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THE ROLE OF PROPHETIC MEDICINE IN TREATMENT OF COMPLICATIONS IN METABOLIC SYNDROME-INDUCED RATS VIA NIGELLA SATIVA AND GINGER

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ABSTRACT

Background: Frequent consumption saturated fatty acids and fructose increase risk of metabolic syndrome (MS). Features of MS include dyslipidemia, visceral obesity, insulin resistance and hypertension. In this study we investigate the role of Nigella sativa and ginger in ameliorating features of MS. **Methods:** High-fructose high-fat fed diet was used for induction MS which was certain after 8 weeks. Four group animals were used: normal control, MS control group given saline, MS groups given Nigella sativa (4ml/kg) and ginger (500mg/kg) daily for 4 weeks. Markers chosen for assessment included effect on body weight gain, insulin, glucose, adiponectin levels and lipid profile. Also peroxisome proliferator-activated receptor-gamma (PPARγ) protein expressions and glucose transporter 4 (GLUT4) content were estimated. In addition, Blood pressure, heart rate, LDH and CK-MB were estimated. Also renal function test and antioxidant activity were evaluated. In addition, to CRP and fibrinogen determined. **Results:** Nigella sativa and ginger caused decrease in both MS-induced increase in body weight and glucose. The drugs used increased adiponectin and decreased insulin level and resistance, with correction of MS-induced hyperlipidemia. There is an increase in PPARγ protein expression and GLUT4 compared with MS control group. Furthermore, both drugs caused decrease in both MS-induced increase in heart rate and blood pressure. They reduced albumin, creatinine, BUN, uric acid and MDA with increased SOD and GSH. Drugs also decreased fibrinogen and CRP compared with MS control group. **Conclusion:** Nigella sativa and ginger ameliorate cardiac and renal complication of MS via their antioxidant activity and increase in GLUT4 and PPARγ expression.

KEYWORDS

Metabolic syndrome, Nigella sativa, Ginger and Antioxidant activity.

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INTRODUCTION

The prevalence of metabolic syndrome (MS) became worldwide mainly due to the obesity epidemic[1]. Although there was no accepted central mechanism for the pathogenesis of the metabolic syndrome, two features; the visceral obesity and

impaired insulin stand out as potential etiologies underlying the abnormalities of MS[2].

Metabolic syndrome also, recognized as a pro-inflammatory and prothrombotic state, although both features are not included in the formal definition[3].

Underlying factors for fructose-induced insulin resistance are varied. Fructose is more lipogenic than glucose, leading to greater elevations of triglycerides (TG) content in the skeletal muscle and in turn to insulin resistance[4].

Glucose uptake into skeletal muscle is primarily through glucose transporter 4 (GLUT-4), which is modulated by insulin signaling or the alternative pathway via activation of AMP-activated protein kinase (AMPK)[5].

Activation of AMPK leads to increased glucose uptake and fatty acid influx into cells and is accompanied by up-regulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a potent transcriptional cofactor in regulating mitochondrial biogenesis and function[6].

Ventricular dilatation, ventricular hypertrophy, decreased ventricular contractile function, and infiltration of inflammatory cells in heart were induced by fructose feeding[7].

Insulin resistance has been proposed as predictor for the development of hypertension[8]. Starch carbohydrate content in laboratory rodent diet when substituted with fructose resulted in increased blood pressure after a period of 6-8 weeks. The effects of high fructose intake have been reported to be concentration and time-dependent[9].

Vascular dysfunction due to a high fructose diet has been reported in the rat and it is observed that vascular dysfunction in metabolic syndrome is accompanied by increased vasoconstrictor sensitivity and excessive production of vascular superoxide anions[10].

It is evident that chronic inflammation state may contribute to the illnesses associated with obesity, namely atherosclerosis, dyslipidemia and insulin resistance[11]. Additionally, CRP is an independent, strong predictor and mediator of cardiovascular diseases[12].

Functional changes including albuminuria and elevated plasma creatinine and thickening of glomeruli and morphological changes including fatty infiltration have been reported after 60 days of fructose feeding in rat[13,14].

Free radical reactions have been involved in the pathogenesis of many human diseases, including, renal disorders, diabetes and cardiovascular disorders[15].

Each cell have been endowed with adequate protective mechanisms against effects of free radicals. Superoxide dismutase (SOD), thiols, catalase, glutathione reductase, glutathione peroxidase and disulfide bonding are buffering systems in every cell[16].

Nutraceuticals provide a rich source of antioxidants to protect against the action of ROS as they can scavenge free radicals and reduce free radical formation[17]. Nigella sativa and ginger were chosen in this study. As nigella sativa (NS) seeds possess antioxidant and hypotensive activity[18]. Moreover, NS is known for its hepatoprotective[19], immunomodulatory effects[20] and anti-diabetic activity[21]. Similarly ginger has the potential to treat hyperlipidemia[22], platelet aggregation[23] and hypertension[24]. Also, ginger is reported to possess anti-inflammatory, hypoglycemic activity[25], renoprotective[26] and immunomodulatory effects[27]. Furthermore they exert antithrombotic activity[28].

This study was designed to investigate the effect of some antioxidants on the cardiovascular effects of metabolic syndrome in rats as what was mentioned in the Holy Quran and Sunnah.

The Prophet Mohamed may God's prayers and peace be upon him, came with the goodness of the religion and the world and from that he urged what is in the benefit of the bodies and forbade everything that spoils them, so he commanded and desired medication.

Many quranic verses in the Book of God Almighty talking about the bliss of Paradise and what God has prepared for His pious servants, the Almighty

said: (And they give them drink in it a cup that was made of ginger).

The hadith about the black seed is very interesting, for it has been authenticated from the Prophet, peace be upon him, with his call for treatment with it and that it is a cure for every disease. And we stop at the words of the Prophet, may God bless him and grant him peace, "a cure for every disease''. Abu Hurairah narranted that the Messenger of Allah (s.a.w) said:

"Use this black seed. For indeed it contains a cure for every disease except As-Sam" And As-Sam is death.

And after I was keen to adhere to the scientific method based on experience and to prove what is true from the Sunnah of the Prophet, peace be upon him, in the topics of medication, to see the extent of compatibility between the correct hadith and what science has proven by experience and proof.

MATERIAL AND METHODS

Animals

Male Sprague Dawley rats (n= 30) weighting 200 to 230g were used in the present study. Rats were purchased from the animal house of the National Research Center Institute (Cairo, Egypt). The animals were housed under conventional laboratory conditions on a 12 hours light/dark cycle and constant temperature (22 ± 1ºC). The experimental design was carried out according to the regulation of ethic committee of faculty of Pharmacy Cairo University.

Drugs and chemicals

Nigella sativa oil was purchased from Pharco Pharmaceuticals, (Alexandria, Egypt), Ginger was obtained from (Arab company for pharmaceuticals and Medicinal plants), (Sharkeya, Egypt). Metformin was obtained from Minapharm Pharmaceutical, (Cairo, Egypt). Fructose was obtained from El Nasr Pharmaceutical, (Cairo, Egypt). Heart rate and blood pressure was indirectly measured by non-invasive blood pressure monitor (ML 125 NIBP, AD Instruments, Australia) from the tail of conscious rats by the tail-cuff technique. Albumin, creatinine, blood urea nitrogen (BUN), uric acid, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), C-reactive protein (CRP) and fibrinogen kits were purchased from Spectrum Diagnostics, (Obour, Egypt). Glutathione (GSH), MDA and SOD activity were estimated. Kits were purchased from (Biodiagnostic, Egypt). Insulin, adiponectin, PPARγ and GLUT4 enzyme-linked immunosorbent assay (ELISA) Kits were purchased from Bioassay Technology Laboratory Company, (Shanghai, China). Total cholesterol (TC), triglyceride, high-density lipoprotein-cholesterol level (HDL-C) and glucose kits were purchased from Spectrum Diagnostics, (Obour, Egypt).

Experimental design

A high-fat diet consisting of standard rodent chow in addition to 10% fat, 3% NaCl, and fructose 20% solution in drinking water was used to induce MS in rats by feeding for 8 weeks according to modified method described by Calvo-Ochoa *et al*[29].

Diet and fructose solution were prepared every day. Rats were provided with a high-fructose high-fat diet (HFHFD) for 8 weeks. Rats were randomly allocated into five groups (six rats each) as follows:

Group 1

This group received normal laboratory diet, tap water ad libitum and given saline daily during the time of experiment.

Group 2

This group fed HFHFD for 12 weeks and given saline daily during the time of experiment.

Group 3

This group fed HFHFD for 12 weeks and Nigella sativa oil (4ml/kg) for the last 4 weeks[30].

Group 4

This group fed HFHFD for 12 weeks and ginger (500mg/kg) for the last 4 weeks[31].

At the end of medication, the animals were fasted for 12 hour weighed and blood samples were withdrawn from the retro-orbital plexus under light anesthesia[32]. Plasma was separated by centrifugation at (1,509g, 15 min, 4ºC) and divided into small aliquots that were stored for the estimation of the levels of GSH, MDA and SOD. In addition, the separated plasma was used for the

estimation of creatinine, BUN, uric acid, albumin, LDH, CK-MB, CRP and fibrinogen.

Furthermore systolic blood pressure and heart rate of animals were indirectly measured by the tail-cuff technique, where tail of the animals were warmed for 30 min at 28ºC to dilate the tail artery in a thermostatically controlled heating cabinet (Ugo Basille, Italy) for better detection of tail artery pulse, the tail was passed through a miniaturized cuff and tail-cuff sensor that was connected to an amplified pulse was recorded during automatic inflation and deflation of the cuff. The average of three measurements was taken at each occasion. Heart rate was recorded automatically by a counter triggered by pulse wave.

Biochemical assays

Plasma sample were used for estimation of the level of creatinine, BUN, uric acid, albumin, LDH, CK-MB, CRP and fibrinogen.

An aliquot of heparinized blood was used for estimating its glutathione (GSH) contents and the other aliquot was centrifuged for separation of plasma and red blood cells for measurement of lipid peroxide content as MDA nmol/ml plasma. The remaining RBCs pellets were used to assess the SOD activity.

Percentage of body weight gain and organ weights were calculated. Serum samples were used for estimation of the levels of fasting glucose, insulin, TC, TG, HDL-C and adiponectin.

In addition, homeostasis model assessment of insulin resistance (HOMA-IR) score as an indicator of insulin resistance was calculated according to the equation provided by Matthews *et al*[33]. Quantitative insulin sensitivity check index (QUICKI) was calculated according to the equation provided by Mc Auley *et al*[34].

LDL-C and VLDL were calculated from the formula described by Friedewald *et al*[35] where LDL-C=TC-HDL + TG/5)

VLDL = TG/5.

PPARγ and GLUT4 were assayed in tissues homogenate using ELISA kits.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance followed by Tukey's post hoc test using SPSS software v21 (SPSS Inc, Chicago, IL). Data were expressed as mean ± standard deviation (SD) and P values of less than 0.05 were considered as statistically different.

RESULTS AND DISCUSSION

At the end of 8 weeks feeding of HFHFD, The body weight gain and relative organ mass were significantly higher in non-treated MS-induced rats when compared to normal-control rats (Table No.2). After oral treatment for 4 weeks of MS-induced rats with NS (4ml/kg), ginger (500mg/kg) suppressed body weight gain by 67% and 65% respectively when compared with the non-treated MS-induced group was observed. The non-treated MS-induced rats had significantly higher relative liver, heart and visceral fat weight than normal control group (Table No.2). Meanwhile MS-induced rats treated with the NS and ginger exhibited decrease in relative liver, heart and in visceral adipose tissue weight.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference.

Between the control and the treated groups were carried out using one-way ANOVA. Relative organ weight = (organ weight/body weight) × 100.

*Statistically significant from the MS-induced rats treated with HFHFD only at $P < 0.05$.

#Statistically significant from the control values at $P < 0.05$.

Non-treated MS-induced group showed higher serum glucose level than normal control (Table No.3). Significant reduction in glucose level was observed in MS-induced rats treated with NS and ginger by 64% and 57% respectively when compared to MS-induced group (Table No.3).

Serum insulin level of non-treated MS-induced group was significantly increased compared to those in normal control group. In comparison to the MS-induced group, NS and ginger administration to MS-induced rats significantly reduced serum insulin level by 75% and 40% respectively.

HOMA-IR in the non-treated MS-induced rats was significantly higher than the normal control group (Table No.3). MS-induced rats given NS and ginger nearly normalized the HOMA-IR index. A statistically significant decrease in QUICKI index was observed in non-treated MS-induced rats than those in normal control group. MS-induced group treated with NS and ginger give significantly ($P<0.05$) elevated level of QUICKI index compared to non-treated MS-induced rats.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at $P < 0.05$.

#Statistically significant from the control values at $P < 0.05$.

There was significant reduction of PPARγ expression in non-treated MS-induced rats as compared to normal control group (Table No.4). Meanwhile, significant increase of PPARγ expression was observed in MS-induced group treated with NS and ginger by 353% and 420% respectively when compared to non-treated MS-induced group.

The amount of tissue GLUT4 in non-treated MS-induced group was significantly reduced compared to normal control group. Meanwhile significant increase in tissue GLUT4 was observed in MS-induced group treated with NS and ginger 814% and 512% respectively when compared to non-treated MS-induced group.

Serum adiponectin level of non-treated MS-induced group didn't give significant reduction compared to those observed in normal control group. MS-induced group treated with NS and ginger showed significant increased serum adiponectin level by 1212% and 1256% respectively when compared to non-treated MS-induced group.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at $P < 0.05$.

#Statistically significant from the control values at $P < 0.05$.

MS-induced rats showed a significant increase in levels of cholesterol, triglyceride LDL-C, VLDL-C and decrease in HDL-C in comparison with normal control group (Table No.5). In comparison to non-treated MS-induced group, oral administration of NS and ginger showed a significant decrease in the levels of cholesterol by 64% and 55% respectively. Triglyceride level also decreased by 58% and 51% respectively when compared to non-treated MS-induced group. Furthermore, LDL-C level was suppressed by 95% and 87% respectively when compared to non-treated MS-induced group. VLDL-C level was decreased ($P<0.05$) by 59% and 31% respectively when compared to non-treated MS-induced group. On the other hand an increase in HDL-C by 288% and 244% respectively when compared to non-treated MS-induced group was observed.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at $P < 0.05$.

#Statistically significant from the control values at $P < 0.05$.

During the 8 weeks feeding of HFHFD, normal control rats demonstrated a systolic blood pressure value of 115±1.87 (mm Hg) (Table No.6). Maintaining rats on HFHFD for 12 weeks increased systolic blood pressure by 57% compared to normal control (Table No.6). Nigella sativa and ginger treated groups showed a significant ($P<0.05$) decrease in systolic blood pressure by 45% and 31% respectively when compared to MS-induced group.

Rats kept on normal laboratory chow exhibited diastolic blood pressure value of 70±7.69 (mm Hg) (Table No.6). Metabolic syndrome was associated with an elevation in diastolic blood pressure level by 36% compared to normal control (Table No.6).

Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in the levels of diastolic blood pressure by 34% and 26% respectively when compared to MS-induced group.

Maintaining rats on normal laboratory chow exhibited mean blood pressure value of 85±5.25 (mm Hg) (Table No.6). Meanwhile MS-induced rats exhibited a significant increase in mean blood pressure by 45% compared to normal control (Table No.6). Administration of Nigella sativa and ginger under the same condition caused a significant (P<0.05) decrease in mean blood pressure compared to the MS-induced rats by 39%, 28% respectively.

Normal control rats demonstrated a heart rate value of 309±13.87 (beat/min) (Table No.6). Meanwhile, MS-induced rats exhibited an increase in heart rate by 40% compared to normal control (Table No.6). Administration of Nigella sativa and ginger under the same condition caused a significant (P<0.05) decrease in heart rate compared to the MS-induced rats by 65%, 56% respectively.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference.

Between the control and the treated groups were carried out using one-way ANOVA. Relative organ weight = (organ weight/body weight) × 100.

*Statistically significant from the MS-induced rats treated with HFHFD only at P < 0.05.

#Statistically significant from the control values at P < 0.05.

Rats kept on normal laboratory chow exhibited total CK-MB value of 101.5±4.32 (U/l) (Table N o.7). Metabolic syndrome was associated with an elevation in CK-MB level by 210% compared to normal control (Table No.7). Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in the levels of CK-MB by 75% and 60% respectively when compared to MS-induced group.

Maintaining rats on normal laboratory chow exhibited LDH value of 115.67±2.31 (U/l) (Table No.7). Meanwhile MS-induced rats exhibited a significant increase in LDH level by 132% compared to normal control (Table No.7). Administration of Nigella sativa and ginger under the same condition caused a significant (P<0.05) decrease in LDH level compared to the MS-induced rats by 75% and 70% respectively.

Normal control rats demonstrated a CRP value of 2.77±0.13 (mg/l) (Table No.7). Maintaining rats on HFHFD for 12 weeks increased CRP level by 432% compared to normal control (Table No.7). Nigella sativa and ginger, treated groups showed a significant (P<0.05) decrease in the Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried.

Out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at P < 0.05.

#Statistically significant from the control values at P < 0.05.

Rats kept on normal laboratory chow exhibited creatinine value of 0.55±0.02 (mg/dl) (Table No.8). Metabolic syndrome was associated with an elevation in creatinine level by 42% compared to normal control (Table No.8). Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in the levels of creatinine by 67% and 72% respectively when compared to MS-induced group.

Maintaining rats on normal laboratory chow exhibited uric acid value of 1.13±0.06 (mg/dl) (Table No.8). Meanwhile MS-induced rats exhibited a significant increase in uric acid level by 340% compared to normal control (Table No.8). Administration of Nigella sativa and ginger under the same condition caused a significant (P<0.05) decrease in uric acid level compared to the MS-induced rats by 74% and 61% respectively.

Normal control rats demonstrated a BUN value of 17.97±2.44 (mg/dl) (Table No.8). Maintaining rats on HFHFD for 12 weeks increased BUN level by 13% compared to normal control (Table No.8). Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in the levels of BUN by 50% and 39% respectively when compared to MS-induced group.

Rats kept on normal laboratory chow exhibited albumin value of 3.58±0.23 (g/dl) (Table No.8). Metabolic syndrome was associated with reduction

in albumin level by 15% compared to normal control (Table No.8). Nigella sativa and ginger treated groups showed a significant (P<0.05) increase in the levels of albumin by 18%, 16% respectively when compared to MS-induced group.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at P < 0.05.

#Statistically significant from the control values at P < 0.05.

Normal control rats demonstrated a blood fibrinogen value of 227.33 ± 1.63 (mg/dl) (Table No.9). MS-induced rats demonstrated an increase in the blood fibrinogen level by 62% compared to normal control (Table No.9). Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in the levels of fibrinogen by 48%, 44% respectively when compared to MS-induced group.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at P < 0.05.

#Statistically significant from the control values at P < 0.05.

Normal control rats demonstrated MDA value of 1.59±0.07 (nmol/ml) (Table No.10). Maintaining rats on HFHFD for 12 weeks increased MDA by 214% compared to normal control (Table No.10). Nigella sativa and ginger treated groups showed a significant (P<0.05) decrease in MDA by 85%, 78% respectively when compared to MS-induced group.

Rats kept on normal laboratory chow exhibited glutathione value of 9.813±0.63 (mg/dl) (Table No.10). Metabolic syndrome was associated with a lowered glutathione level by 31% compared to normal control (Table No.10). Nigella sativa and ginger treated groups showed a significant (P<0.05) increase in the levels of glutathione by 469%, 382% respectively when compared to MS-induced group.

Maintaining rats on normal laboratory chow exhibited SOD value of 11.57±0.51 (U/ml) (Table No.10). Meanwhile MS-induced rats exhibited a significant decrease in SOD by 32% compared to normal control (Table No.10). Administration of Nigella sativa and ginger under the same condition caused a significant (P<0.05) increase in SOD level compared to the MS-induced rats by 638% and 350% respectively.

Results are expressed as mean ± SD (n = 6). The statistical comparison of difference between the control and the treated groups were carried out using one-way ANOVA.

*Statistically significant from the MS-induced rats treated with HFHFD only at P < 0.05.

#Statistically significant from the control values at P < 0.05.

Discussion

Feeding rats with HFHFD resulted in hyperglycemia, hyperinsulinemia and hyperlipidemia associated with decreased adiponectin, GLUT4 and PPARγ protein expression.

Fructose does not stimulate insulin secretion in short term however; insulin resistance and obesity induced by fructose feeding resulted in compensatory hyperinsulinemia[36].

Reduction of GLUT-4 and PPAR-γ expression in MS-induced rats could lead to decreased insulin sensitivity and glucose uptake. It was reported that GLUT-4 translocation does not take place efficiently and GLUT-4 transporters remain inside, where they are not functioning[37]. This results in decreased uptake of glucose by muscle cells, which contributes significantly to the elevated blood glucose levels[38].

Similarly the significant decrease in expression of PPAR-γ in MS-induced rats leads to decreased insulin sensitivity and decreased glucose uptake. Previous data reported that high fructose consumption disturbs normal hepatic carbohydrate metabolism leading to disturbance in glycolytic pathway which may enhance the rate of de novo TG synthesis and decrease the expression of PPAR-γ.

PPAR-γ plays an important role in differentiation of fat cell, storage of lipid and insulin sensitivity[39].

The antiadipose activity of NS which caused the weight loss is related to the decrease of serum lipids and glucose levels. Previous study revealed that methanolic extract and the commercial oil of NS displayed appetite-reducing components inducing the loss of weight[40].

Previous study reported that NS reduced plasma lipids concentrations[41]. The mechanisms of NS favorable effects may be due to its choleretic activity as reported by Kaatabi *et al*[42].

Administration of NS to MS-induced rats increased PPARγ protein expression. Previous studies reported that NS to rats fed a high-fat diet improved insulin resistance by that thymoquinone, a bioactive constituent of NS which interact with the ligand-binding pocket of PPAR γ, which is reported to be critical for its activity[43]. In addition Benhaddou-Andaloussi reported that NS stimulated PPARγ expression in cultured adipocytes and increased the total amount of GLUT-4 glucose transporters in skeletal muscle[44].

In addition, NS in MS-induced group resulted in an increase of adiponectin[45]. Ginger decreased the glucose level in MS-induced rats with reduced insulin level and resistance. Increased insulin sensitivity was also seen in this study and as reported before[46]. Improvement of insulin resistance by ginger could be related to the observed increase in adiponectin, GLUT4 and PPARγ expression.

Ginger significantly decreased MS-induced hyperlipidemia which was also reported before[47]. The hypocholesterolemic effects of ginger stem from the inhibition of cellular cholesterol synthesis. The attenuation of cholesterol synthesis results in augmenting the LDL receptor activity, which leading to the elimination of LDL from plasma.

The mechanism of hypolipidemic action of ginger may be due to inhibition of dietary lipid absorption in the intestine or stimulation of biliary secretion of cholesterol and excretion of cholesterol in feces[48].

Furthermore, Ginger stimulates glucose uptake and increases translocation of GLUT-4 in membrane surface of the cells together with small increases in total GLUT-4 protein expression[49]. Activation PPARγ expression by ginger may be due to presence of 6-shogaol which was identified as PPARγ activator which founded to be a novel effect[50].

Feeding rats with HFHFD in the present study, resulted in metabolic syndrome manifested by elevated oxidative stress, blood pressure and heart rate. HFHFD-fedrats also showed an increase in fibrinogen and CRP associated with changes in kidney function such as hyperuricaemia and albuminuria.

During insulin resistance, there is an imbalance in glucose metabolism that generates chronic hyperglycemia, which in turn triggers oxidative stress and causes an inflammatory response that leads to cell damage[51].

It has been suggested that hyperinsulinemia is associated with alterations of myocardial metabolism leading to increased myocardial free fatty acids oxidation resulting in lipotoxicity and predisposition to cardiac hypertrophy and dysfunction[52]. The most possible mechanisms for the cardiovascular effect of hyperinsulinemia are that it can cause renal sodium retention, increasing cardiac preload. It also activates the renin-angiotensin system, sympathetic nervous system, promotes oxidative stress and stimulates cardiac fibroblasts, increases heart rate and cardiac overload[53].

The current data revealed that HFHFD caused oxidative stress as shown by marked decrease in GSH, SOD and increase in MDA. Several studies have reported that persistent hyperglycemia can cause high production of ROS which may lead to cellular oxidative damage including DNA, lipids and protein[54].

The results of the present study showed that HFHFD induced kidney dysfunction as indicted by elevation of creatinine, uric acid, BUN and reduction of albumin levels. Elevated serum uric acid levels are thought to be a potential mechanism linking fructose consumption to MS[55].

The HFHFD in the present work resulted in increase in fibrinogen and CRP level indicting

cardiovascular changes. CRP has a role in the modulation of the harmful effect of oxidized LDL on endothelial function, contributing to oxidative stress and the subsequent production of free radicals that may contribute to damage and endothelial dysfunction and to oxidation of the lipoproteins in atherosclerotic lesions[56].

Fibrinogen, an acute-phase reactant like CRP, rises in response to a high cytokine state. Thus, prothrombotic and pro-inflammatory states may be metabolically interconnected[57].

The administration of NS to MS-induced rats provoked a significant reduction of blood pressure associated with reduction of heart rate, LDH, CK-MB and reduction of CRP as well as fibrinogen. Furthermore NS improved of renal function and oxidative stress biomarkers.

In the present study, administration of NS significantly decreased MS-induced increase in blood pressure. Several mechanisms can explain the ability of NS to counteract hypertension accompanying metabolic syndrome: (i) antioxidant activity of thymoquinone, polyphenol and flavonoids in NS that cause nitric oxide production and vasodilator effect[58], (ii) presence of linoleic acid that affects ionic fluxes across the vascular endothelial cells[59], (iii) calcium channel-blocking activity by NS[60], (iv) inhibition of angiotensin-converting enzyme by flavonoids[61], (v) cardiovascular depressant action of the oil mediated centrally in the brain either directly or indirectly via mechanisms involving serotoninergic and muscarinic receptors[18], (vi) diuretic and cardiac depressant properties[62] and (vii) suppression of α-adrenoceptor-mediated phenylephrine-induced rise in the arterial BP[63].

In the present study, administration of NS decreased heart rate, CK-MB and LDH level indicating improvement of cardiovascular changes. Such therapeutic potential of NS oil in rats is in line with study of Bader[64] who reported a reduction in SBP, CK-MB, LDH, increase in tissue Na+/K+/ATPase activity and plasma No level suggesting the prevention of myocardial injury. NS exhibited protective effect against ischemia which was evident by decreased level of LDH[30]. The decrease in the heart rate may occur by activating cholinergic mechanisms[65].

The administration of NS improved kidney function as manifested by significant decrease in BUN, creatinine and uric acid level with increase in albumin level. It has been reported that NS, as diuretic, accelerated the process of dissolving the preformed stones by curing and preventing the formation of new stones in the urinary system[66]. Moreover, NS prevented the degenerative changes in renal tissues induced by ethylene glycol[67]. The nephroprotective effect of NS could be possibly due to antioxidant effect[68].

The administration of NS significantly decreased MS-induced increase in CRP level. The anti-inflammatory effect of NS is related to the inhibition of prostaglandins, leukotrienes and oxygen radicals by thymoquinone which may be responsible for anti-inflammatory activity of essential oil[69].

In the present study, NS administration caused a significant reduction in fibrinogen level. Muralidharan-Chari *et al*[70] reported an anticoagulant effect after oral administration of powdered NS seeds. Such findings are supported by Shakeri *et al*[71] who found that the methanol soluble portion of NS oil showed inhibitory effects on arachidonic acid induced-platelet aggregation and blood coagulation and had more potent activity than aspirin.

The administration of NS provoked a significant increase in GSH and SOD and decrease in MDA level which further proves previously reported data of Rahmani and Aly[72] who have documented that pretreatment with TQ, the main active constituent in nigella oil, protected organs against oxidative damage induced by a variety of free radical generating agents.

Previous study revealed that, ginger improves blood circulation and relaxes muscles surrounding blood vessels[73]. In rabbit thoracic aorta preparation, ginger relaxed the phenylephrine-induced vascular contraction[74]. Shaban *et al*[75] clarified that ginger has a strong positive effect in lowering blood

pressure. The hypotensive effect of ginger may be exerted by inhibition of ACE, inhibitory outcome by stimulus of muscarinic receptors and obstruction of Ca+2 channels. Oloyede *et al*[47]. Another postulated mechanism may be due to induction of vasodilatation by increasing nitric oxide release[76].

It has been reported that ginger showed cardiac protection in isoproterenol induced myocardial infarction through attenuation of the release of cardiac biomarkers in serum LDH and CK-MB via the antioxidant activity which prevented lipid peroxidation, stabilized the cardiac membrane and prevented the leakage of cardiac enzymes[77]. Amran *et al*[78] reported that gingerols and shogaols may be responsible for ginger cardio protective effect. Zingerone, one of ginger components reduced the abnormalities in heart histology and the increase in the cardiotoxicity indices, serum LDH and CK-MB activities by ameliorated the state of oxidative stress[78].

In the present study, oral administration of ginger caused a significant improvement in renal function, represented by the significant decrease in serum creatinine, urea and BUN. Yang *et al*[79] reported that ginger administration diminished chronic fructose consumption-induced kidney injury attenuated proximal tubular damage, focal cast formation and interstitial fibrosis through suppression of renal over expression of pro-inflammatory cytokines. The nephroprotective effect of ginger may be due to increased levels of GSH, SOD and serum protein[80]. This protection is mediated either by potentiation of renal antioxidant defense system or by their direct free radical scavenging activity and regeneration of renal tubular epithelial cells[23].

In the present study, ginger administration caused a significant reduction in fibrinogen level. Marx *et al*[81] reported that ginger as well as individual ginger compounds have an effect on platelet aggregation.

Some authors have reported that the concentration of inflammatory markers including CRP were reduced in the group treated with ginger[82]. The active constituents of ginger including phenolic compounds such as gingerol, paradol and shogaol may be responsible for the anti-inflammatory activity[83]. The anti-inflammatory action of ginger is related to direct inhibition of COX activity and suppression of TNF-α production[82].

In the current study, administration of ginger provoked a significant increase in GSH and SOD, and a decrease in MDA level which is in accordance with Gholampour *et al*[84] who reported that consumption of ginger stimulated liver tissue of rats to increase defense enzymes such as superoxide dismutase and catalase, in addition to glutathione.

Table No.1: Nutritional composition of diets

S.No	Nutrient composition	Normal control	HFHFD
1	Fat (%)	4	14
2	Carbohydrates (total) (%)	50	50
3	Fructose (%)	0	20
4	Maltodextrin 10 (%)	15	15
5	Protein (%)	22	22

Abbreviation: HFHFD, high-fructose high-fat diet.

Table No.2: Effect of Nigella sativa and ginger on body weight gain and relative organs weight in MS-induced rats

S.No	Parameters/ Treatment	Body eight gain (g)	Relative Liver weight (g)	Relative Heart weight (g)	Relative Visceral fat tissue weight (g)
1	Normal control	52±5.94*	0.022±0.32	0.002±0.02*	0.018±0.26*
2	MS-induced group	100±13.57#	0.043±0.35#	0.06±0.04#	0.34±0.19#
3	Nigella sativa group (4ml/kg)	-43±15.05*@#	0.024±0.24*#	0.002±0.02@#	0.02±0.11*@#
4	Ginger group (500 mg/kg)	-35±10.84*#	0.032±0.18*#	0.003±0.03	0.021±0.18*@#

Abbreviations: ANOVA, analysis of variance; MS, metabolic syndrome.

Table No.3: Effect of Nigella sativa and gingeron blood glucose homeostasis in MS-induced rats

S.No	Parameters/ Treatment	Blood glucose (mg/dl)	Insulin (mU/l)	HOMA-IR	QUICKI
1	Normal control	74.33±2.48*	7.02±0.39*	1.28±0.00*	0.37±0.00*
2	MS-induced group	164.27±3.56#	26.42±2.2#	10.61±0.02#	0.27±0.00#
3	Nigella sativa group (4ml/kg)	57.7±1.56*@#	6.55±0.42*@	0.92±0.00*@	0.39±0.00*@#
4	Ginger group (500mg/kg)	69.85±5.67*#	15.8±0.85*#	2.69±0.00*#	0.33±0.00*#

Abbreviations: ANOVA, analysis of variance; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index.

Table No.4: Effect of Nigella sativa and ginger on biomarkers affecting insulin resistance MS-induced rats

S.No	Parameters /Treatment	Adiponectin (mg/l)	GLUT-4 (ng/ml)	PPAR γ(ng/ml)
1	Normal control	6.35±0.18	7.53±0.3*	8.58±0.65*
2	MS-induced group	4.68±0.17	4.33±0.22#	3.06±0.18
3	Nigella sativa group (4ml/kg)	35.17±1.47*#	39.6±1.6*@#	13.85±0.76*@#
4	Ginger group (500 mg/kg)	36.33±2.15*#	26.5±1.8*@#	15.92±1.42*@#

Abbreviations: ANOVA, analysis of variance; GLUT-4, glucose transporter 4; MS, metabolic syndrome; PPARγ, peroxisome proliferator-activated receptorγ.

Table No.5: Effect of Nigella sativa and ginger on lipid profile in MS-induced rats

S.No	Parameters / Treatment	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL (mg/dl)
1	Normal control	82±1.43*	79.85±1.6*	30.05±2.2*	36.06±2.71*	15.97±0.32*
2	MS-induced group	199.33±6.74#	156±1.41#	13.5±2.7#	154.63±8.6#	31.2±0.28#
3	Nigella sativa group (4ml/kg)	71.67±3.77*@#	63.67±2.16*@#	52.48±2.0*@#	6.45±0.43@#	12.73±0.43*@#
4	Ginger group (500 mg/kg)	81.67±6.73*@	76.5±3.08*@#	46.52±3.65@#	19.85±6.1*@#	15.3±0.61*@#

Abbreviations: ANOVA, analysis of variance; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MS, metabolic syndrome; VLDL, very low density lipoprotein.

Table No.6: Effect of Nigella sativa and ginger on blood pressure and heart rate in MS-induced rats

Parameters / Treatment		Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Mean blood pressure (mm Hg)	Heart rate (beat/min)
Normal control		115±1.87	70±7.69	85±5.25	309±13.87
MS-induced	Control	180±7.35#	95±5.47#	123±6.23#	433±9.81#
	+ Nigella sativa (4ml/kg)	99±7.3#*	63±4.08*	75±4.64*	153±2.16#*
	+ Ginger (500mg/kg)	124±9.07*	70±4.64*	88±6.31*	190±2.16#*

Abbreviations: ANOVA, analysis of variance; MS, metabolic syndrome. Levels of CRP by 86% and 83% respectively when compared to MS-induced group.

Table No.7: Effect of Nigella sativa and ginger on pathophysiological cardiovascular parameters in MS-induced rats

Parameters / Treatment		CK-MB (U/l)	LDH (U/l)	CRP (mg/l)
Normal control		101.5±4.32	115.67±2.31	2.77±0.13
MS-induced	Control	315.07±15.15#	268.83±6.24#	14.73±1.64#
	+ Nigella sativa (4ml/kg)	78.5±3.39#*	67.83±3.31#*	2.08±0.08*
	+ Ginger (500mg/kg)	126.33±2.16#*	81.33±2.58#*	2.57±0.21*

Abbreviations: ANOVA, analysis of variance; CK-MB, Creatine kinase-MB; LDH, Lactate dehydrogenase, CRP;C reactive protein; MS, metabolic syndrome.

Table No.8: Effect of Nigella sativa and ginger on kidney function in MS-induced rats

Parameters / Treatment		Creatinine (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Albumin (g/dl)
Normal control		0.55±0.02	1.13±0.06	17.97±2.44	3.58±0.23
MS-induced	Control	0.78±0.03#	4.97±0.11#	20.32±3.6#	3.05±0.14#
	+ Nigella sativa (4ml/kg)	0.26±0.03#*	1.31±0.12#*	10.22±1.63#*	3.6±0.2*
	+ Ginger (500 mg/kg)	0.22±0.02#*	1.95±0.12#*	12.30±1.9#*	3.53±0.35

Abbreviations: ANOVA, analysis of variance; BUN; blood urea nitrogen; MS, metabolic syndrome.

Table No.9: Effect of Nigella sativa and ginger on fibrinogen in MS-induced rats

Parameters / Treatment		Fibrinogen (mg/dl)
Normal control		227.33±1.63
MS-induced	Control	369.17±7.83#
	+ Nigella sativa (4ml/kg)	190.67±3.93#*
	+ Ginger (500 mg/kg)	205.83±4.66#*

Abbreviations: ANOVA, analysis of variance; MS, metabolic syndrome.

Table No.10: Effect of Nigella sativa and ginger on oxidative stress paramaters in MS-induced rats

Parameters / Treatment		MDA (nmol/ml)	GSH (mg/dl)	SOD (u/l)
Normal control		1.59±0.07	9.813±0.63	11.57±0.51
MS-induced	Control	4.99±0.44#	6.74±0.43#	7.84±0.36#
	+ Nigella sativa (4ml/kg)	0.76±0.05#*	38.39±1.25#*	57.83±2.17#*
	+ Ginger (500 mg/kg)	1.09±0.04#*	32.5±1.4#*	35.31±2.49#*

Abbreviations: ANOVA, analysis of variance; MDA, Malondialdehyde; GSH, Glutathione reduced; SOD, Superoxide Dismutase; MS, metabolic syndrome.

CONCLUSION

In conclusion, NS and ginger for 4 weeks decreased insulin resistance and reduce glucose level compared with metformin. They improve the hyperlipidemia and insulin sensitivity. The increase in adiponectin, GLUT4 and PPAR protein expression may be responsible for these effect. In addition, NS and ginger for 4 weeks decreased blood pressure and heart rate and improve the renal function. These effects could be related to antioxidant activity.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

BIBLIOGRAPHY

1. El-Bilbeisi A H. The prevalence of metabolic syndrome and its related factors among adults in Palestine: A meta-analysis, *Eth J Hea Sci,* 27(1), 2017, 77.
2. Castro A. V. B, Kolka C M, Kim S P and Bergman R. N. Obesity, insulin resistance and comorbidities? Mechanisms of association, *Arq Bras Endo Metabol,* 58(6), 2014, 600.
3. Russo I. The prothrombotic tendency in metabolic syndrome: Focus on the potential mechanisms involved in impaired haemostasis and fibrinolytic balance, *Scientifica,* 2012, 2012, 525374.
4. Tappy L and Le K A. Metabolic effects of fructose and the worldwide increase in obesity, *Physi Rev,* 90(1), 2010, 23-46.
5. Samuel V T, Shulman G I. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux, *J Clin Invest,* 126(1), 2016, 12-22.
6. Supruniuk E, Mikłosz A, Chabowski A. The implication of PGC-1α on fatty acid transport across plasma and mitochondrial membranes in the insulin sensitive tissues, *Front Physiol,* 8, 2017, 923.
7. Saleh R, Merghani B H and Awadin W. Effect of high fructose administration on histopathology of kidney, heart and aorta of rats, *J Adv Vet Anim Res,* 4(1), 2017, 71.
8. Zhou M S, Wang A and Yu H. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? *Diabetol Metab Syndr,* 6(1), 2014, 12.
9. Wong S K, Chin K Y, Suhaimi F H, Fairus A and Ima-Nirwana S. Animal models of metabolic syndrome: A review, *Nutr Metab,* 13(1), 2016, 65.
10. Marcus Y, Shefer G, Sasson K, Kohen F, Limor R, Pappo O and Fridkin M. Angiotensin 1-7 as means to prevent the metabolic syndrome: lessons from the fructose-fed rat model, *Diabetes,* 62(4), 2013, 1121.
11. Makki K, Froguel P and Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: Cells, cytokines and chemokines, *ISRN Inflamm,* 2013, Article ID: 139239, 2013, 1-13.
12. Madjid M and Fatemi O. Components of the complete blood count as risk predictors for coronary heart disease: In-depth review and update, *Tex Heart Inst J,* 40(1), 2013, 17-29.
13. Sanchez-Lozada L G, Tapia E, Jimenez A, Bautista P, Cristobal M, Nepomuceno T and Herrera-Acosta J. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats, *Am J Physiol Renal Physiol,* 292(1), 2007, F423-429.
14. Nizar J M, Shepard B D, Vo V T and Bhalla V. Renal tubule insulin receptor modestly promotes elevated blood pressure and markedly stimulates glucose reabsorption, *JCI Insight,* 3(16), 2018, e95107.

15. Phaniendra A, Jestadi D B and Periyasamy L. Free radicals: Properties, sources, targets, and their implication in various diseases, *Indian J Clin Biochem,* 30(1), 2015, 11-26.
16. Espinosa-Diez C, Miguel V, Mennerich D, Kietzmann T, Sanchez-Perez P, Cadenas S and Lamas S. Antioxidant responses and cellular adjustments to oxidative stress, *Redox Biol,* 6, 2015, 183-197.
17. Ganji A, Salehi I, Nazari M, Taheri M and Komaki A. Effects of Hypericumscabrum extract on learning and memory and oxidant/antioxidant status in rats fed a long-term high-fat diet, *Metabolic Brain Disease,* 32(4), 2017, 1255-1265.
18. Leong X F, Rais Mustafa M and Jaarin K. Nigella sativa and its protective role in oxidative stress and hypertension, *Evidence-Based Complementary and Alternative Medicine,* 2013, 2013, 120732.
19. Mollazadeh H and Hosseinzadeh H. The protective effect of Nigella sativa against liver injury: A review, *Iranian Journal of Basic Medical Sciences,* 1(12), 2014, 958-966.
20. Boskabady M H, Keyhanmanesh R, Khameneh S, Doost 7 dar, Y and Khakzad M R. Potential immunomodulation effect of the extract of Nigella sativa on ovalbumin sensitized guinea pigs, *Journal of Zhejiang University Science B,* 12(3), 2017, 201-209.
21. El Rabey H A, Al-Seeni M N and Bakhashwain A S. The antidiabetic activity of Nigella sativa and propolis on streptozotocin-induced diabetes and diabetic nephropathy in male rats, *Evidence-Based Complementary and Alternative Medicine,* 2017, 2017, 5439645.
22. Eissa F A, Choudhry H, Abdulaal W H, Baothman O A, Zeyadi M, Moselhy S S and Zamzami M A. Possible hypocholesterolemic effect of ginger and rosemary oils in rats, *African Journal of Traditional, Complementary and Alternative Medicines,* 14(4), 2017, 188-200.
23. Marx W, Mc Kavanagh D, Mc Carthy A L, Bird R, Ried K, Chan A and Isenring L. The effect of ginger (Zingiber officinale) on platelet aggregation: A systematic literature review, *PLoS One,* 10(10), 2015, e0141119.
24. Akinyemi A J, Ademiluyi A O and Oboh G. Aqueous extracts of two varieties of ginger (Zingiberofficinale) inhibit angiotensin I-converting enzyme, iron (II) and sodium nitroprusside-induced lipid peroxidation in the rat heart *in vitro*, *Journal of Medicinal Food,* 16(7), 2013, 641-646.
25. Hosseinian S, Roshan N M, Khazaei M, Shahraki S, Mohebbati R and Rad A K. Renoprotective effect of Nigella sativa against cisplatin-induced nephrotoxicity and oxidative stress in rat, *Saudi Journal of Kidney Diseases and Transplantation,* 29(1), 2018, 19-29.
26. Hassanali Z, Ametaj B N, Field C J, Proctor S D and Vine D F. Dietary supplementation of n-3 PUFA reduces weight gain and improves postprandial lipaemia and the associated inflammatory response in the obese JCR: LA-cp rat, *Diabetes, Obesity and Metabolism,* 12(2), 2010, 139-147.
27. Sakai C, Ishida M, Ohba H, Yamashita H, Uchida, H, Yoshizumi M and Ishida, T. Fish oil omega-3 polyunsaturated fatty acids attenuate oxidative stress-induced DNA damage in vascular endothelial cells, *PloS One,* 12(11), 2017, e0187934.
28. Tanka-Salamon A, Komorowicz E, Szabo L, Tenekedjiev K and Kolev K. Free fatty acids modulate thrombin mediated fibrin generation resulting in less stable clots, *PloS One,* 11(12), 2016, e0167806.
29. Calvo-Ochoa E, Hernandez-Ortega K, Ferrera P, Morimoto S and Arias C. Short-term high-fat-and-fructose feeding produces insulin signaling alterations accompanied by neurite and synaptic reduction and astroglial activation in the rat hippocampus, *Journal of Cerebral Blood Flow and Metabolism,* 34(6), 2014, 1001-1008.

30. Ahmed M A and Hassanein K M. Cardio protective effects of Nigella sativa oil on lead induced cardio toxicity: Anti-inflammatory and antioxidant mechanism, *J Physiol Pathophysiol,* 4(5), 2013, 72-80.
31. Thomson M, Al-Amin Z M, Al-Qattan K K, Shaban L H and Ali M. Anti-diabetic and hypolipidaemic properties of garlic (Allium sativum) in streptozotocin-induced diabetic rats, *Int J Diabetes and Metabolism,* 15(3), 2007, 108-115.
32. Van Herck H, Baumans V, Brandt C J W M, Boere H A G, Hesp A P M, Van Lith H A and Beynen A C. Blood sampling from the retro-orbital plexus, the saphenous vein and the tail vein in rats: Comparative effects on selected behavioural and blood variables, *Laboratory Animals,* 35(2), 2001, 131-139.
33. Friedewald W T, Levy R I and Fredrickson D S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, *Clinical Chemistry,* 18(6), 1972, 499-502.
34. Matthews D R, Hosker J P, Rudenski A S, Naylor B A, Treacher D F and Turner R C. Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man, *Diabetologia,* 28(7), 1985, 412-419.
35. Mc Auley K A, Williams S M, Mann J I, Walker R J, Lewis-Barned N J, Temple L A and Duncan A W. Diagnosing insulin resistance in the general population, *Diabetes Care,* 24(3), 2001, 460-464.
36. Elliott S S, Keim N L, Stern J S, Teff K and Havel P J. Fructose, weight gain and the insulin resistance syndrome, *Am J Clin Nutr,* 76(5), 2002, 911.
37. Tunduguru R and Thurmond D C. Promoting glucose transporter-4 vesicle trafficking along cytoskeletal tracks: PAK-Ing them out, *Front Endocrinol,* 8, 2017, 329.
38. Olson A L. Regulation of GLUT4 and insulin-dependent glucose flux, *ISRN Mol Biol,* 2012, Article ID: 856987, 2012, 1-13.
39. Dornas W C, De Lima W G, Pedrosa M L and Silva M E. Health implications of high-fructose intake and current research, *Adv Nutr,* 6(6), 2015, 729-737.
40. Bano F, Wajeeh M, Baig N, Naz H, Akhtar N and Hajra N. Antiobesity, antihyperlipidemic and hypoglycemic effects of the aqueous extract of Nigella Sativa seeds (Kalongi), *J Biochem Mol Biol,* 42(4), 2009, 136-140.
41. Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M and Ashtary-Larky, D. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa), *Chinese Journal of Natural Medicines,* 14(10), 2016, 732-745.
42. Khan A R, Lateef Z N A A, Al Aithan M A, Bu-Khamseen M A, Al Ibrahim I and Khan S A. Factors contributing to non-compliance among diabetics attending primary health centers in the Al Hasa district of Saudi Arabia, *Journal of Family and Community Medicine,* 19(1), 2012, 26-32.
43. Prabhakar P, Reeta K H, Maulik S K, Dinda A K and Gupta Y K. Protective effect of thymoquinone against high-fructose diet-induced metabolic syndrome in rats, *European Journal of Nutrition,* 54(7), 2015, 1117-1127.
44. Salama R M, Schaalan M F, Ibrahim M E, Khalifa A E and Elkoussi A A. Effectiveness of telmisartan as an adjunct to metformin in treating type II diabetes mellitus in rats, *Open Journal of Endocrine and Metabolic Diseases,* 3(3), 2013, 186-196.
45. Ezz E A, El-Mahdy A A, Abbas O A. Nigella sativa and panax ginseng supplementation ameliorate induced-hyperlipidemia in male rats, *Arab Journal of Nuclear Sciences and Applications,* 49(3), 2016, 237-249.
46. Rani M P, Krishna M S, Padmakumari K P, Raghu K G and Sundaresan A. Zingiber officinale extract exhibits antidiabetic potential via modulating glucose uptake, protein glycation and inhibiting adipocyte differentiation: An *in vitro* study, *Journal of*

the Science of Food and Agriculture, 92(9), 2012, 1948-1955.
47. Singh P, Srivastava S, Singh V B, Sharma P and Singh D. Ginger (Zingiber officinale): A Nobel herbal remedy, *Int J Curr Microbiol App Sci,* 7, 2018, 4065-4077.
48. Yang H. Advances in research on lipid-lowering mechanisms of eight medicinal plants, *In AIP Conference Proceedings,* 2058(1), 2019, 020007.
49. Li Y, Tran V H, Duke C C, B D, Roufogalis. Gingerols of Zingiber officinale enhance glucose uptake by increasing cell surface GLUT4 in cultured L6 myotubes, *Plantamedica,* 78(14), 2012, 1549-1555.
50. Wei C K, Tsai Y H, Korinek M, Hung P H, El-Shazly M, Cheng Y B and Chang F R. 6-Paradol and 6-shogaol, the pungent compounds of ginger, promote glucose utilization in adipocytes and myotubes and 6-paradol reduces blood glucose in high-fat diet-fed mice, *International Journal of Molecular Sciences,* 18(1), 2017, 168.
51. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C and Zuniga F A. Association between insulin resistance and the development of cardiovascular disease, *Cardiovasc Diabetol,* 17(1), 2018,1-14.
52. Han L, Liu J, Zhu L, Tan F, Qin Y, Huang H and Yu Y. Free fatty acid can induce cardiac dysfunction and alter insulin signaling pathways in the heart, *Lipids Health Dis,* 17(1), 2018, 185.
53. Brands M W and Manhiani M M. Sodium-retaining effect of insulin in diabetes, *Am J Physiol Regul Integr Comp Physiol,* 303(11), 2012, R1101-1109.
54. Ullah A, Abad K and Ismail K. Diabetes mellitus and oxidative stress-A concise review, *Saudi Pharm J,* 24(5), 2016, 547-553.
55. Lim J S, Mietus-Snyder M, Valente A, Schwarz J M and Lustig R H. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome, *Nat Rev Gastroenterol Hepatol,* 7(5), 2010, 251-264.
56. Lubrano V and Balzan S. Consolidated and emerging inflammatory markers in coronary artery disease, *World J Exp Med,* 5(1), 2015, 21-32.
57. Ding L, Zhang C, Zhang G, Zhang T, Zhao M, Ji X and Xue F. A new insight into the role of plasma fibrinogen in the development of metabolic syndrome from a prospective cohort study in urban Han Chinese population, *Diabetol Metab Syndr,* 7(1), 2015, 1-8.
58. Shabana A, El-Menyar A, Asim M, Al-Azzeh H and Al Thani H. Cardiovascular benefits of black cumin (Nigella sativa), *Cardiovasc Toxicol,* 13(1), 2013, 9-21.
59. Abbasnezhad A, Niazmand S, Mahmoudabady M, Soukhtanloo M, Rezaee S A and Mousavi S M. Nigella sativa seed decreases endothelial dysfunction in streptozotocin-induced diabetic rat aorta, *Avicenna J Phytomed,* 6(1), 2016, 67-76.
60. Najmi A, Nasiruddin M, Khan R A and Haque S F. Therapeutic effect of Nigella sativa in patients of poor glycemic control, *Asian J Pharm Clin Res,* 5(3), 2012, 224-228.
61. Mohtashami A, Mahaki B, Azadbakht L and Entezari M H. Effects of bread with Nigella sativa on lipid profiles, apolipoproteins and inflammatory factor in metabolic syndrome patients, *Clin Nutr Res,* 5(2), 2016, 89-95.
62. Abbasnezhad A A, Niyazmand S, Abadi M, Soukhtanloo M, Rezaee S A and Mousavi S. M. Comparison the effect of hydroalcholic extract of nigella sativa l. seed and metformin on blood biochemical parameters in streptozotocin-induced diabetic rats, *Horizon Med Sci J,* 20(4), 2015, 243.
63. Bader A A. Anti-ischemic properties of Nigella sativa against cardiac and non-cardiovascular ischemia, *International Journal of Pharmacology and Toxicology,* 5(1), 2015, 53-61.
64. Al-Rasheed N M, Abdelkarem H M, Fadda L M, Mohamed A M, Bassiouni Y, Ali H M and Gafeer A H. Amelioration of insulin,

leptin and adiponectin levels in experimental metabolic syndrome model by some drugs, *Indian J Pharm Sci,* 78(6), 2016, 701-707.
65. Benhelima A, Kaid-Omar Z, Hemida H, Benmahdi T and Addou A. Nephroprotective and diuretic effect of Nigella sativa L seeds oil on lithiasicwistar rats, *Afr J Trad Comp Altern Med,* 13(6), 2016, 204-214.
66. Hayatdavoudi P, Rad A K, Rajaei Z and Hadjzadeh M A R. Renal injury, nephrolithiasis and Nigella sativa: A mini review, *Avicenna J Phyt,* 6(1), 2016, 1-8.
67. Mahood A K S. Histological study of the effect of Nigella sativa on diabetic nephropathy in rats, *Medical Journal of Tikrit,* 18(2), 2012, 154-168.
68. Gholamnezhad Z, Shakeri F, Saadat S, Ghorani V and Boskabady M H. Clinical and experimental effects of Nigella sativa and its constituents on respiratory and allergic disorders, *Avicenna J Phytomed,* 9(3), 2019, 195-212.
69. Muralidharan-Chari V, Kim J, Abuawad A, Naeem M, Cui H and Mousa S. Thymoquinone modulates blood coagulation *in vitro* via its effects on inflammatory and coagulation pathways, *Int J Mol Sci,* 17(4), 2016, 1-13.
70. Shakeri F, Khazaei M and Boskbady M H. Cardiovascular effects of nigella Sativa L and its Constituents, *Indian J Pharm Sci,* 80(6), 2018, 971.
71. Rahmani A H and Aly S M. Nigella sativa and its active constituents thymoquinone shows pivotal role in the diseases prevention and treatment, *Asian J Pharm Clin Res,* 8(1), 2015, 48-53.
72. Tabassum N and Ahmad F. Role of natural herbs in the treatment of hypertension, *Pharmacogn Rev,* 5(9), 2011, 30-40.
73. Zadeh J B and Kor N M. Physiological and pharmaceutical effects of Ginger (Zingiberofficinale Roscoe) as a valuable medicinal plant, *Euro J Exp Bio,* 4(1), 2014, 87-90.
74. Shaban M I, EL-Gahsh N F A and El-sol A E H. Ginger: It's Effect on blood pressure among hypertensive patients, *IOSR Journal of Nursing and Health Science,* 6(5), 2017, 79-86.
75. Oloyede H O B, Ajiboye T O and Salau A K. Potential roles of garlic and ginger in the management of metabolic syndrome, Transaction *of the Nigerian Society of Biochemistry and Molecular Biology,* 1(1), 2015, 1-18.
76. Subbaiah G V, Mallikarjuna K, Shanmugam B, Ravi S, Taj P U and Reddy, K. S. Ginger treatment ameliorates alcohol-induced myocardial damage by suppression of hyperlipidemia and cardiac biomarkers in rats, *Phcog Mag,* 13(1), 2017, S69-S75.
77. Amran A Z, Jantan I, Dianita R and Buang F. Protective effects of the standardized extract of Zingiber officinale on myocardium against isoproterenol-induced biochemical and histopathological alterations in rats, *Pharm Biol,* 53(12), 2015, 1795-1802.
78. Soliman A F, Anees L M and Ibrahim D M. Cardio protective effect of zingerone against oxidative stress, inflammation and apoptosis induced by cisplatin or gamma radiation in rats, *Naunyn Schmiedebergs Arch Pharmacol,* 391(8), 2018, 819-832.
79. Hamed M A, Ali S A and Saba El-Rigal N. Therapeutic potential of ginger against renal injury induced by carbon tetrachloride in rats, *Scientific World Journal,* 2012, Article ID: 840421, 2012.
80. Abd-Allah G A, El-Bakry K A, Bahnasawy M H and El-Khodary E R. Protective effects of curcumin and ginger on liver cirrhosis induced by carbon tetrachloride in rats, *Int. J. Pharmacol,* 12(4), 2016, 361-369.
81. Maan B and Acharya A. To evaluate the effect of ginger (Zingiberofficinale) on body mass index and status of C-reactive protein in diabetes mellitus, *Global Journal for Research Analysis,* 7(1), 2018, 1-2.

82. Prasad S and Tyagi A K. Ginger and its constituents: Role in prevention and treatment of gastrointestinal cancer, *Gastroenterol Res Pract,* 2015, 142979, 2015.
83. Mazidi M, Gao H K, Rezaie P and Ferns G A. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: A systematic review and meta-analysis, *Food Nutr Res,* 60(1), 2016, 32613.
84. Gholampour F, Ghiasabadi F B, Owji S M and Vatanparast J. The protective effect of hydroalcoholic extract of Ginger (Zingiber officinale Rosc.) against iron-induced functional and histological damages in rat liver and kidney, *Avicenna J Phytomed,* 7(6), 2017, 542-553.

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