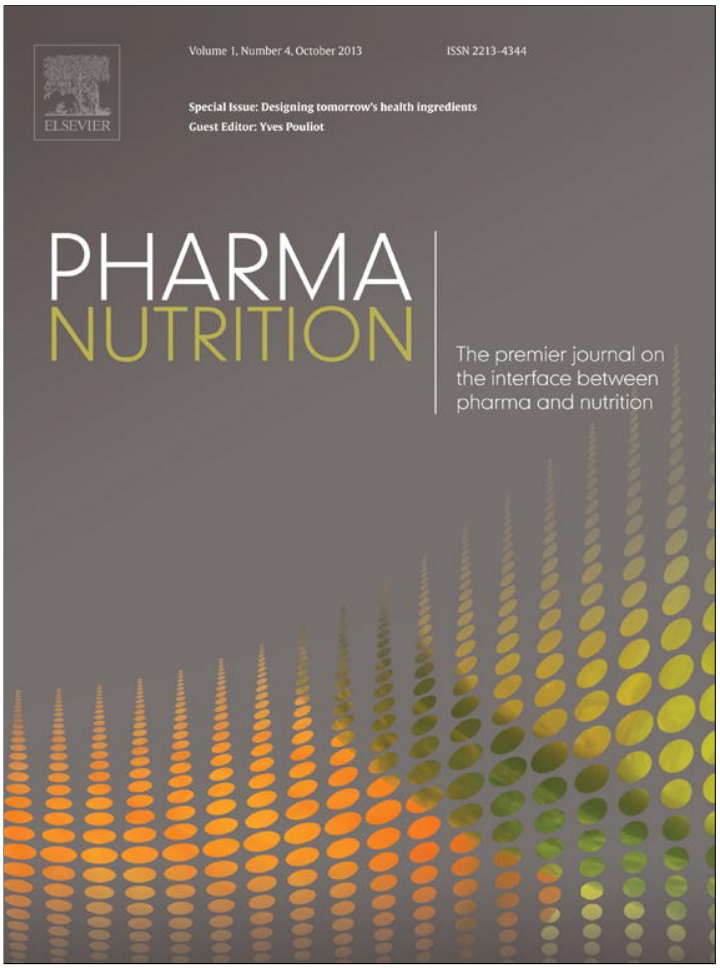

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Polyphenols and type 2 diabetes: A prospective review

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ABSTRACT

Nutritional overload and a sedentary life-style are directly associated with the growing prevalence of type 2 diabetes (T2D). However, a diet rich in fruits and vegetables is inversely correlated to the incidence of T2D, being these beneficial effects largely attributed to phenolic compounds. Human studies using the most promising polyphenol-rich foods to ameliorate T2D have not been as successful as *in vitro* and animal studies have pointed out, evidencing the need for new approaches in order to reduce this current gap. Nevertheless, modern techniques have not only optimized the extraction and the characterization of phenolic metabolites, but have also allowed a better understanding of the impact of polyphenols on the gut microbiota. In this article we provide an overview of the mechanisms implicated in the beneficial metabolic effects of polyphenols and we highlight the investigation of the metabolomes associated to the ingestion of polyphenol-rich foods. These strategies will help in the identification of bioactive phenolic metabolites from various fruits and plants, leading to the discovery of novel cultivars to generate more potent functional foods and nutraceuticals against T2D.

1. Introduction

Typical habits of modern societies push individuals toward nutritional overload and a sedentary life-style. This disturbing reality is evidenced by the exponential rise in the prevalence of type 2 diabetes (T2D), which is estimated to reach the appalling rate of 300 million cases by 2030 [1]. An increasing risk of developing T2D and cardiovascular disease is frequently a consequence of a combination of pathological conditions known as metabolic syndrome, which comprises obesity, hyperglycemia, glucose intolerance, dyslipidemia and hypertension [2]. Furthermore, it is consensual that an interplay between genetic background and environmental influences (*e.g.* sedentary habits and excess of energy intake) promotes insulin resistance, considered as an early manifestation of T2D [3–5]. Insulin resistance is related to a low-grade subclinical inflammation, evidenced by an increased release and action of proinflammatory cytokines, proteins which can impede insulin action in skeletal muscle, liver and adipose tissue [6–10]. Obesity-linked T2D is associated with macrophage infiltration in adipose tissue leading to the release of pro-inflammatory cytokines and activation of inflammatory signaling pathways [9,11,12]. A growing body of evidence also indicates that the intestinal epithelium is also subject to inflammation in obesity and that changes in the gut microflora may be the underlying cause. Indeed, recent studies suggest that dysbiosis, changes in the composition and/or activity of gut microbiota, affect host metabolism, linking genes, environment and the immune system [13,14]. For instance, it is now recognized that gut microbiota-derived lipopolysaccharide (LPS) is a key factor involved in the onset and progression of inflammation in obesity.

Recent research strongly supports the concept that the consumption of fruits and plant-derived foods is inversely correlated with T2D prevalence and the occurrence of cardiometabolic complications [15–19]. It has been suggested that 90% of T2D cases could be potentially prevented by lifestyle modifications [20], including increased physical activity, weight loss and consuming a diet rich in plant-derived foods (*e.g.* whole grains, fruits and vegetables) [21]. Implementation of a fruit-based diet against obesity and T2D would not only help adherence to a dietary treatment but could also help raise the awareness about some relatively uncommon fruits from traditional diets of indigenous and/or economically disadvantaged populations [22]. Nevertheless, human studies using the most promising plant-derived foods in order to improve chronic diseases like T2D and its cardiovascular complications have not been as successful as *in vitro* and animal

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studies had promised [23]. In this review we aim to discuss recent evidences of the antidiabetic effects of some phenolic phytochemicals and to provide a prospective view on the potential of dietary fruits or fruit-based functional foods as a nutritional strategy to prevent or treat T2D. We will emphasize the use of metabolomic approaches and determination of gut microbiomes to help decipher the nature of the polyphenolic metabolites involved in the health effects of fruits as well as the underlying mechanisms behind their antidiabetic actions, thus aiming to reduce the current gap between promising *in vitro* and animal studies and the limited success of previous human trials.

2. Polyphenols

The beneficial health effects of plant-derived products have been largely attributed to polyphenolic compounds, as well as vitamins, minerals and dietary fibers [24–28]. Although the positive role of antioxidant vitamins in the metabolic syndrome is still controversial [29–31], interesting data suggests that high levels of vitamin D are related to a lower risk of developing T2D [32]. Despite the relevance of other phytochemicals than polyphenols to the health-supporting effects of fruits and vegetables, this review will particularly focus on the importance of polyphenols as active molecules against T2D. Polyphenols occur as products of the plant secondary metabolism in response to biotic and abiotic stress [33,34]. Phenolic phytochemicals can exist as simple phenolic acids (*i.e.* hydroxybenzoic acids or hydroxycinnamic acids) or as flavonoids, C6-C3-C6 molecules with two aromatic rings (*i.e.* rings A and B) linked by three carbons usually arranged as an oxygenated heterocycle (*i.e.* ring C). Flavonoids are classified according to the degree of oxidation of the ring C into anthocyanins, flavonols, flavones, flavanols (also named catechins), flavanones and isoflavones; they also occur as oligomers and polymers (*i.e.* tannins), classified as condensed tannins (also known as proanthocyanidins or procyanidins) or hydrolysable tannins [35,36]. Proanthocyanidins are polymers of catechins, and their structure is dependent both on the kind of monomer and the type of linkage between monomers; hydrolysable tannins consist of a central core constituted by a polyol (*e.g.* flavonoid, sugar) and a phenolic carboxylic acid esterifying the core molecule. Stilbenoids (*e.g.* resveratrol) and lignans comprise two other classes of non-flavonoid polyphenols. Most flavonoids are present in nature as O-glycosides and other conjugates (catechins are an exception), which contribute to their complexity and the large number of individual molecules that have been identified (>5000) [37].

Phenolic phytochemicals are generally thought to be poorly absorbed after dietary intake [36]. In fact, using very high concentration of polyphenols in *in vitro* studies does not represent *in vivo* conditions. It is important to consider both the nature and the bioavailability of polyphenols in order to unveil their physiological effects in target organs and cells. Once ingested, phenolic compounds are partly absorbed by the stomach and small intestine (Fig. 1) [36], and hydrolysis of the glycoside moiety seems to be a requisite step for absorption at this level. Hence, type and position of the sugar linked to flavonoids and the degree of polymerization or galloylation of flavanols (catechins) have been

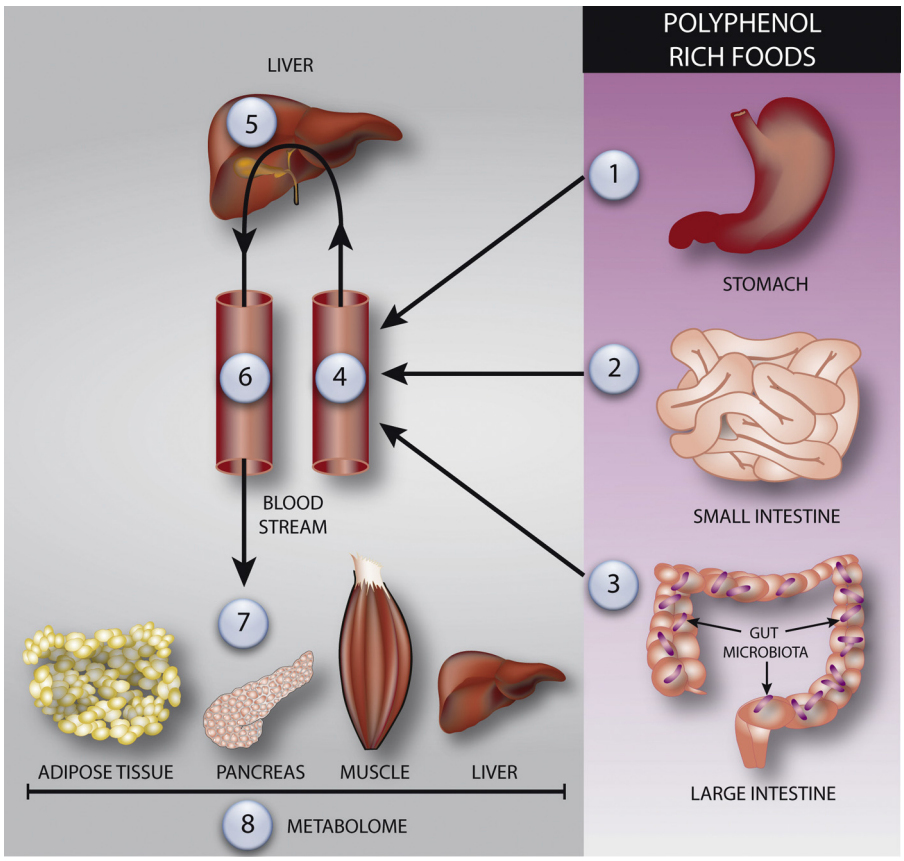

Fig. 1. After intake, some polyphenols are directly absorbed through the stomach and the small intestine (1, 2). The gut microbiota present in the small intestine is not represented in this figure. The majority of the ingested polyphenols reach the large intestine, thereafter undergoing intensive gut microbiota metabolization prior to absorption (3). Some polyphenols are thought to stimulate the growth and activity of bacteria in the digestive tract in ways to be beneficial to health (*i.e.* prebiotic effect). Polyphenols coming from microbial transformation, as well as stomach and intestinal absorption, reach the liver through the enterohepatic circulation (4), being thus subjected to phase I and II biotransformation in the liver (5). Polyphenol metabolites derived from liver metabolization reach the blood stream (6) to be thereafter distributed through peripheral tissues in order to exert beneficial metabolic effects (7). The identification of the polyphenol metabolites present in the peripheral blood and in the tissues (*i.e.* metabolome) is crucial to understand the antidiabetic effects of polyphenols and also essential in order to synthetize nutraceuticals and functional foods in the future (8).

shown decisive for absorption. The flavonol quercetin has been the most extensively studied, but it appears that other flavonoid subclasses follow similar mechanisms. The ATP-binding cassette transporter multidrug resistance protein (MRP), together with intestinal SGLT1, have been implicated in flavonoid absorption [38]. Endogenous β-glucosidases present in the intestinal brush border (*i.e.* lactase phloridzin hydrolase – LPH and cytosolic-β-glucosidase – CBG] are capable of hydrolyzing flavonoids to generate more lipophilic, thus absorbable, aglycones [39,40]. As CBG is a cytosolic enzyme, SGLT1 transport would be necessary in order to allow the β-glucosidase action of this enzyme [41]. Polyphenols which are not directly absorbed reach the colon to be intensively metabolized by gut microbiota into a complex series of end-products that support a significant effect on the functional ecology of symbiotic partners that can affect host physiology (Fig. 1) [42]. Gut microbiota exhibits a much greater and distinct repertoire of metabolizing enzymes, thus being capable of undergoing O- and C-deglycosylation, ester and amide hydrolysis, deglucuronidation of large flavonoids and fermentation of the flavonoid backbone. Fermentation allows breakage of aromatic rings followed by the release of phloroglucinol, hydroxylated forms of phenylpropionate and phenylacetate, short-chain fatty acids, lactate, succinate, oxaloacetate, ethanol, CO_2 and H_2 [42].

An important comparative study showed that the best absorbed polyphenols are, in descending order, gallic acid, isoflavones, catechins, flavanones and quercetin glucosides. Hence, gallic acid, quercetin glucosides, catechins, free hydroxycinnamic acids and anthocyanins are mostly absorbed in the stomach and small intestine, reaching C_{max} in about 1.5 h. Rutin (*i.e.* quercetin-3-O-rutinoside) and flavanones are highly dependent on the release of aglycones by the gut microbiota prior to absorption, reaching C_{max} in about 5.5 h. Interestingly, gallic acid, catechins and flavanones hardly accumulate, while quercetin is able to considerably build up in the plasma [36]. Anthocyanins, which predominantly occur as 3-O-glycoside and 3,5-di-O-glycoside forms in nature, are thought to be poorly bioavailable, but it is important to consider that their rapid degradation probably underestimates their plasmatic levels [38]. It is noteworthy that anthocyanins have been reported intact in plasma, being capable of accumulating in different organs [43–45].

After absorption, polyphenols undergo extensive biotransformation by enterocytes and liver (Fig. 1), a necessary step aiming to increase hydrophilicity therefore favoring urinary excretion. Sulfation, glucuronidation, methylation and glycine-conjugation are the most common biotransformation reactions [42]. Importantly, liver may play a larger role in the metabolism of flavonoids absorbed in the small intestine compared to metabolism of compounds taken up by colon [35]. Polyphenols are not able to saturate metabolic pathways similarly to drugs, thus hindering the establishment of high plasma levels [46]. The exact polyphenol metabolite profile in plasma is often not assessed and poorly understood, although these metabolites probably have more potent properties than polyphenols in their core state [47,48]. Flavonoid amount in the gastro-intestinal tract reaches concentrations equal or frequently greater than μM values, with a high presence of oligomers/polymers of flavonoids along with by-products of colonic microbiota. On the other hand, in the plasma and extracellular fluid, the concentration of polyphenols remains approximately in the μM range, with little presence of oligomers/polymers but abundant in products of enterocyte and liver metabolism. In the intracellular environment, polyphenols are probably present at nM or pM concentrations, while oligomers/polymers are absent with products of reconjugation still playing an important role [49]. Finally, absorption of flavonoids may be influenced by dosage, vehicle of administration, prior diet, food matrix, gender and differences in the gut microbial populations [35,50].

3. Polyphenols and type 2 diabetes: overview of potential mechanisms of action

It has been proposed that consumption of phenolic compounds could help explain the so-called French paradox since people in France have lower cardiovascular events despite their relatively high intake of dietary fat as compared to many other countries. Indeed, resveratrol, quercetin and catechins are abundant polyphenols in red wine, and a positive relation between the consumption of these compounds and longevity have been proposed [51]. However, the physiological mechanisms involved in the beneficial effects of polyphenols still remain poorly understood.

The health benefits of polyphenols are generally attributed to both non-specific mechanisms, dependent upon a broad antioxidant activity, and specific mechanisms, which comprise interactions with key signaling proteins [52]. Moreover, the *in vitro* activity of polyphenols strongly suggests that their role extends much beyond their ability to limit oxidative processes as they have been also shown to modulate metabolic enzymes, nuclear receptors, gene expression and multiple signaling pathways [53]. Indeed polyphenols have been suggested to ameliorate important hallmarks of T2D (*e.g.* fasting and postprandial hyperglycemia) by inhibiting disaccharidases (*i.e.* α-amylase and α-glucosidase) in the intestinal lumen [24]. This can limit the digestion of polysaccharides in the diet, therefore reducing the absorption of simple sugars. On the other hand, skeletal muscle represents a significant mass of tissue and an increase in this tissue's uptake of glucose contributes significantly to keep blood sugar at low levels; this being also true, albeit to a lesser extent, for uptake of glucose by adipose tissue. Interestingly, polyphenols may also exert important antidiabetic effects by improving glucose uptake in muscle and adipocytes [24]. The liver is an important player in the onset of the dyslipidemic and hyperglycemic conditions that characterizes T2D, being hepatic insulin resistance notably related to reduced glucose storage and enhanced glucose production. Polyphenols may also exert antidiabetic effects by increasing hepatic glucokinase activity, which augments glucose utilization to promote energy storage in the form of glycogen, and by suppressing hepatic glucose output (*i.e. gluconeogenesis*) [24]. Additionally, chronic hyperglycemia and hyperlipidemia can exert deleterious effects on β-cell function, respectively referred to as glucotoxicity and lipotoxicity. Over time, both contribute to the progressive deterioration of glucose homeostasis characteristic of T2D [54,55]. In this sense, polyphenols have been suggested to protect pancreatic β-cells from glucotoxicity and to improve insulin secretion, thus alleviating T2D by acting on insulin secreting cells [24].

Considering that obesity-linked T2D is associated with a low-grade inflammatory state [6–10], it has also been proposed that polyphenols can protect against T2D through anti-inflammatory effects [56–58]. For instance, polyphenols such as curcumin, capsaicin, gingerol, catechins, resveratrol and quercetin have been shown to exert anti-inflammatory effects by directly blocking mitogen-activated protein kinase (MAPK) pathways, NFκB activity and the expression of inflammatory cytokines [59–74]. Interestingly, the anti-inflammatory effects of capsaicin, resveratrol and genistein have been suggested to involve, at least in part, direct activation of peroxisome proliferator-activated receptor γ (PPARγ)[63,64,75,76]. PPARγ is a major regulator of various aspects of lipid metabolism and adipocyte differentiation, but it is also implicated in the inhibition of inflammatory genes like inducible nitric oxide synthase (iNOS), AP-1, NFκB and MAPK [77–80]. PPARγ is a target of Thiazolidinediones (TZD), a widely used class of antidiabetic drugs [77]. The isoflavones genistein and daidzein, extracted mostly from soybeans, are also well established

PPARγ ligands. In addition, other phytochemicals such as ψ-baptigenin, hesperidin, 2′-hydroxy chalcone and possibly some metabolites of quercetin have also been suggested to be PPARγ ligands [81]. However, similarly to endogenous ligands of PPARγ, the *in vitro* binding and activation of PPARγ by these compounds does not necessarily mean that they can reach concentrations that can induce PPARγ-mediated effects *in vivo*.

Anthocyanins are flavonoids abundantly present in berries and whose intake has been estimated to be 180–215 mg per day among the US population [82]. This consumption exceeds the estimated intake of 23 mg per day of other flavonoids such as luteolin, kaempferol, myricetin, apigenin and quercetin [83]. Anthocyanins are well recognized for their anti-oxidative and anti-inflammatory properties and have been shown to ameliorate obesity-related pathologies in rodent models [84–88]. Lefevre and colleagues orally administrated a low dose (2.15 mg/kg) of an anthocyanin-rich extract in mice fed a high fat high cholesterol diet and performed a broad microarray analysis of gene expression. Interestingly, they showed that anthocyanin administration led to alterations in substrate metabolism in liver by modulation of specific nuclear hormone receptors and transcription factors such as liver X receptor, PPARα, PPARδ, PPARγ, sterol regulatory element binding protein (SREBP)-1c and PPARγ coactivators 1α and 1β [89]. They also reported downregulation of genes involved in the oxidative stress and endoplasmic reticulum (ER) stress in liver, as well as downregulation of pathways implicated in inflammatory responses in liver and in muscle [89]. It is noteworthy that the so-called unfolded protein response (UPR) is activated by endoplasmic reticulum (ER) stress, which is a consequence of an imbalance between ER protein folding capacity and ER protein load; moreover ER stress is activated in various tissues under obesity and T2D-related conditions activating inflammatory pathways by JNK-NFκB-dependent mechanisms [90]. Another important feature linking inflammation and obesity-induced T2D is the increased immune cell infiltration in the adipose tissue. Infiltrating macrophages, as well as other immune cells and adipocytes, participate in the release of cytokines and biologically active molecules (*e.g.* NO, TNF-α, IL-6 and IL-1) implicated in the chronic inflammatory state associated with insulin resistance [9,11,12]. In this context, cyanidin-3-O-β-glucoside and its main metabolite (*i.e.* protocatechuic acid, PCA) have been reported to reduce macrophage infiltration in mice *via* downregulation of CC chemokine receptor 2 (CCR2), while cyanidin-3-O-β-glucoside alone has been shown to inhibit IκBα phosphorylation *in vitro*, thereby suppressing NFκB activity and reducing LPS-stimulated TNFα and IL-6 expression [91,92]. More recently, it has been proposed that PCA, a product of cyanidin-3-O-β-glucoside metabolism by the gut microbiota, can limit atherosclerosis by a microRNA-dependent mechanism regulating ABCA1 and ABCG1 receptor-mediated cholesterol efflux [93]. Since another ATP-binding cassette transporter (*i.e.* multidrug resistance protein – MRP) has been implicated in flavonoid absorption [38], it would be interesting to evaluate if microRNA-mediated regulation of ABC transporters would affect flavonoid absorption. The potential involvement of microRNA in the mechanisms behind beneficial actions of flavonoids may hold great promise for T2D prevention.

Another important mechanism of action of polyphenols relates to potential effects on a class of proteins known as Sirtuins. Sirtuin1 (SIRT1) is a type III protein deacetylase implicated in anti-aging and anti-inflammatory effects and whose activity brought into evidence an interesting target against T2D and other chronic diseases. Over the last decade, resveratrol, a non-flavonoid polyphenol abundant in grapes and cranberry, has been shown to directly activate SIRT1 *in vivo* and to exert calorie restriction-like benefits [94–96]. On the other hand, recent data suggest that resveratrol is not a direct activator of SIRT1, but rather a positive regulator of AMP-activated kinase (AMPK), a master regulator of glucose and lipid metabolism and capable of activating SIRT1 [97–102]. Hence, quercetin, catechins, butein, piceatannol and myricetin have been shown to activate SIRT1 [103–106], probably as a result of AMPK regulation. Indeed, polyphenols are known to play a defensive role in plants, acting against potential biological threats by disrupting energy transduction pathways, such as mitochondrial oxidative phosphorylation [107]. This effect is a consequence of mitochondrial proton gradient dissipation (*i.e.* uncoupling effect) and/or inhibition of the electron transport chain or ATP synthase [107–109]. Such mitochondrial effects result in a reduction in the ATP/AMP ratio, which activates AMPK [110,111]. Several polyphenols likely use this mechanism as shown *in vitro* (*e.g.* curcumin [112–114], capsaicin [115], catechins [115,116], resveratrol [117], genistein [115], quercetin [22]) and *in vivo* (*e.g.* genistein [118], quercetin [119,120]) to stimulate glucose uptake and oxidation, fatty acid catabolism and inhibition of adipogenesis. Nevertheless, it is important to consider that the beneficial effects arising from mitochondrial proton gradient dissipation are possible if the inhibition of energy transduction pathways is mild and transient, generating the so-called "straightforward hormetic effect" [22,121,122]. Intense mitochondrial uncoupling effect could lead to excessive production of protons and depletion in intracellular ATP, triggering metabolic acidosis. Interestingly, Howitz and Sinclair consider the "straightforward hormetic effect" unlikely as the primary mode of action, at least for mammals and their responses to the most common dietary phytochemicals, since compounds as quercetin and resveratrol are abundant and nontoxic foodstuffs, even when administrated in pure forms [123,124]. In order to explain how plant molecules interact with and regulate key modulators of mammalian physiology, Howitz and Sinclair proposed the xenohormetic theory. In brief, the polyphenol content in a plant provides a chemical signature of the state of the environment, since the synthesis of polyphenols is driven in response to biotic and abiotic stress. After ingestion of plants, polyphenols come into contact with receptors and enzymes. Xenohormesis is explained by the fact that stress-induced plant compounds tend to upregulate pathways that provide stress resistance in animals, suggesting that plant consumers, after being subjected to a selective pressure to do so, may have mechanisms to perceive these chemical cues and react to them in ways that are beneficial [124].

In 2001, Brownlee suggested an unifying hypothesis, attributing to mitochondrial generation of reactive oxygen species (ROS) several molecular mechanisms related to the pathogenesis of T2D (*i.e.* PKC and NFκB activation, polyol and hexosamine pathway flux, advanced glycosylation end-products formation) [125]. Interestingly, capsaicin (abundant in chili peppers), genistein (a soybean isoflavone) and catechins (abundant in green tea) have all been shown to induce uncoupling protein 2 (UCP2) expression in WAT, therefore suggesting an UCP2-dependent buffering of ROS in mitochondria [126–128]. Furthermore, polyphenols may be capable of inducing natural antioxidant defenses by the body as reflected by stimulation of synthesis of glutathione or activation of antioxidation enzymes like glutathione-S-transferase, thioreductases and peroxidases [129–131].

Insulin resistance and T2D are strongly associated with positive energy balance and the accumulation of visceral/ectopic fat [2]. Therefore, increasing energy expenditure and limiting energy storage in visceral fat and non-adipose tissues constitutes a valid antidiabetic strategy. Activation of brown adipose tissue (BAT) which can dissipate stored lipids as heat (*i.e.* thermogenesis), as well as transdifferentiation of WAT into a BAT-like tissue (*i.e.* "browning" or brown remodeling of WAT) have recently re-gained interest as potential modulators of energy balance and adiposity

[132]. Catechins, abundantly present in green tea, are thought to inhibit catechol-o-methyl transferase (COMT), an enzyme that degrades norepinephrine (NE), therefore increasing the presence of NE within the synaptic cleft and leading to prolongation of NE-induced thermogenesis and fat oxidation in BAT. In fact, ingestion of green tea catechins is related to increased energy expenditure, a shift from carbohydrate to fat oxidation and increased urinary excretion of NE [133–137]. Additionally, capsaicin (abundant in chili peppers) and genistein (a soybean isoflavone) have also been shown to increase energy expenditure [126–128], and a reduction in body mass gain was detected in gray mouse lemur primates after resveratrol administration [138]. Recently, a SIRT1-dependent PPARγ deacetylation has been shown as a form of selective PPARγ modulation, leading to induction of BAT genes and repression of visceral WAT genes associated with insulin resistance [139]. In the face of these evidences, it is reasonable to speculate that polyphenols, by AMPK-SIRT1-PPARγ-dependent mechanisms, might exert a myriad of anti-inflammatory, anti-obesity, anti-steatosis and hypoglycemic effects, and that such effects are most likely a consequence of a synergistic action of various metabolites of polyphenols.

4. Polyphenols and gut microbiota

A role for the gut microbiota in the etiology of obesity and T2D has been proposed by Backhed and colleagues when they showed that germ-free mice had 40% less total body fat than conventionally raised mice, even when their caloric intake was 29% higher than the normal group. After gut colonization, previously germ-free mice displayed a 57% increase in total body fat, a 2.3-fold increase in hepatic triglycerides and a dramatic increase in insulin resistance, without affecting food consumption or energy expenditure [140]. Thus, gut microbiota is now considered an important player in the interplay between genetic changes and environmental challenges as well as in the immune-metabolic perturbations of obesity and related inflammatory disorders. Obese individuals have a typical imbalance in their gut microbiota profile characterized by an increased number of bacteria belonging to the phylum *Firmicutes* along with a drop in the number of bacteria from the phyla *Bacteroidetes* and *Proteobacteria* [141–143]. However, the proposed link between the gut microbiomes and obesity is far from being consensual: there are studies showing lower *Firmicutes*/*Bacteroidetes* ratio in overweight human adults compared to lean subjects [144] and no relation between weight loss and changes in the *Firmicutes*/*Bacteroidetes* ratio [145]. Despite this debate, "obese" microbiomes are thought to (i) impact on signals modulating genes involved in lipid metabolism (*e.g.* suppressing intestinal secretion of fasting-induced adipose factor (FIAF), which is capable of preventing fat storage and stimulating fat mobilization); (ii) to modulate energy harvest and nutrient availability, as a result of increased bacterial capacity of breaking otherwise indigestible polysaccharides, along with increased gut permeability and reduced gut mobility; (iii) to be associated with increased bacterial lipopolysaccharide (LPS) absorption, which may trigger the gut/adipose inflammatory axis in obesity-linked T2D (*i.e.* metabolic endotoxemia) [146,147]. Interestingly, genetic models of diabetic mice fed a standard chow diet still develop metabolic endotoxemia, providing strong evidence that the gut microbiota contributes to inflammation even without excessive dietary fat intake [148,149]. It is interesting to mention that gram negative *Bacteroidetes* and *Proteobacteria* species were shown to increase in association with *Bacilli* and *Lactobacillus* classes (both belonging to the phylum *Firmicutes*) [150]. This increased presence of gram negative bacteria is consistent with elevated circulating LPS in obesity. Clearly, more studies are warranted to fully appreciate the role of the gut microbiota in the development of obesity-related inflammation and T2D.

Diet can positively modulate intestinal microbiota through the consumption of probiotics (*i.e.* live microorganisms) and prebiotics (*e.g.* oligosaccharides and dietary fiber) [151,152]. Because *Firmicutes* species possess a disproportionately smaller number of glycan-degrading enzymes than *Bacteroidetes* species, it was hypothesized that polyphenols, which occur predominantly attached to sugars, might reshape gut microbiota toward a "lean" microbiome [153]. The ability of *Bacteroidetes* species to utilize diverse glycans depends on polysaccharide utilization *loci* (PULs), which assemble genes and encode functions necessary to detect, bind, degrade and import carbohydrate species encountered in the gut habitat, either from the diet or from host (*e.g.* glycans associated with mucus) [154]. The intestinal prevalence of *Bacteroidetes* species associated with polyphenol-rich diets might be related to an increased capacity of glycan degradation attributed to such species, thus constituting a possible mechanism by which polyphenols exert their weight lowering and anti-diabetic effects. Interestingly, while polyphenols are generally related to the growth of *Bacteroidetes* species, benzoic acids (*e.g.* ferulic acid, hydroxycinnamic acid) suppress the growth of *Firmicutes* species [154].

Increased level of *Bifidobacteria* is related with improved glucose tolerance and diminished inflammatory tone in prebiotic-treated mice [155,156]. In rats and in humans, blueberry extract, a rich source of anthocyanins and proanthocyanidins, has been shown to increase the population of *Lactobacilli* and *Bifidobacteria* in feces [157]. Proanthocyanidin-rich extracts have also been shown to increase *Bifidobacteria* population in humans [158,159]. Neyrinck and colleagues showed that an ellagitannin/ellagic acid-rich pomegranate peel extract also increased *Bifidobacteria* intestinal population in Balb/c mice [160]. Indeed, *Bifidobacteria* poorly express proteolytic and lipolytic enzymes, but are able to digest oligosaccharides containing uncommon linkages (*e.g.* hemicellulose, inulins, branched starches) therefore generating short chain fatty acids (SCFA) which could be related with several beneficial effects [161]. Increased populations of *Lactobacilli*/*Bifidobacteria* have been related with inhibition of procarcinogenic enzymatic activities, inhibition of pathogen growth (*i.e.* barrier effect) and stimulation of vitamin synthesis. Furthermore, Qin and colleagues showed that T2D subjects have a decline in butyrate-producing bacteria and an increase in several opportunistic pathogens [162]. Interestingly, the high β-glucosidase activity of *Bifidobacteria* has been implicated in the metabolism of anthocyanins [161], which would favor the generation of more absorbable aglycones along with the increase in *Bifidobacteria* population. Additionally, there is some evidence that *Bifidobacteria* would benefit from a low oxidation potential environment provided by anthocyanins and other polyphenols [163].

The ability of dietary polyphenols to interact with gut microbiomes and induce ecological changes suggests that phenolic phytochemicals do not need to be absorbed in order to exert anti-diabetic effects. Interestingly, higher molecular sizes (due to elevated degree of polymerization) and greater abundance of A-type bonds in polymeric proanthocyanidins have been shown as promising key factors for the attenuation of lipid digestion by inhibiting pancreatic lipase activity [164–166]. This effect would take place in the intestinal lumen, thus not requiring polyphenol absorption prior to the event.

5. Prospective view on polyphenol research

T2D is a multifactorial disease characterized by a concomitant impairment of metabolic functions of several organs. The antidiabetic effects of phenolic phytochemicals are likely due to the integration of several complementary mechanisms. It is a daunting task to elucidate the mode of actions of these polyphenolic compounds given their large numbers and the

specific regulation of their bioavailability as determined by their absorption and biotransformation. This may contribute to the relative failure of reproducing the beneficial effects of polyphenols found *in vitro* in animal models and human trials [47]. Importantly, the wide range of health-supporting properties of phenolic phytochemicals are attributed to the complementary, additive and/or synergistic effects of multiple polyphenols, being also possibly dependent on combined actions on several cellular/molecular targets [53]. In this context, Fujimura and colleagues used a metabolomic approach in order to identify the relation between bioactivity and metabolome (*i.e.* the array of metabolites) of forty-three kinds of Japanese green tea cultivars [167]. Unfortunately, their parameter for measuring bioactive potential was a single *in vitro* analysis. Metabolomic approaches are outstanding tools that could be helpful if applied in order to describe blood plasma or tissue metabolite profile after the ingestion of promising polyphenol-rich foods. We emphasize that the biological effects of polyphenols should not be merely attributed to the native compounds present in foods, but rather to their metabolites of various origins gaining access to the circulation to reach their tissue and cellular targets (Fig. 1) [168].

Given the extensive biotransformation of phenolic phytochemicals by the gut microbiota, it is of great interest to understand the metabolomes arising from bacterial metabolization of polyphenols in the colon. Moco and colleagues have compiled data concerning the use of metabolomic approaches in order to identify metabolites derived from the metabolism of coffee and cocoa by the gut microbiota [42]. This approach should be extended to studying gut microbiota-driven metabolomes associated with other polyphenol-rich plant derivatives. However, the composition of the gut microbiota varies among individuals [169], potentially impacting on polyphenol biotransformation in a personalized fashion. Strong interindividual variability was found in the metabolome produced after *in vitro* fermentation of polyphenol-rich extracts using human feces samples [170]. Therefore, specific microbiomes may be associated with better effects arising from a given polyphenol extract. This is suggested by a recent study in which oral administration of fermented milk products in mice was found to cause minimal changes in microbiota configuration but to produce significant changes in expression of microbiome-encoded enzymes involved in numerous metabolic pathways. These results were further confirmed by using gnotobiotic mice carrying human intestinal bacterial species [171]. The use of gnotobiotic mice would be valuable to relate intestinal microbiomes to polyphenol metabolites originated from microflora metabolism, thus helping to clarify interindividual variability. In addition, a more profound analysis of metatranscriptomes is needed to elucidate the impact of polyphenols on gut microbiomes. Such investigation, coupled with the use of gnotobiotic models reproducing more closely the human condition, would greatly increase our understanding about the mechanisms of action of phenolic phytochemicals and the specific role of the gut microbiota in the antidiabetic effects of these plant bioactives.

Finding applicable methodologies enabling to access and to decipher the metabolites obtained after consumption of a polyphenol-rich food is imperative. Although the knowledge about the phenolic composition of our diet has been extended over the last decades, as indicated by the volume of data in the Phenol-Explorer and the United States Department of Agriculture (USDA) phytonutrients databases, more studies concerning the bioavailability and the metabolism of phenolic compounds are needed to provide a satisfying overview on this subject. However, interesting advances have been made in order to obtain a better understanding of the bioavailability of polyphenols with the recent addition of pharmacokinetic informations on the Phenol-Explorer database [172]. In the past, evidences on the absorption of phenolic compounds used to be predominantly provided by the variation of the plasmatic antioxidant status following the consumption of phenolic-rich foods [173]. Such an approach has been largely criticized [174] and direct measurements of phenolic metabolites using high-performance liquid chromatography (HPLC) methods, coupled with diode array detection (DAD) or mass spectrometry (MS) detection, have been privileged since then. The current development of new technologies for the extraction of plasma and tissue's phenolic metabolites, such as micro-elution solid phase extraction (μSPE), associated with the use of ultra-performance liquid chromatography (UPLC) and tandem MS methodology, now allows the simultaneous characterization of numerous metabolites in biological fluids in a small volume of sample, even at low concentrations, and in a short period of time [175].

6. Conclusions

A great array of polyphenols, mostly derived from biotransformation, may exert anti-diabetic effects either through direct effects (*i.e.* dependent on absorption) or indirect effects (*i.e.* dependent on gut microbiota modulation and pancreatic lipase inhibition). Metabolomic approaches will be valuable to define the polyphenol-derived circulating metabolites behind the beneficial effects of these plant molecules and the role of gut microbiota-dependent metabolism. A broader analysis of polyphenol impact on gut microbiota could also be achieved by more sophisticated determinations of the gut microbiota metatranscriptomes. The use of gnotobiotic models carrying human gut bacteria along with a wider comprehension of the polyphenol metabolomes would help diminish the lack of translation between cellular and animal studies and human trials. These strategies will help in the identification of bioactive polyphenol metabolites from various fruits and plants and could lead to the discovery of novel cultivars to generate more potent functional foods and nutraceuticals to prevent T2D and other inflammatory disorders in obese patients.

Layperson's summary

Unhealthy nutrition habits, coupled with a sedentary life-style, impact on the incidence of obesity, the most important cause of type 2 diabetes (T2D). However, diets rich in fruits and vegetables have been shown to reduce the risks for obesity and T2D. These beneficial effects are partly attributed to molecules generally known as polyphenols. Understanding which polyphenols are behind the heath-supporting effects of plant-derived foods and how they act is crucial in order to generate nutraceuticals, functional foods or to improve cultivars in the future. Nevertheless, human studies using the most promising plant-derived foods aiming to ameliorate chronic diseases like T2D and its cardiovascular complications have not been so successful as *in vitro* and animal studies have pointed out. There are new techniques and insights that could improve the investigation of the plethora of molecules present in the blood stream after intake of polyphenol-rich foods. This is an important step in order to reduce the current gap between promising *in vitro* and animal studies and the limited success of previous human trials.

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