BENEFICIAL EFFECTS OF POLYPHENOLS IN METABOLIC SYNDROME—A REVIEW

Mehmed Abtulov, Stefka Valcheva-Kuzmanova

Department of Pharmacology and Clinical Pharmacology and Therapeutics, Faculty of Medicine, Medical University of Varna

ABSTRACT

INTRODUCTION: Polyphenols (PPs) are plant-derived chemical compounds bearing one or more phenolic rings. The most commonly presented dietary PPs include anthocyanins, flavonols, flavanols and phenolic acids. Studies have shown that polyphenols exert a variety of actions including antioxidant, anti-inflammatory, antimicrobial, antiproliferative, cancer protective, cardioprotective, lipid-lowering, and glucose-lowering. Metabolic syndrome (MetS) is a global health issue associated with an increased risk of cardiovascular diseases, type 2 diabetes, and certain types of cancer.

AIM: The purpose of this paper is to summarize the current knowledge about the beneficial effects of different polyphenols on the clinical manifestations of metabolic syndrome.

MATERIALS AND METHODS: Literature in PubMed, Google Scholar and ScienceDirect has been studied and analyzed.

RESULTS: Most data about the beneficial effects of polyphenols is derived from preclinical studies. The clinical trials involving polyphenolic compounds in subjects with MetS are limited, comprise a small number of participants, and the duration is short.

CONCLUSION: Numerous studies show promising effects of polyphenols in improving the biochemical and clinical abnormalities associated with metabolic syndrome but larger, more precise, better controlled clinical trials are necessary to reveal their benefits in clinical practice.

Keywords: *polyphenols, metabolic syndrome*

Address for correspondence:
Mehmed Abtulov
Faculty of Medicine
Medical University of Varna
55 Marin Drinov St
9002 Varna
e-mail: Mehmed.Abtulov@mu-varna.bg

Received: August 28, 2021
Accepted: September 3, 2021

INTRODUCTION

Polyphenols (PPs) are plant-derived chemical compounds bearing one or more phenolic rings. They exert different physiological functions in plants such as protection against microbial infections and UV sunlight as well as attraction of pollinators (1). PPs are found in a variety of foods and beverages, notably in berries, grapes, citrus fruits, red fruits, vegetables, green tea, coffee, and wine (2-3). In general,

PPs are divided into 2 groups: flavonoids and non-flavonoids (Table 1) (4). The most commonly presented dietary PPs include anthocyanins (in berries, red grapes, black currants), flavonols (in berries, grapes, apple, tomatoes, onion, tea, red wine), flavanols (in blueberries, bananas, apples, peaches, tea), and phenolic acids (in fruits, vegetables, coffee) (3-5). Studies have revealed that they exert antioxidant, anti-inflammatory, antimicrobial, antiproliferative, cancer protective, cardioprotective, and antidiabetic effects (6-8).

Table 1. Classification of polyphenols

Polyphenols	
Flavonoids	***Non-flavonoids***
Flavones: apigenin, luteolin, tangeritin, nobiletin, sinensetin	**Phenolic acids**: chlorogenic acid, neochlorogenic acid, caffeic acid, ferulic acid, vanillic acid, curcumin
Flavonols: quercetin, myricetin, rutin, morin, kaemferol	**Stillbenes**: resveratrol
Flavan-3-ols (flavanols): catechin, epicatechin, epigallocatechin	**Lignans**: secoisolariciresinol, matairesinol, lariciresinol, pinoresinol
Isoflavones: daidzein, genistein	
Flavanones: hesperidin, naringenin, eriodictyol	
Anthocyanins: cyanidin, malvidin, delphinidin, peonidin	

Metabolic syndrome (MetS) is a progressive disorder which is associated with development of type 2 diabetes mellitus (T2DM), cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea (OSA), polycystic ovary syndrome (PCOS), neuropsychiatric and oncological disorders (10-16). Epidemiological studies have shown that in subjects with MetS the risk of T2DM is increased 2-fold, whereas the incidence of cardiovascular complications is increased 4-fold. (17).

Pathogenesis of Metabolic Syndrome

Consumption of calorie-dense foods and beverages along with physical inactivity contribute to development of abdominal obesity, which in turn leads to insulin resistance (IR) (18). IR remains the main pathogenic mechanism in the development of MetS. It is characterized by impaired metabolic effects of insulin in different target tissues and organs. In the presence of IR, lipolysis in the white adipose tissue is activated, which causes the release of an excessive amount of free fatty acids (FFAs) in the circulation. FFAs reach insulin-dependent tissues and block insulin-mediated glucose uptake through the GLUT-4 glucose transporter. Hyperglycemia induces hyperinsulinemia, which in turn increases the absorption of sodium and water in the kidneys, stimulates the activity of the sympathetic nervous system, and intensifies the insulin resistance. In the liver, increased FFA influx activates gluconeogenesis and the production of very low-density (VLDL) and low-density (LDL) lipoproteins, suppresses that of high-density lipoproteins (HDL). Glycogen levels in the muscles decrease and lipid levels increase (19).

Metabolic syndrome is also considered as a low-grade inflammatory state (20). Abdominal (visceral) adipose tissue is a source of cytokines, chemokines, hormonal elements, and various proteins. Some of these products possess an anti-inflammatory activity (adiponectin), others—pronounced pro-inflammatory activity (leptin, resistin, inhibitor of plasminogen activator-1, C-reactive protein, interleukins such as IL-1, IL-6; TNF-α, fibrinogen, serum amyloid A). In MetS, the levels of pro-inflammatory mediators are elevated and those of anti-inflammatory mediators are decreased (21). Inflammatory molecules produced by the visceral adipose tissue lead to oxidative stress, endothelial dysfunction, hypercoagulability, and a further reduction of insulin sensitivity. Taken together, all of these events contribute to the development of hypertension, hyperglycemia, dyslipidemia, as well as other disorders associated with MetS.

Management of Metabolic Syndrome

The management of MetS includes lifestyle modifications, weight loss approaches, and treatment of co-morbidities (22). Lifestyle modifications aim at: behavioral changes, calorie restriction, and optimal physical activity. Behavioral changes include a proper diet (reduced consumption of processed foods/pastry/saturated fats, increased consumption of fruits, vegetables, whole grains, legumes, fish and other seafood), reduced to moderate alcohol consumption, smoking cessation, and cognitive-behavioral therapy. In cases with strict indications, medications or surgical interventions are used. Pharmacological treatment of MetS aims to normalize body weight, to improve insulin sensitivity and glycemic control, to lower blood pressure, and to correct dyslipidemia.

Despite different available treatment options, there is no definitive treatment of MetS. Therefore, there is a growing interest in seeking newer therapeutic agents, including phytotherapeutic ones. Studies have shown that PPs might be beneficial in patients with MetS.

AIM

In the present paper, the current knowledge about the beneficial effects of different polyphenols on the clinical manifestations of metabolic syndrome is summarized, based on the information from scientific databases such as PubMed, Google Scholar and ScienceDirect.

RESULTS

Polyphenols and Obesity/Dyslipidemia

In the last years, PPs have attracted research interest due to their numerous health benefits. A number of studies have demonstrated the role of PPs in weight control and lipid metabolism. Most data are available for catechins, anthocyanins, resveratrol and curcumin.

Catechins. Tea is one of the most commonly consumed beverages worldwide. *Camellia sinensis* leaves are a plant source for different types of tea—white, green, oolong or black. Green tea is a well-known source of catechins. The most abundant one in green tea is epigallocatechin gallate (EGCG) (23). Effects of EGCG have been studied in cell cultures, animal and human studies (24). In cell cultures, EGCG inhibits the proliferation and differentiation of adipocytes. It also increases the amount of brown adipose tissue (possesses thermogenic and lypolytic effects) in the body (25). Adenosine monophoshate (AMP)-activated protein kinase (AMPK) is a key regulator of energy metabolism. Its activation through AMP results in the upregulation of enzymes involved in catabolic pathways and downregulation of enzymes involved in anabolic pathways. AMPK inhibits acetyl-CoA carboxylase and suppresses fatty acid synthesis. On the other hand, it directly inhibits the HMG-CoA reductase, a key regulator of hepatic cholesterol synthesis (26). EGCG activates AMPK and stimulates fatty acid oxidation in 3T3-L1 cells (27). Experimental studies with animals confirmed the weight-reducing and antidyslipidemic effects of EGCG. In high-fat diet (HFD) models of obesity and in knock-out leptin deficient (ob/ob) mice, the administration of EGCG reduced the overall body fat tissue and body weight, the cholesterol and TG levels, the accumulation of TG in the liver and decreased the insulin resistance (28-30) Additionally, catechins were found to inhibit the intestinal absorption of lipids (26).

A cross-sectional study among 1210 adults who consumed green tea at least once a week resulted in a significant reduction in the overall body fat and in the waist-to-hip ratio (WHR) compared to non-habitual drinkers (31). Another study with a duration of 14 years showed that the continuous consumption of catechins decreased the BMI (32).

Anthocyanins. Anthocyanins are water-soluble molecules found in various types of fruits (berry fruits, chokeberry, grape, black currant, cherry, plum) and vegetables (red cabbage, red onion, and sweet potato) (33). The beneficial activities of anthocyanins can significantly be affected by various food processing technologies such as pasteurization, concentration and drying (34-35). The anthocyanin cyanidin (CND) and its derivatives, such as cyanidin 3-glucoside (C3G), are the most common anthocyanins in nature, giving a dark blue color to a number of fruits and vegetables (36). In rats with experimentally-induced MetS, CND reduced the clinical features of MetS—such as body weight and serum TG levels (37). These effects could be attributed to the activation of lipoprotein lipase in blood plasma and skeletal muscle and the inhibition of the same enzyme in

adipose tissue (38). *Scazzocchio et al.* found that C3G exerted insulin-like effects (increased GLUT-4 translocation and improved skeletal muscle uptake) by activating peroxisome proliferator-activated receptor-gamma (PPAR-γ). Adiponectin levels also increased. This contributed to improvement in insulin sensitivity (39). Consumption of blueberries, containing the anthocyanins peonidin, petunidin or malvidin, improved metabolic parameters in a genetic model of obesity (C57BL/6). These anthocyanins are supposed to disrupt the mitochondrial proton gradient and mitochondrial respiration in adipose tissue, thereby increasing energy expenditure and reducing the weight (40).

Resveratrol. Resveratrol is a stilbene-type of PP. Rich in resveratrol are red grapes, red wine, and nuts. Its powerful antioxidant and anti-inflammatory effects have been suggested to be useful in the prevention and treatment of MetS (41). In the 3T3-L1 cell line, resveratrol suppressed the activity of fatty acid synthase, lipoprotein lipase, decreased TG accumulation, and activated AMPK, thus inhibited lipogenesis. It also decreased the expression of nuclear factor-kappa B (NF-κB) and the levels of the proinflammatory interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (42-44). In animals with diet-induced models of obesity, resveratrol resulted in fat and weight reduction, decreased fat accumulation in the liver, decreased blood lipid levels, and improved glycemic control (45-46). However, such favorable changes were not achieved in some of the experiments. This is attributed to the duration of the studies and the dose of resveratrol taken (47-48.).

A few randomized, placebo-controlled clinical trials with resveratrol supplementation were conducted in order to estimate the effect of this PP on body weight. *Tome-Carneiro et al.* studied the role of resveratrol in three large studies and concluded that chronic daily consumption of resveratrol improved lipid status, modulated the inflammatory response, and stimulated fibrinolysis (49-50). However, these effects might have also been due to other beneficial ingredients in the grapes, used in these studies as a resveratrol source. Another randomized study found beneficial effects of 30-day consumption of resveratrol on metabolism in obese men (decrease of blood glucose level, fasting insulin, HOMA-IR, TG, and fatty acids) (51).

Curcuminoids. Curcumin is the most important PP in *Curcuma longa* (turmeric), consumed as a spice in India and other countries. A number of preclinical and clinical studies have suggested that curcumin and other curcuminoids might be beneficial in metabolic disturbances associated with MetS.

In 3T3-L1 cell cultures, curcumin treatment suppressed the differentiation of preadipocytes to adipocytes and decreased the expression of PPAR-γ (52). In the same cells, curcumin decreased inflammatory responses by inhibiting the release of monocyte-chemoattractant protein-1 (MCP-1) (53). In preclinical studies, curcumin use showed beneficial effects on the body weight. In one experiment, two-week pretreatment with curcumin and related compounds (curcuminoids) reduced the fat accumulation in epididymal adipose tissue and suppressed lipid accumulation in the liver, probably due to stimulated β-oxidation of free fatty acids. Other studies have revealed that curcumin administration in HFD-induced obesity and ob/ob obese mice suppressed inflammation, increased adiponectin release and improved insulin resistance (54-55).

Despite the numerous animal studies demonstrating the anti-obesity effects of curcuminoids, the number of clinical studies is limited. *Mohammadi et al.* were the first to investigate their effects in obese subjects. In these patients, the BMI and TG levels were significantly reduced (56). Later, other authors confirmed the weight-reducing potential of these compounds and supposed that acting as anti-inflammatory agents they improve insulin resistance (57-58). A meta-analysis from 2019 showed that curcumin intake effectively reduced body weight, BMI, waist circumference, leptin levels, and increased adiponectin levels (59). It is worth mentioning that chronic curcumin consumption might lead to hepatotoxicity, skin allergic eruptions or gastrointestinal distress (60). Although the Mediterranean diet (abundant in PPs) is associated with weight loss, most trials found no effect of PPs on body weight and lipid profile in subjects with MetS. (61-66).

The mechanisms of anti-obesity and antihyperlipidemic effects of polyphenols are summarized in Table 2.

Table 2. Mechanisms of the anti-obesity and lipid-lowering effects of polyphenols

Affected Process	Mechanisms	Reference
Food intake (**suppressed**)	Increased release of cholecystokinin	(67)
Calorie loss/Energy expenditure (**increased**)	Inhibition of pancreatic lipase and lipid absorption in the small intestine; upregulation of UCPs	(68-69)
Lipogenesis (**inhibited**)	AMPK-activation	(70)
Lipolysis (**inhibited**)	Increased expression of AMPK, HSL, CPT-1, UCP-1/2, SIRT1	(24, 69-71)
Fatty acid β-oxidation (**stimulated**)	Upregulation of HSL, CPT-1, UCP-1/2, adiponectin; decrease in the level of malonyl-CoA (inhibitor of fatty acid β-oxidation)	(69, 71-73)
Adipocyte differentiation and growth (**inhibited**)	Downregulation of PPAR-γ, C/EBPα; adipocyte cell cycle arrest	(24)
Intestinal cholesterol absorption (**inhibited**)	Inhibition of intestinal cholesterol influx transporter (NPC1L1)	(74)
Cholesterol synthesis (**inhibited**)	Inhibition of HMG-CoA reductase and SREBP1c	(24)
Cholesterol and bile acid fecal excretion (**stimulated**)	Decreased micellar solubility of cholesterol	(75)
Reverse cholesterol transport—from peripheral tissues to liver (**stimulated**)	Upregulation of SR-BI, ABCA1, ABCG1 and ApoA1	(24, 76-77)

***Legend**: ABCA1—ATP-binding cassette transporter subfamily A member 1; ABCG1—ATP-binding cassette transporter subfamily G member 1; AMPK—adenosine monophosphate kinase; ApoA1—apolipoprotein A1; C/EBPα—CCAT (cytosine-cytosine-adenosine-adenosine-thymidine)-enhancer-binding protein-alpha; CPT-1—carnitine palmitoyltransferase 1; HSL—hormone-sensitive lipase; NPC1L1—Niemann-Pick C1-Like 1 protein; PPAR-γ—peroxisome proliferator activated receptor-gamma; SIRT1—sirtuin 1; SR-BI—scavenger receptor class B type I (HDL receptor); SREBP1c—sterol regulatory element-binding protein-1; UCP—uncoupling protein.*

Polyphenols and Insulin Resistance/ Hyperglycemia

In states of insulin resistance, insulin is not able to lower the blood glucose level. This occurs due to the inability of the hormone: (1) to transport glucose from the systemic circulation into insulin-dependent tissues through GLUT-4-mediated glucose transport; (2) to induce glycogen synthesis; (3) to suppress glycogen breakdown; (4) to inhibit gluconeogenesis; (5) to activate lipogenesis; (6) to suppress lipolysis. Studies have demonstrated that PPs can improve IR and glycemic control (78).

Meta-analyses and systematic reviews showed that foods rich in (-)-epicatechin and EGCG such as cocoa and green tea increased insulin sensitivity and decrease blood glucose levels. Insulin levels and IR (measured with Homeostatic Model Assessment-Insulin Resistance—HOMA-IR; ≥ 2.5 is considered a marker for IR) were significantly lower after regular consumption of dark chocolate rich in EGCG. Continuous regular daily consumption of green tea (15 to 60 days) was associated with improved insulin profile but such an effect was not observed after a short exposure (< 15 days). Another systemic review showed that anthocyanin intake significantly reduced both plasma insulin levels and HOMA-IR in adults. Researches also confirmed the role of phenolic acids in enhancement of insulin effects but again only in high doses. The data concerning the effects of stilbenes, quercetin and hesperidin on insulin sensitivity are also conflicting (78).

The PPs act by different mechanisms to improve insulin resistance and glucose homeostasis (78). First, they decrease carbohydrate degradation and absorption in the small intestine. There are numerous publications which demonstrate the α-amylase and α-glucosidase-inhibiting activities of different PPs. A few in vitro experiments have demonstrated their GLUT2 and SGLT2-inhibiting activities (79). Second, some PPs affect glucose transport.

Quercetin and green tea catechins stimulate GLUT-4-mediated glucose transport in insulin-dependent tissues. Furthermore, quercetin increases the expression of GLUT-4. Third, PPs are potential enhancers of insulin secretion and insulin-signaling pathways. For instance, vanillic acid stimulates PKA and suppresses K_{ATP} in pancreatic β-cells and promotes insulin release; phenolic acids, genistein, and anthocyanins promote postprandial glucagon-like peptide 1 (GLP-1) secretion; catechins inhibit dipeptidyl peptidase-4 (DPP-4, an enzyme responsible for the inactivation of GLP-1) and prolong the plasma half-life of GLP-1;quercetin increases the activity of insulin receptor substrate-1 (IRS-1) and enhances GLUT-4 expression (80-83). PPs such as cinnamic acid, catechin, and EGCG have additionally demonstrated gluconeogenesis-inhibiting effects (84-85). Other probable insulin-sensitizing mechanisms are the powerful antioxidant and anti-inflammatory effects of PPs.

A review from 2018 (86) summarizes that polyphenolic compounds inhibit NF-κB expression, suppress mitogen-activated protein kinase (MAPK), mammalian target of rapamycin complex-1 (mTORC1), JAK/STAT and phospholipase A2-mediated inflammatory pathways. They exert an antioxidant effect by stimulating the endogenous antioxidant enzymes and inhibiting reactive oxygen species production. All these effects improve insulin resistance and lower blood glucose level.

Polyphenols and Arterial Hypertension

High arterial blood pressure is considered an important risk factor in patients with MetS. There is a rising number of studies showing a correlation between PP intake and arterial blood pressure lowering. For example, a cross-sectional study among 2618 individuals conducted in Iran concluded that high PP consumption was inversely associated with systolic (SBP) and diastolic (DBP) blood pressure (87). Another study among 2573 patients with type 2 diabetes mellitus confirmed that high PP intake was associated with lower mean SBP and DBP compared to the individuals with lower PP intake (88). Meta-analyses showed that a significant blood pressure-lowering effect was observed with dietary consumption of isoflavones, anthocyanins, phenolic acids, and lignans. Such an effect was demonstrated also for soybeans, berries, pomegranate juice, coffee, tea, and seeds (sesame, flaxseeds) (89-95). In subjects with MetS, two-month dietary intake of chokeberry (*Aronia melanocarpa*) significantly decreased blood pressure (96). A similar result was achieved by cinnamon (97). Quercetin also had a beneficial effect on blood pressure (98).

Despite the numerous studies demonstrating the positive impact of PPs on blood pressure, the data are not conclusive and some studies have yielded conflicting results. For instance, a meta-analysis concluded that blueberry supplementation (anthocyanins, respectively) did not lower the arterial blood pressure (99). Another meta-analysis showed that soy isoflavones decreased SBP but not DBP and the effects were observed in hypertensive but not in normotensive individuals (100). In one trial, resveratrol supplementation did not improve blood pressure in individuals with MetS, it even caused slight increase in DBP (101). These contradictory results might be associated with the pharmaceutical formulations of the extracts (pills), or with the duration of the trials (acute or chronic), or both.

The mechanisms involved in the blood pressure-lowering effects of PPs are summarized in Table 3.

Table 3. Mechanism of antihypertensive effects of polyphenols

Class of Polyphenols	Mechanisms	Reference
Flavonoids	Inhibition of endothelial NADPH oxidase and increased release of NO; impairment of ACE/AT II-receptor activity	(102-103)
Isoflavones	Interaction with estrogen-response element and increased NO production	(104)
Anthocyanins	Regulation of NOS; inhibition of endothelial cell apoptosis	(102-103, 105)

***Legend**: ACE—angiotensin-converting enzyme; AT II—angiotensin II; NO—nitric oxide; NOS—nitric oxide synthase.*

CONCLUSION

Polyphenols are ubiquitously present in the nature. High intake of polyphenol-rich foods is inversely associated with the incidence of a number of clinical conditions (cardiovascular diseases, type 2 diabetes, obesity, non-alcoholic fatty liver disease, cancer) including metabolic syndrome. Literature data collected from scientific databases review the promising effects of polyphenols in improving the biochemical and clinical abnormalities associated with metabolic syndrome. However, larger, more precise, better controlled clinical trials are necessary to demonstrate their benefits in clinical practice.

REFERENCES

1. Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly) phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal. 2013;18(14):1818-92. doi: 10.1089/ars.2012.4581.
2. Silva RFM, Pogačnik L. Polyphenols from food and natural products: neuroprotection and safety. Antioxidants (Basel). 2020; 9(1):61. doi: 10.3390/antiox9010061.
3. Williamson G. The role of polyphenols in modern nutrition. Nutr Bull. 2017;42(3):226-35. doi: 10.1111/nbu.12278.
4. Liu K, Luo M, Wei S. The bioprotective effects of polyphenols on metabolic syndrome against oxidative stress: Evidences and perspectives. Oxid Med Cell Longev. 2019;2019:6713194. doi: 10.1155/2019/6713194.
5. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47. doi: 10.1017/jns.2016.41.
6. Cherniack EP. Polyphenols and aging. In: Malavolta M, Mocchegiani E, editors. Molecular basis of nutrition and aging: A volume in the molecular nutrition series. Academic Press; 2016. pp. 649-57.
7. Chan SG, Murphy PA, Ho SC, Kreiger N, Darlington G, So EK, et al. Isoflavonoid content of Hong Kong soy foods. J Agric Food Chem. 2009;57(12):5386-90. doi: 10.1021/jf803870k.
8. Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr. 2005;81(1 Suppl):317S-25S. doi: 10.1093/ajcn/81.1.317S.
9. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Metabolic syndrome and non-cardiac vascular diseases: an update from human studies. Curr Pharm Des. 2014;20(31):4944-52. doi: 10.2174/1381612819666131206100750.
10. Marott SC, Nordestgaard BG, Tybjærg-Hansen A, Benn M. Components of the metabolic syndrome and risk of type 2 diabetes. J Clin Endocrinol Metab. 2016;101(8):3212-21. doi: 10.1210/jc.2015-3777.
11. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119(10):812-9. doi: 10.1016/j.amjmed.2006.02.031.
12. Benedict M, Zhang X. Non-alcoholic fatty liver disease: an expanded review. World J Hepatol. 2017;9(16):715-32. doi: 10.4254/wjh.v9.i16.715.
13. Vgontzas AN, Bixler EO, Chrousos GP. Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev. 2005;9(3):211-24. doi: 10.1016/j.smrv.2005.01.006.
14. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270-84. doi: 10.1038/nrendo.2018.24.
15. Farooqui AA, Farooqui T, Panza F, Frisardi V. Metabolic syndrome as a risk factor for neurological disorders. Cell Mol Life Sci. 2012;69(5):741-62. doi: 10.1007/s00018-011-0840-1.
16. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012;35(11):2402-11. doi: 10.2337/dc12-0336.
17. Dommermuth R, Ewing K. Metabolic syndrome: systems thinking in heart disease. Prim Care. 2018;45(1):109-29. doi: 10.1016/j.pop.2017.10.003.
18. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. Nutr Today. 2015;50(3):117-28. doi: 10.1097/NT.0000000000000092.
19. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415-28. doi: 10.1016/S0140-6736(05)66378-7.
20. Sharma P. Inflammation and the metabolic syndrome. Indian J Clin Biochem. 2011;26(4):317-8. doi: 10.1007/s12291-011-0175-6.
21. Reddy P, Lent-Schochet D, Ramakrishnan N, McLaughlin M, Jialal I. Metabolic syndrome is an inflammatory disorder: a conspiracy between

adipose tissue and phagocytes. Clin Chim Acta. 2019;496:35-44. doi: 10.1016/j.cca.2019.06.019.

22. Aguilar-Salinas CA, Viveros-Ruiz T. Recent advances in managing/understanding the metabolic syndrome. F1000Res. 2019 3;8:F1000 Faculty Rev-370. doi: 10.12688/f1000research.17122.1.

23. Chen Z, Zhu QY, Tsang D, Huang Y. Degradation of green tea catechins in tea drinks. J Agricult Food Chem. 2001;49(1):477-82. doi: 10.1021/jf000877h.

24. Wang S, Moustaid-Moussa N, Chen L, Mo H, Shastri A, Su R, et al. Novel insights of dietary polyphenols and obesity. J Nutr Biochem. 2014; 25(1):1-18. doi: 10.1016/j.jnutbio.2013.09.001.

25. Meydani M, Hasan ST. Dietary polyphenols and obesity. Nutrients. 2010; 2(7):737-51. doi: 10.3390/nu2070737.

26. Ching Y, Davies S, Hardie D. Analysis of the specificity of the AMP-activated protein kinase by site-directed mutagenesis of bacterially expressed 3-hydroxy 3-methylglutaryl-CoA reductase, using a single primer variant of the unique-site-elimination method. Eur J Biochem. 1996;237(3):800-8. doi: 10.1111/j.1432-1033.1996.0800p.x.

27. Murase T, Misawa K, Haramizu S, Hase T. Catechin-induced activation of the LKB1/AMP-activated protein kinase pathway. Biochem Pharmacol. 2009;78(1):78-84. doi: 10.1016/j.bcp.2009.03.021.

28. Bruno R, Dugan C, Smyth J, DiNatale D, Koo S. Green tea extract protects leptin-deficient, spontaneously obese mice from hepatic steatosis and injury. J Nutr. 2008;138(2):323-31. doi: 10.1093/jn/138.2.323.

29. Axling U, Olsson C, Xu J, Fernandez C, Larsson S, Strom K, et al. Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. Nutr Metab. 2012;9(1):105. doi: 10.1186/1743-7075-9-105.

30. Bose M, Lambert JD, Ju J, Reuhl KR, Shapses SA, Yang CS. The major green tea polyphenol, (–)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. J Nutr. 2008;138(9):1677-83. doi: 10.1093/jn/138.9.1677.

31. Wu CH, Lu FH, Chang CS, Chang TC, Wang RH, Chang CJ. Relationship among habitual tea consumption, percent body fat, and body fat distribution. Obes Res. 2003;11(9):1088-95. doi: 10.1038/oby.2003.149.

32. Hughes L, Arts I, Ambergen T, Brants H, Dagnelie P, Goldbohm R, et al. Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands cohort study. Am J Clin Nutr. 2008;88(5):1341-52. doi: 10.3945/ajcn.2008.26058.

33. Wu X, Prior R. Systematic identification and characterization of anthocyanins by HPLC-ESI-MS / MS in common foods in the United States: fruits and berries. J Agric Food Chem. 2005;53(7):2589-99. doi: 10.1021/jf048068b.

34. Yousuf B, Gul K, Wani AA, Singh P. Health benefits of anthocyanins and their encapsulation for potential use in food systems: a review. Crit Rev Food Sci Nutr. 2016;56 (13):2223-30. doi: 10.1080/10408398.2013.805316.

35. Azzini E, Giacometti J, Russo GL. Antiobesity effects of anthocyanins in preclinical and clinical studies. Oxid Med Cell Longev. 2017; 2017:2740364. doi: 10.1155/2017/2740364.

36. Fanning KJ, Topp B, Russell D, Stanley R, Netzel M. Japanese plums (Prunus salicina Lindl.) and phytochemicals - breeding, horticultural practice, postharvest storage, processing and bioactivity. J Sci Food Agric. 2014;94(11):2137-47. doi: 10.1002/jsfa.6591.

37. Bhaswant M, Fanning K, Netzel M, Mathai ML, Panchal SK, Brown L. Cyanidin 3- glucoside improves diet-induced metabolic syndrome in rats. Pharmacol Res. 2015;102:208-17. doi: 10.1016/j.phrs.2015.10.006.

38. Wei X, Wang D, Yang Y, Xia M, Li D, Li G, et al. Cyanidin-3-O-β-glucoside improves obesity and triglyceride metabolism in KK-Ay mice by regulating lipoprotein lipase activity. J Sci Food Agric. 2011;91(6):1006-13. doi: 10.1002/jsfa.4275.

39. Scazzocchio B, Varì R, Filesi C, D'Archivio M, Santangelo C, Giovannini C, et al. Cyanidin-3-O-β-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPARγ activity in human omental adipocytes. Diabetes. 2011;60(9):2234-44. doi: 10.2337/db10-1461.

40. Skates E, Overall J, DeZego K, Wilson M, Esposito D, Lila MA, et al. Berries containing anthocyanins enhanced methylation profiles are more effective at ameliorating high fat diet-induced metabolic damage. Food Chem Toxicol. 2018;111:445-53. doi: 10.1016/j.fct.2017.11.032.

41. van der Spuy WJ, Pretorius E. Is the use of resveratrol in the treatment and prevention of obesity premature? Nutr Res Rev. 2009;22(2):111-17. doi: 10.1017/S0954422409990084.

42. Rayalam S, Yang JY, Ambati S, Della-Fera MA, Baile CA. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. Phytother Res. 2008;22(10):1367-71. doi: 10.1002/ptr.2503.

43. Chen S, Li Z, Li W, Shan Z, Zhu W. Resveratrol inhibits cell differentiation in 3T3-L1 adipocytes via activation of AMPK. Can J Physiol Pharmacol. 2011;89(11):793-9. doi: 10.1139/y11-077.

44. Kang L, Heng W, Yuan A, Baolin L, Fang H. Resveratrol modulates adipokine expression and improves insulin sensitivity in adipocytes: relative to inhibition of inflammatory responses. Biochimie. 2010;92(7):789-96. doi: 10.1016/j.biochi.2010.02.024.

45. Alberdi G, Rodriguez VM, Miranda J, Macarulla MT, Arias N, Andres-Lacueva C, et al. Changes in white adipose tissue metabolism induced by resveratrol in rats. Nutr Metab. 2006;8(1):29. doi: 10.1186/1743-7075-8-29.

46. Kim S, Jin Y, Choi Y, Park T. Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice. Biochem Pharmacol. 2011;81(11):1343-51. doi: 10.1016/j.bcp.2011.03.012.

47. Kjær TN, Ornstrup MJ, Poulsen MM, Stødkilde-Jørgensen H, Jessen N, Jørgensen JOL, et al. No beneficial effects of resveratrol on the metabolic syndrome: a randomized placebo-controlled clinical trial. J Clin Endocrinol Metab. 2017;102(5):1642-51. doi: 10.1210/jc.2016-2160.

48. da Silva IV, Rodrigues JS, Rebelo I, Miranda JPG, Soveral G. Revisiting the metabolic syndrome: the emerging role of aquaglyceroporins. Cell Mol Life Sci. 2018;75(11):1973-88. doi: 10.1007/s00018-018-2781-4.

49. Tome-Carneiro J, Gonzalvez M, Larrosa M, Garcia-Almagro FJ, Aviles-Plaza F, Parra S, et al. Consumption of a grape extract supplement containing resveratrol decreases oxidized LDL and ApoB in patients undergoing primary prevention of cardiovascular disease: a triple-blind, 6-month follow-up, placebo-controlled, randomized trial. Mol Nutr Food Res. 2013;56(5):810-21. doi: 10.1002/mnfr.201100673.

50. Tome-Carneiro J, Gonzalvez M, Larrosa M, Yanez-Gascon MJ, Garcia-Almagro FJ, Ruiz-Ros JA, et al. Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: a triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease. Cardiovasc Drugs Ther. 2013;27(1):37-48. doi: 10.1007/s10557-012-6427-8.

51. Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 2011;14(5):612-22. doi: 10.1016/j.cmet.2011.10.002.

52. Kim C, Le T, Chen C, Cheng JX, Kim KH. Curcumin inhibits adipocyte differentiation through modulation of mitotic clonal expansion. J Nutr Biochem. 2011;22(10):910-20. doi: 10.1016/j.jnutbio.2010.08.003.

53. Woo HM, Kang J-H, Kawada T, Yoo H, Sung MK, Yu R. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes. Life Sci. 2007;80(10):926-31. doi: 10.1016/j.lfs.2006.11.030.

54. Weisberg S, Leibel R, Tortoriello D. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinol. 2008;149(7):3549-58. doi: 10.1210/en.2008-0262.

55. Shao W, Yu Z, Chiang Y, Yang Y, Chai T, Foltz W, et al. Curcumin prevents high fat diet induced insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway in adipocytes. PLoS One. 2012;7(1):e28784. doi: 10.1371/journal.pone.0028784.

56. Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M, et al. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytother Res. 2013;27(3):374-9. doi: 10.1002/ptr.4715.

57. Sahebkar A, Mohammadi A, Atabati A, Rahiman S, Tavallaie S, Iranshahi M, et al. Curcuminoids modulate pro-oxidant-antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. Phytother Res. 2013;27(12):1883-8. doi: 10.1002/ptr.4952.

58. Ganjali S, Sahebkar A. Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. Sci World J. 2014;2014:6. doi: 10.1155/2014/898361.

59. Akbari M, Lankarani KB, Tabrizi R, Ghayour-Mobarhan M, Peymani P, Ferns G, et al. The effects of curcumin on weight loss among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2019;10:649. doi: 10.3389/fphar.2019.00649.

60. Liddle M, Hull C, Liu C, Powell D. Contact urticaria from curcumin. Dermatitis. 2006;17(4):196-7. doi: 10.2310/6620.2006.06004.

61. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA. 2004;292(12):1440-6. doi: 10.1001/jama.292.12.1440.

62. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, et al. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J Nutr. 2010;140(9):1582-7. doi: 10.3945/jn.110.124701.

63. Kolehmainen M, Mykkänen O, Kirjavainen PV, Leppänen T, Moilanen E, Adriaens M, et al. Bilberries reduce low-grade inflammation in individuals with features of metabolic syndrome. Mol Nutr Food Res. 2012;56(10):1501-10. doi: 10.1002/mnfr.201200195.

64. Sivaprakasapillai B, Edirisinghe I, Randolph J, Steinberg F, Kappagoda T. Effect of grape seed extract on blood pressure in subjects with the metabolic syndrome. Metabolism. 2009;58(12):1743-6. doi: 10.1016/j.metabol.2009.05.030.

65. Barona J, Aristizabal JC, Blesso CN, Volek JS, Fernandez ML. Grape polyphenols reduce blood pressure and increase flow-mediated vasodilation in men with metabolic syndrome. J Nutr. 2012;142(9):1626-32. doi: 10.3945/jn.112.162743.

66. Basu A, Du M, Sanchez K, Leyva MJ, Betts NM, Blevins S, et al. Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. Nutrition. 2011;27(2):206-13. doi: 10.1016/j.nut.2010.01.015.

67. Al Shukor N, Ravallec R, Van Camp J, Raes K, Smagghe G. Flavonoids stimulate cholecystokinin peptide secretion from the enteroendocrine STC-1 cells. Fitoterapia. 2016;113:128-31. doi: 10.1016/j.fitote.2016.07.016.

68. Martinez-Gonzalez AI, Alvarez-Parrilla E, Díaz-Sánchez ÁG, de la Rosa LA, Núñez-Gastélum JA, Vazquez-Flores AA, et al. In vitro inhibition of pancreatic lipase by polyphenols: a kinetic, fluorescence spectroscopy and molecular docking study. Food Technol Biotechnol. 2017;55(4):519-30. doi: 10.17113/ftb.55.04.17.5138.

69. Stevens JF, Revel JS, Maier CS. Mitochondria-centric review of polyphenol bioactivity in cancer models. Antioxid Redox Signal. 2018;29(16):1589-1611. doi: 10.1089/ars.2017.7404.

70. 70. Zang M, Xu S, Maitland-Toolan KA, Zuccollo A, Hou X, Jiang B, et al. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. Diabetes. 2006;55(8):2180-91. doi: 10.2337/db05-1188.

71. Bustanji Y, Issa A, Mohammad M, Hudaib M, Tawah K, Alkhatib H, et al. Inhibition of hormone-sensitive lipase and pancreatic lipase by Rosmarinus officinalis extract and selected phenolic constituents. J Med Plants Res. 2010;4(21):2235–42. doi: 10.5897/JMPR10.399.

72. Tian C, Ye X, Zhang R, Long J, Ren W, Ding S, et al. Green tea polyphenols reduced fat deposits in high fat-fed rats via erk1/2-PPARγ-adiponectin pathway. PLoS One. 2013;8(1):e53796. doi: 10.1371/journal.pone.0053796.

73. Li BH, Ma XF, Wang Y, Tian WX. Structure-activity relationship of polyphenols that inhibit fatty acid synthase. J Biochem. 2005;138(6):679-85. doi: 10.1093/jb/mvi171.

74. Kobayashi S. The effect of polyphenols on hypercholesterolemia through inhibiting the transport and expression of Niemann-Pick C1-Like 1. Int J Mol Sci. 2019;20(19):4939. doi: 10.3390/ijms20194939.

75. Ogawa K, Hirose S, Nagaoka S, Yanase E. Interaction between tea polyphenols and bile acid inhibits micellar cholesterol solubility. J Agric Food Chem. 2016;64(1):204-9. doi: 10.1021/acs.jafc.5b05088.

76. Zhao W, Haller V, Ritsch A. The polyphenol PGG enhances expression of SR-BI and ABCA1 in J774 and THP-1 macrophages. Atherosclerosis. 2015;242(2):611-7. doi: 10.1016/j.atherosclerosis.2015.08.025.

77. Burke MF, Khera AV, Rader DJ. Polyphenols and cholesterol efflux: is coffee the next red wine? Circ Res. 2010;106(4):627-9. doi: 10.1161/CIRCRESAHA.109.215855.

78. Williamson G, Sheedy K. Effects of polyphenols on insulin resistance. Nutrients. 2020;12(10):3135. doi: 10.3390/nu12103135.

79. Johnston K, Sharp P, Clifford M, Morgan L. Dietary polyphenols decrease glucose uptake by human intestinal Caco-2 cells. FEBS Lett. 2005;579(7):1653-7. doi: 10.1016/j.febslet.2004.12.099.

80. González-Abuín N, Martínez-Micaelo N, Margalef M, Blay M, Arola-Arnal A, Muguerza B, et al. A grape seed extract increases active glucagon-like peptide-1 levels after an oral glucose load in rats. Food Funct. 2014;5(9):2357-64. doi: 10.1039/c4fo00447g.

81. Fujii Y, Osaki N, Hase T, Shimotoyodome A. Ingestion of coffee polyphenols increases postprandial release of the active glucagon-like peptide-1 (GLP-1(7-36)) amide in C57BL/6J mice. J Nutr Sci. 2015;4:e9. doi: 10.1017/jns.2014.71.

82. Rehman K, Ali MB, Akash MSH. Genistein enhances the secretion of glucagon-like peptide-1 (GLP-1) via downregulation of inflammatory responses. Biomed Pharmacother. 2019;112:108670. doi: 10.1016/j.biopha.2019.108670.

83. Ryan CM, Khoo W, Stewart AC, O'Keefe SF, Lambert JD, Neilson AP. Flavanol concentrations do not predict dipeptidyl peptidase-IV inhibitory activities of four cocoas with different processing histories. Food Funct. 2017;8(2):746-56. doi: 10.1039/c6fo01730d.

84. Cheng DM, Kuhn P, Poulev A, Rojo LE, Lila MA, Raskin I. In vivo and in vitro antidiabetic effects of aqueous cinnamon extract and cinnamon polyphenol-enhanced food matrix. Food Chem. 2012;135(4):2994-3002. doi: 10.1016/j.foodchem.2012.06.117.

85. Li X , Li S , Chen M , Wang J , Xie B , Sun Z. (-)-Epigallocatechin-3-gallate (EGCG) inhibits starch digestion and improves glucose homeostasis through direct or indirect activation of PXR/CAR-mediated phase II metabolism in diabetic mice. Food Funct. 2018;9(9):4651-63. doi: 10.1039/c8fo01293h.

86. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients. 2018;10(11):1618. doi: 10.3390/nu10111618.

87. Sohrab G, Hosseinpour-Niazi S, Hejazi J, Yuzbashian E, Mirmiran P, Azizi F. Dietary polyphenols and metabolic syndrome among Iranian adults. Int J Food Sci Nutr. 2013;64(6):661-7. doi: 10.3109/09637486.2013.787397.

88. Vitale M, Masulli M, Rivellese AA, Bonora E, Cappellini F, Nicolucci A, et al. Dietary intake and major food sources of polyphenols in people with type 2 diabetes: The TOSCA.IT Study. Eur J Nutr. 2018;57(2):679-88. doi: 10.1007/s00394-016-1355-1.

89. Kou T, Wang Q, Cai J, Song J, Du B, Zhao K, et al. Effect of soybean protein on blood pressure in postmenopausal women: a meta-analysis of randomized controlled trials. Food Funct. 2017;8(8):2663-71. doi: 10.1039/c6fo01845a.

90. Huang H, Chen G, Liao D, Zhu Y, Xue X. Effects of berries consumption on cardiovascular risk factors: a meta-analysis with trial sequential analysis of randomized controlled trials. Sci Rep. 2016;6:23625. doi: 10.1038/srep23625.

91. Sahebkar A, Ferri C, Giorgini P, Bo S, Nachtigal P, Grassi D. Effects of pomegranate juice on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2017;115:149-61. doi: 10.1016/j.phrs.2016.11.018.

92. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, Bes-Rastrollo M, et al. Long-term coffee consumption is associated with decreased incidence of new-onset hypertension: a dose-response meta-analysis. Nutrients. 2017;9(8):890. doi: 10.3390/nu9080890.

93. Liu G, Mi XN, Zheng XX, Xu YL, Lu J, Huang XH. Effects of tea intake on blood pressure: a meta-analysis of randomised controlled trials. Br J Nutr. 2014;112(7):1043-54. doi: 10.1017/S0007114514001731.

94. Khosravi-Boroujeni H, Nikbakht E, Natanelov E, Khalesi S. Can sesame consumption improve blood pressure? A systematic review and meta-analysis of controlled trials. J Sci Food Agric. 2017;97(10):3087-94. doi: 10.1002/jsfa.8361.

95. Ursoniu S, Sahebkar A, Andrica F, Serban C, Banach M, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Effects of flaxseed supplements on blood pressure: A systematic review and meta-analysis of controlled clinical trial. Clin Nutr. 2016;35(3):615-25. doi: 10.1016/j.clnu.2015.05.012.

96. Stull A, Cash K, Johnson W, Champagne C, Cefalu W. Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. J Nutr. 2010;140(10):1764-8. doi: 10.3945/jn.110.125336.

97. Ziegenfuss T, Hofheins J, Mendel R, Landis J, Anderson R. Effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome in pre-diabetic men and women. J Int Soc Sports Nutr. 2006;3(2):45-53. doi: 10.1186/1550-2783-3-2-45.

98. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr. 2009;102(7):1065-74. doi: 10.1017/S0007114509359127.

99. Zhu Y, Sun J, Lu W, Wang X, Wang X, Han Z, et al. Effects of blueberry supplementation on blood pressure: a systematic review and meta-analysis of randomized clinical trials. J Hum Hypertens. 2017;31(3):165-71. doi: 10.1038/jhh.2016.70.

100. Taku K, Lin N, Cai D, Hu J, Zhao X, Zhang Y, et al. Effects of soy isoflavone extract supplements on blood pressure in adult humans: systematic review and meta-analysis of ran-domized placebo-controlled trials. J Hypertens. 2010;28(10):1971-82. doi: 10.1097/HJH.0b013e32833c6edb.

101. van der Made SM, Plat J, Mensink RP. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: a randomized, placebo-controlled crossover trial. PLoS One. 2015;10(3):e0118393. doi: 10.1371/journal.pone.0118393.

102. Yousefian M, Shakour N, Hosseinzadeh H, Hayes AW, Hadizadeh F, Karimi G. The natural phenolic compounds as modulators of NADPH oxidases in hypertension. Phytomedicine. 2019;55:200-13. doi: 10.1016/j.phymed.2018.08.002.

103. Vendrame S, Klimis-Zacas D. Potential factors influencing the effects of anthocyanins on blood pressure regulation in humans: a review. Nutrients. 2019;11(6):1431. doi: 10.3390/nu11061431.

104. Pilšáková L, Riečanský I, Jagla F. The physiological actions of isoflavone phytoestrogens. Physiol Res. 2010;59(5):651-64. doi: 10.33549/physiolres.931902.

105. Martin S, Giannone G, Andriantsitohaina R, Martinez MC. Delphinidin, an active compound of red wine, inhibits endothelial cell apoptosis via nitric oxide pathway and regulation of calcium homeostasis. Br J Pharmacol. 2003;139(6):1095-102. doi: 10.1038/sj.bjp.0705347.