Where to look into the puzzle of polyphenols and health? The postbiotics and the gut microbiota associated with human metabotypes.

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Abstract

The full consensus on the role of dietary polyphenols as human health-promoting compounds remains elusive. The two-way interaction between polyphenols and gut microbiota (GM) (i.e., modulation of GM by polyphenols and their catabolism by the GM) is determinant in polyphenols' effects. The identification of human metabotypes associated with a differential gut microbial metabolism of polyphenols has opened new research scenarios to explain the inter-individual variability upon polyphenols consumption. The metabotypes unequivocally identified so far are those involved in the metabolism of isoflavones (equol and(or) *O*-desmethylangolesin producers vs. non-producers), and ellagic acid (urolithin metabotypes, including producers of only urolithin-A (UM-A), producers of urolithin-A, isourolithin-A, and urolithin-B (UM-B), and non-producers (UM-0)). Besides, the microbial metabolites (phenolic-derived postbiotics) such as equol, urolithins, valerolactones, enterolactone and enterodiol, and 8-prenylnaringenin, among others, can exert differential health effects. We update the knowledge and take position here on i) the two-way interaction between GM and polyphenols, ii) the evidence between phenolic-derived postbiotics and health, iii) the role of

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metabotypes as biomarkers of GM and the clustering of individuals depending on their metabotypes (metabotyping) to explain polyphenols' effects, and iv) the gut microbial metabolism of catecholamines to illustrate the intersection between personalized nutrition and precision medicine.

1. Introduction

Phenolic compounds are non-nutrient phytochemicals widely consumed in the human diet.[1] Polyphenols (strictly speaking, those compounds with more than one phenolic moiety) are the most abundant and probably also relevant dietary phenolics in the context of human health. In the last decades, non-controlled observational studies, the saturation of reviews and meta-analyses (regrettably many of them led by authors with questionable opinion leadership on this specific topic), and especially a massive output of in vitro studies, have built a seemingly solid basis to claim the beneficial effect of (poly)phenols on human health.[2] Although an increasing number of studies on animal models and randomized human interventions suggest the protective effect of a (poly)phenol-rich dietary pattern, the precise dose of either the combination or specific (poly)phenols required to exert the effects is still unknown. To date, this preventive effect against the development of chronic degenerative diseases (cancer, neurodegenerative, and cardiometabolic diseases) has not been proven unequivocally.[3] Indeed, human studies assaying well-known polyphenols such as resveratrol, isoflavones, curcumin, proanthocyanidins, and ellagitannins, among others, have yielded heterogeneous and often controversial results.[4-6] Perhaps, there may be even many more 'no effects' studies that have not been published due to the lack of appeal for such 'negative' results. The point is: why does a full consensus on (poly)phenols' health benefits remain elusive? In the context of diet and health, the answer lies in the multifaceted interrelation between (poly)phenols and health, which involves various crucial points: i) how can prevention be measured?,[7] ii) the human inter-individuality, i.e., our genetic makeup and physiological status (healthy, disease risk, type of disease, etc.), iii) lifestyle (physical activity, dietary pattern including the food matrix, etc.), iv) heterogeneity in methodological approaches (trial designs, analytical protocols, etc.), and v) the two-way interaction

between (poly)phenols and gut microbiota (modulation of the microbiota by polyphenols and metabolism of polyphenols by the microbiota).[8,9] Finally, the significance of the resulting potentially active metabolites upon catabolism of (poly)phenols by the gut microbiota is emerging, i.e., the phenolic-derived postbiotics (such as urolithins and equol, among others). Overall, the above complex equation yields an extremely high variability in the metabolic fate of (poly)phenols with somehow unpredictable effects on human health.[10,11]

In the present review, we update the information and take position on i) the two-way interaction between the gut microbiota and (poly)phenols, ii) the current evidence between phenolic postbiotics and health, iii) the role of human metabotypes as biomarkers of the gut microbiota and the clustering of individuals depending on their metabotypes (metabotyping) to explain (poly)phenols' effects, and iv) the gut microbial metabolism of the phenolic compounds catecholamines to illustrate the intersection between personalized nutrition and precision medicine.

2. The two-way interaction between phenolics and gut microbiota: what we know so far

The gut microbiota transforms most dietary polyphenols in the intestine of humans and other mammals. This conversion is often essential for the absorption and biological activity of these compounds. Different studies show how gut microbiota converts different polyphenols into smaller molecules called microbial metabolites (i.e., phenolic-derived postbiotics). These studies include intervention studies in humans and animals as well as in vitro cultures using fecal inocula. Some of the bacterial species involved in polyphenol transformations have been identified, and the modulation of the gut microbial ecology by polyphenol consumption has been demonstrated. However, recent investigations have shown large inter-individual differences in the production of bioactive postbiotics from dietary polyphenols because of the specific gut microbiome of each individual. Therefore, the potential biological activity derived from polyphenols intake is conditioned by the gut microbiome ecology of each individual.

2.1. Gut microbial metabolism of phenolics: enzymes involved and metabolites produced

Phenolics are generally found conjugated to organic acids and sugars that are usually not absorbed unless they are hydrolyzed. Gut microbiota can deconjugate glycosides, glucuronides, and organic acids resulting in the release of the corresponding aglycones.[8,12] The gut microbiota further transforms these aglycones through reactions of ring and lactone fission, dehydroxylation, reduction, decarboxylation, demethylation, and isomerization, among others.[8,12-15] Microbial transformations are different depending on the phenolic structure (flavonoids or non-flavonoids), polymerization degree, and spatial configuration.

Flavonoids, including flavonols, flavanones, flavan-3-ols, isoflavones, anthocyanins, and flavones, contain a common structure consisting of two benzene rings (A and B) linked through a heterocyclic pyrone *C*-ring.[12,14] Most of the flavonoids in foods occur as glycosides, mainly *O*-glycosides but also *C*-glycosides (**Table 1**).[14-42] Exceptions to this are flavan-3-ols, which are not conjugated but can form oligomeric and polymeric structures called proanthocyanidins or condensed tannins as a whole or procyanidins, prodelphinidins or propelargonidins when they are only composed of (epi)catechin, (epi)gallocatechin or (epi)azfelechin, respectively. Gut microbiota is able to breakdown the flavonoid *C*-ring in different positions, releasing a higher number of simple phenolics derived from A and B rings. The hydroxylation pattern of the B-ring, as well as its position, affects the type of phenolic compounds produced. After *C*-ring-fission, flavonoids can be further metabolized by the gut microbiota through demethylation and dehydroxylation reactions (**Table 2**).[21,23,26,30,32-34,36-39,43-79] Simpler phenolic compounds derived from A and B rings are released as a product of this microbial degradation of flavonoids in the gut. The majority of these metabolites consist of acid or aldehyde phenolics with 1, 2, and(or) 3 hydroxyl and methyl ester radicals.[8,12]

Non-flavonoid phenolics, including hydrolyzable tannins, lignans, stilbenes, hydroxycinnamates, and hydroxy-benzoic acid derivatives, conform a phenolic group with higher heterogeneity than flavonoids in both structure and polymerization level. Indeed, non-flavonoids are an example of the enormous diversity of phenolic structures commonly found in plant foods, and their microbial

metabolism requires a more detailed study. Thus, depending on their chemical complexity, they are more or less absorbed in the small intestine, and consequently, the gut microbiota has different opportunities to metabolize them.

Hydrolyzable tannins are the most complex phenolics, and they include gallotannins and ellagitannins (ETs). Gut bacteria hydrolyze the ester bonds present in tannins (tannin acyl hydrolase activity).[80] Complex ellagitannins such as punicalagin and pedunculagin can also be hydrolyzed by microbial tannases (Table 1), although this has not been unequivocally proven in humans so far. In contrast, deconjugation of tannin-*C*-glycosides such as castalagin and vescalagin has not been described yet, but something similar to flavone *C*-glycosides hydrolysis by the gut microbiota could happen. After hydrolysis of tannin-*O*-glycosides, gallic acid from gallotannins and ellagic acid (EA) from ETs are further transformed by the gut microbiota (Table 2). Gallic acid can undergo decarboxylation and dehydroxylations. Similarly, EA can be dehydroxylated to render the metabolites called nasutins, in which two hydroxyls have been removed.[80] However, EA is also further transformed by lactone-ring cleavage and decarboxylation to produce pentahydroxy-urolithin (Uro-M5), which is a key intermediate in the production of the different urolithins. From Uro-M5, consecutive dehydroxylations finally lead to the main metabolites detected in vivo, which are the dihydroxy-urolithins urolithin A (Uro-A) and isourolithin A (IsoUro-A) and 3-hydroxy-urolithin, also known as urolithin B (Uro-B) (**Figure 1**).[80-82]

Lignans *O*-glycosides are also hydrolyzed by the gut microbiota to render diphenolic compounds with a 1,4-diarylbutane structure such as pinoresinol, secoisolariciresinol, matairesinol, lariciresinol, isolariciresinol, and syringaresinol.[83] Microbial activities on lignans also include reductions and demethylations, followed by dehydroxylation and lactonization reactions (Table 2).[84] For example, pinoresinol and lariciresinol are transformed by the gut microbiota via four distinct types of chemical reactions, i.e., benzyl ether reduction, guaiacol demethylation, catechol dehydroxylation, and diol lactonization.[84] Therefore, a complex metabolic pathway involving several precursors and intermediary metabolites, various conjugation patterns, and diverse bacterial species are needed to

yield the final products enterodiol and enterolactone (the so-called enterolignans or mammalian lignans) from dietary lignans.[85]

Stilbenes, based on a C6-C2-C6 polyphenolic structure, are also transformed by the gut microbiota. Among stilbenes, *trans*-resveratrol is the main compound studied due to its acknowledged health-benefits.[4,86,87] Resveratrol *O*-glucosides such as *trans*-piceid (*trans*-resveratrol-3-*O*-β-D-glucopyranoside) are also hydrolyzed into the resveratrol aglycone by the gut microbiota (Table 1).[74] Conversely, resveratrol can be glycosylated in the gut to produce piceid again. Piceid and resveratrol are absorbed and extensively conjugated, being the sulfate and glucuronide derivatives the primary circulating metabolites. On the other hand, gut bacteria metabolize resveratrol and its precursors, including piceid, yielding certain derivatives such as dihydroresveratrol, dihydropiceid, 3,4'-dihydroxy-*trans*-stilbene and 3,4'-dihydroxydihydro-stilbene (lunularin) through reduction reactions (Table 2).[74]

Hydroxycinnamates are abundant non-flavonoid dietary compounds. The most common dietary C6-C3 hydroxycinnamates include *p*-coumaric acid (4-hydroxycinnamic acid), caffeic acid (3,4-dihydroxycinnamic acid), ferulic acid (4-hydroxy 3-methoxycinnamic acid) and sinapic acid (4-hydroxy 3,5-dimethoxycinnamic acid), and their esters with quinic, tartaric and malic acids (chlorogenic and caftaric acids, etc.) among others. Hydroxycinnamates that esterify sugars and hydroxylated acids (quinic, tartaric, malic) are hydrolyzed by bacterial esterases (e.g., cinnamoyl esterases),[41] and then metabolized to reduce the double bond to give rise to phenylpropionic acid acids (Tables 1 and 2). However, the reduction of the double bond or the opening and decarboxylation of the quinic acids can also occur before the action of the esterases.[88] The side-chain shortening of phenylpropionic acid takes place through β-oxidation at different levels of the degradation pathway.[15,89] Finally, hydroxycinnamates metabolites are decarboxylated to produce hydroxybenzenes such as catechol (1,2-dihydroxyphenol). Dehydroxylation usually occurs before reduction and decarboxylation to remove the hydroxyl at the C4-position of the caffeic acid residue.[12]

Although there are potentially thousands of different phenolic compounds in the diet, they are typically transformed into a much smaller number of final metabolites.[12] Hydroxy-benzoic acids are the common microbial degradation metabolites obtained in the gut from flavonoid and non-flavonoid phenolics. Besides, these simple metabolites are also commonly found in most fruits. These phenolics are further transformed by microbial decarboxylase enzymes when a free hydroxyl group is present in 4-position. This is the case of gallic acid (3,4,5-trihydroxybenzoic acid), protocatechuic acid (3,4-dihydroxybenzoic), and vanillic acid (3-methoxy-4-hydroxybenzoic acid), which are transformed in pyrogallol (1,2,3-trihydroxyphenol), catechol (1,2-dihydroxyphenol) and *O*-methylcatechol, respectively.[12]

2.2. Gut microbial metabolism of phenolics: the gut bacteria involved and their modulation by phenolics

Overall, many transformations of xenobiotics, such as phytochemicals (including phenolic compounds), pharmaceuticals, pollutants, etc., share common rules of biotransformation in the gut and may be performed by different phylogenetic groups of gut microbes (see Koppel et al.[90] for a review summary on the chemical transformation of xenobiotics by the human gut microbiota). However, in the case of phenolics, the metabolism of each specific compound by the gut microbiota depends not only on the general chemical structure but also on the number, type, and position of specific functional groups, stereoisomerism, and polymerization degree. Besides, it is also necessary the presence of particular bacterial species/strains capable of performing specific transport of the molecule inside, as well as the existence of specific enzymatic machinery to catalyze the different reactions on the phenolic core. Several studies have been performed to identify the microorganisms associated with phenolic transformations (Tables 1 and 2). However, bacterial species implicated in the transformation of many phenolic compounds are still unknown.

Bacterial species involved in the hydrolysis of flavonoids and non-flavonoids conjugated with organic acids and sugars are listed in Table 1. Species belonging to the four most abundant phyla in the human intestine (Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria) can hydrolyze flavonoid and non-flavonoid *O*-glycosides. Interestingly, several *Lactobacillus* and *Bifidobacterium*

spp., highly recognized by their beneficial properties, as well as *Enterococcus*, are involved in *O*-glycoside hydrolysis. Glycosylated phenolics can serve as the sole carbon and energy source of microorganisms, with the attached sugar moieties being preferentially fermented.[14] This could explain the microbial modulation ('prebiotic-like') effects of different phenolic glycosides observed for these and other bacterial groups of the gut microbiota. Some polyphenols carry sugar moieties other than glucose, such as rutinoside (α-L-rhamnosyl-(1->6)-β-D-glucoside) or neohesperidoside (2-α-L-rhamnosyl-(1->2)-β-D-glucoside). Gut microorganisms acting on these phenolics possess α-rhamnosidases in addition to β-glucosidases.[12,14] This is the case of some species of *Lactobacillus* such as *L. plantarum* and some of *Bifidobacterium*, such as *B. pseudocatenulatum* (Table 1). Screening approaches reveal that the activity may be strain-specific.[16,91,92] The hydrolysis of *C*-glycoside phenolics by gut bacteria is less efficient than that of *O*-glycosides, and only some species of the Firmicutes phylum have been related (*Enterococcus* sp., *Eubacterium cellulosolvens*, and *Lactococcus* sp.). In contrast, species from different phyla are involved in ester hydrolysis, including Firmicutes, Actinobacteria, and Proteobacteria (Table 1).

After deconjugation, polyphenols are further transformed by the gut microbiota, and bacterial species or strains reported to catalyze these reactions are listed in Table 2. Interestingly, bacterial species of only two phyla (Firmicutes and Actinobacteria) have been related to these aglycone transformations despite involving very diverse enzymatic activities (*C*-ring and lactone fission, demethylation, decarboxylation, reductions, etc.). Besides, while the species of the Actinobacteria phylum, involved in phenolic deconjugation, belong to the Bifidobacteriaceae family, most of the species of the Actinobacteria phylum, responsible for the transformation of aglycones, belong to Eggerthellaceae family except for the reduction of isoflavones to equol where some *Bifidobacterium* species (*B. animalis, B. longum, B. pseudolongum*) also have this ability. Bacterial genera from the new family Eggerthellaceae family were previously considered within the Coriobacteriaceae family. Thus, the class Coriobacteriia containing the family Coriobacteriaceae has been divided into the Eggerthellales ord. nov. (including the family Eggerthellaceae fam. nov) and the emended order Coriobacteriales (including the emended family Coriobacteriaceae and Atopobiaceae fam. nov.).[93]

Therefore, because of the division of the class Coriobacteriia, bacterial species described as polyphenol transformers have been regrouped within the Eggerthellales ord. nov., while phylogenetic neighbors, not associated with polyphenol conversion (*Atopobium, Olsenella,* and *Collinsella*), are clustered into the emended order Coriobacteriales. Further research should be performed to elucidate the potential health benefits of species from the class Coriobacteriia and especially from the Eggerthellaceae family due to their ability to produce bioactive metabolites from several dietary polyphenols. As an example, two neurodegenerative disorders, Alzheimer's disease, and multiple sclerosis, have recently been associated with a depletion of *Adlercreutzia equolifaciens*, an equol-producing bacterium from Eggerthellaceae family.[94,95]

The gut microbiota composition depends on several factors such as diet, treatment with antibiotics or other medications, physical activity, pregnancy, postpartum, type of delivery, and breastfeeding, among others.[96-98] Functional foods represent an interesting option to modulate the gut microbiota. The diet, via microbial fermentation, modulates the gut ecology. In this line, the modulating effects of dietary fiber have primarily been investigated. Gut bacteria produce short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate, through dietary fiber fermentation.[99] Apart from dietary fiber, several studies in the last decade reported that dietary polyphenols are also relevant in the modulation of the gut microbiota.[12,15,97,100,101] As an example, polyphenols and particularly hydrolyzable and condensed tannins, promote the growth of lactobacilli and bifidobacteria in different in vitro models, preclinical and human intervention studies with polyphenol-rich foods, including cocoa, tea, grapes, wine, berries, pomegranates, and nuts have been performed.[97] Different mechanisms explaining the modulating effects of polyphenols have been suggested such as being a source of sugar in the case of conjugated polyphenols but also antimicrobial activity of different polyphenols such as flavan-3-ols (iron-chelating compound) or anthocyanins (inactivation of the membrane protein and loss of function)[102] or resveratrol (anti-adhesive activity).[103] Consequently, the concept of prebiotics, previously restricted to carbohydrates, has been updated and new and broader definition allows including polyphenols as potential prebiotics: '*A prebiotic is a non-digestible compound that, through its metabolization by microorganisms in the gut modulates*

composition and(or) activity of the gut microbiota, thus conferring a beneficial physiological effect on the host'.[104]

2.3. The case of catecholamines

There are relevant aromatic amino acids with crucial physiological activities that share with other dietary phenolics the interactions with gut microbiota, leading to potential inter-individual variability. This is the case of the neurotransmitters catecholamines, and it is a paradigmatic example to illustrate the intersection between personalized nutrition and precision medicine.

L-tyrosine (tyrosine), and the related drugs L-dopa (levodopa) and dopamine are phenolic amino acids or derivatives from them by decarboxylation. Tyrosine can be synthesized from phenylalanine in humans by the enzyme aromatic amino acid hydroxylase, and levodopa from tyrosine after the action of the enzyme tyrosine hydroxylase, which is the rate-limiting step in the biosynthesis of the catecholamines dopamine, norepinephrine, and epinephrine, and it is present in the brain, all sympathetically innervated tissues, and in the adrenal medulla. Levodopa can be further decarboxylated by the enzyme L-aromatic amino acid decarboxylase to yield dopamine. From dopamine, the enzyme dopamine β-hydroxylase catalyzes the formation of norepinephrine (noradrenaline), which is demethylated by the enzyme phenylethanolamine *N*-methyltransferase to yield epinephrine (adrenaline).[105] In addition to the endogenous biosynthetic pathways, tyrosine, levodopa, and dopamine are also present in the diet. Tyrosine occurs in many protein-rich foods (cheese, meat, beans, nuts, eggs, dairy products, and whole grains). There are also some foods particularly rich in levodopa such as faba beans and other legumes,[106] and dopamine in bananas and avocados.[107]

Tyrosine is also the precursor of *p*-tyramine, which is responsible for some unwanted side effects and is synthesized by an amino acid decarboxylase (TDC) that can be of human and gut bacterial origins. The decarboxylation of levodopa to dopamine by small intestine bacteria limits levodopa bioavailability in Parkinson's disease patients since dopamine produced in the gut is not able to cross the intestinal wall (**Figure 3**). In turn, dopamine accumulation in the gut can promote oxidative

deamination to yield the toxic intermediate 3,4-dihydroxyphenylacetaldehyde.[108] Therefore, the metabolic steps catalyzed by microbial enzymes can be related to differences in the small intestine microbiota composition and function, and can contribute to the intra- and inter-individual variability in the therapeutic efficacy against Parkinson's disease.[109]

It has been recently reported that levodopa is converted into dopamine in the small intestine by several bacterial strains that have the enzyme TDC.[110] The small intestine microbiota mainly includes species of *Enterococcus* and *Lactobacillus*. TDC has been detected in the genome of *Enterococcus*, *Lactobacillus*, and *Staphylococcus*. The TDC activity is particularly high in *Enterococcus faecalis*, *Enterococcus faecium*, and is also detected in *Lactobacillus* spp., although at smaller levels. *E. faecalis* is the dominant bacterium responsible for the levodopa decarboxylation in the complex human gut microbial communities.[109,110] The abundance of *E. faecalis* and its enzyme TDC predicts the considerable inter-individual variability in levodopa metabolism observed in complex human gut microbiota samples.[109]

After the conversion of levodopa into dopamine in the small intestine, dopamine can be further metabolized by bacterial catechol dehydroxylase, a molybdenum-dependent enzyme (Dadh), to *m*-tyramine whose accumulation could produce unknown biological consequences. This enzymatic activity is present in some strains of *Eggerthella lenta*, while it is absent in others.[109] The activity has also been tested in related bacterial species such as *Eggerthella sinensis*, *Paraeggerthella hongkongensis*, and *Gordonibacter pamelaeae*. A 100% conversion of dopamine into *m*-tyramine was shown in *E. sinensis* and *P. Hongkonensis*. However, *Gordonibacter*, a genus that dehydroxylates ellagic acid leading to urolithins[60,61] and lignans to produce the mammalian lignan enterodiol,[84] was not active on dopamine.[109] The same study[109] also demonstrated that single-nucleotide polymorphisms (SNPs) might influence catechol dehydroxylation, which could increase the inter-individual variability dramatically. The Dadh-SNP at position 506 (Arg 506) metabolized dopamine, while samples that carried the Ser 506 did not.

2.4. Relevant phenolic-derived postbiotics

There is a growing interest in the identification and better understanding of the human health benefits exerted by probiotic-derived microbial metabolites known as 'postbiotics,' which have been associated with many of the beneficial effects on host health of the gut bacteria that produce these postbiotics.[111-113] Therefore, postbiotics are those metabolic products resulting from the metabolic activity of gut bacteria, including SCFA (propionate, butyrate, acetate, etc.), proteins/peptides/amino acids (i.e., glutathione), carbohydrates (i.e., galactose-rich polysaccharides), vitamins/co-factors (i.e. B-group vitamins), organic acids (i.e., propionic and 3-phenyl-lactic acid), as well as molecules or metabolites released after bacterial lysis including teichoic acids, exopolysaccharides, peptidoglycan-derived peptides, and other cell wall components (i.e., p40 and p75 molecules, lactocepin, polysaccharide A, lipoteichoic acid).[111,112,114] The current evidence suggests that many of these postbiotics could exert physiological benefits, mainly for maintaining gut health through antioxidant, antimicrobial, anti-inflammatory, anti-proliferative, and immunomodulatory activities. However, their mechanisms of action are not fully elucidated yet.[112,114]

In the last years, among postbiotics derived from food products, phenolic-derived metabolites produced by the gut microbiota are gaining attention as crucial mediators to understand the link between polyphenols consumption and health benefits as well as to unravel the host-gut microbiota interactions.[8,115-118] Remarkably, these phenolic-derived postbiotics might mediate the health benefits of dietary polyphenols due to, at least partly, their higher bioavailability and may also modulate the gut microbiota ecology with subsequent impact on both intestinal and systemic chronic disorders.[8,115,116] In this regard, outstanding progress has been made in the identification of biological activities of novel postbiotics among a vast number of phenolic-derived metabolites generated by the gut microbiota, highlighting those derived from isoflavones, ellagitannins, and lignans that present both specificity and individual variability in their production. Many in vitro studies have reported the potential health benefits exerted by the postbiotics derived from isoflavones (equol and to a lesser extent, *O*-desmethylangolensin, ODMA), ellagitannins (mainly Uro-A), lignans (enterodiol and enterolactone), and hop prenylflavonoids (8-prenylnaringenin, 8PN). These effects are mainly

mediated by antioxidant, anti-inflammatory, anti-cancer, cardioprotective, neuroprotective, and estrogenic activities.[80,119-121] However, in vivo evidence on their health effects is still scarce and very limited in humans.[8,122]

Table 3 gathers the limited evidence provided by those human trials conducted with pure metabolites.[123-133] As expected, only a few trials have been developed using equol, as well as one recent trial with Uro-A together with two randomized clinical trials conducted with 8PN (Table 3). To date, no human trials have been conducted using the rest of other well-known phenolic-derived postbiotics such as IsoUro-A, Uro-B, ODMA, enterolignans, dihydroresveratrol, phenylvalerolactone derivatives, phenylvaleric acids, phenylpropionic acids, phenylacetic acids, or hydroxy-benzoic acids.

Equol is the most studied phenolic-derived postbiotic in humans so far (Table 3). To date, the major evidence suggests beneficial effects of equol supplementation in the protection against menopausal symptoms. Although the molecular mechanisms related to these effects have not been fully elucidated, animal studies suggest that the estrogenic activity of equol is behind the reported effects (**Table S1**, Supporting Information). Besides, contradictory evidence has been reported on its effect on blood pressure, blood lipids, and vascular function. Two trials have reported the improvement of cardiometabolic risk biomarkers in both equol- and non-equol producers.[129,130] For example, in a randomized, double-blinded, placebo-controlled, and crossover study, Usui et al.[130] described a significant decrease in glycated hemoglobin A1c, serum LDL-cholesterol and cardio-ankle vascular index score in 49 Japanese overweight-obese subjects with metabolic syndrome features after daily oral intake of 10 mg S-equol for 3 months (Table 3). Remarkably, the effects were more prominent in the subgroup of female equol non-producers.[130] In contrast to Usui et al.,[130] Hazim et al.[131] reported acute vascular benefits in 14 healthy equol-producers men after the administration of isoflavones and associated the effect with peak circulating equol concentrations after 2 h of the intake (although the isoflavones supplement did not contain synthetic S-equol). Interestingly, the administration of synthetic equol (40 mg) did not exert any effect in equol non-producers. However, in the parallel assay, no isoflavones were administered to equol non-producers

or synthetic equol to the equol-producers, and thus, the unequivocal vascular direct effects of equol (dependently or not of the equol-related metabotype) are still lacking (Table 3).

In the last decade, urolithins have attracted attention as potential bioactive microbial metabolites.[80] Overall, the highest evidence has been reported for the Uro-A's anti-inflammatory activity, and in a lesser extent, its antioxidant activity, supported by intestinal inflammation rodent models, whose benefits also include the preservation of the colonic architecture and intestinal barrier, prebiotic effect, etc. (Table S1, Supporting Information). Besides, physiologically relevant mechanistic in vitro studies have corroborated this activity and the underlying molecular mechanisms involved. However, to date, there are no human studies to confirm this potential anti-inflammatory effect.[80]

The first human trial was recently carried out with an oral Uro-A supplement, supported by a private company, that reported the improvement of mitochondrial and cellular health by regulating gene expression associated with cellular and mitochondrial function (Table 3).[123] Moreover, the recent identification of the safety of Uro-A in both preclinical and human studies,[123,134,135] together with its recent recognition as GRAS (generally recognized as safe) for its use as ingredient in several food products by the Food and Drug Administration (FDA), predict an increase in the clinical trials to evaluate the specific health effects of urolithins in the coming years. However, similar to the trials with equol, the future trials dealing with urolithins should consider the specific individuals' metabotypes to evaluate the possible role of the associated microbiota in the postbiotic effects (as further commented in the present review).

Among the limited human evidence, it is important to highlight two trials that were conducted with the potent phytoestrogen 8PN, showing both endocrine and immunomodulatory effects after a single oral dose of 8PN (Table 3).[132,133] Remarkably, the intake of 8PN was well tolerated and associated with a low incidence of adverse events, which reinforced the use of this phenolic-derived postbiotic in future trials to evaluate its potential beneficial effects.

Overall, although the health-promoting evidence of dietary (poly)phenols is increasing, there is still much to consider the use of its derived postbiotics as an effective alternative against chronic diseases.

3. Human polyphenol-related metabotypes as biomarkers of the gut microbiota

In the context of polyphenols' metabolism and health, the term 'metabotype' refers to a differential gut microbial metabolism of polyphenols. Bolca et al.[136] initially coined this term and was further re-visited by Espín et al.,[8] who described metabotype as a metabolic phenotype defined by i) the existence of specific metabolites derived from the gut microbiota, characteristic of the precursor polyphenol metabolism, and ii) by the associated microbial ecology in terms of composition and activity, which in turn, could exert a distinctive impact on human health.[8] Therefore, the term metabotype involves a feature that is less influenced by external factors and refers to a qualitative criterion (i.e., production vs. non-production, but no high vs. low metabolite excretion) concerning the particular microbial ecology that harbors each specific individual.

It is becoming evident that human subjects respond differentially to dietary interventions because there is no one-size-fits-all diet, and the effects might be determined by the specific host and gut microbiota features.[137,138] In this regard, an increasing number of studies reveal the need for clustering human subjects into known metabotypes (metabotyping) as a strategy to explain, at least partially, the inter-individual variability of the effects observed after consumption of dietary polyphenols.[139-141] This approach, i.e., tailored polyphenol-rich diets for specific individuals, could explain some controversial studies regarding the polyphenol effects by linking metabotypes to the concept of 'personalized nutrition', i.e., the prevention and even the management of some diseases from a nutritional point of view.[8,139,142,143]

As previously commented, the gut microbiota is a crucial piece in the complex puzzle of polyphenols and health. Besides, the unequivocal role of phenolic-derived postbiotics is far from been unequivocally proven. Therefore, the main driver in the effects observed after polyphenol

consumption is still unclear, i.e., the specific phenolic-derived postbiotics, the particular microbiota associated with human metabotypes, or maybe both.

3.1. How many polyphenol-related metabotypes are there? Specific phenolic-derived postbiotics.

The so-called enterotypes, driven by *Bacteroides*, *Prevotella*, and *Ruminococcus* have also been proposed to stratify the population according to their microbiome and suggested to be functional markers.[144] Currently, the enterotypes as distinctive functional microbiome signatures are under debate, and the latest studies suggest the existence of microbial community gradients rather than specific enterotype clusters.[145]

As previously shown, there are gut microbial communities involved in the metabolism of polyphenols, such as ellagitannins, isoflavones, proanthocyanidins, lignans, flavanones, proanthocyanidins, and prenylflavonoids (Tables 1 and 2). As in the case of enterotypes, the metabolism of flavanones,[146,147] lignans,[59,148] and proanthocyanidins[149] can also lead to inter-individual variations by a metabolite production gradient (a continuous variation among individuals). However, no differential human metabotypes are present in the metabolism of these phenolics. The gut microbiota metabolism of proanthocyanidins is paradigmatic to illustrate the lack of polyphenol-related metabotypes. These flavonoids, especially in the case of oligomeric proanthocyanidins, reach the colon almost intact and are sequentially metabolized by the gut microbiota to yield a cascade of metabolites, i.e., phenylvalerolactone derivatives, phenylvaleric acids, phenylpropionic acids, phenylacetic acids, and benzoic acids (**Figure 2**).[149,150,152] The final metabolites in this catabolic pathway are not specific to proanthocyanidin catabolism, but they are also common to the gut microbial catabolism of many other polyphenols (flavonoids and non-flavonoids).[153] Therefore, the binary response of metabotypes is not accomplished, i.e., the presence vs. absence of unique metabolites. Although phenylvalerolactones have been proposed as biomarkers of proanthocyanidin intake,[154,155] these metabolites are intermediates in the catabolic pathway, being further metabolized to unspecific final metabolites. This means that the analysis of intermediates, including

phenylvalerolactones, is influenced by many variables such as the source and concentration of proanthocyanidins, the lag period between the last intake of precursor and the sample analysis, the concomitant intake of other food compounds, etc., which lead to misleading results concerning the qualitative and quantitative production of metabolites.[149]

Likewise, flavanone metabolism, as in the case of hesperidin, also yields high and low metabolite (hesperetin) excreters, which is mainly determined by the rhamnosidase activity of the gut microbiota and the solubility of the hesperidin-containing food matrix.[146] However, hesperetin is also an intermediate metabolite in the catabolism of hesperidin. It can be further metabolized to unspecific phenylpropionic, phenylacetic and hippuric acid derivatives so that even in those 'low hesperetin excreters,' we cannot rule out the possible apparent paradox dealing with a possible high hesperetin production concomitant with rapid catabolism giving rise to a low excretion of hesperetin (Figure 2). Similarly, the presence of potential lignan-related metabotypes has not been reported so far. The metabolism of lignans such as secoisolariciresinol diglucoside does not produce specific metabolites, but a gradient of intermediates to get the final enterodiol and enterolactone metabolites, which seem to be produced by the entire population in greater or lower extent (Figure 2).[85]

Hops prenylflavonoids is another particular case in which the presence of metabotypes has not been sufficiently demonstrated. Various in vitro and animal studies have reported the non-enzymatical conversion of xanthohumol (X) into its isomer, isoxanthohumol (IX), which is enzymatically demethylated to yield the potent phytoestrogen 8PN (Figure 2).[67] Although the human gut microbial *Eubacterium limosum* is involved in the in vivo synthesis of 8PN,[68] however, three main issues prevent the clear establishment of possible human 8PN-related metabotypes: i) low amounts of 8PN can be already present in the food product (hops and beer),[156] ii) 8PN can also be formed by the action of human cytochromes,[157] and iii) 8PN is not the final catabolite but another intermediate since it can be further metabolized by *Eubacterium ramulus* to yield *O*-desmethylxanthohumol (DMX) and *O*-desmethyl-*α*,*β*-dihydroxanthohumol (DDXN) as recently described in vitro (Figure 2).[151] This latter point should be confirmed in vivo. Overall, at this moment and following the definition of

'metabotype,' we can conclude that no human metabotypes can be clearly associated with the metabolism of hops prenylflavonoids.

To date, the metabolism of polyphenols based on specific gut microbial ecologies that produce distinctive metabolites only occurs in two cases unambiguously, i.e., ellagic acid and the isoflavone daidzein (Figure 1).[80,119,158] In the case of the gut microbial metabolism of ellagic acid, three urolithin-related metabotypes (UMs) have been defined to date depending on the final postbiotics produced: i) metabotype A (UM-A), characterized by the production of only Uro-A as final urolithin, ii) metabotype B (UM-B) that yields Uro-B and IsoUro-A in addition to Uro-A, and iii) metabotype 0 (UM-0), whose individuals do not produce these final urolithins.[8,80,158] Therefore, these metabotypes are characterized by i) the capacity of producing the postbiotic urolithins (producers vs. non-producers) and ii) the type of urolithin produced (only Uro-A vs. Uro-A + IsoUroA + Uro-B). Recently, novel urolithins have been discovered, namely urolithin M6R (4,8,9,10-tetrahydroxyurolithin), M7R (4,8,9-trihydroxyurolithin), and urolithin AR (4,8-dihydroxyurolithin). These metabolites are common to both UM-A and UM-B and require a bacterial 3-dehydroxylase activity for their production.[81] Whether these minor urolithins represent a novel metabolic feature for volunteer stratification deserves further research.

The distribution of UMs in the population is critically affected by aging, as recently reported in a large cohort (n = 839), mainly Caucasians and aged from 5 to 90 years.[159] Remarkably, the percentage of individuals with UM-0 (10%) remains approximately constant from 5 to 90 years of age. However, the proportion of UM-B at an early age (15%) progressively increases up to 45% from 40 to 90 years of age, which is concomitant with a decrease of UM-A from 85% up to 55%. This shift from UM-A to UM-B becomes more noticeable from 20 to 40 years of age, and from that age, the proportion of UM-0, UM-A, and UM-B (10%, 55%, and 45%, respectively) remains approximately unaltered.[159] UMs are stable within individuals over time and a challenge of a high dose of an ellagitannin-containing product such as pomegranate extract or walnuts can shift individuals from apparent UM-0 to either UM-A or UM-B, although these individuals were not genuine UM-0 but very low urolithin excreters.[139] Preliminary observations associated UM-B with higher BMI and

gastrointestinal pathologies, driven by gut dysbiosis.[158,160] However, the association between UMs and obesity was not unequivocally confirmed in the large cohort (n = 839) that included healthy volunteers and patients as well as a substantial amount of subjects from each weight status, i.e., normoweight, overweight, and obesity.[159] To date, no clear association between UMs and diet, sex, or ethnicity has been reported.

Regarding the metabolism of isoflavones, the equol- and ODMA-producer metabotypes have been identified so far.[119,161] These metabolites are specific from daidzein metabolism. However, the metabolites 6'-hydroxy-ODMA and 5-hydroxy-equol can also be produced from genistein[162] and have not been considered in the stratification of the population, according to the metabolism of isoflavones (Figure 1). To date, the ODMA- and equol-producer metabotypes have been reported to be independent of each other.[163] The capacity to harbor ODMA- producing bacteria seems to be not associated with the capacity to harbor equol-producing bacteria. The distribution of these metabotypes in the Caucasian population has been estimated to be around 30% for equol-producers and 80-90% for ODMA-producers after the consumption of soy-containing products, a distribution stable over time within individuals despite the consumption of high isoflavone-containing products.[164-167] However, the proportion of equol-producers is higher (50-60%), and that of ODMA-producers is slightly lower in Asians than in Western populations.[168-171] Overall, the number of precise combinations regarding daidzein-related metabotypes is not clear so far, i.e., equol-producers vs. equol non-producers (which is the most common stratification criterion), ODMA-producers vs. ODMA non-producers, or strictly equol-producers vs. strictly ODMA-producers. Besides, the possible catabolism of ODMA to smaller metabolites, which are common final metabolites in the microbial catabolism of many other dietary phenolics (i.e., phloroglucinol, *p*-hydroxyphenyl propionic acid, etc.; Figure 1) could alter the distribution of the ODMA-metabotype in the population. While S-equol has been reported to be hydroxylated by the mammalian cytochrome P450 (CYP), no smaller catabolites from S-equol have been clearly identified.

Different studies have associated the incidence of the equol- or ODMA-producer metabotypes with dietary patterns and sociodemographic characteristics of the population such as age, education level,

anthropometric values (height, weight, and BMI) and race or ethnicity.[169] However, no clear associations for any particular factor have been consistently detected across studies.[119] Although Frankenfeld et al.[166] described that the ODMA-producer, but not the equol-producer metabotype, was associated with obesity in adults, the same group reported that obese individuals were more likely to be ODMA non-producers.[172] It seems that there are many variables potentially involved in the distribution of daidzein-related metabotypes so that more controlled studies in larger cohorts from different geographical origins are required.

3.2. Polyphenol-related metabotypes, the gut microbiota associated and consequences to human health

While the identification of metabotypes and stratification of subjects based on their capacity to produce specific phenolic-derived postbiotics has been clearly established for ellagitannins-ellagic acid and daidzein, however, the impact on the health of these metabotypes has been scarcely approached. The characterization of the gut microbiota associated with polyphenol-related metabotypes is mandatory to explore the differential role of these specific microbial ecologies in human health. However, much remains to be said about this topic, as this approach has just begun. To date, the evidence that correlates, at least partially, a given polyphenol-related metabotype with specific polyphenol health effects, using randomized clinical trials, has only been reported for ellagitannins[139] and daidzein.[119,130] However, this association has been established indirectly.

González-Sarrías et al.[139] described the improvement of a panel of cardiometabolic risk biomarkers (total cholesterol, LDL-cholesterol, non-HDL cholesterol, apolipoprotein B, and oxidized-LDL-cholesterol, among others) in overweight-obese subjects (n=49) after pomegranate extract consumption. However, this effect was observed only in UM-B individuals after the stratification of volunteers by their UMs. Remarkably, these effects were not associated with urolithin concentrations in plasma, urine, or feces. This agrees with other studies that also explored the association between urolithin occurrence in plasma, urine, feces or colonic tissues and cancer-related markers and metabolic endotoxemia in colorectal cancer patients (n=45),[173,174] metabolic endotoxemia in

overweight-obese individuals (n=49),[175] and blood lipid profile in healthy subjects (n=32).[176] Overall, the lack of clear association is plausible due to the highly variable turnover of these microbial metabolites and their occurrence in the bloodstream and other biological reservoirs, especially in studies with a design of short-term follow-up to observe acute effects (hours or few days). However, another trial conducted in 10 healthy males who consumed red raspberries associated the effects on flow-mediated dilation (FMD) with the plasma occurrence of ellagic acid (4.6 nM at 2 h), and Uro-A glucuronide and Uro-A sulfate (41 nM urolithin conjugates at 24h), and suggested that urolithins might be responsible for the observed effects. Remarkably, no association was found between FMD and the other 67 circulating phenolic metabolites (mainly phenolic acids that reached 120 μM at 24h).[177] In addition to the tiny contribution of urolithins vs. the rest of phenolic acids (only 0.034%), it seems somehow contradictory that the same authors previously suggested the link between circulating phenolic metabolites (mainly phenolic acids) and the improvement of FMD after blueberry consumption in healthy individuals (n=21).[178] While raspberry intake seems to improve FMD; however, the association between FMD and circulating urolithins seems to be casual rather than causal.

A recent study has characterized the human gut microbial ecology associated with UMs and also compared divergences and similarities with enterotypes in 249 normoweight, overweight, and obese individuals.[179] While the diversity and richness were not different between the enterotypes *Bacteroides*, *Prevotella*, and *Ruminococcus* at the genus level, UM-0 showed lower diversity and richness than UM-B and UM-A individuals. Overall, the distribution and gut microbiota composition of UMs and enterotypes were not coincident. UM-0 was mainly characterized by its low diversity and lower abundance (< 1%) of some genera, including *Phascolarctobacterium*, *Bilophila, Alistipes,* and *Butyricimonas* in comparison with UM-B and UM-A.

The Coriobacteriia class was increased in UM-B versus UM-A and UM-0 and was positively associated with total-cholesterol, LDL-cholesterol, and BMI.[179-181] These could explain the results reported in previous studies, which showed that overweight-obese UM-B individuals had higher blood total cholesterol levels than UM-A and UM-0.[139,182]

Various pro-inflammatory microbes such as *Methanobrevibacter, Methanosphaera, Parvimonas*, and Gammaproteobacteria were also increased in UM-B vs. UM-A. Besides, total-cholesterol, LDL-cholesterol, apolipoprotein-B, and non-HDL-cholesterol were positively associated with *Slackia* (a Coriobacteriia genus), whose abundance was increased in UM-B vs. UM-A. On the other hand, Eubacteriaceae, which was increased in UM-A vs. UM-B, was positively correlated with apolipoprotein-A.[179] Overall, all these results potentially associate UM-A with a 'protective' metabotype, and UM-B with a dysbiotic-prone metabotype to cardiometabolic impairments, which could support previous findings that reported a higher cardiovascular risk in UM-B vs. UM-A individuals.[139,182]

In the line of the UM-depending response of individuals to polyphenol consumption, García-Mantrana et al.[140] have reported that walnuts consumption after only three days modulated the gut microbiota of healthy volunteers in a UM-depending manner and increased SCFA production. Remarkably, the walnut intervention increased *Bifidobacterium*, *Blautia,* and microbes of the Coriobacteriia class, including *Gordonibacter*, exclusively in UM-B, which was more sensitive than UM-A to walnuts consumption, while some members of the Lachnospiraceae family decreased only in UM-A individuals.[140]

The gut microbiota is significantly altered during pregnancy and after childbirth.[183] Recently, Cortés-Martín et al.[98] described that UMs assessment could be a tool to anticipate the restoration capacity of the gut microbiota, and the anthropometric values of mothers up to 12 months after delivery. Notably, some UM-B bacteria were inversely associated with a reduction of the waist (*Methanobrevibacter* and *Olsenella*), and waist-to-hip ratio, BMI, and waist (Clostridiaceae, *Clostridium sensu stricto*, and *Anaerobacter*). Consequently, UM-B was associated with a more robust and less modulating capacity of microbial and anthropometric profiles than UM-A. On the contrary, UM-A women normalized their gut microbiota and anthropometric values to a greater extent than UM-B, through the 1-year follow-up postpartum. [98]

A recent review of meta-analysis encourages soy intake as part of a healthy diet because 'isoflavone consumption is more beneficial than harmful'.[167] Unfortunately, this study did not take

into account the inter-individual variability based on the metabotypes related to equol and(or) ODMA production. Although some studies did not find any correlation between these metabotypes and health effects,[170,184] an increasing number of studies associate daidzein-related metabotypes mainly with cardiovascular risk.[185-188] Overall, the current evidence suggests that equol and(or) ODMA producers may have a lower risk than non-producers as comprehensively reviewed by Frankenfeld.[119] However, some associations might be conjectural due to the cross-sectional design of the studies. For example, a cross-sectional study reported that equol and ODMA producers had better cardiovascular health profiles than non-producers in 595 Chinese postmenopausal women with prehypertension or untreated hypertension, independently of lifestyle factors.[186] Another cross-sectional study in 272 Japanese men described the inverse association between the equol-producer metabotype, but not isoflavones intake and coronary artery calcification.[187] As mentioned in a previous section, Usui et al.[130] described a significant improvement of cardiometabolic risk biomarkers after daily oral intake of S-equol for 3 months (Table 3), and the effects were more noticeable in those equol non-producers females.[130] On the contrary, Hazim et al.[131] suggested that equol exerted vascular benefits only in equol-producers men. However, the design of that study prevented unambiguously such a conclusion. Miller et al.[172] also suggested the association of the ODMA non-producer metabotype with obesity in those peri- and postmenopausal women that harbored a specific gut microbial ecology not capable of metabolizing daidzein to ODMA, although no specific dietary intervention was performed. Overall, these observations cannot conclude whether the presence of the microbial community associated with equol and(or) ODMA production is somehow involved in the effects exerted by the corresponding postbiotics equol and ODMA. Therefore, more dietary intervention studies that stratify the individuals, according to their equol- and ODMA-metabotype, are critical to explaining the effects exerted by dietary isoflavones. To date, whether the effects are exerted by the metabolites dependently or not of the associated microbiota, requires further research.

A recent cross-sectional study has described for the first time the overall difference (both composition and functional) in the gut microbiota between the equol-producer and non-producer metabotypes as well as their possible association with blood lipids.[189] Unfortunately, this study did

not take into account the ODMA metabotype as an important feature of daidzein metabolism. In contrast to UMs, no significant difference in bacterial richness was found between the equol-producer and non-producer metabotypes. In this 99 Chinese group, the equol-producer metabotype was not affected by the intake of isoflavones for 3 days. Perhaps, this is a too short isoflavone challenge to modify a metabotype status, but this approach could be valid to identify those very low equol-producers. The equol-producer metabotype was enriched in *Prevotella*, *Megamonas*, *Allistipes*, *Desulfovibrio*, *Collinsella*, and *Eubacterium*, among others. In contrast, the non-producer metabotype was enriched in the family Lachnospiraceae, as well as the genus *Eggerthella* and several species from *Ruminococcus* and *Bacteroides*. Metabolic pathways (mainly general biosynthetic pathways) also showed significant dissimilarity between both metabotypes, being seven of them metabolic pathways associated with the equol concentration in urine. Besides, equol-producing related species such as *Adlercreutzia equolifaciens* and *Bifidobacterium bifidum* showed higher abundance in the equol-producer metabotype vs. the non-producer.[189] Individuals from the equol-producer metabotype showed a lower prevalence of dyslipidemia than non-producers (27% vs. 50%), and some microbes were statistically associated with serum lipids. However, these authors did not find any association between microbial composition and functionality with BMI, smoking habit, age, and gender. The only difference was obviously associated with the production of equol.[189] Overall, causal conclusions regarding the involvement of the microbiota cannot be obtained from a cross-sectional design.

4. Final remarks and future directions

Human metabotypes associated with differential gut microbial ecologies are at the crossroad of the metabolism and biological activity of polyphenols. Mounting evidence suggests that the variations in the gut microbiota ecology among individuals can affect polyphenol metabolism capacity, but at the same time, polyphenol-related metabotypes can indirectly reflect the individuals' gut microbiome and the individuals' health status. Therefore, polyphenol-related metabotypes could be considered as biomarkers of a specific type of microbiota with a distinctive impact on health. For this reason, the clustering of individuals according to polyphenol-related metabotypes (metabotyping), could be a

useful tool to predict the functionality and status of gut microbiota and to understand better the effects of bioactive compounds and the large inter-individual variation observed. Various crucial issues need further research:

To date, ellagic acid is unequivocally the precursor of urolithins. However, the in vivo hydrolysis of ellagitannins to release ellagic acid is questionable, and thus, whether the gut microbiota involved in urolithin formation can act directly in vivo on ellagitannins to form urolithins remains unclear.

UM-0 seems to be quite stable over time. In contrast, the distribution of UM-A and UM-B depends on aging. The capacity to produce equol has been reported to be stable over time within individuals, but not the precise distribution of the daidzein-related metabotypes. Therefore, additional research is needed to confirm the stability of daidzein-related metabotypes from early to old ages. The long-term impact of lifestyle and other variables (smoking, diet, physical activity, disease, etc.) on these metabotypes has not been sufficiently investigated. Overall, the knowledge on ODMA is by far much lower than that on equol. Besides, the possible contribution of genistein-derived metabolites (5-hydroxy-equol or 6'-hydroxy-ODMA) to the variability of the population in the metabolism of isoflavones should be studied in greater depth.

Eggerthella lenta, which plays a relevant role in the bioactivation of plant lignans,[84] can metabolize dopamine through a catechol dehydroxylation reaction leading to m-tyramine accumulation, with biological effects still poorly understood. At this point, inter-individual variability in dietary polyphenol metabolism by the gut microbiota joints with that of endogenous phenolic neurotransmitters and phenolic-related drugs. The impact of specific SNPs on gut microbial dopamine metabolism, and probably other phenolics, suggests that merely detecting functional genes may not accurately predict the activities encoded by the human gut microbiome and highlights the importance of studying enzymes from this community. Parallel to polyphenol-related metabotypes, the identification of possible drug-related metabotypes could pave the way to develop specific strategies in the context of 'precise medicine'.

To date, most studies establish associations between gut microbiota and various disease-related characteristics. However, the causal involvement of a specific gut microbiota ecology (including

polyphenol-related metabotypes) in the etiology and(or) prevention of (metabolic) diseases lacks for humans.

While there has been a substantial advance in the structural features of the human gut microbiota using metagenomics, however, there are gaps regarding the meaningful relationship between taxonomic and functional profiles of the gut microbiota. In this regard, there is a need to provide more information on the metabolic map of the gut (metabolic reactions), which could help in the prediction of functional properties. To date, the prediction of functional properties based on rather rough (i.e., genus-level) taxonomic profiles, and also based on snapshot fecal samples, could be questionable. In this regard, metatranscriptomics, metaproteomics, and metabolomics are disciplines to be integrated for characterizing the functional profile of the human gut microbiome.

To date, there is a need to expand our knowledge regarding the gut microbiota (both taxonomic and functional) profiles from other gut segments since fecal samples are representative of the entire tract.

The evidence supporting the specific contribution of phenolic-related postbiotics in health, whether or not dependent on the microbiota associated in their production, is still too limited to be conclusive. In this starting 'postbiotics era', although the in vivo activity of these metabolites cannot be discarded, there is stronger evidence to consider them as biomarkers of specific human polyphenol-related metabotypes rather than unambiguously bioactive metabolites with differential impact on human health.[190]

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Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Table S1. Biological activity of urolithins, equol and ODMA in rodent models

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

gut microbiota, polyphenols, metabotypes, equol, urolithins

Figure Captions

Figure 1. Catabolic pathways of (**A**) ellagic acid to urolithins, and (**B**) the isoflavones daidzein and genistein to equol/ODMA or 5-hydroxy-equol/6'hydroxy-ODMA, respectively. For a detailed description of the pathways, check the studies by García-Villalba et al.[81] for the catabolism of ellagic acid to urolithins, and Lee et al.[82] for the catabolism of isoflavones. The circles specifically enclose the final urolithins for each metabotype (red, UM-B; blue, UM-A). D(G)R, daidzein/genistein reductase; DH(G)R, dihydrodaidzein/genistein reductase; THD(G)R, tetrahydrodaizein/genistein reductase; CYP450, mammalian cytochrome P450; 4-HPPA, 4-hydroxyphenyl propionic acid.

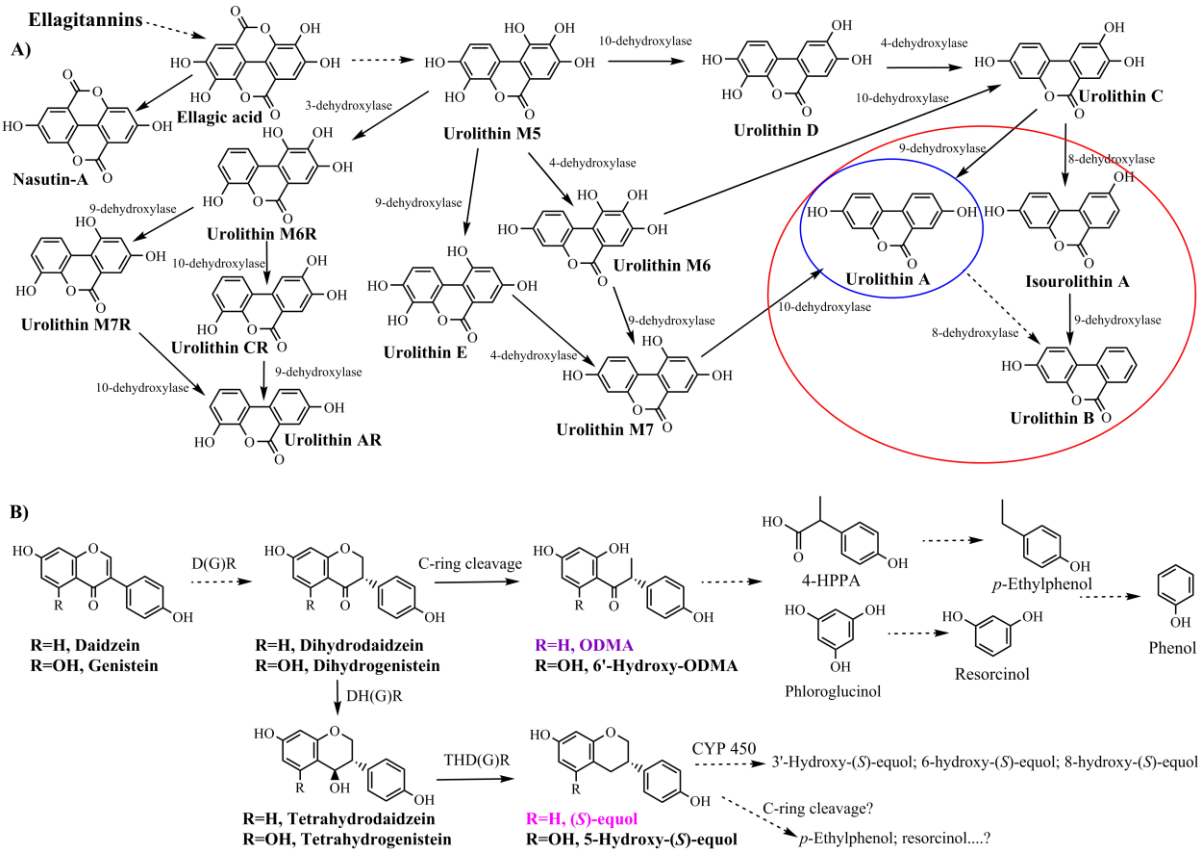

Figure 2. Summarized catabolic pathways of dietary polyphenols non-related to gut microbiota metabotypes. (**A**) Proanthocyanidins and flavan-3-ols (catechin),[150] (**B**) citrus flavanones (hesperidin),[146] (**C**) lignans (secoisolariciresinol)[85,148] and (**D**) prenyl-flavanones (xanthohumol).[151] HPP-2-ol, 1-(hydroxyphenyl)-3-(2",4",6"-trihydroxyphenyl)-propan-2-ol; PV, phenylvalerolactone; HPV, hydroxyphenyl valerolactone; DHPV, dihydroxyphenylvalerolactone; HPV, hydroxyphenylvalerolactone; 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.

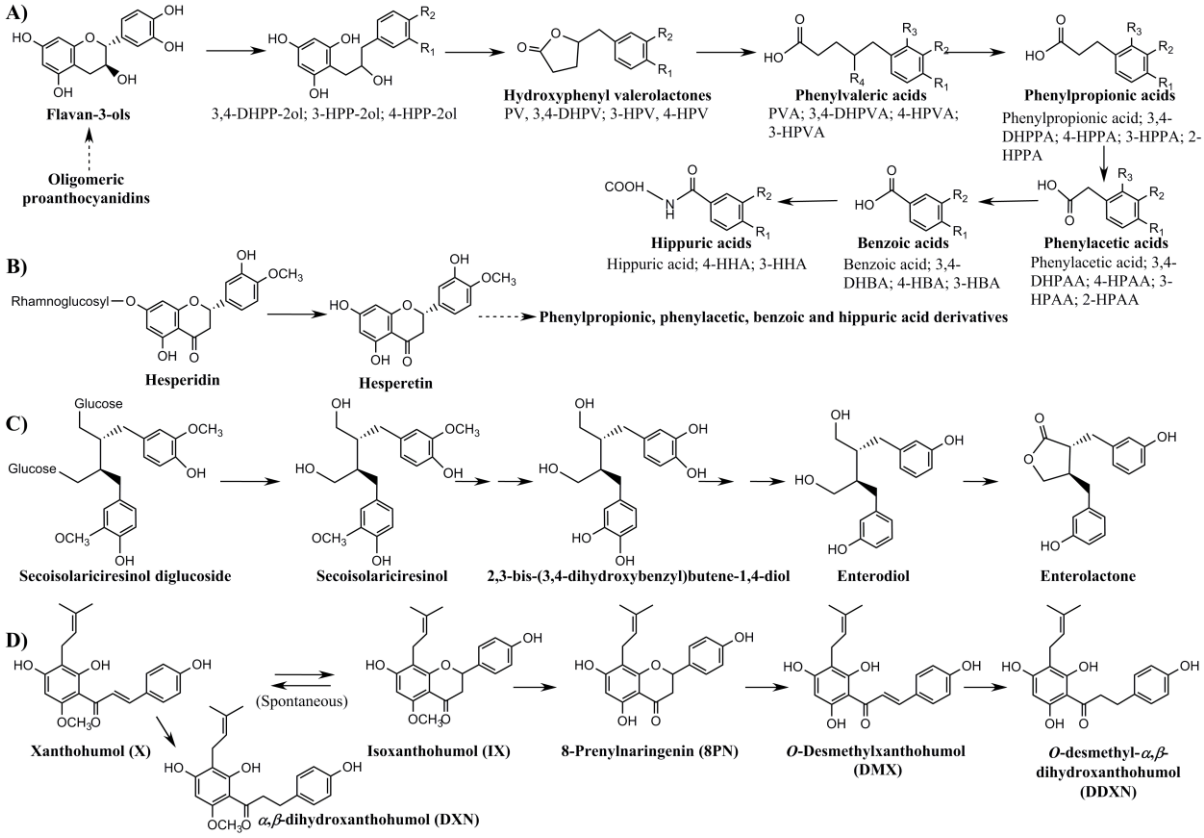

Figure 3. Intestinal microbial metabolism of L-dopa.

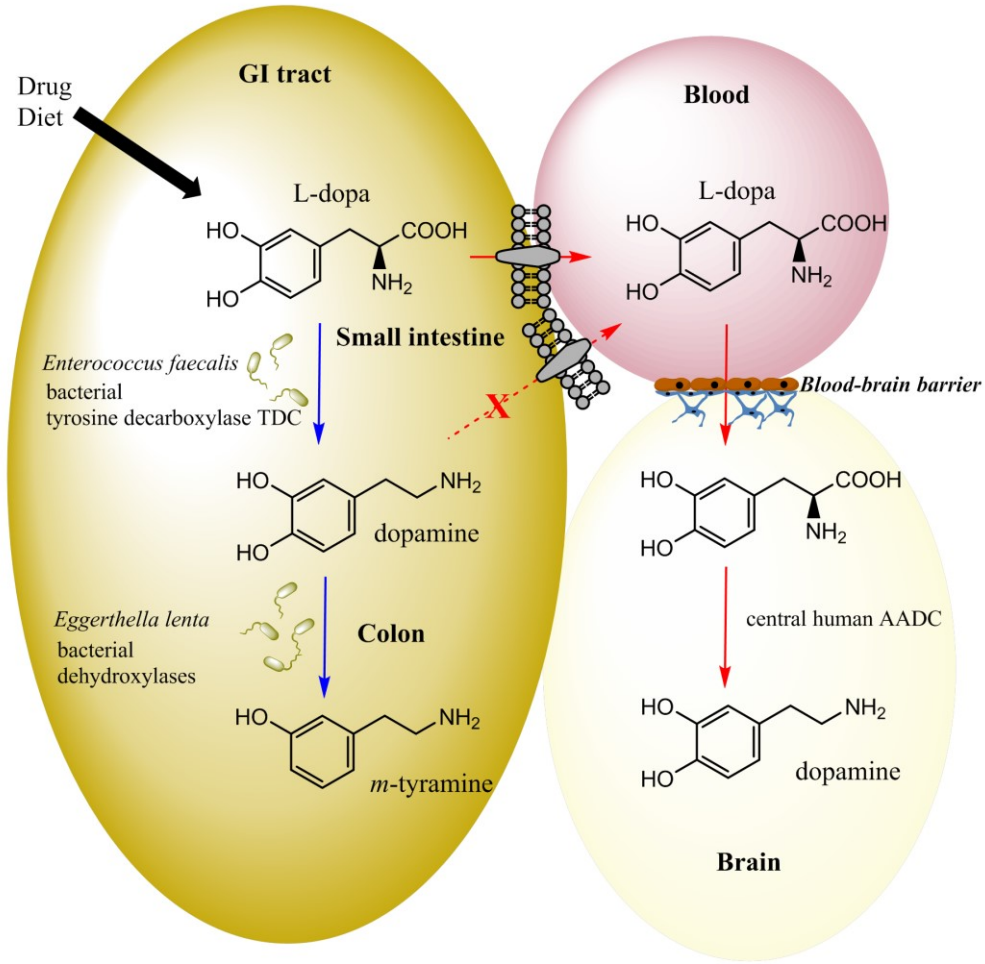

Table 1. Hydrolysis of conjugated phenolics by the human intestinal microbiota.

Reaction	Phenolic family*	Phylum	Order	Family (Species)	References
***O*-glycosidase**	Flavonols, Flavanones, Dihydrochalcones, Isoflavones, Anthocyanins, Ellagitannins, Lignans, Stilbenes	Firmicutes	Clostridiales	Clostridiaceae (*Clostridium sphenoides, C. saccharogumia, C. cocleatum)*	[14,16-38]
				Enterococcaceae (*Enterococcus casseliflavus, E. avium, E. faecalis)*	
				Eubacteriaceae (*Eubacterium rectale, E. ramulus, E. cellulosolvens)*	
				Lachnospiraceae (*Blautia* sp.)	
			Lactobacillales	Lactobacillaceae (*Lactobacillus acidophilus, L. plantarum, L. casei, L. leichmanii*)	
		Bacteroidetes	Bacteroidales	Bacteroidaceae (*Bacteroides ovatus, B. fragilis, B. distasonis, B. uniformis)*	
				Porphyromonadaceae (*Parabacteroides distasonis)*	
		Actinobacteria	Bifidobacteriales	Bifidobacteriaceae (*Bifidobacterium angulatum, B. animalis, B. catenulatum, B. pseudocatenulatum, , B. longum, B. pseudolongum, B. infantis, B. breve, B. dentium, B. adolescentis, B. bifidum)*	

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		Proteobacteria	Enterobacteriales	Enterobacteriaceae (*Enterobacter cloacae)*	
***C*-glycosidase**	Flavones, Isoflavones	Firmicutes	Clostridiales	Enterococcaceae (*Enterococcus* sp.)	[21,22,27,39,40]
				Eubacteriaceae *(Eubacterium cellulosolvens)*	
			Lactobacillales	Streptococcaceae (*Lactococcus* sp.)	
Glucuronidase	Ellagitannins	Proteobacteria	Enterobacteriales	Enterobacteriaceae (*Escherichia coli)*	[25]
Esterase	Hydroxycinnamates	Firmicutes	Lactobacillales	Lactobacillaceae *(Lactobacillus gasseri)*	[12,41,42]
		Actinobacteria	Bifidobacteriales	Bifidobacteriaceae (*Bifidobacterium lactis)*	
		Proteobacteria	Enterobacteriales	Enterobacteriaceae (*Escherichia coli)*	

Table 2. Enzymatic reactions catalyzed by the human intestinal microbiota on phenolic aglycones.

Reaction	Phenolic family*	Phylum	Order	Family (Species)	References
***C*-Ring cleavage**	Flavonols, Flavanones, Dihydrochalcones, Flavan-3-ols, Isoflavones, Anthocyanins	Firmicutes	Clostridiales	Clostridiaceae (*Clostridium butyricum*)	[21,30,32-34, 43-58]
				Eubacteriaceae (*Eubacterium ramulus, Eubacterium oxidoreducens*)	
				Lachnospiraceae (*Butyrivibrio* sp.)	
				Ruminococcaceae (*Flavonifractor plautii*)	
			Lactobacillales	Lactobacillaceae *(Lactobacillus plantarum*)	
		Actinobacteria	Eggerthellales	Eggerthellaceae *(Adlercreutzia equolifaciens, Eggerthella* spp. *SDG-2, Eggerthella lenta, Slackia equolifaciens)*	
Lactone cleavage	Ellagitannins	Actinobacteria	Eggerthellales	Eggerthellaceae (*Gordonibacter urolithinfaciens, Gordonibacter pamelaeae, Ellagibacter isourolithinifaciens*)	[59-62]
Lactonization	Lignans	Firmicutes	Clostridiales	Clostridiaceae (*Lactonifactor longoviformis*)	[63]
Dehydroxylation	Flavanones, Flavan-3-ols, Tannins, Lignans, Hydroxycinnamates	Firmicutes	Clostridiales	Clostridiaceae (*Clostridium butyricum*)	[23,38,47,52,54, 59-64]
				Eubacteriaceae (*Eubacterium ramulus*)	
				Lachnospiraceae (*Butyrivibrio*)	
				Ruminococcaceae (*Flavonifractor plautii*)	
		Actinobacteria	Eggerthellales	Eggerthellaceae (*Adlercreutzia equolifaciens, Eggerthella lenta, Gordonibacter urolithinfaciens, Gordonibacter pamelaeae, Ellagibacter isourolithinifaciens*)	
Demethylation	Flavanones, Flavonols, Flavan-3-ols, Anthocyanins, Lignans	Firmicutes	Clostridiales	Clostridiaceae (*Clostridium* sp.*)*	[23,26,63-69]
				Eubacteriaceae (*Eubacterium limosum, Eubacterium callanderi*)	
				Lachnospiraceae (*Blautia producta, Blautia* sp.)	
				Peptostreptococcaceae (*Peptostreptococcus productus*)	
			Lactobacillales	Lactobacillaceae (*Lactobacillus*)	
				Streptococcaceae *(Streptococcus*)	
Decarboxylation	Tannins, Benzoic acids, Hydroxycinnamates	Actinobacteria	Eggerthellales	Eggerthellaceae (*Gordonibacter urolithinfaciens, Gordonibacter pamelaeae, Ellagibacter isourolithinifaciens*)	[59-62,70]
Reduction	Isoflavones, Lignans,	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae **(***Bifidobacterium animalis, Bifidobacterium longum, Bifidobacterium pseudolongum*)	[36,37,39,63, 71-79]

Stilbenes	Eggerthellales	Eggerthellacea (*Adlercreutzia equolifaciens, Eggerthella lenta, Slackia equolifaciens, Slackia isoflavoniconvertens*)

Table 3. Human evidence on the effects of relevant phenolic-derived postbiotics

Phenolic-derived postbiotics	Human evidence	Study design	Reference
Urolithin A	✓ *Improvement of mitochondrial and cellular health*: upregulation of skeletal muscle mitochondrial gene expression and improvement of systemic plasma acylcarnitines associated with cellular and mitochondrial function.	Phase 1, randomized, double-blind, placebo-controlled study. N=60 healthy male and female elderly volunteers. Both single and multiple dosing of Uro-A (250, 500 and 1,000 mg) were orally administered each day for 4 weeks.	[123]
S-Equol	✓ *Improvement of menopausal symptom and mood states*: the anxiety scores of EP were lower than those of non-EP. Decrease of depression scores, tension-anxiety, depression-dejection and fatigue, and increase of vigor.	Randomized, double-blind, placebo-controlled study. N=127 pre/peri/post-menopausal women. Equol supplement for 12 weeks (10 mg of equol per day or three times per day).	[124]
S-Equol	✓ *Improvement of bone health*: attenuation of urinary DPD, a marker of bone resorption, slightly decrease of bone loss, but does not affect serum sex and thyroid hormone concentrations. Treatment with 10 mg/day prevents a decrease in bone mineral density in the entire body.	Double-blind, randomized, placebo-controlled study. N=93 non-EP postmenopausal women. Tablets containing 2, 6, or 10 mg of S-equol per day for 1 year.	[125]
S-Equol	✓ *Improvement of menopausal symptoms*: decrease of hot flush frequency and severity of hot flushes and neck or shoulder muscle stiffness.	Multicenter, randomized, double-blind placebo-controlled study. N=126 non-EP postmenopausal women. 10 mg/d of S-equol for 12 weeks.	[126]
S-Equol	✓ *Improvement of menopausal symptoms*: decrease of hot flash frequency and improvement of muscle and joint pain score.	Randomized, double-blind, active comparator trial.	[127]

		N=102 postmenopausal women. 10, 20 or 40 mg/d of S-equol for 8 weeks.	
S-Equol	✓ *Effect on skin aging*: decrease of wrinkle area and depth.	Randomized, double-blind, placebo-controlled study. N=101 non-EP postmenopausal women. 10 or 30 mg/d of S-equol for 12 weeks.	[128]
S-Equol	✓ *Effect on bone and cardiovascular parameters*: reduction in arterial stiffness especially in higher risk groups (moderate and high risk for arteriosclerosis, hypertriglyceridemia, bone resorption). No significant differences between EP and non-EP. Increase levels of TC, LDL-c and HDL-c.	Prospective observational study. N=74 outpatient women. 10 mg/d of S-equol for 1 year.	[129]
S-Equol	✓ *Cardioprotective effect*: decrease of HbA1c, serum LDL-c levels and CAVI score. These effects were higher in the subgroup of female equol non-producers. No effect on BMI, systolic BP, diastolic BP, FPG, TC, HDL-c, triglycerides, adiponectin, leptin and CRP levels.	Randomized, double-blinded, placebo-controlled, crossover study with no washout period. N=49 overweight or obese outpatients. Tablets containing 10 mg of S-equol were orally administered each day for 12 weeks.	[130]
S-Equol	✓ *Non acute vascular benefits*: No changes on hemodynamic and vascular measures (RHI, diastolic and systolic BP, CO, AI, and cfPWV).	Parallel, placebo-controlled study. N=28 men at moderate cardiovascular risk. 40 mg of S-equol to non-EPs. Acute study (2 h).	[131]
8PN	✓ *Endocrine effect*: decrease of LH serum concentrations at the highest dose (750 mg).	Randomized, double-blind, placebo-controlled, dose-escalation design. N=6 healthy postmenopausal women. Micronized 8-PN was given orally in doses of 50, 250 or 750 mg. Acute study (up to 48 h).	[132]
8PN	✓ *Inmunomodulatory effect*: increase of the number of living PBMC.	Randomized, double-blind, placebo-controlled, crossover trial study. N=16 healthy volunteers. Single oral dose of 500 mg of 8-PN (6 h).	[133]