

Potential role of phytochemicals in metabolic syndrome prevention and therapy

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Abstract: Metabolic syndrome (MetS) is a set of cardiovascular risk factors which severely increases the risk of type II diabetes, renal disease and cardiovascular disease. Over the last decades, the role of dietary bioactive substances in features of MetS has been extensively investigated. Due to their multiple properties, these plant-derived natural compounds have demonstrated to provide positive effects in obesity, diabetes, renal and in cardiovascular disease. Catechins of green tea and caffeine reduce body mass index and waist circumference. Catechins, anthocyanins and proanthocyanidins of cocoa reduce blood pressure and blood glucose. Curcumin and silymarin exert hepatoprotective effects. Monacolins of red yeast rice are effective cholesterol-lowering agents. However, inconsistent or conflicting results have been found in clinical trials when other promising compounds in vitro or in animal studies, such as policosanol, curcumin or silymarin, were used. Low oral bioavailability of substances, ineffective dosages, inadequate treatment duration and insufficient statistical approach may explain the lack of effectiveness observed in some human studies. Further clinical studies are needed to better understand the role of bioactive compounds in the prevention and management of MetS.

Keywords: metabolic syndrome, bioactive substances, nutrition, cardiovascular risk

Introduction

Metabolic syndrome (MetS) is defined as a cluster of metabolic disorders related to increased risk of cardiovascular disease, type 2 diabetes mellitus, renal disease and cognitive deficits.¹ The condition includes hypertension, high blood glucose, excess of abdominal fat, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C). In 1998, WHO firstly proposed a definition for MetS.² Over the last 20 years, other organizations have developed different definitions for this condition. In 2001, the National Cholesterol Education Program Adult Treatment Panel III included in the MetS criteria the fasting blood plasma glucose level.³ Subsequently, the International Diabetes Federation proposed a new definition of the MetS, listing ethnic group-specific thresholds for waist circumference to define central adiposity.⁴ The American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) established that MetS is diagnosed when three or more of the following criteria are present: waist circumference >102 cm in men, and >88 cm in women, blood pressure $\geq 130/\geq 85$ mmHg, triglyceride (TG) plasma level ≥ 150 mg/dL (1.7 mmol/L), HDL cholesterol <40 mg/dL (1.03 mmol/L) in men, and <50 mg/dL (1.29 mmol/L) in women, and fasting plasma glucose ≥ 100 mg/dL (5.6 mmol/L) or history of diabetes mellitus or taking antidiabetic medications (Table 1).⁵

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Table I Definitions of metabolic syndrome

WHO 1999	IGT or DM, and/or IR, together with two or more of the following criteria: <ul style="list-style-type: none"> • HDL-cholesterol <0.9 mmol/L (35 mg/dL) in men, <1.0 mmol/L (40 mg/dL) in women • Triglycerides >1.7 mmol/L (150 mg/dL) • Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI > 30 kg/m • Blood pressure >140/90 mmHg
NCEP ATP III 2001	Three or more of the following criteria: <ul style="list-style-type: none"> • Blood glucose greater than 5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose • HDL-cholesterol <1.0 mmol/L (40 mg/dL) in men, <1.3 mmol/L (50 mg/dL) in women or drug treatment for low HDL-C • Blood triglycerides >1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides • Waist >102 cm (men) or >88 cm (women) • Blood pressure >130/85 mmHg or drug treatment for hypertension
AHA/NHLBI 2004	Three or more of the following criteria: <ul style="list-style-type: none"> • Waist circumference >102 cm in men and >88 cm in women • Blood pressure \geq130/\geq85 mmHg or specific medication • Triglyceride plasma level \geq150 mg/dL (1.7 mmol/L) • HDL-cholesterol <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women • Fasting plasma glucose \geq100 mg/dL (5.6 mmol/L) or history of diabetes mellitus or taking antidiabetic medications
IDF 2005	<i>IDF definition are very similar to NCEP ATP III except in the waist parameter of 102 vs 94 cm in men and 88 vs 80 cm in women.</i>

Abbreviations: AHA/NHLBI, American Heart Association/National Heart, Lung, and Blood Institute; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; IGT impaired glucose tolerance; IR, insulin resistance; NCEP ATP III, Cholesterol Education Program Adult Treatment Panel III.

During the past several decades, the prevalence of metabolic syndrome has markedly increased worldwide. The global prevalence of this disorder is reported between 14% and 32%, which increases with aging in both sexes.^{6,7}

Insulin resistance (IR) plays a key role in the pathophysiology of the MetS and it is considered to be a causative factor also for non-alcoholic fatty liver disease (NAFLD), conditions often associated with MetS.⁸ IR leads to higher levels of serum insulin and glucose and favors the development of diabetes mellitus; moreover, hyperinsulinemia results in excessive renal sodium retention and elevations in blood pressure.⁹

It is not still clear what causes MetS, but it is known that a chronic, subclinical inflammation is associated with MetS. Liver, intestine and adipose tissue are the three major sites that have been involved in initiating of chronic inflammation in MetS.¹⁰ Adipose tissue excess induces a proinflammatory state due to hypertrophy of adipocytes.¹¹ Hypertrophic adipocytes secrete proinflammatory cytokines, such as tumor necrosis factor alpha (TNF α), IL-6, IL-8 and MCP-1. Proinflammatory cytokines cause serine phosphorylation of insulin receptor substrate-1 via nuclear factor κ B (NF κ B) and Jun N-terminal kinase signaling inducing IR.¹² Adipocyte hypertrophy causes hypoxia and thus can induce cell necrosis with the production of TNF α , IL-6, plasminogen activator inhibitor-1 (PAI-1),

and macrophage infiltration.¹³ In turn, TNF α enhances IR in adipose cells.

NAFLD is often found in patients with metabolic syndrome.¹⁴ Most patients with NAFLD remain asymptomatic but about the 20% progress to non-alcoholic steatohepatitis (NASH), a chronic hepatic inflammation.¹⁵ Both MetS and NAFLD are associated with alterations in the gut flora and its related biological pathways. Changes in intestinal inflammation, gut permeability, energy provision, anaerobic fermentation and IR have been described.¹² Substances derived from the gut microbiota such as lipopolysaccharides, peptidoglycan and bacterial DNA can reach the liver through the portal vein and activate the Kupffer cells, activating an inflammatory cascade that favors NASH and IR.¹⁶

The gut microbiota can affect IR via several mechanisms. For example, the stimulation of toll-like receptors by bacterial lipopolysaccharides induces the activation of serine kinases, leading to IR through serine phosphorylation of insulin receptor substrate-1.¹⁷

First-line treatment of MetS consists of lifestyle changes, including diet and physical activity. The Mediterranean diet and other dietary regimens rich in vegetable-derived products were shown to prevent MetS.^{18,19} The favorable effects of these diets are thought to be related to their content of bioactive substances,

monounsaturated and polyunsaturated fatty acids.²⁰ Although low-density lipoprotein cholesterol (LDL-C) does not explicitly belong to MetS, subjects with MetS have a high concentration of small dense LDL particles and a low LDL-C/HDL-C ratio,²¹ both powerful atherogenic risk factors. When lifestyle changes alone are unsuccessful, phytochemicals can contribute to improve lipid profile.

Bioactive compounds are plant secondary metabolites found in foods able to modulate metabolic processes. Research on phytochemicals suggests their possibility as therapeutic and preventive agents against diseases including inflammation, oxidative stress, dyslipidemia and IR. This review addresses current knowledge about the phytochemicals in the treatment of MetS components and in other alterations that often are associated with MetS, such as NAFLD and high cholesterol levels.

Bioactive compounds: classes and dietary sources

Polyphenols

Most bioactive natural substances are polyphenols. They are a large group of secondary metabolites of plants that are generally involved in defense mechanisms against ultraviolet radiation or pathogens. More than 8000 polyphenolic compounds have been identified in various plant species.

Polyphenols may be classified according to the number of phenol rings of their molecular structure and on the basis of functional groups linked to these rings in two main classes: flavonoids and non-flavonoids (phenolic acids, stilbenes and lignans).

Flavonoids have a common basic structure consisting of two aromatic rings (A and B) bound together by three carbon atoms that form an oxygenated heterocycle (ring C). These substances are widely present in the plants and they are responsible for the attractive colors of the flowers, fruits and leaves. Until now more than 4000 varieties of flavonoids have been identified. Flavonoids may be divided into 6 subclasses based on the type of heterocycle involved: flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (catechins and proanthocyanidins).²²

Phenolic acids are divided into two subclasses: derivatives of benzoic acid and derivatives of cinnamic acid. The hydroxybenzoic acid content of edible plants is low in most cases, except for certain red fruits, black radish and onions. Tea is a rich source of gallic acid. Hydroxybenzoic

acids are constituent of hydrolyzable tannins (gallotannins in mangoes and ellagitannins in red fruit including strawberries, raspberries and blackberries).²³

The most common hydroxycinnamic acids are p-coumaric, caffeic, ferulic and sinapic acids.²⁴ They are found in the free form almost exclusively in processed food. They are glycosylated derivatives or esters of quinic acid, shikimic acid and tartaric acid. Caffeic acid occurs in foods mainly as an ester with quinic acid called chlorogenic acid, a compound that is found in several types of fruit and in high amounts in coffee. Ferulic acid is the most abundant phenolic acid found in cereal grains, which are its main dietary source.

Stilbenes consist of two benzene rings connected by a two-carbon methylene bridge. The provision of stilbenes with the human diet is quite low. Most stilbenes in plants act as antifungal phytoalexins, compounds that are synthesized in response to infection or injury. Resveratrol (3,4',5-trihydroxystilbene), the stilbene most studied, is largely found in berries, grapes and in red wine as *cis* and *trans* isomeric forms, mostly glycosylated.²⁵

Lignans are formed of 2 phenylpropane units. Several lignans, such as secoisolariciresinol, are considered to be phytoestrogens. Oleaginous seeds (linseed) are the richest source of lignans while legumes, cereals, vegetables (garlic, asparagus, carrots) and fruit (pears, prunes) as minor sources.²⁶

Other bioactive compounds

Some terpenoids and sterols derived from terpenoid precursors have been used for the treatment of the MetS features.²⁷ Terpenoids consist of five-carbon isoprene units and so can also be called "isoprenoids". Molecules with multiples of 5 carbons and particularly with single carbon side chains belong to this group. The carotenoids are a large family of yellow to orange pigments built up from eight isoprene units (40 carbons). Beta-carotene is best-known as the pigment of the carrot and it is a precursor of vitamin A. Phytosterols, including phytostanols and their esters, are more complex terpenoids occurring in plant cell membranes and present in the highest amounts in vegetable oils, nuts and seeds. Sitosterol, campesterol and stigmasterol are the most frequent plant sterols in food and represent about in media 65%, 30% and 3% of dietary intake.²⁸

Monacolin K and other monacolins are natural statins produced by *Monascus purpureus* yeast and found in the red yeast rice (RYR) used in China and other Asian

countries for centuries as a traditional medicine. They are a class of molecules with a polyketide structure, able to inhibit hydroxymethyl glutaryl-coenzyme A reductase, the key enzyme in cholesterol biosynthesis.²⁹

Policosanol (PC) is a mixture of very long chain aliphatic alcohols (24–34 carbons) originally isolated from sugarcane (*Saccharum officinarum* L.). The major components of the policosanol mixture are octacosanol (60–70%, w/w), triacontanol (10–20%, w/w) and hexacosanol (4–10%, w/w). PC can also be extracted from a variety of other natural sources such as bee wax, rice bran and wheat germ.³⁰

Treatment of metabolic syndrome by bioactive compounds

Polyphenols

Several foods and beverages containing polyphenols have been found to be useful in the MetS features. Green tea, nuts, red wine, grape seeds, berries and dark chocolate, which contain both flavanol monomeric forms (catechins) and their oligomers (proanthocyanidins), are the main sources of these substances.³¹ Green tea, that is sourced from the fresh leaves of the *Camellia sinensis* L. plant, contains high levels of flavanols (catechins) and the alkaloid caffeine, both virtually able to produce metabolic effects.

Nagao et al³² reported a significant reduction of body weight, BMI, waist circumference and body fat mass in men treated for 12 weeks with a green tea extract (catechins 690 mg per day) compared with the control group (catechins 22 mg per day). As caffeine has been found to influence the energy balance by increasing energy expenditure and decreasing energy intake,³³ the authors adjusted caffeine intake in both groups and ascribed the effects to catechin intake.

Basu et al³⁴ treated 35 MetS subjects randomly assigned to three groups: control, green tea beverage and green tea extract. After 8 weeks, body weight and BMI decreased significantly both in green tea beverage group (-2.5 ± 0.7 kg and -0.9 ± 0.3 kg/m² respectively) and in green tea extract group (-1.9 ± 0.6 kg and -0.7 ± 0.2 kg/m² respectively) compared to controls, without changes in body fat and waist circumference. Suliburska and coworkers³⁵ observed that the 12 weeks of supplementation with 378 mg of green tea containing 208 mg of epigallocatechin gallate (EGCG) per day significantly decreased BMI and waist circumference in obese patients.

The effects of the tea on body weight depend mainly on the effect of caffeine and catechins on the adrenergic

system. Caffeine (1,3,7 trimethylxantine) is a purine alkaloid inhibiting the phosphodiesterase enzyme that hydrolyzes cyclic adenosine monophosphate (cAMP) to AMP.³⁶ cAMP signal is activated by beta-adrenergic stimulation, inducing some adrenergic effects including appetite reduction and increase of energy expenditure and lipolysis.³⁷ Moreover, caffeine enhances the expressions of the uncoupled proteins that increase thermogenesis through enabling phosphodiesterase inhibition and protein kinase A activating by cAMP.³⁶ The thermogenic effect of caffeine is prolonged 30–150 mins after caffeine consumption, according to the dose.³⁸ The catechins of green tea interfere also with catecholamine inactivation, inhibiting the catechol-O-methyl transferase enzyme (COMT) and inducing a adrenergic overstimulation.³⁹ Similar to the caffeine-induced inhibition of phosphodiesterase, the COMT inactivation increases the energy expenditure, fat oxidation and lipolysis.³⁶

On the other hand, the studies that evaluated the effects of different doses of the green tea catechins on the energy expenditure⁴⁰ and on body mass index (BMI) and waist circumference⁴¹ showed no significant effect. In a study evaluating the effects in thermogenesis of different EGCG doses (90, 200, 300, or 400 mg) administered mixed to 200 mg of caffeine. Compared to placebo without caffeine, the 24 hrs of energy expenditure in EGCG and caffeine groups raised by 8% and this increase was similar to all doses of EGCG in the mixtures.⁴²

Few studies evaluated the effects of green tea catechins free from caffeine on thermogenesis. Boschmann et al.⁴³ treated 6 obese subjects with EGCG 300 mg daily for 2 days without observing a significative change in the preprandial and postprandial energy expenditure.

The effect of green tea on energy expenditure seems to occur when the green tea catechin is administered combined with caffeine. In a study, 31 thin young males and 31 thin young females were given 94 mg EGCG and 100 mg caffeine-containing thermal drink, 3 times daily for 3 days. Following the consumption of thermal drink, a significant increase (4.6%) in 24 hrs of energy expenditure was found.⁴⁴

One of the most important limitations of the studies examining the effect of green tea catechins and caffeine components on the thermogenesis is considered the variability among individuals about the habitual consume of caffeine and/or catechins. To verify this hypothesis, 76 overweight and moderately obese subjects on weight maintenance after body weight loss were treated with a

green tea–caffeine mixture (270 mg EGCG +150 mg caffeine per day).⁴⁵ Thermogenesis was lower and body weight regain was higher in the subjects that regularly consume high amounts of caffeine (>300 mg/day).

The studies on the effects of green tea on the lipid profile have shown controversial effects. Green tea supplementation was shown to improve the lipid profile by reducing significantly LDL-cholesterol in some trials^{34,35,46,47} and/or TGs.^{35,46,48} On the other hand, other studies did not find improvement in lipid profile using green tea.^{32,49,50} Green tea also reduces oxidative stress and cardiac remodeling in dialysis patients⁴⁶ and counteracts inflammation in the nervous system.⁵²

Anthocyanins are water-soluble bioactive compounds widely found in various vegetables and fruits, including grapes, plums, cherries, cranberries, strawberries, blueberries, blackberries, elderberries, currants, beetroot, red cabbage and red onions. These substances have antioxidant property due to their ability to transfer electrons or to donate the hydrogen atoms from various hydroxyl groups to free radicals.⁵³ Animal studies showed that anthocyanins are mainly absorbed in the intact glycosidic form and they are found in the systemic circulation within 0.25–2 hrs. Their plasma concentration declines rapidly within 2 hrs upon a single oral administration in rats.⁵⁴

Blueberries (*Vaccinium myrtillus* L.) are fruits rich in anthocyanidins, chlorogenic acid, flavonoids and stilbenes, such as pterostilbene and resveratrol. Studies on blueberries showed several preventive and therapeutic properties, including the reduction of oxidative stress and inflammatory responses,⁵⁵ protecting against cardiovascular disorders, hypertension⁵⁶ and diabetes.⁵⁷

Blueberry-enriched diet evidenced a protective effect on the MetS-related pro-inflammatory status in the obese Zucker rat increasing adiponectin expression and suppressing liver expression of NF- κ B.⁵⁸ An in vivo study showed that blueberry reduced TGs, body weight gain, liver weight, abdominal fat mass, and improved adipose and skeletal muscle peroxisome proliferator activated receptor activities involved in glucose uptake and in glucose and fat oxidation in obese rats.⁵⁹ A meta-analysis of 32 clinical studies evidenced that anthocyanidin-rich foods ameliorate glycemic control and exert favorable effects on low-density plasma cholesterol (LDL-C) level.⁶⁰ In a randomized controlled study, 48 patients with MetS were supplemented with freeze-dried and fresh strawberries for 8 weeks daily decreased total cholesterol, LDL-C, small low-density lipoprotein particles and circulating levels of vascular cell

adhesion molecule respect to controls.⁶¹ Castro-Acosta et al⁶² in a randomized, controlled, double-blinded cross-over trial showed that apple and blackcurrant polyphenols decreased postprandial glucose, insulin and C-peptide excursion and probably due to inhibition of intestinal glucose transport. An anthocyanin-rich beverage (açai berries beverage) was administered to 37 subjects with MetS for 12 weeks.⁶³ The plasma levels of interferon gamma (IFN- γ) and urinary level of 8-isoprostane were decreased. However, all parameters related to the glucose and lipid metabolisms were found to be unchanged after intake of the beverage.

Pomegranate (*Punica granatum* Linn) is a fruit cultivated since ancient times throughout the Mediterranean region. Pomegranate is rich in polyphenols such as ellagitannins and anthocyanin and therefore it has been proposed in the prevention and treatment of MetS. In vivo studies evidenced that pomegranate reduces blood glucose, increases insulin sensitivity, inhibits α -glucosidase and enhances the glucose transporter type 4 activity.⁶⁴ Moreover, pomegranate exerts anti-inflammatory effects, acting through the modulation of peroxisome proliferator-activated receptor pathways⁶⁴ and a recent trial evidenced that this fruit reduces blood pressure in subjects with MetS.⁶⁵ Cocoa is a rich source of polyphenols such as catechins, anthocyanins and proanthocyanidins. Epidemiological data and short-term human intervention studies evidenced that the cocoa polyphenols exert cardiovascular benefits of in humans.⁶⁶ Vasodilation is the main vascular effect observed as a consequence of nitric oxide (NO) release following acute cocoa ingestion.⁶⁷ Dark chocolate was more effective than white chocolate in lowering the flow-mediated dilation and the blood pressure.⁶⁸ Cocoa polyphenols exert antioxidant and anti-inflammatory effects acting on some important signaling pathways such as toll-like receptor 4/NF κ B signal transduction and activation of transcription.⁶⁹ Cocoa polyphenols induce release of NO through the activation of endothelial NO synthase which, in turn, accounts for vasodilation and cardioprotective effects. In healthy individuals, the consumption of 45 g of flavonoid-rich dark chocolate increased coronary flow velocity reserve respect to flavonoid-free white chocolate.⁷⁰ Cocoa can reduce blood pressure through several mechanisms. Increase in NO may explain the anti-hypertensive effects of cocoa.⁷¹ Moreover, flavanols and flavonol are able to inhibit angiotensin-converting enzyme activity in vitro.⁷²

Many studies found that cocoa, provided as chocolate bar or beverage, exerts favorable effects on glucose control. Cocoa and its flavonols improved insulin sensitivity

and reduced blood glucose, insulin, and HbA1c in normoglycemic and prediabetic subjects and in patients with type 2 diabetes mellitus within 2–4 weeks.^{72,73} Despite these data, studies on long-term effects of cocoa are lacking. Interestingly, when epicatechin were utilized alone, no significant glycemic improvement was observed,^{74–76} meaning that synergistic combination of the bioactive compounds of cocoa is necessary to achieve the clinical effects.⁷⁷ Studies in vitro and in animal models showed that polyphenols can induce an improvement of MetS features through several mechanisms including inhibition of digestive enzymes and intestinal glucose transporters,⁷⁸ stimulation of incretin response, improvement of insulin signaling and modulation of gut microbiota.⁷⁹

Curcumin is a polyphenol with several biologic activities derived from rhizomes of turmeric (*Curcuma longa* L.). In turmeric, there are two other analogs along with curcumin, called curcuminoids: demethoxycurcumin and bisdemethoxycurcumin.⁸⁰ Curcumin and curcuminoids have low oral bioavailability due to limited intestinal absorption and rapid metabolism.⁸¹

Clinical studies have shown that this polyphenol exerts anti-inflammatory, anticancer, hypoglycemic, antioxidant, antiviral and antimicrobial activities, indicating that curcumin is a therapeutic potential against a wide range of human diseases.⁸² Curcumin has been also shown to directly interact with numerous cell signaling molecules involved in inflammation, cancer and other diseases.⁸³ Moreover, curcumin modulates the activity of several transcription factors, growth factors, inflammatory cytokines, protein kinase and other enzymes.⁸⁴ Several clinical studies have investigated the use of curcumin in the components of MetS. Yang et al⁸⁵ in a randomized double-blind controlled trial evaluated the effect of 1950 mg daily of curcumin extract (95% curcuminoids) on weight, glucose and lipid profile in patients with MetS. After 12 weeks of treatment, the levels of HDL-C were significantly increased, while the levels of LDL-C were decreased. In a previous randomized double-blind controlled study, the supplementation with curcumin did not show any significant improvement on total cholesterol, LDL-C, HDL-C and TGs in 75 acute coronary syndrome patients.⁸⁶

In a systematic review and meta-analysis, Melo et al⁸⁷ evidenced that the supplementation of curcuminoids and/or curcumin decreased the concentrations of HbA1c without affecting homeostatic model assessment of insulin resistance (HOMA-IR). The administration of isolated

curcumin or combined curcuminoids was both effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia (pre-diabetes, diabetes or metabolic syndrome), but not in non-diabetic or euglycemic individuals. Unlike curcumin and curcuminoids, in this meta-analysis, the use of turmeric extracts was not effective.

In order to improve curcumin bioavailability, the substance was administered combined with piperine or as phytosomes. Piperine could improve curcumin bioavailability reducing liver conjugation and consequently its elimination by urine.⁸⁸ Phytosomes are complexes of bioactive natural compounds and phospholipids. The amphipathic nature of phospholipids improves the bioavailability and protects the bioactive substances from degradation in the digestive tract.⁸⁹ Panahi et al⁹⁰ treated with curcumin (1000 mg/day) plus piperine (10 mg/day) 50 diabetic patients for a period of 3 months, evidencing a significant reduction in serum levels of glucose, HbA1c, C-peptide and transaminases compared with the placebo group. Recently, Cicero et al⁹¹ treated with 200 mg of phytosomal curcumin and 8 mg of piperine per day 80 overweight subjects. HOMA-IR, waist circumference, blood pressure, TG, HDL-C, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase and serum cortisol significantly improved compared to the baseline.

Olive oil is considered as a functional food that, in addition to high level of oleic acid, contains minor components biologically active, such as vitamins and polyphenols. The phenol content in olive oil varies between oils. In refined oils, phenolic substances may be present at concentrations of approximately 62±12 mg/kg, whereas in high-quality extra-virgin olive oils, the concentration may be much higher.⁹² Olive oil contains over 230 chemical compounds, including tocopherols, fatty alcohols, triterpenic alcohols, squalene, plant sterols and polyphenols such as oleuropein and its metabolites hydroxytyrosol and tyrosol.⁹³ Polyphenols, in particular hydroxytyrosol and tyrosol, have been evidenced anti-inflammatory effects and may also influence cell proliferation and apoptosis in cancer cell.⁹⁴

In the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet (PREDIMED) study, extra-virgin olive oil improved blood pressure, glycaemic control, endothelial function, and oxidative stress, decreased triglycerides, total and LDL-C, increased HDL-C and reduced inflammatory markers such as C-reactive protein and

IL-6.⁹⁵ In the large multi-center clinical trial EUROLIVE study (Effect of Olive Oil Consumption in European Populations), the consumption of olive oil with different phenolic concentrations increased HDL-C, decreased total cholesterol and oxidative stress markers and decreased TG plasma levels in a dose-dependent manner.⁹⁶ A recent

meta-analysis of 30 intervention studies demonstrated that the impact of olive oil on glucose, TGs, and LDL-C is mediated through an adherence to the Mediterranean diet, with the only effect of olive oil polyphenols being the increase of HDL-cholesterol and the improvement of the antioxidant and inflammatory status of the subject.⁹⁷

Some flavonoids and phenolic acids contained in elderflower extract, such as kaempferol, quercetin and their glucosides, can enhance the glucose and oleic uptake in human skeletal muscle cells and in hepatocytes in vitro.⁹⁸ If these pieces of evidence will be confirmed by clinical trials, elderflower extract could be usefully employed as ingredient of supplements or functional food against diabetes or glucose abnormalities in MetS.

Other bioactive compounds

Milk thistle

Milk thistle (*Silybum marianum* L.) is a plant that has been used for centuries as a herbal treatment in liver and biliary tract diseases.⁹⁹ Fruits and seeds of milk thistle contain the main active components of *S. marianum* that are a mixture of flavonolignans, called silymarin, containing silibinin A and B, isosilybin A and B, silychristin and silydianin. Silymarin has antioxidant and anti-inflammatory effects,¹⁰⁰ promotes hepatocyte regeneration and inhibits fibrogenesis and then it is considered to have hepatoprotective effects.¹⁰¹ Animal studies showed that *S. marianum* can be effective in the treatment of MetS characteristics, including high glucose and lipid plasma levels, high blood pressure and liver steatosis.¹⁰²

A meta-analysis of 6 randomized and controlled clinical trials evaluated the effects of silymarin in patients with hepatic diseases.¹⁰³ A statistically significant reduction of 0.26 IU/mL ($p=0.007$) of ALT and 0.53 IU/mL ($p=0.000$) of AST plasma level after using the silymarin was observed, though with no clinical relevance. In another meta-analysis of 8 randomized controlled trials involving 587 patients with NAFLD treated with silymarin was reported a reduction of the AST (6.5 U/mL, $p=0.02$) and ALT (-9.6 U/mL, $p=0.02$) levels more significantly than the control group.¹⁰⁴ Clinical trials evaluating the effects of milk thistle extracts showed no significant effects on

blood pressure.^{105,106} Clinical studies on the silymarin use in diabetic patients reported controversial data, so that further studies are needed for more investigation.¹⁰²

Policosanols

Dietary supplements containing PC extracted by sources other than sugarcane have been marketed in recent years as cholesterol-lowering agents. Their composition in long-chain aliphatic primary alcohols differs little among the different sources and octacosanol is the main aliphatic primary alcohol in all policosanols mixtures and it is thought to be the most active component.

The mechanism behind the PC-induced cholesterol lowering has not yet been fully elucidated yet. Studies on humans and rats show that PC decreases in vitro LDL oxidation.¹⁰⁷ Other studies examining the antioxidant activity of sugarcane PC failed to support previous positive findings, reporting no significant change of oxidation state in LDL from humans treated with sugarcane PC supplements.^{108,109} Early clinical studies have shown that oral administration of sugarcane PC within a range of 5–20 mg/day reduces plasma total cholesterol and LDL-C levels and increases HDL-C in healthy, hypercholesterolaemic and diabetic patients.^{110–112}

Reports comparing sugarcane PCs with statins showed the same efficacy in LDL-C lowering, whereas sugarcane PCs have a greater efficacy than statins in increasing HDL-C.^{113–115} Sugarcane PC-induced cholesterol reduction seems to be dose-dependent in a dose range of 5–20 mg/day.

Others have not been able to reproduce the same evidence regarding PC supplementation. Indeed, the effects of PC on plasma cholesterol levels have been questioned by the results of several randomized controlled trials performed in Europe and the US that failed to find any significant effect of PC on plasma cholesterol levels in different clinical conditions.^{116–119} The lack of cholesterol-lowering efficacy has been confirmed for both sugarcane PC and for PC extracted from other sources.^{120,121} In 2011, EFSA rejected a claim on the beneficial effects of sugarcane PC for the lack of evidence of a cause-effect relationship between their supplementation and plasma cholesterol reduction.¹²² Recently, two studies showed that the short-term treatment with cuban policosanols can reduce blood pressure both in spontaneously hypertensive rat¹²³ and in healthy men,¹²⁴ also improving lipid profile.

Phytosterols

Phytosterols are natural sterols that occur in the cells of all plants where they play an important role in stabilizing the biological membranes. A western-type diet contains about

60–500 mg of plant phytosterols.¹²⁵ Serum phytosterol levels in humans range from 7 to 41 $\mu\text{mol/L}$ (2.9–17.0 mg/L).¹²⁶ Only a negligible amount of phytosterols is absorbed in the healthy human gut. Phytosterols are absorbed under similar conditions needed for cholesterol absorption and compete for cholesterol in absorptive micelles resulting in reduced solubility of cholesterol.¹²⁷ The transfer of plant sterols from the mixed micelles into the enterocytes occurs by the same intestinal membrane transporter, the Niemann-Pick C1-Like 1 protein, and then they compete with cholesterol for entry into cells.¹²⁸

The low absorption of phytosterols compared to cholesterol is due to their expulsion from the enterocytes back in the gut lumen via the ATP-binding cassette transporters.¹²⁹

Dietary intake of phytosterols in humans can lower blood cholesterol by reducing intestinal absorption. In 1953, Pollack reported a mean reduction of 25% of total cholesterol in 26 healthy men consuming between 5 and 10 g/day of sitosterol for between 8 days and 8 months.¹³⁰ Afterward, many studies evaluated the effects of phytosterols on lipid metabolism disorder and atherogenesis in humans and in laboratory animals.

The use of phytosterols in supplements and in food fortification has been limited due to their low solubility. To increase the solubility of nonesterified phytosterols in foods, formulation of emulsions, microemulsions and suspension is currently utilized.¹³¹ Most of the studies on phytosterols have evidenced their LDL-C-lowering effects, while HDL-C levels do not seem to be influenced by these compounds.¹³² Phytosterols can affect TG plasma levels. In a review of 19 studies, dietary phytosterols reduced TGs by 0.8–28% compared to the baseline values, with a greater effect in the hypertriglyceridemic subjects.¹³³

A recent meta-analysis of 20 studies found no effect of phytosterols on high-sensitivity C-reactive protein levels, an inflammatory biomarker associated with atherosclerosis and coronary heart disease.¹³⁴ Similarly, phytosterols have not demonstrated benefit on endothelial function.¹³⁵

Few intervention studies on phytosterol food fortification or supplementation and cardiovascular mortality are present in literature. The studies that have investigated the association of blood concentrations of phytosterols and risk of cardiovascular diseases reported a direct correlation between phytosterol plasma level and increased cardiovascular risk in some cases^{136–138} and no association in others.¹³⁹ A meta-analysis of these studies did not show a significant association between serum concentration of

sitosterol or campesterol and cardiovascular risk.¹⁴⁰ Data from the European Prospective Investigation into Cancer and Nutrition-the Netherlands study, energy-adjusted dietary intake of naturally occurring phytosterols was not associated with risk of cardiovascular disease, coronary heart disease or myocardial infarction.¹⁴¹ However, it must be considered that this population consumed a low amount of phytosterols (mean intake of 296 mg/day) with a narrow range of intake (mean intake of 231 to 366 mg/day from lowest to highest quintile). A meta-analysis of 41 randomized controlled trials involving 3306 subjects reported that sterol and stanol consumption decreased plasma beta-carotene and other carotenoid concentrations but does not affect tocopherol, retinol and vitamin D plasma levels.¹⁴² Recently, Tao et al¹⁴³ reported that, despite a 50% reduction in plasma cholesterol, the accumulation of stigmasterol leads to cardiac injury and promote mortality in a rodent model of phytosterolemia (disease characterized by elevated levels of dietary plant sterols in the blood) suggesting a role of phytosterol as potential risk factor for cardiovascular disease when absorbed in large amount.

The main clinical studies on plant substances and MetS are summarized in Table 2. The effects of plant and phytochemicals on the different components of MetS and associated conditions are represented in Table 3.

Conclusion

Some natural bioactive compounds including polyphenols, silymarin and monacolins could have a beneficial effect on the main features of MetS such as obesity, dyslipidemia, IR, impaired glucose tolerance, liver steatosis and hypertension through different mechanisms.

Green tea catechins, caffeine, berries anthocyanins and cocoa polyphenols evidenced benefits in some characteristics of MetS. RYR monacolins are effective in the treatment of hypercholesterolemia. Curcumin has been shown to interfere with several pathogenetic mechanisms of MetS, but its effectiveness is reduced by poor bioavailability. Combination with piperine or phytosome formulations can improve curcumin absorption and then its effectiveness in metabolic alterations (Figure 1).

In some cases, randomized controlled trials do not confirm the promising effects reported in the previous animal or in vitro studies. Several factors can explain these discrepancies, including poor bioavailability of substances, use of low dosages, inadequate treatment duration and inappropriate statistical approach. Further

Table 2 Phytochemicals and metabolic syndrome: clinical trials

Aim	Treatment	Result	Reference
<i>Catechins</i>			
To evaluate the effect of catechins on body fat reduction	Oolong tea with green tea extract (690 mg catechins daily) or oolong tea containing (22 mg catechins daily) for 12 weeks	BW, BMI, waist circumference, body fat mass and subcutaneous fat area were significantly lower in the green tea extract group than in the control group	32
To compare the effects of supplementation of green tea on BW, blood glucose and lipid profile, and oxidative stress in obese subjects with MetS	Green tea (4 cups daily), or green tea extract (2 capsules and 4 cups water/d) for 8 weeks	Green tea beverage consumption or extract supplementation significantly decreased BW and BMI. Green tea beverage lowered lipid peroxidation versus controls	34
To evaluate the effects of green tea extract on the lipid profile, blood glucose and antioxidant status of obese patients	379 mg of green tea extract (EGCG 208 mg) daily for 3 months	Green tea extract supplementation induced the reduction of BMI, waist circumference, TC, LDL-C, TG, and increased the total antioxidant level	35
To investigate the effect of dietary supplementation with EGCG on IR, and associated metabolic risk factors in man	400 mg capsules of EGCG twice daily for 8 weeks	EGCG treatment had no effect on insulin sensitivity, IR, or glucose tolerance but reduced diastolic BP	41
To investigate the effect of a green tea–caffeine mixture on BW maintenance after BW loss in moderately obese subjects	Green tea–caffeine mixture (EGCG 270 mg + 150 mg caffeine per day) or placebo.	High caffeine intake was associated with BW loss. In habitual low caffeine consumers, the green tea–caffeine mixture improved BW maintenance, partly through thermogenesis and fat oxidation	45
<i>Anthocyanins</i>			
To evaluate the freeze-dried strawberry supplementation in improving BP, plasma glucose level, and dyslipidemia in obese subjects with MetS	4 cups of freeze-dried strawberry beverage (50 g freeze-dried strawberries approximately 3 cups fresh strawberries) daily for 8 weeks	Strawberry supplementation significantly decreased TC and LDL-C, small low-density lipoprotein particles, and circulating levels of vascular cell adhesion molecule. Serum glucose, TG, HDL-C, BP and waist circumference were not affected	56
To investigate the apple and blackcurrant polyphenol-rich drinks in reducing postprandial blood glucose, insulin, C-peptide and GIP concentration	2 polyphenol-rich drinks containing fruit extracts: either apple polyphenols 1200 mg or apple polyphenols 600 mg + blackcurrant anthocyanins 600 mg	Polyphenol-rich drinks significantly decreased postprandial blood glucose, insulin, C-peptide and GIP	61
To determine the modulation of lipid and glucose metabolism, oxidative stress and inflammation, by an açai beverage	25 mL twice per day of a placebo control or açai beverage (1139 mg/L gallic acid equivalents of total polyphenolics) for 12 weeks	Plasma level of interferon gamma and urinary level of 8-isoprostane, were significantly decreased after 12 weeks of açai consumption compared to the placebo control. No significant modification of biomarkers for lipid and glucose metabolism was observed	63

(Continued)

Table 2 (Continued).

Aim	Treatment	Result	Reference
<i>Proanthocyanidins</i>			
To evaluate the acute effects of solid dark chocolate and liquid cocoa intake on endothelial function and BP in overweight adults	In phase 1: solid dark chocolate bar (containing 22 g cocoa powder) or a cocoa-free placebo bar. In phase 2: sugar-free cocoa (containing 22 g cocoa powder), sugared cocoa (containing 22 g cocoa powder) or a placebo	Solid dark chocolate and liquid cocoa ingestion improved endothelial function (measured as flow-mediated dilatation). BP decreased after the ingestion of dark chocolate and sugar-free cocoa compared with placebo	68
To compare the effects of either dark or white chocolate bars on BP and glucose and insulin responses to an oral-glucose-tolerance test in healthy subjects	100 g dark chocolate bars, which contained approximately 500 mg polyphenols, or 90 g white chocolate bars for 15 days	HOMA-IR was significantly lower and QUICKI was significantly higher after dark than after white chocolate ingestion. Systolic BP was lower after dark than after white chocolate ingestion	74
To evaluate the effects of 3-month treatment with epicatechin-rich cocoa in oxidative stress.	18 g of natural cocoa powder (100 mg epicatechin) daily for 3 months	Treatment with with epicatechin-rich cocoa increased the glutathione levels and decreased the nitrotyrosilation and carbonylation of proteins	76
To examine the effects of chocolate on lipid profiles, weight and glycemic control in individuals with type 2 diabetes	45 g chocolate with or without a high polyphenol content for 8 weeks	HDL-C increased significantly with high polyphenol chocolate with a decrease in the TC:HDL-C ratio. No changes were seen in BW nor in glycemic control	77
<i>Curcumin</i>			
To evaluate the effect of a curcumin extract for 12 weeks on BW, blood glucose, and lipid profiles in patients with MetS	Turmeric extract capsule (630 mg of curcumin) thrice daily	HDL-C and TG significantly increased and the LDL-C significantly reduced after 12 weeks of treatment. BW and glucose homeostasis did not improve	85
To evaluated the effect of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in type 2 diabetes patients	Curcuminoids 500 mg/day co-administered with piperine (5 mg/day) or placebo for 3 months	Significant reduction in serum levels of blood glucose, HbA1c, C-peptide and transaminases in curcuminoids compared with the placebo group	90
To test the effect of phosphatidylserine- and piperine-containing curcumin phytosomes on metabolic parameters related to IR	Phytosomal curcumin (curcumin 200 mg, phosphatidylserine 120 mg, phosphatidylcholine 480 mg and piperine 8 mg) for 8 weeks	In the curcumin group fasting plasma insulin, HOMA-IR, BW, TG, HDL-C, liver transaminases, gamma-GT, index of liver steatosis and serum cortisol improved compared to the baseline. Fasting plasma insulin, TG, liver transaminases, fatty liver index and serum cortisol level also significantly improved compared with the placebo-treated group	91

Abbreviations: BMI, body mass index; BP, blood pressure; BW, body weight; EGCG, epigallocatechin gallate; GIP, gastrointestinal peptide; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Table 3 Effects of plant substances on the components of metabolic syndrome and associated conditions

Components	Plants/substances	Mechanisms	References
Abdominal obesity	Caffeine	Adrenergic stimulation	36,38
	Tea (catechins)	Adrenergic stimulation	33–35
Impaired glucose tolerance	Berries (anthocyanins, flavonoids, stilbenes)	Slowing carbohydrate digestion and absorption; stimulating insulin secretion via AMPK pathway; decreasing cell oxidative damage	62
	Pomegranate (ellagitannins, anthocyanins)	Inhibition of α -glucosidase; increasing glucose transporter type 4 activity ⁶⁴	64
	Cocoa	Slowing carbohydrate digestion and absorption; stimulation of incretin response; improvement of insulin signaling, modulation of gut microbiota.	73,74,78,79
	Curcuma (curcumin) Olive oil (polyphenols)	Improvement of IR via TNF α reduction Slowing carbohydrate digestion and absorption; improvement of IR via anti-inflammatory activity	87,96 95
Hypertriglyceridemia	Olive oil (MUFAs, polyphenols)	Increasing VLDL catabolism	95,96
Low levels of HDL-C	Curcuma (curcumin)? Olive oil (polyphenols)	-Improvement of HDL metabolism	85,86,91 95–97
High blood pressure	Cocoa (catechins, proanthocyanidins, flavonols) Pomegranate (ellagitannins, anthocyanins) Olive oil (polyphenols)	Activation of endothelial NO synthase; inhibition of angiotensin-converting enzyme	67–72 95
		Reduction of serum angiotensin-converting enzyme (ACE) activity	
		Increasing NO levels	
		Increasing NO levels	
<i>Associated conditions</i>			
Fatty liver	Curcuma (curcumin) Milk thistle	Antioxidant and antiinflammatory effects; inhibition of fibrogenesis	90,91 104
Chronic inflammation	Tea, catechins	Modulation signaling of inflammatory response pathways, antioxidant activity	51,52
	Berries (anthocyanins, flavonols, stilbenes)	NF-kB suppression	63
	Pomegranate (ellagitannins, anthocyanins)	Modulating peroxisome proliferator-activated receptor pathways	64
		Modulation of toll-like receptor pathway	69
		Reduction of TNF α ; inhibition of COX and LOS	97
	Cocoa (catechins, proanthocyanidins, flavonols) Curcuma (curcumin) Olive oil (polyphenols)	Inhibition of COX; reduction of inflammatory gene expression	
LDL-C/small LDL	Tea, catechins	Reduction of lipid intestinal absorption, upregulation of LDL receptors;	34,35,46–48
	Berries (anthocyanins, flavonoids, stilbenes)	protection of lipid from oxidative damage	60,61,63
		Inhibition of cholesterol synthesis via activation of AMPK	130,132–
	Phytosterols	Inhibition of intestinal cholesterol absorption	135

Abbreviations: AMPK, 5' adenosine monophosphate kinase; COX, cyclooxygenase; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance; LOS, lipooxygenase; MUFAs, monounsaturated fatty acids; NAFLD, nonalcoholic fatty liver disease; NF-kB, nuclear factor kB; NO, nitric oxide; TNF α , tumor necrosis factor alpha; VLDL, very low-density lipoprotein.

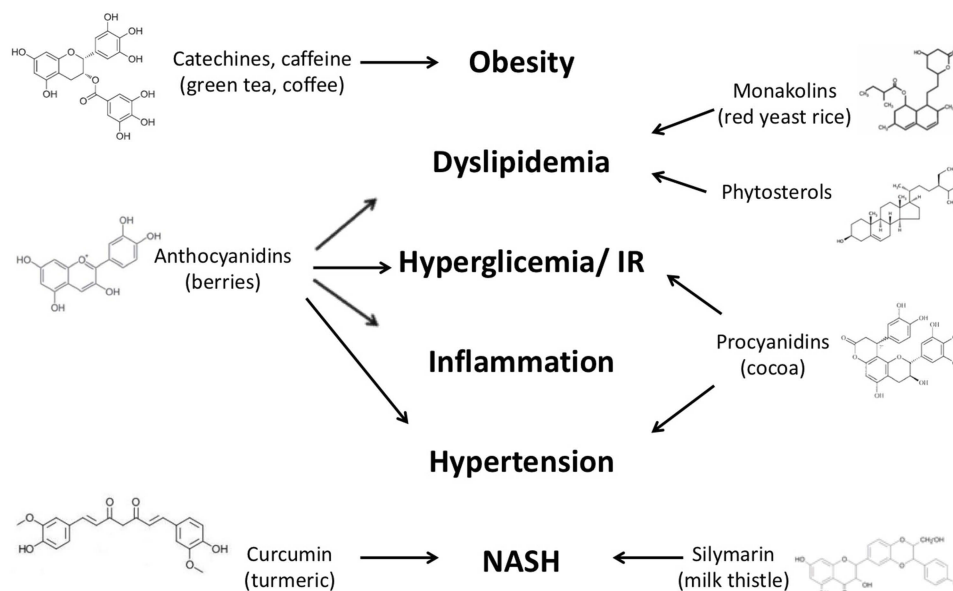


Figure 1 Effect of natural bioactive compounds on the main features of MetS.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; cAMP, cyclic adenosine monophosphate; COMT, catechol-O-methyl transferase enzyme; EGCG, epigallocatechin gallate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistance; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; NAFLD, non alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-kB, nuclear factor kB; PAI-1, plasminogen activator inhibitor-1; PC, policosanols; TG, triglycerides; TNF α , tumor necrosis factor alpha.

long-term randomized and well-designed trials are needed to better understand the role of bioactive compounds in the prevention and treatment of MetS, and alternatives in the supplement formulations are desirable to improve the bioavailability of these substances.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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