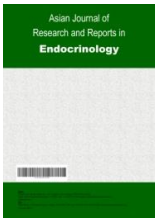

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Nigella sativa and Ginger Increase GLUT4 and PPARγ in Metabolic Syndrome-induced Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author EAZ designed the study, performed the statistical analysis, wrote the protocol, managed the analyses of the study, managed the literature searches and wrote the first draft of the manuscript. Authors HAAEL and AAAS designed the study, wrote the protocol, and reviewed the first draft of the manuscript and author AEMKEM managed the analyses of the study. Author AAZ managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Increased fructose intake has been linked to epidemiology of insulin resistance, type 2 diabetes mellitus, renal damage and metabolic syndrome (MS). As oxidative stress plays a pivotal role in the pathology of insulin resistance, the present study was conducted to investigate the effects of Nigella Sativa (NS) and ginger, as potent antioxidants on fructose induced MS in rats. **Methods**: Male rats were fed with high-fructose high-fat fed diet for 8 weeks. By the end of the 8th week, rats were divided into four groups; one was left untreated (normal control) and MS control group treated with saline, MS groups given Nigella sativa (4 ml/kg), and ginger (500 mg/kg) daily for 4 weeks. Markers chosen for assessment included effect on body weight gain, glucose, insulin, adiponectin levels, and lipid profile. Also glucose transporter 4 (GLUT4) content and peroxisome

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proliferator-activated receptor-gamma (PPARγ) protein expressions were estimated.
Results: Nigella sativa and ginger ameliorated some manifestation of MS including increase in body weight, glucose, insulin level and resistance. In addition, both drugs lowered insulin resistance induced hyperlipidemia and increased adiponectin level. Drugs also increased GLUT4 and PPARγ protein expression compared with MS control group.
Conclusion: Nigella sativa and ginger ameliorated parameters of MS. They improve the lipid profile and insulin sensitivity via increased adiponectin, GLUT4 and PPARγ expression.

Keywords: Metabolic syndrome; Nigella sativa; ginger; Insulin resistance; lipid.

1. INTRODUCTION

Metabolic syndrome (MS) is characterized by insulin resistance, hyperlipidemia, obesity and increased risk for developing non-alcoholic fatty liver disease, type 2 diabetes mellitus, cardiovascular and renal diseases [1]. Consumption of large amounts of dietary fructose is one of major factors that contribute to the development of obesity, and MS [2].

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 [3].

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) [4].

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 co-activator 1-alpha (PGC-1α), a potent transcriptional cofactor in regulating mitochondrial biogenesis and function [5].

There has been a lot of interest into potential strategies to treat and prevent metabolic syndrome, including non-pharmacological interventions [6]. Nigella sativa and ginger were chosen in this study. As *Nigella sativa* (NS) seeds possess antioxidant and hypotensive activity [7]. Moreover, NS is known for its hepatoprotective [8], immunomodulatory effects [9], and anti-diabetic activity [10]. Similarly ginger has the potential to treat hyperlipidemia [11], platelet aggregation [12], and hypertension [13]. Also, ginger is reported to possess anti-inflammatory, hypoglycemic activity [14], renoprotective [15], and immunomodulatory effects [16]. Furthermore they exert antithrombotic activity [17]. The aim of the study was to investigate the role of Nigella sativa and ginger compared with metformin on MS-induced insulin resistance.

2. MATERIALS AND METHODS

2.1 Animals

Adult male Sprague Dawley rats weighting 200 to 230 g were used. They were purchased from the animal house of the National Research Center Institute (Cairo, Egypt). During the study, the animals were housed under appropriate laboratory conditions of controlled humidity, temperature and light.

2.2 Drugs and Chemicals

Nigella sativa oil and Ginger were used in the study. (Metformin was purchased from Minapharm Pharmaceutical, (Cairo, Egypt). Fructose was purchased from El Nasr Pharmaceutical, (Cairo, Egypt). Insulin, adiponectin, GLUT4, and PPARγ 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).

2.3 Experimental Design

Rats were divided into five groups each consisting of 6 rats. Rats in the first group were fed with normal laboratory chow whereas rats in the remaining groups were fed with a high-fructose high-fat diet (HFHFD) composed 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. [18] After 8

weeks of diet initiation, animals in the four groups were treated as follows:

- Normal control group: this group received normal laboratory diet, tap water ad libitum and given saline daily during the time of experiment.
- MS-induced group: this group fed HFHFD for 12 weeks and given saline daily during the time of experiment.
- Nigella sativa group: this group fed HFHFD for 12 weeks and Nigella sativa oil (4ml/kg) for the last 4 weeks [19].
- Ginger group: this group fed HFHFD for 12 weeks and ginger (500 mg/kg) for the last 4 weeks [20].

At the end of study, blood samples were withdrawn from the retro-orbital plexus of all rats [21]. Serum was separated by centrifugation at (3000 rpm, 15 min, 4°C) and divided into small aliquots that were stored for the estimation.

2.4 Biochemical Assays

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. Quantitative insulin sensitivity check index (QUICKI) was calculated according to the equation provided by McAuley et al.

LDL-C and VLDL were calculated from the formula described by Friedewald et al. where
LDL-C=TC−(HDL + TG/5)
VLDL = TG/5.

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

2.5 Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Results were analyzes using one-way analysis of variance followed by Tukey's post hoc test using SPSS software. For all statistical tests, the level of significance was set at $P < 0.05$.

3. RESULTS

At the end of 8 weeks feeding of HFHFD, The body weight gain and relative organ weight were significantly higher in non-treated MS-induced rats when compared to normal-control rats (Table 1). After 4 weeks of oral treatment of MS-induced rats with NS (4ml/kg), ginger (500 mg/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 1). Meanwhile, MS-induced rats treated with the NS and ginger exhibited decrease in relative liver, heart, and in visceral adipose tissue weight.

Non-treated MS-induced group showed higher serum glucose level than normal control (Table 2). Significant reduction in glucose level was seen in MS-induced rats treated with NS and ginger by 64%, and 57 % respectively when compared to MS-induced group (Table 2).
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 2). MS-induced rats given NS and ginger nearly normalized 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.

There was significant reduction of PPARγ expression in non-treated MS-induced rats as compared to normal control group (Table 3). 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.

Table 1. Effect of Nigella sativa and ginger on body weight gain and relative organs weight in MS-induced rats

Parameters/ Treatment	Body eight gain (g)	Relative Liver weight (g)	Relative Heart weight (g)	Relative Visceral fat tissue weight (g)
Normal control	52±5.94*	0.022±0.32	0.002±0.02*	0.018±0.26*
MS-induced group	100±13.57#	0.043±0.35#	0.06±0.04#	0.34±0.19#
Nigella sativa group (4ml/kg)	-43±15.05*@#	0.024±0.24*#	0.002±0.02@#	0.02±0.11*@#
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. 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.

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

Table 2. Effect of Nigella sativa and ginger on blood glucose homeostasis in MS-induced rats

Parameters/ Treatment	Blood glucose (mg/dl)	Insulin (mU/l)	HOMA-IR	QUICKI
Normal control	74.33±2.48*	7.02±0.39*	1.28±0.00*	0.37±0.00*
MS-induced group	164.27±3.56#	26.42±2.2#	10.61±0.02#	0.27±0.00#
Nigella sativa group (4ml/kg)	57.7±1.56*@#	6.55±0.42*@	0.92±0.00*@	0.39±0.00*@#
Ginger group (500 mg/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. 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 3. Effect of Nigella sativa and ginger on biomarkers affecting insulin resistance MS-induced rats

Parameters / Treatment	Adiponectin (mg/l)	GLUT-4 (ng/ml)	PPAR γ (ng/ml)
Normal control	6.35±0.18	7.53±0.3*	8.58±0.65*
MS-induced group	4.68±0.17	4.33±0.22#	3.06±0.18
Nigella sativa group (4ml/kg)	35.17±1.47*#	39.6±1.6*@#	13.85±0.76*@#
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. 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 4. Effect of Nigella sativa and ginger on lipid profile in MS-induced rats

Parameters / Treatment	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL (mg/dl)
Normal control	82±1.43*	79.85±1.6*	30.05±2.2*	36.06±2.71*	15.97±0.32*
MS-induced group	199.33±6.74#	156±1.41#	13.5±2.7#	154.63±8.6#	31.2±0.28#
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*@#
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. 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.

compared to those observed in normal control group [22,23]. 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.

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 4). 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.

4. DISCUSSION

Feeding rats with HFHFD resulted in hyperglycemia, hyperinsulinemia, and hyperlipidemia associated with decreased adiponectin, GLUT4, and PPARγ protein expression [23,24].

Fructose does not stimulate insulin secretion in short term however; insulin resistance and obesity induced by fructose feeding resulted in compensatory hyperinsulinemia [25].

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 [26]. This results in decreased uptake of glucose by muscle cells, which contributes significantly to the elevated blood glucose levels [27].

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 [28].

The antiadipose activity of NS 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 [29].

Previous study reported that NS reduced plasma lipids concentrations [30]. The mechanisms of NS favorable effects may be due to its choleretic activity as reported by Khan et al. [31].

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 [32]. In addition Benhaddou-Andaloussi reported that NS stimulated PPARγ in cultured adipocytes and increased the total amount of GLUT-4 glucose transporters in skeletal muscle. [33]

In addition, NS in MS-induced group resulted in an increase of adiponectin.[34] 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 [35]. 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 [36]. 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, 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 [37].

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 [38]. Activation PPAR γ expression by ginger may be due to presence of 6-shogaol which was identified as PPARγ activator which founded to be a novel effect [39].

5. CONCLUSIONS

In conclusion, NS and ginger for 4 weeks decreased insulin resistance and reduce glucose level compared with metformin. They improve the lipid profile and insulin sensitivity. These effects could be related to increased adiponectin, GLUT4, and PPAR protein expression. The NS treated group showed more activity than ginger treated group in ameliorating MS parameters.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It’s not applicable.

ETHICAL APPROVAL

The study was carried out according to the regulation of ethic committee of faculty of Pharmacy Cairo University (Approval number: PT 1305).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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