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POSITION PAPER

Effects of polyphenols on cardio-metabolic risk factors and risk of type 2 diabetes. A joint position statement of the Diabetes and Nutrition Study Group of the Italian Society of Diabetology (SID), the Italian Association of Dietetics and Clinical Nutrition (ADI) and the Italian Association of Medical Diabetologists (AMD)

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Abstract *Aim:* A large body of evidence supports a role of polyphenols in the prevention of chronic diseases, i.e. type 2 diabetes (DMT2), cardiovascular diseases and some types of cancer. In the present manuscript, the effect of polyphenol/phenolic compounds on the main cardio-metabolic risk factors (body weight, blood pressure, blood glucose concentrations, plasma lipids, inflammation and oxidative stress) in humans will be discussed.
Data synthesis: Epidemiological evidence supports the beneficial effects of polyphenol-rich diets in the prevention of T2D risk. However, the available evidence from randomized controlled clinical trials did not allow the identification of specific phenolic compounds or polyphenol-rich foods that effectively improve cardio-metabolic risk factors. The most promising results in terms of the management of cardio-metabolic risk factors derive from RCTs based on a long-term intake of polyphenol-rich foods and beverages. Therefore, future studies should focus on a diet containing different classes of polyphenols rather than a specific food or phenolic compound. The hypothesis is that a polyphenol-rich diet may have a pleiotropic effect on cardiometabolic risk factors thanks to the specific action of different polyphenol subclasses.
Conclusion: The lack of conclusive evidence on the effectiveness of polyphenols in the management of cardio-metabolic risk factors does not allow recommendation of their use as supplements to reduce T2D and CVD risk. However, the daily consumption of naturally polyphenol-

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rich foods and beverages might be advised according to the current nutritional dietary recommendation.

Introduction

Polyphenols account for a huge family of plant-derived compounds that have at least one aromatic ring with one or more hydroxyl groups attached. Based on their chemical structure they are classified into flavonoids-which include several subclasses as flavones, flavonols, flavan-3-ols, flavanones, isoflavones and anthocyanins, and phenolic acids, stilbenes, lignans and other polyphenols (Fig. 1).

Flavonoids are the most representative class of polyphenol of the human diet. The main dietary sources are fruits (in particular berries and citrus fruits) and vegetables, but a large amount can be found also in dark chocolate, extra-virgin olive oil, and some beverages (tea, coffee and wine) [1].

In recent decades, mounting evidence indicated that higher intake of polyphenol-rich foodstuff is closely related to a reduction of chronic-degenerative diseases, i.e. type 2 diabetes (T2D), cardiovascular diseases (CVD) and some type of cancer [2–4]. As a consequence, consumers from developed countries increased their awareness of the role of polyphenols in promoting health [5].

The average dietary intake of polyphenols in Western populations range from 500 to 1000 mg/day [4,6] while more plant-based diets provide greater amount of polyphenol as demonstrated by plasma concentration of phenolic metabolites in vegan and vegetarian individuals [7]. However, since low adherence to plant-based food recommendations has been reported in several populations [8,9], polyphenol intake may be scant. As a

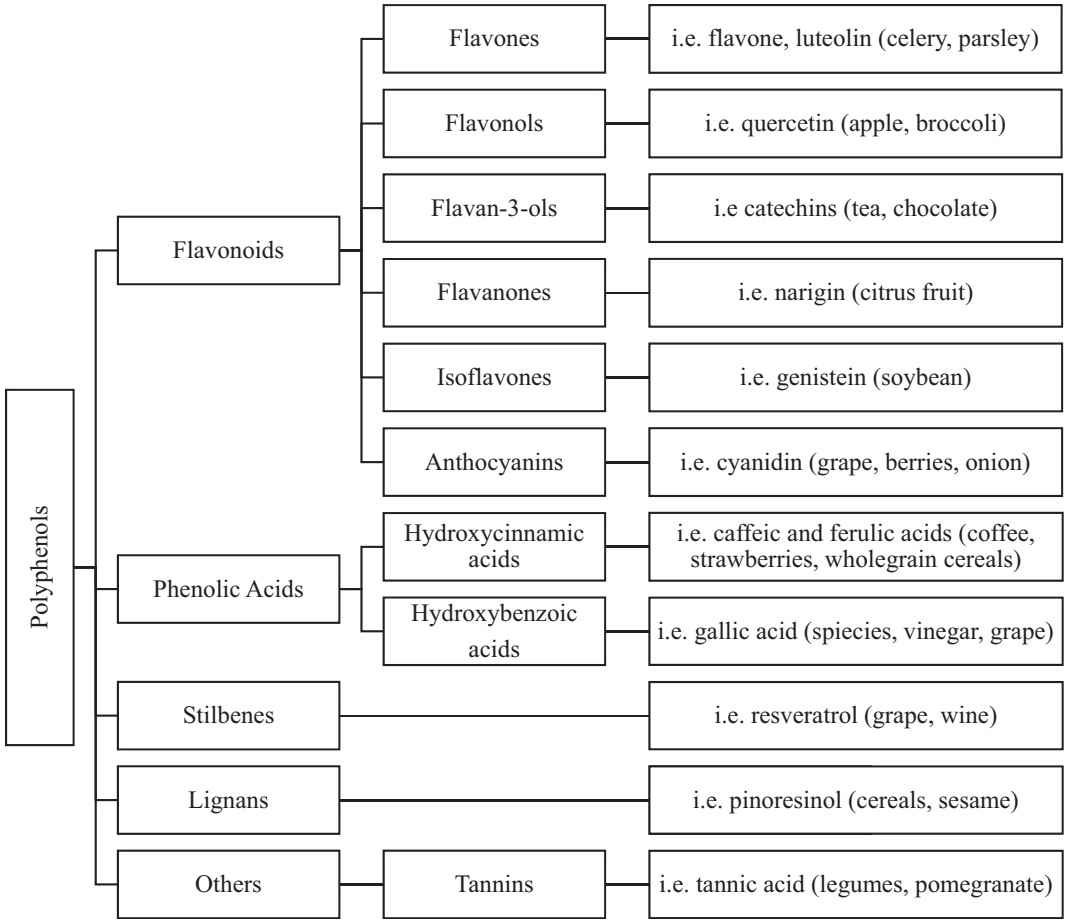

Figure 1 Polyphenols classification and food sources.

consequence, due to the growing interest for their effects on health, polyphenol-based supplements consumption has dramatically increased worldwide. Although health benefits may arise from the use of different polyphenol-based supplements, their consumption might be also associated with possible risks. Indeed, some studies reported pro-oxidant effects induced by polyphenols (generally known for their antioxidant effects) and/or inhibiting activity on enzymes involved in drug metabolism, thus having an important impact on the pharmacokinetic data and toxicity of these drugs [5].

Moreover, the independent buying and use of supplements might encourage patients under pharmacological treatment to reduce or discontinue their medications without a prior consultation with doctors. Finally, the large and uncontrolled availability of supplements (i.e. e-commerce, pharmacies and drugstores) and the possibility that their use may be suggested by health-care professionals (physicians, nutritionists, dietitians, nurses) but also friends, relatives, or self-decided might predispose to the risk of incorrect consumption of these preparations and to potential side effects.

Therefore, the purpose of this position paper is to: 1) critically evaluate whether polyphenol intake is effective for T2D prevention and the management of cardio-metabolic risk factors; 2) point out if the increase of polyphenol intake should be recommended trough dietary changes and/or supplements. For this purpose we reviewed evidence coming from observational studies, randomized clinical trials (RCTs) and meta-analyses in humans.

A literature search was conducted using PubMed databases for epidemiological studies and randomized controlled clinical trials and meta-analyses on adults published in the English language. We used as keywords “dietary polyphenols” or “polyphenols” and separate search terms for each of the cardiovascular risk factors. The search yielded 123 epidemiological studies for “polyphenols” OR “polyphenols AND “diabetes mellitus, type 2″, 141 articles for “polyphenols and body weight ”, 163 articles for “polyphenols and blood glucose”, 123 articles for “polyphenols and plasma lipids”, 132 articles for “polyphenols and blood pressure”, 140 studies for “polyphenols and inflammation”.

This document includes: (1) the meta-analyses of randomized clinical trials; 2) clinical trials not available in the meta-analyses that added significant information to the current knowledge on the effects of polyphenols on health.

Type 2 diabetes risk

In the last decades, a role of polyphenols in type 2 diabetes (T2D) risk reduction has been argued thanks to their effects on fasting and postprandial blood glucose concentrations [10–12].

Several epidemiological studies indicate that polyphenols-rich diets, including whole grains, vegetables, fruit, extra-virgin olive oil, coffee, tea, or chocolate, are tightly associated with a reduction in T2D, CVD and some type of cancer risk [3,13–15]. In addition, evidence from medium-term clinical trials (6–8 weeks) showed an improvement of the main metabolic parameters - i.e. blood glucose and lipid, and blood pressure - in individuals with and without T2D [16–19].

However, large cohort studies provide conflicting results on the effectiveness of polyphenol in T2D prevention and blood glucose control. Indeed, a meta-analysis of prospective cohort studies reported that daily consumption of flavonoids from different food sources reduced risk of type 2 diabetes by 9%. In a dose–response analysis, an increase intake of 500 mg/day was associated with a significant 5% reduction of T2D risk [17] (Table 1). This result is in line with those obtained in two previous studies considering total flavonoids and their subclasses. In particular, anthocyanidin-rich fruit intake (blueberries and apples) reduced the risk of T2D by 23% in daily *vs.* weekly/monthly consumers [20,21] (Table 1). Conversely, in the Women's Health Study (38,018 American women) neither the consumption of flavonoids nor their main subclasses (flavonols and flavones) or single phenolic compounds (quercetin, kaempferol, myricetin, apigenin and luteolin) was associated with a significant reduction inT2D risk in 8.8 years follow-up [22].

Likewise, in the Iowa Women's Health Study no association was found between flavonoids and their subclasses and T2D risk in post-menopausal women [23].

Finally, the results of the Nurses' Health Study I and II showed a 39–48% reduction of T2D in subjects having more urinary phenolic metabolites during a mean follow-up 4.6 years. However, the association did not persist in the long-term follow-up (4.6–11.4 years) [24].

Nevertheless, epidemiological studies focusing on phenolic acids, mainly from coffee and tea, gave more convincing results on the beneficial association between polyphenol and low T2D risk [25–28]. A recent meta-analysis of 28 prospective studies on 1109272 subjects without diabetes showed a 33% reduction of T2D in

Table 1 Association between polyphenol intake and risk of diabetes: meta-analyses of prospective cohort studies.

	n. studies	Follow-up	Polyphenol sources	Cases/cohort	Exposure range (mg/d) or frequency (times/week)	Adjusted RRs (95% CI)
Liu YJ, 2014 [18]	6 prospective cohorts' studies	8.8–28 years	Total Flavonoid intake	18.146/284.806	Q1 = 8.85 Q5 = 770.3	1.00 0.91 (0.87–0.96)
Wedick NM, 2012 [21]	3 prospective cohorts' studies	16–24 years	Anthocyanidin-rich fruit intake	12.611/200.894	Q1 = <1 time/month Q5 = >5 times/week	1.00 0.77 (0.65–0.93)
Ding M, 2014 [29]	28 prospective cohorts' studies	10 months to 20 years	Cups of coffee	45.335/1.109.272	Q1 = 1 cup Q5 = 6 cups	1.00 0.67 (0.61–0.74)

habitual coffee drinkers (1–6 cups of coffee/day), with and without caffeine, compared to non-consumers [29] (Table 1). As for tea, in particular green tea, the daily consumption of 3–4 cups reduced T2D risk by 16% comparing consumers and non-consumers [30,31].

Finally, in a British cohort study a significant reduction of T2D was observed only when tea and coffee consumption was pooled whereas no effect was detected considering the intake of the single beverage [32].

As for the association between polyphenols and blood glucose control, the available evidence is still scant. An observational study involving 3000 subjects with T2D showed that the consumption of total polyphenols and their subclasses was associated with lower glycosylated hemoglobin (HbA1c) concentrations [33]. Moreover, daily consumption of coffee or tea was associated with a significant reduction of blood glucose and insulin, as well as an improvement in insulin resistance [34–36].

Cardio-metabolic risk factors

Undoubtedly, polyphenols are known for their antioxidant activity which will not be discussed in this position statement. However, they have been shown to influence also the main cardio-metabolic risk factors, such as body weight, blood glucose, lipid profile, blood pressure and inflammation.

Body weight

In recent years, polyphenols have been pointed out as potentials modulators of energy metabolism and, therefore, of body weight control. Indeed, several *in vitro* and animal models have shown that polyphenols can inhibit adipocyte differentiation, increase fatty acids oxidation, increase thermogenesis and energy expenditure, and inhibit the digestive enzyme activity [37–39]. However, to date, few human studies evaluated the effect of polyphenols on body weight regulation. Furthermore, the available evidence is still inconsistent due to the huge variability in study design, sample size, type of participants, time of exposure and polyphenol sources.

As an example, in a 4-week RCT in overweight individuals, the consumption of apple juice (750 ml/day containing 802 mg of polyphenols) reduced body fat with no changes in body weight, body mass index and waist circumference [40] (Table 2). Likewise, orange juice intake (500 ml/day containing 250 mg of anthocyanins) did not induce weight loss in non-diabetic subjects after 12 weeks [41].

Conversely, a 12-weeks supplementation with citrus extract (900 mg/day Sinetrol XPur) containing mainly flavanones (hesperidin and naringin) significantly affected body weight (−3.8%), waist circumference (−7.5%) and abdominal fat (−9.7%) compared to placebo in obese individuals [42] (Table 2). In line with this result, in a 16-week placebo-controlled RCT with a flavonoid-rich extract (1000 mg/day HolisFiit, derived

Table 2 Effects of polyphenols on body weight and body composition: intervention studies.

	Sources (polyphenols dose)	Participants	Study Design	Duration (weeks)	Main outcomes
Barth SW, 2012 [40]	Apple juice (802 mg/day) vs Control Drink	68 obese men	RCT parallel group	4	Δ (%) body weight: −0.3 ± 0.1 *vs* −0.2 ± 0.1; ns Δ (%) body fat: −1.0 ± 1.3 vs −0.2 ± 0.9*
Cases J, 2015 [42]	Sinetrol XPur (900 mg/day) vs Placebo	25 overweight men	RCT parallel group	12	Δ (%) body weight: −3.75 ± 0.81 *vs* −1.76 ± 0.61* Δ (%) abdominal fat: −9.74 ± 3.84 *vs* −4.81 ± 1.74* Δ (%) waist circumference: −7.50 ± 2.00 *vs* −2.11 ± 0.48*
Wang H, 2010 [44]	Green Tea (886 mg/day) vs Control Drink	182 overweight subjects	RCT parallel group	13	Δ (%) body weight: −1.7 *vs* 0.14*
Maki CK 2009 [45]	Green Tea (625 mg/day) vs Control Drink	128 overweight/obese subjects	RCT parallel group	12	Δ (%) waist circumference: −2.0 *vs* −0.2* Δ (%) body weight: −2.3 *vs* 1.6; ns Δ (%) total abdominal fat area: −7.7 *vs* −0.3* Δ (%) subcutaneus fat area: −6.2 *vs* 0.8*
Nagao T, 2005 [46]	Green tea extract (690 mg/day) vs Control (22 mg/day)	35 overweight/obese subjects	RCT parallel group	12	Δ (cm) waist circumference: −3.4 ± 0.5 *vs* −1.6 ± 0.4*
Brown AL, 2011 [48]	Decaffeinated green tea extract (800 mg/day) vs Placebo	64 overweight/obese men	RCT cross-over	6	Δ (kg) body weight: −0.327 ± 1.89 *vs* −0.038 ± 1.88*
Chen IJ, 2016 [49]	Decaffeinated green tea extract (857 mg/day) vs Placebo	77 overweight/obese women	RCT parallel group	12	Δ (%) body weight: −0.85 ± 2.13 *vs* −0.05 ± 8.15; ns Δ (%) body mass index: −0.89 ± 2.15 vs −0.1 ± 8.15; ns

RCT: randomized controlled trial; Δ = change from baseline; *statistically significant polyphenols *vs* control; ns = not statistically significant.

from citrus fruits, green tea and black carrots) a reduction of body weight (−1.6%) and body fat (−5.3%) was detected [43].

Green tea catechin-based RCTs provided more convincing results. As a matter of fact, long-term consumption (90 days) of 2 cups of green tea/day (886 mg of catechin) significantly reduced waist circumference (−1.9 cm) and body weight (−1.2 kg) in overweight Asian individuals [44]. In addition, the improvement of anthropometric parameters (body weight, BMI, waist circumference and abdominal fat were observed in two 12-week RCTs [45,46]. Green tea extracts providing the 800−870 mg of catechin induced the same effects after 8-12-week supplementation in obese subjects [47−49] (Table 2).

Nevertheless, some studies did not observe any improvement of anthropometry after catechins supplementation [50−52].

This may be due mainly to the confounding effect of caffeine in green tea that could have influenced the effect of catechins. In fact, caffeine has shown to increase energy expenditure and thermogenesis thus influencing body weight [53]. A meta-analysis of 15 RCTs showed that a significant reduction of body weight, BMI and waist circumference was observed only with the administration of caffeine-containing green tea (catechin: 583−714 mg/day) in a mean period of 12 weeks [54].

In addition, the ethnicity of the participants could have played a role since the results obtained on the Caucasian population are less consistent than those observed in Asian populations. In this light, it has been suggested that the thermogenic activity of green tea may be linked to the differences in the allele frequencies of the A2A receptor for adenosine and to the polymorphisms of the catechol-O-methyltransferase among the different ethnic groups [50].

Resveratrol, the typical phenolic compound in grapes, wine and even some red fruits, has been proposed as body weight regulator. In fact, the results of *in vitro* and animal studies have shown that it can inhibit pre-adipocytes differentiation and lipogenesis, decrease adipocytes proliferation, stimulate lipolysis and beta-oxidation of fatty acids [55]. However, evidence from human clinical trials is quite limited and inconsistent. Furthermore, significant weight loss was achieved only when resveratrol is consumed as food supplement [56−58].

In conclusion, the conflicting results are mainly due to the wide variability of studies (i.e. ethnic groups, sources, and the influence of other bioactive compounds). Hence, the current evidence does not allow to confirm the beneficial effect of polyphenols in body weight regulation. Nevertheless, the results suggest a potential role of polyphenols in body weight maintenance rather than weight loss.

Blood glucose

Several studies have evaluated the effects of polyphenols on glucose and insulin metabolism in healthy subjects, as well as individuals with metabolic syndrome (MS) or with type 2 diabetes.

Firstly, in individual at high cardio-metabolic risk, a medium-term polyphenol-rich diet (3 g/day) has shown to significantly improve glucose response to an OGTT-challenge, likely through an improved insulin sensitivity and early insulin secretion as compared to a control diet (~300 mg/day of total polyphenols) [17].

As for specific phenolic compounds, evidence came mainly from RCTs evaluating the effects of flavan-3-ols from green tea and cocoa.

A meta-analysis of 22 clinical trials [59], including 1584 individuals, showed that the consumption of green tea − independently from caffeine − significantly reduced fasting blood glucose concentration (−1.48 mg/dl) in short and in long-term trials (3−24 weeks). No effect was observed on fasting insulin, HbA1c or insulin resistance (Table 3). This result was confirmed by Liu and colleagues [60] in a meta-analysis of 17 clinical trials where green tea or catechins improved blood glucose control (evaluated as HbA1c concentration) in healthy, overweight/obese and/or diabetic subjects (Table 3).

Looking at cocoa, the meta-analysis by Hooper et al. [19] showed a reduction of fasting insulin and HOMA index in subjects at cardiovascular risk after the consumption of cocoa-derived products (cocoa powder, chocolate flavan-3-ols) (Table 3).

Therefore, the results of these meta-analyses supported the role of flavan-3-ols from green tea and cocoa, as beneficial modulators of glucose metabolism. The effect is independent from caffeine and it is greater when “pharmacological” doses of epigallocatechins (230−1.200 mg/day) are supplemented.

As for resveratrol, the main phenolic compound in grapes and wine, short and medium-term RCTs clearly demonstrated that daily consumption of resveratrol reduced blood glucose concentrations in healthy subjects and in individuals with T2D. As a matter of fact, the meta-analysis by Zhu et al. [61] showed that resveratrol supplementation (4−12 weeks) significantly reduced fasting blood glucose (−5.52 mg/dl), insulin concentrations (−0.64 U/mL) and the HOMA index (−0.52) in 283 subjects with T2D (Table 3). Moreover, the subgroup analysis showed that the improvement in fasting glucose was dose-dependent, with the greatest effect obtained with more than 100 mg/day of resveratrol. However, no effect on HbA1c was observed. In line with these results, two medium term RCTs, confirmed the effectiveness of resveratrol supplementation in the improvement of glucose homeostasis in individuals with T2D. This effect was obtained with the daily consumption of 600 mg of grape seed extract [62] as well as 150 ml of resveratrol-containing beverages (grape juice, wine, and non-alcoholic wine) [63].

As for high risk subjects (individuals with Metabolic Syndrome or some metabolic abnormalities), a reduction of fasting and postprandial insulin was detected after medium-term consumption of red grape pomace (20 g/day) [64] or red wine (300 ml/day, polyphenols: 798 Eq Gallic Acid/day) [65].

Table 3 Effects of polyphenols on fasting glucose and insulin, HOMA index and HbA1c: meta-analyses of intervention studies.

	Sources (polyphenol range)	n. studies	Participants	Duration (weeks)	Δ Glucose (mg/dl) (95% CI)	Δ Insulin (μU/ml) (95% CI)	Δ HOMA index (95% CI)	Δ HbA1c (%) (95% CI)
Zheng XX, 2013 [59]	Green tea catechins (236–1207 mg/day)	22 RCT	1.584 subjects, overweight/obese, MS, diabetes and prediabetes	3–24	−1,48* (−2.57, −0.40)	−0.04 (−0.36, 0.45)	−0.05 (−0.37, 0.26)	−0.04 (−0.15, 0.08)
Liu K, 2013 [60]	Green tea and green tea extracts (208–1207 mg/day)	17 RCT	1.133 subjects, healthy, overweight/obese, diabetes,	2–24	−2.0* (−3.0, −1.0)	−0.40 (−1.27, 0.46)	−0.04 (−0.67, 0.59)	−0.30* (−0.37, −0.22)
Hooper L, 2012 [19]	Cocoa, cocoa derived products and flavan-3-ols	11 RCT glucose 5 RCT insulin 6 RCT HOMA 6 RCT HbA1c	459 subjects healthy, overweight, hypertension, diabetes, dyslipidemia, CHD	2–18	0.0 (−4.0, 3.0)	−2.65* (−4.65, −0.65)	−0.67* (−0.98, −0.36)	nr
Zhu X, 2017 [61]	Resveratrol (8–3000 mg/day)	9 RCT	283 subjects with T2D	4–12	−5.0* (−0.9, −1.0)	−0.64* (−0.95, −0.32)	−0.52* (−1.0, −0.04)	−1.10 (−2.46, 0.26)

Δ = mean change *vs.* control; CHD: coronary heart disease; MS: Metabolic Syndrome; RCT: randomized controlled trial; T2D: type 2 diabetes; *statistically significant; nr = not reported.

Recently, an acute study in healthy subjects has observed a reduction of postprandial insulin response (−31%) and an increased insulin sensitivity (36%) after a test meal preceded by the oral supplementation with a grape pomace-based drink rich in anthocyanins not containing resveratrol [66].

In conclusion, the overall results suggested that polyphenols can improve several parameters related to blood glucose control, in particular fasting glucose and insulin, or HbA1c. The main mechanisms behind these effects are linked to: a) the reduction of carbohydrate digestion triggered by the inhibition of intestinal enzyme; b) the enhancement of glucose uptake; c) decreased gluconeogenesis; d) increased insulin secretion. However, further longer-term studies considering larger population are needed to confirm the effectiveness of polyphenol in the long-term.

Plasma lipids

Growing evidence suggest that the beneficial role of polyphenols in cardiovascular risk reduction is linked to their ability to reduce LDL-cholesterol while increase HDL-cholesterol. In fact, the results of *in vitro* and animal studies have shown that polyphenols may reduce Apo B-containing lipoproteins and increase HDL cholesterol concentrations [67].

A naturally polyphenol-rich diet (3 g/day) significantly reduced fasting and postprandial triglycerides in individuals at high cardiometabolic risk, whereas no effect on LDL and HDL cholesterol was detected [16].

As previously reported, cocoa and chocolate are important source of polyphenols, in particular flavan-3-ols (catechins, anthocyanins and proanthocyanidins). The short-medium term effects (2–18 weeks) of cocoa polyphenols on lipids were evaluated in three meta-analyses of RCTs, in which the flavan-3-ols content ranged from 166 to 2110 mg/day [19,68,69] (Table 4).

In brief, the consumption of cocoa/dark chocolate reduced LDL-cholesterol and marginally total cholesterol, while had no effect on HDL-cholesterol and triglycerides. However, in the meta-analyses by Hooper and colleagues [19], an increase in HDL cholesterol (+1 mg/dl) was detected in long-term studies. Hence, these results suggested that cocoa polyphenols partially affect lipid profile even though differences between RCTs are quite large.

As for tea, animal studies showed that catechins inhibit lipid biosynthesis and intestinal cholesterol absorption [70]. However, the evidence in humans is quite controversial (Table 4). A meta-analysis of 14 RCTs on 1136 subjects showed that consumption of green tea and/or its extracts significantly reduced total and LDL-cholesterol (−7.20 mg/dl and −2.19 mg/dl, respectively), with no effect on HDL [71]. In contrast, a meta-analysis of RCTs in 600 subjects (healthy, individuals with mild hypercholesterolemia, T2D and coronary artery disease) showed that the consumption of black tea or its extracts reduced only LDL cholesterol levels (−5.57 mg/dl) but did not affect total cholesterol and HDL levels [72].

Table 4 Effects of polyphenols on lipid profile: meta-analyses of intervention studies.

	Sources (polyphenol range)	n. studies	Participants	Duration (weeks)	Δ Total cholesterol (mg/dl) (95% CI)	Δ LDL-cholesterol (mg/dl) (95% CI)	Δ HDL-cholesterol (mg/dl) (95% CI)
Zheng XX, 2011 [71]	Green tea and green tea extracts	14 RCT	1.136 subjects healthy and at high cardiometabolic risk	3–12	−7.20* (−8.19, −6.21)	−2.19* (−3.16, −1.21)	0.25 (−0.73, 0.23)
Wang D, 2014 [72]	Black tea and black tea extracts (77.5–1350 mg/day)	15 RCT	605 subjects healthy, hypercholesterolemia, T2D e CHD	3–24	−2.53 (−11.47, 6.40)	−5.57* (−9.49, −1.66)	0.56 (−3.46, 4.58)
Jia L, 2010 [68]	Dark chocolate and cocoa-derived products	8 RCT	215 subjects healthy, prehypertension, hypertension, diabetes	2–18	−5.82 (−12.39, 0.76)	−5.87* (−11.13, −0.61)	1.12 (−2.70, 4.95)
Tokede OA, 2011 [69]	Dark chocolate and cocoa	10 RCT	320 subjects healthy, overweight, hypertension	2–12	−6.23* (−11.60, −0.85)	−5.90* (−10.47, −1.32)	−0.76 (−3.02, 1.51)
Hooper L, 2012 [19]	Cocoa, cocoa derived products and flavan-3-ols	21 RCT	986 subjects healthy, overweight, hypertension, diabetes, dyslipidemia, CHD	2–18	−2.0 (−4.0, 1.0)	−3.0 (−5.0, 0.0)	1.0 (0.0, 2.0)
George ES, 2018 [74]	Polyphenol-rich olive oil	12 RCT	subjects healthy and at high cardiometabolic risk	3–12	−4.5* (−6.54, −2.39)	−3.54 (−7.27, 0.19)	2.37* (0.41, 5.04)
Sahebkar A, 2013 [93]	Resveratrol (8–1500 mg/day)	7 RCT	282 subjects diabetes, dyslipidemia, hypertension, MS, CHD	4–24	−8.70 (−21.54, 4.14)	−3.22 (−12.56, 6.12)	−0.26 (−4.25, 3.73)

Δ = mean change vs. control; CHD: coronary heart disease; MS: Metabolic Syndrome; RCT: randomized controlled trial; T2D: type 2 diabetes; *statistically significant.

More recently, a double-blind RCT, 1-year catechin supplementation (1315 mg/day catechins of which 843 mg/day of EGCG) significantly reduced total cholesterol (−2.1%), LDL (−4.1%) and non-HDL cholesterol (−3.1%) [73]. Interestingly, the greatest effect was observed in participants with higher cholesterol concentrations (≥200 mg/dl) at baseline. Therefore, the results of these studies suggest that green tea, but not black tea, may improve lipid profile.

Looking at other sources of polyphenols, extra-virgin olive-oil has shown a potential role as plasma lipid-modulator. As a matter of fact, in a recent meta-analysis of 26 RCTs [74], daily consumption of polyphenol-rich oil reduced total cholesterol (−4.5 mg/dl) and increase HDL cholesterol (on average 2.37 mg/dl). However, it should be noted that most of the studies included in the meta-analysis derived only from two cohorts in the European Mediterranean area; therefore, the benefits of olive oil-polyphenols need to be confirmed in non-Mediterranean populations.

Undoubtedly, fruit represent important polyphenols-rich foods, mainly flavonols, anthocyanins and proanthocyanidins. Berries have shown to increase significantly HDL-cholesterol concentrations in overweight/obese subjects in medium-term RCTs [75]. Considering specific type of berries, strawberries extracts exhibited a great lowering-effect on total and LDL-cholesterol (−10% and −11%, respectively) [76], as well as on triglyceride in individuals with high cardiometabolic risk [77]. Otherwise, no effect was observed on fasting lipids concentration [77] (Table 4).

No significant changes in plasma lipids were reported after the consumption of other type of berries, i.e. blueberries [78,79] and grape powder [80].

Moreover, citrus fruits have been identified as potential cholesterol-lowering compounds because of their flavanones content (naringin and hesperidin) [81]. However, evidence from RCTs did not confirm the beneficial effects of citrus fruit-extract supplementation in humans [82,83].

Recently, apple polyphenols (mainly procyanidins), have also shown a potential lipid-lowering effect when they are supplemented as extracts [84], whereas no effects were observed after apple-juice consumption [85].

As for grape, more studies are available, but the results are not conclusive. In particular, Castilla and colleagues [86,87] reported a significant improvement of several lipid parameters (total, LDL- and HDL-cholesterol, Apo B-100 and Apo A-1) after 14 day-supplementation with concentrated grape juice (640 mg of polyphenols) in healthy subjects and in hemodialysis patients. On the contrary, short-term RCTs (2 weeks) carried out in healthy subjects and/or with coronary artery disease detected an increase in fasting triglycerides with no effects on total cholesterol and its fractions (LDL and HDL) [88,89].

Similarly, grape-extracts-based interventions in individuals with high cardio-metabolic risk did not provide convincing results [90–92] Finally, a meta-analysis of 7 RCTs considering individuals with diabetes, dyslipidemia,

hypertension and coronary artery disease (n = 282) showed that resveratrol supplementation did not influence any of the lipid parameters [93] (Table 4).

In conclusion, the evidence available so far do not establish the lipid-lowering effect of polyphenols. Nevertheless, some animals and in *vitro* models have shown that polyphenols can inhibit pancreatic lipase, reducing fat digestion and cholesterol absorption, and consequently the secretion of chylomicrons and LDL due to reduced lipid availability in hepatocytes [94,95].

Studies focusing on tea, cocoa/dark chocolate and olive oil suggest a beneficial effect of polyphenol on lipid profile. However, further high-quality studies are needed to confirm this effect and to establish the effective dose to be consumed.

Blood pressure

Blood pressure (BP) control reduces the incidence of cardiovascular complications. Recently, observational studies have suggested a possible favorable effect of polyphenols on systolic (SBP) and diastolic (DBP) BP. In particular, an inverse relationship between the intake of polyphenols and BP has been detected in a large cohort of individuals with T2D [33]. Moreover, a cross-sectional study showed that the highest consumption of tea or 4-O-methylgallic acid (a biomarker of tea intake) is associated with significantly lower rates of SBP in 218 women [96].

As for tea polyphenols, two meta-analyses [97,98] clearly showed that tea consumption (1–24 weeks) significantly reduced PAS and PAD in normotensive and hypertensive individuals (Table 5).

Greater reduction of BP levels was obtained in RCTs with cocoa and cocoa-derived products [99,100], even in a more recent meta-analyses [19] a reduction of PAD but not PAS was detected.

Interestingly, Rodriguez-Mateos et al. [101] evaluated the effects on BP of two cocoa-extracts with different degrees of polymerization. The results showed that monomeric component improved endothelial function, vessel rigidity and PAS in healthy subjects, suggesting that the reduction of CVD risk linked to the consumption of cocoa-derived products is driven by this flavanols.

The effects of grape polyphenols on BP were evaluated in 3 meta-analyzes [102–104] (Table 5). Overall, the evidence showed that grape-polyphenol significantly affected PAS and PAD levels. The effect was greater in obese subjects and in individuals with metabolic syndrome (Zhang et al., 2016), and when low doses (<733 mg/day) are supplemented [102].

Finally, olive-oil polyphenols have been extensively studied. Their beneficial effect on BP has been observed after the long-term consumption of olive oil (30–50 ml/day) in normotensive or low-hypertensive individuals [105], and hypertensive patients with stable coronary artery disease [106]. Recently, the lowering-BP effect of olive-polyphenol in healthy individuals has been

Table 5 Effects of polyphenols on blood pressure: meta-analyses of intervention studies.

	Sources (polyphenol range)	n. studies	Participants	Duration (weeks)	Δ Systolic blood pressure (mmHg) (95%CI)	Δ Diastolic blood pressure (mmHg) (95%CI)
Liu G, 2014 [97]	Green and black tea	25 RCT	1.476 subjects healthy, hypertension, dyslipidemia and CHD	1–24	−1.8* (−2.4, −1.1)	−1.4* (−2.2, −0.6)
Peng X, 2014 [98]	Green tea (208–1207 mg/day)	13 RCT	1.367 subjects prehypertension, hypertension	3–12	−1.98* (−2.94, −1.01)	−1.92* (−3.17,-0.68)
Desch S, 2010 [99]	Cocoa derived products	10 RCT	297 subjects healthy, prehypertension, hypertension	2–18	−4.5* (−5.9, −3.2)	−2.5* (−3.9, −1.2)
Ried K, 2009 [100]	Cocoa and dark chocolate (30–1000 mg/day)	15 RCT	476 subjects healthy and hypertension	2–12	−3.2 ± 1.9* (M±SE)	−2.0 ± 1.3* (M±SE)
Hooper L, 2012 [19]	Cocoa, cocoa derived products	22 RCT	918 subjects healthy, overweight, CHD hypertension, diabetes, dyslipidemia,	2–18	−1.50 (−3.43, 0.3)	−1.60* (−2.77, −0.43)
Li SH, 2015 [102]	and flavan-3-ols Grape extracts (150–1.400 mg/day)	10 RCT	561 subjects healthy, hypertension, MS	2–16	−1.48* (−2.79, −0.16)	−0.50 (−1.46, 0.46)
Feringa HH, 2011 [103]	Grape seed extracts	9 RCT	390 subjects hypertension, MS, diabetes, hypercholesterolemia	2–24	−1.54* (−2.85, −0.22)	−0.65 (−1.67, 0.36)
Zhang H, 2016 [104]	Grape seed extracts (100–2000 mg/day)	16 RCT	810 subjects healthy, prehypertension, hypertension, MS	2–16	−6.07* (−10.7, −1.4)	−2.8* (−4.4, −1.18)

Δ = mean change vs. control; CHD: coronary heart disease; MS: Metabolic Syndrome; RCT: randomized controlled trial; *statistically significant.

confirmed also with the supplementation of olive-derived extracts (136 mg of oleuropein and 6 mg of hydroxytyrosol) [107].

In conclusion, the overall results suggest that polyphenols contained in tea, cocoa, dark chocolate, grapes and olive oil have favorable effects on blood pressure, likely through the improvement of endothelial vasodilation.

However, further long-term RCTs evaluating different doses of polyphenols are needed to definitively establish whether polyphenols can improve blood pressure.

Inflammation

Scientific evidence indicates that low-grade chronic inflammation, named subclinical inflammation, is strictly related to the development of chronic-degenerative diseases, primarily T2D and CVD.

So far, meagre evidence is available from RCTS evaluating polyphenols effects on inflammatory markers.

As an example, only three studies were carried out with green tea. The results showed no significant changes of inflammatory status after short- and medium-term consumption of green tea in adult smokers [108], in obese women [109] or in individuals with T2D [110].

Regarding cocoa-derived products, the available evidence suggest that cocoa polyphenols reduced some inflammatory biomarkers (IL-1β, IL-10, ICAM-1, MCP-1, VCAM-1 or P-selectin) in individuals with higher-grade of inflammation (individuals with hypercholesterolemia or end-stage renal disease) than in healthy subjects [111–114].

As for fruit polyphenols, short term RCTs (1–4 weeks) focusing on blueberries, grapes, rhamnus, apple and pomegranate have shown a significant reduction in inflammation markers, including IL-6, PCR and tumor necrosis factor (TNF-α) in healthy or hyperinsulinemic subjects, and individuals at high-cardiometabolic risk [115–121]. However, other studies observed no difference of the same markers [80,85].

Medium and long-term RCTs (5 weeks–18 months) with the supplementation with fruit polyphenols (as food or extracts) provided conflicting results independently from the source of polyphenol (grapes, raisins, strawberries, blueberries, citrus fruits, aronia and pomegranate), study population (healthy subjects, individuals with cardiovascular risk factors or end-stage renal disease). Indeed, a significant reduction in inflammation was found in six studies [122–127] whereas no changes were observed in seven trials [78,79,128–132].

Finally, a meta-analysis of 5 randomized trials [133] reported no significant PCR changes after an intervention with pomegranate juice.

Looking at other polyphenol, red wine and resveratrol have been accounted for their anti-anti-inflammatory and anti-atherogenic effects. In healthy adults, 4-week red wine intake significantly reduced PCR and IL-6 levels, improved the response of platelet and leukocyte adhesion molecules (sP-selectin and sE-selectin) [65,134,135]. However, considering resveratrol as supplement, a meta-analysis of 11 randomized controlled trials [136] observed no effect on PCR concentrations.

In conclusion, the conflicting results provided by RCTs do not support the anti-inflammatory activity of dietary polyphenols.

Conclusions

Epidemiological evidence supports the beneficial effects of polyphenol-rich diets in the prevention of T2D risk.

So far, the results provided by RCTs did not allow the identification of specific phenolic compounds or polyphenol-rich foods that effectively improve cardiometabolic risk factors. The major flaws related to the studies are: poor-quality of study planning, inadequate sample size, and huge variability of polyphenol amount.

The most promising results in terms of the management of cardio-metabolic risk factors derive from RCTs based on the long-term intake of polyphenol-rich foods and beverages. Therefore, future studies should focus on a diet containing different classes of polyphenols rather than a specific food or phenolic compound. The hypothesis is that a polyphenol-rich diet may have a pleiotropic effect on cardiometabolic risk factors thanks to the specific action of different polyphenol subclasses.

In conclusion, the lack of conclusive evidence on the effectiveness of polyphenols in the management of cardiometabolic risk factors does not allow recommending their use as supplements to reduce T2D and CVD risk. However, the daily consumption of naturally polyphenol-rich foods and beverages might be advised according to the current nutritional dietary recommendation. In this light, the Mediterranean diet or other plant-based diets may represent the gold standard for adequate polyphenol dietary intake.

Conflicts of interest

None declared.

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