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Medicinal utility and cardiovascular protection of pomegranate or ginger in the treatment of diabetic/obese rats

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Abstract

Diabetes and obesity are representing a major public health problem that is on rise worldwide. In this work, a comparison study was occurred between normal control ones, diabetic/obese animals group (without treatment), diabetic/obese rats group treated with 500mg pomegranate/kg b.wt by the aid of oro-gastric tube for one month and diabetic/obese rats group treated with 400mg ginger/kg b.wt by the aid of oro-gastric tube for one month to evaluate the alterations in the carbohydrate profile, lipids picture, heart enzymes activity and cardiac markers associated with the changes in oxidative and antioxidant status in the heart tissues due to experimentally initiation of diabetes/obesity (DM/Ob). Initiation of diabetes/obesity was occurred in rats by the administration of both streptozotocin/nicotinamide to induce diabetes and cholesterol/cholic acid to induce obesity. Comparing to diabetic/obese rats group, significant corrections were occurred in studied parameters after diabetic/obese rats treated by pomegranate or ginger for one month. These findings are consistent with the concept that pomegranate or ginger is hypoglycemic and hypolipidemic agents. The fundamental mechanisms of these properties were explained with obtainable modern researches.

Keywords : Diabetes mellitus, Obesity, Pomegranate, Ginger, Rats.

1. Introduction

Advanced glycation end products (AGEs) are created by the Maillard process; a non-enzymatic response between ketone cluster of the glucose or aldehydes and oxidation of proteins, lipids and nucleic acids [1]. They are proficient of modulating various cellular processes. Increment formation and accumulation of AGEs has been reported to occur in conditions such as diabetes mellitus. Furthermore, AGEs may be a major reason in the

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progress of metabolic complications rate in diabetes. Moreover, AGEs are formed and elevated permanently in the body according to the concentration of sugar in blood and degree of disease as illustrated in (Figure 1) [2]. Recently, the correlation between the increment of AGEs and pronouncing cardio-vascular complications in diabetes was postulated by several authors [3,4,5]

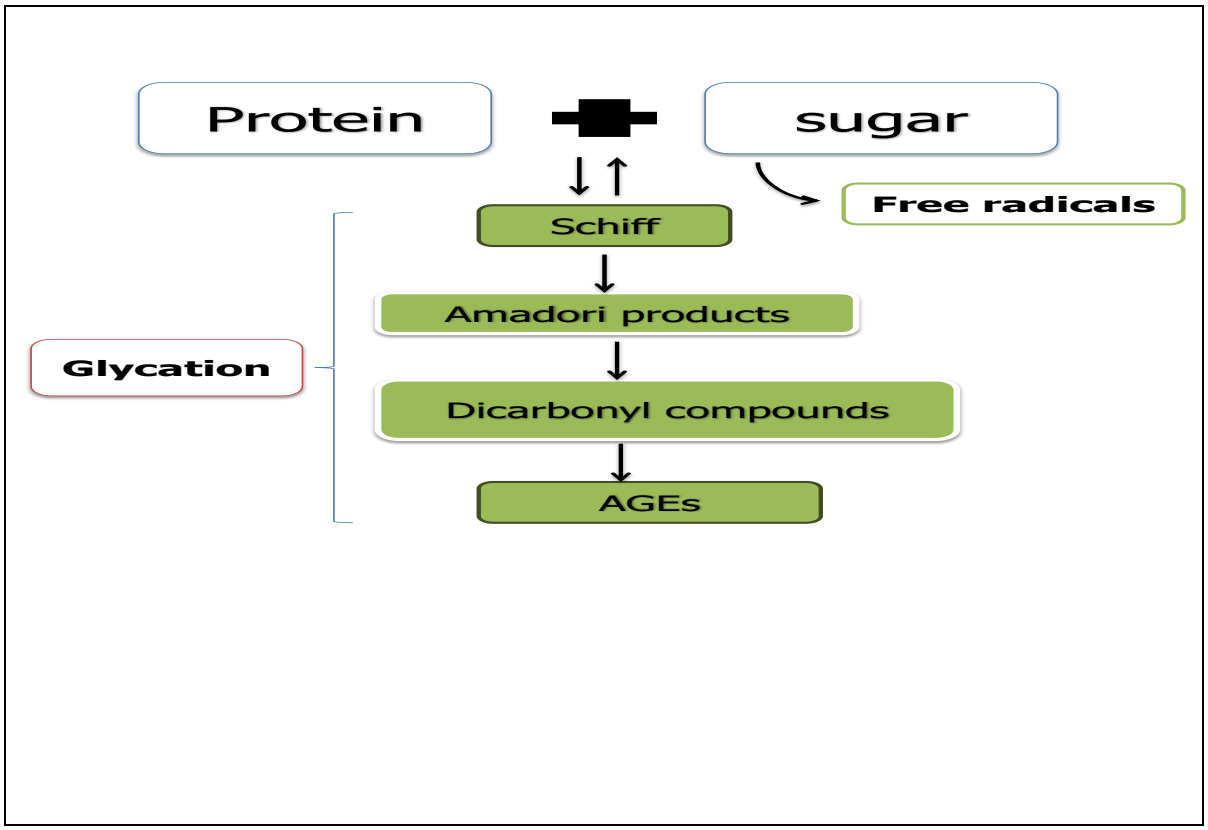

Figure 1. illustrated the formation of AGEs.

Alternative medicine (Traditional medicine) comes from the Egyptians, Chinese, Indians, Greeks and Romans around about 4000BC. The antioxidant activity of herbs has been extensively researched aspect. This action may be due to the great amount of phenolic compounds in herbs [6]. Herbs and their constituent compounds can act through certain actions as raising the activities of endogenous protective enzymes, shielding DNA from free radical-induced structural destruction and encourage the self-damage of aberrant cells (apoptosis) as well as decreasing tumor growth. Some authors reported that the ability of herbs to act as cardiovascular protective agents (hypoglycemic, hypolipidemic, anti-platelet aggregation and anti-thrombotic). They also pointed to that some herbs and their

components possess anti-inflammatory role by stopping the progress of many chronic diseases and health troubles due to the increment of free radicals production [7].

Pomegranate (*Punica granatum L.*) is usually cultured in Asia, Mediterranean area and Southwest of America [8]. Numerous investigations noted enhancement in diabetic patients after intake of pomegranate juice. These improvements may be attributed to the decline in the oxidative status and inflammation [9,10]. Pomegranate is contained several polyphenols and antioxidant agents which have the ability to stimulate β-cells to secrete insulin [11]. Some authors evaluated the anti-diabetic effects of pomegranate [12,13]. They explained these data to the activities of polyphenols and antioxidant agents in pomegranate by declining oxidative stress and formation of lipid peroxidation as well as decreasing nuclear factor kappa-β (NF-κβ) activity [14,15]. Furthermore, several authors demonstrated the presence of polyphenols [gallotannins, ellagitannins (2,3-hexahydroxydiphenoyl and 4,6 gallagylglucoside), gallagyl esters, hydroxycinnamic acids and hydroxybenzoic acids, gallic acid, ellagic acid, caffeic acid, chlorogenic acid, p-coumaric acid, aglycone, and ferulic acid], anthocyanosides [cyanidin-3-glucoside, cyanidin-3,5-diglucoside, cyanidin 3-rutinoside, cyanidinpentoside, delfinidin-3,5-diglucoside, delfinidin-3-glucoside, pelargonidin-3-glucoside and pelargonidin-3,5-diglucoside], flavonols and flavones [catechin, epicatechin, gallocatechin, kaempferol, quercetin and apigenin], alkaloids [pseudopelletierine, pelletierine, isopelletierine, methylpelletierine, 1-pelletierine, dl-pelletierine and methylisopelletierines], organic acids [citric acid, L-malic acid, oxalic acid, ascorbic acid, quinic acid, fumaric acid, tartaric acid and succinic acid], lignans (furofuran, dibenzylbutyrolactone and dibenzylbutane), minerals (Ca, P, K, N, Mg & Na) and active steroid components in pomegranate by using HPLC and LC-MS/MS analysis [16,17].

Ginger (*Zingiber officinale*) is generally used as a spice. In ancient, ginger rhizome is usually used as a herbal medicine [18]. It contains several vitamins, minerals and proteolytic enzymes. Several authors postulated a remarkable decline in the oxidative stress in diabetic rats after treated with ginger [19,20]. They explained these data to the hypoglycemic and hypolipidemic properties of ginger. In diabetic rats treated with ginger, a considerable decline in the serum glucose, cholesterol, and triacylglycerol concentrations associated with elevation in serum HDL-cholesterol levels when compared with diabetic rats (without treatment) were recorded [21,22,23]. Some authors were identified several

compounds in ginger such as; gingerols, shogaols, paradols, dihydroparadols, 3-dihydroshogaols, acetyl derivatives of gingerols, gingerdiols, mono- and di-acetyl derivatives of gingerdiols, 1-dehydrogingerdiones, diarylheptanoids, zingiberene, phellandrene and methyl ether derivatives of some of these compounds as well as (4,6,7,8 &10)-gingerols [24,25].

This study was undertaken to get medicinal utility of pomegranate or ginger on diabetic/obese rats and their capacity to decrease the dual impact of the existence of diabetes and obesity which lead to multi-organs dysfunction in rats.

2. Material and Methods

2.1 Chemicals and Herbs

Streptozotocin (STZ), nicotinamide (NT) and cholic acid were bought from Sigma-Aldrich (St. Louis, MO, USA). Cholesterol was purchased from El-Nassr Pharm.Co., Egypt. Pomegranate powder was purchased from Kanegrade, Ltd Ingredients House Caxton Way, Stevenage Hertfordshire, England. Ginger was procured in the form of 30 tablets each contained 400mg ginger (MEPACO Company, Enshas, Sharkeya, Egypt).

2.2 Plant material

200ml boiling distilled water was added to 3gm powder pomegranate, left it for 10 minutes, and filtered. The filtrate was dried at 40-45C0 in the incubator. The chemical and structural composition of pomegranate peels powder consists of (total phenols 15,05g, ellagic acids 2,89 g, punicalagin 3,05, gallic acid 0,89g, chlorogenic acid 0,02, coumaric acid 0,047g)/100g of dry matter.

10 gm of ginger powder were soaked in 100ml [10%] hot water [88 C○] in awater bath for 6 h. Then ,itis filtered by capron silica cloth 150 µ. The filtrate was stored in dark bottles in the refrigerator at [4C○].

2.3. Ethical Approval

The study was approved by the Ethics Committee of and the animals were kept in accordance with the University guidelines on the use and care of animals in research.

2.4. Animals

This work was carried out on forty adult male albino rats (*Rattus rattus*) as a rat model for induction of diabetes and obesity together. The animals were obtained from the Serum and Antigen Laboratories at Helwan with an average weight of 140±10g and 12±1 weeks of age. They were allowed seven days pre-experiment period to acclimatize the laboratory conditions in order to avoid any complications along the course of' the experiment. The animals were caged in wire bottom galvanized metal wall boxes under controlled environmental and nutritional conditions (25°C and 55-60% relative humidity). They were fed on a standard laboratory animal diet according to NRC [26]. Food and fresh tap water was available and replenished daily. All animal procedures were conducted in accordance with the standards set forth in the guidelines for the care and use of experimental animals by the Committee for the Purpose of Control and Supervision of Experiments on Animals and the National Institutes of Health-Ain Shams University.

2.5. Experimental design and Protocol

The animals were randomly divided into two main divisions. In the first division, ten rats were fed on a standard rodent ration (basal diet) only and served as normal control group (Group 1). While, the second division of animals (thirty rats) was fed on a basal diet supplemented with 2% dietary cholesterol together injected with cholic acid (I/M) for one month to induce obesity associated as described by Beynen *et al.* [27]. At the same time, the animals in this division were also injected intraperitoneal (i.p) with 60mg streptozotocin (STZ)/kg b.wt as a single dose which freshly dissolved in cold citrate buffer, pH 4.5. After 15min of STZ injection, animals were injected i.p by 110mg nicotinamide/kg/b.wt. (prepared in normal saline) to induce diabetes mellitus type-2. The rats were considered to be diabetic if their serum glucose levels were more than 250 and less than 300mg/dL. This model was created by Masiello *et al.* [28] and confirmed by several authors [29,30]. This animals group was served as diabetic/obese (DM/Ob) rats. After one month of induction diabetes/obesity in the animals, the DM/Ob rats were further divided into 3 equal groups, 10 rats for each.

Group (2): the animals group was not further treated for another one month and served as recovery diabetic/obese (DM/Ob) rats group.

Group (3): DM/Ob animals group was received 500mg pomegranate/kg b.wt/day by the aid of oro-gastric tube for one month as described by several authors [31,32]. This rats group served as DM/Ob+P group.

Group (4): DM/Ob rats group was received 400mg ginger/kg b.wt/day by the aid of oro-gastric tube for one month to previously mentioned methodology [33]. This rats group served as DM/Ob+G group.

2.6. Tissue and Blood sampling

At the end of investigational time, rats were slightly anaesthetized by diethyl ether. Blood samples were collected from the heart in clean dry test tubes containing ethylene diethyl tetraacetic acid (EDTA). Other blood samples left to clot and centrifuged at 10,000 rpm for 20 minutes to obtain sera. Sera were separated and kept at -20°C for the biochemical parameters. After sacrifice, hearts were removed, washed with cool saline solution (0.9% NaCl) and kept at -80°C till assessments.

2.7. Biomarker Analysis

Serum concentrations of glucose, total cholesterol (T-Ch), triglycerides (TG), high-density lipoproteins-cholesterol (HDL-Ch), low-density lipoproteins-cholesterol (LDL-Ch), creatine kinase (CK), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) were determined using commercial kit purchased from Spainreact (Santa Coloma, Spain) and adopting the instructions supplied by the manufacturer. Serum rat levels of C-peptide, glycation end products (GEPs), resistin (Res), leptin (Lept), adiponectin (Adp), heart-fatty acid binding protein (H-FABP) and endothelin-1 (ET-1) as well as rat glycated haemoglobin (HbA1C) concentration in blood were measured using a solid phase enzyme linked immunosorbent assay (ELISA) and following the manufacturer instructions. These commercial rat kits were procured from CUSABIO Technology LLC., USA. Serum total nitric oxide (TNO) level was determined by the aid of commercial kit bought from BioVision Inc., Milpitas, USA, following the instruction of manufacturer. Moreover, glutathione (GSSG/GSH), superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) concentrations were estimated in heart tissues according to manufacturer instructions. These commercial kits were purchased from Cell BioLabs, Inc., USA.

2.8. Statistical analysis

The obtained data in the different groups were statistically compared by ANOVA (one way analysis of variance) followed by Duncan's multiple range tests to evaluate the alterations in the studied parameters as a result of induction DM/Ob in rats as well as to estimate the enhancement roles of pomegranate or ginger on diabetic/obese rat groups. These data were expressed as mean±SE and significance was defined as $P<0.05$. Statistical analyses were calculated using computerized SPSS program (Windows Version, 20).

3. Results

3.1. Carbohydrate profile

The induction of DM/Ob in rats caused a significant ($p<0.05$) increment in the serum levels of glucose, and HbA1C (Table 1). While, C-peptide level was remarkable declined as a result of induction DM/Ob in rats. Moreover, considerable improvements were occurred in the levels of the serum glucose, C-peptide as well as HbA1C concentrations in DM/Ob rat groups which treated with pomegranate or ginger for one month. The best improvements were recorded in all studied pervious parameters in DM/Ob rats group after treated with 500mg pomegranate/kg b.wt/day for one month (Table 1).

Table (1): The therapeutic role of pomegranate or ginger on carbohydrate profile in DM/Ob rats after one month.

Groups	Control	Recovery	Pomegranate	Ginger
Parameters				
Glucose (mg/dL)	123.56±0.591 **D**	324.62±4.167 **A**	177.24±2.430 **C**	251.12±2.056 **B**
HbA1C (ng/ml)	4.298±0.053 **D**	7.459±0.072 **A**	5.318±0.040 **C**	6.068±0.047 **B**
C-peptide (ng/ml)	10.612±0.042 **A**	5.174±0.037 **D**	7.410±0.041 **B**	6.118±0.055 **C**

- Data are expressed as means ± standard error (SE) for 10 rats/group.
- A,B,C,D in each parameter means significant different ($P<0.05$).

3.2. Advanced glycation end products analysis (AGEs)

The induction of DM/Ob in rats caused a significant ($p<0.05$) increment in the serum levels of AGEs (Figure2). Moreover, considerable improvements were occurred in the levels of the serum AGEs in DM/Ob rat groups which treated with pomegranate or ginger for one month. The best improvements were recorded in DM/Ob rats group after treated with 500mg pomegranate/kg b.wt/day for one month (Figure 2).

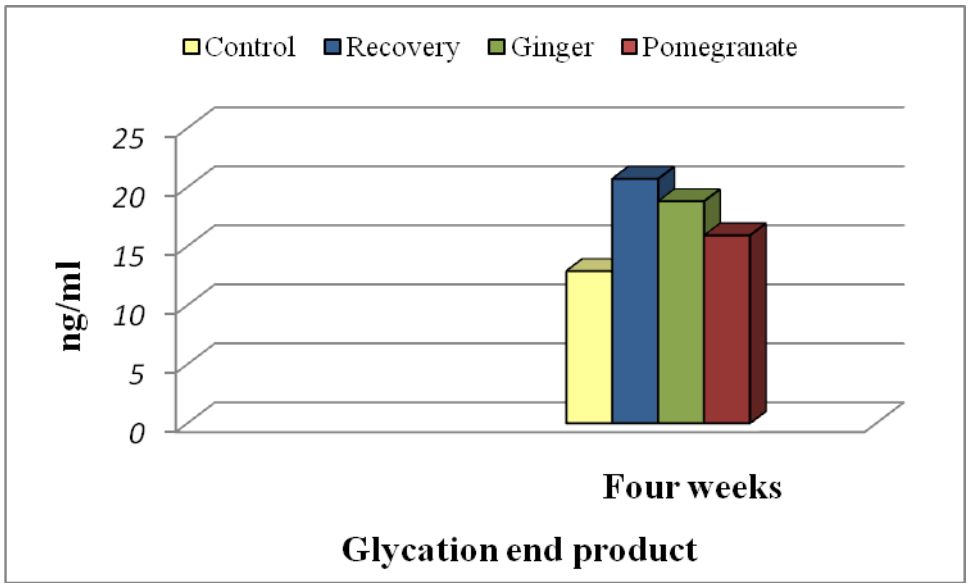

Fig. 2: Effect of ginger and pomegranate on the concentration of advanced glycation end products (AGEs)in DM/Ob rats.

3.3. Lipid profile

A significant ($p<0.05$) elevation in serum levels of T-Ch, TG, HDL-Ch, LDL-Ch, Res and Lept were occurred as a result of induction DM/Ob in rats compared to their corresponding control rats group (Table 2). On the other hand, the serum concentration of Adp was considerable decreased in DM/Ob rats group compared to control ones (Table 2). However, considerable enhancements were recognized in serum T-Ch, TG, HDL-Ch, LDL-Ch, Res, Lept and Adp levels of DM/Ob rat groups after treated by pomegranate or ginger. The greatest correction was obtained in the previous parameters after DM/Ob rats group which received 500mg pomegranate/kg b.wt/day for one month (Table 2).

3.4. Heart profile

The induction of DM/Ob in rats was caused a significant ($p<0.05$) increment in the serum activities of CK, CK-MB, LDH and AST as well as considerable elevation in serum H-FABP and ET-1 levels (Table 3). While, a remarkable decreased in the serum TNO levels in DM/Ob rats was observed compared to normal control animals group (Table 3). The supplementation of pomegranate or ginger to DM/Ob rat led to remarkable correction in the previous parameters (Table 3). The maximum amelioration was obtained in these studied parameters after DM/Ob rats group treated with 500mg pomegranate/kg b.wt/day for one month (Table 3).

Table (2): The therapeutic role of pomegranate or ginger on lipid and hormone profiles in DM/Ob rats after one month.

Groups	Control	Recovery	Pomegranate	Ginger
Parameters				
Total Cholesterol (mg/dL)	55.328±0.229 **D**	101.24±0.896 **A**	77.743±0.659 **C**	92.267±0.703 **B**
Triglycerides (mg/dL)	66.541±0.418 **D**	122.64±0.764 **A**	82.386±0.905 **C**	110.881±0.712 **B**
HDL (mg/dL)	15.226±0.095 **D**	20.488±0.159 **A**	16.262±0.113 **C**	18.924±0.127 **B**
LDL (mg/dL)	26.794±0.169 **D**	56.224±0.348 **A**	45.004±0.267 **C**	51.167±0.309 **B**
Resistin (pg/ml)	3.376±0.028 **D**	8.409±0.059 **A**	6.458±0.037 **C**	7.314±0.046 **B**
Leptin (ng/ml)	287.9±1.821 **D**	604.28±3.247 **A**	454.68±2.667 **C**	586.2±2.421 **B**
Adiponectin (ng/ml)	9.106±0.083 **A**	6.484±0.047 **D**	7.901±0.062 **B**	6.948±0.056 **C**

- Data are expressed as means ± standard error (SE) for 10 rats/group.
- A,B,C,D in each parameter means significant different ($P<0.05$).

Table (3): The therapeutic role of pomegranate or ginger on heart profile in DM/Ob rats after one month.

Groups	Control	Recovery	Pomegranate	Ginger
Parameters				
Creatine kinase (U/L)	94.871±0.468 **D**	221.56±1.948 **A**	150.46±0.903 **C**	185.58±1.948 **B**
Creatine kinase-MB (U/L)	14.923±0.072 **D**	27.018±0.289 **A**	19.564±0.152 **C**	23.958±0.194 **B**
Lactate dehydrogenase (U/L)	237.62±1.194 **D**	502.65±3.407 **A**	385.64±2.313 **C**	472.3±2.561 **B**
Aspartate aminotransferase (U/L)	121.88±1.063 **D**	229.08±3.124 **A**	161.04±1.432 **C**	212.61±2.447 **B**
H-FAPB (ng/ml)	15.314±0.247 **D**	40.634±0.953 **A**	23.454±0.426 **C**	33.264±0.714 **B**
Endothelin-1 (pg/ml)	0.386±0.002 **D**	0.893±0.011 **A**	0.499±0.008 **C**	0.759±0.005 **B**
Total nitric oxide (µM/ml)	56.679±0.784 **A**	35.196±0.317 **D**	49.998±0.602 **B**	41.572±0.429 **C**

- Data are expressed as means ± standard error (SE) for 10 rats/group.
- A,B,C,D in each parameter means significant different ($P<0.05$).

3.5. Oxidative stress and antioxidant enzymes status

In relation to the normal control rats group, a significant ($p<0.05$) decrease in the activities of heart GSH, GSSG, SOD and CAT were reported in DM/Ob rats compared to control rats group (Table 4). In contrast, the induction of DM/Ob in rats caused a significant ($p<0.05$) elevation in the heart MDA level (Table 4). The treatment of DM/Ob rats with pomegranate or ginger led to considerable correction in the heart GSH, GSSG,

SOD, CAT and MDA concentrations. The highest improvements were recorded in these parameters after the DM/Ob rats group treated with pomegranate as shown in Table (4).

Table (4): The therapeutic role of pomegranate or ginger on heart antioxidant and lipid peroxidation status in diabetic/obese rats after one month.

Groups	Control	Recovery	Pomegranate	Ginger
Parameters				
GSH (µM/mg protein)	13.976±0.076 **A**	9.428±0.151 **D**	12.094±0.284 **B**	11.028±0.125 **C**
GSSG (µM/mg protein)	0.0114±0.00029**A**	0.0081±0.00022**D**	0.0099±0.00026**B**	0.0087±0.00023**C**
SOD (U/mg protein)	132.16±0.458**A**	72.218±0.581**D**	99.716±0.823**B**	77.098±0.569**C**
CAT (U/mg protein)	53.086±0.453**A**	31.376±0.349**D**	42.554±0.4178**B**	36.168±0.387**C**
MDA (µM/mg tissue)	10.204±0.047**D**	28.172±0.317**A**	15.168±0.298**C**	23.336±0.260**B**

- Data are expressed as means ± standard error (SE) for 10 rats/group.
- A,B,C,D in each parameter means significant different ($P<0.05$).

4. Discussion

Cardiovascular damage in diabetic patients is dependent on the kind of diabetes mellitus. This damage includes macrovascular complications (cardiovascular disease) or/and microvascular complications (chronic kidney disease, neuropathy and retinopathy) in patients [3,4]. The mechanisms are not entirely clear diabetic/obese peoples. In both rats and mice models as well as inadequate data from some investigations conducted in humans confirmed a dysfunction in hepatic insulin receptor (number and activity) causing destruction in pathway of insulin signaling [2] associated with lipid metabolic disorders by formation of ceramides and diacylglycerols [4]. Both ceramides and diacylglycerols can

inhibit proximal insulin signaling through phosphorylation of insulin receptor substrate and disturbance in the activities of protein C kinase, protein kinase-β, and phosphoinositide-3-kinase [1,4]. The alterations in ceramides and diacylglycerols are recognized in both diabetic and obese patients [2,34].

Advanced glycation end products (AGEs) are diverse compounds and resultant from Maillard reactions [5,35]. The formations of AGEs in diabetic patients lead to pronouncing DM complications. These complications are obtained from the interactions between bi-product of carbohydrate with protein, lipids, or nucleic acids. These interactions cause destruction in structural and function of different macromolecules and lead to increment of oxidative stress and appearance of inflammation as well as endothelial injure [36]. So, the elevation of oxidative stress is considered the main mechanism leading to cardiovascular diseases in diabetic/obese patients [2,3]. In hyperglycemia, NADPH-oxidase is activated also, superoxide anions undergo a series of reactions to produce excessive ROS and oxidative stress [1,4].

In cases of diabetes with cardiovascular diseases, both oxidative stress and inflammation are promoted [1,3]. These authors reported that the formation of ROS is directly or indirectly led to the increment of several factors (nuclear factor kappa-β (NF-κβ), transforming growth factor-β (TGF-β) and changes in the activities of protein kinase-C and mitogen-activated protein kinase. Furthermore, the evolution of cardiovascular diseases in diabetic patients may be due to the elevation in the levels of pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-6). The over-expression genes of these cytokines can lead to promotion of cardiac fibroblast proliferation, elevation in collagen synthesis and finally developing of myocardial fibrosis.

Atherosclerosis is a serious syndrome and usually associated with hyperglycemia, and dyslipidemia. The development of atherosclerosis may be due to the increment of both ROS and AGEs formations associated with imbalance in autonomic and genetic factors [37]. It is supposed that the adipose tissue initiates obesity as a result of inflammation and endothelial dysfunction with over-expression genes of adhesion molecules (ICAM-1, VCAM-1, P-selectin and E-selectin) as well as changes in T-lymphocytes and monocytes [38]. In both diabetes and obesity, the progress of oxidative stress and increment of

inflammation guide to pronounce of vascular endothelial dysfunction. Also, the elevation of inflammation increases leukocyte adhesion. The progress in leukocyte adhesion led to destruction in endothelial signal transduction and redox regulated transcription factors linked with decreasing in NO production and developments of microvascular complications [35]. Moreover, several factors can clarify endothelial dysfunction in diabetes such as hyperglycemia, hyperlipidemia and hyperhomocysteinemia [39,40]. Elevation in the endothelin-1 (ET-1) level can be seen in diabetic/obese patients with pronouncing of cardiac diseases and abnormalities in vascular reactivity [4,41,42].

In the current study, administration of a STZ/NA and cholesterol/cholic acid to induce diabetes mellitus and obesity in rats caused a significant ($p<0.05$) increment in the levels of glucose, AGEs and HbA1C (Table 1). These data may be attributed to the elevation in the hepatic diacylglycerol content, reduction in GSH pool in the hepatocytes and the activities of glyoxalase-I and glyoxalase-II and changes in the levels of circulating adipocytokines (leptin and resistine). Similar results were obtained by several authors [4,42]. They recorded a remarkable decline in both glucose transporters and insulin receptors, elevations in the pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and changes in Toll-like receptors (TLRs) in diabetic patients.

On the other hand, a considerable decline in the serum C-peptide level was recorded in DM/Ob rats group comparing to corresponding control rats group (Table 1). These data may be also due to the achievement of STZ (diabetogenic agent) causing injury in the pancreatic β-cells coupled with extensive DNA injury led to hyperactivity of PARP-1, severe exhausting in NAD^+ and decreasing in ATP production linked with lessening in mitochondrial aconitase activity and potential of mitochondrial membrane. These results are matching with those obtained by Yamagishi & Imaizumi [43] and Perez-Burillo *et al.* [44]. The last authors recognized these facts to the toxic effect of STZ on pancreas causing minimizing in insulin secretion.

A remarkable elevation in serum concentrations of T-Ch, TG, HDL-Ch, LDL-Ch, Res and Lept associated with a significant ($p<0.05$) reduction in Adp level were observed in DM/Ob rats group compared to their corresponding control rats ones (Table 2). These results may be due to increment of free radicals production, lipids peroxidation and *de novo*

lipogenesis as well as mitochondria dysfunction. Furthermore, these data may be attributed to the confusion in the neuropeptide hormones and negative shift in the hypothalamus-pituitary-thyroid axis (HPTA) and. These data are in agreement with several researchers [45,46,47]. The last investigators explained these data to the disturbance in carbohydrates oxidation and glycogen activity and inhibition of insulin production.

As a result of induction DM/Ob in rats, the serum CK, CK-MB, LDH and AST activities and the levels of H-FABP and ET-1 were elevated ($p<0.05$) significantly linked with a remarkable decline in serum TNO level in DM/Ob in rats group comparing to their corresponding control rats group (Table 3). These data may be due to the alterations in the activities of protein kinase-β, mitogen activated protein kinases (MAPK) and phosphoinosotide-3 kinase (PI3K) which led to appearance of apoptosis as a result of the oxidative damage and inflammation associated with reduction in pattern of HDL-cholesterol and creation of endothelial scavenger receptor class-B member-1 (SR-B1). So, the excessive myocardial infraction was occurred as a result of increment ROS production, inhibition in the activity of nitric oxide synathase and appearance of mitochondria dysfunction. Judging from the existing data in this work, similar results were reported by some researchers [48,49,50]. Moreover, several authors obtained analogous data in both diabetic/obese patients and rat models with cardiac dysfunction or heart failure [50,51,52].

In this work, the induction of DM/Ob in rats led to a significant elevation in heart MDA levels accompanied by a marked decrease in heart activities of GSH, GSSG, GPx, SOD and CAT when compared with control rats group (Table 4). Parallel results were reported by several authors [9] who noticed that STZ- diabetic rats in a dose level of 45mg/kg had a depressing effect on activities of SOD and CAT and increment in MDA level. These data may be attributed to increase production of ROS which is implicated in the development and progression of DM [45]. Also, Yan *et al*. [35] and Koch *et al*. [53] noted that diabetes led to pronounce of cardiovascular complications in patients caused of morbidity and mortality due to elevation in the productions of both ROS and AGEs.

In this investigation, the supplementation of 500mg pomegranate/kg b.wt daily for 30 days by the aid of oro-gastric tube in DM/Ob rats group led to a significant ($p<0.05$) improvement in the all studied parameters according to the obtained data in Tables (1-4).

These data were confirmed by several authors [9,10,44,45]. The last authors attributed these results due to the existence of several antioxidant enzymes (sulfonylureas, glucosidase inhibitors and dipeptidyl peptidase-4) and polyphenols compounds (meglitinides, biguanides, thiazolidinediones and sodium glucose cotransporter-2 inhibitors). So, sulfonylureas in pomegranate can bind to potassium-ATP channels leading to the influx of calcium ions with increment of insulin secretion by β-cell in pancreas [47,54,55]. Also, meglitinides in pomegranate can act on different pancreatic β-cell receptors and increase calcium ions influx to promote insulin releasing [54,55]. In addition, biguanides in pomegranate can reduce gluconeogenesis in liver, decrease the absorption of glucose molecule in intestine and increase insulin sensitivity of muscle tissues [46,47,55], Furthermore, thiazolidinediones in pomegranate can act as substrate for binding of PPAR-receptors which correct insulin sensitivity and hepatic glucose level [56,57]. Pomegranate contains on sodium glucose cotransporter-2 inhibitors which can prevent glomerular glucose reabsorption by inhibiting the sodium glucose cotransporter-2 [54]. Moreover, dipeptidyl peptidase-4 (DPP-4) inhibitors in pomegranate can inhibit protease activity of DPP-4 associated with correction in the levels of glucagons and insulin [55].

Additionally, the polyphenols in pomegranate enhance the activity of serum HDL associated paraoxonase-1. This enzyme hydrolyzes lipid peroxides in oxidized-LDL and converts them to a less atherogenic LDL by decreasing the concentration of oxidized-LDL. It can be understood from the data that polyphenols in pomegranate decline the plasma lipids levels as a result of induction diabetes in rats after administration of STZ. Hence, there are direct effects of flavonoids on cholesterol metabolism and the activities of hydroxymethyl glutaryl-CoA reductase and sterol O-acyltransferase [10,47,54]. The last authors postulated that these enzymes are probably the reasons for the flavonoids effect on cholesterol metabolism. Also, plant flavonoids can act as potent inhibitors of low density lipoprotein (LDL) oxidation or of macrophage oxidation [45,46,47]. Sohrab *et al*. [10] and Perez-Ramirez *et al.* [46] postulated that total polyphenol contents in pomegranate were evaluated by gallic acid equivalents determination. They also pointed to the useful polyphenols in pomegranate due to antioxidant potency, free radical scavenging capacity and inhibition of LDL oxidation.

As well, treatment of DM/Ob rats group with 400mg ginger/kg b.wt/day for 30 days by the aid of oro-gastric tube led to a significant ($p<0.05$) enhancement in the all studied parameters according to the obtained data in Tables (1-4). These results were confirmed by numerous authors [20,56,57]. They attributed these effects to antidiabetic/anti-obesity effects through multiple mechanisms that include; elevation of glucose, prostaglandin inhibitory, induction of 5′ adenosine monophosphate-activated protein kinase phosphorylation, promotion of GLUT4 translocation to plasma membrane, suppression of advanced glycation end product formation as a result of increment of ROS levels in pancreatic β-cells, enhancement of fibrinolytic activity, improvement of glucose intolerance, regulation of gluconeogenesis and glycogenolysis and reduction of both thermogenesis and lipids level.

The hypoglycemic effect of dietary ginger was confirmed by many studies [20,21,25.56]. They attributed this effect to the bioactive components in ginger. These components act on decreasing free radical formation in diabetes as well as reducing blood glucose levels [25,56]. The last authors exposed that 6-gingerol in ginger has modulatory effect on insulin release. Also, ginger riches with α- amylase and α-glucosidase. These enzymes are keys in controlling carbohydrate metabolism and inhibit the formation of hyperglycaemia in diabetes. These enzymes are found in ginger and also represented in phenolic contents of gingerol and shogaol [20,24,25]. As well, ginger inhibits the conversion of excess carbohydrates into TG by regulating the expression of carbohydrate response element-binding protein. In addition, ginger contains on niacin which is a nutrient component and plays as a potential active ingredient in lowering serum triglyceride level, increasing clearance of VLDL. Niacin also enhances hepatic uptake of LDL and inhibits cholesterol synthesis [19,20,21,22]. The last authors reported the beneficial treatment of ginger on T-Ch and TG levels in STZ-induced diabetic rats. They attributed these results to the bioactive components in ginger such as; gingerols, shogaols, zingerone, flavonoids and paradols. These components act on the elevation the fecal excretion of cholesterol, obstruct absorption of cholesterol in the gut and inhibition of cellular cholesterol synthesis as well as the elevation in antioxidants activities (SOD and CAT) and reduction of MDA level due to decrease in ROS formation.

5. Conclusion

From the above cited data, it can be concluded that pomegranate and ginger are hypoglycemic and hypolipidemic agents. In comparison, the obtained data in DM/Ob rats group treated with pomegranate are better than those obtained in DM/Ob rats group treated with ginger. These results may be due to strong and potential antioxidant components presented in pomegranate than that existed in ginger.

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7.Conflicts of interest

conflict of interest Declared none.

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الملخص العربي

الفائدة الطبية للرمان أو الزنجبيل فى حماية وعلاج القلب والأوعية الدموية للجرذان المصابة بمرض البول السكري/السمنة

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الملخص العربى:

يعتبر مرض البول السكري والسمنة مشكلة صحية عامة كبرى آخذة في الارتفاع في جميع أنحاء العالم. وفي هذا البحث تم إجراء دراسة مقارنة بين مجموعة الضابطة الطبيعية، مجموعة الحيوانات المصابة بالسكري/السمنة (بدون علاج)، مجموعة الجرذان المصابة بمرض البول السكري/السمنة المعالجة بجرعة ٥٠٠ ملغم من الرمان/كغم من وزن الجسم بواسطة أنبوب فموي معدي لمدة شهر و مجموعة الجرذان المصابة بداء البول السكري والسمنة تعاملت بجرعة ٤٠٠ ملجم زنجبيل/كجم من وزن الجسم بواسطة أنبوب فموي معدي لمدة شهر لتقييم التغيرات في صورة الكربوهيدرات وصورة الدهون ونشاط إنزيمات القلب وعلامات القلب بالإضافة إلى التغيرات في الأكسدة. وحالة مضادات الأكسدة في أنسجة القلب بسبب التحريض التجريبي لمرض البول السكري / السمنة (DM / Ob). مرض البول السكري والسمنة المستحث في الجرذان عن طريق إعطاء كل من الستربتوزوتوسين / النيكوتيناميد للحث على مرض السكري والكولسترول / حمض الكوليك للحث على السمنة.

بالمقارنة مع مجموعة الجرذان المصابة بمرض البول السكري/السمنة، حدثت تحسنات ملحوظة في المعايير المدروسة بعد معاملة الجرذان المصابة بمرض البول السكري/السمنة بالرمان أو الزنجبيل لمدة شهر واحد. تتوافق هذه النتائج مع مفهوم أن الرمان أو الزنجبيل من عوامل الخافضة لنسب السكر ومستويات الدهون في الدم. وقد تمت مناقشة الآليات الأساسية لهذه التأثيرات مع الأبحاث الحديثة المتاحة.