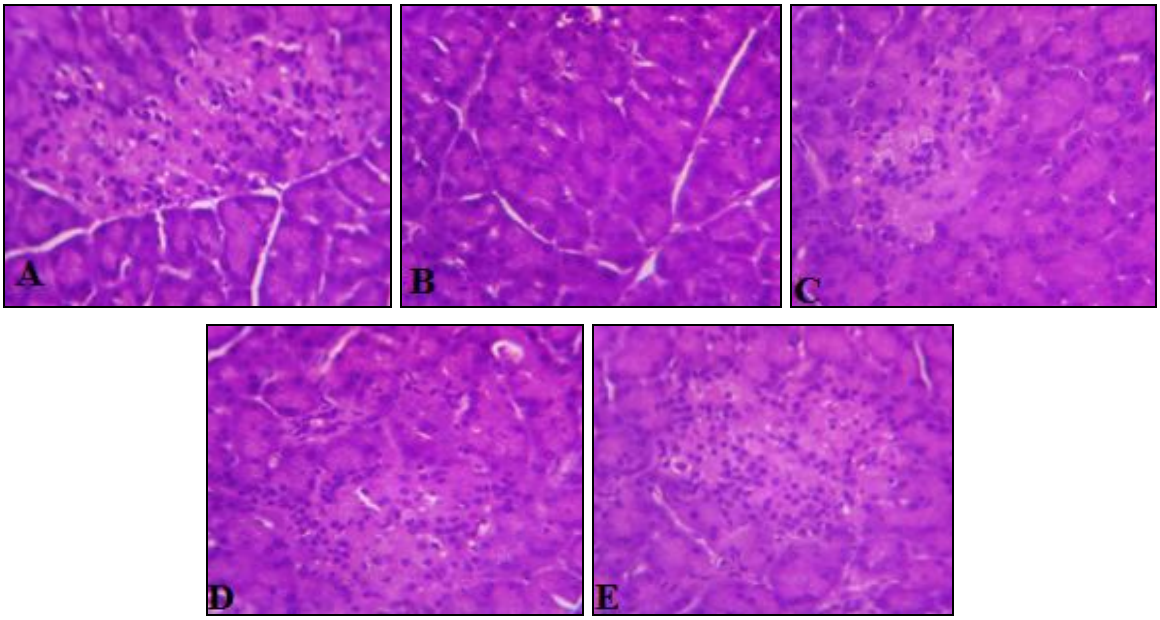


FIG.4: HISTOLOGY OF LIVER

Histopathological observations of Zio and metformin treated pancreas in STZ-induced diabetic rats after 30 days of treatment (H&E staining, 400×). (A) Normal control – normal histological structure of hepatic, hepatic cords, hepatic sinusoids and central vein. (B) Diabetic control - mild sinusoids were observed. (C) Diabetic + Zio 10mg/kg bwt & (D) Diabetic + Metformin 50 mg/kg bw) – have a normal portal & central vein. (E) Zio control – normal histological structure of hepatic, hepatic cords, hepatic sinusoids and central vein.

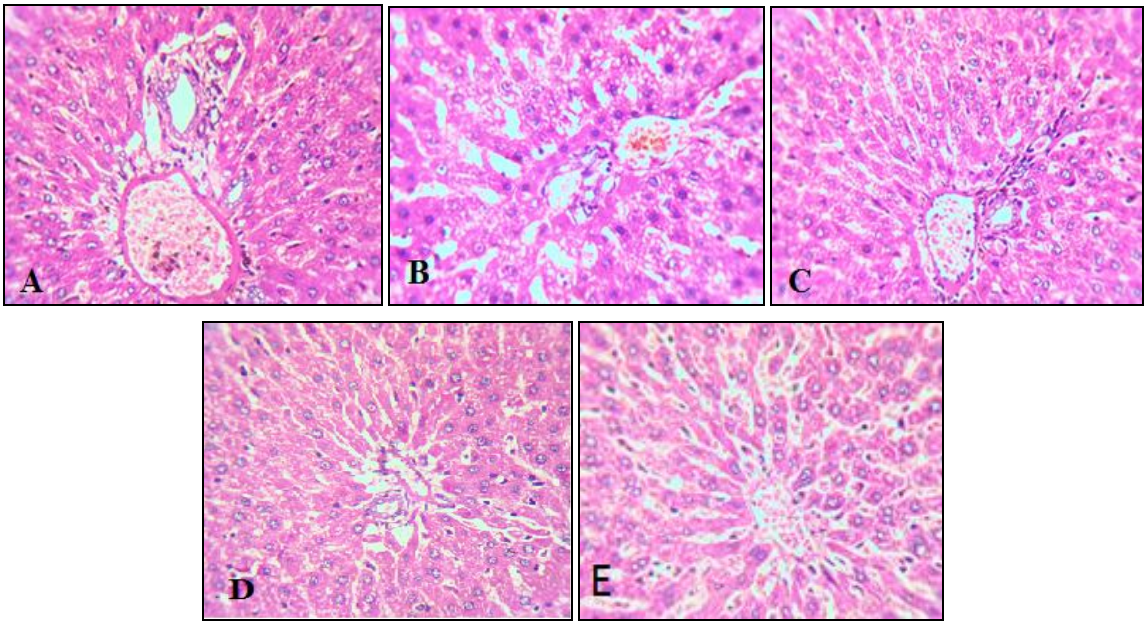
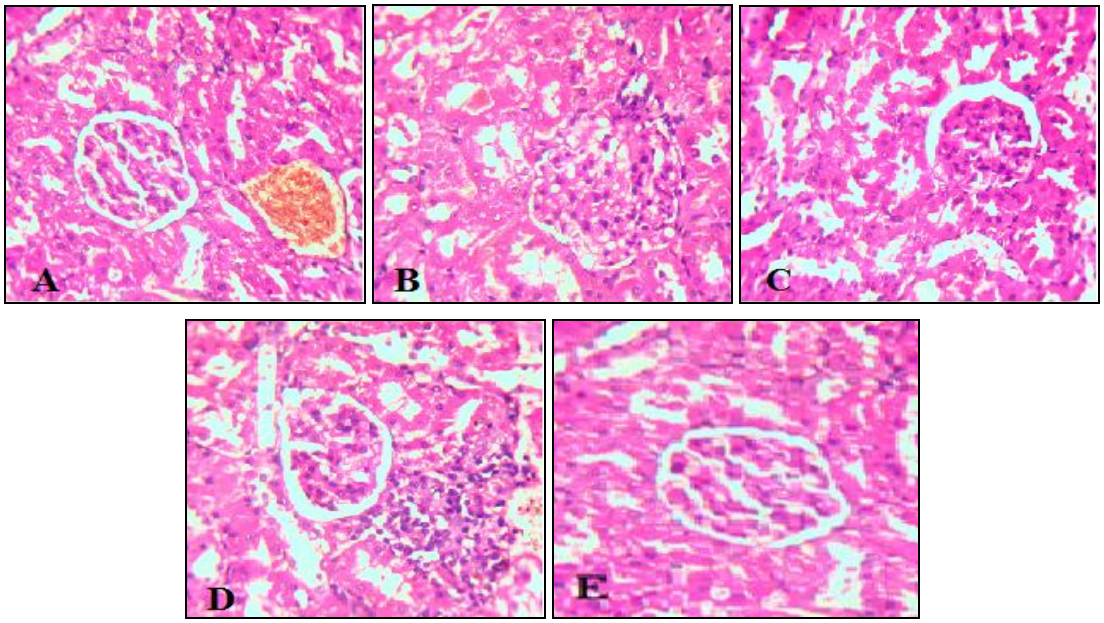


FIG.5: HISTOLOGY OF KIDNEY

Histopathological observations of Zio and metformin treated pancreas in STZ-induced diabetic rats after 30 days of treatment (H&E staining, 400×). (A) Normal control – normal tubule, glomerular, intestium & blood vessels, (B) Diabetic control -showed inflammation of intestium & tubule mild sinusoids were observed. (C) Diabetic + Zio 10mg/kg bwt & (D) Diabetic +

Metformin 50 mg/kg bw) – there was no pathological change occur. (E) Zio control – normal tubule, glomerular, intestium & blood vessels,



DISCUSSION: Hyperlipidemia is a metabolic complication of both clinical and experimental diabetes [35]. The present study was designed to evaluate the effects of Zio on the improvement of blood glucose level and lipid levels. The results of this study showed a significant effect in reducing the blood glucose level in the treated diabetic rats with Zio as well as metformin. The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [36]. Repeated administration of the Zio for 30 days significantly ($p<0.05$) decreased the hypertriglyceridemia and hypercholesterolemia. Hypercholesterolemia and hypertriglyceridemia are mostly found in the diabetes due to lipid abnormalities [37]. These are the major factor involved in rising of coronary heart disease and atherosclerosis, which are the secondary complication accompanying during diabetes [38]. The level of triglyceride increased due to insulin deficiency resultant failure to activate lipoprotein lipase thereby causing hypertriglyceridemia [39].

In diabetes, the deposition of the cholesterol in the peripheral tissue is carrying by LDL and VLDL, peripheral tissue to survive and then excretion of cholesterol done by HDL. Hence increased level of LDL and VLDL is atherogenic. The level of serum lipids was elevated 2 times more as compared to the normal control rats. Treatment of Zio significantly controls the increased level of serum lipids (Triglyceride, Low density lipoprotein, VLDL) and significantly increased the level of HDL in diabetic control rats.

Excess free fatty acids in serum produced by the STZ lowers the insulin-mediated glucose disposal and promote conversion of excess fatty acids into phospholipids and cholesterol in liver. These two substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoprotein [40]. Both increased hepatic production of triglycerides and decreased peripheral removal have been demonstrated. Hypercholesteremia and hypertriglyceridemia have been reported to occur in diabetic rats [41]. A high concentration of cholesterol in human serum is one of the primary factors in the development of atherosclerosis [42]. The marked hyperlipidemia that characterizes the diabetic state may therefore be regarded as a consequence of the uninhibited actions of lipolytic hormones on the fat depot [43].

In our present study demonstrate the lipid levels of both serum and tissue (liver & kidney) levels are maintain in the normal level when compared to the STZ induced diabetic rats. Histopathological studies of tissue organ (Pancreas, Liver, kidney & Adipose) were undertaken it was found that Zio

was non-toxic and regenerate the toxic effect of STZ.

Previous studies of the hypoglycaemic properties of ginger in human subjects and animals have produced variable results. The administration of an ethanolic extract of ginger (100 or 300 mg/kg) to normal rabbits showed potential hypoglycaemic activity (51% decrease in serum glucose) 2 h after administration [44]. In contrast, in another study, non-diabetic patients with coronary artery disease showed no decrease in their blood lipid or sugar levels when treated with a daily dose of 4 g powdered ginger for a period of 3 months [45]. Akhani et al. (2004) have reported that ginger juice exhibits hypoglycemic activity in both normal and STZ-induced diabetic rats. Clearly, the results in the present study confirm the observations of Akhani et al. (2004) [46]. Gingerols can be converted to shogoals and zingerone by dehydration and retro-aldol reaction, respectively. Zingerone and shogaol are found in small amounts in fresh ginger [47, 48]. These ginger components have been shown to have a variety of pharmacological effects, including anti-inflammatory, anti-emetic, cardio tonic and gastro protective properties [49].

The result of present study showed that Zio brings back the blood glucose and cholesterol level to normal in diabetes induced rats. In histopathological studies the Zio treated rats improve the pancreatic islets of beta cells, normal appearance of liver hepatocytes, portal tracts, and central vein & improve the kidney section of tubules, glomeruli, intestium & blood vessels. No previous studies have reported changes in antidiabetic hypolipidemics & histopathologial studies (pancreas, liver& kidney) as a result of Zingerone administration.

CONCLUSION: The result of the present study showed that Zingerone brings back the blood glucose and body weight to normal in diabetes induced rats. It also improved kidney, liver function and hyperlipidemia due to diabetes. After treatment with Zingerone, pancreas, liver & kidney has favorable effect to inhibit the histopathological changes in STZ induced diabetes. Although the exact natural compounds responsible for the hypoglycemic effect of Zingerone still remains speculative, experimental evidence obtained from this study indicates that Zingerone possess antidiabetic property, which also is confirmed by histopathological examination.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

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