

The effects of *Allium cepa* L. (onion) and its active constituents on metabolic syndrome: A review

Amin Galavi¹, Hossein Hosseinzadeh^{2,3}, Bibi Marjan Razavi^{4,3*}

¹ School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

² Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

³ Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

⁴ Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article type:

Review article

Article history:

Received: Mar 10, 2020

Accepted: Aug 17, 2020

Keywords:

Allium cepa L.

Diabetes mellitus

Dyslipidemia

Hypertension

Metabolic syndrome

Obesity

Onion

Quercetin

ABSTRACT

Metabolic syndrome as a clustering disorder includes excess abdominal fat distribution, abnormal insulin and glucose metabolism, disturbed blood lipids, pro-inflammatory state, and hypertension. Regarding to the adverse effects of synthetic medicines, the identification of appropriate healthcare approaches, such as herbal medicines, with fewer side effects is more favorable. *Allium cepa* L. (onion) is a culinary and medicinal herb belonging to the family of *Amaryllidaceae*. Flavonoids such as quercetin and kaempferol, alk(en)yl cysteine sulfoxides including S-methyl cysteine sulfoxide and S-propyl cysteine sulfoxide, cycloalliin, thiosulfinates, and sulfides are main compounds existing in the plant. *A. cepa* and its pharmacologically active constituents display broad-spectrum activities including anti-oxidant, anti-inflammatory, lipid-modifying, anti-obesity, antihypertensive, and antidiabetic effects. Our objective in this review was to find out the role of *A. cepa* and its bioactive phytochemicals as cardiovascular protective agents in different metabolic syndrome risk factors, including hyperlipidemia, high blood glucose, obesity, and hypertension.

► Please cite this article as:

Galavi A, Hosseinzadeh H, Razavi BM. The effects of *Allium cepa* L. (onion) and its active constituents on metabolic syndrome: A review. Iran J Basic Med Sci 2021; 24:3-16. doi: 10.22038/ijbms.2020.46956.10843

Introduction

Metabolic syndrome as a clustering disorder comprises of excess abdominal fat distribution, abnormal insulin and glucose metabolism, disturbed blood lipids, pro-inflammatory state, and hypertension. This syndrome, increases cardiovascular disease (CVD) incidence and mortality by 2-fold and all-cause death by 1.5-fold (1, 2). CVDs account for about 17.8 million annual loss of life all over the world, which makes them the underlying cause of death (3). Based on the modified NCEP (National Cholesterol Education Program) definition, a manifestation of any three or more of five medical conditions presented in Table 1 is required to confirm the clinical diagnosis of metabolic syndrome (4).

Over the last few decades, medicinal herbs are becoming extensively popular among the public and scientific community in both developing and developed countries for being cost-effective, easily accessible, and with relatively lesser adverse effects (5).

Allium cepa L. (onion) is a culinary and medicinal herb belonging to the botanical family of *Amaryllidaceae*. This ancient cultivated plant with edible bulbs is the third most important horticultural crop after potato and tomato and widely consumed throughout the world, mainly for its distinctive flavor (6).

Onion has been utilized during thousands of years for remedial purposes. For instance, it was used by athletes in ancient Greece for purifying their blood

Table 1. Updated National Cholesterol Education Program (NCEP) criteria for metabolic syndrome (4)

Waist circumference	≥102 cm (men), ≥88 cm (women)
Fasting plasma glucose	≥100 mg/dl or pharmacologic therapy
Serum triglycerides	≥150 mg/dl or pharmacologic therapy
Serum HDL-C	<40 mg/dl (men), <50 mg/dl (women) or pharmacologic therapy
Blood pressure	≥130 mm Hg (systolic) or ≥85 mm Hg (diastolic) or pharmacologic therapy

People with at least three of the above five features are considered to have metabolic syndrome

HDL-C= high-density lipoprotein cholesterol

*Corresponding author: Bibi Marjan Razavi. Targeted Drug Delivery Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Tel:+98-51-31801194; Fax: +98-51-38823251; Email: Razavimr@mums.ac.ir

and rubbed down by Roman gladiators to firm up the muscles. Hippocrates, the Greek physician, prescribed onion for diuretic effect, healing wounds, and combating pneumonia. It was recommended by medieval doctors to alleviate cough, headache, snake bite, hair loss, and other diseases (6, 7). In traditional medicine, onion has been used for a large variety of ailments such as headache, fever, toothache, cough, sore throat, flu, baldness, epilepsy, rash, jaundice, constipation, flatulence, intestinal worms, low sexual power, rheumatism, body pain and muscle cramps, high blood pressure, and diabetes (8-10).

The results of composition analyses have indicated that *A. cepa* is rich in two valuable chemical groups called flavonoids and alk(en)yl cysteine sulfoxides. The various layers of several varieties of onion bulbs contain quercetin and kaempferol as main flavonoids with anti-oxidant and free radical scavenging benefits ranging from 14.5 to 5110 and 3.2 to 481 µg/g of dry weight, respectively, so that higher amounts are found in red and violet onions and outer layers. S-methyl cysteine sulfoxide (SMCS), S-propyl cysteine sulfoxide, cycloalliin, thiosulfonates, and sulfides are organo-sulfuric compounds existing in the plant (11, 12). Figure 1 illustrates the chemical structures of major onion isolated ingredients.

Many modern studies have reported that *A. cepa* and its pharmacologically active constituents display broad-spectrum activities, including anti-oxidant (13), anticancer (14, 15), anti-scar (16), hepatoprotective (17), antiplatelet (18), antithrombotic (19), immunoprotective (20), anti-inflammatory (21), anticholelithogenic (22), neuroprotective (23), antibacterial (24), and antifungal (25) properties. They can also be useful in the treatment of allergy (26), asthma (27), hyperuricemia (28), anxiety, depression, and cognitive disorders (29). Onion as a dietary vegetable and its nutraceuticals may assist

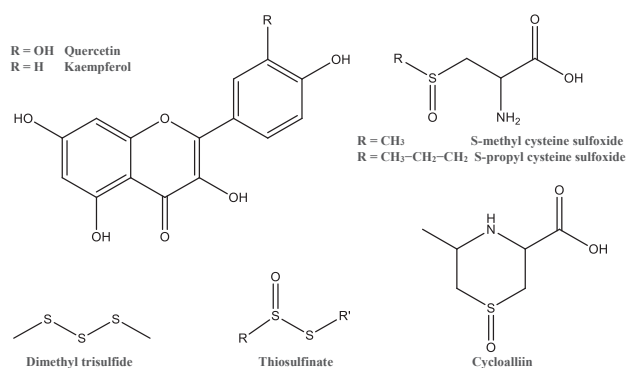


Figure 1. Chemical structures of main flavonoids and sulfur-containing compounds of *Allium cepa*

in cardiovascular risk reduction through anti-oxidant and antithrombotic effects, regulating blood lipids, improvement of endothelial function, and decreasing waistline (30, 31).

The aqueous onion extract was examined to evaluate its toxicity in the hepatic and pulmonary tissues of rats. Intraperitoneal (IP) administration of onion at a high dose (500 mg/kg/day) induced histologic damages and was lethal to 25% of animals after 4 weeks. However, treatment with low doses (50 mg/kg/day), especially when given orally exhibited no toxic effects (32). In human studies, apart from heartburn, no other adverse effects have been reported following the use of onion (33, 34).

This review aimed to find out the role of *A. cepa* and its bioactive phytochemicals as cardiovascular protective agents in different metabolic syndrome risk factors, including hyperlipidemia, high blood glucose, obesity, and hypertension. For this purpose, we revised the most relevant *in vitro*, animal, and human investigations. Tables 2 and 3 report a summary of

Table 2. A summary of onion and its phytoconstituents effects in metabolic syndrome

Effect	Study design	Constituents	Results	Reference
Hypolipidemic	<i>In vitro</i> , human THP-1 cells	Quercetin (0.3 µM)	↑ Protein levels of PPAR-γ, LXRα, and ABCA1, cholesterol efflux to apo-A1 and HDL	(110)
	<i>In vivo</i> , male SD rats (received HCD)	Onion high-pressure processing extract (8.1 g/kg/day) for 6 weeks	↑ Fecal total lipid ↓ Food intake, TC, HDL, and LDL Inhibition of HMG-CoA reductase activity	(111)
	<i>In vivo</i> , albino rats (atherogenic diet)	Onion extract (equivalent to 2 g/kg of dry onion) for 5 days	↓ Cholesterol, TG, and grade of atherosclerotic lesions	(112)
	<i>In vivo</i> , male HCD hamsters	AC powder (5% w/w diet) for 8 weeks	↑ HDL/TC and fecal excretion of neutral and acidic sterols ↓ TC, HDL, non-HDL, non-HDL/HDL, TG, and cholesterol absorption Up-regulation of hepatic SREBP-2, LXRα, and CYP7A1	(113)
	<i>In vivo</i> , HFD mice	Quercetin (100 mg/kg) for 8 weeks	↑ SOD, CAT, GSH ↓ Serum TC, TG, and LDL, hepatic cholesterol, TG, and LPO, atherogenic index, AST, ALT, and ALP	(114)
Anti-obesity	<i>In vitro</i> , 3T3-L1 cells	OPE (100 µg/ml)	↑ CPT-1α and FABP4 mRNA expression ↓ Differentiation of preadipocytes to adipocytes, TG content, and mRNA level of AP2	(115)
	<i>In vivo</i> , obesity-induced HFD mice	Red onion extract	↑ Body muscle percentage and energy expenditure ↓ Weight gain and fat mass accumulation Improvement in skeletal muscle mitochondrial number and function	(116)

Continued Table 2

	<i>In vivo</i> , SD rats (received HFD)	OPE (0.36% or 0.72%) for 8 weeks	↑ mRNA levels of CPT-1 α and UCP1 in adipose tissues ↓ Retroperitoneal, mesenteric, and total visceral fat, final body weight, and mRNA expression of PPAR- γ , FAS, and ACC in adipose tissues	(115)
	<i>In vivo</i> , rats (obesogenic diet)	Combination of quercetin (30 mg/kg/day) and resveratrol (15 mg/kg/day) for 6 weeks	↓ Rate of body weight gain, intra-abdominal and subcutaneous adipose tissue weight Brown-like remodeling of perirenal white adipose tissue	(117)
Hypotensive	<i>In vivo</i> , high-fructose diet rats	Onion extract (400 mg/kg/day) p.o. for 8 weeks	↑ Heart eNOS activity ↓ SBP, plasma TBARS, aortic NADPH oxidase activity	(118)
	<i>In vivo</i> , Wistar HCD rats	Onion powder (100 g/kg diet) for 7 weeks	↑ Erythrocyte SOD and GPx Prevention of impaired endothelium-dependent Ach relaxation in mesenteric arteries	(119)
	<i>In vivo</i> , male SD rats with abdominal aortic constriction	Quercetin (estimated 130 mg/kg) for 21 days	↓ Carotid arterial blood pressure, aortic medial thickness, and cardiac hypertrophy	(120)
Antidiabetic	<i>In vitro</i>	Onion powder and extract	↓ Oxidative stress Inhibition of α -glucosidase activity	(121)
	<i>In vivo</i> , AID rats	AC aqueous extract (200, 250, and 300 mg/kg/day) IP for 6 weeks	↓ FBG, total serum lipids, and TC	(122)
	<i>In vivo</i> , SID Wistar rats	Onion powder (3% w/w diet) for 8 weeks	↑ Rate of weight gain, plasma albumin ↓ FBG, hepatic cholesterol, TG, and phospholipids, relative liver weight, plasma levels of urea, creatinine, phospholipids, and inorganic phosphorus Improvement in some of diabetic nephropathy clinical parameters	(123)
	<i>In vivo</i> , SID rats	Onion essential oil (100 mg/kg) p.o. for 21 days	↑ Insulin, HDL ↓ FBG, TC, TG, LDL, serum NO and TBARS Amelioration of diabetic liver and kidney histology	(124)
	<i>In vivo</i> , AID rabbits	AC aqueous extract (300 mg/kg/day) p.o. for one month	↑ Levels of liver CAT, SOD, GPx, and GSH ↓ FBG, liver content of MDA	(125)
	<i>In vivo</i> , SID rats fed HFD	OPE (1%) for 8 weeks	↑ Muscle glycogen, liver SOD activity and glycogen, GLUT4 and insulin receptor mRNA expression in skeletal muscle ↓ Liver IL-6 protein and MDA, plasma FFA	(126)
	<i>In vivo</i> , male Wistar rats (high-fat-sucrose diet)	Quercetin (30 mg/kg/day) for 6 weeks	↓ Glucose, insulin, HOMA-IR, fructosamine, glucose tolerance test	(127)
	<i>In vivo</i> , obese ob/ob mice	Quercetin (30 mg/kg) IP every other day for 10 weeks	↑ GLUT4 protein content in skeletal muscle and insulin sensitivity ↓ FBG	(128)
	<i>In vivo</i> , SID rats	Quercetin (1 g/kg diet) for 6 weeks	↓ Water intake, FBG Change in body weight No effect on food consumption	(129)
	<i>In vivo</i> , SID Wistar albino rats	Quercetin (15 mg/kg) daily for 4 weeks	↑ TAC, insulin level ↓ Glucose	(130)
	<i>In vivo</i> , high fructose-induced diabetic rats	SMC (100 mg/kg/day) for 2 months	↑ HDL and total antioxidant status ↓ FBG, TC, TG, LDL, VLDL, Liver, kidney, and adipose tissue weight, ALT, AST, and body weight	(131)

↑=increase, ↓=decrease, ABCA1=ATP binding cassette transporter A1, AC=Allium cepa, ACC=acetyl-CoA carboxylase, Ach= acetylcholine, AID= alloxan-induced diabetic, ALP= alkaline phosphatase, ALT= alanine transaminase, AP2= activating protein 2, apo-A1= apolipoprotein A1, AST= aspartate transaminase, CAT= catalase, CPT-1 α = carnitine palmitoyltransferase 1 alpha, CYP7A1= cholesterol 7 α -hydroxylase, eNOS= endothelial nitric oxide synthase, FABP4= fatty acid binding protein 4, FAS= fatty acid synthase, FBG= fasting blood glucose, FFA= free fatty acid, GLUT4= glucose transporter 4, GPx= glutathione peroxidase, GSH= reduced glutathione, HCD= high-cholesterol diet, HDL= high-density lipoprotein, HFD= high-fat diet, HMG-CoA reductase= 3-hydroxy-3-methylglutaryl coenzyme A reductase, HOMA-IR= homeostatic model assessment of insulin resistance, IL-6= interleukin 6, IP= intraperitoneal, LDL= low-density lipoprotein, LPO= lipid peroxidation, LXR α = liver X receptor alpha, MDA= malondialdehyde, NO= nitric oxide, OPE= onion peel extract, p.o.= per os (orally), PPAR- γ = peroxisome proliferator-activated receptor gamma, SBP= systolic blood pressure, SD= Sprague-Dawley, SID= streptozotocin-induced diabetic, SMC= S-methyl-L-cysteine, SOD= superoxide dismutase, SREBP-2= sterol regulatory element binding protein 2, TAC= total anti-oxidant capacity, TBARS= thiobarbituric acid reactive substances, TC= total cholesterol, TG= triglyceride, UCP1= uncoupling protein 1, VLDL= very low-density lipoprotein

Table 3. A summary of clinical studies on *Allium cepa* in metabolic syndrome

Effect	Population	Constituents	Duration	Results	Reference
Hypolipidemic	24 healthy volunteers with mild hypercholesterolemia	100 ml onion juice	8 weeks	↓ Body weight, BMI, body fat, TC, LDL, and oxidative stress No significant effect on TG and HDL	(50)
	12 normal young Korean women	100 mg quercetin (OPE)	2 weeks	↓ TC, LDL, and atherogenic index	(34)
Anti-obesity	72 healthy overweight and obese volunteers	OPE (containing 100 mg quercetin)	12 weeks	↓ Body weight and BMI	(132)
	78 overweight or obese women with PCOS	Quercetin (1000 mg/day)	12 weeks	↓ Weight, BMI, WC, plasma resistin, insulin resistance No significant change in calorie intake	(133)
	70 overweight or obese patients with (pre-)hypertension	OPE powder capsules (containing 54 mg quercetin) three times a day	6 weeks	No significant differences in serum adiponectin, leptin, and insulin, HOMA-IR, and plasma glucose and TNF- α	(134)
	70 healthy Japanese participants	Onion powder (9 g/day)	12 weeks	↓ Visceral fat only in subjects with lower HDL and ALT No significant effect on abdominal fat, body weight, BMI, AST, and ALP	(135)
Hypotensive	70 overweight-to-obese patients with (pre-)hypertension	OPE powder capsules (containing 54 mg quercetin) 3 times a day	6 weeks	↓ SBP and MAP	(136)
	92 healthy male smokers	Quercetin capsules (100 mg/day)	10 weeks	↓ SBP and DBP	(137)
Antidiabetic	84 PCOS women	Quercetin capsules (500 mg) twice a day	12 weeks	↑ ADIPOR1 and ADIPOR2 transcript expression, AMPK activity ↓ Insulin, HOMA-IR	(138)
	15 healthy young men	3.1 g onion extract	Once 30 mins before the OGTT	Without any significant changes in postprandial blood glucose and insulin and 24 rs urinary glucose output	(89)

↑= increase, ↓= decrease, ADIPOR= adiponectin receptor, ALP= alkaline phosphatase, ALT= alanine transaminase, AMPK= AMP-activated protein kinase, AST= aspartate transaminase, BMI= body mass index, DBP= diastolic blood pressure, HDL= high-density lipoprotein, HOMA-IR= homeostatic model assessment of insulin resistance, LDL= low-density lipoprotein, MAP= mean arterial pressure, OGTT= oral glucose tolerance test, OPE= onion peel extract, PCOS= polycystic ovary syndrome, SBP= systolic blood pressure, TC= total cholesterol, TG= triglyceride, TNF- α = tumor necrosis factor alpha, WC= waist circumference

selected studies which focused on *A. cepa* and associated components potential efficacy and mechanisms of action in the context of metabolic syndrome and related complications.

Methodology

The literature review was carried out by searching the databases of PubMed, Scopus, and Web of Science using the following key terms: *Allium cepa*, onion, quercetin, metabolic syndrome, dyslipidemia, cholesterol, diabetes, hyperglycemia, insulin resistance, cardiovascular disease, atherosclerosis, hypertension, and obesity. Articles about the effects of *A. cepa* on metabolic disorders written in the English language without

publication time restriction have been incorporated in this research. The reference lists of the collected articles were also investigated to recognize further studies.

Effects on lipid profile

Dyslipidemia which is characterized by a combination of four abnormalities in serum lipid profile including elevated levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) and low level of high-density lipoprotein cholesterol (HDL-C) raises the incidence of cardiovascular morbidity and mortality (35). Numerous animal and human research projects on the lipid-modifying effect of *A. cepa* have exhibited an important decrease in serum

and hepatic values of TG and cholesterol (36).

***In vitro* studies**

It has been documented that S-propyl cysteine acts as a reducing agent in the release of apolipoprotein B100 (apoB100), TG, cholesterol, and phospholipids from HepG2 cells. Moreover, the inverse relationship between the rate of apoB100 secretion and carbon chain length in S-propyl, S-ethyl, and S-methyl substitutions of cysteine was detected (37). L-glutamyl-L-phenylalanine (EF) dipeptide, which can be found on average in the range of 2.03 to 4.04 mg per 100 g of fresh onion cultivars, suppressed SREBP-1c (sterol regulatory element-binding protein 1c) and its target genes related to lipogenesis by stimulating AMPK (adenosine monophosphate-activated protein kinase) in AML12 cell line. Consequently, EF caused lower fat accumulation in mouse hepatocytes, depending on the used concentration (38). Quercetin is found to provide prophylaxis of atherosclerosis. This flavonoid stimulated cholesterol removal through the expression of PPAR- γ (peroxisome proliferator-activated receptor gamma) and ABCA1 (ATP-binding cassette transporter A1) in human THP-1 macrophages and thus prevented foam cells formation, which is crucial in atherosclerotic plaque development (39). In order to compare the potency of quercetin, estradiol, and three phytoestrogens (genistein, biochanin A, and daidzein) in protecting LDL from oxidative stress, LDL was isolated from the blood of healthy postmenopausal females not receiving hormonal treatment. After induction of oxidation in LDL, malondialdehyde (MDA) was considered as an indicator of oxidative stress level. Quercetin showed the most antioxidative ability, and its potency was almost 8 times that of estradiol and 100 times that of genistein. In the case of biochanin A and daidzein, the required concentration to reduce 50% of MDA was extremely high. The results of this *in vitro* study also indicated that quercetin, in combination with estradiol, had a synergistic effect (40).

Animal studies

In cholesterol-treated rabbits, the three-month use of onion essential oil (1 g/kg/day) was effective in the reduction of plasma cholesterol and fibrinogen values and aorta lipid content. It also markedly induced the rise of blood clotting time and fibrinolytic activity. The superiority of onion over clofibrate (33 mg/kg) was proved in all parameters mentioned above (41). The blood samples of high cholesterol-fed rats showed a significant decrease in TC, LDL-C, TG, and phospholipids and a rise in HDL-C after 6 weeks treatment with 5% and 10% dehydrated onion powder. Furthermore, the concentration of anti-oxidant compounds such as total thiols, glutathione, α -tocopherol, and ascorbic acid in addition to resistance against peroxidation of lipids increased during the examination (42).

The cholesterol-lowering effect of onion peel extract was explored in hypercholesterolemic-diet-given mice for 12 weeks. The results revealed that the oral gavage of 100 and 200 mg/kg of the extract, especially the latter one, ameliorated TG and TC contents and weight of liver, cardiac risk factor (TC/HDL-C), atherogenic

index ((TC - HDL-C)/HDL-C) as well as plasma TC and LDL-C. The possible mechanisms might be the up-regulation of LDL receptor (LDL-R) and cholesterol 7 α -hydroxylase (CYP7A1) expression, and as a result of that, enhanced fecal elimination of cholesterol (43). Red onion extract and quercetin could produce improving effects on paraoxonase 1 (PON1) activity, scavenging of free radicals, LDL oxidation, and lipid peroxidation against oxidative stress induced by HgCl₂ in rats (44). The prolonged administration of quercetin contributes to regulating utilization of fatty acids in rat lung as the target tissue. Receiving 500 mg/kg/day of the flavonoid for 41 weeks led to a rise in the expression of genes associated with catabolism of fatty acids such as LPL (lipoprotein lipase) and ACOX1 (acyl-coenzyme A oxidase 1). This effect was supported by the reduction of free fatty acids concentration in the serum (45). Adding cycloalliin to the atherogenic diet of rats at doses of 0.1% and 0.3% for 14 days considerably resulted in diminished serum TG levels (about 40%) whereas there were not any significant changes in TC, HDL-C, weight and lipid content of liver, and activities of lipogenic enzymes (46). Another study revealed that SMCS has hypolipidemic activities in Sprague-Dawley rats fed a cholesterol-rich diet which is comparable to gugulipid (50 mg/kg/day) as a natural lipid-lowering drug derived from *Commiphora mukul* tree. SMCS (200 mg/kg/day, by gavage for 45 days) significantly reduced activities of total LPL in the adipose tissue and hepatic malic enzyme, serum and tissue levels of free fatty acids, TG, cholesterol, and phospholipids but significantly increased liver glycogen and fecal excretion of bile acids and neutral sterols when compared to the control group (47). In a recent study, the preventive capacity of *A. cepa* against nonalcoholic fatty liver disease (NAFLD) in the presence of risk factors has been demonstrated. Receiving 7% onion powder significantly reversed the elevation in hepatic tumor necrosis factor alpha (TNF- α) gene expression and plasma levels of alanine transaminase (ALT), aspartate transaminase (AST), glucose, insulin, and TG in fat- and sugar-enriched diet rats; while the increase in consumed food, body weight, gamma-glutamyl transferase, alkaline phosphatase (ALP), cholesterol, and LDL-C did not change significantly after 7 weeks of intervention. The analysis of liver histology showed a remarkable enhancement in lobular and portal inflammation, hepatic steatosis, and ballooning degeneration (48). An earlier investigation showed that onion ingestion alone is not enough for treating NAFLD, but in combination with a healthy dietary pattern has therapeutic potential (49).

Clinical studies

Oral daily administration of 100 ml onion juice in volunteers with mild hypercholesterolemia after 8 weeks restrained lipid peroxidation and extended the lag time required for LDL oxidation by reducing oxidative stress. It also decreased the plasma values of TC, LDL-C, and LDL-C/HDL-C ratio by 10.2%, 7%, and 6.8%, respectively, but did not influence TG and HDL-C ($P < 0.05$) (50). The results of a randomized controlled clinical trial on women with polycystic ovary syndrome (PCOS) who were 17-37 years old and had body mass

index (BMI) 25-40 kg/m² represented the health benefits of onion as a hypocholesterolemic agent. Fifty-four patients were randomly divided into control and therapeutic groups. They received 10-15 g (control group) or 40-60 g (high-onion group) fresh red onion twice a day for 2 months. There was a considerable decline in the serum levels of TC and LDL-C within both groups in comparison to before the intervention. Other lipid markers, including TG, HDL-C, and lipoprotein (a) did not change significantly in any of the groups (33). Even a two-week consumption of *A. cepa* peel extract capsules at a dose equivalent to 100 mg quercetin by normal females aged 20 to 25 years led to a significant reduction in TC, LDL-C, and atherogenic index (34).

Taken together, different mechanisms including the activation of AMPK, decrease in malic enzyme and HMG-CoA reductase activities, up-regulation of LDL-R, increasing expression of CYP7A1 enzyme, lowering cholesterol absorption, enhancing fecal elimination of cholesterol, reduction of lipogenesis and lipid peroxidation, modulating catabolism of fatty acids, and inhibition of apoB100 secretion have been proposed for antihyperlipidemic effect of *A. cepa* and its various preparations. Other studies are necessary to pinpoint the exact mechanisms being responsible for onion effectiveness in dyslipidemia.

Effects on obesity

Obesity is a common global health concern. It was estimated that in 2016, the obese population reached over 790 million, and an extra 1.5 billion were overweight. In fact, the prevalence of overweight and obesity combined was nearly 31 percent (51). There is a strong requirement to explore new and efficacious weight-lowering agents because of the limited number of approved safe and efficient drugs, especially for long-term treatment of obesity (52). Research projects have shown the anti-obesity characteristics of onion and phytoconstituents available in this plant such as quercetin and organosulfurs (53, 54).

In vitro studies

In a recent study, Funakoshi and colleagues indicated the potential of quercetin in the prevention of adipogenesis in myosatellite cells (MSCs) *in vitro*. This molecule decreased fat cells quantity, TG/protein ratio, and TG amount in cells. Furthermore, the expression of adipogenesis genes such as PPAR- γ and fatty acid binding protein 4 (FABP4) was down-regulated (55). The peel extract of onion (1, 2, 4 μ g/ml) and its pharmacologically active component quercetin (1, 2, 4 μ g/ml) produced a significant reduction of TG content in 3T3-L1 adipocytes in which effectiveness of the extract was higher than quercetin. Furthermore, glycerol-3-phosphate dehydrogenase (GPDH) activity as an essential enzyme in lipid biosynthesis and mRNA expression of LPL were lowered in this experiment (56). The beneficial effects of quercetin on obesity was demonstrated through down-regulation of C/EBP β (CCAAT/enhancer-binding protein beta), PPAR- γ , C/EBP α , and FABP4 as adipogenesis-related factors and TG synthetic enzymes such as lipin1, DGAT1 (diacylglycerol acyltransferase 1), and LPAAT0 (lysophosphatidic acid acyltransferase). Quercetin

also blocked signaling pathways of MAPK (mitogen-activated protein kinase) (ERK [extracellular signal-regulated kinase] and JNK [c-Jun N-terminal kinase]) and mTOR (mammalian target of rapamycin) as well as the release of pro-inflammatory cytokines including monocyte chemoattractant protein-1 (MCP-1), TNF- α , interleukin-1 beta (IL-1 β), and IL-6 while stimulated the levels of anti-inflammatory cytokines (IL-10) and anti-inflammatory adipokines (adiponectin) in 3T3-L1 cells (57). In another study, although the low concentrations of quercetin (from 0.5 to 10 μ M) were capable of repressing adipogenesis in 3T3-L1 preadipocytes, only the highest concentration (10 μ M) appeared as an anti-adipogenic agent in mature fat cells. This effect of quercetin probably results from inducing expression of sirtuin 1. Sirtuin 1 deacetylates proteins and thereby reduces expression and the activity of lipogenic enzyme fatty acid synthase (FAS) (58).

Animal studies

Yoshinari *et al.* evaluated properties of onion extract against body fatness in male Zucker diabetic fatty rats. Four weeks of treatment with the extract (5% w/w) led to a significant decline in the rate of body weight gain, the ratio of liver to body weight, and adipose tissue (mesenteric, pararenal, and epididymal) without altering the satiation. Additionally, onion and a number of its sulfur compounds such as cycloalliin, S-propyl cysteine sulfoxide, S-methyl cysteine, dimethyl trisulfide, and particularly SMCS, could prevent white adipocytes differentiation (59). The addition of quercetin and red onion extract to the high-fat diet significantly lessened inguinal and epididymal adipose tissue weight in mice. Also, the size, density, and morphology of adipocytes altered in varying degrees (60). Quercetin was able to inhibit lipid and TG deposition besides factors associated with the synthesis of TG in cells of zebrafish (57). An oil/water nanoemulsion preparation of quercetin with 33.5-fold greater oral bioavailability compared to free quercetin was used for anti-obesogenic activity in high-fat diet mice. After 10 weeks receiving a dose of 150 mg/kg/day, without a change in the amount of food consumption, body weight gain was prevented by 23.5%. Also, fat mass loss in different regions of the body was found to be 21.2 to 37.4 percent (61). With regard to brown adipocytes role in modulating energy balance, adipose tissue browning seems a promising strategy against obesity (62). In an investigation by Lee *et al.* it was reported that onion skin extract and quercetin have a facilitating role in the transformation of white adipocytes into brown-like adipocytes. This extract (0.5% w/w) caused the up-regulation of various brown adipocyte genes such as PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), PRDM16 (PR domain-containing 16), UCP1 (uncoupling protein 1), CIDEA (cell death-inducing DFFA-like effector A), and FGF21 (fibroblast growth factor 21) in the adipose tissues of mice fed a fat-enriched diet (63).

Clinical studies

Onion peel extract capsules, consist of 50 mg quercetin, were administered to Korean overweight

and obese participants twice a day for 12 weeks in a double-blind, randomized, placebo-control trial performed in 2013. A decline in BMI and percentage of body fat mass was indicated (64). In a similar study on plasma adipokines, including visfatin, adiponectin, leptin, TNF- α , and IL-4, the only significant change was a rise in adiponectin. However, even this single change occurred in both placebo and intervention groups. It was concluded that inflammatory factors after 12 weeks of supplementation with the extract were unaffected (65).

These studies suggested that several mechanisms such as reduction of fatty acids and TGs biosynthesis, anti-oxidant and anti-inflammatory activity, elevation of adiponectin and energy expenditure, decrease in plasma resistin and insulin resistance, prevention of white adipocytes differentiation, and brown-like remodeling of adipose tissue are involved in anti-obesity properties of onion and its active components. However, further clinical trials are needed to assess the clinical efficacy.

Effects on hypertension

Hypertension is the leading metabolic risk factor for the development of life-threatening CVDs, including coronary artery disease, stroke, atrial fibrillation, vascular dementia, and heart failure (66). The decrease of systolic blood pressure as much as 10 mm Hg results in the significant risk reduction in major CVD events by 20%, heart failure by 28%, stroke by 27%, coronary artery disease by 17%, and all-cause mortality by 13% (67). Although the current antihypertensive medications such as angiotensin-converting enzyme (ACE) inhibitors, diuretics, and calcium channel blockers have been proved to be beneficial in blood pressure control, treatment with these medications is often accompanied by undesirable side effects (68). Blood pressure-lowering phytochemicals are gaining growing attention as preventive and curative agents, mainly for prehypertensive patients (69). Several studies have confirmed the antihypertensive potential of onion and quercetin.

In vitro studies

The inhibition of ACE by two types of onion (white and purple) aqueous extract was assessed. According to the results, both types were able to reduce enzyme activity in a concentration-dependent way (0–1.25 mg/ml) (70). The binding energy of quercetin with the active site of ACE was calculated -8.5 Kcal/mol in comparison to enalapril as standard (-7.0 Kcal/mol). So, this molecule can reduce blood pressure by inhibiting the conversion of angiotensin I to angiotensin II (71). In a study on rat coronary arteries, it was shown that a physiological concentration of quercetin (10^{-7} moles/l) induces vasodilatation. At least part of this effect is because of the rise in endogenous vasoactive prostanoids in the wall of the coronary arterioles (72). Quercetin is found only in the form of conjugated metabolites in plasma, so, it works through these metabolites. Unlike quercetin, its metabolites do not have direct vasorelaxing action in rat aorta. They might be responsible for *in vivo* improvement of endothelial function (73).

Animal studies

The ethanol extract of onion at doses of 0.2, 0.6, 2,

and 6 mg/kg was used intravenously in normotensive anesthetized rats. According to the results, onion dose-dependently reduced heart rate and blood pressure. The mechanism of lowering blood pressure can be due to a decrease in heart rate (74). *A. cepa* skin hydroalcoholic extract decreased blood pressure in fructose-fed hypertensive rats presumably by a reduction in oxidative stress and inhibition of Ca^{2+} influx in the cells of vascular smooth muscle (75). The reduction of blood pressure by crude onion was observed in spontaneously hypertensive rats and those with N^{ω} -nitro-L-arginine methyl ester (L-NAME)-induced hypertension, probably via anti-oxidant properties (76, 77). The anti-oxidant and antihypertensive activities of onion diminished after 60 min boiling (76). The ethanolic extract of *A. cepa* containing 0.8 mg of quercetin per 100 g body weight did not produce enough blood pressure-lowering effect in spontaneously hypertensive rat (78).

Clinical studies

In a randomized controlled study on 22 obese and hypertensive patients, increased systolic and diastolic blood pressure after consumption of a high energy meal was not reduced by the intake of either placebo or 54 mg quercetin (79). The ingestion of 400 mg quercetin increased brachial artery diameter in 15 healthy volunteers depending on dose and time. This flavonoid also induced vasodilation in human arteries *in vitro* (80). In a study on 41 participants with prehypertension and stage 1 hypertension, it was shown that administration of 730 mg/day quercetin for 28 consecutive days significantly lowered blood pressure only in stage 1 hypertensive patients (systolic by 7 ± 2 mm Hg, diastolic by 5 ± 2 mm Hg, and mean arterial pressures by 5 ± 2 mm Hg) while did not have a systemic anti-oxidant influence in both groups (81). The peak effect of receiving an onion macerated in olive oil product equivalent to 2.5 g fresh onion was seen after 5 hrs. At this time, systolic and diastolic blood pressure of 10 subjects with impaired blood fluidity reduced by 10 and 8 mm Hg on average, respectively (82). The incompatible effects of quercetin on blood pressure may be because of apolipoprotein E (APOE) polymorphism. In a double-blind, randomized, placebo-controlled study with a crossover design, 93 overweight or obese adults were treated with 150 mg/day quercetin. The flavonoid controlled blood pressure in APOE3 carriers but was not effective in APOE4 individuals (83).

The above-mentioned investigations have shown hypotensive properties of onion and quercetin which are mediated by several mechanisms such as anti-oxidant activity, ACE inhibitory effect, decreasing heart rate, increasing endothelial nitric oxide, blocking of calcium channels, and vasodilation. More human studies with larger sample size are needed to establish the effects on high blood pressure. In addition, hypotensive properties of other onion phytochemicals would need to be examined in future studies.

Effects on diabetes and hyperglycemia

There has been a rising trend in the prevalence of age-standardized diabetes mellitus in adults during 1980-2014. According to estimates,

the number of diabetic adults elevated from 108 to 422 million worldwide over this period, and it is expected that it will exceed 700 million in 2025 (84). Diabetes mellitus and its micro-and macrovascular complications, including cardiovascular and kidney diseases, retinopathy, loss of vision, neuropathy, foot ulcers and amputation are important morbidity and mortality causes (85).

In vitro studies

Anti-protein glycation of bovine serum albumin with D-fructose and anti-oxidant properties of 25 herbs have been measured. Among them, the skin of *A. cepa* showed the most anti-glycating potential and scavenging capacity of free radicals using 1,1-Diphenyl-2-picrylhydrazyl (DPPH) test with $IC_{50} = 16.8 \pm 5.0$ and 4.49 ± 0.59 $\mu\text{g/ml}$, respectively (86). The inhibitory activity of quercetin and different parts and sizes of onion were seen on porcine pancreatic α -amylase. Furthermore, it was found that outer layers of onions and smaller ones possess more enzymatic activity inhibition (87). Rat intestinal α -glucosidase was inhibited with IC_{50} values 1.27 and 0.15 mg/ml by ethanolic extract of onion skin and quercetin, respectively (88). Sodium-glucose linked transporter (SGLT1) and glucose transporter 2 (GLUT2) play key roles in intestinal glucose absorption. Onion extract inhibited human SGLT1 expressed in *Xenopus laevis* oocytes in a concentration-dependent manner with a maximum effect of 86% at 1 mg/ml. The inhibition of expressed human GLUT2 in oocytes by 0.25 mg/ml concentration of onion extract was 78%. Among the onion flavonols, the highest levels of SGLT1 and GLUT2 suppression were observed by quercetin-4'-O-glucoside and aglycone quercetin, respectively. Onion extract was able to reduce glucose transport into mouse jejunal intestinal sections competitively and reversibly (89). Glucose transporter 4 (GLUT4), which is regulated by insulin, transports glucose from the blood into fat and muscle cells. An *in vitro* study revealed that the ethanolic extract of *A. cepa* bulbs stimulates glucose uptake through GLUT4 in L6 myotubes in a dose and time reliant pattern. The insulin-like activities of the extract were exerted by increasing phosphorylation of insulin receptor- β , insulin receptor substrate-1, and protein kinase B (Akt) together with the elevation of GLUT4 content and translocation of this protein to the cell surface (90).

Animal studies

Several studies have evidenced the health beneficial hypoglycemic action of onion and its functional constituents in animal models (91-95). Thirty mins after consuming sucrose solution (2.0 g/kg) by five-week-old Sprague-Dawley male rats, the ethanolic extract of onion skin and quercetin (both 0.5 g/kg) showed a significant reduction in blood glucose comparable with acarbose (5.0 mg/kg) as an efficient drug for postprandial hyperglycemia. One hr after administration, the lowering blood glucose effect of the extract disappeared but acarbose maintained glycemia near base value for about 2 hrs (88). In another animal study on alloxan diabetic rats which treated by 100, 300 and 600 mg/kg daily doses of aqueous extract

of *A. cepa* for 21 days, a decrease in serum levels of glucose, LDL, TG, TC, AST, ALT, and ALP along with an increase in HDL value was reported. The maximum dose of the extract and 2 mg/kg glibenclamide exhibited approximately the same efficacy. The fraction of the plant containing a kaempferol glycoside improved the diabetic condition (96). A meta-analysis was performed in 2008 on antidiabetic activities of onion extract and SMCS in diabetic rats. The findings showed that onion extract and SMCS significantly contributed to the control of blood glucose and body weight (97). Both quercetin and red onion extract as a food supplement in C57BL/6J mice on a high-fat diet for 9 weeks provoked a reduction in methylation of PGC-1 α promoter and the augmentation of NT-PGC-1 α expression (98). Quercetin (0.2% w/w almost equal to 1000 mg/day in humans according to dose conversion factor provided by FDA (Food and Drug Administration)) was added to the high-fat diet of C57BL/6J male mice for a period of 10 weeks. It reduced hyperglycemia, hyperinsulinemia, creatinine, and inflammatory indicators such as C-reactive protein. Increase in acyl-coenzyme A oxidase 1 (ACOX1) gene expression in the liver was also observed while no significant alterations occurred in energy expenditure, body weight, and lipid profile (99). Because of the low bioavailability of curcumin, its beneficial antidiabetic properties in combination with piperine and quercetin were evaluated on induced diabetes in rats. After 4 weeks of daily oral feeding by this mixture (CPQ) at the dose of 100 mg/kg, amelioration in fasting plasma glucose, glucose tolerance, LDL, HDL, TG, cholesterol, water, food intake and weight loss was observed in comparison with diabetic control and the animals receiving only curcumin. Obtained results were similar to those of 10 mg/kg/day glibenclamide. It was concluded that small amounts of quercetin and piperine in CPQ may exert their effects by lowering the metabolism of curcumin (100). Thiosulfinate (20 and 40 mg/kg) in diabetic rats possibly through non-competitive α -glucosidase inhibition and pancreatic beta cells stimulation showed improvements in postprandial glycemic control, glucose tolerance, and insulin secretion with an effect comparable to 10 mg/kg acarbose (101). S-methyl cysteine (100 mg/kg/day, orally for 60 days) along with a significant decline in blood glucose, insulin plasma concentration, TNF- α , and HOMA-IR (homeostatic model assessment of insulin resistance) showed anti-oxidant properties in rats receiving high-fructose diet. For example, a significant decrease in the serum amount of MDA and an increase in the levels of reduced glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT) were detected (102).

Some researchers have studied the effects of *A. cepa* and its bioactive constituents on diabetic complications. For example, Gomes *et al.* showed that quercetin could be useful for the management of diabetic nephropathy. This polyphenol (10 mg/kg/day, orally for 28 days) showed improvement in renal function by reducing proteinuria, the plasma concentration of creatinine, uric acid, and urea as well as increasing creatinine clearance in streptozotocin-induced diabetic nephropathy mice. Among them, modifications in creatinine-related factors were significant. Treatment

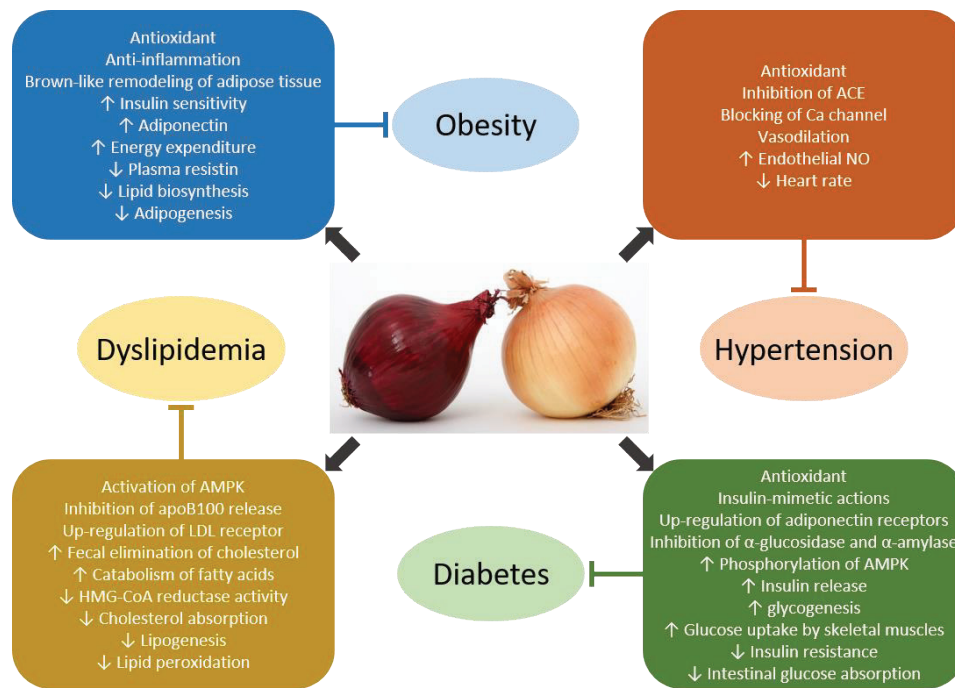


Figure 2. Proposed mechanisms of *Allium cepa* and its main compounds on metabolic syndrome components

with quercetin also significantly decreased kidney weight/body weight ratio, glomerulosclerosis, and the formation of apoptotic renal cells. They demonstrated that the anti-oxidant behavior of quercetin could lead to renoprotective results (103). The daily IP injection of aqueous onion extract (500 mg/ml/kg) to diabetic rats for 28 days showed a significant lowering effect on elevated serum amount of thromboxane B2 (TXB2). This extract also resulted in reducing the synthesis of TXB2 and aggregation of platelets, which was induced by collagen and arachidonic acid *in vitro* (104). The ethanolic seed extract of *A. cepa* in streptozotocin-induced diabetic Wistar male rats (200, 400 mg/kg/day, orally for 4 weeks) improved reproductive system performance by affecting factors such as seminiferous tubular diameter, luminal diameter, the volume density of lumen together with raising the generation of primary spermatocytes and spermatids (105). In an experiment which was conducted on mice, onion exhibited neuroprotective benefits in the prevention and therapy of diabetic neuropathy. In addition to the amelioration of hyperalgesia and hyperglycemia, levels of thiobarbituric acid reactive substances (TBARS) and serum nitrite decreased, and GSH level increased. According to the results, the neuroprotection impact of onion might be correlated with its anti-oxidant and hypoglycemic effects (106).

Clinical studies

High blood glucose can be induced by taking some medications. Jafarpour-Sadegh *et al.* in a randomized, triple-blind, placebo-controlled clinical trial study showed that dietary raw yellow onion at the doses of 100 to 160 g/day based on BMI index for 8 weeks significantly improved doxorubicin-induced insulin resistance and hyperglycemia in patients with breast cancer undergoing chemotherapy (107). In a clinical

trial which was performed on 84 patients suffering from type 1 and 2 diabetes mellitus with an average age of 44 ± 3.87 years, the intake of 100 g raw red onion improved oral glucose tolerance and fasting blood sugar after 4 hrs (108). An onion meal in people with lactose intolerance diminished the maximum blood glucose to a greater extent than those who could tolerate lactose (44.2% versus 19.3%, $P < 0.05$). It can be due to the decomposition of quercetin glucosides into quercetin in lactose-tolerant subjects and further inhibition of GLUT2 by glucosylated compounds (109).

Overall, *A. cepa* and its active components may be regarded as prophylactic or therapeutic agents against diabetes through different mechanisms including anti-oxidant, α -glucosidase and α -amylase inhibitory effect, up-regulation of adiponectin receptors, reducing insulin resistance and glucose absorption from intestine, elevation in the liver and muscle glycogen content, increasing insulin secretion and phosphorylation of AMPK, insulin-mimetic actions and GLUT4 translocation in skeletal muscles. Moreover, they exhibit benefits in diabetic complications by renal and neural protective effects, enhancing the function of the male reproductive system, and prevention of atherosclerosis. Unfortunately, there is a lack of clinical-based evidence to support improving complications of diabetes by onion.

Figure 2 shows the mechanisms of action through which onion and onion-derived compounds mediate their biological activities on metabolic syndrome.

Conclusion

The current review article summarized diverse cell, animal, and human studies to realize the role of *A. cepa* and its major ingredients in metabolic syndrome. Based on the gathered data, it has been concluded that onion can be helpful in the prevention and treatment of dyslipidemia, high blood pressure, diabetes mellitus,

and obesity as metabolic syndrome disorders and subsequently CVDs on account of anti-oxidant, anti-inflammatory, and vasodilatory properties, increasing insulin release and response, reduction of cholesterol and glucose absorption, modulating the metabolism of lipids and carbohydrates, and inhibition of adipogenesis. These effects are chiefly attributed to the ability of controlling associated signaling pathways, transcription factors, genes expression, enzymes and receptors activities. Additional clinical investigations with sufficient human population and duration are needed to be accomplished to prove the effectiveness and safety of *A. cepa*, especially in the case of potential interaction with conventional drugs.

Acknowledgment

The authors are thankful to Vice Chancellor of Research, Mashhad University of Medical Sciences, Mashhad, Iran, for their supports.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

- Samson SL, Garber AJ. Metabolic syndrome. *Endocrinol Metab Clin North Am* 2014; 43:1-23.
- Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 56:1113-1132.
- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1736-1788.
- Grundty SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112:2735-2752.
- Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 2014; 4:177.
- Teshika JD, Zakariyyah AM, Zaynab T, Zengin G, Rengasamy KR, Pandian SK, et al. Traditional and modern uses of onion bulb (*Allium cepa* L.): a systematic review. *Crit Rev Food Sci Nutr* 2019; 59:S39-S70.
- Upadhyay RK. Nutraceutical, pharmaceutical and therapeutic uses of *Allium cepa*: a review. *Int J Green Pharm* 2016; 10:S46-S64.
- Ahmed N, Mahmood A, Ashraf A, Bano A, Tahir SS, Mahmood A. Ethnopharmacological relevance of indigenous medicinal plants from district Bahawalnagar, Punjab, Pakistan. *J Ethnopharmacol* 2015; 175:109-123.
- Josabad Alonso-Castro A, Jose Maldonado-Miranda J, Zarate-Martinez A, Jacobo-Salcedo Mdel R, Fernandez-Galicia C, Alejandro Figueroa-Zuniga L, et al. Medicinal plants used in the Huasteca Potosina, Mexico. *J Ethnopharmacol* 2012; 143:292-298.
- Ayyanar M, Ignacimuthu S. Ethnobotanical survey of medicinal plants commonly used by Kani tribals in Tirunelveli hills of Western Ghats, India. *J Ethnopharmacol* 2011; 134:851-864.
- Prakash D, Singh BN, Upadhyay G. Anti-oxidant and free radical scavenging activities of phenols from onion (*Allium cepa*). *Food Chem* 2007; 102:1389-1393.
- Breu W. *Allium cepa* L. (onion) Part 1: Chemistry and analysis. *Phytomedicine* 1996; 3:293-306.
- Lee B, Jung JH, Kim HS. Assessment of red onion on anti-oxidant activity in rat. *Food Chem Toxicol* 2012; 50:3912-3919.
- Ren KW, Li YH, Wu G, Ren JZ, Lu HB, Li ZM, et al. Quercetin nanoparticles display antitumor activity via proliferation inhibition and apoptosis induction in liver cancer cells. *Int J Oncol* 2017; 50:1299-1311.
- Wang R, Yang L, Li S, Ye D, Yang L, Liu Q, et al. Quercetin inhibits breast cancer stem cells via downregulation of aldehyde dehydrogenase 1A1 (ALDH1A1), chemokine receptor type 4 (CXCR4), mucin 1 (MUC1), and epithelial cell adhesion molecule (EpCAM). *Med Sci Monit* 2018; 24:412-420.
- Draeos ZD. The ability of onion extract gel to improve the cosmetic appearance of postsurgical scars. *J Cosmet Dermatol* 2008; 7:101-104.
- Peng Z, Gong X, Yang Y, Huang L, Zhang Q, Zhang P, et al. Hepatoprotective effect of quercetin against LPS/d-GalN induced acute liver injury in mice by inhibiting the IKK/NF-kappaB and MAPK signal pathways. *Int Immunopharmacol* 2017; 52:281-289.
- Ro JY, Ryu JH, Park HJ, Cho HJ. Onion (*Allium cepa* L.) peel extract has anti-platelet effects in rat platelets. *Springerplus* 2015; 4:17.
- Lee SM, Moon J, Chung JH, Cha YJ, Shin MJ. Effect of quercetin-rich onion peel extracts on arterial thrombosis in rats. *Food Chem Toxicol* 2013; 57:99-105.
- Kumar VP, Venkatesh YP. Alleviation of cyclophosphamide-induced immunosuppression in Wistar rats by onion lectin (*Allium cepa* agglutinin). *J Ethnopharmacol* 2016; 186:280-288.
- Khajah MA, Orabi KY, Hawai S, Sary HG, El-Hashim AZ. Onion bulb extract reduces colitis severity in mice via modulation of colonic inflammatory pathways and the apoptotic machinery. *J Ethnopharmacol* 2019; 241:112008.
- Reddy RRL, Srinivasan K. Dietary fenugreek and onion attenuate cholesterol gallstone formation in lithogenic diet-fed mice. *Int J Exp Pathol* 2011; 92:308-319.
- Singh T, Goel RK. Neuroprotective effect of *Allium cepa* L. in aluminium chloride induced neurotoxicity. *Neurotoxicology* 2015; 49:1-7.
- Kim JH. Antibacterial action of onion (*Allium cepa* L.) extracts against oral pathogenic bacteria. *J Nihon Univ Sch Dent* 1997; 39:136-141.
- Shams-Ghahfarokhi M, Shokoohamiri MR, Amirrajab N, Moghadasi B, Ghajari A, Zeini F, et al. *In vitro* antifungal activities of *Allium cepa*, *Allium sativum* and ketoconazole against some pathogenic yeasts and dermatophytes. *Fitoterapia* 2006; 77:321-323.
- Kaiser P, Youssof MS, Tasduq SA, Singh S, Sharma SC, Singh GD, et al. Anti-allergic effects of herbal product from *Allium cepa* (bulb). *J Med Food* 2009; 12:374-382.
- Oliveira TT, Campos KM, Cerqueira-Lima AT, Cana Brasil Carneiro T, da Silva Velozo E, Ribeiro Melo IC, et al. Potential therapeutic effect of *Allium cepa* L. and quercetin in a murine model of *Blomia tropicalis* induced asthma. *Daru* 2015; 23:18.
- Haidari F, Rashidi MR, Keshavarz SA, Mahboob SA, Eshraghian MR, Shahi MM. Effects of onion on serum uric acid levels and hepatic xanthine dehydrogenase/xanthine oxidase activities in hyperuricemic rats. *Pak J Biol Sci* 2008; 11:1779-1784.
- Samad N, Saleem A. Administration of *Allium cepa* L. bulb attenuates stress-produced anxiety and depression and improves memory in male mice. *Metab Brain Dis* 2018; 33:271-281.
- Jain S, Buttar HS, Chintameneni M, Kaur G. Prevention of cardiovascular diseases with anti-inflammatory and anti-oxidant nutraceuticals and herbal products: An overview of pre-clinical and clinical studies. *Recent Pat Inflamm Allergy Drug Discov* 2018; 12:145-157.
- Tang GY, Meng X, Li Y, Zhao CN, Liu Q, Li HB. Effects of

- vegetables on cardiovascular diseases and related mechanisms. *Nutrients* 2017; 9:857.
32. Thomson M, Alnaqeeb MA, Bordia T, Al-Hassan JM, Afzal M, Ali M. Effects of aqueous extract of onion on the liver and lung of rats. *J Ethnopharmacol* 1998; 61:91-99.
 33. Ebrahimi-Mamaghani M, Saghafi-Asl M, Pirouzpanah S, Asghari-Jafarabadi M. Effects of raw red onion consumption on metabolic features in overweight or obese women with polycystic ovary syndrome: A randomized controlled clinical trial. *J Obstet Gynaecol Res* 2014; 40:1067-1076.
 34. Kim J, Cha YJ, Lee KH, Park E. Effect of onion peel extract supplementation on the lipid profile and antioxidative status of healthy young women: a randomized, placebo-controlled, double-blind, crossover trial. *Nutr Res Practice* 2013; 7:373-379.
 35. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. *Prim Care* 2013; 40:195-211.
 36. Srinivasan K. Dietary spices as beneficial modulators of lipid profile in conditions of metabolic disorders and diseases. *Food Funct* 2013; 4:503-521.
 37. Han SY, Hu Y, Anno T, Yanagita T. S-propyl cysteine reduces the secretion of apolipoprotein B100 and triacylglycerol by HepG2 cells. *Nutrition* 2002; 18:505-509.
 38. Lee YG, Cho J, Hwang EJ, Jeon T, Moon J. Glu-Phe from onion (*Allium Cepa* L.) attenuates lipogenesis in hepatocytes. *Biosci Biotechnol Biochem* 2017; 81:1409-1416.
 39. Sun L, Li E, Wang F, Wang T, Qin Z, Niu S, et al. Quercetin increases macrophage cholesterol efflux to inhibit foam cell formation through activating PPAR γ -ABCA1 pathway. *Int J Clin Exp Pathol* 2015; 8:10854-10860.
 40. Arteaga E, Villaseca P, Rojas A, Marshall G, Bianchi M. Phytoestrogens possess a weak anti-oxidant activity on low density lipoprotein in contrast to the flavonoid quercetin *in vitro* in postmenopausal women. *Climacteric* 2004; 7:397-403.
 41. Bordia A, Arora SK, Kothari LK, Jain KC, Rathore BS, Rathore AS, et al. The protective action of essential oils of onion and garlic in cholesterol-fed rabbits. *Atherosclerosis* 1975; 22:103-109.
 42. Vidyavati HG, Manjunatha H, Hemavathy J, Srinivasan K. Hypolipidemic and anti-oxidant efficacy of dehydrated onion in experimental rats. *J Food Sci Technol* 2010; 47:55-60.
 43. Kang HJ, Pichiah BT, Abinaya RV, Sohn HS, Cha YS. Hypocholesterolemic effect of quercetin-rich onion peel extract in C57BL/6J mice fed with high cholesterol diet. *Food Sci Biotechnol* 2016; 25:855-860.
 44. Jaiswal N, Rizvi SI. Onion extract (*Allium cepa* L.), quercetin and catechin up-regulate paraoxonase 1 activity with concomitant protection against low-density lipoprotein oxidation in male Wistar rats subjected to oxidative stress. *J Sci Food Agr* 2014; 94:2752-2757.
 45. De Boer VCJ, Van Schothorst EM, Dihal AA, Van Der Woude H, Arts ICW, Rietjens IMCM, et al. Chronic quercetin exposure affects fatty acid catabolism in rat lung. *Life Sci* 2006; 63:2847-2858.
 46. Yanagita T, Han S, Wang YM, Tsuruta Y, Anno T. Cycloalliin, a cyclic sulfur imino acid, reduces serum triacylglycerol in rats. *Nutrition* 2003; 19:140-143.
 47. Kumari K, Augusti KT. Lipid lowering effect of S-methyl cysteine sulfoxide from *Allium cepa* Linn in high cholesterol diet fed rats. *J Ethnopharmacol* 2007; 109:367-371.
 48. Emamat H, Foroughi F, Eini-Zinab H, Hekmatdoost A. The effects of onion consumption on prevention of nonalcoholic fatty liver disease. *Indian J Clin Biochem* 2018; 33:75-80.
 49. Emamat H, Foroughi F, Eini-Zinab H, Taghizadeh M, Rismanchi M, Hekmatdoost A. The effects of onion consumption on treatment of metabolic, histologic, and inflammatory features of nonalcoholic fatty liver disease. *J Diabetes Metab Dis* 2016; 15:25.
 50. Lu TM, Chiu HF, Shen YC, Chung CC, Venkatakrishnan K, Wang CK. Hypocholesterolemic efficacy of quercetin rich onion juice in healthy mild hypercholesterolemic adults: A pilot study. *Plant Foods Human Nutr* 2015; 70:395-400.
 51. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017; 390:2627-2642.
 52. Joo JK, Lee KS. Pharmacotherapy for obesity. *J Menopausal Med* 2014; 20:90-96.
 53. Marrelli M, Amodeo V, Statti G, Conforti F. Biological properties and bioactive components of *Allium cepa* L.: Focus on potential benefits in the treatment of obesity and related comorbidities. *Molecules* 2018; 24:119.
 54. Williams DJ, Edwards D, Hamernig I, Jian L, James AP, Johnson SK, et al. Vegetables containing phytochemicals with potential anti-obesity properties: A review. *Food Res Int* 2013; 52:323-333.
 55. Funakoshi T, Kanzaki N, Otsuka Y, Izumo T, Shibata H, Machida S. Quercetin inhibits adipogenesis of muscle progenitor cells *in vitro*. *Biochem Biophys Res* 2018; 13:39-44.
 56. Bae CR, Park YK, Cha YS. Quercetin-rich onion peel extract suppresses adipogenesis by down-regulating adipogenic transcription factors and gene expression in 3T3-L1 adipocytes. *J Sci Food Agr* 2014; 94:2655-2660.
 57. Seo MJ, Lee YJ, Hwang JH, Kim KJ, Lee BY. The inhibitory effects of quercetin on obesity and obesity-induced inflammation by regulation of MAPK signaling. *J Nutr Biochem* 2015; 26:1308-1316.
 58. Eseberri I, Miranda J, Lasa A, Churruga I, Portillo MP. Doses of quercetin in the range of serum concentrations exert delipidating effects in 3t3-l1 preadipocytes by acting on different stages of adipogenesis, but not in mature adipocytes. *Oxid Med Cell Longev* 2015; 2015.
 59. Yoshinari O, Shiojima Y, Igarashi K. Anti-Obesity Effects of Onion Extract in Zucker Diabetic Fatty Rats. *Nutrients* 2012; 4:1518-1526.
 60. Forney LA, Lenard NR, Stewart LK, Henagan TM. Dietary quercetin attenuates adipose tissue expansion and inflammation and alters adipocyte morphology in a tissue-specific manner. *Int J Mol Sci* 2018; 19:895.
 61. Pangen R, Kang SW, Oak M, Park EY, Park JW. Oral delivery of quercetin in oil-in-water nanoemulsion: *In vitro* characterization and *in vivo* anti-obesity efficacy in mice. *J Funct Foods* 2017; 38:571-581.
 62. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 2009; 360:1509-1517.
 63. Lee SG, Parks JS, Kang HW. Quercetin, a functional compound of onion peel, remodels white adipocytes to brown-like adipocytes. *J Nutr Biochem* 2017; 42:62-71.
 64. Lee JS, Cha YJ, Lee KH, Yim JE. Onion peel extract reduces the percentage of body fat in overweight and obese subjects: a 12-week, randomized, double-blind, placebo-controlled study. *Nutr Res Practice* 2016; 10:175-181.
 65. Kim KA, Yim JE. The effect of onion peel extract on inflammatory mediators in Korean overweight and obese women. *Clin Nutr Res* 2016; 5:261-269.
 66. Blacher J, Levy BI, Mourad JJ, Safar ME, Bakris G. From epidemiological transition to modern cardiovascular epidemiology: hypertension in the 21st century. *Lancet* 2016; 388:530-532.
 67. Etehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387:957-967.
 68. Aslam M, Ahmad M, Mobasher F. Efficacy and tolerability of antihypertensive drugs in diabetic and nondiabetic patients. *J Pharm Bioallied Sci* 2017; 9:56-65.
 69. Chen ZY, Peng C, Jiao R, Wong YM, Yang N, Huang Y. Anti-

- hypertensive nutraceuticals and functional foods. *J Agr Food Chem* 2009; 57:4485-4499.
70. Oboh G, Ademiluyi AO, Agunloye OM, Ademosun AO, Ogunsakin BG. Inhibitory effect of garlic, purple onion, and white onion on key enzymes linked with type 2 diabetes and hypertension. *J Diet Suppl* 2018;1-14.
71. Muhammad SA, Fatima N. In silico analysis and molecular docking studies of potential angiotensin-converting enzyme inhibitor using quercetin glycosides. *Pharmacogn Mag* 2015; 11:S123-S126.
72. Monori-Kiss A, Monos E, Nádasy GL. Quantitative analysis of vasodilatory action of quercetin on intramural coronary resistance arteries of the rat *in vitro*. *PLoS ONE* 2014; 9:e105587.
73. Lodi F, Jimenez R, Moreno L, Kroon PA, Needs PW, Hughes DA, et al. Glucuronidated and sulfated metabolites of the flavonoid quercetin prevent endothelial dysfunction but lack direct vasorelaxant effects in rat aorta. *Atherosclerosis* 2009; 204:34-39.
74. Brankovic S, Radenkovic M, Kitic D, Veljkovic S, Ivetic V, Pavlovic D, et al. Comparison of the hypotensive and bradycardic activity of ginkgo, garlic, and onion extracts. *Clin Exp Hypertension* 2011; 33:95-99.
75. Naseri MKG, Arabian M, Badavi M, Ahangarpour A. Vasorelaxant and hypotensive effects of *Allium cepa* peel hydroalcoholic extract in rat. *Pakistan J Biol Sci* 2008; 11:1569-1575.
76. Kawamoto E, Sakai Y, Okamura Y, Yamamoto Y. Effects of boiling on the antihypertensive and anti-oxidant activities of onion. *J Nutr Sci Vitaminol* 2004; 50:171-176.
77. Sakai Y, Murakami T, Yamamoto Y. Antihypertensive effects of onion on NO synthase inhibitor-induced hypertensive rats and spontaneously hypertensive rats. *Biosci Biotechnol Biochem* 2003; 67:1305-1311.
78. Kivirantat J, Huovinen K, Seppänen-Laakso T, Hiltunen R, Karppanen H, Kilpeläinen M. Effects of onion and garlic extracts on spontaneously hypertensive rats. *Phytother Res* 1989; 3:132-135.
79. Brull V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Muller C, et al. Acute intake of quercetin from onion skin extract does not influence postprandial blood pressure and endothelial function in overweight-to-obese adults with hypertension: a randomized, double-blind, placebo-controlled, crossover trial. *Eur J Nutr* 2017; 56:1347-1357.
80. Perez A, Gonzalez-Manzano S, Jimenez R, Perez-Abud R, Haro JM, Osuna A, et al. The flavonoid quercetin induces acute vasodilator effects in healthy volunteers: Correlation with beta-glucuronidase activity. *Pharmacol Res* 2014; 89:11-18.
81. Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T. Quercetin reduces blood pressure in hypertensive subjects. *J Nutr* 2007; 137:2405-2411.
82. Kalus U, Pindur G, Jung F, Mayer B, Radtke H, Bachmann K, et al. Influence of the onion as an essential ingredient of the Mediterranean diet on arterial blood pressure and blood fluidity. *Drug Res* 2000; 50:795-801.
83. Egert S, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. *J Nutr* 2010; 140:278-284.
84. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016; 387:1513-1530.
85. American Diabetes Association. Microvascular complications and foot care: standards of medical care in diabetes. *Diabetes Care* 2019; 42:S124.
86. Kim HY, Kim K. Protein glycation inhibitory and antioxidative activities of some plant extracts *in vitro*. *J Agr Food Chem* 2003; 51:1586-1591.
87. Jaiswal N, Rizvi SI. Amylase inhibitory and metal chelating effects of different layers of onion (*Allium cepa* L.) at two different stages of maturation *in vitro*. *Ann Phytomed Int* 2017; 6:45-50.
88. Kim SH, Jo SH, Kwon YI, Hwang JK. Effects of Onion (*Allium cepa* L.) Extract administration on intestinal alpha-glucosidases activities and spikes in postprandial blood glucose levels in SD rats model. *Int J Mol Sci* 2011; 12:3757-3769.
89. Schulze C, Bangert A, Schwanck B, Vollert H, Blaschek W, Daniel H. Extracts and flavonoids from onion inhibit the intestinal sodium-coupled glucose transporter 1 (SGLT1) *in vitro* but show no anti-hyperglycaemic effects *in vivo* in normoglycaemic mice and human volunteers. *J Funct Foods* 2015; 18:117-128.
90. Gautam S, Pal S, Maurya R, Srivastava AK. Ethanolic extract of *Allium cepa* stimulates glucose transporter typ 4-mediated glucose uptake by the activation of insulin signaling. *Planta Med* 2015; 81:208-214.
91. Augusti KT. Effect of alloxan diabetes of allyl propyl disulphide obtained from onion. *Naturwissenschaften* 1974; 61:172-173.
92. Augusti KT, Roy VCM, Semple M. Effect of allyl propyl disulphide isolated from onion (*Allium cepa* L.) on glucose tolerance of alloxan diabetic rabbits. *Experientia* 1974; 30:1119-1120.
93. Jain RC, Vyas CR. Letter: Hypoglycaemia action of onion on rabbits. *Br Med J* 1974; 2:730.
94. Karawya MS, Abdel Wahab SM, El-Olemy MM, Farrag NM. Diphenylamine, an antihyperglycemic agent from onion and tea. *J Nat Prod* 1984; 47:775-780.
95. Kumari K, Augusti KT. Antidiabetic effects of s-methylcysteine sulfoxide on alloxan diabetes. *Planta Med* 1995; 61:72-74.
96. Ikechukwu OJ, Ifeanyi OS. The Antidiabetic effects of the bioactive flavonoid (Kaempferol-3-O-beta-D-6{P-Coumaroyl} Glucopyranoside) isolated from *Allium cepa*. *Recent Pat Antiinfect Drug Discov* 2016; 11:44-52.
97. Kook S, Kim GH, Choi K. The antidiabetic effect of onion and garlic in experimental diabetic rats: Meta-analysis. *J Med Food* 2009; 12:552-560.
98. Devarshi PP, Jones AD, Taylor EM, Stefanska B, Henagan TM. Quercetin and quercetin-rich red onion extract alter Pgc-1 alpha promoter methylation and splice variant expression. *PPAR Res* 2017 ;2017:3235693.
99. Snyder SM, Zhao B, Luo T, Kaiser C, Cavender G, Hamilton-Reeves J, et al. Consumption of quercetin and quercetin-containing apple and cherry extracts affects blood glucose concentration, hepatic metabolism, and gene expression patterns in obese C57BL/6J high fat-fed mice. *J Nutr* 2016; 146:1001-1007.
100. Kaur G, Invally M, Chintamaneni M. Influence of piperine and quercetin on antidiabetic potential of curcumin. *J Complement Integr Med* 2016; 13:247-255.
101. Al-Malki AL. inhibition of alpha-glucosidase by thiosulfinate as a target for glucose modulation in diabetic rats. *Evid Based Complement Altern Med* 2016; 2016:7687915.
102. Thomas S, Senthilkumar GP, Sivaraman K, Bobby Z, Paneerselvam S, Harichandrakumar KT. Effect of S-Methyl-L-cysteine on oxidative stress, inflammation and insulin resistance in male Wistar rats fed with high fructose diet. *Iran J Med Sci* 2015; 40:45-50.
103. Gomes IBS, Porto ML, Santos MCLFS, Campagnaro BP, Pereira TMC, Meyrelles SS, et al. Renoprotective, anti-oxidative and anti-apoptotic effects of oral low-dose quercetin in the C57BL/6J model of diabetic nephropathy. *Lipids Health Dis* 2014; 13.
104. Jung YS, Kim MH, Lee SH, Baik EJ, Park SW, Moon CH. Antithrombotic effect of onion in streptozotocin-induced diabetic rat. *Prostag Leukotr Ess* 2002; 66:453-458.
105. Fallah V, Mahabadi JA, Mahabadi MY, Kashani HH, Nikzad

- H. Protective effect of *Allium cepa* (Onion) seeds (AC) extract on histopathology of testis in STZ-induced male rats. *Int J Morphol* 2017; 35:1517-1524.
106. Bhanot A, Shri R. A comparative profile of methanol extracts of *Allium cepa* and *Allium sativum* in diabetic neuropathy in mice. *Pharmacognosy Res* 2010; 2:374-384.
107. Jafarpour-Sadegh F, Montazeri V, Adili A, Esfehiani A, Rashidi MR, Pirouzpanah S. Consumption of fresh yellow onion ameliorates hyperglycemia and insulin resistance in breast cancer patients during doxorubicin-based chemotherapy: A randomized controlled clinical trial. *Integr Cancer Ther* 2017; 16:276-289.
108. Taj Eldin IM, Ahmed EM, Elwahab HMA. Preliminary study of the clinical hypoglycemic effects of *Allium cepa* (red onion) in type 1 and type 2 diabetic patients. *Environ Health Insights* 2010; 4:71-77.
109. Hoffman R, Ranjbar G, Madden AM. Inhibition of the glycaemic response by onion: A comparison between lactose-tolerant and lactose-intolerant adults. *Eur J Clin Nutr* 2016; 70:1089-1091.
110. Lee SM, Moon J, Cho Y, Chung JH, Shin MJ. Quercetin up-regulates expressions of peroxisome proliferator-activated receptor γ , liver X receptor α , and ATP binding cassette transporter A1 genes and increases cholesterol efflux in human macrophage cell line. *Nutr Res* 2013; 33:136-143.
111. Jung H, Wee JH, Kim K, Sung H, Shin H. Effect of onion (*Allium cepa*) ultra-high pressure processing and hot water extracts on the serum cholesterol level in high cholesterol-fed rats. *Food Sci Biotechnol* 2015; 24:287-294.
112. Lata S, Saxena KK, Bhasin V, Saxena RS, Kumar A, Srivastava VK. Beneficial effects of *Allium sativum*, *Allium cepa* and *Commiphora mukul* on experimental hyperlipidemia and atherosclerosis-a comparative evaluation. *J Postgrad Med* 1991; 37:132-135.
113. Guan L, Chung HY, Su YL, Jiao R, Peng C, Chen ZY. Hypocholesterolemic activity of onion is mediated by enhancing excretion of fecal sterols in hamsters. *Food Funct* 2010; 1:84-89.
114. Sikder K, Das N, Kesh SB, Dey S. Quercetin and beta-sitosterol prevent high fat diet induced dyslipidemia and hepatotoxicity in Swiss albino mice. *Indian J Exp Biol* 2014; 52:60-66.
115. Moon J, Do HJ, Kim OY, Shin MJ. Antiobesity effects of quercetin-rich onion peel extract on the differentiation of 3T3-L1 preadipocytes and the adipogenesis in high fat-fed rats. *Food Chem Toxicol* 2013; 58:347-354.
116. Henagan TM, Cefalu WT, Ribnicky DM, Noland RC, Dunville K, Campbell WW, et al. *In vivo* effects of dietary quercetin and quercetin-rich red onion extract on skeletal muscle mitochondria, metabolism, and insulin sensitivity. *Genes Nutr* 2015; 10:451.
117. Arias N, Picó C, Teresa Macarulla M, Oliver P, Miranda J, Palou A, et al. A combination of resveratrol and quercetin induces browning in white adipose tissue of rats fed an obesogenic diet. *Obesity* 2017; 25:111-121.
118. Vazquez-Prieto MA, Rodriguez Lanzi C, Lembo C, Galmarini CR, Miatello RM. Garlic and onion attenuates vascular inflammation and oxidative stress in fructose-fed rats. *J Nutr Metab* 2011; 2011:475216.
119. Gonzalez-Pena D, Angulo J, Vallejo S, Colina-Coca C, de Ancos B, Sanchez-Ferrer CF, et al. High-cholesterol diet enriched with onion affects endothelium-dependent relaxation and NADPH oxidase activity in mesenteric microvessels from Wistar rats. *Nutr Metab* 2014; 11:57.
120. Jalili T, Carlstrom J, Kim S, Freeman D, Jin HF, Wu TC, et al. Quercetin-supplemented diets lower blood pressure and attenuate cardiac hypertrophy in rats with aortic constriction. *J Cardiovasc Pharmacol* 2006; 47:531-541.
121. Wu HR, Xu BJ. Inhibitory effects of onion against α -glucosidase activity and its correlation with phenolic antioxidants. *Int J Food Prop* 2014; 17:599-609.
122. Ozougwu JC. Anti-diabetic effects of *Allium cepa* (onions) aqueous extracts on alloxan-induced diabetic *Rattus norvegicus*. *J Med Plants Res* 2011; 5:1134-1139.
123. Babu PS, Srinivasan K. Influence of dietary capsaicin and onion on the metabolic abnormalities associated with streptozotocin induced diabetes mellitus. *Mol Cell Biochem* 1997; 175:49-57.
124. El-Soud NA, Khalil M. Antioxidative effects of *Allium cepa* essential oil in streptozotocin induced diabetic rats. *Macedonian J Med Sci* 2010; 3:344-351.
125. Ogunmodede OS, Saalu LC, Ogunlade B, Akunna GG, Oyewopo AO. An evaluation of the hypoglycemic, anti-oxidant and hepatoprotective potentials of onion (*Allium cepa* L.) on alloxan-induced diabetic rabbits. *Int J Pharmacol* 2012; 8:21-29.
126. Jung JY, Lim Y, Moon MS, Kim JY, Kwon O. Onion peel extracts ameliorate hyperglycemia and insulin resistance in high fat diet/streptozotocin-induced diabetic rats. *Nutr Metab* 2011; 8:18.
127. Arias N, MacArulla MT, Aguirre L, Martínez-Castaño MG, Portillo MP. Quercetin can reduce insulin resistance without decreasing adipose tissue and skeletal muscle fat accumulation. *Genes Nutr* 2014; 9:361.
128. Anhê GF, Okamoto MM, Kinote A, Sollon C, Lellis-Santos C, Anhê FF, et al. Quercetin decreases inflammatory response and increases insulin action in skeletal muscle of ob/ob mice and in L6 myotubes. *Eur J Pharmacol* 2012; 689:285-293.
129. Shetty AK, Rashmi R, Rajan MGR, Sambaiah K, Salimath PV. Antidiabetic influence of quercetin in streptozotocin-induced diabetic rats. *Nutr Res* 2004; 24:373-381.
130. Khaki A, Fathiazad F, Ahmadi-Ashtiani HR, Rezazadeh S, Rastegar H, Imani AM. Compartments of quercetin & *Allium cepa* (onion) on blood glucose in diabetic rats. *J MedPlants* 2010; 9:107-112.
131. G PS, Thomas S, K S, Sankar P, Bobby Z. Study the effect of s-methyl L-cysteine on lipid metabolism in an experimental model of diet induced obesity. *J Clin Diagn Res* 2013; 7:2449-2451.
132. Choi EY, Lee H, Woo JS, Jang HH, Hwang SJ, Kim HS, et al. Effect of onion peel extract on endothelial function and endothelial progenitor cells in overweight and obese individuals. *Nutrition* 2015; 31:1131-1135.
133. Khorshidi M, Moini A, Alipoor E, Rezvan N, Gorgani-Firuzjaee S, Yaseri M, et al. The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. *Phytother Res* 2018; 32:2282-2289.
134. Brull V, Burak C, Stoffel-Wagner B, Wolfram S, Nickenig G, Muller C, et al. No effects of quercetin from onion skin extract on serum leptin and adiponectin concentrations in overweight-to-obese patients with (pre-)hypertension: a randomized double-blinded, placebo-controlled crossover trial. *Eur J Nutr* 2017; 56:2265-2275.
135. Nishimura M, Muro T, Kobori M, Nishihira J. Effect of daily ingestion of quercetin-rich onion powder for 12 weeks on visceral fat: A randomised, double-blind, placebo-controlled, parallel-group study. *Nutrients* 2019; 12.
136. Bruell V, Burak C, Stoffel-Wagner B, Wolfram S, Nickenig G, Mueller C, et al. Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-) hypertension: a randomised double-blinded placebo-controlled cross-over trial. *British J Nutr* 2015; 114:1263-1277.
137. Lee KH, Park E, Lee HJ, Kim MO, Cha YJ, Kim JM, et al. Effects of daily quercetin-rich supplementation on cardiometabolic risks in male smokers. *Nutr Res Pract* 2011; 5:28-33.
138. Rezvan N, Moini A, Gorgani-Firuzjaee S, Hosseinzadeh-

Attar MJ. Oral quercetin supplementation enhances adiponectin receptor transcript expression in polycystic ovary

syndrome patients: A randomized placebo-controlled double-blind clinical trial. *Cell J* 2018; 19:627-633.