Research Article **CODEN: AJPCFF** **ISSN: 2321 – 0915**

Asian Journal of Phytomedicine and Clinical Research

Journal home page: www.ajpcrjournal.com

https://doi.org/10.36673/AJPCR.2020.v08.i03.A13

TREATMENT WITH *NIGELLA SATIVA* AND GINGER IMPROVE CARDIAC AND RENAL COMPLICATIONS IN METABOLIC SYNDROME-INDUCED RATS

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ABSTRACT

Background: Frequent consumption of fructose and saturated fatty acids increase risk of metabolic syndrome (MS). Features of MS include insulin resistance, dyslipidemia, visceral obesity, and hypertension. The aim of this study was to investigate the role of *Nigella sativa* and ginger in ameliorating features of MS. **Methods:** Induction of MS in rats by high-fructose high-fat fed diet was certain after 8 weeks. Animals were divided into four groups: normal control, MS control group given saline, MS groups given *Nigella sativa* (4ml/kg), and ginger (500mg/kg) daily for 4 weeks. Blood pressure, heart rate, CK-MB, and LDH were estimated. Also renal function 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 blood pressure and heart rate. They reduced creatinine, BUN, uric acid, albumin, and MDA with increased GSH, and SOD. Drugs also decreased CRP, and fibrinogen compared with MS control group. **Conclusion:** *Nigella sativa* and ginger ameliorate cardiac and renal complication of MS via their antioxidant activity.

KEYWORDS

Metabolic syndrome, *Nigella sativa*, Ginger and Antioxidant activity.

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INTRODUCTION

The prevalence of metabolic syndrome (MS) has increased worldwide mainly due to the obesity epidemic[1]. Although there was no accepted central underlying mechanism for the pathogenesis of the metabolic syndrome, two features; the visceral obesity and impaired insulin in particular stand out

as potential etiologies underlying the associated abnormalities of MS[2].

Many authorities also recognize metabolic syndrome as a pro-inflammatory and prothrombotic state, although these features are not included in the formal definition[3].

Fructose feeding induced ventricular dilatation, ventricular hypertrophy, decreased ventricular contractile function, and infiltration of inflammatory cells in heart[4].

Insulin resistance has been proposed as a strong predictor for the development of hypertension[5]. Substituting the starch carbohydrate content in laboratory rodent diet with fructose resulted in elevated blood pressure within a period of 6-8 weeks. The effects of high fructose feeding have been reported to be concentration and time-dependent[6].

Vascular dysfunction due to a fructose-rich diet has been reported in the rat, and it is recognized that vascular dysfunction in metabolic syndrome is associated with increased vasoconstrictor sensitivity and production of vascular superoxide anions[7].

It is evident that this state of chronic inflammation may contribute to the chronic illnesses associated with obesity, namely atherosclerosis, dyslipidemia and insulin resistance[8]. Additionally, CRP is emerging as an independent and strong predictor and mediator of cardiovascular diseases[9].

Sanchez-Lozada *et al*[10], reported functional changes including elevated plasma creatinine and albuminuria and morphological changes including fatty infiltration and thickening of glomeruli have been reported after 60 days of fructose feeding in rat[11].

Oxygen-derived free radical reactions have been implicated in the pathogenesis of many human diseases/disorders, including cardiovascular disorders, renal disorders and, diabetes[12].

Nature has endowed each cell with adequate protective mechanisms against any harmful effects of free radicals. Superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase, thiols, and disulfide bonding are buffering systems in every cell[13].

Plants provide a rich source of antioxidants to overcome the action of ROS as they can reduce free radical formation and scavenge free radicals[14]. *Nigella sativa* and ginger were chosen in this study. As nigella sativa (NS) seeds possess antioxidant and hypotensive activity[15]. Moreover, NS is known for its hepatoprotective[16], immunomodulatory effects[17], and anti-diabetic activity[18]. Similarly ginger has the potential to treat hyperlipidemia[19], platelet aggregation[20], and hypertension[21]. Also, ginger is reported to possess anti-inflammatory, hypoglycemic activity[22], renoprotective[23], and immunomodulatory effects[24]. Furthermore they exert antithrombotic activity[25]. The aim of the study was to investigate the role of *Nigella sativa* and ginger compared with metformin on MS-induced insulin resistance.

MATERIAL AND METHODS

Animals

Thirty male Sprague Dawley rats weighting 200 to 230g were used in the current study. They were purchased from the animal house of the National Research Center Institute (Cairo, Egypt). During the study, the animals were housed under conventional laboratory conditions on a 12 hours light/dark cycle and constant temperature (22 ± 1°C). 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 purchased from (Arab company for pharmaceuticals and Medicinal plants (MEPACO-MEDI FOOD), (Sharkeya, Egypt). Metformin was purchased from Minapharm Pharmaceutical, (Cairo, Egypt). Fructose was purchased 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).

Experimental design

MS was induced by feeding rats a high-fat diet consisting of standard rodent chow in addition to 10% fat, 3% NaCl, and fructose 20% solution in drinking water for 8 weeks according to modified method described by Calvo-Ochoa *et al*[26].

Diet and fructose solution were freshly 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 I

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

Group II

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

Group III

This group fed HFHFD for 12 weeks and Nigella sativa oil (4ml/kg) for the last 4 weeks[27].

Group IV

This group fed HFHFD for 12 weeks and ginger (500mg/kg) for the last 4 weeks[28].

At the end of treatment, the animals were fasted for 12 hour weighed and blood samples were withdrawn from the retro-orbital plexus under light anesthesia[29]. Plasma was separated by centrifugation at (1,509g, 15 min, 4°C) 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 28°C 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 at least 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.

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

During the 8 weeks feeding of HFHFD, normal control rats demonstrated a systolic blood pressure value of 115±1.87 (mm Hg) (Table No.2). Maintaining rats on HFHFD for 12 weeks increased systolic blood pressure by 57% compared to normal control (Table No.2). *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.2). Metabolic syndrome was associated with an elevation in diastolic blood pressure level by 36% compared to normal control (Table No.2). *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.2). Meanwhile MS-induced rats exhibited a significant increase in mean blood pressure by 45% compared to normal control (Table No.2). 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.2). Meanwhile, MS-induced rats exhibited an increase in heart rate by 40% compared to normal control (Table No.2). 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.

Rats kept on normal laboratory chow exhibited total CK-MB value of 101.5±4.32 (U/l) (Table No.3). Metabolic syndrome was associated with an elevation in CK-MB level by 210% compared to normal control (Table No.3). *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.3). Meanwhile MS-induced rats exhibited a significant increase in LDH level by 132% compared to normal control (Table No.3). 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.3). Maintaining rats on HFHFD for 12 weeks increased CRP level by 432% compared to normal control (Table No.3). Nigella sativa, and ginger, treated groups showed a significant (P<0.05) decrease in the levels of CRP by 86 %, and 83% respectively when compared to MS-induced group.

Rats kept on normal laboratory chow exhibited creatinine value of 0.55±0.02 (mg/dl) (Table No.4). Metabolic syndrome was associated with an elevation in creatinine level by 42% compared to normal control (Table No.4). *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.4). Meanwhile MS-induced rats exhibited a significant increase in uric acid level by 340% compared to normal control (Table No.4). 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.4). Maintaining rats on HFHFD for 12 weeks increased BUN level by 13% compared to normal control (Table No.4). *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.4). Metabolic syndrome was associated with reduction in albumin level by 15% compared to normal control (Table No.4). *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.

Normal control rats demonstrated a blood fibrinogen value of 227.33 ± 1.63 (mg/dl) (Table No.5). MS-induced rats demonstrated an increase in the blood fibrinogen level by 62% compared to normal control (Table No.5). *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.

Normal control rats demonstrated MDA value of 1.59±0.07 (nmol/ml) (Table No.6). Maintaining rats on HFHFD for 12 weeks increased MDA by 214%

compared to normal control (Table No.6). *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.6). Metabolic syndrome was associated with a lowered glutathione level by 31% compared to normal control (Table No.6). 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.6). Meanwhile MS-induced rats exhibited a significant decrease in SOD by 32% compared to normal control (Table No.6). 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.

DISCUSSION

In the present study, 8 weeks of feeding rats with HFHFD 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[30].

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[31]. 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[32].

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[33].

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[34].

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[35].

Fibrinogen, an acute-phase reactant like CRP, rises in response to a high cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected[36].

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, polyphenols, and flavonoids in NS that cause nitric oxide production and vasodilator effect[37], (ii) presence of linoleic acid that affects ionic fluxes across the vascular

endothelial cells[38], (iii) calcium channel-blocking activity by NS[39], (iv) inhibition of angiotensin-converting enzyme by flavonoids[40], (v) cardiovascular depressant action of the oil mediated centrally in the brain either directly or indirectly via mechanisms involving serotoninergic and muscarinic receptors[15], (vi) diuretic and cardiac depressant properties[15], and (vii) suppression of α-adrenoceptor-mediated phenylephrine-induced rise in the arterial BP[41].

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[42] 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[43]. The decrease in the heart rate may occur by activating cholinergic mechanisms[44].

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[45]. Moreover, NS prevented the degenerative changes in renal tissues induced by ethylene glycol[46]. The nephroprotective effect of NS could be possibly due to antioxidant effect[47].

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[48].

In the present study, NS administration caused a significant reduction in fibrinogen level. Muralidharan-Chari *et al*[49], reported an anticoagulant effect after oral administration of powdered NS seeds. Such findings are supported by Shakeri *et al*[50]. 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[51] 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.

Tabassum and Ahmad[52] revealed that, ginger improves blood circulation and relaxes muscles surrounding blood vessels. In rabbit thoracic aorta preparation, ginger relaxed the phenylephrine-induced vascular contraction[53]. Shaban *et al*[54]. 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*[55]. Another postulated mechanism may be due to induction of vasodilatation by increasing nitric oxide release[56].

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[57]. Amran *et al*[58] 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[59].

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*[59] 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[60]. 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[61].

In the present study, ginger administration caused a significant reduction in fibrinogen level. Marx *et al*[20]. Reported that ginger as well as individual ginger compounds have an effect on platelet aggregation.

Maan and Acharya[62] have reported that the concentration of inflammatory markers including CRP were reduced in the group treated with ginger. The active constituents of ginger including phenolic compounds such as gingerol, paradol, and shogaol may be responsible for the anti-inflammatory activity[63].

The anti-inflammatory action of ginger is related to direct inhibition of COX activity and suppression of TNF-α production[64].

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*[65] 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 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. 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 $P < 0.05$.

Table No.3: 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 (500 mg/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. 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 $P < 0.05$.

Table No.4: 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 (500mg/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. 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 $P < 0.05$.

Table No.5: 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. 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 $P < 0.05$.

Table No.6: Effect of *Nigella sativa*, and ginger on oxidative stress parameters 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. 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 $P < 0.05$.

CONCLUSION

In conclusion, NS and ginger for 4 weeks decreased blood pressure and heart rate. They improve the renal function. These effects could be related to antioxidant activity.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Department of Pharmacy, Ministry of Health, Kafr El Shiekh General Hospital, Kafr El-Shaikh, Egypt for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Please cite this article in press as: Eman Adel Zayed *et al*. Treatment with *Nigella Sativa* and ginger improve cardiac and renal complications in metabolic syndrome-induced rats, *Asian Journal of Phytomedicine and Clinical Research,* 8(3), 2020, 119-131.