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## Obesity Comorbidity/Nutrition

# Effects of dietary polyphenols on metabolic syndrome features in humans: a systematic review

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## Summary

Dietary polyphenols constitute a large family of bioactive substances potential beneficial effect on metabolic syndrome (MetS). This review summarizes the results of clinical studies on patients with MetS involving the chronic supplementation of a polyphenol-rich diet, foods, extracts or with single phenolics on the features of MetS (obesity, dyslipidemia, blood pressure and glycaemia) and associated complications (oxidative stress and inflammation). Polyphenols were shown to be efficient, especially at higher doses, and there were no specific foods or extracts able to alleviate all the features of MetS. Green tea, however, significantly reduced body mass index and waist circumference and improved lipid metabolism. Cocoa supplementation reduced blood pressure and blood glucose. Soy isoflavones, citrus products, hesperidin and quercetin improved lipid metabolism, whereas cinnamon reduced blood glucose. In numerous clinical studies, antioxidative and anti-inflammatory effects were not significant after polyphenol supplementation in patients with MetS. However, some trials pointed towards an improvement of endothelial function in patients supplemented with cocoa, anthocyanin-rich berries, hesperidin or resveratrol. Therefore, diets rich in polyphenols, such as the Mediterranean diet, which promote the consumption of diverse polyphenol-rich products could be an effective nutritional strategy to improve the health of patients with MetS. © 2016 The Authors. Obesity Reviews published by John Wiley & Sons Ltd on behalf of World Obesity

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## Introduction

With abdominal obesity reaching epidemic proportions (1), there are increased risks of cardiovascular morbidity and mortality via complex interrelationships with unfavourable metabolic consequences. Metabolic syndrome (MetS) is a clustering of cardio-metabolic risk factors, including abdominal obesity, insulin resistance, dyslipidemia and hypertension and is a key phenotype leading to atherogenic and diabetogenic profiles (2,3). MetS depends on many parameters such as age, gender, ethnicity, socioeconomic status and the definition used to identify MetS. The rapidly growing

prevalence of MetS, and the increased cardiovascular risks it entails, is a major public health concern (4).

Global strategies initially approach the treatment of MetS by focussing on lifestyle changes, including diet and physical activity. This is followed by pharmacological intervention. Diets recommending increased fruit and vegetable consumption over a long-term period are very attractive and efficient in inducing health benefits (5,6). The Mediterranean diet, rich in plant-derived products, was shown to prevent MetS (7,8). Its beneficial effects are related to the high content of bioactive compounds, monounsaturated and polyunsaturated fatty acids and polyphenols (9).

Epidemiological studies associated an increased consumption of polyphenol-rich foods and beverages with a reduction of cardiovascular diseases (10–12). Among polyphenol-rich foods and beverages, tea received particular attention and meta-analysis enlightened that a higher intake of green or black tea is associated with a lower risk of stroke (13) and type 2 diabetes (14). There is large body of evidence attributing anti-obesity, anti-diabetic, anti-hypertensive, anti-hyperlipidemic and anti-inflammatory effects to polyphenols (15).

The present review summarizes the results of clinical studies on the chronic supplementation of polyphenol-rich diet, foods, extracts and molecules in features of MetS. Molecular and physiological mechanisms are discussed. As MetS is characterized by an altered oxidative/antioxidant status and by subclinical chronic inflammation, both of which are responsible for the development of atherosclerosis, we review the impact of polyphenol supplementation on these associated complications.

### Metabolic syndrome: definition and associated complications

As reviewed by Kassy et al. (16), a number of definitions of MetS have been published by different organizations. These include the World Health Organization, the National Cholesterol Education Program Adult Treatment Panel III, the International Diabetes Federation and the American Heart Association/National Heart, Lung, and the Blood Institute. The definition of MetS was standardized (17). A person has MetS when three or more of the following five cardiovascular risk factors have been diagnosed: (i) central obesity (waist circumference: men  $\geq 102$  cm; women  $\geq 88$  cm); (ii) elevated triglycerides ( $\geq 150$  mg dl<sup>-1</sup>); (iii) diminished high-density lipoprotein (HDL) cholesterol (men  $< 40$  mg dl<sup>-1</sup>; women  $< 50$  mg dl<sup>-1</sup>) (or treated for dyslipidemia); (iv) systemic hypertension ( $\geq 130/\geq 85$  mm Hg) (or treated for hypertension); and (v) elevated fasting glucose ( $\geq 100$  mg dl<sup>-1</sup>) (or treated for hyperglycaemia).

### Polyphenols: classes and dietary sources

Polyphenols are a large group of bioactive plant compounds displaying a wide variety of diverse structures which belong to two main classes: non-flavonoids (especially phenolic acids, stilbenes and lignans) and flavonoids which are characterized by the basic C6-C3-C6 skeleton (Table 1). The two aromatic rings within the flavonoid structure are linked by a heterocyclic ring, which differs in the degree of oxidation and leads to the following sub-classification: flavones, flavonols, isoflavones, flavanones, anthocyanins and flavanols, usually called catechins. In plant food products, the major forms are conjugated either with acid-alcohol or with glycosides. Moreover, polyphenols are also found as oligomers

and polymers, usually called tannins. These are divided into hydrolysable tannins (derived from gallic and ellagic acids) and condensed tannins (derived from catechin and usually called procyanidins). The diversity and the complexity of phenolic compounds leads to difficulties in their quantification, but the mean total polyphenol intake in the French diet was estimated at  $1193 \pm 510$  mg d<sup>-1</sup>, or  $820 \pm 335$  mg d<sup>-1</sup> when expressed as aglycone equivalents (18) and ranged from 584 mg d<sup>-1</sup> for Greek women and 1786 mg d<sup>-1</sup> for Danish men (19). The main dietary sources associated with the main phenolic structures are reported in Table 1.

### Effects of polyphenols and associated mechanisms on the main features of metabolic syndrome

#### Central obesity

As reported in Table 2, numerous clinical interventions have investigated the effects of polyphenol-rich intake on anthropometric variables, weight, body mass index (BMI), waist circumference and body fat mass in MetS subjects. Clearly, clinical studies pointed towards significant beneficial effects of green tea on BMI (21–28) and waist circumference (21,24–28). In a study by Basu et al. (22), 35 MetS subjects were randomly assigned to three groups (1): control, (2) green tea (beverage) and (3) green tea extract given for 8 weeks. Subjects who consumed green tea (beverage or extract) decreased significantly their body weight ( $-2.5 \pm 0.7$  in green tea beverage and  $-1.9 \pm 0.6$  kg in green tea extract compared with controls) and BMI ( $-0.9 \pm 0.3$  in green tea beverage and  $-0.7 \pm 0.2$  kg in green tea extract compared with controls) without changes in body fat and waist circumference. Nagao et al. (21) have previously confirmed a significant reduction of body weight, BMI, waist circumference and body fat mass in men who took a green tea extract compared with the control group. As caffeine was adjusted in both groups, the authors evidenced the role of catechin-polyphenols in the green tea extract. In the trial conducted by Suliburska et al. (26), 12 weeks of green tea extract supplementation resulted in decreases in BMI and waist circumference in men, even when the dose of catechins was around three times lower than that tested in the trial conducted by Nagao et al. (21). Interestingly, green tea catechin consumption also enhanced exercise-induced changes ( $\geq 180$  min week<sup>-1</sup> moderate intensity exercise, including  $\geq 3$  supervised sessions per week) in abdominal fat in overweight and obese adults compared with the control beverage group (least squares mean [95%CI]:  $-7.7$  [ $-11.7$ ,  $-3.8$ ] vs.  $-0.3$  [ $-4.4$ ,  $3.9$ ] in catechin and control groups respectively) (29). Green tea, which is unfermented and mainly consumed in Asia, is rich in catechins, especially in (-)-epigallocatechin 3-O-gallate (EGCG), the major phenolic compound, (-)-epigallocatechin, (-)-epigallocatechin 3-O-gallate,

**Table 1** Polyphenolic classes and their main dietary sources

Class	Sub-class	Main dietary sources
Non-Flavonoids	Hydroxycinnamic acids	Fruits: blueberry, cranberry, pear, cherry (sweet), apple, orange, grapefruit, cherry juice, apple juice, lemon, peach and cider Vegetables: potato, lettuce and spinach Others: coffee and tea
	Hydroxybenzoic acids	Fruits: strawberry, raspberry, grape juice (black/green) and pomegranate juice
	Stilbenes	Fruits: grapes and rhubarbOthers: red wine and peanuts
	Lignans	Cereals: rye, wheat, oat, barley and soybeanFruits: apricots and strawberries
	Flavones	Vegetables: broccoli and cabbageOthers: nuts and seeds,
Flavonoids	Flavones	Fruits: celery and olives
	Flavonols	Vegetables: hot peppers and celery heartsSpices and herbs: parsley, oregano, rosemary and thyme
		Fruits: apples, apricots, grapes, plums, bilberries, blackberries, blueberries, cranberries, olive
		elderberries, currants, cherries, blackcurrant juice, apple juice and ginkgo biloba
		Vegetables: capers, celery, chives, onions, red onions, dock leaves, fennel, hot peppers, cherry tomatoes, spinach, sweet potato leaves, turnip (green), endive, leek, lettuce, celery, broccoli, Hartwort
		leaves and kaleLegumes: beansCereals: buckwheat
	Isoflavones	Spices and herbs: dill weedOthers: red wine, tea (green, black), tea (black beverage) and cocoa powder
		Fruits: grape seed/skinLegumes and derived products: soybean, soy nuts, soy flour/bread, tofu, miso, soy milk and tofu yogurt
	Flavanones	Citrus fruits and juices: lemon, lime orange, orange, grapefruit and tangerineSpices and herbs: peppermint
	Anthocyanidins	Fruits: blackberries, black currant, blueberries, black grape, elderberries, strawberries, cherries, plums, cranberry, pomegranate juice and raspberry
Tannins	Flavanols	Others: red wine Fruits: apples, apricots, grapes, peaches, nectarines, pears, plums, raisins, raspberries, cherries, blackberries, blueberries and cranberries
	Procyanidins (Condensed tannins)	Others: red wine, tea (green, black), chocolate (dark, milk), white wine and cocoa Fruits: grape (dark/light) seed/skin, apple juice, strawberries,
		raspberries, walnuts, muscadine grape, peach, blackberry (juices/jams/jellies) and plum
		Legumes: chick pea, black-eyed peas and lentils,
	Ellagitannins (hydrolysable tannins)	Others: red wine, white wine, cocoa, chocolate, oak-aged red wine, tea, cider, tea and coffee Fruits: pomegranate

**Table 2** Effects on cardiometabolic features of polyphenol-rich intake given to subjects with metabolic syndrome

Polyphenols	Exposition/day duration	Participants N (Male)/age	BMI	WC	BP	LDL-C	HDL-C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
Diet rich in foods and beverages with a high content of polyphenols PP	2.9 mg PP8 weeks	86 (33) 35–70 years	ns	ns	ns	ns	ns	↓	ns	↓	Urinary 8-isoprostane ns	na		20
Green tea	Extract (690 mg catechins) 12 weeks	32 (32) 24–46 years	↓	↓	na	ns	ns	ns	ns	ns	↓ MDA	leptin ns, PAI-1 ns	↓ body fat mass and subcutaneous fat area	21
	4 cups (928 mg catechins) or extract (870 mg catechins) 8 weeks	35 (8) 42.8 years	↓	ns	ns	↓	ns	ns	ns	na	↓ MDA, ↓HNE ↑ plasma antioxidant, ↑ GSH	adiponectin nsCRP ns, IL6 ns, IL1-β ns, leptin ns	↓Large very LDL TG ↓HDL TGVCAM-1 ns, ICAM-1 ns	22,23
	1000 mg Puerh tea (capsules) 8 weeks	90 (41) 18–70 years	↓	↓	ns	↓	ns	↓	↓	na	↓ MDA, ↑ SOD	↓ CRP, ↓ IL6, ↑ IL10	↓ apoB-100	24
	3 g (3 sachets) 2 months	4560 years	↓	↓	na	ns	ns	ns	ns	na				25
	Extract (208 mg EGCG) 12 weeks	46 (46) 30–60 years	↓	↓	ns	↓	ns	↓	ns	na	↑ antioxidant level,	na	↑ Zn, ↑ Mg, ↓ Fe	26
	Greenselect 100 (49) 46.5 years	100 (49) 46.5 years	↓	↓	↓	↓	↑	↓	↓	na	↓ Plasma free radicals	na		27
	Phytosome, (300 mg) 24 weeks	70 59.2 years	↓	↓	na	ns	ns	ns	ns	na				28
	999 mg Puerh tea extract (capsules) 3 months	128 (67) 21–65 years	↓	↓	ns	ns	ns	↓	na	na	na	na	↓ body fat mass and subcutaneous fat	29
(+ exercise)	Extract (625 mg catechins) 12 weeks	70 (40)	ns	na	ns	↓	ns	ns	ns	na	na	na	na	30
Black tea	Puerh tea (1.5 g d <sup>-1</sup> ) 3 months	49 (18), 18–65 years	ns	ns	↓	ns	ns	ns	↓	↓	Fat oxidation ns	na		31
Cocoa	eq 902 mg flavanols 6 weeks	49 (18), 18–65 years	ns	ns	↓	ns	ns	ns	↓	↓	↑ Fat oxidation	na	↓ body fat ↓ abdominal body fat ↑ endothelial function	31
	same conditions than above + exercise	21 (14) 54.9 years	na	na	↓	na	na	na	na	na	na	na	↑ endothelial function	32
Cocoa	beverage (701 mg vs. 22 mg catechins) 7 d	40 (40)	na	na	na	na	na	na	↓	na	↓F <sub>2</sub> -isoprostane	IL6 ns	leucocytes ns	33
	idem + pre-exercise													

**Table 2.** (Continued)

Polyphenols	Exposition/day duration	Participants N (Male)/age	BMI	WC	BP	LDL-C	HDL-C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
(+ myo-inositol + soy isoflavones)	30 mg cocoa polyphenols 6 months	30 (0) 56 years	ns	ns	ns	ns	↑	↓	↓	na	na	↓ visfatin, ↓ resistin	↓ bone specific alkaline phosphatase	34
Berries	500 g strawberries 8 weeks	30 (2) 47 years	ns	ns	ns	↓	ns	ns	ns	na	↓ ox-LDL, ↓ TBARS, ↓ MDA	adiponectin ns	↑ Small LDL particles (CAM-1 ns, ↓ VCAM-1)	22,23
	300 mg aronia extract 2 months	25	↓	ns	↓	↑	↑	↓	↑	na	↑ SOD, ↑ GPX, ↓ CA, ↓ TBARS	CRP ns	↓ endothelin ↑ fibrinogen	35
	480 mL cranberry juice 8 weeks	3652 years	na	na	ns	ns	ns	ns	ns	na	↑ plasma antioxidant capacity, ↓ ox-LDL, ↓ MDA, ↓ HNE	CRP ns, IL6 ns	na	23
	Berries (bilberry BB and sea buckthorn) 44.2 years	80 (0)	↓	↓	na	na	na	na	↓	↓	na	↓ TNF $\alpha$	↓ GHbA $_{1c}$ ↓ VCAM-1	36
	Smoothie blueberry 6 weeks	32 (5) 54 years	ns	ns	ns	ns	ns	ns	ns	↓	na	↑ adiponectin for BB	na	37
	grape powdered 252 g grape 8 weeks	24 (24) 30–70 years	ns	ns	↓	ns	ns	ns	ns	na	na	CRP ns, TNF $\alpha$ ns, MCP-1 ns	↑ endothelial function	33,38,51
Citrus	Citrus-based juice (300 mL)	53 (24) 50–65 years	na	na	na	↓	↓	ns	ns	na	↓ ox-LDL	↑ IL10, ↑ adiponectin in men without dyslipidemia	↓ homocysteine	52
Cinnamon	Cinnulin PF® 12 weeks	22 (11) 46 years	na	na	↓	ns	ns	ns	↓	na	na	↓ CRP	↓ body fat mass	53
	1.5 g 12 weeks	4045 years	na	na	↓	ns	↓	↓	↓	na	na	↓ hs-CRP	↓ total cholesterol	54
Soy isoflavones	soy-based meal 12 weeks	100 (20) 35–65 years	↓	↓	ns	↓	ns	na	na	na	na	na	↓ body fat mass	55
Daidzein D, genistein G	5 mg equol+0.8 mg D+1 mg G+2.2 mg glycitein 12 weeks	54 (16) 59.4 years	ns	↓	ns	↓	ns	ns	↓	na	na	CRP ns, adiponectin ns, leptin ns	↓ HbA $_{1c}$ ↑ aortic stiffness (cardio-ankle vascular index)	56
Genistein	36 mg 3/6 months	12 (0) 18–32 years	ns	ns	na	↓	ns	ns	ns	ns	na	na	↓ total cholesterol	57
Quercetin	150 mg 6 weeks	96 (42) 45 years	na	na	↓	↓	↓	ns	ns	na	↓ ox-LDL	↓ TNF $\alpha$ , CRP ns	na	58

Table 2. (Continued)

Polyphenols	Exposition/day duration	Participants N (Male)age	BMI	WC	BP	LDL- C	HDL- C	TG	BG	IR	Oxidative markers	Inflammatory markers	Other markers	References
Hesperidin	500 mg 3 weeks	28 (15) 52 years	ns	ns	ns	↓	↓	ns	↓	↓	na	↓ CRP, ↓ serum amyloid ↓ soluble E-selectin	↓ BP in apo ε3ε3 genotype ↑ endothelial function	41 59
Epigallocatechin gallate	800 mg 8 weeks	88 (88) 40–65 years	ns	ns	↓	ns	ns	ns	ns	ns	na	na		60
Resveratrol	Longevinex (eq 100 mg resveratrol) 3/6 months 2 weeks	34	ns	ns	ns	ns	ns	ns	ns	ns	na	hsCRP ns, IL-6 ns	↑ endothelial function	61
		11 28–55 years	na	na	na	na	na	ns	ns	ns	na	na	↓ apoB- 100 and apoB- 48 production ↓ fat mass	62
	500 mg 3 months 150 mg 4 weeks	24 45 (25) 61 years	↓	↓	na	na	na	na	↓	↓	na	na		63
			ns	ns	↓	ns	ns	ns	ns	ns	CRP ns, IL- 6 ns, TNF α ns, E-and P-selectin ns, ICAM-1 ns, VACAM-1 ns			64
Resveratrol R+ Epigallocatechin gallate E	200 mg R + 282 mg E 3 d	18 (9) 33 years	na	na	na	na	na	na	na	na	na	na	↑ fasting and postprandial energy expenditure in men	65

BMI, body mass index; BP, blood pressure; BG, blood glucose; EGCG, epigallocatechin gallate; ↓, significant augmentation or diminution; ↓↑, significant augmentation or diminution; ns, not significant; IR, insulin resistance; LDL-HDL-C, low and high density lipoprotein cholesterol; na, not assayed or not reported; MDA, malonyl dialdehyde; SOD, superoxide dismutase; hs CRP, highly sensitive C-reactive protein; TNF, tumour necrosis factor; MCP, monocyte chemoattractant protein; HbA<sub>1c</sub>, glycated haemoglobin A1c; ICAM, intercellular adhesion molecule; TG, triglycerides; VCAM, vascular cell adhesion molecule; WC, waist circumference.



(-)-epicatechin, (+)-gallocatechin, but also in 5-O-galloylquinic acid, and 5-caffeoylquinic acid and diverse flavonols (66,67). However, the trial conducted with 800 mg of EGCG had no significant effect on BMI and waist circumference (68) even though its beneficial effects were demonstrated in experimental studies in animal models, as reported by Legeay et al. (69). These diverging results could be because of the dose, but also because green tea has other polyphenolic compounds, as previously reported, and their mixture could be more efficient than the single EGCG. The combination of catechin-polyphenols and caffeine with green tea was demonstrated to stimulate thermogenesis lead to increased 24 h energy expenditure and fat oxidation in humans (70), by mechanisms attributed to their actions on different molecular pathways: via inhibiting the phosphodiesterase-induced degradation of cAMP, and inhibiting catechol O-methyltransferase, an enzyme that degrades norepinephrine (71). Tea polyphenols may stimulate cellular energy expenditure that could reduce body-weight gain and suppress the expression of fatty acid synthase (72). Intake of Puerh tea (fermented) for 3 months was also associated with a slight reduction of body weight (-2.05 kg) and BMI (-0.73), but only in men and without the improvement of other metabolic parameters (30). Fermented tea commonly named black tea, which is largely consumed in Western countries, contains the same compounds than green tea, but with lower amounts of catechins, because of their oxidation during fermentation step. Theaflavins and thearubigins, which result from the oxidation of flavanols, are other major polyphenols in black tea (66,67). This quantitative and qualitative composition could explain the less pronounced effects of black tea compared with green tea. Interestingly, Yang et al. (73) hypothesized two types of effect, which could explain the biological differences between teas. The first one concerns the decrease of macronutrient absorption at intestine level leading to the reduction of caloric intake by polyphenols; the aflavins and thearubigins of black tea could be particularly involved. The second mechanism may involve bioavailable polyphenols, which, by their action on AMP-activated protein kinase activation, could decrease gluconeogenesis and fatty acid synthesis, increase catabolism and consequently, reduce body weight. While trials evidenced the beneficial action of tea on anthropometric parameters, cocoa-drink with a high dose of flavanols did not affect body composition (31) nor augment the effect of exercise on body composition (31). The addition of myositol and soy isoflavones to cocoa supplementation also had no effect. Berry supplementation with strawberries (74), cranberries (75) or blueberry smoothies (37) did not change weight or body composition in MetS subjects. However, decreased weight and waist circumference were reported after bilberry supplementation in overweight-obese women (delta changes calculated by the subtraction of wash out value from the value obtained at the end of the supplementation were -0.2 kg for body weight and -1.2 cm for waist circumference) (36). One explanation of those differences may be because of the level of

anthocyanidin between these berries. Supplementation of citrus-based juice, known to be rich in vitamin C and flavanones (especially hesperidin), had also no effect on anthropometric parameters (52). Studies by Ziegenfuss et al. (53) in pre-diabetic men and women and Askari et al. (54) in non-alcoholic fatty liver disease patients conducted on cinnamon supplementation did show a significant decrease in body weight and waist circumference, whereas soy isoflavone supplementation had a beneficial effect on both these anthropometric parameters compared with the control group (55). MetS subjects in the 12-week soy isoflavone supplementation and control MetS were followed up at 4-week intervals and seen at screening, at 4, 8 and 12 weeks. The treatment group had significant greater losses of body weight at week 12 (-7.1 vs. -2.5 kg in experimental and control groups) and body fat at weeks 8 and 12 compared with controls (-3.0 vs. -1.7 kg and -4.3 vs. -1.4 kg in experimental and control groups at weeks 8 and 12 respectively) (55). The beneficial effect was heightened after 12 weeks. Decreased waist circumference was only significant after 12 weeks. Weight reduction has been also observed in a group of diabetic patients where three meals per day were replaced with a soy meal (76). Another study compared weight loss in obese men and women after soy or casein meals (77), but there was no difference in weight loss and body composition between both protein meals. Thus, the role of soy isoflavones in weight management remains questionable even if in rodents, isoflavone administration decreased fat accumulation (78). Interestingly, the effect of equol, a key metabolite of soy daidzin, was tested in non-equol producers corresponding to people who cannot convert daidzin into S-equol through their intestinal bacterial flora (56). In fact, great interindividual variability in the ability to produce equol from soy isoflavone (79) was found. Usui et al. (56) have shown a significant beneficial effect of S-equol supplementation on the waist circumference of non-equol producers displaying MetS, although a significant reduction was also observed in the placebo group because of one patient with a strong waist circumference reduction. When taking phenolic molecules only, there was no effect in different studies conducted with genistein (57), quercetin (58), hesperidin (59), EGCG (60) and resveratrol for most of the trials (61,62,64). However, one trial with 500 mg of resveratrol during 3 months produced significant decreased anthropometric features (body weight, BMI, fat mass and waist circumference) than baseline values (63). This was certainly because of the high dose given compared with the previous studies (61,62,64). The combination of two polyphenols, resveratrol and EGCG also had no effect on BMI and waist circumference (65), but the authors reported a significant rise in fasting and postprandial energy expenditure in men. While no changes have been reported using resveratrol in most of the previously mentioned intervention studies, Konings et al. (80) have found a beneficial effect on the adipose tissue function after administering resveratrol to 11 obese men for 30 d. Thus,



resveratrol supplementation resulted in a modification of adipose tissue morphology with a decrease in adipocyte size. Furthermore, the authors reported a down-regulation of Wnt and Notch signalling pathways, suggesting an increased adipogenesis.

### Blood pressure: diastolic and systolic

Given that hypertension is one of the main cardiovascular risk factors in the patients with MetS, its management could be achieved by adopting a healthy lifestyle including a higher intake of fruit, vegetables and whole cereals, all known rich sources of fibres and polyphenols. However, the role of polyphenols on the blood pressure of patients with MetS remains difficult to isolate. When considering a diet naturally rich in polyphenols (close to  $3\text{ g d}^{-1}$ ) blood pressure was unchanged (20) and when focussing on specific foods or beverages, tea had no effect while cocoa lowered blood pressure (31,34). While cocoa supplementation decreased diastolic blood pressure (DBP) ( $-1.6\text{ mm Hg}$ ) and systolic blood pressure (SBP) ( $-1.2\text{ mm Hg}$ ) in the high-flavanol cocoa MetS group, these changes were independent of exercising (31). Berry et al (32) conducted a randomized, double-blind, cross-over trial to test the acute effects of cocoa flavanols on blood pressure responsiveness to exercise. Area under the curve for DBP response to exercise was significantly lower in high-flavanol (701 mg) than low-flavanol cocoa (22 mg) ( $743 \pm 1098$  vs.  $2359 \pm 822\text{ mm Hg.s}$  respectively) in 21 patients with borderline/mild hypertension, whereas there was no change in SBP and mean arterial pressure. Although the best dose and food matrix were not well established, it seems that a high dose of flavanols was required to obtain a beneficial effect on blood pressure. The study conducted by D'Anna et al. (34) with 30 mg of cocoa flavanols had no effect on blood pressure even with the addition of soy isoflavones. To strengthen dose-effect role, a two-month polyphenol-rich olive oil diet led to a significant decrease in SBP ( $-7.91\text{ mm}$ ) and DBP ( $-6.65\text{ mm Hg}$ ) in 24 young women with high-normal BP or stage 1 essential hypertension (81). The meta-analysis performed by Petrone et al. (82) including 23 randomized and control trials was consistent with a beneficial effect of dark chocolate and cocoa products on endothelial function and thus on blood pressure. Following berry supplementation (strawberry, cranberry, bilberry, sea buckthorn or blueberry), blood pressure remained unchanged in MetS subjects apart from chokeberry (*Aronia melanocarpa*), which lowered both DBP and SBP after 2 months (37). Grape polyphenol extract also produced an improvement in blood pressure with a mean decrease of  $5\text{ mm Hg}$  in SBP. Although modest, this change was nevertheless clinically significant. Indeed, a reduction in DBP of  $2\text{ mm Hg}$  has been calculated to reduce the risk of stroke and CHD by 15 and 6% respectively (83). Cinnamon was also shown to improve blood pressure (53), whereas

citrus-based juice supplementation still had no effect (52). In terms of the flavonoid tested, soy isoflavones (55) and hesperidin (59) were not effective, whereas a daily intake of  $150\text{ mg}$  of quercetin for 6 weeks had a beneficial effect on blood pressure (58). These effects were more pronounced in younger MetS adults aged 25–50 years compared with the whole group and to (pre)-hypertensive MetS subjects defined as  $\text{SBP} \geq 120$  or  $\text{DBP} \geq 80\text{ mmHg}$ . DBP decreased after 8 weeks of EGCG treatment ( $-2.5\text{ mmHg}$ ) in patients with MetS (60). There was no change of blood pressure in 34 MetS individuals who consumed resveratrol for 6 months (61), whereas DBP increased following  $150\text{ mg}$  of daily resveratrol intake for 4 weeks (84). All the results of intervention studies point towards the ability of dietary polyphenols to improve endothelial dilatory function associated with increased bioavailability of nitric oxide (NO) as was shown for cocoa flavanols (85). The enhancing effect of dietary polyphenols on the endothelial synthesis of NO was reported in an intervention sub-study of 200 high cardiovascular risk participants conducted as part of the Predimed trial : effects of Mediterranean diet on the primary prevention of cardiovascular disease, in which a Mediterranean diet enriched with extra virgin olive oil or nuts were beneficial on blood pressure (86).

### Dyslipidemia

Based on catechin-polyphenol consumption, green tea supplementation was shown to improve lipid profile by reducing significantly LDL-cholesterol in trials conducted by Basu et al. (22), Chu et al. (24), Suliburska et al. (26) and Belcaro et al. (27) and/or triglycerides in trials undertaken by Chu et al. (24), Suliburska et al. (26) and Belcaro et al. (27) and Maki et al. (29). Furthermore, no significant effect was observed for HDL cholesterol, although Basu et al. (22) reported an upwards trend. Other studies found no improvement in lipid profile using green tea (21,25,28) and cocoa (31). However, the combination of cocoa polyphenols with soy isoflavones and myoinositol was efficient on triglycerides level (34). It should be noted that Di Renzo et al. (87) recently showed that regular consumption of dark chocolate had a beneficial effect on HDL cholesterol and lipoprotein ratios in women with normal weight obese syndrome. Among berries, only strawberries and chokeberries improved serum lipids (35,74). Twenty-seven middle-aged MetS subjects with high BMI (mean  $37.5\text{ kg m}^{-2}$ ) were given  $50\text{ g d}^{-1}$  of freeze-dried strawberries for 8 weeks (74). This resulted in 10% and 11% reductions in total cholesterol and LDL cholesterol respectively, whereas it had no effect on triglycerides, HDL cholesterol or very LDL cholesterol levels. An important result was a 14% decrease in small LDL particle concentrations which are specifically atherogenic (74). In the trial conducted by Broncel et al. (35) enrolling 25 MetS subjects, administering aronia extract significantly reduced total cholesterol, LDL-cholesterol and

triglycerides after two months, whereas HDL-cholesterol did not change significantly. No significant changes in serum lipids were found for other berries such as cranberries (75), blueberries (37), bilberries, sea buckthorn (36) and grape powder (38). Considering these trials, it is difficult to understand the beneficial role of anthocyanins in lipid improvement because strawberries and cranberries displayed the lowest anthocyanin contents among the berries tested whereas chokeberries and bilberries had the highest levels (39). However, strawberries were reported to have the highest content of total polyphenols among fruit consumed in France (40), suggesting the action of other phenolic structures. The dose and the food matrix could influence the bioavailability of polyphenols and their effect on lipid metabolism (39). Two studies on cinnamon supplementation gave different results on lipid profile (53,54). Interestingly, isoflavone, flavone or flavanone supplementation pointed towards improved lipid profiles (55–59). A reduction of LDL-cholesterol was observed in MetS subjects following isoflavone supplementation with a soy-based meal (55) or a 30 mg genistein administration (57) or administering S-equol to non-equol producers (56). Egert et al. (58) reported the effect of a 6-week supplementation with quercetin ( $150 \text{ mg d}^{-1}$ ) given to 93 MetS subjects with little difference in serum lipid levels. Reanalysis of their data suggested that those subjects with specific apolipoprotein-E genotypes had differential lipid responses to quercetin (41). Flavanone supplementation, with 300 mL citrus juice or hesperidin at  $500 \text{ mg d}^{-1}$  for three weeks, showed a significant reduction in total cholesterol and LDL cholesterol (59). Resveratrol was shown to be inactive on lipid metabolism. However, resveratrol has been reported to decrease triglyceride-rich lipoprotein apoB100 and apoB48 concentrations (62). Considering all the results, catechin-polyphenols of tea and flavonoids could contribute to a beneficial effect on lipid metabolism. The mechanisms at intestinal level would be the reduction effect of polyphenols on lipid availability, cholesterol absorption and chylomicron secretion. It has been reported that polyphenols could constrain the digestion of fats by inhibiting the pancreatic lipases (42). Moreover, impaired lipid availability in hepatocytes by polyphenols seems to contribute to reduced hepatic very LDL secretion. Polymeric catechins, namely proanthocyanidins, were shown to be able to suppress the expression of miR-33a and miR-122 (43). MiR-33a and miR-122 are two key regulators of lipid metabolism in the liver corresponding to the ATP-binding cassette transporter ABCA1 targets genes, fatty acid synthase and peroxisome proliferator-activated receptor PPAR $\beta/\delta$  respectively (44).

### Blood glucose and insulin resistance

With regards to fasting glucose and/or insulin resistance, clinical studies of polyphenol supplementation have reported controversial results. Neither green tea nor EGCG treatment

in patients with MetS had an effect on insulin sensitivity, secretion or glucose tolerance and on insulin resistance in the majority of clinical trials, apart from those conducted by Vieira Senger et al. (25) and Belcaro et al. (27). By contrast, cocoa products were reported to have a beneficial effect on glycaemia. Decreased insulin resistance assessed by HOMA2 ( $-0.31\%$ ) was observed in high-flavanol cocoa (902 mg) supplementation in obese individuals (31), highlighting the dose-dependent effect of polyphenols on blood glucose changes. Acute dark chocolate consumption prior to prolonged exercise also enhanced insulin sensitivity compared with chocolate consumption alone (33). Berry consumption gave conflicting results; fasting glucose was unchanged after strawberry (74) and cranberry (75) supplementation but was lower after a sea buckthorn diet (36). Using a hyperinsulinemic euglycemic clamp with a blueberry diet, Stull et al. (37) reported improved insulin sensitivity without any change in body weight, suggesting that bioactive blueberry substances had a direct effect on increasing whole-body insulin action. Concerning citrus-juice (52), fasting glucose was unchanged while hesperidin supplementation improved glycemia and insulin resistance (59). Cinnamon-extract supplementation for 12 weeks reduced fasting glucose in 22 MetS subjects (53). This decrease was confirmed in a trial conducted by Askari et al. (54). Single phenolic molecule tested on patients with MetS had no effect apart from hesperidin, as previously mentioned, and high doses of resveratrol (500 mg) in the 3-month trial carried out by Méndez-del Villa et al. (63). Dose–effect may partly explain the lack of results in numerous trials. Polyphenols, as reviewed by Hanhineva et al. (45), could act on different targets such as the intestine, by inhibiting glucose absorption via the sodium-dependent glucose transporter SGLT1, the pancreas, by protecting  $\beta$ -cells from glucotoxicity, the liver by suppressing glucose release from liver storage and peripheral tissues by improving glucose uptake via the glucose transporter GLUT4. These mechanisms could explain the inverse association between a higher consumption of berries and the risk of type 2 diabetes as reported in a prospective study by Mursu et al. (46).

### Associated complications

#### *Oxidative stress*

Because polyphenols are poorly absorbed and extensively metabolized, their antioxidant effects are attributed to the regulation of redox enzymes by reducing reactive oxygen species production from mitochondria, NADPH oxidases and uncoupled endothelial NO synthase in addition to multiple up-regulated antioxidant enzymes (47). Moreover data supporting the oxidative stress-reducing effects of polyphenols was promising in reducing plasma isoprostanes and thiobarbituric acid-reacting substances (TBARS), malonyl dialdehyde (MDA), 4-hydroxy nonenal (HNE) or oxidized

low-density lipoprotein (ox-LDL). Not all clinical trials reported significant reductions in oxidative stress in MetS subjects, especially for those carried out using a single phenolic compound. While green tea beverages or extract supplementations were shown to induce antioxidative responses in MetS subjects enrolled in several clinical trials (23,24,26,27), this did not apply to cocoa products. Among berries, strawberry, aronia and cranberry treatments reduced lipid oxidation (lower Ox-LDL, lower TBARS or lower MDA) and improved antioxidant status (increased superoxide dismutase and a 47% increase in plasma antioxidant capacity) in MetS individuals (35,75). As reported by Sivaprakasipallai et al. (48), the higher the baseline ox-LDL was, the greater the decrease in ox-LDL with a high dose of grape seed extract. Six months of citrus juice supplementation also induced lower ox-LDL. Egert et al. (41) used quercetin supplementation and reported decreased ox-LDL in apoE3 and apoE4 groups of MetS subjects. As ox-LDL was involved in the initiation and progression of atherosclerosis, polyphenols may thus represent natural dietary sources of potent antioxidants to improve the antioxidative status in MetS subjects.

### Inflammation

Visceral obesity is characterized by chronic local and systemic inflammation. It seems well established that a rise in pro-inflammatory cytokines may be connected to enlarged adipose tissue and increased risk of coronary disease. A polyphenol-rich diet is currently recommended as having a beneficial impact on inflammation (9,49). However, results from various clinical trials conducted on patients with MetS reported no overall effect on the most common inflammation biomarkers following polyphenol supplementation. As a systemic inflammation marker, highly sensitive C-reactive protein (CRP) stimulates the production of other inflammatory cells and reduces the expression of endothelial nitric oxide synthase (eNOS). No significant change was noted after green tea supplementation (except in the trial conducted by Chu et al. (24)), cranberries (75), aronia (35), blueberries (37), quercetin (58) and resveratrol (61,64). Following citrus-based juice and hesperidin supplementation, CRP was significantly decreased and was associated to improved endothelial function in MetS individuals (59). Concerning the circulatory tumour-necrosis factor (TNF- $\alpha$ ) associated inflammation, while blueberries (37) and grapes (38) did not produce any change in TNF- $\alpha$ , bilberries and sea buckthorn (36) or quercetin (41) significantly reduced its level. Furthermore, no study in MetS subjects reported changes in interleukin-6 (IL-6) following green tea, cranberry or grape supplementation (23,38,75). It has been suggested that the lack of changes may be because of the baseline inflammatory value and/or that the anti-hypertensive treatment usually received by the patients may explain the absence of additional effects due its anti-inflammatory

effects (23). However, it is interesting to note an increased anti-inflammatory cytokines (IL-10 and adiponectin) production after 4 weeks of grape supplementation (38), 6 months of citrus juice supplementation (52) or after regular consumption of dark chocolate (87). As regards to these controversial findings, the higher dose of polyphenols or the adaptation of lifestyle with the greater physical activity may influence adiposity, turning to be one of the better anti-inflammatory strategies for patients with MetS.

### Vascular dysfunction

MetS is associated with endothelial-dependent and endothelial-independent dysfunction, affecting both the macrovascular and microvascular systems (50). As reported in Table 2, some clinical interventions have investigated the effects of polyphenol-rich intake on vascular dysfunction in MetS subjects. Clearly, clinical trials pointed towards significant beneficial effects of polyphenols on endothelial dysfunction (31,32,51,59) and adhesion modulation (36,74). In fact, supplementation of cocoa-drink with a high dose of flavanols improved flow mediated dilation, an established measure of endothelial function, acutely (2 h post-dose) by 2.4% and chronically (over 12 weeks) by 1.6% in patients with MetS (31). Grape polyphenols also increased flow-mediated dilation in 25 MetS subjects (51). Following oral hesperidin administration (500 mg once daily for three weeks), flow mediated dilation increased in MetS subjects ( $10.26 \pm 1.19$  vs.  $7.78 \pm 0.76\%$ ,  $p=0.02$ ) (59). In 34 MetS individuals, resveratrol consumption for 6 months improved flow-mediated dilation (61). According to vasoconstriction effect, administering aronia extract during 2 months in 25 MetS subjects significantly reduced plasma endothelin-1 (35). Moreover, vascular cell adhesion molecule (VCAM) and/or intercellular adhesion molecule [ICAM]) decreased after berries supplementation, for strawberries (74) or buckthorn (36). However, green tea intervention did not affect VCAM and ICAM (22). Several mechanisms, mostly based on *in vitro* studies, have been described to explain the protective effects of polyphenols on endothelium and vascular smooth muscle cells. Polyphenols increase the production of vasodilatory substances such as NO and endothelium-derived hyperpolarizing factor by stimulating the phosphorylation of Akt, AMP kinase and eNOS, prevent ROS-mediated degradation of NO by decreasing the expression of NADPH oxidase, blunt vasoconstrictive and pro-inflammatory responses (47).

### Conclusions and future directions

Cross-over and randomized controlled trials in MetS subjects with single phenolic compound or specific food/beverage/extract do not provide strong evidence for the promising protective effects of polyphenols on cardiovascular diseases as reported in numerous animal and cell studies. Different factors could be involved: (i) the

characteristics of the selected MetS population under study; (ii) insufficient statistical power; (iii) inadequate treatment duration, (iv) the use of suboptimal dosages and (v) low bio-availability supplementation with a single molecule; and (vi) improper administration of micronutrients relative to meal ingestion. However, the present review highlights that polyphenols, usually at higher doses, could have a beneficial effect on the main features of MetS through different actions on (i) anthropometric features with tea (green and black); (ii) blood pressure with cocoa; (iii) lipid metabolism with green tea and soy isoflavones, citrus products/flavanones with quercetin; and (iv) blood glucose with cocoa and cinnamon. Because of the composition complexity of tea, cocoa, soy and citrus products, it is difficult to emphasize the bioactivity of a specific polyphenol. The more beneficial effect of a dietary polyphenol-rich plant product compared with a single molecule could be explained by the co-existence of diverse phenols molecules and other bioactive substances, which could (i) confer to a better chemical stability within the matrix, notably for highly oxidizable catechins and (ii) provide additive or synergistic effects. Mixture of phenolic compounds may have synergistic effects for certain functions, such as reported by Yang et al (73) for AMP kinase, which could be activated by other phenols than EGCG, such as resveratrol, curcumin or capsaicin. Aside, because polyphenols are highly metabolized through the products of microbial breakage in the intestine or hepatic transformation, these are phenolic metabolites that reach target tissues, making the circulating pool of potential bioactive phenolic phytochemicals most distinct from the native molecules. The measurement of the phenolic metabolome in humans would point out which phenolic molecules are present in the plasma/urine of humans followed the intake of polyphenol-rich foods (green tea, cocoa, citrus, apple...) and should facilitate the provision of clearer evidence on the relations between food composition and risk of major chronic diseases such as cancer, cardiovascular diseases or diabetes and shed new light on the causes of such diseases (46). Moreover, some polyphenol supplementations may improve antioxidant and inflammatory status. With regard to all these results, it is difficult to establish the best dose and the ideal food matrix and mode of supplementation. Moreover, further research is needed to evaluate the possible preventive effects of a higher consumption of polyphenols by a combination of their diverse dietary sources (green tea, dark chocolate, berries, citrus fruits...). Because gut microbiota has been demonstrated to play a key role in the development of several pathologies (49), and, in particular, has been recently identified as a possible new cardiovascular disease risk factor (50), the role concerning the interaction of polyphenols with microbiota might be considered in the dietary management of MetS (51,88). It has been estimated that only 5–10% of total polyphenol intake is absorbed in the small intestine (88).

The remaining polyphenols (90–95% of total polyphenol intake) may accumulate in the large intestinal lumen up to the millimolar range where, together with conjugates excreted into the intestinal lumen through bile, they are subjected to the enzymatic activities of the gut microbial community (88). Recent studies have in fact suggested that both the phenolic substrates supplied to gut bacteria through different dietary intake patterns and the aromatic metabolites produced may modulate and cause fluctuations in the composition of the microflora populations through selective prebiotic effects and antimicrobial activities against gut pathogenic bacteria (89–94) that could influence its involvement in health problems. Gut microbiota could therefore be an interesting target for exploring the potential role of polyphenols in metabolic balance and weight loss.

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