BENEFICIAL EFFECTS OF POLYPHENOLS IN METABOLIC SYNDROME—A REVIEW

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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

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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,
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Polyphenols (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), flavonoids (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-densi-
**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 lipolytic effects) in the body (25). Adenosine monophosphate (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). Scaccio 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-kB) and the levels of the proinflammatory interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (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.
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 glucoseogenesis-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.

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