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THE ROLE OF PROPHETIC MEDICINE IN TREATMENT OF COMPLICATIONS IN METABOLIC SYNDROME-INDUCED RATS VIA FENUGREEK AND OMEGA-3 OIL

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ABSTRACT

Background: Frequent consumption of western diet containing saturated fatty acids and increase risk of metabolic syndrome (MS). Features of MS include visceral obesity, insulin resistance, dyslipidemia, cardiovascular complication 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 alienated into four groups: normal control, MS control group given saline, MS groups given fenugreek oil (4 ml/kg), and omega-3 (260 mg/kg) daily for 4 weeks. Parameters chosen for assessment included effect on body weight gain, glucose, insulin, 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, CK-MB, and LDH were estimated. Also renal function tests and antioxidant activity were evaluated. Additionally, CRP, and fibrinogen were determined. **Results:** Fenugreek oil and omega-3 caused decrease in both MS-induced increase in body weight and glucose. They reduced insulin level and resistance with increased adiponectin, and correction of MS-induced hyperlipidemia. Drugs also increased GLUT4 and PPARγ protein expression compared with MS control group. Furthermore, both drugs 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. Also, both fenugreek and omega-3decreased CRP, and fibrinogen compared with MS control group. **Conclusion:** Fenugreek oil and omega-3ameliorate cardiac and renal complication of MS via their antioxidant activity and increase in GLUT4 and PPARγ expression.

KEYWORDS

Metabolic syndrome, Fenugreek oil, Omega-3 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 fatty acid influx and glucose uptake 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].

Functional food provide a rich source of antioxidants to protect against the action of ROS as they can scavenge free radicals andreduce free radical formation[17].

Fenugreek (Trigonella foenum-graecum L. Leguminosae) is one of the oldest medicinal plants with medicinal activities such as hypocholesterolemic, antibacterial, gastric stimulant, anorexigenic, antidiabetic, galactogogue, hepatoprotective and anticancer. These beneficial physiological effects including the antidiabetic and hypocholesterolemic effects of fenugreek are mainly attributable to the intrinsic dietary fiber constituent which have promising nutraceutical value[18,19].

Omega-3 polyunsaturated fatty acids (PUFAs) are long chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in plants and marine sources[20]. The best prevention of cardiovascular diseases appears to be achieved by replacing saturated fat with omega-3 unsaturated fatty acids[21]. Similarly, increased intakes of marine omega-3 can result in decreased triglycerides, fibrinogen and platelet aggregation, which are considered to be beneficial for cardiovascular diseases[22].

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, God, the Most Merciful said: (It is He who has subjected the sea to you, so that you eat of its soft flesh and bring up from it ornaments which you wear. And you see the ships plowing their course through it in order that you seek His bounty and give thanks). Also Allah, the Most Merciful said, (Made lawful to you is the fished of the sea and its food, an enjoyment for you and for travelers. But you are forbidden the hunted of the land whilst you are on pilgrimage. Have fear of Allah, before whom you shall all be assembled). In addition Allah, the Most Merciful said (The two seas are not alike. One is fresh, sweet and pleasant to taste, while the other is salt and bitter. Yet, from each you eat fresh flesh and bring forth out of it ornaments for you to wear. And you see the ships plow their course through it so that you may seek His bounty and in order that you give thanks).

On the authority of Ibn Omar (may God be pleased with him) that the Prophet may God's prayers and peace be upon him, said: "Two dead bodies and two bloods are permitted for us. As for the two dead bodies, they are whales and locusts, and as for the two bloods, they are the liver and the spleen." And in the answer of the Prophet, peace be upon him, to the questions of one of the Jewish rabbis, as narrated by Anas (may God be pleased with him) on the authority of the Prophet, may God's prayers and peace be upon him, he said: (As for the first food that the people of Paradise will eat, it is an increase in the liver of a whale)

The hadith about the fenugreek 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 many disease. And we stop at the words of the Prophet about fenugreek, may God bless him and grant him peace, "If the people knew of its benefits, they would buy it for its weight in gold."

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±1°C). The design of the experiment was carried out according to the regulation of ethic committee of faculty of Pharmacy Cairo University.

Drugs and chemicals

Fenugreek oil was purchased from local herbal store, Haraz (Egypt), Omega-3 oil was purchased from (Montana Pharmaceuticals, Egypt). Metformin was obtained from Minapharm Pharmaceutical, (Cairo, Egypt). Fructose was purchased from El Nasr Pharmaceutical, (Cairo, Egypt).Blood pressure and heart rate were 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, uric acid, blood urea nitrogen (BUN), 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 using Kits purchased from (Biodiagnostic, Egypt).Adiponectin, 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).

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 giving the modified diet for 8 weeks according to modified method described by Calvo-Ochoa *et al*[23].

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 four groups (six rats each) as follows:

Group 1: this group received tap water ad libitum, normal laboratory diet, 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 fenugreek oil (4ml/kg) for the last 4 weeks[24].

Group 4: this group fed HFHFD for 12 weeks and omega-3(260 mg/kg) for the last 4 weeks[25].

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[26]. 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 using 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. 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.

Calculation of percentage of body weight gain and organ were determined. 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*[27]. Quantitative insulin sensitivity check index (QUICKI) was calculated according to the equation provided by McAuley *et al*[28].

LDL-C and VLDL were calculated from the formula described by Friedewald *et al*[29] 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

At the end of 8 weeks of feeding of HFHFD, The body weight gain and relative organ mass were significantly higher in non-treated MS-induced group when compared to normal-control group (Table No.2). After 4 weeks of oral treatment of MS-induced rats with fenugreek oil (4ml/kg),

omega-3 (260mg/kg) suppressed body weight gain by 92%%, and 83% 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 fenugreek and omega-3 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 seen in MS-induced rats treated with fenugreek oil and omega-3 by 59%, and 58% 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, fenugreek oil and omega-3administration to MS-induced rats significantly reduced serum insulin level by 67%, and 68% 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 fenugreek oil and omega-3nearly 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 fenugreek oil and omega-3give 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 fenugreek oil and omega-3by 314%, and 185% 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 fenugreek oil and omega-3281% and 658% 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 fenugreek oil and omega-3 showed significant increased serum adiponectin level by 718%, and 548% 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 fenugreek and omega-3 showed a significant decrease in the levels of cholesterol by 57%, and 60% 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 87%, and 87 % respectively when compared to non-treated MS-induced group. VLDL-C level was decreased (P<0.05) by 50%, and 52% respectively when compared to non-treated MS-induced group. On the other hand an increase in HDL-C by 267%, and 222% 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). Fenugreek, and omega-3treated groups showed a significant (P<0.05) decrease in systolic blood pressure by 28% %, and 36% 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). Fenugreek, and omega-3treated groups showed a significant (P<0.05) decrease in the levels of diastolic blood pressure by 24%, 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 Fenugreek, and omega-3 under the same condition caused a significant (P<0.05) decrease in mean blood pressure compared to the MS-induced rats by 24 %, 31% 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 Fenugreek, and omega-3under the same condition caused a significant (P<0.05) decrease in heart rate compared to the MS-induced rats by 60%, 62% 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 No.7). Metabolic syndrome was associated with an elevation in CK-MB level by 210% compared to normal control (Table No.7). Fenugreek, and omega-3treated groups showed a significant (P<0.05) decrease in the levels of CK-MB by 59%, and 74% 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 Fenugreek, and omega-3under the same condition caused a significant (P<0.05) decrease in LDH level compared to the MS-induced rats by 67 %, and 71% 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). Fenugreek, and omega-3, treated groups showed a significant (P<0.05) decrease in the levels of CRP by 82 %, and 80% 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 $P < 0.05$.
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). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) decrease in the levels of creatinine by 49%, and 42% 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 Fenugreek, and omega-3under the same condition caused a significant ($P<0.05$) decrease in uric acid level compared to the MS-induced rats by 67 %, and 65% 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). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) decrease in the levels of BUN by 25 %, and 28% 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). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) increase in the levels of albumin by 20%, 23% 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). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) decrease in the levels of fibrinogen by 52%, 42% 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). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) decrease in MDA by 75 %, 75% 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 10). Fenugreek, and omega-3treated groups showed a significant ($P<0.05$) increase in the levels of glutathione by 364%, 403% 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 Fenugreek, and omega-3under the same condition

caused a significant (P<0.05) increase in SOD level compared to the MS-induced rats by 391%, and 317% 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, hyperlipidemia, and hyperinsulinemia concomitant 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[30].

Reduction of PPAR-γ expression and GLUT-4 content 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[31]. This results in decreased uptake of glucose by muscle cells, which contributes significantly to the elevated blood glucose levels[32].

Furthermore, 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[33].

The administration of omega-3 to MS-induced rats provoked a significant reduction of blood glucose associated with reduction of insulin level and reduction of HOMA-IR as well as increased QUICKI. Reduction of blood glucose level may be due to improved insulin sensitivity in rats[34].

The antiadipose activity of omega-3 associated with a decrease in inflammation within the adipose tissue, induction of mitochondrial biogenesis, and upregulated adiponectin expression[35]. The underlying mechanism omega-3 antiadipose activity may be related to content of EPA and DHA, which reduced the abdominal adiposity, and total body fat and increased insulin sensitivity[36].

Previous study reported that omega-3 and fish oils reduced plasma lipids concentrations[37]. The mechanisms of omega-3 favorable effects may be due to incorporation into the membrane phospholipid fraction and TG lipid droplets of adipocytes[38].

Administration of omega-3 to MS-induced rats increased PPARγ protein expression. Previous studies reported that omega-3 to rats fed a high-fat diet improved insulin resistance by decreasing content of fat and maintaining normal phosphatidylinositol-3′ kinase activity as well as increasing expression and translocation of GLUT4[39]. In addition, omega-3 in MS-induced group resulted in an increase of adiponectin[40].

L-Carnitine 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[41]. Improvement of insulin resistance by L-carnitine could be related to the observed increase in adiponectin, GLUT4, and PPARγ expression.

In the present study, the administrations of omega-3 to MS-induced rat lead to a significant increase in GSH, and SOD, and decrease in MDA level. Lalia and Lanza[42] showed that treatment with Omega-3for 13 weeks increased the activity of antioxidant enzymes in a spontaneously hypertensive obese rat model of the metabolic syndrome.

The administration of omega-3 provoked a significant decreased MS-induced increase in level of CRP. Similar findings are observed by Kelley *et al*[43] who showed that treatment with omega-3 lowered the plasma CRP and inflammatory markers.

The administration of omega-3 in the present study, lead to significant decreased MS-induced hypertension. Omega-3 fatty acids have been associated with a mild decrease in systolic blood pressure and a decrease in diastolic blood pressure[44]. The suggested mechanisms of antihypertensive effect of omega-3 involve improvement in autonomic function by augmentation of vagal tone, improvement in left ventricular diastolic filling, alterations on the cardiac electrophysiological pathways, increase in urinary sodium, decrease in plasma renin activity, increase in endothelial nitric oxide production, and decrease in arteriosclerosis[45-47].

The prostaglandins derived from EPA antagonize the effect of arachidonic acid-derived prostaglandins, thromboxanes, and leukotrienes mediate vasoconstriction, platelet aggregation, and synthesis of inflammatory mediators. Omega-3 appears to suppress the activity of angiotensin-converting enzyme, leading to reduction in angiotensin II production and inhibition of aldosterone secretion[48,49].

Omega-3 improved hyperuricaemia, albuminuria, and kidney functionin the present study. The current results are in harmony with the results of Hu *et al*[50], who suggested that omega-3 fatty acids significantly reduced the risk of end-stage renal disease and was associated with a lower risk of proteinuria.

In the present study, omega-3 administration caused a significant reduction in fibrinogen level. The current results are in harmony with the previous study by Larson *et al*[50], who showed that omega-3 fatty acids had an antithrombotic effect, particularly a diminution in thromboxane A2, which produces platelet aggregation and vasoconstriction.

The administration of fenugreek seed extracts have the potential to slow enzymatic digestion of carbohydrates, reduce gastrointestinal absorption of glucose, and thus reduce post-prandial glucose levels and HbA1c[51]. In diabetic rats, trigonelline ingestion increased insulin sensitivity and reduced blood glucose levels[52].

The administration of fenugreek oil provoked a significant increase in GLUT-4 expression which may lead to decreased IR and increased glucose uptake. Kouzi *et al*[53], showed that 4-hydroxyisoleucine contained in fenugreek stimulated glucose uptake by enhancing the translocation of GLUT-4 to the cell surface via a PI3-K/Akt-dependent mechanism.

Furthermore, enhanced PPAR-γ expression by fenugreek was observed in this study may play a key role in maintaining glycemic control. Diosgenin raised PPAR-γ level in white adipose tissue[54]. Tharaheswari *et al*[55] found that methanolic extract of fenugreek increased PPAR-γ mRNA levels in high fat fed rats.

A highly significant increase in adiponectin level was observed in animals supplied with fenugreek oil. Arshadi *et al*[56] and Knott *et al*[57] reported that fenugreek supplementation increased adiponectin expression in subcutaneous adipose tissue.

The antiadipose activity of fenugreek fiber significantly increased satiety and decreased hunger leading to reduction in body weight as observed. Mathern *et al*[58] postulated that galactomannan present in seeds flushes out the sugars from the body before it enters the blood stream, thus resulting in weight loss. Furthermore it has been suggested that weight loss induced by fenugreek may be due to reduction of intestinal fat absorption or inhibition of pancreatic lipase activity[59] or reducing appetite by decreasing the levels of leptin in the adipose tissue[60]. Also, it was reported that saponins present in fenugreek suppressed the appetite signals in the hypothalamus leading to reduced food intake and body weight gain[61,62].

In addition fenugreek significantly improved lipid profile. Kumar *et al*[63] reported that galactomannan, and polyphenols contained in fenugreek seeds regulated dyslipidemia in obese and diabetic rodents. The hypolipidemic effect of fenugreek on adipocytes and liver cells may be related to enhanced LDLR-mediated LDL uptake which is responsible for improvement in serum lipid profile and body weight. Fenugreek lowered the hepatic TGs and cholesterol levels by increasing the

excretion of bile acids and cholesterol in the feces of rats in a dose-dependent manner[54,64].

Additionally, fenugreek hypolipidemic effect might be due to the activation of several enzymes, such as lecithin-cholesterol acyltransferase, TG lipase, and lipoprotein lipase[65,66]. Also, saponin present in fenugreek reduces cellular triglyceride accumulation by stimulating AMPK phosphorylation[67].

The administration of fenugreek oil provoked a significant increase in GSH, and SOD, and decrease in MDA level. Free radical scavenging activity of fenugreek is due to phenolic compounds present in the seeds[68]. Reduction of oxidative stress by fenugreek may also due to improvement of hyperglycemia and improvement of insulin resistance.

The administration of fenugreek oil significantly decreased CRP level indicating anti-inflammatory activity. This effect could be exhibited by diosgenin, which was found to attenuate inflammation and promote differentiation in the adipocytes[69].

The administration of fenugreek oil significantly decreased MS-induced hypertension and heart rate. The hypotensive effect of fenugreek was mediated through serotonin antagonism[70]. Recent studies have shown that, diosgenin contained in fenugreek protects vascular function by attenuating aortic calcification, increasing the expression of endothelial NO synthase, and inhibiting differentiation in aortic vascular smooth muscle cells[71,72].

Cardio-protective effect of fenugreek was evidenced by their blocking potential on renin-angiotensin system and nitric oxide metabolites in circulation[73].

Fenugreek also improved the glycogen content and hexokinase activity in muscle and caused a significant reduction in CK-MB isoenzyme activity in serum suggesting the potential protective effects of fenugreek against peripheral tissue damage[55].

In the present study, fenugreek oil improved hyperuricaemia, albuminuria, and kidney function. The results of the present study are in agreement with Konopelniuk *et al*[74] who reported that the beneficial effects of fenugreek galactomannan were evidenced by their capacity to inhibit diabetes-induced kidney injury through lowering the urea and creatinine content in plasma. The improvement in kidney dysfunction induced by fenugreek administration could be related to its ability to increase the activities of antioxidants in the kidneys[75].

In the present study, fenugreek oil administration caused a significant reduction in fibrinogen level leading to improvement of kidney function. Eldin *et al*[76] stated that, fenugreek aqueous extract in different concentrations inhibits clot formation and increases prothrombin time. They suggested that, anticoagulant effect of fenugreek may be attributed to several coumarin compounds that have been noted in the seeds.

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 fenugreek oil and omega-3on 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	Fenugreek oil group (4ml/kg)	8±14.07*#	0.026±1.66*	0.002±0.02*	0.029±0.23*#
4	Ginger group (500mg/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 fenugreek oil and omega-3 on 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	Fenugreek oil group (4ml/kg)	67.67±2.73*#	8.62±0.4*#	1.42±0.08*	0.36±0.00*
4	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.

Table No.4: Effect of fenugreek oil and omega-3 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	Fenugreek oil group (4ml/kg)	21.92±1.42*	16.5±1.87*#	13.5±1.26*#
4	Ginger group (500mg/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 fenugreek oil and omega-3on 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	Fenugreek oil group (4ml/kg)	85.33±2.58*	78.17±3.18*	49.5±2.16*#	20.2±2.4*#	15.63±0.63*
4	Ginger group (500mg/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 fenugreek oil and omega-3 on blood pressure and heart rate in MS-induced rats

S.No	Parameters / Treatment		Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Mean blood pressure (mm Hg)	Heart rate (beat/min)
1	Normal control		115±1.87	70±7.69	85±5.25	309±13.87
2	MS-induced	Control	180±7.35#	95±5.47#	123±6.23#	433±9.81#
3	MS-induced	+ Fenugreek oil group (4ml/kg)	130±1.86#*	130±1.86#*	91±8.06*	174±1.86#*
4	MS-induced	+ Omega-3 (260 mg/kg)	115±2.16*	70±6.89*	85±4.79*	164±2.73#*

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

Table No.7: Effect of fenugreek oil and omega-3 on pathophysiological cardiovascular parameters in MS-induced rats

S.No	Parameters / Treatment		CK-MB (U/l)	LDH (U/l)	CRP (mg/l)
1	Normal control		101.5±4.32	115.67±2.31	2.77±0.13
2	MS-induced	Control	315.07±15.15#	268.83±6.24#	14.73±1.64#
3	MS-induced	+ Fenugreek oil group (4ml/kg)	129.5±3.39#*	129.5±3.39#*	2.08±0.08*
4	MS-induced	+ Omega-3 (260 mg/kg)	81.67±4.08#*	77.83±3.97#*	2.92±0.22*

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 fenugreek oil and omega-3 on kidney function in MS-induced rats

S.No	Parameters / Treatment		Creatinine (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Albumin (g/dl)
1	Normal control		0.55±0.02	1.13±0.06	17.97±2.44	3.58±0.23
2	MS-induced	Control	0.78±0.03#	4.97±0.11#	20.32±3.6#	3.05±0.14#
3	MS-induced	+ Fenugreek oil group (4ml/kg)	0.4±0.03#*	1.65±0.13#*	15.24±2.34#*	3.67±0.21*
4	MS-induced	+ Omega-3 (260 mg/kg)	0.45±0.02#*	1.73±0.19#*	14.67±1.86#*	3.75±0.39*

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

Table No.9: Effect of fenugreek oil and omega-3 on fibrinogen in MS-induced rats

S.No	Parameters / Treatment		Fibrinogen (mg/dl)
	Normal control		227.33±1.63
1	MS-induced	Control	369.17±7.83#
2	MS-induced	+ Fenugreek oil group (4ml/kg)	176.33±4.65#*
3	MS-induced	+ Omega-3 (260 mg/kg)	212.33±6.37#*

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

Table No.10: Effect of fenugreek oil and omega-3 on oxidative stress paramaters in MS-induced rats

S.No	Parameters / Treatment		MDA (nmol/ml)	GSH (mg/dl)	SOD (u/l)
1	Normal control		1.59±0.07	9.813±0.63	11.57±0.51
2	MS-induced	Control	4.99±0.44#	6.74±0.43#	7.84±0.36#
3		+ Fenugreek oil group (4ml/kg)	1.27±0.08#*	31.24±0.95#*	38.5±1.8#*
4		+ Omega-3 (260 mg/kg)	1.25±0.07#*	33.91±2.42#*	32.73±1.12#*

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

CONCLUSION

In conclusion, fenugreek oil and omega-3 for 4 weeks decreased insulin resistance and reduce glucose level compared with metformin. They improve the hyperlipidemia and insulin sensitivity. These effects could be related to increased adiponectin, GLUT4, and PPAR protein expression. In addition, fenugreek oil and omega-3 for 4 weeks decreased blood pressure and heart rate and improve the renal function. These effects could be correlated to antioxidant activity.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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