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Original Article

Promising effects of Persian shallot extract on the serum markers and blood pressure of patients with metabolic syndrome: a double-blinded randomized controlled trial

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Abstract

OBJECTIVE: To evaluate the effect of Persian shallot extract on the serum markers and blood pressure of patients with metabolic syndrome (MetS).

METHODS: Fifty patients with MetS diagnosis were randomly assigned to the intervention (Persian shallot extract) and the control (placebo) group. Both groups received treatment for three months. Before the study and at the end of the study, 5 mL peripheral blood was taken from each patient. The measured factors included total antioxidant capacity (TAC), superoxide dismutase enzyme (SOD), malondialdehyde, oxidized low-density lipoprotein (Ox-LDL), apolipoprotein H (Apo-H), fasting blood glucose (FBS), total cholesterol, triglycerides, high-density lipoprotein (HDL), LDL, and systolic and diastolic blood pressure.

RESULTS: At baseline, the evaluated parameters were not significantly different between the intervention and control groups. At the end of the study, the mean serum levels of malondialdehyde and ox-LDL were significantly lower in the intervention group. The mean FBS, cholesterol, triglycerides, and LDL were significantly lower in the intervention group. The mean TAC and HDL were significantly higher in the intervention group ($P < 0.05$). Moreover, the intervention group significantly reduced systolic and diastolic blood pressure. No other significant association was observed.

CONCLUSION: Persian shallot extract has several beneficial effects in MetS patients, including optimizing oxidative balance, reducing blood pressure, fasting blood sugar, and blood lipid profile

Keywords: shallots; medicine, Persian; metabolic syndrome; antioxidants

1. INTRODUCTION

Metabolic syndrome (MetS) is a major health problem that involves 20%-30% of the world's population.[1] It is defined by a cluster of interconnected conditions, including high blood sugar, low blood high-density lipoprotein (HDL), high triglycerides (TG), high blood pressure, and large waist circumference, which collectively increase the risk of cardiovascular disorders and type 2 diabetes.[2] MetS is associated with diseases such as nonalcoholic fatty liver disease (NAFLD),[3] polycystic ovarian syndrome,[4] and hypogonadism.[5] According to multivariate analysis, the risk of sudden death increases by 68% in MetS.[6]

In spite of its significant health impact and financial burden, the pathogenesis of MetS is not completely understood. Even so, dyslipidemia, insulin resistance, sedentary behavior, high-calorie diet, inflammatory factors, and oxidative stress are suggested as the underlying risk factors of MetS.[7, 8]

The role of oxidative stress in the pathogenesis of many disorders, including MetS has become more prominent in recent years.[9-11] Higher levels of oxidants and lower levels of antioxidants have been demonstrated in the blood circulation of MetS patients.[12] Cumulative evidence supports the hypothesis that oxidative stress

could be an early event in the pathogenesis of MetS rather than a by-product of the metabolic system.[13] As a result, several studies have focused on oxidative stress as a therapeutic target in MetS patients, mainly through antioxidant supplementation.[14-16]

Allium hirtifolium Boiss (Persian shallot) is an *Allium* species in the *Lilacea* family, native to Iran. The most prominent members of this family are garlic, onion, and shallot, which have long been used for therapeutic purposes.[17] Sulfur-rich chemicals are the main therapeutic components in shallot extract.[18] The sulfur-rich component named allicin is responsible for many therapeutic properties of shallot extract, such as reducing plasma cholesterol, blood pressure, and platelet aggregation.[19] Linolenic, linoleic, palmitoleic, stearic, and oleic acids, saponins, sapogenins, and flavonoids (such as quercetin and kaempferol) are the other components of Persian shallot with a variety of acknowledged therapeutic properties.[17] The antioxidative effects of Persian shallot have also been demonstrated in several investigations.[20-23]

The beneficial effects of Persian shallot extract in various disorders such as diabetes,[24, 25] cancer,[26] enterococcus faecalis,[27] and trichomonas[28] have been demonstrated in earlier studies. To the best of our knowledge, no study has been performed to evaluate the effect of Persian shallot extract on MetS patients. In this trial, we aimed to explore how supplementation with Persian shallot extract affects oxidative balance in MetS patients. We also evaluated the effect of Persian shallot extract on the other parameters of MetS, including fasting blood glucose (FBS), total cholesterol, TG, HDL, and low-density lipoprotein (LDL).

2. PATIENTS AND METHODS

2.1. Study design

This randomized, double-blind clinical trial was approved by the review board of our institute under the code IR.RUMS.REC.1398.019. The protocol of the study was registered in the Iranian Registry of Clinical Trials under the code IRCT20171023036967N2. Participants provided written consent before inclusion in the study.

2.2. Patients' characteristics

The weight, height, and waist size of patients were measured using a digital scale and tape measure with an accuracy of 0.1 kg and 0.5 cm, respectively. Age, sex, and body mass index (BMI) were obtained and recorded. Systolic and diastolic blood pressure was also measured by a digital sphygmomanometer with an accuracy of 1 mm Hg. The demographic characteristics of the two study groups were not significantly different (Table 1).

2.3. Preparation of Persian shallot hydroalcoholic extract

Fresh shallots were obtained from Kangavar, Kermanshah, Iran. Preparation of the extract was done by the Persian Institute of Research and Development in Chemical Industries at 56 ℃ for 6 h. In brief, the shallot bulbs (60 kg) were first ground. Then, an adequate volume of 70% ethanol was added to reach a final volume of 200 liters. Subsequently, the concentrated extract was pulverized by a spray dryer. After that, 600 mg of shallot extract powder was poured into gelatin capsules.

2.4. Intervention

The intervention group of the study received two gelatin capsules daily containing 600 mg of Persian shallot hydroalcoholic extract. The placebo group received two cellulose-filled gelatin capsules (600 mg) daily. Both groups received the pills for a duration of three months. Before the intervention and at the end of the intervention, 5 mL venous blood was taken from each patient in fasting condition, and after centrifugation for 10 min at 3000 rpm, the serum samples were put into microtubes and stored at －20 ℃ for biochemical analysis.

2.5. Outcome measures

The primary outcome measured the oxidative status of the patients by the evaluation of total antioxidant capacity (TAC), superoxide dismutase enzyme (SOD), malondialdehyde (MDA), oxidized low-density lipoprotein (Ox-LDL), and apolipoprotein H (Apo-H) using detection kits (ZellBio, Berlin, Germany) and according to the manufacturer's protocols.

2.6. SOD measurement

The measurement of SOD in the mentioned kit is based on the production of superoxide radicals produced in the xanthine and xanthine oxidase system, which reacts with nitroblue tetrazolium (NBT) and creates diformazan precipitate (NBTH2). By adding serum to the test sample, the production of purple color was inhibited by SOD, which was measured in terms of the percentage inhibition of NBTH2 production at the wavelength of 560 nm.

2.7. Ox-LDL measurement

The enzyme-linked immunosorbent assay (ELISA) technique and a two-site enzyme immunoassay were used to measure Ox-LDL. After pairing the Ox-LDL present in the sample with the coated antibody the well, labeled anti-human apolipoprotein B antibody was added. After incubation and washing again, the conjugate in the microplate was determined by adding 5, 5, 3, 3-tetramethylbenzidine and the reaction was stopping by acid. Finally the absorbance was measured at a wavelength of 450 nm.

2.8. TAC measurement

This kit works by the colorimetric method and based on the reduction of Fe^{3+} to Fe^{2+} by antioxidant compounds Ferric Reducing Ability of Plasma method. TAC of serum samples was calculated to the instructions of the

manufacturer of the ELISA kit using, the prepared standard curve. Each sample was prepared twice and read at a wavelength of 490 nm.

2.9. MDA measurement

This kit functions based on the reaction of malondialdehyde with thiobarbituric acid (TBARS) at high temperatures. Malondialdehyde is measured colorimetrically at 535 nm by an ELISA reader.

2.10. Apolipoprotein H (APOH) measurement

APOH serum level was measured using a matched pair antibody *via* the APOH human ELISA kit (ZellBio, Berlin, Germany).

The secondary outcome measured biochemical parameters of MetS, including FBS, cholesterol, TG, HDL, and LDL-C with corresponding kits (Pars Azmoon, Tehran, Iran) and an autoanalyzer by photometric method. Systolic and diastolic blood pressure was also among the secondary outcome measures. The persons in charge of evaluating the outcome measures were blinded to the treatment allocation of patients.

2.11. Sample size and statistical analysis

The sample size was calculated according to the mean and standard deviation of LDL obtained from the study of Eftekhari *et al*,[29] who evaluated the impact of *Allium hirtifolium* on the parameters of MetS. Accordingly, 25 patients in each group was found to be enough to detect a significant difference between the two groups using an independent *t*-test at a power of 80% and type I error of 0.05.

SPSS for Windows, version 20 (IBM Corp., Armonk, NY, USA) was used for statistical comparison of data between the two study groups. Descriptive data were presented as mean ± standard deviation or number and percentage. The Shapiro-Wilk test was used to test the normality of distribution for each variable. An independent *t*-test or its nonparametric counterpart (the Mann-Whitney *U* test) was used to compare the variables between the intervention and placebo groups. The paired *t*-test or its nonparametric counterpart (the Wilcoxon test) was used to compare the average variables before and after the intervention in each group. Qualitative variables were compared using Pearson's χ^2 test. Finally, analysis of covariance was used to compare the overall average score of FBS and HDL in the two groups, taking into account the confounding effect of the average index before the intervention. Levene's test was also used to check the assumption of homogeneity of variance. A P value of < 0.05 was considered significant.

3. RESULTS

The study population included individuals with a primary diagnosis of MetS according to the National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP/ ATPⅢ) criteria. Exclusion criteria were malignancy, thyroid or cardiovascular disorders, liver and kidney diseases, smoking, pregnancy, breastfeeding, and taking anti-inflammatory or antidepressant drugs. If the patients were taking certain medications, they were asked to continue taking the drug at the prescribed dose during the study period. Over-the-counter medications, vitamins, dietary supplements, and herbal supplements were forbidden from two weeks before the start of the study. Patients were randomly assigned to the case (intervention) or the control (placebo) group using the permuted blocks procedure (Figure 1). Participants were blinded to treatment allocation.

Demographic characteristics were evaluated in the both intervention and placebo groups, and there was no significant difference between these two groups (Table 1). At baseline, the primary and secondary measures of outcomes were not significantly different between the intervention and placebo groups except for FBS and HDL (Table 2). Considering the significant difference in FBS and HDL between the two groups before the intervention, multivariate covariance analysis was used to compare these indices after the intervention. After controlling the effect before the intervention related to FBS and HDL, the results of this test showed that this type of intervention has an effect on the level of FBS and HDL after the intervention, with the average FBS and HDL decreasing and increasing, respectively, more noticeably in the intervention group than in the placebo group (Table 3).

At the end of the study, the mean serum levels of malondialdehyde and oxLDL were significantly lower in the intervention group in comparison with the placebo group ($P = 0.003$ and $P = 0.026$, respectively). The mean Apo-H was not significantly different between the intervention and placebo groups ($P = 0.995$). The mean TAC was significantly higher in the intervention group ($P < 0.001$), but SOD was not significantly different between the two study groups ($P = 0.065$).

The mean FBS, cholesterol, TG, and LDL were significantly lower in the intervention group in comparison with the placebo group ($P = 0.027$, $P = 0.026$, $P < 0.001$, and $P = 0.003$, respectively). The mean HDL was significantly higher in the intervention group ($P = 0.006$). Systolic and diastolic blood pressure were significantly lower in the intervention group ($P < 0.001$, $P = 0.048$, respectively).

4. DISCUSSION

In this study, we evaluated the impact of Persian shallot hydroalcoholic extract on the laboratory indices of MetS. According to our results, this extract significantly improved the oxidative balance in MetS patients, mainly through elevation of TAC and reduction of MDA and ox-LDL. In addition, serum levels of FBS, TG, cholesterol, and LDL significantly decreased after treatment with the extract, while the serum levels of HDL significantly increased. Blood pressure was also reduced following the treatment.

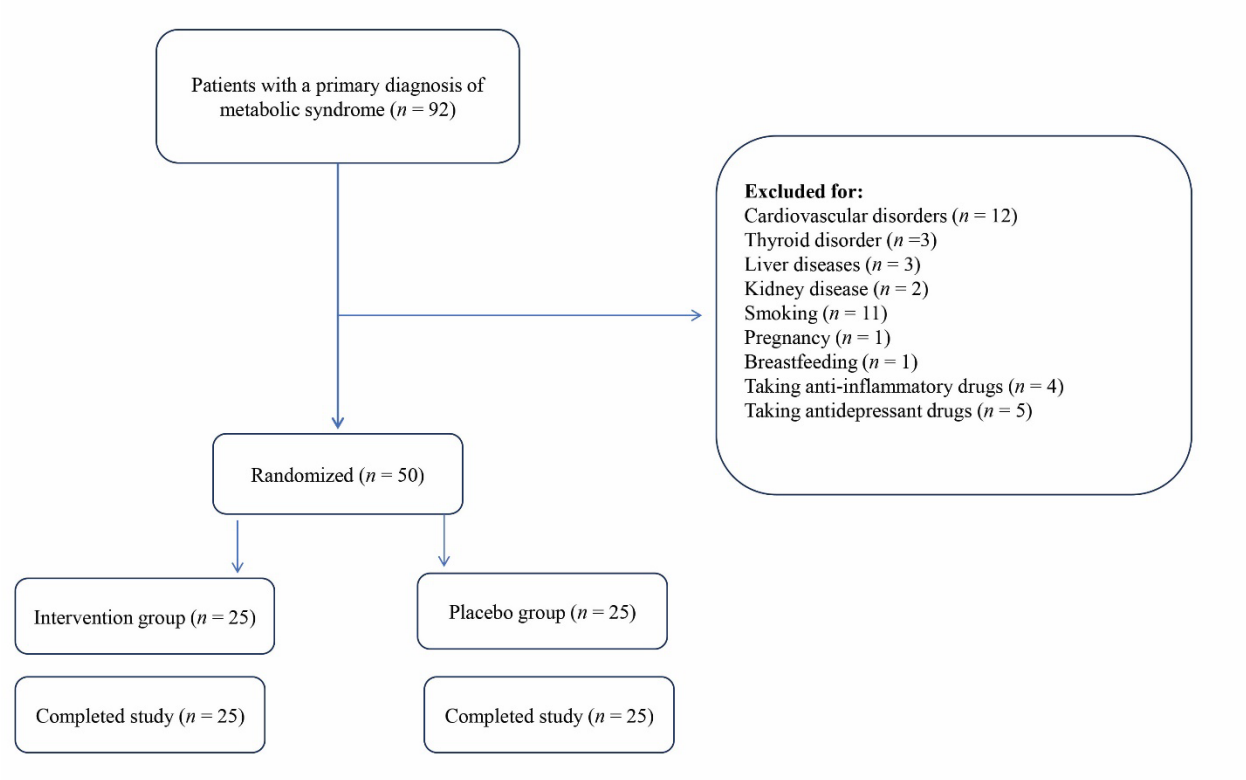

Figure 1 Flow chart of the study
Placebo group received gelatin capsules filled with cellulose (600 mg) twice a day for 12 weeks. Intervention group received gelatin capsules filled with Persian shallot extract (600 mg) twice a day for 3 months.

Table 1 Comparison of demographic characteristics between the intervention and placebo group

Variable		Placebo group (n = 25)	Intervention group (n = 25)	[a]P value
Age (years)		43.8±7.3	45.1±6.9	0.51
Sex [n (%)]	Male	11 (44)	12 (48)	0.50
	Female	14 (56)	13 (52)	
Height (cm)		167.2±8.9	170.9±9.5	0.26
Weight (Kg)		78.5±10.3	81.5±10.4	0.11
BMI (kg/m^2)		26.9±0.9	27.4±1.5	0.16
Waist circumference (cm)		97.4±5.2	98.9±6.1	0.23
Systolic blood pressure (mm Hg)		132.5±4.8	132.5±5.0	0.91
Diastolic blood pressure (mm Hg)		82.3±1.5	82.7±1.9	0.38

Notes: placebo group received gelatin capsules filled with cellulose (600 mg) twice a day for 12 weeks. Intervention group received gelatin capsules filled with Persian shallot extract (600 mg) twice a day for 3 months. BMI: body mass index. Data are presented as mean ± standard deviation or number (%). $P < 0.05$ is considered significant. [a]$P < 0.05$, between the two groups.

The therapeutic effects of herbal extracts have been examined in a variety of disorders, and their beneficial impacts have been acknowledged.[30-32] Persian shallot is a native and endemic herb of Iran with several therapeutic implications. In traditional medicine, it was used for the treatment of various disorders, including rheumatic and inflammatory arthritis, gout, stomach pain, psoriasis, and hemorrhoid. In modern medicine, it has been known to have a variety of health benefits, including anticarcinogenic, antioxidative, antibiotic, hypoglycemic, and hypolipidemic potential.[26, 33,34]

Mahmoodi *et al* [35] evaluated the effect of Persian shallot extract on blood sugar, HbA1c, insulin, triiodothyronine (T3), and thyroxine (T4) in diabetic rats. After 30 d, serum levels of FBS and HbA1c significantly decreased in the treatment group. Serum levels of insulin and T3 showed a slight increase, while the serum level of T4 declined. They attributed these beneficial effects to the antioxidant capacity of Persian shallot induced by its phenolic and diallyl disulfide content.Similarly, in the present study, we observed a significant reduction in serum FBS following treatment with Persian shallot extract.

The phytochemical constituents of Persian shallot, such as phenol, allicin, and pyruvic acid, have high antioxidant activity. Panahandeh *et al* [36] evaluated the phytochemical constituents and antioxidant activity of 13 ecotypes of Persian shallot from different regions of Iran. According to their results, average contents of allicin, pyrovic acid and total phenol of extracts per g fresh

Table 2 The comparison of the outcome measures before and after the intervention between and within intervention and Placebo groups

Variable	Intervention group (n = 25)			Placebo group (n = 25)			Between two groups	
	Before	After	P value[a]	Before	After	P value[a]	P value (before)[b]	P value (after)[b]
Serum levels of MDA (μmol/L)	5.17±0.78	3.81±0.75	<0.001	4.87±0.66	4.45±0.67	<0.001	0.146	0.003
Total antioxidant capacity (μmol/L)	0.62±0.11	1.03±0.19	<0.001	0.61±0.12	0.71±0.11	<0.001	0.823	<0.001
SOD activity level (U/mL)	43.69±5.27	45.58±6.03	0.159	41.45±6.39	42.14±6.80	0.571	0.154	0.065
Serum ox-LDL levels (ng/L)	278.39±32.22	241.32±37.71	<0.001	277.77±41.19	264.70±33.95	0.002	0.953	0.026
Serum level of Apo-H (ng/mL)	19.12±2.86	17.15±2.56	0.001	18.08±2.55	17.15±2.17	0.080	0.180	0.995
FBS (mg/dL)	116.96±8.88	99.12±8.77	<0.001	110.44±10.67	105.36±10.54	<0.001	0.023	0.027
Serum cholesterol level (mg/dL)	213.36±19.49	191.52±16.56	<0.001	210.24±17.57	201.56±17.83	<0.001	0.627	0.026
Serum HDL level (mg/dL)	40.56±2.61	45±3.34	<0.001	42.32±2.77	42.56±2.61	0.109	0.026	0.006
Serum LDL level (mg/dL)	120.32±12.36	108.64±10.90	<0.001	121.40±11.19	117.16±10.62	<0.001	0.748	0.003
Serum TG level (mg/dL)	193.20±14.24	171.52±13.58	<0.001	191.12±17.51	189.00±17.81	0.236	0.647	<0.001
Systolic blood pressure (mm Hg)	132.52±5.00	125.88±4.20	<0.001	132.52±4.80	132.12±5.04	0.412	1.00	<0.001
Diastolic blood pressure (mm Hg)	82.72±1.90	81.64±1.35	0.001	82.28±1.45	82.48±1.47	0.197	0.380	0.048

Notes: placebo group received gelatin capsules filled with cellulose (600 mg) twice a day for 3 months; Intervention group received gelatin capsules filled with Persian shallot extract (600 mg) twice a day for 3 months. MDA: malondialdehyde; SOD: superoxide dismutase; Ox-LDL: oxidized low-density lipoprotein; Apo-H: apolipoprotein-H; FBS: fasting blood sugar; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride. Data are presented as mean ± standard deviation and $P < 0.05$ is considered significant. [a] Paired t-test or Wilcoxon test were applied for comparison and analysis within each group. [b]Independent t-test or Mann-Whitney U test were applied for comparison and analysis between the intervention and Placebo groups.

Table 3 Results of the covariance test to compare the mean total score of FBS and HDL-C after the intervention in the placebo and intervention groups

Variable	Type Ⅲ sum of squares	Df (degree of freedom)	Mean square	F test	P value	Partial eta squared
FBS before the intervention	3679.44	1	3679.437	207.61	<0.001	0.82
	1629.17	1	1629.17	91.93	<0.001	0.66
HDL before the intervention	390.58	1	390.58	441.43	<0.001	0.90
	208.11	1	208.11	235.21	<0.001	0.83

Notes: placebo group received gelatin capsules filled with cellulose (600 mg) twice a day for 3 months (n = 25); intervention group received gelatin capsules filled with Persian shallot extract (600 mg) twice a day for 3 months (n = 25). FBS: fasting blood sugar; HDL: high-density lipoprotein. F-test: Covariance test using for comparison and analysis between the intervention and Placebo groups. $P < 0.05$ is considered significant.

weight were 2.12 mg, 84.41 μmol and 0.647 mg gallic acid equivalent, respectively and antioxidant activity was 63.717%. Among the analyzed antioxidants, SOD activity had the most quantity (61.5 U mg-1 protein).

Also, Persian shallot extract significantly increased hepatic catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase activities in the intervention zebrafish group compared to fish fed the control diet.[20] Consistent with the results of earlier studies, serum TAC levels were significantly higher in the treatment group of the present study.[22, 37]

Allicin, as a major component of Persian shallot, has shown a beneficial effect on major cardiovascular risk factors, including systolic blood pressure and triglyceride levels.[38-41]

Sánchez-Gloria *et al*,[41] showed that in experimental models of hyperlipidemia, allicin improved the lipid profile, and decreased hyperinsulinemia. Allicin could contribute to the treatment of CVD through its effects on dyslipidemia, which is a common risk factor in obesity, hepatic steatosis, type 2 diabetes, and metabolic syndrome. Allicin increased the phosphorylation of adenosine monophosphate-activated protein kinase, protein kinase A, and the AMP response element-binding

protein in a cell culture of hepatic lipotoxicity. In contrast, it decreased the expression levels of genes involved in lipogenesis, including sterol regulatory element-binding protein 1 and the proteins SREBP-2, acetyl-CoA carboxylase, fatty acid synthase, stearoyl-CoA desaturase-1, and peroxisome proliferator-activated receptor γ.[42] In another study, Shi *et al*,[43] showed that allicin treatment reduced body weight gain and fat accumulation (visceral and subcutaneous) and improved the glucose tolerance test, insulin response and lipid profile, which is consistent with the results of our study. It also protects cardiomyocytes and endothelial cells from apoptosis through inhibition of intracellular ROS production in a dose-dependent manner. In endothelial cells and cardiomyocytes cultures, allicin reduces MDA and increases nitric oxide (NO) release and endothelial nitric oxide synthase (eNOS) expression.[44] In an experimental model of chronic kidney disease, allicin upregulated nuclear factor erythroid 2-related factor 2, catalase, SOD, and heme oxygenase-1, which was associated to decrements in oxidized proteins and lipid peroxidation in kidney tissue, improving the renal function.[45]

Also, Nazeri *et al* [46] showed that allicin is able to play a role in cholesterol homeostasis by influencing the expression of proteins involved in the pathways of cholesterol synthesis, transport, and degradation. Allicin has a potent antihypertensive effect exerted through the improvement of endothelial function and the modulation of proteins and substances associated with vasoactive responses.[41,47,48] Since these risk factors are shared between MetS and cardiovascular disorders, it could be concluded that Persian shallot might improve MetS symptoms through improvement in cholesterol and glucose homeostasis, and oxidative balance, i.e., elevation of TAC and reduction of MDA.

According to preclinical and clinical studies, flavonoids are capable of inhibiting carbohydrate digestions and glucose absorptions, along with the regulation of insulin secretions *via* multiple signaling pathways.[49] He *et al* [50] showed that the flavonoids, can suppress *α*-glucosidase activity. Quercetin is a flavonoid that is another component of Persian shallot*,* which exhibits antioxidant and antihypertensive effects and reduces visceral fat.[51] The hypoglycemic action of quercetin involves the inhibition of intestinal carbohydrate digestion, glucose transporter activity, and glucose production in the liver and the improvement of glucose utilization in peripheral tissues and protection against pancreatic islet damage.[49, 52]

The main limitation of the study was the small number of patients. Although the patients' number was enough to detect a significant difference, a larger number of patients will better describe the benefits of Persian shallot extract in MetS patients.

In conclusion, Persian shallot extract has several benefits in MetS patients, including the reduction of blood sugar, cholesterol, TG, and LDL and elevation of serum levels of HDL. Systolic and diastolic blood pressure was significantly reduced following the treatment with Persian shallot extract. Moreover, the antioxidative capacity of the serum significantly increased, while its oxidative activity markedly decreased. The results suggest promising potentials for Persian shallot extract, as an adjuvant in the treatment of MetS patients.

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