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Effect of Ginger and Cinnamon on Induced Diabetes Mellitus in Adult Male Albino Rats

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Keywords

- STZ
- Metformin
- Ginger
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- Diabetes mellitus
- Fat diet

Abstract

Background: Diabetes Mellitus is the most common endocrine disorder. It is a pathological state leads to long term complications causing damage of different tissue and organs as heart and blood vessels. Ginger is one of the most important plants with several medicinal, nutritional and ethnomedical values. Cinnamon contains proteins, carbohydrates, vitamins [A, C, K, B3], Minerals like Calcium, Iron, Magnesium, Manganese, Phosphorous, Sodium and Zinc. **Aim of the work:** Evaluation the effects of ginger and cinnamon extracts administration on diabetic adult male albino rats. **Materials and Methods:** Seventy adult male albino rats of local strain were divided into equal seven groups as follow: Group I: served as control group received normal saline, Group II: high fat diet control group, Group III: high fat diet diabetic control group, Group IV: High fat diet, diabetic and metformin group, Group V: high fat diet, diabetic and ginger group, Group VI: high fat diet, diabetic and cinnamon group and Group VII: high fat diet, diabetic, ginger and cinnamon group. **Results:** Metformin, ginger and cinnamon administration to diabetic rats leads a significant decrease of blood glucose level, glycated hemoglobin level, cholesterol, TG, LDL, atherosclerosis index, atherogenic index, MDa, TNF α and CRP levels associated with significant increase in serum insulin and catalase levels. **Conclusion:** Metformin, ginger and cinnamon have a protective effect against abnormalities in diabetic rats due to its antioxidant properties.

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INTRODUCTION

Diabetes mellitus [DM] is a complex chronic illness characterized by presence of a state of persistent hyperglycemia occurring from deficiencies in insulin secretion, action or both and accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins [1].

DM induces pathognomonic changes in the microvasculature, by increasing the thickness of the capillary basement membrane, leading to the development of diabetic micro-angiopathy [2].

Ginger is herbaceous rhizomatous perennial, reaching up to 90 cm in height under cultivation. Rhizomes are aromatic, thick lobed, pale yellowish, bearing simple alternate distichous narrow oblong lanceolate leaves. The herb develops several lateral shoots in clumps, which begin to dry when the plant matures. Leaves are long and 2 - 3 cm broad with sheathing bases, the blade gradually tapering to a point. Inflorescence solitary, lateral radical pedunculate oblongcylindrical spikes. Flowers are rare, rather small, calyx superior, gamosepalous, three toothed, open splitting on one side, corolla of three subequal oblong to lanceolate connate greenish segments [3].

Cinnamon derived from a Greek word that means sweet wood, comes from the inner bark of tropical evergreen cinnamon trees. cinnamon is a genus of the Lauraceae family, many of whose members are used as spices. It is one of the most widely used flavoring agents used in the food and beverage industry worldwide and well recognized for its medicinal properties since antiquity [4]. It has been used as traditional folk herbs in food industry as antioxidant and spicy agent. It also has been used widely in the traditional medicine to treat digestive problems, anti-inflammatory, anti-bacterial, anti-fungal and blood glucose and lipids lowering agent [5].

The present study was designed to evaluate the effect of ginger and cinnamon extracts administration on diabetic adult male albino rats.

MATERIALS AND METHODS

Animals and experimental design:

Seventy adult male albino rats of local strain were brought from Nile Pharmaceuticals Company, Cairo, Egypt and chosen to be the model of the present work. All rats were about the same age and healthy, their weight ranging between 130 - 160 gm [average weight 145 gm]. They were housed in stainless steel cages [20 × 32 × 20 cm for every 5 rats] at room temperature, good ventilation and received water and commissural rat chow diet with the natural light dark cycle. They were left for two weeks in the laboratory room before the onset of the experiment for acclimatization. Rats were divided into equal 7 groups as follow;

Group I [control group]: Rats fed on normal rat chow diet for 12 weeks.

Group II [high fat diet control group]: Rats fed on high fat diet for 12 weeks **[6]**.

Group III [high fat diet [HFD] diabetic control group]: Rats were fed on high fat diet for 12 weeks and they received single intraperitoneal injection of 30 mg/kg streptozotocin [STZ] after the 4th week **[7]**.

Group IV [high fat diet, diabetic and metformin group]: Rats were fed on high fat diet for 12 weeks. After the 4th week rats received single intraperitoneal injection of 30 mg/kg STZ, then

they received 150 mg/kg metformin by oral gavage daily for 8 weeks **[8]**.

Group V [high fat diet, diabetic and ginger group]: Rats were fed on high fat diet for 12 weeks. After the 4th week rats received single intraperitoneal injection of 30 mg/kg STZ, then they received 300 mg/kg ginger extract by oral gavage daily for 8 weeks **[9]**.

Group VI [high fat diet, diabetic and cinnamon group]: Rats were fed on high fat diet for 4 weeks. After the 4th week rats received single intraperitoneal injection of 30 mg/kg STZ, then they received 200mg/kg cinnamon extract by oral gavage daily for 8 weeks **[10]**.

Group VII [high fat diet, diabetic, ginger and cinnamon group]: Rats were fed on high fat diet for 12 weeks. After the 4th week rats received single intraperitoneal injection of 30 mg/kg STZ, then they received ginger and cinnamon extracts by oral gavage daily for 8 weeks.

Diet: Composition of the experimental diet [g/kg diet] was according to the formula of **Kim et al**. [**6]**. It included the normal diet for control rats [fat 5%, carbohydrates 65%, proteins 20.3%, fiber 5%, salt mixture 3.7% and vitamin mixture 1%]. Obesity induced by high fat diet [HFD] contained fat 46%, carbohydrates 24%, proteins 20.3%, fiber 5%, salt mixture 3.7%, vitamin mixture 1%. Normal and high fat diet constituents were purchased from El-Gomhoria Company, Cairo, Egypt. High fat diet was preserved at 4○C until used.

Induction of diabetes: Type II diabetes was induced in rats by receiving high-fat diet for 4 weeks, then receiving single intraperitoneal injection of a 30 mg/kg STZ **[7].**

Ginger extract preparation: Ginger powder was purchased from a local market. Then 10 gm were soaked in 100ml [10%] hot water [88○ C] in water bath for 6 h. Then filtered by capron silica cloth 150 µ. This diluted extracts [in water 1:10] were administered to rats by feeding needle [oral gavage]. The filtrate was stored in dark bottles in the refrigerator at [4○C]. These procedures were repeated each week **[11]**.

Cinnamon extract preparation: Cinnamon powder was purchased from a local market. Then 10g were weighed and mixed with 100 ml of water and kept in a water bath at 60○C for two hours, then filtered by capron silica cloth 150 µ. This diluted extracts [in water 1:10] were administered to rats by feeding needle [oral gavage]. The filtrate was stored in dark bottles in the refrigerator at [4○C]. These procedures were repeated each week **[5]**.

Calculation of Body mass index [BMI]: Rats were lightly anaesthetized with Diethyl ether, then weighed and the naso-anal lengths were measured on a calibrated platform to calculate the body mass index [BMI = body weight [gm] / length^2 [cm^2]] **[12]**.

Blood and tissue collection: At the end of experimental period, all rats were fasted overnight and anesthetized by placing in an anesthetic box filled with ether vapor. Ether vapor was maintained by periodically applying liquid ether to a cotton wool on the base of the box. Blood was withdrawn from the retro-orbital plexus using heparinized capillary tube for determination of blood glucose [**13],** glycated hemoglobin levels **[14].** To obtain serum, blood was left to clot and centrifuged at 5000 rate per minute for 10 minutes. Serum was sucked out into Eppendorf tubes and

stored frozen at -20ºC [**15]** until assayed for determination of total cholesterol **[16]**, TG **[17]**, HDL **[18]**, LDL[**19]**, serum insulin level [**20]**, malondialdehyde [**21],** catalase [**22],** C-reactive protein **[23]** and tumor necrosis factor α **[24]**.

Statistical analysis: Data input and analysis were done using Statistical Package for the Social Sciences [SPSS] version "24" computer program. All results were expressed as mean ± standard error. Mean values of the different groups were compared using one way analysis of variance. Least significant difference [LSD] post hoc analysis was used to identify significantly different mean values. P value < 0.05 was accepted to denote a significant difference.

RESULTS

Results of the present work showed that feeding rats with HFD for 4 weeks led to statistically significant increase in body weight, weight gain, weight gain percentage, length and body mass index [BMI] in group II [HFD control] when compared to group I [control] **[Table 1].**

Concerning glycemic state, feeding of rats with high fat diet for 4 weeks led to insignificant changes in the mean values of blood glucose, HbA1c, serum insulin, HOMA-IR and HOMA- β between group II [HFD control] and group I [control]. As regards lipid profile, oxidative stress and inflammatory status, the present study showed that feeding of rats with high fat diet for 4 weeks led to statistical significant increase in total cholesterol, triglyceride, LDL, atherosclerosis index, atherogenic index, MDA, TNFα and CRP associated with significant decrease of HDL and catalase in group II [HFD control] when compared to group I [control] **[Table 2].**

Administration of metformin, ginger and cinnamon led to significant decrease of blood glucose and glycated hemoglobin associated with significant increase of insulin, HOMA-IR and HOMA-B when compared with other group **[Table 3].**

Administration of metformin, ginger and cinnamon led to significant decrease of TC, TG, LDL, atherosclerosis index and atherogenic index when compared with other group **[Table 4].**

In HFD and HFD diabetic group; MDA, TNF α and CRP increased significantly when compared with group I associated with significant decrease of catalase level. Administration of metformin, ginger, cinnamon or combination to HFD and HFD diabetic groups led to statistical significant decrease of MDA, TNF α and CRP levels when compared with group II and III associated with significant increase of catalase level when compared with group II and III **[Table 5].**

Table [1]: Anthropometric measures after 4 weeks of HFD in groups I and II [Mean ± SE].

	Group I	**Group II**	**P value**
	Mean ± SE	**Mean ± SE**	
Weight [gm]	**166.5 ± 1.93**	**257.3 ± 3.16**	**<0.001***
Weight gain [gm]	**37.6 ± 1.45**	**125.6 ± 4.33**	**<0.001***
Weight gain %	**29.23 ± 1.25**	**95.92 ± 4.6**	**<0.001***
Length [cm]	**15.66 ± 0.14**	**16.17 ± 0.12**	**0.01***
BMI [kg/m^2]	**6.79 ± 0.11**	**9.85 ± 0.16**	**<0.001***

* = Significant difference between the two groups.
SE = Standard error.
Group I: Control group.
Group II: HFD group.

Table [2]: Comparison between groups I and II regarding all parameters of the study after 4 weeks

Parameters	Group I	Group II	P value
	Mean ± SE	Mean ± SE	
Blood glucose [mg/dl]	100.9 ± 3.12	103.4 ± 2.21	0.52
HbA1c [%]	4.87 ± 0.28	4.93 ± 0.24	0.87
Serum insulin [µIU/L]	10.41 ± 0.53	10.43 ± 0.48	0.98
HOMA-IR	1.38 ± 0.06	1.39 ± 0.06	0.89
HOMA- β	95.8 ± 7.01	90.1 ± 5.12	0.53
Total cholesterol [mg/dl]	81.6 ± 1.8	165.0 ± 4.3	<0.001*
Tri glyceride [mg/dl]	72.1 ± 1.34	155.6 ± 3.52	<0.001*
LDL [mg/dl]	29.8 ± 1.79	103.5 ± 3.39	<0.001*
HDL [mg/dl]	37.37 ± 0.27	30.38 ± 1.2	<0.001*
Atherosclerosis index	0.79 ± 0.05	3.47 ± 0.21	<0.001*
Atherogenic index	2.18 ± 0.06	5.5 ± 0.27	<0.001*
MDA [nmol/L]	18.1 ± 0.25	45.98 ± 1.09	<0.001*
Catalase [nmol/L]	36.19 ± 0.29	28.09 ± 0.26	<0.001*
TNF α [pg/ml]	53.5 ± 0.39	97.2 ± 0.53	<0.001*
CRP [mg/L]	5.52 ± 0.21	7.57 ± 0.24	<0.001*

Number of rats in each group = 10.
*** = Significant to group I.** **Group I: Control.**
SE = Standard error. **Group II: HFD control**

Table [3]: Blood glucose, HbA1c, serum insulin, HOMA-IR and HOMA-β of the studied groups at the end of the experiment.

	Blood glucose [mg/dl]	HbA1c [%]	Serum insulin [µIU/L]	HOMA-IR	HOMA-β
Group I [Mean ± SE]	92.12±8.57	4.44±0.55	10.46±0.67	1.31±0.23	92.0±2.87
Group II [Mean ± SE]	102.34±9.17	5.11±1.42	10.9±1.65	1.54±0.09	78.36±8.7
Group III [Mean ± SE]	319.2 ± 17.42 *#	10.64 ± 0.45 *#	3.73 ± 0.16 *#	0.85 ± 0.04 *#	5.53 ± 0.72 *#
Group IV [Mean ± SE]	247.2 ± 10.29 *#○	5.0 ± 0.56 ○	6.69 ± 0.29 *#○	1.16 ± 0.07 *#○	13.06 ± 1.1 *#○
Group V [Mean ± SE]	275.4 ± 10.37 *#○Δ	7.15 ± 0.13 *#○Δ	5.3 ± 0.28 *#○Δ	1.05 ± 0.06 *#○	8.87 ± 0.65 *#○Δ
Group VI [Mean ± SE]	269.2 ± 7.78 *#○Δ	7.14 ± 0.4 *#○Δ	5.6 ± 0.39 *#○Δ	1.11 ± 0.08 *#○	9.71 ± 0.58 *#○Δ
Group VII [Mean ± SE]	249.9 ± 4.7 *#○♦●	6.7 ± 0.14 *#○Δ	6.62 ± 0.29 *#○♦●	1.14 ± 0.03 *#○	12.36 ± 0.69 *#○♦●

*** = Significant to group I.** **# = Significant to group II.**
○ = Significant to group III. **Δ = Significant to group IV.**
♦ = Significant to group V. **● = Significant to group VI.**
Group I: Control. **Group II: HFD control.**
Group III: HFD diabetic control. **Group IV: HFD, diabetic and metformin.**
Group V: HFD, diabetic and ginger. **Group VI: HFD, diabetic and cinnamon.**
Group VII: HFD, diabetic, ginger and cinnamon. **SE = Standard error.**

Table [4]: Lipid profile of the studied groups at the end of the experiment.

	TC [mg/dl]	**TG** [mg/dl]	**LDL** [mg/dl]	**HDL** [mg/dl]	**Atherosclerosis index**	**Atherogenic index**
Group I [Mean±SE]	86.25±3.27	75.6±4.03	29.25±3.05	40.87±6.29	3.19±0.81	2.37±0.31
Group II [Mean±SE]	172.4±3.16 *	164.7±3.2 *	111.2±3.15 *	28.2±0.85 *	3.99±0.21 *	6.15±0.25 *
Group III [Mean±SE]	193.2±2.5 *	161.1±3.1 *	112.8±1.9 *	28.1±1.32 *	5.52±1.2 *#	6.2±1.45 *
Group IV [Mean±SE]	105.8±2.7 *#○	97.4±2.46 *#○	45.5±2.1 *#○	40.8±0.72 #○	1.12±0.05 *#○	2.59±0.06 #○
Group V [Mean±SE]	124.6±1.01 *#○Δ	115.0±1.19 *#○Δ	63.2 ± 1.5 *#○Δ	38.4±1.12 #○	1.66±0.08 *#○Δ	3.27±0.1 *#○Δ
Group VI [Mean±SE]	121.9±1.64 *#○Δ	111.6±1.29 *#○Δ	60.0±1.47 *#○Δ	39.58±0.54 #○	1.52±0.05 *#○Δ	3.08±0.06 *#○Δ
Group VII [Mean±SE]	106.3±1.58 *#○♦●	96.6±1.4 *#○♦●	46.0±1.38 *#○♦●	41.08±0.62 #○♦●	1.12±0.04 *#○♦●	2.58±0.05 #○♦●

* = Significant to group I. # = Significant to group II.
○ = Significant to group III. Δ = Significant to group IV.
♦ = Significant to group V. ● = Significant to group VI.
Group I: Control. Group II: HFD control.
Group III: HFD diabetic control. Group IV: HFD, diabetic and metformin.
Group V: HFD, diabetic and ginger. Group VI: HFD, diabetic and cinnamon.
Group VII: HFD, diabetic, ginger and cinnamon. SE = Standard error.

Table [5]: MDA, catalase, TNF α and CRP of the studied groups at the end of the experiment.

	MDA [nmol/L]	**Catalase [nmol/L]**	**TNF α [pg/ml]**	**CRP [mg/L]**
Group I [Mean ± SE]	18.3±0.75	35.63±1.41	52.5±1.6	5.49±1.43
Group II [Mean ± SE]	55.4±5.86 *	26.71±1.18 *	104.75±16.42 *	7.98 ± 0.12 *
Group III [Mean ± SE]	56.03 ± 1.28 *	22.29 ± 0.54 *#	107.86± 1.26 *	8.19±0.82 *
Group IV [Mean ± SE]	22.5 ± 0.4 *#○	33.55±0.56 #○	58.03±0.63 #○	5.67 ± 0.15 #○
Group V [Mean ± SE]	39.15 ± 0.8 *#○Δ	28.47±0.66 *○Δ	88.2 ± 0.83 *#○Δ	6.9 ± 0.15 *#○Δ
Group VI [Mean ± SE]	37.33 ± 0.91 *#○Δ	28.57±0.45 *○Δ	86.8 ± 0.98 *#○Δ	6.96±0.13 *#○Δ
Group VII [Mean ± SE]	24.4±0.63 *#○♦●	29.05±0.64 *#○Δ	61.54±0.67 #○♦●	5.7±0.13 #○♦●

* = Significant to group I. # = Significant to group II.
○ = Significant to group III. Δ = Significant to group IV.
♦ = Significant to group V. ● = Significant to group VI.
Group I: Control. Group II: HFD control.
Group III: HFD diabetic control. Group IV: HFD, diabetic and metformin.
Group V: HFD, diabetic and ginger. Group VI: HFD, diabetic and cinnamon.
Group VII: HFD, diabetic, ginger and cinnamon. SE = Standard error.

DISCUSSION

The present work aimed to study the effect of administration of ginger and cinnamon extracts on diabetic adult male albino rats.

Results of the present work showed that HFD for 4 weeks led to statistical significant increase in body weight, weight gain, length and body mass index [BMI]. These results were in consistence with a study was done by Subramaniam et al. [25] to develop a rat model that replicates the natural history and metabolic characteristics of human type 2 diabetes. In this study, rats were divided into two groups and fed with commercially available normal pellet diet [12% calories as fat], while other group fed on HFD [58% calories as fat], for a period of 2 weeks. The HFD-fed rats exhibited significant increase in body weight, basal plasma glucose, insulin, triglycerides and total cholesterol levels as to rats fed on normal diet.

A study had been done by Coelho et al. [26] showed that HFD has role in obesity. They stated that an excess of body fat tissue may be related not only to energy intake and energy expenditure in humans, as stated but also to the type of diet, especially HFD, which may lead to various metabolic alterations such as hyperphagia in humans, reduced lipolytic activity in fat tissue, reduction in leptin secretion and/or sensitivity, hypothalamic neuron apoptosis, impairment of mitochondrial metabolism, insulin resistance, and obesity.

Results of the present work showed that HFD led to statistical significant increase in total cholesterol, Triglyceride, Low density lipo-protein [LDL], atherosclerosis index and atherogenic index. These results agreed with Ramalho et al. [27] who reported that HFD led to significant increase in total cholesterol, triglyceride and LDL.

Another study was made by Kennedy et al. [28] revealed that mice that received HFD for 14 weeks had excess weight gain more than mice received ketogenic diet or normal chew. This may be due to decreased expression of genes that responsible for fatty acid oxidation pathways and increase in lipid synthesis pathways. In addition, leptin levels were markedly increased in HFD animals with other mice.

Dyslipidemic changes occurs in obesity may be due to the increased triacylglycerol, content of the liver due to increased influx of excess NEF as into the liver, lipid alterations have been considered as contributory factors to oxidative stress in obesity. Increased production of reactive oxygen species as well as reduced antioxidant defense mechanisms have been suggested to play a role in both humans and animal models of obesity [29].

Results of the present work showed that HFD led to statistical significant increase in malondialdehyde [MDa], tumor necrosis factor alpha [TNFα] and C-Reactive protein associated with significant decrease of catalase. These results agreed with Olorunnisola et al. [30] who reported that HFD increased MDa associated with decreased level of catalase. This finding can be explained by compensatory adaptation of organism to oxidative stress in HFD. The increased lipid peroxidation lead to inactivation of the enzymes by crosses linking with MDa; this will cause an increased accumulation of superoxide, H_2O_2 and hydroxyl radicals which could further stimulate lipid peroxidation [31].

Sivakumar and Anuradha [32] reported that, a significant increase in TNF-α was observed in rats fed on high fructose diet [60% of diet] for 60 days. These results may be related to that, high fructose diet consumption may lead to Steatosis or fat overload in the hepatocytes which results in activation of stress/inflammatory pathways that trigger the resident macrophages in the liver [Kupffer cells] for inflammatory reactions [33]. The rise in TNF-α in fructose-fed rats could be related to nuclear factor-kappa [NF-KB] activation which in turn is attributed to the rise in Reactive Oxygen Species [ROS] levels and oxidative stress. NF-KB activation increased the expression of a large number of pro-inflammatory cytokines and stimulation of inflammatory cascade have been observed in fructose-fed rats [34].

In the present study, injection of Streptozotocin [STZ] led to significant decrease of body weight. These results were in agreement with the findings of Husni et al. [35] and Yang and Hyung-Sub [36] who observed marked decrease body weight in streptozotocin induced diabetic rats. Due to absolute or relative deficiency of insulin and decreased production of aTP and protein synthesis decreases in all tissues [37].

Soliman [38] noticed that untreated diabetic rats showed severe body weight loss. This characteristic weight loss in diabetic rats could be due to degradation and catabolism of fats and proteins. Thus, increased catabolic reactions leads to muscle wasting which may be the major cause for weight loss in diabetic rats. However, extract-treated groups showed a sign of recovery in the body weight which suggests the protective effect of the extract by preventing it from muscle wastage and other macromolecular degradations.

In the present study STZ injection led to significant increase in blood glucose level and glycated hemoglobin level [Hba1c] associated with significant decreased in serum insulin level, HOMa-IR and HOMa- β. These results in agreement with Sekkin et al. [39] who found that a single injection of STZ leads to development of DM indicated by an elevation of random blood glucose level, elevation of glycated hemoglobin level [Hba1c] and decreased serum insulin level. This occurs due to destruction of β cells within 24 hour, damage of islets cells and triggering an inflammatory process leading to macrophage and subsequent lymphocyte infiltration caused by STZ. Oxidative damage induced by STZ in rats is closely associated with chronic inflammation leading to potential tissue damage [40].

STZ induced diabetes by preventing glucose oxidation or reduction of insulin biosynthesis and secretion. The toxicity of STZ is due to DNa alkylation at 6 O-position of guanine which results in fragmentation of DNa and defects of the beta cells. also, STZ act as an intracellular nitric oxide [NO] donor and generates reactive oxygen species [ROS]. The action of both NO and ROS may also contribute to DNa fragmentation and other damages caused by STZ [41].

In the present study STZ injection led to significant increase in cholesterol, TGs and LDL associated with in-significant decreased of HDL. These results were compatible with Saleh and Maged [42] who reported that cholesterol, TGs and LDL levels showed significant elevations in diabetic animals when with normal ones. also, Akmali et al. [43] reported that elevated serum cholesterol and TGs levels occur in diabetes when with normal control group.

The decreased levels of HDL and increased level of LDL are indicators of disturbed lipoprotein metabolism. HDL has anti-atherosclerotic action and facilitates the removal of cholesterol from blood vessels. Thus, an elevated level of LDL, cholesterol and triglycerides elevate the risk of atherosclerosis [44]. The elevated serum level of free fatty acids could be attributed to inhibition of β oxidation by cadmium. The free fatty acids level increases in the liver mitochondria, followed by its discharge into the circulatory system [45].

Impairment in insulin sensitivity due to high concentration of lipids in the cells is responsible for the elevated cardiovascular risk in diabetes mellitus. Thus, the altered lipid and lipoprotein pattern observed in diabetic rats could be due to defect in insulin secretion and/or action. accumulation of cholesterol and phospholipids in liver due to elevated plasma free fatty acids has been reported in diabetic rats. Hyperglycemia is an important contributor for the cardiovascular diseases [CVD] risk [46].

Several mechanisms have been implicated in the underlying detrimental effects of hyperglycemia-induced tissue damage. activation of the renin–angiotensin–aldosterone system [RaaS], polyol- and advanced glycation end product [aGE]-dependent pathways, the hexosamine pathway flux, activation of protein kinase C [PKC] and nicotinamide adenine dinucleotide phosphate [NaDPH] oxidases, also referred to as NaDPH oxidase [NOX]. These have been demonstrated to cause significant disruption of the regulatory processes that control homeostasis and stimulate several detrimental cellular signaling events [47].

In the present study, STZ injection led to significant elevation of MDa level associated with significant decrease of catalase level. These results were in agreement with Lo et al. [48] who reported a decreased catalase level and increased level of MDa in diabetic rats. The decrease in the activity of this antioxidants can lead to increase superoxide anion and hydrogen peroxide in biological systems, which in turn generate hydroxyl radicals resulting in lipid peroxidation. CaT is responsible for the reduction of H2O2 for protecting cells against highly reactive OH radicals [37]. Oxidative stress in diabetes is caused by hyperglycemia inducing increased free radical formation [49].

In the present study, TNF alpha and CRP elevated in diabetic rats. These results in-agreement with Edrees et al. [50] who noticed TNF-α and CRP increased in diabetic rats. Oxidative stress causes production of abnormal cytokine production as TNF-α that produced by the liver in response to inflammation El-Komy and Mouafi [51] reported that TNF-α production was increased in oxidative damages. TNF-α stimulate neutrophil infiltration and nuclear factor kappa B [NF-kB] production. Moreover, TNF-α plays a major role in the activation of caspases which are important in the induction of cell apoptosis [52].

In the present study, metformin, ginger and cinnamon administration to diabetic rats led to significant increase in the body weight associated with significant decrease of TC, TG, LDL, atherosclerosis index and atherogenic index. These results agreed with Shirali et al. [53] who reported that metformin improves lipid profile through activation of adenosine mono phosphate protein kinase [aMPK] that is effective in insulin signaling, energy balance of the whole body and

metabolism of lipids. activated aMPK inhibits acetyl-COa carboxylase [aCC] through phosphorylation of Ser-79 resulting in reduction of malonyl-COa level and activation of CTP-1 enzyme and thus inhibits lipogenesis. In addition, metformin provides the possibility of oxidation of fatty acids through activates lipoprotein lipase [LPL] to break down VLDL in to free fatty acids [FFa].

Metformin reduces level of cholesterol in patients with T2DM. This means that activated aMPK reduces synthesis of cholesterol through phosphorylation and inhibition of HMG-COa reductase [cytosolic enzyme of cholesterol biosynthesis]. as well as, activated aMPK reduces biosynthesis of triacylglycerol [TaG] in liver and then reduces concentration of TG in diabetics [54].

Ginger improve lipid profile in diabetes due to the pharmacological action of ginger which elevates the activity of hepatic cholesterol-7α-hydroxylase which is the rate-limiting enzyme in the biosynthesis of bile acids and stimulates the conversion of cholesterol to bile acids [55]. Moreover, ginger antihypercholesterolemic effect may be due to the inhibition of cellular cholesterol synthesis, this may be due to the presence of niacin in ginger, niacin causes increased clearance of VLDL, lower TG levels, increase hepatic uptake of LDL, and inhibition of cholesterogenesis [9].

Also, these results in agreement with Shatwan et al. [56] who noticed that cinnamon and ginger lower the elevated levels of TC, TG and LDL in rats. The possible potential mechanism underlying the hypolipidemic effect of them could be due to their high contents of polyphenols [cinnamon] and of gingerols and shogaols [ginger] which inhibit the intestinal absorption of cholesterol with subsequent hypocholesterolemic activity.

Oral administration of cinnamon and ginger to obese diabetic rats caused hyperinsulinemia. The hyperinsulinimic effect of both could be possibly explains their antiobesity effect, which was evident in this study, as obesity is commonly linked with hyperinsulinemia [57].

In the present study, metformin, ginger and cinnamon administration to diabetic rats led to significant decrease in the blood glucose level, glycated hemoglobine associated with significant increase of insulin level. These results in-agreement with Yang et al. [58] who reported that metformin reduces hyperglycemia primarily by inhibiting hepatic gluconeogenesis. It also increases insulin sensitivity, enhances peripheral glucose uptake [by inducing the phosphorylation of GLUT4 enhancer factor], and reduces insulin-induced suppression of fatty acid oxidation

These results also, in-agreement with Son et al. [59] who noticed ginger decreased blood glucose and glycated hemoglobin levels in diabetes. The hypoglycemic effect of ginger by increased the activity of glycolytic enzymes [glucokinase, phosphofructokinase, pyruvate kinase] [55].

Also, cinnamon increases the production of glucose-6-phosphate dehydrogenase [G-6-PDH] in the liver in which G-6-PDH leads to reduce glucose transporting by pentose phosphate pathway [pentose shunt] and storage of glucose as a glycogen in the liver. It activate the function gluco-kinase enzyme which in turn stimulates glucose transporters [GLUT4] for entering of glucose to the hepatic cells [glycogenesis] and

adipocytes lead to increase in glycogen storage available for energy production [60].

Bugudare et al., [61] found that cinnamon reduced blood glucose in diabetic rats when used alone or combined with metformin drugs. Moraveji et al. [62] observed that lowering postprandial glucose effect of cinnamon exhibited by suppression of alpha-glycosidase enzyme to enhancing the metabolism of glycogenesis in liver and decrease the circulating glucose.

In the present study, metformin, ginger and cinnamon administration to diabetic rats led to significant decrease in the MDa and TNF alpha associated with significant increase of catalase and CRP level. These results in-agreement with Onyeka et al. [63] who reported metformin increased catalase and decreased MDa. Increase in their activities is an indication of their ability to scavenge ROS, thus contributing to the protective effect against oxidative stress and preventing further damage to membrane lipids.

Ginger prevents the production of free radicals, neutralizes, and scavenges free radicals produced in the body and chelats prooxidant transition metals as iron. Gingerols and shogaols are the major bioactive flavonoids present in ginger, they suppress the accumulation of reactive oxygen and/or nitrogen species in the cells. The 6-gingerol treatment regulates the overexpression of TNF-α [64].

The significant decrease in MDA level in hypercholesterolemic rats treated with cinnamon attributed to its antioxidant activity as cinnamon contains polyphenols which are potent antioxidant compounds which can help to reduce the oxidative damage caused by free radicals [65].

Cconclusions: In the present study STZ developed diabetes and pancreatic islet loss and reduction of insulin-producing beta cell mass are relevant aspects to diabetic pathogenesis. Oxidative stress plays an important role in the pathogenesis of diabetes. The presented results suggested that metformin, ginger and cinnamon administration might be beneficial for reducing diabetic complications by preventing oxidative damage. Metformin, ginger and cinnamon administration have a marked effect on improvement of blood glucose, insulin, antioxidant levels and lipid profile. This might be due to increasing insulin secretion, increasing tissue sensitivity to the hormone and decreasing hepatic fat biosynthesis. These hypoglycemic, hypolipidemic and anti-hypertensive effects of metformin, ginger and cinnamon could improve diabetic mortality and morbidity.

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