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Main drivers of (poly)phenol effects on human health: metabolite production and/or gut microbiota-associated metabotypes?

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Despite the high human interindividual variability in response to (poly)phenol consumption, the cause-and-effect relationship between some dietary (poly)phenols (flavanols and olive oil phenolics) and health effects (endothelial function and prevention of LDL oxidation, respectively) has been well established. Most of the variables affecting this interindividual variability have been identified (food matrix, gut microbiota, single-nucleotide-polymorphisms, *etc.*). However, the final drivers for the health effects of (poly)phenol consumption have not been fully identified. At least partially, these drivers could be (i) the (poly)phenols ingested that exert their effect in the gastrointestinal tract, (ii) the bioavailable metabolites that exert their effects systemically and/or (iii) the gut microbial ecology associated with (poly)phenol metabolism (*i.e.*, gut microbiota-associated metabotypes). However, statistical associations between health effects and the occurrence of circulating and/or excreted metabolites, as well as cross-sectional studies that correlate gut microbial ecologies and health, do not prove a causal role unequivocally. We provide a critical overview and perspective on the possible main drivers of the effects of (poly)phenols on human health and suggest possible actions to identify the putative actors responsible for the effects.

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1. Introduction

Historically, dietary (poly)phenols, such as flavonoids, evolved from possible compounds with vitamin-like properties to non-essential nutrients[1] (check the comprehensive and excellent review on the metabolism and bioactivity of flavonoids from a historical perspective by Williamson *et al.*[2]). Later, (poly)phenols were considered anti-nutrients with potential mutagen and carcinogenic activities.[3] However, this perception changed when epidemiological studies showed an inverse relationship between the consumption of plant foods and cancer risk,[4] and primarily cardiovascular disease (CVD) risk.[5] Together with early experimental studies, these observations endorsed the health-promoting effects observed from the flavonoid content of fruits and vegetables, and the most plausible mechanism of action was attributed to the antioxidant activity of flavonoids.[5–7] In the late 1990s and early 2000s, there was a massive output of *in vitro* studies describing the free radical scavenging capacity of (poly)phenol-rich plant extracts, establishing a potential health claim based merely on the content of (poly)phenols in foods.[8–11] Later, ADME (absorption, distribution, metabolism, and excretion) studies showed that (poly)phenols are poorly bioavailable, *i.e.*, the proportion of intact (poly)phenolic compounds ingested that reach the bloodstream is low.[12–16] Upon absorption, phase-II enzymes extensively metabolise (poly)phenols, yielding conjugated metabolites that can show some activity but are much lower than their food-occurring phenolic precursors.[17–20] This evidence questions the reliability of thousands of *in vitro* results based on non-physiological conditions, *i.e.*, the assay of food-occurring (poly)phenols instead of their physiologically relevant conjugates.[21] Unfortunately, this useless approach persists.

To date, a substantial number of human studies and *meta*-analyses have discussed the preventive effects of (poly)phenol-containing foods against cardiometabolic diseases and, to a lesser extent, against some types of cancer and neurodegenerative diseases.[22–33] However, there is controversy and not all the studies reach conclusive links between (poly)phenols and health, even for the same outcome, *e.g.*, vascular function, performed by the same research group and assaying the same

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pure flavonoid, *e.g.* epicatechin.[34,35] Overall, most systematic reviews and *meta*-analyses on (poly)phenols and health highlight the finding of some "promising" or "potential" health effects, but conclude with the same call of caution: "*...more high-quality research is needed...*", "*...further well-designed randomised and controlled trials are required...*"

A well-established cause-and-effect relationship between most (poly)phenols consumed and their possible beneficial effects remains elusive. In this regard, many of their related health claims have been rejected by the European Food Safety Agency (EFSA). Indeed, except for a few examples of health benefits, including protection of low-density lipoprotein cholesterol (LDLc) particles from oxidative damage by olive oil phenolics such as hydroxytyrosol,[36] and improvement of endothelial function by cocoa flavanols,[37] most of the health effects of dietary (poly)phenols have not been unequivocally proven. Even in these cases, the final triggering metabolite for the effects is unknown. Beyond antioxidant activity, many mechanisms for the action of (poly)phenols have been described, including the modulation of inflammatory mediators, fat metabolism, and transcription factors,[38–40] but the actual mechanisms behind the effects have not been fully established. We do not aim here to review possible determinants affecting (poly)phenols effects, an issue extensively reviewed in recent years under the COST Action POSITIVe activities.[41–43] However, it is not yet clear whether the effects observed after polyphenol-rich food consumption are mainly exerted by: (i) the ingested phenolics, (ii) their phase-II derived metabolites, (iii) the greater or lesser amount of phenolic-derived metabolites produced by the microbiota (metabolite gradient), and/or (iv) the specific gut microbiota associated with the metabolism of (poly)phenols (the so-called gut microbiota metabotypes).

Therefore, we aim to provide an overview and perspective to address which player(s), *i.e.*, metabolite production and/or gut microbiota-associated metabotypes, could be responsible for the observed health effects in humans upon (poly)phenol consumption.

2. Interindividual variability in response to (poly)phenol consumption: in search of the putative driver responsible for the effects

It has long been known that the clinical response to drug administration varies widely between individuals.[44] Similarly, increasing evidence began to appear on interindividual variability in the metabolism of certain dietary (poly)phenols, such as isoflavones,[45] flavanones,[46] tea catechins,[47] and ellagitannins,[48] among others. In parallel, other studies also began to throw controversy about the statistical significance of the observed effects due to the large standard deviations of the results obtained.[22] In this regard, the wide range of (poly)phenol structures was suggested to be a crucial factor that impacts their metabolism and could be behind the wide variability in the effects on biomarkers of CVD risk.[49–51] However, despite dietary (poly)phenols being structurally different, many share the same multi-target action mechanisms.[2] Finally, there is notable interindividual variability in response to (poly)phenol consumption. Overall, this avoids claiming that (poly)phenols exert health effects for the entire population, which could be behind the rejection by EFSA of many health claims for (poly)phenols. Instead, the participation of many specific variables leads us to personalised dietary recommendations that consider a complex mixture of individuals' conditions (sex, age, genetic makeup, lifestyle, physiological status, and gut microbiota) and other aspects (food matrix and processing, dietary patterns, *etc.*).[41,43,52–57] It seems that not all of these conditions and aspects necessarily contribute equally. However, the possible weight of importance for each contributor is not known.

In the last decade, the two-way interaction between (poly)phenols and gut microbiota (modulation of the microbiota by (poly)phenols and metabolism of (poly)phenols by the microbiota) has attracted attention as a new piece in the puzzle of (poly)phenols and health.[43,53,58,59] In the search for the main actor(s) involved in the final (poly)phenol health effects, growing evidence has identified their derived microbial metabolites as a possible connection to establishing the bioactivity of (poly)phenols. However, the two-way interaction between the gut microbiota and dietary (poly)phenols is also the main driver of the interindividual variation detected.[43,59,60] In addition to the possible bioactivity exerted by the ingested (poly)phenols and/or their derived microbial derivatives, each individual's gut microbiota, including that involved in (poly)phenol metabolism, is also relevant to explain the final effects. For example, the daidzein-derived metabolite equol was suggested as being more bioactive than its daidzein precursor and seemed to be predominant in some individuals capable of producing equol (*i.e.*, "equol producers").[61] Similarly, the presence of urolithins in the bloodstream was initially claimed as a plausible explanation behind the effects observed after consumption of foods containing the non-bioavailable urolithin precursors ellagitannins.[48,62] However, not all individuals produce the same urolithins, nor harbour the same associated gut microbiota.[43,63]

While the determinants affecting the individuals' response to (poly)phenol consumption have been comprehensively identified,[41,42] the relationship between effects and the (poly)phenols ingested and/or their derived metabolites is not conclusive. The questions to ask are: Which is (are) currently accepted as the final molecule(s) responsible for the effects after (poly)phenol consumption? Is there a consensus? It is not clear if the effects are exerted by the ingested phenolics and/or their microbial metabolites, and in both cases, if the phase-II conjugates participate actively, or if the effects are mediated by indirect signalling cascades where it is not necessary for the direct interaction of the molecule with the systemic target. It seems that the studies that associate the observed activity with the simultaneous presence of circulating

(or excreted) phenolic metabolites or their microbial derivatives may be affected by many variables that prevent a well-established cause-and-effect relationship. In this regard, although local effects can have an impact on a systemic level, and *vice versa*, the likely site of the action exerted by the (poly)phenol ingested, *i.e.*, gastrointestinal or systemic, could be the first criterion to search for a possible cause-and-effect relationship.

2.1. Effects of dietary (poly)phenols on the gastrointestinal tract

Most (poly)phenols (90%) might exert their potential benefits in the gastrointestinal (GI) tract because they are poorly absorbed and are retained for a longer time than other food compounds in the gut, where they suffer microbial transformations.[43,58] Several strategies have been developed to improve the solubility and transport of dietary (poly)phenols through the GI tract and their delivery efficiency to specific intestinal regions.[64] The microbial conversion of (poly)phenols in the intestine often results in metabolites with greater bioavailability than their precursors and, therefore, with potential activity beyond the GI tract. These microbial transformations are different depending on the phenolic structure (flavonoids or non-flavonoids), polymerisation degree, the spatial configuration of the compound, and gut microbial composition of the host.[43,58] Several mechanisms of action of the (poly)phenols and their microbial metabolites on intestinal health have been investigated and summarised in the last decade.[65–70] Some of their molecular mechanisms of action against gut inflammation are the reduction of oxidative stress, the inhibition of the secretion of inflammatory cytokines (TNF-α, IL-6, IL-8 and IL-1β), suppression of NF-κB activation, positive regulation of Nrf2, modulation of immune function, and protection of the intestinal barrier.[68,70,71] Furthermore, the intestinal barrier protection by (poly)phenols and their metabolites indirectly limits the translocation of antigens and bacterial pathogens and the infiltration of bacterial lipopolysaccharides (LPS) into the bloodstream, which could reduce metabolic endotoxemia and host inflammation. The molecular mechanisms (epigenetics, inflammation, mRNA expression, and gut microbes) of several (poly)phenols have also been reviewed, such as curcumin and resveratrol against colorectal cancer (CRC).[66,67,69] Although (poly)phenols, their microbial metabolites, and short-chain fatty acids (SCFAs) co-exist in the colon, it is unknown if there are *in vivo* synergistic interactions that reduce inflammation and protect the gut barrier. It is also unknown in what proportion most (poly)phenols and their derived metabolites contribute to the protective effect on the GI tract because most intervention studies are performed with the food (poly)phenols. Therefore, both (precursors and microbial metabolites) co-exist in the colon. Furthermore, the ratio of precursor/derived metabolites varies among individuals depending on their gut microbiota, whose composition is specific at the individual level. The higher absorption rate and anti-inflammatory activity of (poly)phenol microbial metabolites suggest they could play a more crucial role than precursors in preserving intestinal health and mitigating gut inflammatory conditions. However, it could depend on the host's ability to produce these microbial metabolites, which differs from one individual to another depending on their gut microbiota composition, which in turn depends on many factors such as health, age, lifestyle, *etc*. According to this, some (poly)phenol microbial metabolites such as urolithin A (Uro-A) (a microbial metabolite of ellagic acid and ellagitannins) and hydrocaffeic acid (a microbial metabolite of caffeic acid and chlorogenic acid) have been reported to be effective in treating gut inflammation in dextran sodium sulfate (DSS)-induced colitis modelled in rats.[72,73] Indeed, Uro-A supplementation was more effective than pomegranate extract for ameliorating the inflammation. Besides this, a clear effect was also observed on inflammatory markers, antioxidant status, microbiota, and gene expression in the DSS-pomegranate extract group. The authors suggested that the effect could be due to either the remaining ellagic acid or the ellagitannin fraction that could reach the colon together with the small amount of Uro-A produced by the gut microbiota.[73] Similarly, the only study of the chemopreventive effect of ellagitannin-containing pomegranate extract in CRC patients has revealed that the pomegranate extract counterbalanced the expression of several CRC-related genes in cancerous colon tissues. However, this effect was not associated with the urolithin level in colon tissues or with urolithin metabotypes (UMs).[74] In most cases, microbial metabolites (*e.g.*, Uro-A) could be the main active intestinal anti-inflammatory and chemopreventive compounds related to the consumption of (poly)phenols (*e.g.*, ellagitannins) in healthy people. However, in gut dysbiosis (*e.g.*, inflammatory bowel diseases (IBD) and CRC) and producers of low quantity or no metabolites, the precursors together with a low amount of microbial metabolites could act synergistically.

Most human studies do not unequivocally show the specific effect of metabolites in the GI tract because they were performed with their precursor (poly)phenols. However, the molecular mechanisms of some metabolites have been identified using *in vitro* and animal studies. In this regard, Uro-A decreased inflammation markers (iNOS, cycloxygenase-2, PTGES and PGE_2) both in the colonic mucosa of rats after oral administration and in an intestinal inflammatory cell model, and upregulated tight junction proteins in HT-29 cells.[73,75,76] Besides this, hydrocaffeic acid intake has been shown to attenuate colitis by reducing inflammatory cytokines, including TNF-α and IL-8, and dihydro ferulic acid inhibited lipid peroxidation and DNA damage in colon mucosa after carrageenan-induced colitis, diminishing the expression of TNF-α, IL-1β and IL-8 and oxidative DNA damage in the distal colon mucosa.[72] Hydroxybenzoic acids are the common microbial degradation metabolites obtained in the gut from flavonoid and non-flavonoid phenolics and are commonly found in most fruits.[43] Some metabolites' potential mechanism of action, including 3,4-dihydroxyphenylpropionic acid and 3,4-dihydroxyphenylacetic acid, has been investigated. These metabolites significantly decreased the secretion of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 in LPS-stimulated peripheral

blood mononuclear cells obtained from healthy people, suggesting their usefulness to alleviate IBD.[77] According to these studies, it was suggested that a diet rich in these metabolite precursors (*i.e.*, pomegranate, artichoke, cocoa, apples, strawberries, *etc*.) could exert anti-inflammatory effects and attenuate intestinal inflammation in humans. However, in some cases, the physiological activities of microbial phenolic-derived metabolites could not be higher than those of their precursor (poly)phenols. In an *in vitro* colon model, flavonoids (flavanols, theaflavin, quercetin, rutin and hesperidin) of citrus, green and black tea were catabolised to 4-hydroxyphenylacetic acid, 3-methoxy-4-hydroxyphenylacetic acid, 3,4-dihydroxyphenylacetic acid, and other catabolites with lower anti-proliferation effects than the corresponding parent flavonoids on colon cancer cell lines.[78]

The gut microbial imbalance (*i.e.*, gut dysbiosis) has been associated with IBD, irritable bowel syndrome, CRC, allergies, obesity, metabolic syndrome and neurodegenerative diseases, among others.[79–81] A healthy, diverse, and stable gut microbiota is essential in maintaining the homeostasis of the gut barrier and regulating the gut-brain axis.[82,83] Besides other gut bacteria such as *Faecalibacterium prausnitzii* and *Bacteroides thethaiotamicron*, lactobacilli and bifidobacteria are considered beneficial in human health, helping to improve gut barrier function and the host immune system, prevent diarrhoea or allergies, activate pro-vitamins, and modulate lipid metabolism.[79] The impact of dietary (poly)phenols on the gut microbial ecology and the mechanism underlying the putative beneficial effects on the GI tract and extra-intestinal diseases have been recently reviewed.[64,84] Several (poly)phenol-rich foods increase gut microbiota diversity, improve the relative abundance of beneficial bacteria such as lactobacilli and bifidobacteria, and inhibit the pathogenic species. However, the precise association of (poly)phenols with benefits for the GI tract through gut microbiota modulation has been suggested but not unequivocally proven. In a human intervention study, cocoa flavanols promoted the growth of lactobacilli and bifidobacteria (intestinal barrier protectors) and reduced C-reactive protein (CRP) concentrations, an inflammatory blood biomarker and a hallmark of the acute phase inflammatory response. Changes in CRP concentrations were significantly linked to changes in lactobacilli counts.[85] Other human intervention studies showed that an ellagitannin-rich pomegranate extract decreased plasma LBP in overweight-obese subjects,[86] and patients with newly diagnosed CRC.[87] Changes in LBP were significantly associated with the increase of *Faecalibacterium*, one of the main SCFA-producing bacteria, especially butyrate.[86] It is known that the gut microbiota interacts with the host through microbial metabolites such as SCFAs from dietary fibre and metabolites produced from dietary (poly)phenols. It has been well established that SCFAs are the primary candidates in the crosstalk between bacteria and the intestine.[88] SCFAs are an important source of energy for colonocytes and play a significant role in regulating tight junction proteins (claudin-1, occluding and zonula occludens-1), critical in preserving the integrity of the intestinal barrier.[79,89] Several bacteria contribute to SCFA production. Modulation of growth and/or metabolic activity of SCFA-producing bacteria and, therefore SCFA production, has been associated with fibre consumption and the presence of (poly)phenols in the diet. For instance, red wine (poly)phenols significantly increased the number of faecal lactobacilli, bifidobacteria, and butyrate-producing bacteria (*F. prausnitzii* and *Roseburia*) at the expense of less desirable groups of bacteria such as LPS producers (*Escherichia coli* and *Enterobacter cloacae*).[90] Different studies have shown that some (poly)phenols either interfered with or enhanced these positive effects of fibre.[84] For instance, a combination of apple (poly)phenolic fraction (epicatechin, procyanidins, and chlorogenic acid) with apple pectin showed an additive effect on SCFA production in rat cecum size.[84,91] Conversely, strawberry ellagitannins thwarted the positive effects of dietary fructooligosaccharides, while anthocyanin-rich strawberry extracts enhanced the beneficial effects of a fructooligosaccharide-rich diet.[92,93] Factors such as the state of health (composition and functionality) of the gut microbiota and its enormous complexity of interactions with the host show the difficulty of demonstrating the *in vitro* effects of dietary (poly)phenols in the human GI tract.

2.2. Effects of dietary (poly)phenols on systemic targets

Before entering the bloodstream, dietary (poly)phenols must pass from the gut lumen, which is a crucial bottleneck in their subsequent potential biological activity.[2,94] Most (poly)phenols from plant foods are glycosylated, and the attached sugar moiety is usually released before absorption occurs. The bioaccessibility of (poly)phenols is closely related to their physicochemical structure and the food matrix that contains them, which could interfere with their release ability and intestinal absorption. Once in the enterocyte, the cytochrome P450 (CYP) family of enzymes catalyse phase-I reactions, involving oxidation, reduction, and hydrolysis. Later, the aglycones can undergo phase-II metabolism in enterocytes by enzymatic systems like UDP-glucuronosyltransferases (UGT), acetyltransferases, glutathione-S-transferases (GST), sulfotransferases (SULT), and catechol-*O*-methyltransferases. Besides this, members of the ATP-binding cassette (ABC) superfamily are considered gatekeepers governing (poly)phenol absorption, their excretion, and, in many cases, their entry into target organs.[95,96] ABC transporters can limit the absorption of (poly)phenols, their aglycones or derived metabolites by driving efflux back into the lumen (Pgp, MRP2 and BCRP) or transporting them from the intracellular compartment to the bloodstream (MRP3).[96–98] Once in the bloodstream, phenolic metabolites can be subjected to additional phase-II metabolism, mainly in the liver, where CYP enzymes and ABC transporters can also critically influence the metabolism and fate of (poly)phenol-derived metabolites before urinary excretion.[16,98,99] Finally, the (poly)phenols not absorbed, which can be a substantial amount of those ingested, are metabolised by the gut microbiota, mainly in the colon. The microbial-derived metabolites can be subjected to the same

restrictions and metabolic actions as their phenolic precursors (*i.e.*, absorption, transport, *etc.*). The microbial metabolites are usually excreted in the urine in high quantities, usually over those phenolic metabolites that enter the bloodstream before gut microbial catabolism. Overall, systemic cells can be exposed to these gut microbial-derived phenolics rather than their parent (poly)phenols ingested through plant foods.[2,15,59,99]

2.2.1. The qualitative criterion: gut microbiota metabotypes associated with (poly)phenol metabolism. The term "metabotype" refers to a metabolic phenotype, *i.e.*, the differential metabolic response of individuals to nutritional or pharmacological interventions, defined by their (*epi*)genetics, physiology and/or gut microbiota composition and functionality. Therefore, it is an extensive concept and can concern the gut microbial and host metabolism and subsequent biological activity (synthesis, transport, interaction with receptors, *etc.*) of either endogenous or exogenous compounds. Molecules such as cholesterol, glucose, and xenobiotics (dietary, pharmacological and environmental compounds), among many others, can show distinctive metabotypes.[43,59,100–103] Therefore, the unequivocal identification of metabotypes associated with the metabolism of (poly)phenols by the gut microbiota requires limiting the definition to this specific context, *i.e.*, a metabolic phenotype that gives rise to characteristic metabolites derived from the catabolism of specific (poly)phenols by a particular gut microbial ecology in terms of composition and functionality.[59] Overall, a metabotype associated with the gut microbiota is defined by a qualitative criterion (*i.e.*, producer *vs.* non-producer of specific metabolites) and not by a quantitative criterion (*i.e.*, high producer *vs.* low producer), since the production gradient could be affected by external factors (diet, motility of GI tract, food matrix, sample collection time, *etc.*).[43,55,59]

The metabolism of many (poly)phenols, including flavanones, lignans, prenylflavonoids, proanthocyanidins, anthocyanins and stilbenes, shows high interindividual variability, demonstrated by the presence of a metabolite production gradient that gives rise to the so-called "high producers" and "low producers" of certain metabolites.[55,104–107] However, no gut microbiota-associated metabotypes have been unequivocally described in their metabolism.[43]

Flavanone metabolism, such as hesperidin, yields high and low metabolite (hesperetin) excreters, a process mainly governed by the rhamnosidase activity of the gut microbiota (Fig. 1).[108,109] However, hesperetin is an intermediate, further metabolised to phenolic acids (phenylpropionic, phenylacetic, and hippuric acid derivatives), which are typical final catabolites for many flavonoids.

Therefore, flavanone metabolism does not yield unique microbial metabolites but a metabolite production gradient, depending on the rhamnosidase activity of the individuals' gut microbiota and the physicochemical properties of flavanones, especially their solubility under physiological conditions.[53,104,107,108,110]

Likewise, the metabolism of lignans such as the flaxseed secoisolariciresinol diglucoside does not produce specific metabolites but a gradient of intermediates to get enterodiol and enterolactone, which seems to be produced by the entire population to a greater or lesser extent.[111,112] The presence of unique enterodiol and/or enterolactone-derived catabolites, which could be related to specific gut microbiota-associated metabotypes, has not been identified so far (Fig. 1).[43]

The possible gut microbiota metabotype associated with the metabolism of hops prenylflavonoids, such as xanthohumol and isoxanthohumol, has not been sufficiently demonstrated either. Xanthohumol can be either chemically or enzymatically converted into isoxanthohumol, which the gut microbial *Eubacterium limosum* can demethylate to yield the potent phytoestrogen 8-prenylnaringenin (8PN) (Fig. 1).[113] However, several issues prevent a possible clustering of individuals according to a gut microbiota metabotype associated with the unique production of 8PN. Firstly, the gut microbial *Eubacterium ramulus* can metabolise 8PN to *O*-desmethylxanthohumol and *O*-desmethyl-α,β-dihydroxanthohumol (Fig. 1).[113] Besides this, 8PN can already be present in food products (hops and beer), and finally, 8PN can also be formed by human cytochromes.[114,115]

Avenanthramides (AVAs) are phenolic alkaloids found mainly in whole-grain oat.[116] Recently, Wang *et al.*[117] observed interindividual variations in the metabolism of AVAs to dihydro-AVAs (DH-AVAs) in humans (Fig. 1). These authors identified *F. prausnitzii* as the individual bacterium to metabolise AVAs to DH-AVAs and proposed that the abundance of this species could be helpful to stratify individuals into AVA metabolisers and non-metabolisers after whole-grain oat intake.[117] The authors claimed the term "metabotype" to illustrate the above interindividual variability. However, these results were based on a pharmacokinetic study with only 11 volunteers and 21 *in vitro* faecal fermentation experiments. *F. prausnitzii* is one of the most abundant bacterial species in the human intestinal microbiota of healthy adults, representing more than 5% of the total bacterial population.[118] The chronic consumption of a (poly)phenolic substrate can increase the abundance of the microbial groups involved in its metabolism,[58,119] implying that the continuous consumption of whole-oat could convert non-metabolisers into DH-AVA producers; in this case by the increase of *F. prausnitzii*. Besides this, many microbial groups could catalyse the reduction of the double-bond from AVAs to DH-AVAs in the hydroxycinnamic acid moiety since this is a relatively non-specific reaction (Fig. 1).[58,105,120] Therefore, it is difficult to conceive that changes in the abundance of *F. prausnitzii* could be the limiting step in converting AVAs to DH-AVAs in healthy adults. Although there is interindividual variability in the metabolism of AVAs,[117] the existence of a genuine gut microbiota-associated metabotype for AVA metabolism deserves further research.

Flavan-3-ols (flavanols) and proanthocyanidins from tea, cocoa, grapes, apples, *etc.*, are catabolised into different phenylvalerolactone derivatives.[47,121–123] Although valerolactone-derivatives are characteristic of flavanol metabolism, these metabolites are further transformed to phenolic acid derivatives, as in many other flavonoid metabolic pathways (Fig. 1).[55,124,125]

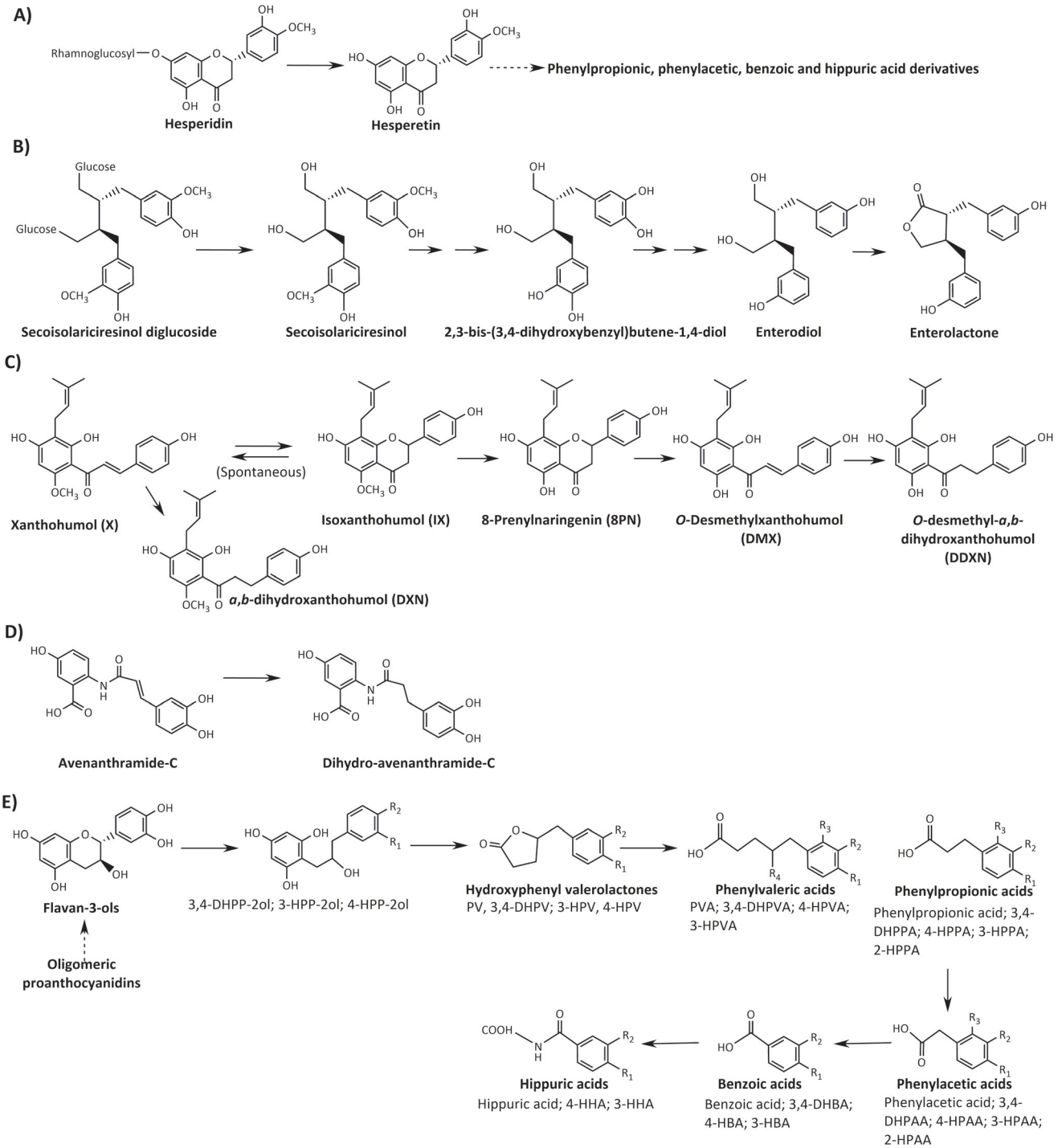

Fig. 1 Summarised catabolic pathways of dietary (poly)phenols non-related to gut microbiota metabotypes. (A) Flavanones (hesperidin), (B) lignans (secoisolariciresinol), (C) prenyl-flavanones (xanthohumol), (D) avenanthramides (avenanthramide-C) and (E) proanthocyanidins and flavan-3-ols (catechin), HPP-2-ol, 1-(hydroxyphenyl)-3-(2′′,4′′,6′′-trihydroxyphenyl)-propan-2-ol; PV, phenylvalerolactone; HPV, hydroxyphenyl valerolactone; DHPV, dihydroxyphenylvalerolactone; PVA, phenylvaleric acid; HPVA, hydroxyphenylvaleric acid; DHPVA, dihydroxyphenylvaleric acid; HPPA, hydroxyphenylpropionic acid; DHPPA, dihydroxyphenylpropionic acid; HPAA, hydroxyphenylacetic acid; DHPAA, dihydroxyphenylacetic acid; HBA, hydroxybenzoic acid; DHBA, dihydroxybenzoic acid; HA, hippuric acid; HHA, hydroxyhippuric acid. Adapted from Cortés-Martín *et al.*[43] with permission from Wiley, copyright March 19, 2020.

Cortés-Martín *et al.*[55] reported several points that prevent the identification of gut microbiota metabotypes associated with the metabolism of flavanols. For example, the binary response of gut microbiota metabotypes is not accomplished in flavanols, *i.e.*, the presence *vs.* absence of unique metabolites, which does not allow the population to be stratified as

producers *vs.* non-producers. As in the case of other (poly) phenols, the production gradient (high and low producers of valerolactone-derived metabolites) gives rise to substantial interindividual variability, in which phase-II polymorphisms and other variables (food matrix, flavanols polymerisation degree, *etc*.) can contribute critically.[55,126,127] Therefore, despite the opinion of other researchers, strictly speaking, there are no gut microbiota metabotypes associated with the metabolism of flavanols. As previously suggested, phase-II enzymes give rise to high interindividual variability and possible potential metabotypes (not associated with the gut microbiota).[53,55,128] However, these possible metabotypes should provide a clear discriminant clustering of individuals and not an additional gradient (*i.e.*, high and low levels) based on, for example, the typical glucuronidation/sulfation ratio.[55,128] The question raised in any possible gradient is always the same: what is the cut-off to consider an individual from one or another "metabotype"? This issue is even more relevant when tentative "metabotypes" have been proposed after the analysis of *in vitro* or *in vivo* samples from a few volunteers ($n \approx 10$–15), which is, unfortunately, the most common scenario in those studies that recurrently use the term "metabotype" in the context of (poly)phenol metabolism.[117,128–130] Indeed, after analysing such small sample sizes, high and low producers could be tentatively identified by specifying an arbitrary limit to establish such a classification. However, in a large cohort, it could be possible that after applying the same cut-off, these same volunteers could be all grouped within the high producers or all of them within the low producers. The establishment of this cut-off is arbitrary and depends on many external factors, as discussed in a further section. For example, for identifying genuine metabotypes, the sensitivity of the analytical procedure is crucial. If the technique is not sensitive enough, especially when the detection limit of a specific metabolite is relatively high, it could lead to the erroneous interpretation that an individual is a non-producer. Besides this, identifying "new" metabotypes based on the absence of a specific metabolite in urine is questionable because polymorphisms in gut transporters involved in phenolic-derived metabolite absorption and excretion can affect the urine excretion profile of metabolites. Therefore, a comparative analysis between urine and faecal excretion is mandatory. Overall, large groups are needed to identify gut microbiota metabotypes associated with the metabolism of (poly)phenols.[43,55,111,131]

The stratification of individuals according to their gut microbiota (poly)phenol metabotypes has been proposed to understand individuals' response to dietary (poly)phenols, which could be crucial in the context of personalised nutrition.[43,119] To date, the metabotypes identified unequivocally are those involved in the metabolism of isoflavones (equol producers *vs.* non-producers), and ellagic acid (UMs, including producers of only Uro-A (UM-A), producers of Uro-A, isourolithin-A (IsoUro-A), and urolithin-B (Uro-B) (UM-B), and urolithin non-producers (UM-0)) (check Cortés-Martín *et al.*[43] for a comprehensive description of these metabotypes). Of course, within each metabotype, a metabolite production gradient also defines tentatively "high" and "low" producers of metabolites. However, the same problem for establishing the boundary between high and low metabolite producers is also found within genuine metabotypes.[43,111,132]

Therefore, the concept of gut microbiota metabotypes associated with (poly)phenol metabolism involves a qualitative criterion with two possible putative players responsible for the (poly)phenol health effects: (i) (poly)phenol-derived metabolites with distinctive biological activity and specifically produced only for some individuals, and/or (ii) the particular gut microbial ecology in terms of composition and functionality, associated with (poly)phenol metabolism, and harboured by specific individuals.

2.2.1.1. Production of distinctive microbial phenolic-derived metabolites. There are two paradigmatic examples regarding the production of phenolic-derived postbiotics produced by specific gut microbiota ecologies: (i) equol-producing individuals (producers) and equol non-producers in the daidzein metabolism, and (ii) urolithin-producing individuals (UM-A and UM-B) *vs.* those individuals not capable of producing urolithins (urolithin non-producers, UM-0) after consuming ellagic acid (Fig. 2). Whether these phenolic-derived postbiotics are the final drivers in the health benefits observed upon isoflavone- or ellagitannin-rich foodstuff consumption deserves further research.[43,59]

The evidence on the role of postbiotics in human health is well consolidated for some compounds, including SCFAs,[133] but still weak for many others.[43,134–137] To date, there is no evidence to support a specific health benefit from producing, qualitatively, one metabolite (*e.g.* equol or Uro-A) compared with others.

While the distribution of UM-A and UM-B is critically affected by ageing, the proportion of individuals with UM-0 (urolithin non-producers) remains constant, about 10%, from 5 to 90 years of age.[131] Therefore, the relatively low number of volunteers with UM-0 in different human studies has prevented the drawing of any statistically significant conclusion regarding the possible impact of non-producing urolithins in the outcomes of the studies.[74,119,138,139]

Regarding the metabolism of isoflavones, the equol- and ODMA-producer metabotypes have been identified so far.[111] It seems that both metabotypes are independent of each other.[140] However, as discussed for flavanols, flavanones, and prenylflavanones, the catabolism of ODMA can also give rise to simpler and unspecific metabolites such as phloroglucinol, 4-hydroxyphenyl propionic acid, *etc*. (Fig. 2), which are common in the microbial catabolism of many other dietary phenolics. Therefore, this fact could compromise a genuine ODMA-metabotype in the population and might have contributed to the inconsistent results linking isoflavone metabotypes and human health outcomes.[43] The percentage of equol producers has been estimated to be around 30% and 50–60% in the Caucasian and Asian populations, respectively.[141,142] Therefore, it could be potentially more feasible to reach statistically significant differences when linking the presence or

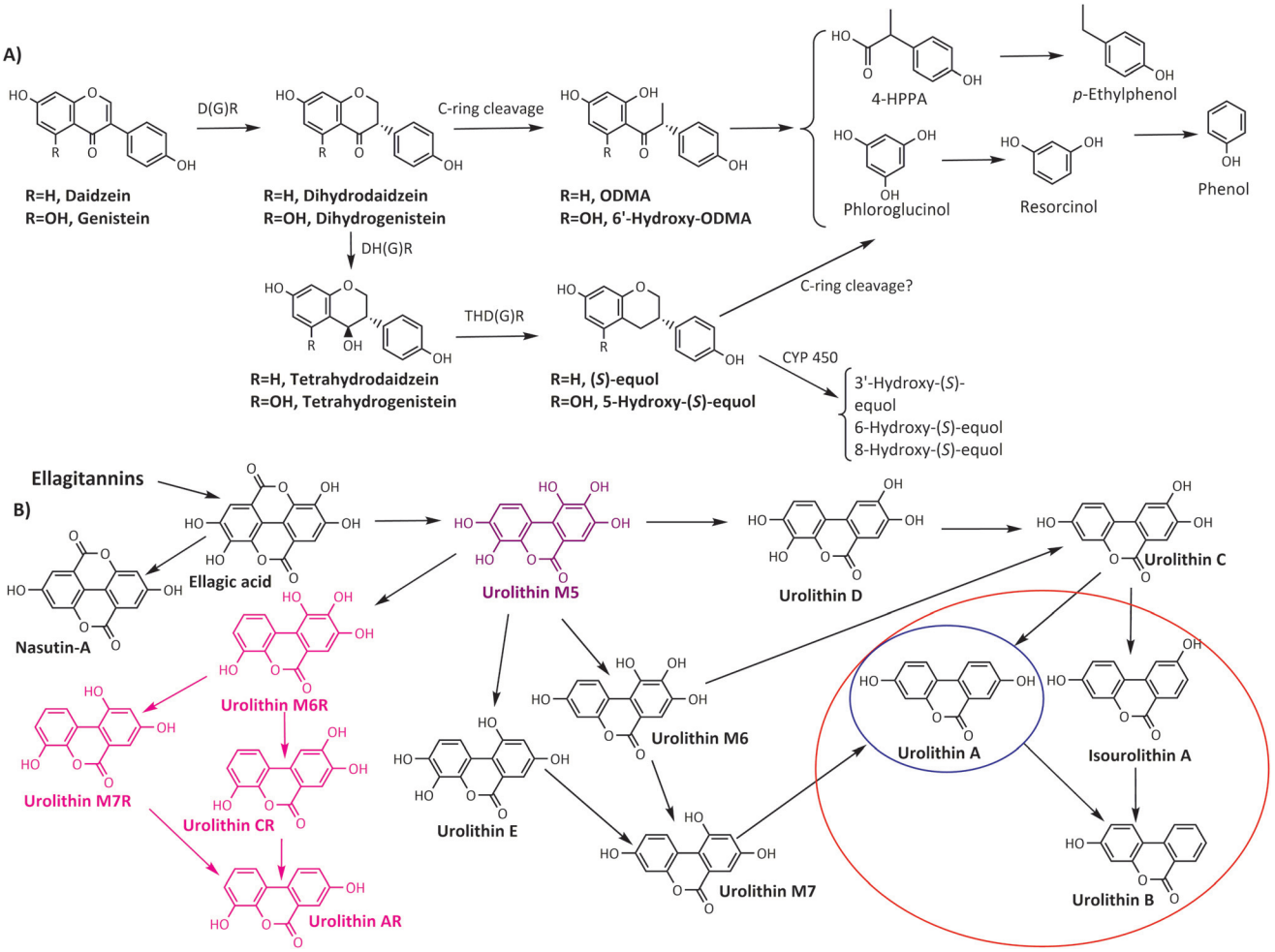

Fig. 2 Summarised catabolic pathways of (A) isoflavones (daidzein and genistein) and (B) ellagic acid to urolithins. The circles specifically enclose the final urolithins for each metabotype (red, UM-B; blue, UM-A). Urolithin M5 (purple) is the only detected urolithin in UM-0. R-urolithins (pink) are those present in individuals with specific 3-dehydroxylase activity (they can be present in both UM-A and UM-B). D(G)R, daidzein/genistein reductase; DH(G)R, dihydrodaidzein/genistein reductase; THD(G)R, tetrahydrodaidzein/genistein reductase; CYP450, mammalian cytochrome P450; 4-HPPA, 4-hydroxyphenyl propionic acid. Adapted from Cortés-Martín *et al.*[43] with permission from Wiley, copyright March 19, 2020.

absence of equol in the results of each study. However, producing a specific microbial-derived metabolite such as equol is linked to harbouring a particular gut microbial ecology.[111,143] Therefore, whether a specific microbial-derived metabolite exerts biological activity, dependently or not of the associated microbiota, requires evaluating the effects upon direct administration of the metabolite.

To date, equol is the most studied phenolic-derived postbiotic in humans. The main evidence suggests improvement of cardiometabolic biomarkers and, particularly, protection against menopausal symptoms.[144–154] However, the precise mechanisms are not yet fully elucidated.[43] A human trial (n = 49) described the improvement of some cardiometabolic risk biomarkers in overweight-obese women after S-equol administration (10 mg), showing more effects in the equol non-producer participants.[149] In contrast, Hazim *et al.*[150] described acute vascular effects in healthy equol-producing men (n = 14) after consuming isoflavones. The effects were associated with peak circulating equol concentrations (although the isoflavones supplement did not contain synthetic S-equol). Remarkably, equol administration (40 mg) did not exert any effect on equol non-producers. However, in the parallel assay, no synthetic equol was administered to the equol-producers or isoflavones to equol non-producers.[150] This means that the acute vascular effects of equol (dependently or not of the equol-related metabotype) have not been demonstrated unequivocally. Two randomised placebo-controlled trials (RCT) specifically recruited equol-producing participants to evaluate isoflavone effects on blood pressure, vascular function,[155] bone metabolism and inflammation.[156] Remarkably, the authors did not observe a significant effect on any cardiovascular risk factor among 253 Chinese equol-producing postmenopausal women that consumed isoflavones for 6 months.[156] Unfortunately, whether the same approach could have exerted some effects on equol non-producers remains unanswered. Recently, an 8.8-years prospective study described that serum isoflavones and equol

were associated with reduced carotid intima-media thickness progression, mediated by sex hormone-binding globulins and systolic blood pressure in 2572 Chinese subjects (40–75 years old).[157] However, a case-control study with pre- and postmenopausal Chinese women (n = 792) only found a statistically significant association between serum daidzein and reduced odds of breast cancer, but not with the rest of the isoflavones or equol.[158]

Urolithins, mainly Uro-A, can exert anti-inflammatory and anti-obesity activities, preserve the intestinal barrier, modulate the gut microbiota, and protect from oxidative stress, among many other activities, in animal models.[73,132,159–161] Besides this, physiologically relevant mechanistic *in vitro* studies support the underlying molecular mechanisms involved.[18–21,162–164] However, there are no human studies to confirm these potential effects.[132] To date, there are two human studies conducted with a commercial oral synthetic Uro-A supplement, funded by a private company. One of them described cellular health improvement by regulating gene expression associated with cellular and mitochondrial function.[165] The second one claimed the consumption of 500 mg of synthetic Uro-A as the solution to achieve more plasma Uro-A-derived conjugates than the single intake of a specific pomegranate juice and after only 6 h,[166] not enough time to achieve a substantial conversion of ellagic acid into Uro-A, which can take around 48 h.[48,167] Besides this, walnut intake would have yielded much more Uro-A production.[168]

Nevertheless, as in equol, future human trials dealing with urolithins should consider the individuals' UMs to evaluate the possible role of the associated gut microbiota in the postbiotic effects. Overall, the *in vivo* activity of phenolic-derived postbiotics cannot be discarded, but the evidence supporting their genuine role in health is still too limited to be unquestionable. In this regard, they could be potential biomarkers of specific human gut microbiota metabotypes associated with the metabolism of (poly)phenols rather than irrefutably bioactive metabolites with differential impact on human health.[169]

2.2.1.2. Specific gut microbial ecologies, associated with the metabolism of (poly)phenols, as possible health drivers. An increasing number of studies encourage the clustering of subjects into known metabotypes (*i.e.*, metabotyping) as a strategy to explain, at least partially, the different response of individuals to dietary compounds, including (poly)phenols.[43,63,102,119,170–172] This approach would allow tailoring of specific (poly)phenol-rich diets for specific individuals by linking metabotypes to the concept of "personalised nutrition", *i.e.*, optimising and aiming the diet individually for the prevention of some diseases.[59,119,173–176]

The current evidence suggests that equol and/or ODMA producers may have a lower cardiovascular risk than non-producers.[111] The capacity of individuals for producing equol seems to be stable at least for 2 years,[177] and the proportion of equol production status might increase with age.[178] However, despite the attempts to correlate the occurrence of the equol- or ODMA-producer metabotypes with dietary patterns and some sociodemographic characteristics of the population, including age, education level and ethnicity, no clear associations have been consistently found.[111,179] The association of the ODMA non-producer metabotype with obesity in *peri-* and postmenopausal women has been previously suggested.[180] These results agree with those observed by Reverri *et al.*,[181] who reported that equol and ODMA non-producers were related to obesity. In the same line, the inverse association between the equol producer metabotype and obesity has been recently suggested in postmenopausal women, using logistic regression analysis with adjustment for lifestyle factors.[182]

More than 10 gut microbes have been reported to be involved in the equol production, including *Adlercreutzia equolifaciens*,[183] *Asaccharobacter celatus* (now *Adlercreutzia equolifaciens* subsp. *celatus*),[184] *Bacteroides ovatus*,[185] *Finegoldia magna*, *Lactobacillus mucosae* (now *Limosilactobacillus mucosae*),[186] *Slackia equolifaciens*, *Slackia isoflavoniconvertens*,[187,188] and *Streptococcus intermedius*.[185] In contrast, reports on gut microbes that specifically produce ODMA, but not equol, are less abundant. This is the case of *Adlercreutzia equolifaciens* IPLA37004, whose genome sequence suggested a deletion in a large part of the equol operon.[189]

Nakatsu *et al.*[190] found a greater abundance of the genera *Bifidobacterium* and *Eubacterium* in equol-producers *vs.* non-producers in 17 postmenopausal women after consuming isoflavone-containing soy bars for one week. Later, Lino *et al.*[178] compared the relative abundance of 8 gut microbes capable of producing equol in 1044 adult subjects. Interestingly, the equol producing intestinal bacteria were present in both equol producers (n = 458) and non-producers (n = 586). However, the species *A. equolifaciens* subsp. *celatus* and *S. isoflavoniconvertens* were significantly more abundant in equol-producers *vs.* non-producers. Overall, a clue from this study could be the existence of a possible threshold abundance of *A. equolifaciens* subsp. *celatus* and *S. isoflavoniconvertens* necessary to produce equol from daidzein.

A cross-sectional study described the difference in the gut microbiota between the equol-producer and non-producer metabotypes in Chinese people (n = 99).[143] Unfortunately, this study did not consider the ODMA metabotype as an important feature of daidzein metabolism. No significant difference in bacterial richness was found between the equol-producer and non-producer metabotypes, and the equol-producer metabotype was not affected by the intake of isoflavones for 3 days. Although this is too short an isoflavone intervention to modify a metabotype status, this finding agrees with Yoshikata *et al.*,[191] who reported that equol production might not depend on the quantity of equol-producing bacteria but the type of these bacteria since equol-producing bacteria were identified in 56 women but only 13 produced equol (*i.e.*, not all strains within the genus identified as potential equol producers are actually capable of metabolising daidzein to produce equol). However, unlike Zheng *et al.*,[143] Yoshikata *et al.*[191] described a higher microbial diversity in equol producers. Besides this, a previous study reported that isoflavone consumption for one month did not induce the ability to

produce equol in postmenopausal women.[192] These results suggest that the conversion of non-producing individuals into equol producers seems to be unlikely.

The equol-producer metabotype shows a higher abundance of the species *A. equolifaciens* and *Bifidobacterium bifidum* than the non-producer.[143] Besides this, the equol-producer metabotype showed a higher abundance of *Prevotella, Megamonas, Allistipes, Desulfovibrio, Collinsella*, and *Eubacterium* genera. In contrast, the equol non-producer metabotype was enriched in the family Lachnospiraceae, the genus *Eggerthella* and several species from *Ruminococcus* and *Bacteroides*. Also, the authors found statistically significant associations between the equol-producer metabotype and lower prevalence of dyslipidaemia *vs.* non-producers (27% *vs.* 50%).[143] However, no associations between microbial composition and functionality with body mass index (BMI), smoking habit, age, and gender were found. Other cross-sectional studies in Chinese postmenopausal women[193] and Japanese men[194] have reported better cardiovascular health profiles for both equol and ODMA producers than non-producers. Sekikawa *et al.*[195] found proportionally inverse associations between equol-producing status (non-producers, low and high) and white matter lesion, but not the amyloid-beta deposition, in 91 normal cognitive elderly Japanese. Unfortunately, the gut microbiota of the participants was not analysed.

A recent study compared faecal samples from 20 individuals with sporadic colorectal adenomas *vs.* 20 without proliferative lesions and observed the presence of *Parabacteroides distasonis*, *Clostridium clostridioforme*, and *Pediococcus pentasaceus* only in controls, while *Bacteroides fragilis* and *Prevotella melaningenica* were present only in those subjects with colorectal adenomas.[196] Remarkably, the authors found undetectable or deficient equol levels in individuals with colorectal adenomas *vs.* control and suggested that equol production could determine a milieu able to contrast the development of colonic mucosa proliferative lesions.[196] Obviously, it is not known whether precancerous signalling could modulate the gut microbiota or a specific gut microbiota played a possible role in the development of lesions, or both. Thus, as in other cross-sectional studies, the causality role of the gut microbial ecologies cannot be unambiguously assumed.

The specific response of individuals, according to their equol and/or ODMA producing status after dietary intervention with isoflavones, are less abundant. Recently, Hayashi *et al.*[197] reported that the interaction of aerobic exercise and equol production status plays an essential role in improving central artery compliance in postmenopausal women. However, the assay was not a crossover, and the sample size was relatively small (27 females performed exercise *vs.* 16 females did not). Reverri *et al.*[198] described the improvement of endothelial function, but not inflammatory biomarkers, independently of the equol and/or ODMA production status of 17 postmenopausal women and men over the age of 45 years at cardiometabolic risk after consuming isoflavones. The same authors distinguished ODMA-only and equol + ODMA producers from non-producers, according to the serum metabolome of the same volunteers, and found a lower metabolic risk in those producer individuals than non-producers.[181] Although it was a randomized and crossover study, the sample size (n = 17) and the absence of a placebo could limit the scope of these results.

A RCT with soy protein supplementation (n = 50) *vs.* placebo (n = 43) for 2 years in men following radical prostatectomy has recently reported no effects on body weight, blood pressure, total serum cholesterol, iron status parameters, calcium, phosphorus, and thyroid hormones.[199] Interestingly, the stratification of subjects on equol production status in the soy group revealed that body weight increased in equol producers compared with non-producers. Besides this, both systolic and diastolic blood pressure decreased only in the equol non-producers.[199] Overall, these results suggest that the capacity to produce equol in middle-aged to older men seemed to be a disadvantage and agree with Usui *et al.*[149], who observed higher cardioprotective effects in the subgroup of women equol non-producers after consuming 10 mg S-equol. However, it should be noted that most participating men were under medication (mainly taking lipid-lowering and anti-hypertensive drugs, not considered as covariates in the analyses),[199] which might affect the gut microbiota and determine the soy effects and equol production. Overall, the possible influence of medication on equol production and isoflavone effects agree with recent results observed for urolithins in polymedicated metabolic syndrome patients after consuming pomegranate.[139] While the percentage of equol producers in Caucasians has been estimated to be about 30%,[141] the proportion of equol producers was much higher in the study of Bosland *et al.*[199]

As commented above, the metabolism of ellagitannins and ellagic acid to produce (or not) distinctive UMs is critically affected by ageing, as reported in a large cohort (n = 839), mainly Caucasians and aged from 5 to 90 years.[131] The percentage (10%) of urolithin non-producers (UM-0) remains constant in the range from 5 to 90 years of age. In contrast, the proportion of UM-A at an early age (85%) progressively decreases up to 55% from 40 to 90 years of age, concomitant with an increase of UM-B from 15% up to 45%. The shift from UM-A to UM-B was more evident from 25 to 35 years of age, and from that age, the proportion of UM-A and UM-B (55% and 45%, respectively) remains approximately unaltered.[131] Although UMs are stable within individuals at a certain age, a challenge of a high dose of ellagitannins for 3 weeks can shift some specific individuals from apparent UM-0 to either UM-A or UM-B.[119] However, we think these individuals were not genuine UM-0 but very low urolithin producers, in which urolithin production was below the limit of detection or their gut microbiota was more sensitive to ellagitannin consumption than other real UM-0 individuals. To date, no clear association between UMs and diet, sex, or ethnicity has been reported. Despite preliminary observations associating UM-B with higher BMI and gut dysbiosis,[200,201] this was not unequivocally confirmed in a large cohort (n = 839) that included healthy volunteers and patients.[131] On the other hand, in a recent study, gut microbiota and UM distribution in mothers were changing through the 1-year follow-up postpartum to resemble the dis-

tribution in the general population previously described.[138] The decrease in the percentage of overweight mothers with UM-B was concomitant with the increase of normoweight mothers with UM-A over time. Although the correlation between UM-B and obesity cannot be unequivocally established, the results of that study suggest that the UM-B dysbiosis-prone metabotype could be a potential contributor to obesity.

The interindividual variability in urolithin production has been related to some dissimilarity in the gut microbiota. Pure cultures of *Gordonibacter* species can metabolise ellagic acid into different urolithins[202] and are positively associated with Uro-A and UM-A in faeces and urine.[63,168] In contrast, the occurrence of IsoUro-A, Uro-B, and UM-B are inversely associated with faecal concentrations of *Gordonibacter* spp.[63,170] *Ellagibacter isourolithinifaciens*, another human gut bacteria of the family Eggerthellaceae, converts ellagic acid into IsoUro-A and is positively associated with IsoUro-A, Uro-B and UM-B.[63,203,204] *Gordonibacter* increase has been described in adults at cardiovascular risk (n = 42) that consumed a diet containing whole walnuts for 2 weeks compared with a standard Western diet in a crossover design.[205] Although the authors suggested that this shift might be involved in the underlying mechanisms associated with the cardiovascular benefits of walnut consumption, no direct link between *Gordonibacter* and any risk marker was provided. In contrast, in another study, faecal *Gordonibacter* concentration positively correlated with HDLc and negatively with both plasma glucose and VLDLc levels in overweight-obese-metabolic syndrome volunteers consuming pomegranate extract or nuts.[170] Lower abundance of *Gordonibacter* among other bacteria was also observed in active Crohn's disease.[206] Du *et al.*[207] reported a higher abundance of the genera *Scardovia*, *Lactobacillus*, *Gordonibacter*, and *Phascolarctobacterium* in 40 Chinese patients with multiple system atrophy compared with healthy controls (n = 40). The authors found a positive statistical association between *Gordonibacter* and the scale for Parkinson's disease autonomic dysfunction (r = 0.195, P = 0.011).[207] However, the authors acknowledged that their cross-sectional study did not reveal any causal relationship between microbiota and multiple system atrophy. In the case of *Ellagibacter*, this genus has been reported to increase after consuming a symbiotic drink (probiotics plus dietary fibre) by healthy postmenopausal Korean women (n = 37) and was inversely associated with the participants' BMI.[208] However, the trial was not placebo-controlled nor crossover, limiting the scope of the results. Overall, there is still a low number of studies on the role of *Gordonibacter* and *Ellagibacter* in human health. Besides this, finding specific associations between some genera or species and some risk factors might not be enough evidence to prove the role of such microbial groups in health.

The comparison of the human gut microbial ecologies associated with UMs has been reported in healthy normoweight, overweight, and obese individuals (n = 249).[63] Unlike the equol-producer and non-producer metabotypes that did not show a significant difference in bacterial richness in a recent study,[143] UM-0 showed lower diversity and richness than UM-A and UM-B subjects.[63] Besides this, UM-0 was also characterised by a lower abundance of the genera *Phascolarctobacterium*, *Bilophila*, *Alistipes*, and *Butyricimonas* than UM-B and UM-A. Remarkably, UM-B showed a higher abundance of the Coriobacteriia class compared with UM-A and UM-0, which was positively associated with total cholesterol (Tchol), LDLc, and BMI.[63,209,210] For example, the genus *Slackia* (belonging to the Coriobacteriia class), whose abundance was increased in UM-B *vs.* UM-A, correlated with Tchol, LDLc, apolipoprotein-B, and non-HDL-cholesterol levels. In contrast, the family Eubacteriaceae, which was increased in UM-A *vs.* UM-B, was positively associated with apolipoprotein-A. UM-B individuals also presented a higher abundance of some pro-inflammatory microbial groups *vs.* UM-A, including *Methanobrevibacter*, *Parvimonas*, Gammaproteobacteria and *Methanosphaera*.[63] These differences in the gut microbial ecologies between UM-A and UM-B support previous results showing higher cardiometabolic risk in overweight-obese UM-B individuals *vs.* UM-A and UM-0.[119,170] Indeed, correlations between baseline CVD risk markers and urolithins were found in overweight-obese individuals. Uro-A (primarily present in UM-A) was positively correlated with apolipoprotein A-I and intermediate-HDLc, while Uro-B and IsoUro-A (characteristic from UM-B) were positively correlated with Tchol, LDLc, apolipoprotein B, VLDLc, IDLc, oxLDL and the apolipoprotein B : apolipoprotein A-I ratio. In metabolic syndrome patients, Uro-A only correlated inversely with glucose.[170]

It is known that the gut microbiota is significantly altered during pregnancy and after childbirth.[211] Interestingly, Cortés-Martín *et al.*[138] described that the restoration capacity of the gut microbiota and the anthropometric values of mothers up to 12 months after delivery depended on their UM. Through the 1-year follow-up postpartum, UM-A women normalised their gut microbiota and anthropometric values to a greater extent than UM-B. For example, *Methanobrevibacter* and *Olsenella* reduction were correlated to waist reduction, and reduction of Clostridiaceae, *Clostridium sensu stricto*, and *Anaerobacter* correlated to the reduction of waist-to-hip ratio, BMI, and waist.[138] These results also suggest that UM-B, in contrast to UM-A, was associated with a dysbiotic-prone microbial ecology and more resilient to change the microbial and anthropometric profiles during postpartum.

Recently, Cortés-Martín *et al.*[212] explored the possible participation of UMs, along with other factors, in the prevalence of obesity in a cohort of children and adolescents (n = 415). A statistical ordinal logistic model revealed that overweight-obesity prevalence was related to being a young boy (9–12 years old) with either UM-B or UM-0, low adherence to the Mediterranean diet (KIDMED score) and high contribution of a specific consortium of 24 single-nucleotide polymorphisms (SNPs) from a total of 53 SNPs related to obesity and cardiometabolic diseases. In contrast, every variable (sex, diet, UMs, SNPs, age, physical activity, *etc.*) was not independently associated with overweight-obesity.[212]

The gut microbial ecologies of UMs have been reported to be differentially modulated upon consumption of walnuts for just 3 days.[213] After consumption, the genera *Bifidobacterium*, *Blautia*, and some gut microbes of the Coriobacteriia class, including the genus *Gordonibacter*, increased exclusively in UM-B. In contrast, UM-A was less sensitive to walnut consumption, and some members of the Lachnospiraceae family decreased only in UM-A individuals.[213]

In the line of the UM-depending response of individuals to (poly)phenol consumption, for the first time, González-Sarrías *et al.*[119] described the improvement of a panel of cardiometabolic risk biomarkers in UM-B individuals, but not in UM-A. In fact, no statistically significant effects were observed before clustering individuals according to their UM. Furthermore, no significant correlations were found between faecal urolithins excretion and improvement of CVD risk markers. However, urinary excreted urolithin conjugates significantly correlated with improvement of CVD risk markers in UM-B individuals, *i.e.*, reduction of Tchol, LDLc, and non-HDLc correlated with urinary excretion levels of Uro-A metabolites, and changes of LDLc also correlated with both Uro-A and IsoUro-A + Uro-B conjugates. However, in UM-A individuals, where CVD risk markers did not change, no correlations were found.

Despite these correlations with CVD risk markers, other studies failed to find a significant correlation between urolithins occurrence in plasma, urine, faeces or colonic tissues and cancer-related markers and metabolic endotoxemia in colorectal cancer patients (n = 45),[74,87] metabolic endotoxemia in overweight-obese individuals (n = 49),[86] and the blood lipid profile in healthy subjects (n = 32).[214]

Recently, Cortés-Martín *et al.*[139] described that UMs distribution was altered in polymedicated metabolic syndrome patients. The gut microbiota of these patients was in dysbiosis, mainly in hypertensive patients with an overabundance of LPS-producing members of the Enterobacteriaceae family.[215] A RCT and crossover trial showed that the polymedication of the patients determined the prebiotic effect of an ellagitannin-rich pomegranate extract as a crucial variable. The metabolic endotoxemia slightly but significantly improved in all the patients after consuming the extract. However, the soluble intercellular adhesion molecule-1 (sICAM-1) only improved in those patients consuming lipid-lowering drugs (LL-), and the patients' medication clearly determined the modulation of the gut microbiota. In this regard, the genus *Lactococcus* increased in patients consuming antidiabetic (AD-), LL- and anti-hypertensive (HP-) drugs, *Bifidobacterium* increased in LL- and AD-consuming patients, and *Clostridium* cluster XIVa decreased in non-LL- and non-HP-consuming patients. Urolithin production (type and amount) was not associated with the effects observed.[139]

Overall, the current evidence, albeit still low, suggests that the gut microbial ecology of UM-A could be "protective", while UM-B could be a potential dysbiotic-prone metabotype to cardiometabolic impairments.[43,63] In general, the lack of clear associations between circulating or excreted urolithin derivatives (and other phenolic-derived metabolites) and specific effects can be somewhat logical due to the highly variable turnover of these metabolites in the bloodstream and other reservoirs.

2.2.2. The quantitative criterion: the production gradient of (poly)phenol-derived metabolites. Another crucial aspect to be considered to identify or explain the (poly)phenols' health effects is the production gradient of the main bioactive metabolites that can reach the circulation and systemic tissues and exert their potential benefits after (poly)phenols intake. Table 1 shows representative human studies that performed quantitative assessments of circulating and/or excreted phenolic-derived metabolites to correlate health outcomes.

As commented before, the metabolism of some classes of polyphenols, including prenylflavonoids, flavanones, flavan-3-ols, lignans, ellagitannins and isoflavones, yields a high variability of metabolites. Therefore, the definition of "low and high producers" has been commonly used to stratify those individuals capable of producing a high or low amount of metabolites, respectively.[43,55,62,104,105,166,195,199,216–218]

However, as previously mentioned, this cut-off concentration is arbitrary and conditioned by external factors, including the lag period between the last intake of (poly)phenolic precursor and the sample analysis, the sensitivity of the analytical procedure and the food matrix. Regarding food matrix effects, flavanone metabolism is a paradigmatic example. The amount of phenolic-derived metabolites in flavanone metabolism is dramatically affected by their solubility. Encapsulation and micronisation of flavanones increase their excretion in subjects, including the so-called "low hesperetin producers".[219]

Recently, the gut microbiota metabolism of eriocitrin, a soluble flavanone mainly present in lemon, has been reported to yield much higher plasma and urinary concentrations of metabolites (eriodyctiol, homoeriodyctiol, and hesperetin) than hesperidin.[107] Therefore, the cut-off for being high or low producers will significantly depend on the solubility of the flavanone. Overall, the consumption of soluble flavanone-rich sources could be a strategy to enhance the metabolite production of those low-flavanone metabolite producers and provide a sufficient circulating concentration metabolite threshold to exert health benefits even in low producer individuals.[107]

There is a certain consensus regarding the intake of some specific (poly)phenols such as epicatechin, hydroxytyrosol and quercetin, among others, and health effects. However, the final driver in the health effects (a specific phenolic-derived metabolite or a mixture) has not been clearly identified. Besides this, and very importantly, the minimum concentration necessary for a specific (poly)phenol to exert health benefits, and even less in the case of its derived metabolites, is unknown. In this line, many trials, mainly based on the presence-absence of phenolic and dose–response studies, suggest that phenolic-derived metabolites that, as expected, are increased in plasma (or urine) after intake could be related to the health outcomes observed. However, among the vast number of studies dealing with (poly)phenols and health, only

Table 1 Representative human studies that performed quantitative assessments of circulating and/or excreted phenolic-derived metabolites to correlate health outcomes

Source and (poly)phenol classes ingested	Design of the study	Health outcome	Phenolic-derived metabolites evaluated	Main correlations	Ref.
Studies that did find a correlation					
Flavanol-rich cocoa drink (100 mL) with high (176 to 185 mg) or low (<11 mg) flavanol content. (Poly) phenol classes: flavan-3-ols and procyanidins	Randomised control trial (RCT), double-blind, crossover and dose–response study. Healthy adults (n = 11). Duration: acute (2 h). Wash out (WO): 1 day	↑NO species and ↑FMD at 2 h after ingestion of 176 to 185 mg flavonols	Plasma flavanol metabolites	Epicatechin, catechin, epicatechin-7-β-D-glucuronide, 4′-*O*-methyl-epicatechin, and 4′-*O*-methyl-epicatechin-β-D-glucuronide correlated with ↑NO increase. ↑FMD correlated with ↑epicatechin and catechin	220
Black tea (5 cups per d of 250 mL). Detailed (poly) phenolic content not provided	RCT and crossover. Adults with mild hyperlipidaemia (n = 21). Duration: acute (5 h) and chronic (4 weeks). No WO period	Significant increase in FMD response after 4-week consumption of black tea, but not acutely	Urinary 4-*O*-methylgallic acid after 5 h and 4 weeks	↑4-*O*-Methylgallic acid excretion was inversely associated with the change in FMD responses after 4 weeks	221
Flavanol-rich cocoa drinks (300 mL; high or low flavanol content, 917 and 37 mg of total flavanols, respectively). (Poly)phenol classes: flavan-3-ols and procyanidins	RCT, double-blind, crossover. Healthy male adults (n = 16). Duration: acute study (assessments at 1, 2, 3, 4, and 6 h after a single-dose). WO: 2 days	Acute significant transient increase of the FMD response at 1–4 h after oral ingestion of the high-flavanol-rich cocoa drink, but not after the low dose	Plasma flavanol metabolites: epicatechin, epicatechin-7-*O*-glucuronide, 4′-*O*-methyl-epicatechin, 4′-*O*-methyl-epicatechin-*O*-glucuronide, catechin	Epicatechin and epicatechin-7-*O*-glucuronide were independent predictors of FMD effects	222
Curcumin (1 or 4 g d^{-1})	RCT, double blind, placebo-controlled. Elderly subjects (n = 36). Duration: 1 and 6 months	Consumption of curcumin did not significantly affect triacylglycerols, Tchol, LDLc, and HDLc	Plasma curcumin metabolites	Curcumin metabolites were correlated with slight increases in Tchol after 1 month	223
Breakfasts rich in olive oils with different phenolic contents (80 or 400 ppm). (Poly)phenol classes: phenolic alcohols, phenolic acids and derivatives. Others: oleuropein, flavones and lignans	RCT, crossover. Hypercholesteraemic adults (n = 21). Duration: postprandial study (assessments at 1 and 2 h after a single-dose). WO: 1 week	Plasma concentrations of the procoagulant activated factor VII (FVIIa) increased less and PAI-1 activity decreased more 2 h after the high-phenol meal than after the low-phenol meal	Plasma tyrosol, hydroxytyrosol, and 3-*O*-methyl-hydroxytyrosol	↑Plasma hydroxytyrosol correlated with ↓FVIIa concentrations after intake of the high phenol olive	224
Olives (approximately 100 g). (Poly)phenol classes: phenolic alcohols, phenolic acids and derivatives, oleuropein, flavones and lignans	Interventional study. Healthy male adults (n = 8). Duration: acute study (assessments at 1, 2, 3 and 4 h after a single-dose)	↑Plasma total antioxidant potential (TAP) at 2 h	Total phenolic compounds in plasma	↑TAP correlated with total (but no individual) phenolic compounds at 4 h	225
Quercetin, epicatechin, or EGCG (200 mg in 300 mL of water).	RCT, crossover. Healthy male adults (n = 12). Duration: acute study (assessments at 2 and 5 h after a single-dose). 1 week of WO	↑Plasma *S*-nitrosothiols, plasma nitrite, and urinary nitrate after quercetin and epicatechin intake. EGCG did not alter any of the measures of NO production. ↓Plasma endothelin-1 concentration after quercetin and epicatechin intake	Plasma quercetin, 3′-*O*-methylquercetin, epicatechin, 3′-*O*-methyl-epicatechin, and EGCG (2 h), and 11 flavonoids and aromatic metabolites in urine (5 h)	↑Plasma *S*-nitrosothiol correlated with ↑plasma quercetin and epicatechin. Plasma nitrite, urinary nitrate, and urinary endothelin-1 were not correlated with plasma flavonoids	226 and 227
Two types of olive oils (25 mL; 22 g d^{-1}) distributed over 3 meals. (Poly)phenol classes: phenolic alcohols, phenolic acids and derivatives, oleuropein, flavones and lignans	RCT double-blind, crossover. Healthy non-smokers adults (n = 36). Duration: 3 weeks. WO: 2 weeks	↓Oxidized LDL (oxLDL), conjugated dienes, and hydroxyl-fatty acids after both olive oil consumption	Phenolics in isolated LDL particles, including hydroxytyrosol and tyrosol derivatives and homovanillic acid	Plasma oxLDL, but not other oxidation markers, were negatively correlated with the sum of phenols in LDL	228
Orange juice or control drink plus hesperidin (500 mL containing 292 mg hesperidin and 47.5 mg narirutin). (Poly)phenol classes: flavanones and flavones	RCT, crossover. Healthy overweight male adults (n = 24). Duration: acute study (assessments at 6 h after a single-dose). WO: 3 days	Both orange juice and drink plus hesperidin ingestion significantly improved postprandial microvascular endothelial reactivity	Plasma hesperetin	Plasma hesperetin and changes in microvascular endothelial reactivity were significantly correlated	229
Cocoa (250 mL; containing 2, 5, 13, or 26 g of cocoa) with 420, 840 or 1470 mg of total (poly)phenols, respectively. (Poly)phenol classes: flavan-3-ols and procyanidins	RCT, double-blind, crossover. Healthy older adults (n = 23). Duration: acute study (assessments at 1 and 2 h after a single-dose). WO: 3 days	↑FMD at 1 and 2 h, after the intake of 5, 13, and 26 g cocoa	Plasma epicatechin	↑Serum total epicatechin correlated with ↑FMD at 1 and 2 h	230

Table 1 *(Contd.)*

Source and (poly)phenol classes ingested	Design of the study	Health outcome	Phenolic-derived metabolites evaluated	Main correlations	Ref.
Blueberry drinks (500 mL; containing 766, 1,278, or 1791 mg total blueberry polyphenols). (Poly)phenol classes: anthocyanins, flavanols, hydroxycinnamic acids and flavonols	RCT, double-blind, crossover. Healthy male adults (n = 10). Duration: acute study (assessments at 1, 2, 4, and 6 h after a 766 mg single-dose)	Biphasic time-dependent significant increase in FMD at 1–2 and 6 h after consumption of 766–1791 mg total blueberry polyphenols	Plasma phenolic acids and aromatic compounds (n = 32)	↑Vanillic and benzoic acids at 1–2 h and hippuric, hydroxyhippuric, and homovanillic acids at 4–6 h were correlated with ↑FMD	231
Quercetin (200 or 400 mg d^{-1})	RCT, double-blind. Healthy adults (n = 15). Duration: acute study (assessments at 2 and 5 h after a single-dose). WO: 1 week	Time-dependent increase in brachial artery diameter after 400 mg of quercetin intake. No changes in blood pressure	Plasma quercetin, quercetin-3′-*O*-glucuronide and isorhamnetin	The change in diameter was correlated with quercetin-3′-*O*-glucuronide at 2 h	232
Strawberry pulp (50 g d^{-1}). (Poly)phenol classes: anthocyanins, ellagitannins and procyanidins	Open-label, controlled, 2-phases study. Healthy adults (n = 31). Duration: 30 days each phase with a 10-day WO period	Strawberry consumption decreased median resting luminol enhanced whole blood chemiluminescence (LBCL), reflecting oxidants generation by circulating phagocytes after two phases	Caffeic acid, homovanillic acid, Uro-A and 4-hydroxyhippuric acid in urine and plasma	Resting LBCL correlated negatively with plasma 4-hydroxyhippuric acid after the first strawberry dose	233
Orange juice (containing either normal or high concentrations of polyphenols (299 and 745 mg d^{-1}, respectively)). (Poly)phenol classes: flavanones and flavones	RCT, double-blind, crossover. Non-smoking overweight or obese adults (n = 100). Duration: 12 weeks. WO: 7 weeks	The intake of both orange juices significantly protected against DNA damage and lipid peroxidation, modified several antioxidant enzymes, and reduced body weight (BMI, WC, and leptin)	Urinary hesperetin and naringenin and their metabolites	↑Urinary hesperetin and naringenin correlated with erythrocyte catalase activity, but not with CoQ_9, LPO, SOD, BMI, WC, urinary 8-iso-PGF2α and 8-OHdG, and malondialdehyde	234
Mixed nuts (30 g d^{-1}). (Poly) phenol classes: ellagitannins and procyanidins	RCT, 2-arms parallel. Adults with at least three metabolic syndrome risk factors (n = 50). Duration: 12 weeks	Nut consumption improved several cardiometabolic risk markers, including hyperlipidaemia and hypertension parameters	Uro-A glucuronide in plasma	Uro-A glucuronide was inversely correlated with basal abdominal adiposity (WC, waist-hip ratio) and impaired glycaemic control	235
Cocoa flavanol-containing drink (450 mg). (Poly) phenol classes: flavan-3-ols and procyanidins	RCT, double-blind, 2-arms parallel. Healthy adults (n = 100). Duration: acute study (assessments at 1 and 2 h; n = 5) and chronic (1 month)	Acute and chronic cocoa flavanol consumption → ↑FMD, and ↓blood pressure, vascular stiffness and cholesterol	Plasma flavanol metabolites, including epicatechin and its related metabolites	↑Plasma flavanols at 2 h and after 1 month was correlated with ↑FMD	236
Cranberry juices (450 mL; containing 409, 787, 1238, 1534, or 1910 mg of (poly) phenols). (Poly)phenol classes: anthocyanidins, proanthocyanidins, flavanols and flavonols	RCT, double-blind, crossover. Healthy male adults (n = 10). Duration: acute study (assessments at 1, 2, 4, 6 and 8 h after a single-dose). WO: 1 week	Acute cranberry juice consumption → ↑FMD with a peak at 4 h and maximal effects with juice containing 1238 mg of total (poly) phenols	Plasma phenolic acids and metabolites (n = 60) from flavan-3-ols, proanthocyanidins, flavonols, and anthocyanins	Twelve metabolites, including dihydro isoferulic acid 3-*O*-sulfate, ferulic acid 4-*O*-sulfate and homovanillic acid sulfate correlated with ↑FMD (all time-points)	237
Soy isoflavones (80 mg aglycone equivalents)	RCT, double-blind, crossover. Healthy male adults equol and non-equol producers (n = 14 each group). Duration: acute study (assessments at 6 and 24 h after a single-dose). WO: 1 week	Carotid-femoral PWV was significantly improved in equol producers at 24 h, but not at 6 h or in equol non-producers	Plasma isoflavones (daidzein, genistein, and glycitein) and the metabolite equol	Carotid-femoral PWV change was significantly associated with plasma equol	150
Resveratrol (150 mg d^{-1})	RCT, double-blind, crossover. Adults with type 2 diabetes (n = 17). Duration: 30 days. WO: 30 days	Hepatic and peripheral insulin sensitivity and intrahepatic lipid content were not affected by resveratrol treatment, while intramyocellular lipid content increased in type 2 diabetes, muscle fibres and SBP tended to decrease	Plasma resveratrol and its metabolites	↓Intrahepatic lipid content correlated with ↑plasma resveratrol	238
Resveratrol (75, 150 or 300 mg)	RCT, double-blind, crossover. Adults with type 2 diabetes (n = 36). Duration: acute study (assessments at 2 h). 1 week of WO period	Resveratrol (75 mg) significantly improved neurovascular coupling capacity	Plasma resveratrol and derived metabolites	↑Neurovascular coupling capacity was correlated with ↑plasma total resveratrol	239
Coffee drink (50 mL; containing 89 or 310 mg of chlorogenic acid (CGA)). (Poly)phenol classes: hydroxycinnamic acids	RCT, crossover. Healthy male adults (n = 15). Duration: acute study (assessments at 1, 3 and 5 h after a single-dose). 1 week of WO period	Biphasic time-dependent significant increase in FMD at 1 and 5 h after low and high dose of CGA	Plasma CGA metabolites (n = 56)	↑Total plasma CGA metabolites correlated with ↑FMD. Individual metabolites were correlated with FMD depending on the time frame	240

Table 1 *(Contd.)*

Source and (poly)phenol classes ingested	Design of the study	Health outcome	Phenolic-derived metabolites evaluated	Main correlations	Ref.
Pomegranate extract (450 g per capsule); 1st dose = 1 capsule per d (160 mg total phenolics) and 2nd dose = 4 capsules per d (640 mg total phenolics). (Poly)phenol classes: ellagitannins and ellagic acid derivatives	RCT, double-blind, dose–response, crossover. Healthy obese or overweight adults (n = 49). Duration: 3 weeks each dose. WO: 3 weeks	The consumption of pomegranate extract exerted a significant dose-dependent reduction of a range of CVD risk biomarkers, but only in UM-B subjects	Faecal, urinary and plasma urolithins	↑Urolithins correlated with ↓CVD risk markers in UM-B individuals. ↓Tchol, LDLc, and non-HDLc correlated with ↑urinary Uro-A excretion, whereas ↓LDLc also correlated with ↑IsoUro-A + Uro-B	119
Aronia extract (500 mg d^{-1}). (Poly)phenol classes: anthocyanins, hydroxycinnamic acids and proanthocyanidins	RCT. Healthy (former smokers) adults (n = 49). Duration: 12 weeks	Aronia consumption significantly reduced fasting plasma Tchol, LDLc, LDL receptor protein in peripheral blood mononuclear cells	Urinary anthocyanins metabolites (n = 9)	↑Peonidin-3-*O*-galactoside, 3-(4-hydroxyphenyl) propionic acid, and cyanidin-3-*O*-galactoside were associated with ↓Tchol and LDLc	241
Cocoa chocolate (90%; 50 g). (Poly)phenol classes: flavan-3-ols and procyanidins	Interventional study. Healthy male adults (n = 18). Duration: acute study (assessments at 4 h after a single-dose)	The acute cocoa intake significantly increased collagen/ADP-induced platelet function closure time, but not collagen/epinephrine	Circulating (*epi*)catechin and phenyl-γ-valerolactone metabolites (n = 13) in plasma	↑(Epi)catechin metabolites and the single (*epi*) catechin-sulfates significantly correlated with ↑collagen/ADP closure time. No correlations were found with phenyl-γ-valerolactones	242
Red raspberry drinks (200 or 400 g containing 201 or 403 mg of total (poly) phenols, respectively). (Poly) phenol classes: ellagitannins, anthocyanidins, flavonols, hydroxycinnamic acids, flavanols and hydroxybenzoic acid derivatives	RCT, double-blind, crossover. Healthy male adults (n = 10). Duration: acute study (assessments at 2 and 24 h after a single-dose). WO: 1 week	↑FMD at 2 and 24 h after consumption of the 200 and 400 g red raspberry drinks	Circulating ellagitannins metabolites (n = 15) and other phenolic metabolites including benzaldehydes, catechols, pyrogallols, flavonols and propionic, benzoic cinnamic, phenylacetic, hippuric acids (n = 59) in plasma	Plasma ellagic acid (4.6 nM) at 2 h (after 200 and 400 g red raspberry), and Uro-A-3-glucuronide and Uro-A-sulfate at 24 h (41 nM) (only after 200 g) correlated with ↑FMD. No association was found between FMD and 67 circulating phenolic metabolites (120 μM at 24 h)	243
Wild blueberry drinks (11 g d^{-1} containing 150 mg of anthocyanins). (Poly)phenol classes: anthocyanins, flavanols, procyanidins, hydroxycinnamic acids and flavonols	RCT, 2-arms parallel, double-blind. Healthy adults (n = 20 in each arm). Duration: acute (2 h) and chronic (1 month)	Acute (2 h) and daily 1-month wild blueberry consumption significantly increased FMD. Chronic consumption significantly lowered 24-hour ambulatory SBP	Plasma anthocyanin metabolites (n = 63)	14 and 21 anthocyanin plasma metabolites correlated with acute and chronic ↑FMD, respectively	244
Aronia (poly)phenol-rich extract (116 mg, 75 g berries) or whole fruit powder (12 mg, 10 g berries daily). (Poly)phenol classes: anthocyanidins, hydroxycinnamic acids, proanthocyanidins and hydroxybenzoic acid derivatives	RCT, double-blind, 3-arms parallel. Healthy male adults (n = 66). Duration: acute (2 h after single-dose) and chronic (12 weeks)	Acute and chronic consumption of aronia whole fruit and extract powder significantly increase in FMD	Plasma phenolic metabolites (n = 63)	20 metabolites after Aronia extract consumption and 5 metabolites after consumption of the whole fruit correlated with acute and chronic ↑FMD	245
Red grape pomace drink (250 mL; containing 1562 g of total (poly)phenols as gallic acid equivalents (GAE). (Poly)phenol classes: anthocyanins, flavan-3-ols, procyanidins, flavonols, and gallic acid	RCT, crossover. Healthy male adults (n = 12). Duration: acute (3 h after single-dose), postprandial (5 h after the standard meal), and 24 h. WO: 1 week	Red grape pomace consumption → ↓Postprandial insulin incremental area and insulin secretion, and ↑insulin sensitivity index (ISI)	Circulating phenolic metabolites (n = 28) in plasma, including phenyl-γ-valerolactones, hydroxybenzoic acids and simple phenols	Only gallic acid correlated inversely with the insulin response and positively with the ISI	246
Blood orange juice or a sugar-matched control drink (200 mL twice daily). (Poly) phenol classes: flavanones, flavones and anthocyanins	RCT, single-blind, crossover trial. Overweight men and women (n = 15). Duration: 2 weeks. WO: 1 week	↑FMD after blood orange juice consumption. Blood pressure, lipid profile, high-sensitivity CRP, and endothelin-1 were not affected	Urinary hesperetin glucuronide and sulfated metabolites	↑Urinary hesperetin-3′-glucuronide and hesperetin-7-glucuronide were correlated with ↑FMD	247
Studies that did not find a correlation					
Black tea (900 mL; 12.9 and 13.3 mg dL^{-1} of total catechin and 150 and 163 mg dL^{-1} of total (poly)phenols for the freeze-dried and freshly brewed tea, respectively). (Poly)phenol classes: flavanols	RCT, crossover. Patients with stable coronary artery disease (n = 66). Duration: acute (450 mL) and chronic studies (assessments at 2 h after a single-dose and after 4 weeks with daily dose). No WO period	Black tea acute and chronic consumption did not improve plasma antioxidant capacity and did not reduce urinary 8-OHdG, or urinary 8-isoprostane levels	Circulating catechin metabolites in plasma: epicatechin, epicatechin gallate, epigallocatechin, and EGCG	Changes in catechin levels did not correlate with changes in endothelial function, plasma markers of oxidative stress, or CRP	248

Table 1 *(Contd.)*

Source and (poly)phenol classes ingested	Design of the study	Health outcome	Phenolic-derived metabolites evaluated	Main correlations	Ref.
EGCG (150 mg twice daily)	RCT, double blind, crossover. Patients with coronary artery disease (n = 42). Duration: acute and chronic studies (2 h after a single-dose and after 2 weeks with daily dose). WO: 1 week	↑Brachial artery FMD two hours after the first dose of 300 mg of EGCG, but was similar to baseline after 2 weeks of treatment (14 h after the last dose)	Circulating EGCG in plasma	↑Plasma EGCG concentration did not correlate with ↑FMD	249
Quercetin (150 mg d^{-1})	RCT, double-blind, crossover. Overweight or obese adults with metabolic syndrome traits (n = 93). Duration: 6 weeks. WO: 5 weeks	↓SBP, pulse pressure, hs-TNF-α, serum HDLc, oxLDL and hs-CRP (but only in subjects with baseline concentrations >2 mg L^{-1}) after quercetin consumption	Circulating flavonol metabolites in plasma: quercetin, isorhamnetin and kaempferol	There was no correlation between markers and plasma quercetin	250
Flavonoid-enriched chocolate (27 g d^{-1}; containing 850 mg flavan-3-ols (90 mg epicatechin) + 100 mg isoflavones (aglycone equivalents)). (Poly)phenol classes: flavan-3-ols, procyanidins and isoflavones	RCT, double-blind, 2-arms parallel. Postmenopausal with type 2 diabetes mellitus patients (n = 93). Duration: 1 year	Equol producers (n = 17) had larger reductions in DBP, mean arterial pressure, and PWV, compared with non–equol producers (n = 30) after flavonoid intervention	Urinary total epicatechin, 3′-methyl epicatechin, 4′-methyl epicatechin, epicatechin sulfates, methyl epicatechin sulfates and isoflavones (daidzein, genistein, and equol)	Urinary equol concentrations tended to be inversely correlated with DBP only in the equol producer individuals (P = 0.08)	251
Pomegranate extract with high or low punicalagin/ellagic acid ratio (900 mg d^{-1}). (Poly)phenol classes: ellagitannins and ellagic acid derivatives	RCT. Colorectal cancer patients (n = 52). Duration: intake of pomegranate extract for 7–30 days (pre-surgery period)	Pomegranate extract consumption modulated colorectal cancer markers expression (genes and miRNAs)	Ellagitannin-derived metabolites (ellagic acid and urolithins) in colorectal tissues	No correlation between miRNA changes and colorectal cancer marker expression with the urolithins detected in the tissues or with individuals' UMs	252 and 74
Green tea beverage, green tea extract, or isolated EGCG (442 mL containing 200 mg of EGCG). (Poly)phenol classes: flavanols	RCT, crossover. Healthy male adults (n = 50). Duration: acute study (assessments at 2 h after a single dose). WO: 3 days	FMD significantly improved after consuming green tea containing 200 mg EGCG, but not after green tea extract or EGCG intake	Plasma catechin metabolites	No correlations between EGCG, epicatechin, epigallocatechin, epicatechin gallate, and the total catechin plasma levels and changes in FMD were observed	253
Pomegranate extract (450 g per capsule); 1st dose = 1 capsule per d (160 mg total phenolics) and 2nd dose = 4 capsules per d (640 mg total phenolics). (Poly)phenol classes: ellagitannins and ellagic acid derivatives	RCT, double-blind, dose–response, crossover. Healthy obese or overweight adults (n = 49). Duration: 3 weeks each dose. WO: 3 weeks	The highest pomegranate extract dose significantly reduced plasma LBP levels	Faecal, urinary and plasma urolithins	No correlation between urolithins and plasma LBP levels was found	86
Pomegranate extract with high or low punicalagin/ellagic acid ratio (900 mg d^{-1}). (Poly)phenol classes: ellagitannins and ellagic acid derivatives	RCT, 2-arms, parallel. Colorectal cancer patients (n = 35). Duration: from 5 to 35 days before surgery	↓LBP levels after daily consumption of pomegranate extract rich in punicalagin	Concentration of ellagic acid and urolithins in plasma, urine and colon tissues	No correlation with LBP levels and any specific urolithin in plasma, urine, or colon tissues	87
Pomegranate extract (320 mg phenolics per d). (Poly)phenol classes: ellagitannins and ellagic acid derivatives	RCT, double-blind and crossover. Metabolic syndrome patients under medication (n = 50). Duration: 4 weeks. WO: 4 weeks	Pomegranate effects depended on the patients' medication. ↓Plasma sICAM levels was found only in LL-patients. ↑*Lactococcus* in AD-, LL- and HP-patients, ↑*Bifidobacterium* in LL- and AD-, while ↓*Clostridium XIVa* in non-LL- and non-HP-patients	Concentration of urolithins in plasma, urine and faeces	No urolithin was associated with any microbial group or plasma inflammatory-metabolic biomarker (sICAM-1, ghrelin, peptide YY TNF-α, leptin, adiponectin, sVCAM-1, RBP4, GLP-1, IL-6, PAI-1, resistin, BDNF, HGF, MCP-1, P-selectin, C-peptide and LBP)	139

8-OHdG, 8-hydroxydeoxyguanosine; AD-, patients under antidiabetic medication; ADP, adenosine-5′-diphosphate; BMI, body mass index; BDNF, brain-derived neurotrophic factor; CGA, chlorogenic acid; CoQ, coenzyme Q; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; EGCG, epigallocatechin gallate; FMD, flow-mediated dilation; GAE, gallic acid equivalents; GLP-1, glucagon-like peptide-1; HDL, high density lipoprotein; HDLc, high density lipoprotein cholesterol; HGF, hepatocyte growth factor, HOMA-IR, homeostatic model assessment of insulin resistance; HP-, patients under anti-hypertensive medication; ISI, insulin sensitivity index; LBP, lipopolysaccharide-binding protein; LDL, low density lipoprotein; LDLc, low density lipoprotein cholesterol; LL-, patients under lipid-lowering medication; LPO, lipid peroxide; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; oxLDL, oxidized LDL; PAI-1, plasminogen activator inhibitor type-1; PGF2α, prostaglandin F2 alpha; PWV, pulse-wave velocity; RCT, randomised control trial; SBP, systolic blood pressure; RBP4, retinol-binding protein-4; sICAM-1, soluble intercellular adhesion molecule-1; SOD, superoxide dismutase; sVCAM-1, soluble vascular adhesion molecule-1; TAP, total antioxidant potential; Tchol, total cholesterol; TNF-α; tumour necrosis factor-α; UM, urolithin metabotype; WC, waist circumference; WO, wash-out.

a few human studies have explored correlations and/or associations between the reached concentrations of these circulating or excreted metabolites and health outcomes (Table 1). Most of these studies that have observed a significant correlation with specific circulating phenolic-derived metabolites belonging to acute studies where the variation in the concentration-time profile of these circulating metabolites is more controlled than chronic studies.

Thus, to date, improvements in flow-mediated dilation (FMD) have been correlated with changes in plasma flavanols and derived metabolites such as epicatechin and its glucuronides following flavanol-rich cocoa consumption.[220,222,230,236] On the contrary, significant increases in plasma catechin metabolite levels did not correlate with changes in endothelial function, plasma markers of oxidative stress, or CRP after acute and chronic black tea or pure EGCG consumption.[248,249] These findings suggest that other (poly)phenolic components of tea may influence vascular health or, perhaps, it is another example of the food matrix effect. In this regard, the increase in urinary 4-*O*-methyl gallic acid was inversely associated with the change in FMD responses after 4-weeks of black tea consumption.[221]

Other studies have also shown acute correlations between FMD and several phenolic acid metabolites such as vanillic, benzoic and hippuric acids, and ferulic and caffeic acid sulfates, among others, after anthocyanin-rich berry intake.[231,237,244,245] Surprisingly, the same authors associated the improvement of FMD in 10 subjects after red raspberry intake with the presence of plasma ellagic acid (4.6 nM) and Uro-A conjugates (41 nM), but not with the pool of plasma phenolic acid metabolites that reached 120 μM.[243] Overall, it is likely that associations will be found between plasma metabolites that increase after consuming the corresponding (poly) phenolic precursor and acute specific effects such as FMD improvements. However, these associations are usually lost in longer studies, even if the effects are also observed. Statistical associations do not necessarily involve causality or clinical relevance. In this regard, the approach of these authors to prove the link between FMD effects and circulating metabolites should be highlighted. They injected the equivalent dose of the pool of metabolites found in human plasma into mice and observed an improvement of FMD in mice, proving the causality role of anthocyanin-derived metabolites.[244]

Urinary excreted flavanone metabolites such as hesperetin 3′-*O*-glucuronide, and hesperetin 7-*O*-glucuronide have also been correlated with relative FMD improvements in overweight subjects after drinking orange juice.[247] As expected, flavanone metabolite excretion increased after orange juice intake. However, whereas orange juice might improve FMD, there is no proven causality between urinary flavanone metabolite excretion and observed effects.

Other acute or postprandial studies have reported correlations between some health outcomes and circulating metabolites such as hesperetin concentrations and changes in microvascular endothelial reactivity after both orange juice and control drink plus hesperidin intake,[229] quercetin-3′-*O*-glucuronide concentrations and an increase in brachial artery diameter after 400 mg of quercetin intake,[232] hydroxytyrosol concentrations with the reduction of the pro-coagulant activated factor VII (FVIIa) concentrations after intake of the olive oil,[224] and gallic acid and the insulin response and insulin sensitivity after red grape pomace intake.[246]

Finally, other studies have not identified the main driver (or drivers) of beneficial effects despite reporting positive correlations. Thus, Wong *et al.*[239] reported in a postprandial study that resveratrol intake improved neurovascular coupling capacity, and the effect was correlated with the total metabolites (free form plus conjugates).[239] A similar aspect was found in an acute interventional study in healthy males that consumed olives, finding a significant correlation between plasma total phenolics and plasma total antioxidant potential (TAP) but not with individual phenolic-derived metabolites, including hydroxytyrosol.[225] Besides this, another RCT reported that equol concentrations were correlated with the change in carotid-femoral pulse-wave velocity (PWV) after soy isoflavones intake, but no effect was observed after free equol intake.[150]

In contrast, correlations between phenolic-derived metabolites and health outcomes are less evident in chronic studies. This fact is remarkable with the lack of studies that correlated improvements in FMD and/or blood pressure, even with flavanol-derived metabolites such as epicatechin. In this regard, one RCT conducted in postmenopausal with type 2 diabetes mellitus patients that consumed flavonoid-enriched chocolate (27 g d^{-1}) plus 100 mg isoflavones for 1 year reported that urinary equol concentrations, but not epicatechin and its metabolites, tended to be inversely correlated with the reduction in diastolic blood pressure, although only in the equol producer individuals.[251] On the contrary, a certain correlation has been found with other cardiometabolic markers such as hyperlipidaemia. Thus, urinary anthocyanin metabolites such as peonidin-3-*O*-galactoside, 3-(4-hydroxyphenyl) propionic acid, and cyanidin-3-*O*-galactoside were correlated with lower plasma Tchol and LDLc in a RCT conducted with 49 healthy former smokers after 12-weeks Aronia consumption.[241] In the same line, another RCT described that the plasma oxLDL concentrations were negatively correlated with the sum of phenolics including hydroxytyrosol and tyrosol derivatives and the homovanillic acid metabolite in LDL particles from 36 healthy volunteers that consumed olive oil for 3 weeks.[228] However, no correlation was found with antioxidant markers. Similarly, in another RCT conducted in 100 overweight or obese adults that consumed either normal or (poly) phenol-enriched orange juice for 12 weeks, no correlation was found with urinary hesperetin and naringenin or their conjugated metabolites and several antioxidant markers and reduction of anthropometric parameters, except for an inverse correlation with erythrocyte catalase activity.[234]

Several RCT trials conducted with pomegranate extracts have tried to correlate different plasma cardiometabolic and inflammatory risk biomarkers regarding urolithins. However, most studies did not find correlations between concentration

changes in urine and plasma of any conjugated urolithin and the evaluated biomarkers.[86,87,139] Besides this, the occurrence of urolithin levels in human CRC tissues was not correlated with the modulation of different miRNAs and CRC marker expression.[74,252] González-Sarrías *et al.*[119] reported that total and single urinary urolithins (Uro-A and B and IsoUro-A) in subjects that belong to UM-B significantly correlated with a reduction in LDLc levels, and specifically for Uro-A with total cholesterol and non-HDLc, after 3-weeks consumption of pomegranate extract. Besides this, the intake of other ellagitannin-rich sources has yielded contradictory results. In this regard, Uro-A glucuronide was inversely correlated with basal abdominal adiposity (WC, waist-hip ratio) and impaired glycaemic control (fasting insulin, HOMA-IR) after 12-weeks consumption of mixed nuts (30 g d^{-1}).[235] However, no correlation was found after 1-month strawberry pulp consumption (50 g d^{-1}) between Uro-A and several antioxidant markers, being the effects negatively correlated with plasma 4-hydroxyhippuric acid concentrations.[233]

Two RCT studies found a correlation between the sum of circulating curcumin metabolites and the change in Tchol,[223] and the increase of intrahepatic lipid content with the plasma resveratrol levels[238] after consuming curcumin and resveratrol for one month, respectively. On the contrary, in another RCT conducted in patients with metabolic syndrome that consumed quercetin for 6 weeks, no correlation was found between improvements in cardiometabolic and inflammatory risk biomarkers with plasma concentrations of quercetin.[250]

3. Conclusions and roadmap

A consistent cause-and-effect relationship has been observed between consuming a few dietary (poly)phenols, including flavanols and phenolics in olive oil, and health effects (endothelial function and prevention of LDL oxidation, respectively). However, this cause-and-effect relationship has not been well established for the rest of the dietary phenolics.

To date, the possible final drivers of the effects, at least partially, *i.e.*, the specifically produced metabolite(s) and/or the gut microbial ecology associated with (poly)phenol metabolism (gut microbiota-associated metabotypes), have not been fully identified. In this regard, several studies have found statistical associations between plasma metabolites and acute effects such as FMD improvements. This association is likely to happen if the precursor (pure (poly)phenol or phenolic-containing food) exerts an effect. In this case, as it is logical to observe the concomitant increase in plasma of the derived phenolic metabolites, the statistical possibility of finding a correlation between effect and metabolite concentration will be high. Likewise, a non-targeted plasma analysis could also yield many possible associations between FMD (or other acute determinations) and the concomitant presence of other plasma metabolites during the assay (*e.g.*, vitamins, amino acids, and many others).

However, these associations are usually lost in longer studies due to the high turnover of phenolic metabolites. Besides this, significant statistical associations do not necessarily involve causality or clinical relevance.

Cross-sectional associations to observe differential health effects depending on the gut microbial ecology are insufficient to prove both causality and temporality in the effects. Due to the vast amount of interfering variables that affect the individuals' response to (poly)phenol consumption, randomised and placebo-control trials are mandatory to establish a causal role between specific gut microbial ecologies (gut microbiota metabotypes) and health effects. In this regard, several points like clustering subjects according to their gut microbiota-associated metabotypes, production of metabolite level, age (since metabotypes might change with age) or phase-II polymorphisms, as well as qualitative and quantitative assessments of the circulating (and excreted) metabolites to find strong correlations should be considered in further RCT studies. No single associations are sufficient to prove causality (even from a RCT). Therefore, RCTs should include a crossover and dose–response design as a first step in demonstrating causality *vs.* apparent statistical associations of circulating metabolites and effects.

The genetic makeup can contribute to defining the impact of dietary (poly)phenols on human health. Therefore, there is a need for investigating the role of polymorphisms of transporters and enzymes involved in the ADME of (poly)phenols. The contribution of these polymorphisms on the existence of specific polyphenol-related metabotypes is uncertain. However, they could modulate the bioavailability of dietary (poly)phenols critically and consequently affect the health effects.

Instead of animal to human, we should perform human to animal translational approaches to prove in animals the causal role of specific phenolic-derived metabolites produced by humans and/or their gut microbiota metabotypes. For example, after consuming dietary (poly)phenols, the human plasmatic phenolic signature should be administered (intravenously or intraperitoneally) to animal models to check a systemic cause-and-effect relationship. Similarly, the qualitative and quantitative profile of phenolic-derived metabolites found in human tumours after consuming dietary (poly)phenols could be injected chronically into tumours of xenograft animal models to verify their specific response to the challenge of phenolic-derived metabolites individually or as a mix.

In the same line, specific gut microbes, a consortium of microbes or faecal transplants characteristic of specific human gut microbiota metabotypes, should be assayed in animal models to demonstrate their causal role in health effects.

Identifying the actual metabolites ultimately responsible for the health effects after (poly)phenol consumption remains elusive. Nevertheless, we believe that the approaches given above, in combination with growing evidence for the biological effects of circulating metabolites, thanks to physiologically relevant mechanistic studies using circulating phenolic-derived metabolites, but not the forms present in foods, will

contribute to identifying the putative drivers responsible for the health effects attributed to (poly)phenols.

Author contributions

Conceptualisation, supervision and validation: J.C.E.; funding acquisition: J.C.E., M.V.S.; investigation: all the authors; writing – original draft: J.C.E., M.V.S., A.G.-S.; writing – review & editing: all the authors.

Conflicts of interest

There are no conflicts to declare.

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