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Received: 3 December 2021 | Revised: 17 June 2022 | Accepted: 21 June 2022

DOI: 10.1111/1541-4337.13006

COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

A look beyond dietary (poly)phenols: The low molecular weight phenolic metabolites and their concentrations in human circulation

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Funding information
European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under grant agreement No 804229. iNOVA4Health Research Unit (LISBOA-01-0145-FEDER-007344), which is cofunded by Fundação para a Ciência e Tecnologia (FCT) / Ministério da Ciência e do Ensino Superior, through national funds, and by FEDER under the PT2020 Partnership Agreement, European Research Council (Starting Grant: FunKeyGut 741623). FCT (2020.04630.BD).

Abstract

A large number of epidemiological studies have shown that consumption of fruits, vegetables, and beverages rich in (poly)phenols promote numerous health benefits from cardiovascular to neurological diseases. Evidence on (poly)phenols has been applied mainly to flavonoids, yet the role of phenolic acids has been largely overlooked. Such phenolics present in food combine with those resulting from gut microbiota catabolism of flavonoids and chlorogenic acids and those produced by endogenous pathways, resulting in large concentrations of low molecular weight phenolic metabolites in human circulation. Independently of the origin, in human intervention studies using diets rich in (poly)phenols, a total of 137 low molecular weight phenolic metabolites have been detected and quantified in human circulation with largely unknown biological function. In this review, we will pinpoint two main aspects of the low molecular weight phenolic metabolites: (i) the microbiota responsible for their generation, and (ii) the analysis (quali- and quantitative) in human circulation and their respective pharmacokinetics. In doing so, we aim to drive scientific advances regarding the ubiquitous roles of low molecular weight phenolic metabolites using physiologically relevant concentrations and under (patho)physiologically relevant conditions in humans.

KEYWORDS
metabolism, microbiota, polyphenols

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1 INTRODUCTION

The human gastrointestinal tract harbors a diverse collection of microorganisms comprising bacteria, viruses, fungi, archaea, and protozoa. This constellation of gut microorganisms is under constant exposure to thousands of dietary molecules, the metabolism of which allows for more complete digestive processes, xenobiotic detoxification, and synthesis of key mediators such as vitamins, bile acids, short-chain fatty acids, amino acids, poly and mono amines, tryptophan metabolites, and phenolic acids (Lee & Hase, 2014). These microbial metabolites are crucial because they provide essential amino acids, are energy sources, facilitate absorption, maintain pH, promote immune maturation, and modulate overall organismal homeostasis (Sorgdrager et al., 2019; Waclawiková & El Aidy, 2018). Nonetheless, such metabolites are not exclusive to the gastrointestinal environment, crossing the epithelial barrier, reaching the circulation, acting on multiple organs throughout the organisms, and being found in multiple fluids such as urine, blood, and the cerebrospinal fluid.

Epidemiological studies addressing fruits and vegetables intake have shown clear associations with health benefits on diabetes (Li et al., 2014), cardiovascular risk (Medina-Remón et al., 2015; Rodriguez-Mateos, Heiss, et al., 2013; Sesso et al., 2022), and neurodegeneration and cognitive function (Macready et al., 2009; Nehlig, 2013; Nooyens et al., 2011; Psaltopoulou et al., 2013; Sloan et al., 2021). Such effects have been historically attributed to the presence of large amounts of (poly)phenols—like flavonoids—in fruits and vegetables (Arts & Hollman, 2005; Kim & Je, 2017; Rodriguez-Mateos, Heiss, et al., 2013). This epidemiological evidence has been backed up by a vast array of in vitro studies using pure, commercially available (poly)phenols, but many of these studies have used supraphysiological concentrations that do not reflect the actual concentrations achievable in human circulation. In turn, animal studies have also shown significant alterations upon exposure to (poly)phenols, but these may have overlooked biotransformation (Kroon et al., 2004). The gut microbiota has been shown to have a major role on biotransformation of (poly)phenols, and several species have been deemed necessary to produce the bioactive forms of circulating metabolites (Del Rio et al., 2013). Among these, one finds (poly)phenol-derived metabolites such as equol and enterolactone, which function as important nonsteroidal hormone modulators (Penttinen et al., 2007; Setchell & Clerici, 2010). Still, one set of (poly)phenol-derived metabolites remain poorly understood: the low molecular weight (LMW) phenolic metabolites. These represent a wide group of molecules that share a common backbone phenolic structure and that can be generated from gut microbiota catabolism of a broad range of (poly)phenols, for example, of flavonols, flavones, anthocyanins, chalcones, chlorogenic acids, and others. Nonetheless, it is important to mention that besides gut microbiota origin, some of these metabolites may appear in circulation due to their presence in the food matrix, since they can be produced in edible plants for example, 4′-hydroxy-3′-methoxycinnamic acid (ferulic acid) and 3′,4′-dihydroxycinnamic acid (caffeic acid). Furthermore, a small portion of these metabolites are also generated from human endogenous sources. Herein, we will describe LMW phenolic metabolites from the three sources without discrimination of their origin since in vivo they represent the same chemical entities ultimately with the same possible biological functions.

An example of endogenously produced LMW phenolic metabolites that also result from microbiota (poly)phenols catabolism are 3′,4′-dihydroxyphenylacetic acid (DOPAC) and 4′-hydroxy-3′-methoxyphenylacetic acid (homovanillic acid) acids that are formed as metabolites of dopamine and that raise questions as to their putative role in neuromodulation in Parkinson's disease. Additionally, microbiota production of benzene-1,2-diol (catechol) and benzene-1,2,3-triol (pyrogallol), two catechol-*O*-methyltransferase inhibitors, also suggests potential involvement in Parkinson's disease (C. Barrow, 2012). Also two metabolites derived from the neurotransmitters epinephrine and norepinephrine, 2-hydroxy-2-(3′,4′-dihydroxyphenyl)acetic acid (dihydroxymandelic acid) and 2-hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)acetic acid (vanillylmandelic acid) have been indicated as LMW phenolic metabolites (Kay et al., 2020). Furthermore, 2′,5′-dihydroxyphenylacetic acid (homogentisic acid) is produced as part of phenylalanine and tryptophane metabolism (Bory et al., 1990). Additionally produced from phenylalanine and tryptophan metabolism, hippuric acid is part of the alternative urea cycle and has shown a significant increase upon consumption of (poly)phenol rich foods (Armstrong et al., 1955; Krupp et al., 2012).

Overall, the major barrier to our understanding of the implications of these LMW phenolic metabolites is the incomplete catalogue of circulating metabolites and their respective concentrations. Hindering the cataloguing of circulating LMW phenolic metabolites are the food matrix effect, interindividual variability on gut microbiota composition, human genetic and epigenetic variation on phase II enzymes (e.g., single nucleotide polymorphisms [SNPs] or methylation of key genes), the lack of a universal protocol for compound quantification in biological samples, the use of enzymatic hydrolysis for quantitative analysis, and the lack of analytical standards, which overall result in laborious, challenging, and ambiguous chemical confirmation. Stable isotope labeling might represent a very

TABLE 1 Bacterial species isolated from human fecal matter capable of (poly)phenol catabolism and respective generated products

Bacterial species	(Poly)phenol Substrate/ Intermediate	Product	Reference
Flavonifractor plautii	1-(3′,4′-dihydroxyphenyl)-3-(2′,4′,6′-trihydroxyphenyl)propan-2-ol	5-(3′,4′-dihydroxyphenyl)-γ-valerolactone 4-hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid	(Kutschera et al., 2011)
	1-(3′,4′-dihydroxyphenyl)-3-(2′,4′,6′-trihydroxyphenyl)propan-2-ol	5-(3′,4′-dihydroxyphenyl)-γ-valerolactone[a] 4-hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid[a]	(Takagaki & Nanjo, 2015)
	Quercetin, taxifolin alphitonin	3′,4′-dihydroxyphenylacetic acid	(Schoefer et al., 2003)
	Apigenin, naringenin phloretin		3-(4′-hydroxyphenyl) propanoic acid benzene-1,3,5-triol
	Luteolin, eriodictyol	3-(3′,4′-dihydroxyphenyl)propanoic acid	
	Naringenin	phenylacetic acid	(Winter et al., 1989)
	Quercetin	3′,4′-dihydroxyphenylacetic acid	
Eubacterium ramulus	Quercetin	3′,4′-dihydroxyphenylacetic acid benzene-1,3,5-triol, acetate butyrate	(Schneider et al., 1999)
	Quercetin, rutin, taxifolin	3′,4′-dihydroxyphenylacetic acid	(Schneider & Blaut, 2000)
	Luteolin, eridictyol	3-(3′.4′-dihydroxyphenyl)propanoic acid	
	Kaempferol	4′-hydroxyphenylacetic acid	
	Naringenin, phloretin	3-(4′-hydroxyphenyl)propanoic acid	
	Quercetin, taxifolin, alphitonin	3′,4′-dihydroxyphenylacetic acid benzene-1,3,5-triol	(Braune et al., 2001)
	Luteolin	3-(3′,4′-dihydroxyphenyl)propanoic acid	
	Eriodictyol	benzene-1,3,5-triol	
	Naringenin, phloretin	3-(4′-hydroxyphenyl)propanoic acid	
Eubacterium oxidoreducens	3,4,5-trihydroxybenzoic acid[1]	benzene-1,2,3-triol	(Krumholz et al., 1987)
	Benzene-1,2,3-triol	benzene-1,3,5-triol	
	Benzene-1,3,5-triol	dihydrophloroglucinol	
	Dihydrophloroglucinol	3-hydroxy-5-oxohexanoate	
Clostridium scindens	Naringenin	phenylacetic acid	(Winter et al., 1989)
Agathobaculum desmolans	Naringenin	phenylacetic acid	
Clostridium perfringens	Quercetin	3′,4′-dihydroxyphenylacetic acid	(Peng et al., 2017)
Lactobacillus gasseri	Chlorogenic acid	3′,4′-dihydroxycinnamic acid	(Couteau et al., 2001)
Clostridium butyricum	Eriodictyol	3-(3′,4′-dihydroxyphenyl)propanoic acid benzene-1,3,5-triol	(Miyake et al., 1997)

(Continues)

TABLE 1 (Continued)

Bacterial species	(Poly)phenol Substrate/ Intermediate	Product	Reference
Catenibacillus scindens	O-desmethylangolensin	Benzene-1,3-diol 2-(4′-hydroxyphenyl)propanoic acid	(Braune & Blaut, 2011)
	6′-hydroxy-o-desmethylangolensin	Benzene-1,3,5-triol 2-(4′-hydroxyphenyl)propanoic acid	
Bacteroides fragilis	Quercetin	3′,4′-dihydroxyphenylacetic acid	(Peng et al., 2017)
Eggerthella sp. SDG-2	3′,4′-dihydroxycinnamic acid	3-(3′,4′-dihydroxyphenyl)propanoic acid 3-(3′-hydroxyphenyl)propanoic acid	(Wang et al., 2001)
Bifidobacterium animalis subsp. lactis	Chlorogenic acid	3′,4′-dihydroxycinnamic acid	(Couteau et al., 2001)
Escherichia coli (three isolates)	Chlorogenic acid	3′,4′-dihydroxycinnamic acid	

[a]both R and S isomers have been detected.

useful strategy to overcome some of these complications, tracking flavonoid metabolites and their dynamics while distinguishing from endogenous metabolite products, like hippuric acid. However, only a few studies have taken advantage of this technology (Czank et al., 2013; R. M. de Ferrars, Cassidy et al., 2014; Ottaviani et al., 2016). Moreover, metabolomic and spectral databases such as Metlin (Smith et al., 2005) or the Human Metabolomics Database (HMDB) (Wishart et al., 2018) represent extremely valuable tools that are constantly being updated with novel metabolite entries, but many more, referred to as the "dark matter," have yet to be unveiled (Peisl et al., 2018). Nonetheless, the use of these databases also presents several pitfalls and limitations. There is a great variability in metabolite identification depending on experimental equipment, incorrect entries, or the use of in silico tools, which do not reflect the experimental fragmentation of the compounds at all (Kuhnert & Clifford, 2022). To this, it should be added the large number of synonyms currently present in the literature that must be harmonized and updated (Kay et al., 2020).

LMW phenolic metabolites represent poorly characterized but important modulators of human physiology. Growing evidence has identified LMW phenolic metabolites as the molecules responsible for health beneficial effects of (poly)phenol consumption (Cortés-Martín et al., 2020; de Ferrars, Cassidy et al., 2014). Different pathways may culminate in the presence of LMW phenolic metabolites in human circulation, for example, directly from the food matrix, catabolism by microbiota, endogenous pathways, or even industrial chemicals and pharmaceuticals (Koppel et al., 2017). In this review, we will systematize the gut bacteria that have been shown capable of generating LMW phenolic metabolites in vitro, pinpoint LMW phenolic metabolites present in human blood after (poly)phenol intake mainly flavonoids and chlorogenic acids, together with their physiological concentrations and pharmacokinetics and, highlight the pressing issues and knowledge gaps to be addressed.

The extensive list of precursor molecules and their origin in the plant kingdom will however be out of the scope of this review as this information has been extensively described in recent years in several reviews (Abdallah et al., 2020; Koppel et al., 2017; Riaz Rajoka et al., 2017) and can be found in multiple databases, that is, Phenol-explorer and Phytohub (da Silva et al., 2016; Rothwell et al., 2013). To facilitate data interpretation and analysis, this review used the metabolite nomenclature recommended by Kay et al. (2020). Overall, we aim to push the evaluation of LMW phenolic metabolites at physiological relevant concentrations in hope to discover their (patho)physiological effects with biological relevant mechanistic studies and possibly contribute to drive future therapies using nutritional counseling, supplementation, pro-biotics, or a combination thereof taking advantage of the potential health properties of these LMW phenolic molecules.

2 | GUT MICROBIOTA AND THE LMW PHENOLIC METABOLITES

LMW phenolic metabolites resulting from microbiota catabolism can arise from dietary sources mainly those containing flavonoids, as has been shown using isotopically labeled flavonoid molecules (Czank et al., 2013; R. M. de Ferrars, Cassidy et al., 2014; Ottaviani et al., 2016) and chlorogenic acids (Ludwig et al., 2013). Flavonoids are abundant in edible fruits and vegetables such as oranges, grapes, apples, tomato, mango, or berries (e.g., strawberry,

blueberry, raspberry) (Neveu et al., 2010; Rothwell et al., 2013). In addition, these can be largely complemented by other sources commonly consumed such as cocoa, herbal teas, and fermented beverages like wine (Neveu et al., 2010; Rothwell et al., 2013). Likewise, significant amounts of chlorogenic acids can be found in the same sources including coffee, wine, drupes, and berries.

Based on their chemical (dis)similarities, LMW phenolic metabolites have been classified into different classes that overall represent different molecular sizes (Kay et al., 2020). As reviewed by Braune and Blaut (2016) for flavonoids, our knowledge on the microbiota species responsible for the first steps in (poly)phenol catabolism is increasing, yet the species and enzymes responsible for the generation of specific phenolic metabolites are still largely unidentified. Several studies have been conducted trying to establish a connection or association between fecal bacteria and (poly)phenol consumption. Such studies employed different methodologies from static batch fermentation cultures to gastrointestinal simulators, animal studies, or even human intervention studies, as previously revised (Dueñas et al., 2015). Moreover, these studies can go much further in understanding how a diet rich in (poly)phenols modulate microbiota and consequent lymphocyte function (Bakuradze et al., 2019; Groh et al., 2020). Such studies are a crucial source of knowledge of how the microbiota system is evolving in a complex environment and highlight microbiota benefiting from the presence of (poly)phenols. However, by having a complex environment, it is difficult to pinpoint the bacteria responsible to produce each particular phenolic metabolite. For this reason, in vitro studies using isolated bacteria from human fecal samples have provided more robust evidence regarding which bacteria are responsible for flavonoid and chlorogenic acid catabolism generating LMW phenolic metabolites and potentially short chain fatty acids (SCFAs) (Table 1).

Bacterial species such as *Flavonifractor plautii* (former *Clostridium orbiscidens*) (Kutschera et al., 2011; Schoefer et al., 2003) were shown to generate 5-(phenyl)-γ-valerolactone and 4-hydroxy-5-(phenyl)valeric acids (Figure 1a) (Kutschera et al., 2011; Schoefer et al., 2003; Takagaki & Nanjo, 2015). *Eubacterium ramulus* (Braune et al., 2005; Schneider & Blaut, 2000; Schoefer et al., 2002; Schoefer et al., 2003), *Clostridium butyricum, Flavonifractor plautii* (Schoefer et al., 2003), *Catenibacillus scindens* (former CG19-1) (Braune & Blaut, 2011), and *E. ramulus* (WANG et al., 2004) are known to generate phenylpropanoic acids. Meanwhile, *Escherichia coli* and *Bifidobacterium animalis subs. lactis* and *Lactobacillus gasseri* produce cinnamic acids from chlorogenic acid (Couteau et al., 2001). The bacteria *E. ramulus* (Schneider et al., 1999) and *F. plautii* (Braune et al., 2001; Schneider & Blaut, 2000; Schneider et al., 1999; Schoefer et al., 2003) have been shown to produce phenylacetic acids. Benzoic acids have been mapped to *B. animalis ssp. lactis* (former *Bifidobacterium lactis*) BB-12, *Lactobacillus casei* LC-01, and *Lactobacillus plantarum* IFPL722, but these have yet to be isolated from human stool samples (Hayashi et al., 2012; Sánchez-Patán et al., 2012). Benzenes such as benzene-1,3,5-triol have been observed to be produced in presence of *E.ramulus* (Schneider et al., 1999) and *C. scindens* (Braune & Blaut, 2011; Maini Rekdal et al., 2019). Meanwhile, *L. plantarum* isolated from human saliva harboring the *ldp* (lactobacillus plantarum decarboxylase) gene were also capable of producing benzene-3,4,5-triol and benzene-1,2-diol from 3,4,5-trihydroxybenzoic acid and 3,4-dihydroxybenzoic acid, respectively (Jiménez et al., 2013). Lastly, *E. ramulus, E. oxidoreducens*, and *F. plautti* have the capacity to degrade benzene-1,3,5-triol into SCFAs (Braune & Blaut, 2016), which ones are of particular relevance when one considers the possibility of LMW phenolic metabolites generating SCFAs and their potential health effects (Dalile et al., 2019).

Across the limited number of available studies reporting the formation of LMW phenolic metabolites, the flavonols, that is, quercetin, has been one of the most often used substrate (Table 1). Interestingly, despite the use of different bacterial species (i.e., *F, plautti*, *E. ramulus*, *C. perfringens*, or *B. fragilis)* and different concentrations and reaction times (from 4.8 h to 72 h), the produced LMW phenolic metabolites was the same: 3′,4′-dihydroxyphenylacetic acid (DOPAC, Supplementary Table 1). Schoefer et al. (2003) also showed that quercetin could be converted to taxifolin and alphitonin, and these can also result in DOPAC (Supplementary Table 1). This suggests the possibility that these species share the same type of reaction which could mean a common/similar enzyme or group of enzymes responsible for the degradation of flavonoids. Moreover, using other flavonoids, flavones, that is, luteolin and eriodictyol or flavanones, that is, naringenin, resulted in a common class of phenolics, phenylpropanoic acids. Interestingly, benzene-1,3,5-triol was also a product of these flavonoid substrates (Table 1). However, whether this reaction uses the same enzyme is still unknown.

A particular class of LMW phenolic metabolites are 5-(phenyl)-γ-valerolactone and 4-hydroxy-5-(phenyl)valeric acid, which seem to only be generated from flavan-3-ols (Kutschera et al., 2011). Nonetheless, their production required the formation of an intermediary by *E. ramulus* before *F. plautti* could produce a racemic mixture of these phenolics. Notwithstanding, *E. ramulus* did not seem to produce this class of metabolites.

Globally, although the evidence suggests that the metabolic capacity of different bacteria is similar in producing the same type of reaction in the phenolic ring, the enzymes have not been so far identified. Moreover, the

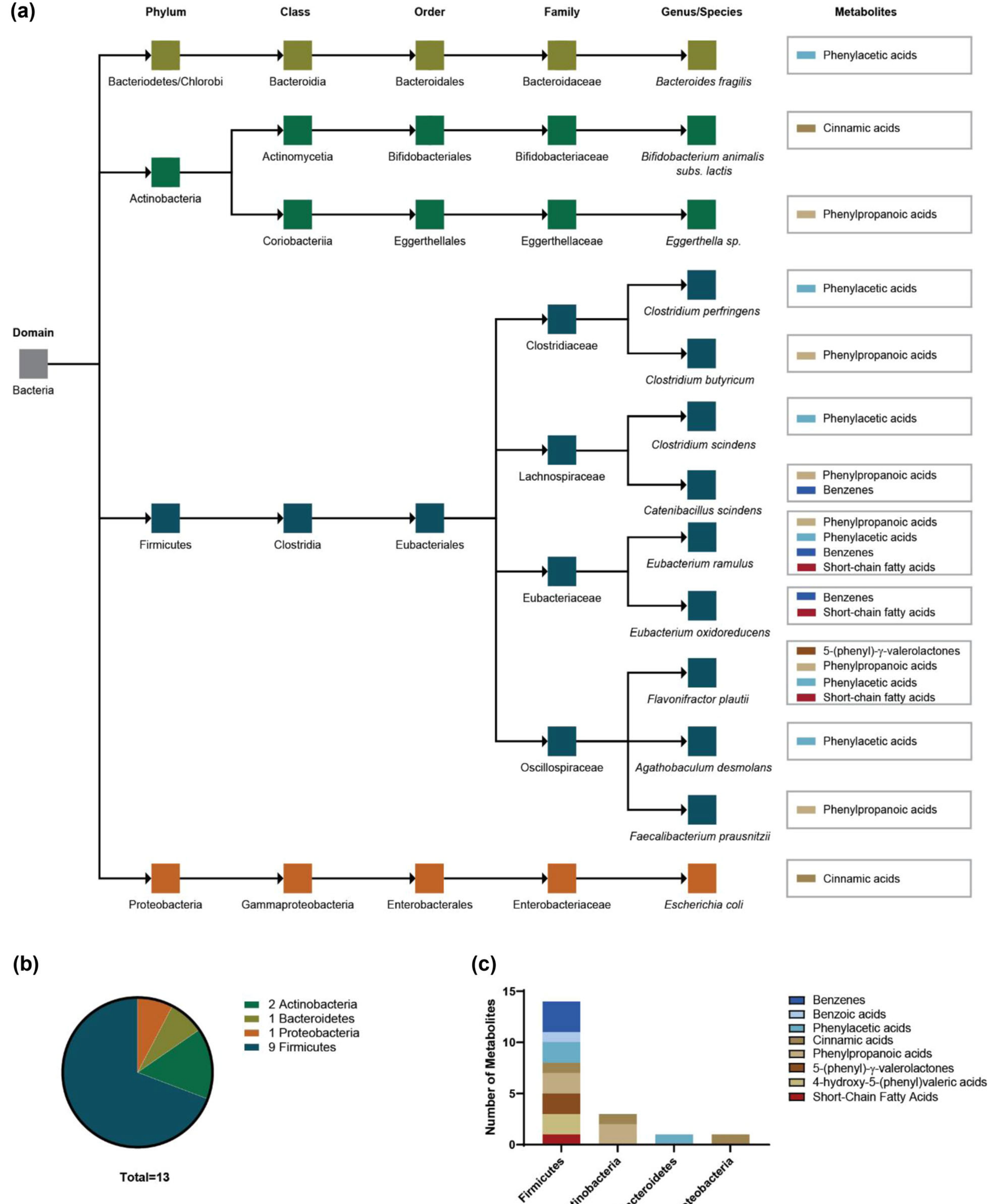

FIGURE 1 Gut microbiota bacterial species across different phyla identified as producers of LMW phenolic metabolites. (**a**) Phylogenetic tree of the 13 gut bacterial species from human fecal samples with known capacity to produce LMW phenolic metabolites and its respective phenolic metabolite class (Table 1). (**b**) Distribution of the 13 species across four different phyla: Firmicutes, Actinobacteria, Bacteroidetes and Proteobacteria. (**c**) Number of LMW phenolic metabolite according to phenolic class distributed across the four bacterial different phyla. Additional details about the LMW phenolic metabolites produced and the substrates used can be found in Table 1 and Supplementary Table 1

same bacteria can transform different substrates to originating the same product. Overall, 13 different bacterial species have been identified across all major phyla present in the human gut: Bacteroidetes, Actinobacteria, Proteobacteria, and Firmicutes (Figure 1a,b). Here, the majority and the most diverse group of LMW phenolic metabolites have been identified as originated by Firmicutes metabolism (Figure 1c). Possibly this is due to their relatively high abundance in the human intestine: Firmicutes 64%, Bacteroidetes 23%, Proteobacteria 8%, and Actinobacteria 3% (Duda-Chodak et al., 2015) or the fact the processes that increase the bioavailability of flavonoids, that is, *C*- and *O*-deglycosylation have been mainly found in firmicutes (Braune & Blaut, 2016). Moreover, *C*-ring fission has until now only been appointed to Firmicutes and Actinobacteria (Cortés-Martín et al., 2020; Duda-Chodak et al., 2015). In contrast, certain bacteria capable of chlorogenic acid catabolism have been identified (e.g., *Faecalibacterium prausnitzii*), however all the resulting metabolites are still unknown (Tomas-Barberan et al., 2014).

Considering the metabolic pathways involved in LMW phenolic metabolite production that have come to be predicted and refined over the past two decades (Carregosa et al., 2019; Crozier & Spencer, 2016; Del Rio et al., 2013; Manach et al., 2005; Williamson & Manach, 2005; Williamson et al., 2018), our knowledge on which bacterial species are capable of such transformations and the mechanisms herein involved is still rather limited (Figure 2). For example, transformation of 2-(phenyl)ethanol into phenylacetic acid by bacteria has been proven using human fecal samples, but the metabolizing species are yet to be pinpointed (Mosele et al., 2014). Using in vitro fermentation, Di Pede et al. (2022) showed the resulting products of several proanthocyanins and flavan-3-ols along time, but the bacteria species responsible were not elucidated Likewise, even though the conversion of cinnamic acids into vinyl phenol has been reported across several bacteria and yeast species isolated from food, soil, and plants, the same was not found using human fecal samples (Mishra et al., 2014). It is possible that many of the already-identified bacteria from gut microbiota produce many more LMW phenolic metabolites still to be identified. This is particularly true due to the limited number of flavonoids used as substrates until now (Table 1) as they represent a very small percentage of the known dietary flavonoids (da Silva et al., 2016; Neveu et al., 2010; Rothwell et al., 2013). Moreover, other factors might play an important role on our lack of knowledge such as the use of stool samples for gut microbiota isolation, resulting in the underrepresentation of small intestine bacteria, hiding interesting information, or the difficulties in growing and meeting the needs of many anaerobic bacteria, not fully recapitulating the gut environment.

All in all, the gut microbiota plays a key role in (poly)phenol metabolism, so that variability at the LMW phenolic metabolites level is thought to drive interindividual variability in health and disease. Unfortunately, challenges pertaining to the isolation of certain bacteria, in particular the ones of low abundance, their identification, and lack of nomenclature uniformization have precluded the exploitation thereof.

3 | LMW PHENOLIC METABOLITES CROSS THE INTESTINAL MEMBRANES AND REVEAL ANTI-INFLAMMATORY PROPERTIES

Independently of the origin, directly from food, resulting from gut microbiota, or formed by endogenous pathways in the host, LMW phenolic metabolites are present in human circulation. In contrast with dietary flavonoids that may be transported by ATP-binding cassette transporters (ABC) and organic anion transporters (OAT) (Williamson et al., 2018), the exact mechanisms via which circulating LMW phenolic metabolites cross the host cell membranes is unknown. Passive permeability has been considered important judging by the modeling based on the physicochemical properties of several LMW phenolic metabolites from different classes including phenols, benzoic acid, phenylacetic acid, and cinnamic acid (Carecho et al., 2021; Selby-Pham et al., 2017). However, OAT transport has also been reported for LMW phenolic metabolites as revised in Carecho et al. (2021). Accordingly, modulation of OAT1 (SLC22A6), OAT3 (SLC22A8), and OAT4 (SLC22A11) by LMW phenolic metabolites such as 3,4,5-trihydroxybenzoic acid and hippuric acid has been reported (Wang & Sweet, 2012). Of particular note, the two LMW phenolic metabolites 3′,4′-dihydroxyphenylacetic acid and 4′-hydroxy-3′-methoxyphenylacetic acid, have also been described to be transported across the blood-brain barrier by OAT3 (Mori et al., 2003; Ohtsuki et al., 2002). However, this data refers mainly to LMW phenolic metabolites shared between dietary consumption and endogenous pathways, meaning that much remains to be unveiled.

Before reaching circulation, LMW phenolic metabolites undergo entero-hepatic circulation, whereby they can be further modified by intestinal and hepatic cells via phase I and II metabolic reactions (Figure 3). Examples thereof include conjugation with glucuronic acid by glucuronosyltransferases (UGT) (Wong et al., 2010), methyl by catechol-*O*-methyltransferase (COMT), sulfate

FIGURE 2 Biotransformation pathway from parent compounds (grey) to progressively smaller low molecular weight phenolic metabolites (blue), culminating in the production of short chain fatty acids (green). Microbiota from human feces capable of producing low molecular weight phenolic metabolites are shown by grey arrows while respective LMW phenolic metabolites are shown in Table 1 and the respective concentration and reaction times in Supplementary Table 1. Gray dashed arrows represent known metabolic conversions with unidentified human microbiota origin. SCFA—short chain fatty acids

by sulfotransferase (SULT), and glycine by glycine *N*-benzoyltransferase (GLYAT) (Czank et al., 2013). However, downstream of entero-hepatic circulation and systemic distribution, the potential effects of LMW phenolic metabolites have not been fully elucidated. In contrast, other metabolites (e.g., tryptophan, SCFAs) have been shown to play a role in immune and nervous system maturation and modulation (Fung et al., 2017; Roager & Licht, 2018). Notably, the production of SCFAs from LMW phenolic metabolites by *F. plautti* and *E. oxireducens* (Table 1) seems to be of particular relevance in regulating the vagal tone (Silva et al., 2020). Likewise, the production of LMW phenolic metabolites common to endogenous dopamine metabolism byproducts such as 3′,4′-dihydroxyphenylacetic acid again implicates LMW phenolic metabolites in vagal tone regulation. This regulation of endogenous 3′,4′-dihydroxyphenylacetic acid has been reported after consumption of other (poly)phenols,

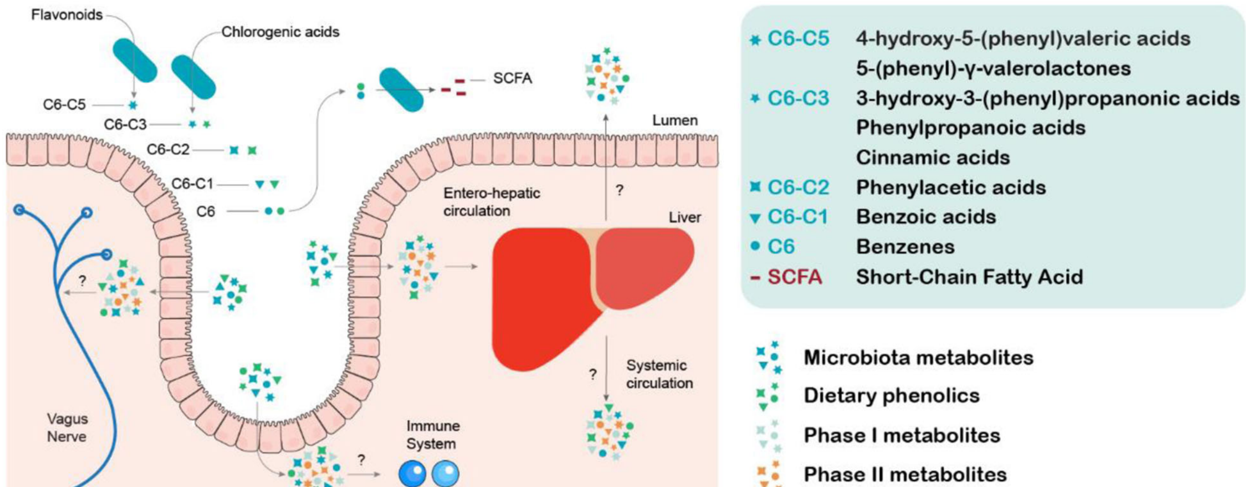

FIGURE 3 LMW phenolic metabolites are converted into short chain fatty acids (SCFA) or absorbed by intestinal epithelium entering entero-hepatic circulation undergoing phase I and II metabolic reactions before being redirected to the gut or reaching systemic circulation

like rosmarinic acid (Hase et al., 2019) and curcumin (Rajeswari & Sabesan, 2008), in models of Parkinson's disease.

When it comes to their putative local anti-inflammatory properties, the use of 3,4,5-trihydroxybenzoic acid and 4′-hydroxy-3′-methoxycinnamic acid have been shown to suppress colitis in mice (Pandurangan et al., 2015) and rats, respectively (Sadar et al., 2016) using physiological relevant concentrations. In zebrafish, 3,4,5-trihydroxybenzoic acid and 4′-hydroxy-3′-methoxycinnamic acid reduce neutrophil infiltration in a cholesterol model of inflammatory bowel disease (IBD) (Silva et al., 2021). Phloroglucinol (benzene-1,3,5-triol) has shown nonspecific antispasmodic effects and was effective in reducing IBD symptoms alone (Jafri et al., 2006) or in combination with 1,3,5-trimethoxybenzene (Chassany et al., 2007). Immune modulation by LMW phenolic metabolites can be traced up until microglia in the brain, revised in Carregosa et al. (2019). Moreover, the potential health benefits of these metabolites in reducing neuroinflammation and neurodegeneration in different animal models have also been revised in Carregosa et al. (2021).

In summary, LMW phenolics consumed from the matrix combine with those resulting from microbiota fermentation, which could be further metabolized by the microbiota–entero-hepatic system before being distributed by the systemic circulation, have an increasingly recognized role in immune and neuronal modulation in organs not restricted to the gastrointestinal system (Figure 3). The health effects of such metabolites, for example, on the vagus nerve and the immune system, remain poorly understood.

4 | INTERVENTION STUDIES IDENTIFYING AND QUANTIFYING THE LMW PHENOLIC METABOLITES IN BLOOD

To guide future in vitro and in vivo studies in dissecting the health benefits and mechanisms of action of LMW phenolic metabolites, at physiologically relevant concentrations, it becomes imperative to characterize certain distribution parameters, most notably their maximal circulating concentrations (C_{max}), time to peak maximal concentration (T_{max}), and the circulation time in humans. Although this information is available in the literature, it is spread across multiple studies, and this is reflected by several in vitro studies using supraphysiological concentrations that cannot be achievable in blood circulation or target tissues through dietary or even supplementation means. By addressing this matter and summarizing the physiological conditions for LMW phenolic metabolites, we ensured and maximize the translation potential of the data obtained. For precisely this reason, we have decided not to interpolate data from urinary samples, as these usually represent concentrations far higher than those achieved in circulation (Guerreiro et al., 2022).

We have searched PubMed for human intervention studies, which have identified and quantified LMW phenolic metabolites in human blood using diets rich in (poly)phenols or using flavonoid supplementation. In total, we have identified 42 intervention studies that employed either (i) dietary sources such as fruits or derivates thereof (e.g., juice, fruits, cake, coffee) in a single dose (Supplementary Table 2), (ii) dietary sources

in multiple doses (Supplementary Table 3), or (iii) supplementation using plant extracts or pure flavonoids in capsules (Supplementary Table 4) (Azzini et al., 2010; Bresciani et al., 2017; Caccetta et al., 2000; Castello et al., 2018; Curtis et al., 2019; Czank et al., 2013; Rachel M. de Ferrars, Czank et al., 2014; R. M. de Ferrars, Cassidy et al., 2014; de la Torre et al., 2003; R. Feliciano et al., 2017; R. Feliciano, Istas, et al., 2016; R. P. Feliciano, A. Boeres, et al., 2016; Henning et al., 2013; Keane et al., 2015; Koli et al., 2010; Lang et al., 2013; Li et al., 2000; Loke et al., 2009; Ludwig et al., 2015; McKay et al., 2015; Mueller et al., 2017; Ottaviani et al., 2016; Pereira-Caro et al., 2020; Pimpão et al., 2015; Prymont-Przyminska et al., 2016, 2014; Rodriguez-Mateos et al., 2016, 2014; Rodriguez-Mateos, Rendeiro, et al., 2013; Russell et al., 2009; Sandhu et al., 2018; Scherbl et al., 2016; Stalmach et al., 2012, 2009, 2014; Suárez et al., 2009; Urpi-Sarda et al., 2009; van der Pijl et al., 2015; van Duynhoven et al., 2014; Vitaglione et al., 2007; Zhang & Zuo, 2004; Zhong et al., 2017).

Overall, in these dietary intervention studies, a diversity of different foods was used including cranberry, blueberry, strawberry, raspberry, grapes, or oranges, either intact, delivered as juice, or even used in some more elaborate baked products. Coffee and herbal teas were also often used as a source of flavonoids and chlorogenic acids, respectively. This diversity of different arrangements is synonymous of a wide range of total (poly)phenol content (Supplementary table 2, 3 and 4). Noteworthy, while some studies included an in-depth analysis of the (poly)phenol content in the matrix looking into an array of different phenolics, a substantial number of studies did not perform this analysis nor reported the total amount of (poly)phenols in the matrix. Those detailing some information did so reporting total (poly)phenol content by different methods including Folin–Ciocalteu, dimethylaminocinnamaldehyde (DMCA), or HPLC (Supplementary Tables 2, 3 and 4). This variability between methodologies may also imply some variability by over- or underestimating total (poly)phenol content. Meanwhile, another common description is the total anthocyanin concentration commonly measured by HPLC. This measurement results from the quantification of the most abundant anthocyanins which in most cases result from the quantification of cyanidin and its glucosides. This also includes some variability as may be reported by the total amount of each anthocyanin, only cyanidin after glycosylation treatment of the matrix, or by measuring cyanidin plus its glucosides by HPLC. On the other hand, the (poly)phenols present in coffee are expressed as total amount of chlorogenic acids and as such it is the major metric used to quantify total (poly)phenols. In contrast to studies using dietary sources, intervention studies using pure compounds or capsules have a well-defined characterization of the matrix used (Supplementary Table 4).

Regarding the identification and quantification of LMW phenolic metabolites from blood samples, a variety of different methodologies have been used to extract the metabolites from blood including solid phase extraction or liquid–liquid extraction (Supplementary tables 2, 3 and 4). Most importantly some studies reported the use of enzymatic treatment (sulfatases and β-glucuronidases). This was used to increase the concentration of phenolics and thus increase their detectability, nonetheless, by doing so, the identification and quantification of such sulfate and glucuronide conjugates were lost and the quantification of LMW phenolic metabolites might be biased depending on LMW phenolic metabolites having a free hydroxyl group for sulfate or glucuronide conjugation. Besides, these enzymatic treatments may entail an overestimation of the LMW phenolic metabolites levels. Since these studies still report useful information, we have still used this data, yet have identified using this type of treatment as in Supplementary Tables 2, 3 and 4. Three other important factors were also noted: (i) since sulfate and glucuronide conjugation arise from hydroxyl groups on the phenolic structure, several isomers have been observed across multiple studies. However, due to the lack of proper standards, many studies have used one isomer to quantify other isomers or reported the quantification of the mixture of isomers. This fact may contribute to values different from the real circulating concentrations for each specific isomer (specifically by the different signals between isomers in HPLC-MS). This type of quantification was not excluded from our dataset, but have been noted in supplementary tables 2, 3 and 4; (ii) Some LMW phenolic metabolites have chiral centers: 5-(phenyl)-γ-valerolactones, 4-hydroxy-5-(phenyl)valeric acid, 3-hydroxy-3-(phenyl)propanoic acid, 2-hydroxy-2-(phenylacetic acid), and 2-(phenyl)propanoic acid. To the best of our knowledge, no study has been capable of clearly distinguishing and reporting the quantification of the isolated stereoisomers; (iii) The LMW phenolic metabolite cinnamic acid has two isomer configurations E and Z. The number of studies reporting the standard configuration used are exceptionally low and most refer to the trans configuration.

Finally, several types of systems and detectors have been used to quantify LMW phenolic metabolites. These usually include HPLC and GC, but NMR has also been used (Supplementary Table 1, 2, 3 and 4). Most studies herein revised have used authentic standards to quantify LMW phenolic metabolites, although it is common practice to use standards with similar structures, that is, isomers. Nonetheless, it was clear that some studies had a larger

portfolio of standards available for analysis and/or also focused on untargeted metabolomics, while some focus on a more restricted set of metabolites.

Another difference between studies is the request of a run-in phase intended to wash-out previous evidence of (poly)phenols and LMW phenolic metabolites. This varies between a simple statement of a low (poly)phenol content diet to an extensive list of dietary products recommended to be avoided by the participants. This period ranged from 2 weeks to 24 h, while some studies did not report the use of a wash-out period. Most of the interventions requested participants to perform an overnight fasting (i.e., 8 to 12 h) to washout traces of the previous meal. A sample of fasting blood, before the intervention was also collected in a large number of studies to subtract any LMW phenolic metabolites still present in circulation. Together these two factors, wash-out period and fasting, ensure that the LMW phenolic metabolites detected originated from the intervention and not from previous meals.

Blood collection across all studies ranged from 2 up to 48 h. For multiple dose intervention studies and single dose intervention studies, using blood collection timepoints above 4/ 6 h, it is important to register what participants eat during the intervention. A very limited number of studies have reported a detailed description of the dietary regime used during the time blood was collected from the participants, but this was an exceedingly rare occasion. This is even more important in multiple dose dietary intervention. In any case, most studies stated the use of a (poly)phenol-free diet during the intervention.

5 | LMW PHENOLIC METABOLITES: BLOOD DISTRIBUTION AND PHARMACOKINETICS

Overall, 137 LMW phenolic metabolites have been identified and/or quantified in human circulation across all studies (Figure 4a and Table 2). In respect to their chemical classification, these were grouped into 16 phenolic classes: benzenes (14 metabolites), benzaldehydes (5 metabolites), benzoic acids (38 metabolites), phenylacetic acids (12 metabolites), cinnamic acids (19 metabolites), phenylpropanonic acids (19 metabolites), hippuric acids (5 metabolites), 5-(phenyl)-γ-valerolactones (12 metabolites), 5-(phenyl)valeric acids (1 metabolite), 4-hydroxy-5-(phenyl)valeric acids (2 metabolites), 3-hydroxy-3-(phenyl)propanoic acids (2 metabolites), 2-(phenyl)propanoic acids (1 metabolite), 2-(4-hydroxyphenoxy)propanoic acids (1 metabolite), cinnamoyl glycine (1 metabolite), 4-ethylbenzenes (2 metabolites), and 2-(phenyl)ethanols (4 metabolites) (Figure 4a and Table 2). For the sake of simplicity, ambiguous chemical structures that could represent different isomers are herein counted as a single entity, with three metabolites falling in this situation: 3-methoxybenzene-1,2-diol-sulfate (mixture of 3-methoxyphenol-2-sulfate and 2-methoxyphenol-6-sulfate), 4-methylbenzene-1,2-diol-sulfate (mixture of 4-methyphenol-2-sulfate and 5-methylphenol-2-sulfate), and 2-(3′,4′-dihydroxyphenyl)ethanol-glucuronide (a possible mixture of 2-(3′-hydroxyphenyl)ethanol-4′-glucuronide, 2-(4′-hydroxyphenyl)ethanol-3′-glucuronide, and 3′,4′-dihydroxyphenylmethyl hydrogen sulfate (Table 2).

Single dose dietary intervention studies recapitulate acute intake of dietary products, being the easiest intervention to employ and thus representing the majority of studies (26 studies). A total of 99 LMW phenolic metabolites have been discovered across single dose dietary intervention studies (Figure 4b, Supplementary Table 5). However, single dose intervention studies do not allow for microbiota composition adaptation and thus might be biased by interindividual differences in microbiota composition. In turn, the use of dietary intervention studies employing multiple doses might allow for adaptive microbiota composition changes, culminating in a more uniform microbiota composition and hypothetically in a more uniform generation of phenolic metabolites (Tomás-Barberán et al., 2016; Zoetendal & de Vos, 2014). Here, multiple dose intervention studies require longer preparation, comprise higher costs, and are biased by the more variable intake of other foods by volunteers or lack of compliance. A total of 7 studies using multiple doses of foods rich in (poly)phenols and flavonoids (e.g., black tea, cocoa, strawberry, blueberry, or blackcurrant) exploring the concentration of LMW phenolic metabolites in human circulation have been reported to date (R. Feliciano, Istas, et al., 2016; Henning et al., 2013; Koli et al., 2010; Prymont-Przyminska et al., 2016, 2014; Sandhu et al., 2018; Urpi-Sarda et al., 2009). In these, 60 LMW phenolic metabolites were quantified (Figure 4c, Supplementary Table 6). Alternatively, intervention studies with plant extracts or pure flavonoids have been especially useful when aiming at the identification of metabolites that can be directly traced back to a particular flavonoid family or distinguishing from LMW phenolic metabolites present directly in the food matrix (Bresciani et al., 2017; Czank et al., 2013; Rachel M. de Ferrars, Czank, et al., 2014; R. M. de Ferrars, Cassidy, et al., 2014; Loke et al., 2009; Ottaviani et al., 2016; van der Pijl et al., 2015). Although, it should be noted that such studies often administer flavonoid concentrations higher than those achieved with dietary interventions. Nonetheless, these studies allow for the use of isotopically labeled flavonoids, which helps with identifying the originated phenolic metabolites. For example, using (^{13}C)-cyanidin-glucoside, it was possible

TABLE 2 LMW phenolic metabolites identified and quantified in human blood across the different intervention studies. The reported C_{max} and T_{max} values refer to the highest reported values in the literature among single dose intervention studies, multiple dose intervention studiesm and/or from intervention studies using capsules, extracts, or pure phytochemicals (see footnote)

Class	LMW metabolite	C_{max} (nM)	T_{max} (h)	Reference
Benzenes	benzene-1,2-diol	3269 ± 2507[b]	–	(Loke et al., 2009) [e]
	phenol-2-sulfate	24555 ± 3775	7.1 ± 0.4	(R. P. Feliciano, A. Boeres, L. Massacessi, G. Istas, M. R. Ventura, C. N. dos Santos, et al., 2016)
	phenol-2-glucuronide	129 ± 50	0.75	(Lang et al., 2013)
	methoxybenzene-2-sulfate	343 ± 74	0.75	(Lang et al., 2013)
	methoxybenzene-2-glucuronide	24 ± 12	0.5	(Lang et al., 2013)
	benzene-1,2,3-triol	6500 ± 4400	8.8 ± 5.5	(van der Pijl et al., 2015) [e]
	benzene-1,2-diol-3-sulfate	652 ± 328	6	(Pimpão et al., 2015)
	benzene-1,3-diol-2-sulfate	11430 ± 6678	6	(Pimpão et al., 2015)
	benzene-1,3-diol-2-glucuronide	19[b]	5	(van Duynhoven et al., 2014)
	1-methoxybenzene-2,3-diol-sulfate	2879 ± 1807[d]	6	(Pimpão et al., 2015)
	2-methoxyphenol-3-sulfate	1969 ± 982	6	(Pimpão et al., 2015)
	3,4-dimethoxyphenol	18805 ± 6934[b]	2	(Loke et al., 2009) [e]
	4-methylbenzene-1,2-diol-sulfate	4951 ± 1503[d]	10.7 ± 0.0	(Feliciano et al., 2017)
	1,3,5-trimethoxybenzene	10353 ± 4514[b]	–	(Loke et al., 2009)
Benzaldehydes	4-hydroxybenzaldehyde	574 .4 ± 58.1	10.0 ± 3.0	(Zhong et al., 2017)
	3,4-dihydroxybenzaldehyde	34 ± 10 61082 ± 55838[b]	4.1 ± 2.6 –	(R. P. Feliciano, A. Boeres, L. Massacessi, G. Istas, M. R. Ventura, C. N. dos Santos, et al., 2016) (Loke et al., 2009) [e]
	4-hydroxy-3-methoxybenzaldehyde	1025 ± 525 28258 ± 24808[b]	– 2[b]	(Suárez et al., 2009) (Loke et al., 2009) [e]
	3-methoxybenzaldehyde-4-sulfate	37045 ± 22365	–	(Suárez et al., 2009)
	2,4,6-tihydroxybenzaldehyde	46.6 ± 4.7 582 ± 536[b]	0.5 ± 0.3 2.8 ± 1.1[b]	(Zhong et al., 2017) (R. M. de Ferrars, Cassidy et al., 2014)
Benzoic acids	benzoic acid	36030	0.75	(Zhang & Zuo, 2004)
	2-hydroxybenzoic acid	7649.08	0.75	(Zhang & Zuo, 2004)
	2-methoxybenzoic acid	2211 ± 1052	2	(Loke et al., 2009) [e]
	3-hydroxybenzoic acid	96 ± 31 1030.0 ± 138.0[a] 1273 ±1198[b]	1.8 ± 0.7 2[a] 2[b]	(Feliciano et al., 2017) (Sandhu et al., 2018) (Loke et al., 2009) [e]
	3-methoxybenzoic acid	3626 ±1660[b]	2[b]	(Loke et al., 2009) [e]
	4-hydroxybenzoic acid	2500 ±700 9730 ± 500[a] 28885 ± 18445[b]	1.9 ±0.3 0[a] 2[b]	(Azzini et al., 2010) (Urpi-Sarda et al., 2009) (Loke et al., 2009) [e]

(Continues)

TABLE 2 (Continued)

Class	LMW metabolite	C_{max}(nM)	T_{max}(h)	Reference
	4-methoxybenzoic acid	29.3 ± 3.1 131916± 12345[b]	5.7 ± 3.5 2[b]	(Zhong et al., 2017) (Loke et al., 2009) [e]
	benzoic acid-4-sulfate	56.7 ± 9.4 196 ± 15.48[b]	3.0 ± 0.7 3[b]	(Castello et al., 2018) (Rachel M. de Ferrars, Czank et al., 2014)
	benzoic-4-glucuronide	74 ± 20[b]	10.9 ±3.4[b]	(R. M. de Ferrars, Cassidy et al., 2014)
	2,3-dihydroxybenzoic acid	12024 ± 4055	2.0 ± 0.6	(Feliciano et al., 2017)
	2,4-dihydroxybenzoic acid	5450	4.5	(Zhang & Zuo, 2004)
	2,5-dihydroxybenzoic acid	1459 ± 622	5.6 ± 0.8	(Feliciano et al., 2017)
	2,6-dihydroxybenzoic acid	26 ± 7[b]	2[b]	(Loke et al., 2009) [e]
	2,3-dimethoxybenzoic acid	3834 ± 3399[b]	2[b]	(Loke et al., 2009) [e]
	2,6-dimethoxybenzoic acid	1062 ± 902[b]	2[b]	(Loke et al., 2009) [e]
	2-hydroxy-4-methoxybenzoic acid	1 ± 0.07[b]	2[b]	(Rachel M. de Ferrars, Czank et al., 2014)
	3,4-dihydroxybenzoic acid	16000	1	(Keane et al., 2015)
	3,4-dihydroxybenzoic acid-sulfate	1055 ± 972[d]	4	(Pimpão et al., 2015)
	3-hydroxybenzoic acid-4-glucuronide	68 ± 61[b]	3.8 ± 0.8[b]	(R. M. de Ferrars, Cassidy et al., 2014)
	4-hydroxybenzoic acid-3-sulfate	408.5 ± 68.7	2.1 ± 0.3	(Castello et al., 2018)
	4-hydroxybenzoic acid-3-glucuronide	3.1 ± 0.6 15 ± 1.75[b]	3.0 ± 0.8 2[b]	(Castello et al., 2018) (Rachel M. de Ferrars, Czank et al., 2014)
	3-hydroxy-4-methoxybenzoic acid	447 ± 58 650 ± 510[b]	2 2[b]	(R. Feliciano, Istas et al., 2016) (Loke et al., 2009) [e]
	4-methoxybenzoic acid-3-glucuronide	48.6 ± 3.2	1.4 ± 0.1	(Zhong et al., 2017)
	4-hydroxy-3-methoxybenzoic acid	11877 ± 0.21	0.7 ± 0.3	(McKay et al., 2015)
	3-methoxybenzoic acid-4-sulfate	1576 ± 368	1.3 ± 0.3	(Feliciano et al., 2017)
	3-methoxybenzoic acid-4-glucuronide	169.2 ± 17.9	1.4 ± 0.3	(Zhong et al., 2017)
	3,4-dimethoxybenzoic acid	202 ± 193[b]	2[b]	(Loke et al., 2009) [e]
	3,5-dihydroxybenzoic acid	400 ± 268[b]	2[b]	(Loke et al., 2009) [e]
	3,5-dimethoxybenzoic acid	512 ± 247[b]	2[b]	(Loke et al., 2009) [e]
	3,4,5-trihydroxybenzoic acid	124 ± 31.9 1200 ± 1000[b]	3.8 ± 0.7 1.3 ± 0.5[b]	(Castello et al., 2018) (van der Pijl et al., 2015)
	1,2,4-trihydroxybenzoic acid	159 ± 115[b]	2[b]	(Loke et al., 2009) [e]
	1,3,5-trihydroxybenzoic acid	138 ± 91[b]	0[b]	(Loke et al., 2009) [e]
	3,4-dihydroxy-5-methoxybenzoic acid	79 ± 25	1.0 ± 00	(Mueller et al., 2017)
	3,5-dihydroxy-4-methoxybenzoic acid	300 ±138 1300 ± 800[b]	2 1.7 ± 0.5[b]	(Pimpão et al., 2015) (Loke et al., 2009) [e]
	4-hydroxy-3,5-dimethoxybenzoic acid	777 ± 182	1.0 ± 00	(Mueller et al., 2017)
	4-methoxy-3-hydroxybenzoic acid-5-sulfate	2028 ± 1095	2	(Pimpão et al., 2015)
	3-hydroxy-4,5-dimethoxybenzoic acid	77 ± 62[b]	2[b]	(Loke et al., 2009) [e]

(Continues)

TABLE 2 (Continued)

Class	LMW metabolite	C_{max}(nM)	T_{max}(h)	Reference
	2,3,4-trihydroxybenzoic acid	91 ± 88[b]	2[b]	(Loke et al., 2009) [e]
	2,4,5-trimethoxybenzoic acid	351 ± 346[b]	2	(Loke et al., 2009)
Phenylacetic acids	phenylacetic acid	10349 ± 3761 20320 ±1200[a] 80360 ± 24113[b]	5.7 ± 2.4 0[a] 2[b]	(Feliciano et al., 2017) (Urpi-Sarda et al., 2009) (Loke et al., 2009) [e]
	2′-hydroxyphenylacetic acid	2281 ± 2091[b]	2[b]	(Loke et al., 2009)
	2′-methoxyphenylacetic acid	15267 ± 12817[b]	2[b]	(Loke et al., 2009)
	3′-hydroxyphenylacetic acid	689 ± 246 2318 ± 2231[b]	7.6 ± 2.2 2[b]	(Feliciano et al., 2017) (Loke et al., 2009) [e]
	3′-methoxyphenylacetic acid	84649 ± 76184[b]	2[b]	(Loke et al., 2009)
	4′-hydroxyphenylacetic acid	2606 ± 1407	2.7 ± 0.5	(Feliciano et al., 2017)
	3′,4′-dihydroxyphenylacetic acid	476 ± 138 4170 ± 2600[a]	7.3 ± 2.3 –	(Feliciano, Istas et al., 2016)
	4′-hydroxy-3′-methoxyphenylacetic acid	1756 ± 1003	15.6 ± 3.4	(Feliciano et al., 2017)
	3′-methoxy-4′-hydroxyphenylacetic acid	199 ± 192[a]	0[a]	(Henning et al., 2013) [e]
	3′-methoxyphenylacetic acid-4′-sulfate	52 ±15	1.2 ± 0.4	(Feliciano et al., 2017)
	3′,4′-dimethoxyphenylacetic acid	2613 ± 2137[b]	2[b]	(Loke et al., 2009)
	3′,4′,5′-trimethoxyphenylacetic acid	292 ± 248	2[b]	(Loke et al., 2009)
Cinnamic acids	cinnamic acid	370 ± 60	1.3 ± 0.4	(Azzini et al., 2010)
	2′-hydroxycinnamic acid	6 ± 1 3528 ± 3295[b]	1.2 ± 0.3 2[b]	(Feliciano, Istas et al., 2016) (Loke et al., 2009) [e]
	3′-hydroxycinnamic acid	29 ± 14 881 ± 878[b]	3.2 ±0.8 2[b]	(Feliciano, Istas et al., 2016) (Loke et al., 2009) [e]
	4′-hydroxycinnamic acid	131 ± 51 940 ± 897[b]	1.0 ± 0.0 2[b]	(Feliciano, Istas et al., 2016) (Loke et al., 2009) [e]
	4′-methoxycinnamic acid	2941 ± 2612[b]	2[b]	(Loke et al., 2009)
	3′,4′-dihydroxycinnamic acid	178 ± 53 3915 ± 2695[b]	0.5 ± 0.2 –	(Stalmach et al., 2012) (Loke et al., 2009) [e]
	4′-hydroxycinnamic acid-3′-sulfate	181 ± 127	1	(Pimpão et al., 2015)
	4′-hydroxycinnamic acid-3′-glucuronide	45 ± 11 4 ± 3[a]	2.7 ± 0.7 –	(Feliciano et al., 2017) (R. Feliciano, Istas et al., 2016)
	3′-hydroxycinnamic acid-4′-sulfate	10 ± 3	17 ± 4	(Scherbl et al., 2016)
	3′-hydroxycinnamic acid-4′-glucuronide	119 ±15	4.8 ± 2.6	(Feliciano et al., 2017)
	3′-Hydroxy-4′-methoxycinnamic acid	7545 ± 3462	14.4 ± 3.8	(Feliciano et al., 2017)
	4′-Methoxycinnamic acid-3′-glucuronide	555 ± 120	3.7 ± 2.5	(Feliciano et al., 2017)
	4′-methoxycinnamic acid-3′-sulfate	76 ± 14	5.6 ± 2.4	(Feliciano et al., 2017)
	4′-Hydroxy-3′-methoxycinnamic acid	416 ± 67 940 ± 370[b]	0.75 11.29 ± 4.2[b]	(Lang et al., 2013) (Czank et al., 2013)

(Continues)

TABLE 2 (Continued)

Class	LMW metabolite	C_{max}(nM)	T_{max}(h)	Reference
	3′-methoxycinnamic acid-4′-sulfate	4865 ± 1508	1.4 ± 0.3	(Feliciano et al., 2017)
	3′-methoxycinnamic acid-4′-glucuronide	364 ± 46	12.2 ± 3.7	(Feliciano et al., 2017)
	3′, 4′-dimethoxycinnamic acid	61 ± 24 647 ± 43[b]	17 ± 5 2[b]	(Scherbl et al., 2016) (Loke et al., 2009) [e]
	4′-hydroxy-3′,5′-dimethoxycinnamic acid	6690	4.5	(Zhang & Zuo, 2004)
	3′,5′-dimethoxycinnamic acid	630 ± 4[b]	2[b]	(Loke et al., 2009)
Phenylpropanoic acids	3-(phenyl)propanoic acid	19 ± 12 1500 ± 1000[b]	6.8 ± 0.1 –	(Pereira-Caro et al., 2020) (van der Pijl et al., 2015)
	3-(2′-methoxyphenyl)propanoic acid	355 ± 307[b]	2[b]	(Loke et al., 2009)
	3-(3′-hydroxyphenyl)propanoic acid	355 ± 57 775 ± 747[b]	5.8 ± 0.5 2[b]	(Stalmach et al., 2012) (Loke et al., 2009) [e]
	3-(3′-methoxyphenyl)propanoic acid	422 ± 274[b]	2[b]	(Loke et al., 2009)
	3-(4′-Hydroxyphenyl)propanoic acid	390606 ± 270423	11.0 ± 3.4	(Feliciano et al., 2017)
	3-(4′-methoxyphenyl)propanoic acid	3827 ± 3463[b]	2[b]	(Loke et al., 2009)
	3-(3′,4′-dihydroxyphenyl)propanoic acid	188 ± 104 200 ± 40[a] 5000 ± 5000[b]	2.6 ± 0.4 0[a] –	(Feliciano et al., 2017) (Urpi-Sarda et al., 2009) (van der Pijl et al., 2015) [e]
	3-(3′,4′-dihydroxyphenyl)propanoic acid-sulfate	678 ± 574[d]	8[d]	(Lang et al., 2013)
	3-(4′-hydroxyphenyl)propanoic acid-3′-sulfate	2181 ± 880	2.8 ± 0.5	(Feliciano et al., 2017)
	3-(4′-hydroxyphenyl)propanoic acid-3′-glucuronide	110 ±13	6.9 ± 0.4	(Feliciano et al., 2017)
	3-(3′-hydroxyphenyl)propanoic acid-4-sulfate	42 ± 9[d]	4.4 ± 0.7	(Stalmach et al., 2012)
	3-(3′-methoxyphenyl)propanoic acid-4′-glucuronide	581 ± 469	9.9 ± 2.8	(Feliciano et al., 2017)
	3-(4′-hydroxy-3′-methoxyphenyl)propanoic acid	878 ± 635 6127 ± 4700[b]	8[d] 2 [b]	(Lang et al., 2013) (Loke et al., 2009) [e]
	3-(3′-Methoxyphenyl)propanoic acid-4′-sulfate	197 ± 96	1.9 ± 0.6	(Feliciano et al., 2017)
	3-(3′-Methoxyphenyl)propanoic acid-4′-glucuronide	581 ± 469	9.9 ± 2.8	(Feliciano et al., 2017)
	3-(3′-hydroxy-4′-methoxyphenyl)propanoic acid	1941 ± 348	–	(R. Feliciano, Istas et al., 2016)
	3-(4′-Methoxyphenyl)propanoic acid-3′-sulfate	149 ± 35	2.8 ± 0.6	(Feliciano et al., 2017)
	3-(4′-Methoxyphenyl)propanoic acid-3′-glucuronide	69 ± 42	9.3 ± 3.7	(Feliciano et al., 2017)
	3-(4′-hydroxy-3′,5′-dimethoxyphenyl)propanoic acid	281 ± 130[b]	2[b]	(Loke et al., 2009) [e]
	3-(3′,4′,5′-trimethoxyphenyl)propanoic acid	69 ± 34[b]	2[b]	(Loke et al., 2009)

(Continues)

TABLE 2 (Continued)

Class	LMW metabolite	C_{max}(nM)	T_{max}(h)	Reference
Hippuric acids	hippuric acid	90567 ± 40359	8.9 ± 2.9	(Feliciano et al., 2017)
	2′-hydroxyhippuric acid	202 ± 192	5.6 ± 0.4	(Feliciano et al., 2017)
	3′-hydroxyhippuric acid	320 ± 84 708 ± 159[a]	2 0[a]	(R. Feliciano, Istas et al., 2016) (R. Feliciano, Istas et al., 2016)
	4′-hydroxyhippuric acid	860 ± 288 3440 ± 3010[a]	– 0.9 ± 0.5[a]	(Feliciano et al., 2017) (Prymont-Przyminska et al., 2014)
	α-hydroxyhippuric acid	4991 ± 1101	1.4 ± 0.3	(Feliciano et al., 2017)
5-(phenyl)-γ-valerolactones	5-(phenyl)-γ-valerolactone-3′-sulfate	69.2 ± 25.2 0.3 ± 0.2[b]	11.0 ± 0.9 5[b]	(Castello et al., 2018) (Bresciani et al., 2017)
	5-phenyl-γ-valerolactone-3′-glucuronide	88.4 ± 44.7	9.1 ± 2.5	(Castello et al., 2018)
	5-(3′,4′-dihydroxyphenyl)-γ-valerolactone	230.54 480 ± 90[a] 300 ± 300[b]	5 0[a] 8[b]	(Li et al., 2000) (Urpi-Sarda et al., 2009) (Wiese et al., 2015) [e]
	5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone	75.82	8	(Li et al., 2000)
	5-(3′-Hydroxyphenyl)-γ-valerolactone-4′-glucuronide	268.4 ± 68.2	5.3 ± 0.6	(Castello et al., 2018)
	5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate	31 ± 10 67 ± 25[a]	2 2[a]	(R. Feliciano, Istas et al., 2016) (R. Feliciano, Istas et al., 2016)
	5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-glucuronide	1171.2 ± 242.7	5.2 ± 0.6	(Castello et al., 2018)
	5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-sulfate	272 ± 56[b]	6.4 ± 1.0[b]	(Ottaviani et al., 2016)
	5-(3′-methoxyphenyl)-γ-valerolactone-4′-glucuronide	36.77 ± 6.12[a]	–	(Urpi-Sarda et al., 2009)
4-hydroxy-5-(phenyl)valeric acids	4-hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid	4 ± 3[b]	7 ± 3[b]	(Wiese et al., 2015) [e]
	4-hydroxy-5-(3′-hydroxyphenyl)valeric acid-4′-glucuronide	56 ± 9	5.9 ± 0.6	(Ottaviani et al., 2016)
5-(phenyl)valeric acids	5-(3′-hydroxyphenyl)valeric acid-4′-glucuronide	54 ± 14	4.9 ± 1.3	(Ottaviani et al., 2016)
3-hydroxy-3-(phenyl) propanoic acids	3-hydroxy-3-(3′-hydroxy-4′-methoxyphenyl)propanoic acid	20 ± 2	7.5 ± 0.1	(Pereira-Caro et al., 2020)
	3-hydroxy-3-(3′-hydroxyphenyl)propanoic acid	628 ± 18	3.5 ± 0.2	(Pereira-Caro et al., 2020)
2-(phenyl) propanoic acids	2-(4′-hydroxyphenyl)propanoic acid	4 ± 1 393 ± 339[b]	– 2[b]	(R. Feliciano, Istas et al., 2016) (Loke et al., 2009) [e]
Cinnamoyl glycine	4′-hydroxy-3′-methoxycinnamoyl glycine (feruloyl glycine)	66 ± 29 5 ± 3[b]	8 2[b]	(Lang et al., 2013) (Bresciani et al., 2017)

(Continues)

TABLE 2 (Continued)

Class	LMW metabolite	C_{max}(nM)	T_{max}(h)	Reference
	cinnamoyl glycine[c]	–	–	(Bacurau et al., 2013)
4-ethylbenzenes	4-ethylbenzoic acid	4676 ± 3258[b]	2[b]	(Loke et al., 2009)
	4-ethylphenol	2200 ± 626[b]	–	(Loke et al., 2009) [e]
2-(phenyl)ethanol	2-(4′-hydroxyphenyl)ethanol	186.96 ± 93.80	0.58 ± 0.26	(de la Torre et al., 2003) [e]
	2-(4′-hydroxy-3′-methoxyphenyl)ethanol	25.56 ± 13.86	0.88 ± 0.54	(de la Torre et al., 2003) [e]
	2-(3′,4′-dihydroxyphenyl)ethanol-glucuronide	65 ± 5[d]		(Suárez et al., 2009)
	2-(3′,4′-dihydroxyphenyl)ethanol-sulfate	480 ± 200		(Suárez et al., 2009)

Values are shown as the mean ± SD.
[a]Information from multiple dose dietary intervention studies (more details of these studies can be found in the Supplementary Table 3).
[b]Information from intervention studies using capsules, or mixture or isolated flavonoids (more details of these studies can be found in Supplementary Table 4).
[c]Detected not quantified.
[d]Two isomers could be present.
[e]This study uses sulfatase and/or β-glucuronidase that may affect the quantification of this metabolite.

to trace the catabolism of this anthocyanin into LMW phenolic metabolites and their conversion over time, eliminating confounding factors and interfering molecules and in particular endogenous sources (Czank et al., 2013). Likewise, using (2-^{14}C-epicatechin), it was possible to follow the generation of the specific LMW phenolic metabolites of flavan-3-ols such as 5-(phenyl)-γ-valerolactones and 5-(phenyl)valeric acids (Ottaviani et al., 2016). Across these studies, 90 LMW phenolic metabolites have been to date quantified (Figure 4d, Supplementary Table 7).

From all the listed LMW phenolic metabolites some of them were identified and quantified in a small number of participants. This might result from interindividual differences or metabolism of some drugs, for example, aspirin or chemical pollutants. Nonetheless, we have reported these metabolites as they still have physiological relevance.

Due to the diversity of the food sources or otherwise matrixes used, microbiota composition and other factors contributing to interindividual variability, the C_{max} and T_{max} present significant discrepancies between studies. Moreover, it would not be possible to perform a critic and in-depth comparison among studies due to the lack of uniformity in studies performing blood collections immediately after ingestion (e.g., blood collection within the first 8h) compared with those in which the sample collection was performed from time zero up until 24–48 h post-ingestion. This is especially true since most studies did not perform sample collection after 8 h. This variability is very clear with 4′-hydroxyphenylacetic acid, one of such molecules with a wide range of reported T_{max} values, ranging from 0.75 to 13.8 ± 4.0 h (Supplementary Table 8) (R. P. Feliciano, A. Boeres, et al., 2016; Zhang & Zuo, 2004). Such variability can be further noted in the case of LMW phenolic metabolites originating not only from gut microbiota metabolism. For instance, the 4-hydroxy-3-methoxycinnamic acid is present in dietary sources (e.g., tea and coffee) but also produced by gut microbiota (Czank et al., 2013; Neveu et al., 2010; Rothwell et al., 2013). As a result, this metabolite has a bimodal absorption, with two different local maximal C_{max} and T_{max} being observable (R. M. de Ferrars, Cassidy, et al., 2014), and the metabolite has T_{max} ranging from 0.6 ± 0.3 h to 9.0 ± 3.8 h (Feliciano et al., 2017; McKay et al., 2015).

The circulation time, that is, detection time is an important physiological measure that corresponds to the period of time during which the metabolite could be detected and quantified in circulation after the ingestion of (poly)phenol-rich foods/supplements. We have reported circulation time as the factual timepoints where a particular LMW phenolic metabolite has been detected in a blood sample in contrast to predicted half-lives.

Circulation time for a given LMW phenolic metabolite in human circulation may be affected by the pathways leading to their appearance in circulation. At least three different pathways are proposed: (i) LMW phenolic metabolites that are largely present in the food matrix with little to no contribution of gut microbiota; (ii) LMW phenolic metabolites that come from both the matrix and gut microbiota catabolism, and (iii) LMW phenolic metabolites that are originated from gut microbiota processes only. In general, the majority of LMW phenolic metabolites appear in circulation immediately after ingestion up until 2 h post-ingestion (Figure 4e, Supplementary Table 8). This suggests that many LMW phenolic metabolites may be mainly present in the food matrix and result from direct absorption rather than from gut microbiota fermentation processes (Supplementary Table 8). Nonetheless, after the initial 2 h, the mix of matrix and gut

FIGURE 4 Pool of low molecular weight (LMW) phenolic metabolites identified and quantified in human circulation. (**a**) Class distribution of the 137 LMW phenolic metabolites found and quantified in human blood across intervention studies (Table 2 and Supplementary Tables 5, 6 and 7). (**b**) Class distribution of the 99 LMW phenolic metabolites after single administration dietary intervention studies (Supplementary Table 5). (**c**) Class distribution of the 60 LMW phenolic metabolites after multiple dose dietary intervention studies (Supplementary Table 6). (**d**) Class distribution of the 90 LMW phenolic metabolites identified in human circulation after extract or pure flavonoid supplementation (Supplementary Table 7). (**e**) Class distribution of LMW phenolic metabolites over circulation time (Supplementary Table 8)

microbiota starts as seen for example for 3,4-dihydroxybenzoic acid present in the matrix of several foods (Rothwell et al., 2013) and from gut microbiota catabolism of flavonoids (de Ferrars, Cassidy, et al., 2014). Another example is the before-mentioned biphasic LMW phenolic metabolite 4-hydroxy-3-methoxycinnamic acid. On the other hand, LMW phenolic metabolites not present in the matrix and known to appear only from gut microbiota like 5-(phenyl)valeric acids tend to emerge after the initial 2 h (e.g., 2 to 12 h, Supplementary Table 8). Over time, from 8 up to 24/48 h, the diversity of the circulating metabolite pool decreases, possibly due to the metabolic convergence resulting from progressive cleavage into common LMW phenolic metabolites. Interestingly, due to this convergency process, certain LMW phenolic metabolite classes (e.g., benzenes, benzoic acids, and hippuric acids) can stay in circulation for extended periods of time, exceeding 24 h (Figure 4e, Supplementary Table 8).

It is important to note that longer periods such as 24 or 48 h imply multiple meals, and these may affect the data on circulation time. Most intervention studies prepare and report the use of (poly)phenol free meals given to volunteers to address this issue. Studies with isotopically labeled molecules have also confirmed these observations. Albeit hippuric acids are widely recognized as biomarkers of (poly)phenol consumption (Bøhn et al., 2021; Yuan et al., 2022), they are also produced from endogenous pathways, that is, phenylalanine metabolic pathway (Zhang et al., 2021). This may lead to their continuous production in humans and the fact that it is present in longer timepoints. As such without using isotopically labeled molecules, we might be overestimating the circulation time of hippuric acid (among others) due to consumption of (poly)phenol rich foods.

As stated above, intervention studies employ a variety of different strategies (e.g., food source or matrix, prior recommendations/procedures before intervention, blood collection time, samples treatments, quantification methods), a direct comparison between concentrations across studies cannot be performed. Nonetheless, the identification of the most relevant metabolites based on peak concentrations across studies can be of immense value. Overall, the 137 phenolic metabolites identified across all intervention studies were found at concentrations ranging from 1 nM to 390.61 ± 270.42 μM (in the case of 3-(4′-hydroxyphenyl)propanoic acid)) (Feliciano et al., 2017). Most metabolites displayed a C_{max} below 0.1 μM (Figure 5a) and specific metabolite classes such 2-(phenyl)ethanols could only be observed under 0.5 μM for all their representative metabolites. Notably, the number of metabolites is progressively smaller for concentrations from 0.1 to 4.99 μM, but the numbers increase thereafter, with 24 phenolic metabolites found in circulation with C_{max} > 10 μM and 12 phenolic metabolites found with C_{max} > 20 μM: phenol-2-sulfate, 3,4-dihydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 3-methoxybenzaldehyde-4-sulfate, benzoic acid, 4-hydroxybenzoic acid, 4-methoxybenzoic acid, 3,4-dihydroxybenzoic acid, phenylacetic acid, 3′-methoxyphenylacetic acid, 3-(4′-hydroxyphenyl)propanoic acid, and hippuric acid (Figure 5a, Table 2). More than half of the phenolic metabolites were found with C_{max} > 0.5 μM (Figure 5a) and 55 phenolic metabolites (~40%) were found in human circulation with C_{max} > 1 μM. Intriguingly, hippuric acids, benzenes, benzoic acids, phenylacetic acids, and phenylpropanoic acids are the most representative classes of phenolic metabolites, with human circulation maximum concentrations > 10 μM (Figure 5a).

In single dose dietary intervention studies, the majority of the 99 phenolic metabolites identified were found to display a C_{max} < 0.1 μM. In turn, 42 phenolic metabolites were found in circulation with C_{max} above 0.50 μM and 33 displayed C_{max} > 1 μM. Furthermore, 5 metabolites from 5 different classes were found in concentrations > 20 μM (Figure 5b, Table 2): phenol-2-sulfate, 3-methoxybenzaldehyde-4-sulfate, benzoic acid, 3-(4′-hydroxyphenyl)propanoic acid, and hippuric acid. Regarding multiple dose intervention studies, 38 of the 60 phenolic metabolites quantified (> 50%) were found with C_{max} > 0.1 μM. However, only 17 (~28%) were found at concentrations above 0.5 μM. Furthermore, only phenylacetic acid and hippuric acid were found in concentrations > 20 μM (Figure 5c, Table 2) . Here, only for 8 phenolic metabolites, higher peak concentrations were achieved compared to single dose administrations: 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, phenylacetic acid, 3′,4′-dihydroxyphenylacetic acid, 3-(3′,4′-dihydroxyphenyl)propanoic acid, 3′-hydroxyhippuric acid, 4′-hydroxyhippuric acid, and 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate. Notably, when comparing single vs. multiple (daily for 1 month) dietary interventions using the same matrix and cohort, Feliciano and colleagues have shown a significant increase in 8 out of 56 metabolites (benzoic acid, 2,5-dihydroxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, phenol-2-sulfate, hippuric acid, 3′-hydroxyhippuric acid, 4′-hydroxyphenylpropanoic acid-3′-sulfate, 4-methoxycinnamic acid-3-glucuronide) (R. Feliciano, Istas, et al., 2016). In turn, in intervention studies employing plant extracts of pure flavonoids, 40 out of 90 metabolites display a C_{max} > 1 μM (Figure 5d, Supplementary Table 7). In this type of intervention, 8 phenolic metabolites could be identified in concentrations > 20 μM: 3,4-dihydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, benzoic acid, 4-hydroxybenzoic acid, 4-methoxybenzoic acid, phenylacetic acid, 3′-methoxyphenylacetic acid, and 3-(phenyl)propanoic acid. Interestingly from a food safety, supplementation, and drug development perspective, even though these studies have employed flavonoid doses much higher than those normally obtained from diet alone, leading to higher concentrations of LMW phenolic metabolites, as example 3-(4′-hydroxy-3′-methoxyphenyl)propanoic acid that could reach a blood concentration level 11-fold higher than otherwise obtained with dietary interventions (Loke et al., 2009), no signs of toxicity have been reported in any of the revised publications. Here, it should also be mentioned that in the study of Loke et al., the LMW phenolic metabolites were quantified after enzymatic hydrolysis, which undoubtedly leads to an overestimation of the metabolite in question.

Overall, C_{max} values can be significantly biased by a variety of different confounding factors (Supplementary

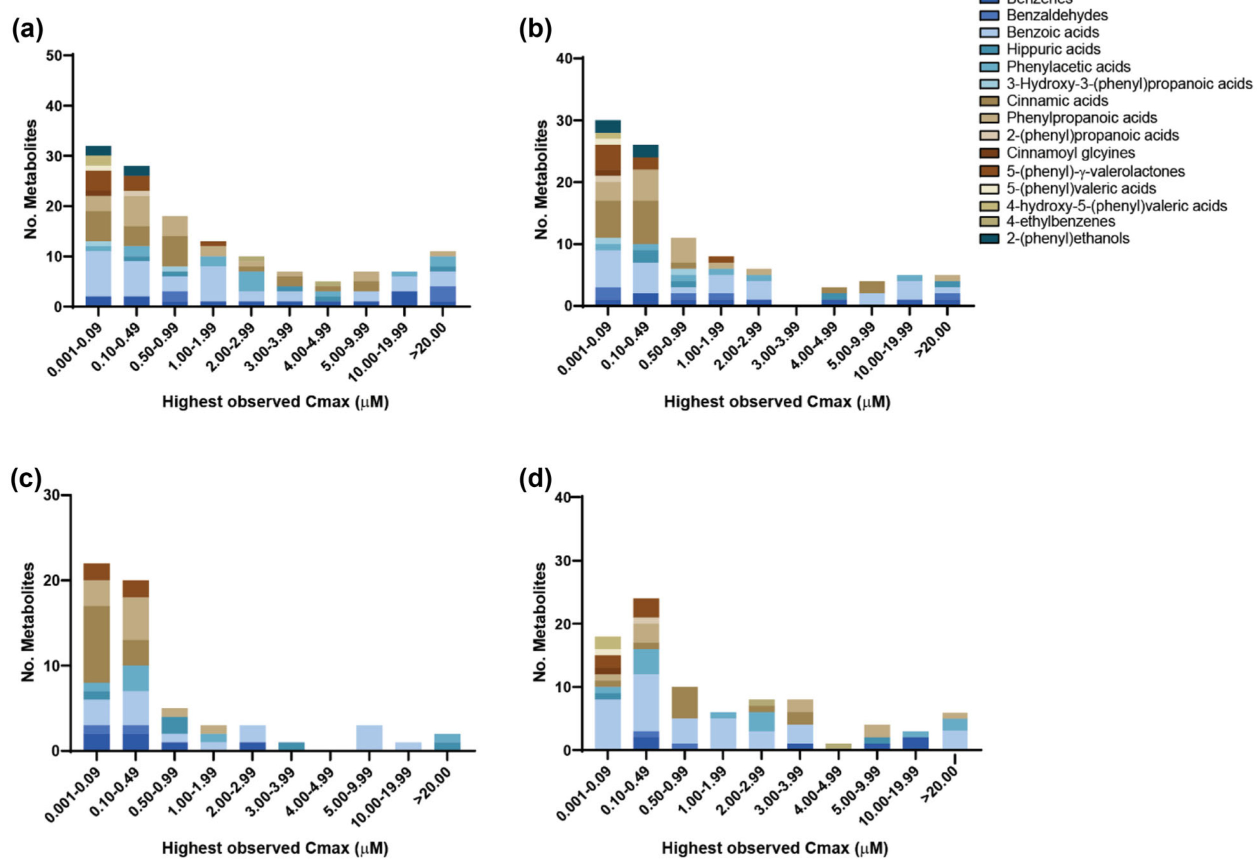

FIGURE 5 A total of 137 low molecular weight (LMW) phenolic metabolites have been detected and quantified in human circulation, ranging from 0.001 μM to 390.61 μM. The number of phenolic metabolites grouped by C_{max} depends on the design of the intervention study. (a) C_{max} ranges for the 138 LMW phenolic metabolites quantified across all intervention studies (Table 2) (b) C_{max} ranges for phenolic metabolites quantified in single dose dietary intervention studies (Supplementary Table 5) (c) C_{max} ranges for the phenolic metabolites quantified in multiple dose dietary intervention studies (Supplementary Table 6) (d) C_{max} ranges for the phenolic metabolites quantified using extract or purified flavonoids administrated via capsules or similar formulations (Supplementary Table 7)

Tables 2, 3 and 4). These include differences in study design, dietary intervention, sample treatment, and intrinsic interindividual variability (e.g., genetics, microbiota composition, dietary regiments, sex, and age) (Almeida et al., 2018; Manach et al., 2017). One major gap identified is the lack of a study comparing C_{max} on individuals with different dietary regiments, for example, vegans, vegetarians, intensive meat eaters, among others. As an example of the dispersion, the reported C_{max} for 2-hydroxybenzoic acid (salicylic acid) varied from 51 nM, using three pieces of blueberry bun (Rodriguez-Mateos et al., 2014), to 7.65 μM using 1.8 L of 27% concentrated cranberry juice (Zhang & Zuo, 2004). The plasma C_{max} is a key pharmacokinetic parameter and necessary to unlock the translation between models and clinical/ non-clinical applications (Liston & Davis, 2017). Nonetheless, another crucial factor to consider when translating from in vivo settings to in vitro models should be the concentration around which the compound consistently can stay in the body (steady-state concentration). Although there is one study describing the steady-state pharmacokinetics for other phenolic compounds (namely resveratrol) twice daily (la Porte et al., 2010), the same was not found for LMW phenolic metabolites. Since multiple dietary sources reflect a regular consumption of (poly)phenols and specifically flavonoids and chlorogenic acids leading to LMW phenolic metabolites in circulation, further studies evaluating steady-state concentration should be addressed. This is especially true since LMW phenolic metabolites remain for hours/days in the body, and probably will appear at higher and more sustained concentrations. Such variability in C_{max} under controlled settings makes it challenging to draw general conclusions about what might be physiological relevant, but such variability is also more likely to reflect real-world scenarios.

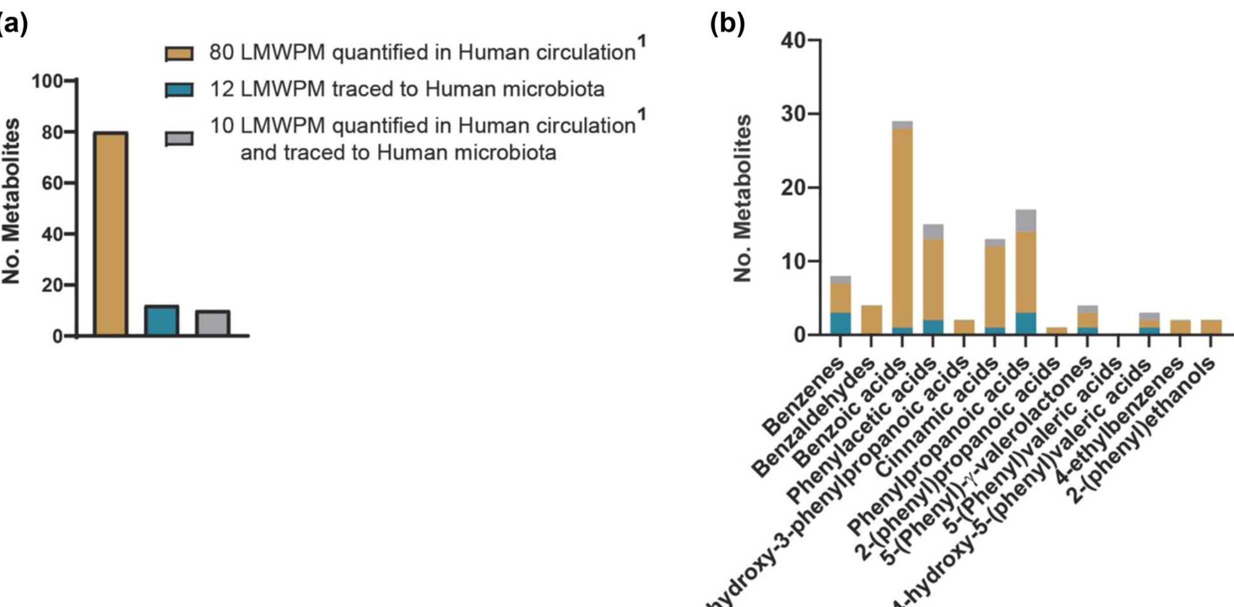

FIGURE 6 The large majority of LMW phenolic metabolites quantified in human circulation have not been traced back to the human microbiota. (a) From the 80 LMW phenolic metabolites quantified in human circulation, only 10 have been traced back to known human microbiota. (b) Number of LMW phenolic metabolites grouped by LMW phenolic metabolite class: quantified in human circulation; traced back to human microbiota; or traced back to human microbiota and quantified in human circulation. [1]The list of confirmed and predicted gut microbiota phenolic metabolites excludes phase II conjugates (i.e., sulfate, glucuronide, and glycine conjugates, as shown Supplementary Table 9)

6 | MISSING KNOWLEDGE ON (POLY)PHENOL METABOLISM BY HUMAN MICROBIOTA

Having identified the LMW phenolic metabolites present in human circulation, it is possible to compare with the LMW phenolic metabolites of confirmed human microbiota origin. However, it should be noted that the 137 phenolic metabolites detected in human circulation include phase II conjugates (i.e., sulfate, glucuronide, and glycine conjugates) that are not expected to be produced by microbiota directly. As such, these blood circulating phase II conjugates have been excluded from the list of predicted microbiota-produced LMW phenolic metabolites (Supplementary Table 9). This list includes a total of 80 LMW phenolic metabolites meaning nearly 58% of all LMW phenolic metabolites might be produced by human microbiota (Figure 6a). Yet, from the list of 80 metabolites, only 10 have been linked to a specific human microbiota species (Figure 6a) although 12 LMW phenolic metabolites have been associated to microbiota, meaning 2 LMW phenolic metabolites have been produced by microbiota but not detected in circulationa that is, the benzenes benzene-1,3,5-triol and benzene-1,3-diol (see Tables 1, 2 and Figure 6a). In addition, benzoic acids was the class with the highest number (26) of LMW phenolic metabolites of unknown bacterial origin (Figure 6b). Noteworthy 16 of the 80 LMW phenolic metabolites were detected only in the first 2 h after the intervention and for that reason it is possible, but not proven, that these 16 LMW phenolic metabolites may be present only in food and not produced by microbiota. These cases have been noted in supplementary table 9.

Analyzing by phenolic classes, some classes were excluded since they are produced exclusively from phase II conjugation, that is, hippuric acids and cinnamoyl glycine derived from glycine conjugation of benzoic acids and cinnamic acids, respectively. The metabolite class 5-(phenyl)valeric acid has no representative LMW phenolic metabolites, since only phase II conjugates were found in circulation (Figure 6b). Benzaldehydes, 3-hydroxy-3-(phenyl)propanoic acid, 2-(phenyl)propanoic acid, 2-(phenoxy)propanoic acid, 4-ethylbenzene, and 2-(phenyl)ethanol were detected and quantified in human circulation but have not yet been associated with any specific human gut microbiota. Importantly, some LMW phenolic metabolites might be present only in the matrix and not generated from microbiota fermentation. Bacteria present in saliva, the stomach, and duodenum are largely mis-represented and should also be focused in future works. Furthermore, the role of fungi, archaea, and protozoa is still largely unknown. All these factors may account

for an unknown number of molecules and additional studies addressing the LMW phenolic metabolites produced and producers should be performed in the future.

7 | OVERVIEW OF THE PATHWAYS GENERATING THE LMW PHENOLIC METABOLITES

The pharmacokinetics of the 137 LMW phenolic metabolites unveils certain gaps in knowledge regarding their production. An overall tendency of convergence into smaller and common metabolites over time is a trend observed in (poly)phenol metabolism across studies. Certain metabolites (e.g., benzenes, benzoic acids, and hippuric acids) tend to appear at higher concentrations and might have higher potential to modulate (patho)physiological processes at the organismal level (Carregosa et al., 2019; Ottaviani et al., 2016). In parallel, many of the LMW phenolic metabolite classes displayed in Figure 7 can undergo phase I metabolism or phase II conjugation with sulfate, glucuronide, or glycine. Hippuric acid, the glycine conjugate of benzoic acid, is the most predominant form of phase II conjugation reaching concentrations above 50 μM. Interestingly, sodium benzoate (benzoic acid) has been used to treat urea cycle disorders as alternative means to excrete urea via the production of hippuric acid (Häberle et al., 2012). Although LMW phenolic metabolites can be produced by endogenous pathways, the high levels of hippuric acid achieved with these intervention studies suggest that a dietary regimen might help patients with this disorder.

Regarding excretion, LMW phenolic metabolites tend to be expeled in urine and feces, but isotopic labeling reveals that certain metabolites can also be excreted as CO_2 (Czank et al., 2013). Here, further evidence on the intermediate conversion of metabolites into SCFAs is required but of extreme relevance, as the confirmation thereof would significantly expand on the ubiquitous roles of LMW phenolic metabolites.

8 | LIMITATIONS AND FUTURE DIRECTIONS

Overall, only 13 gut-microbiota bacterial species from human fecal samples have been identified to produce LMW phenolic metabolites from dietary (poly)phenols. The number of different bacterial species identified is surprisingly low and understudied deserving more attention. Here, it should be noted that many gut bacteria are not culturable, which hinders their comprehensive study. Nevertheless, with an increase in large culture collections, it should become easy to achieve this goal in the future. The characterization of microbiota species could be furthered by the investigation of the enzymes mapped to already-known microbiota species and their metabolism of phenolic compounds. With this in mind, genetic and bioinformatic tools ought to provide robust pipelines to study such bacterial species (Goris et al., 2021). Nonetheless, bioinformatic tools will also require confirmation by in vitro studies dissecting molecular mechanisms of the involved enzymes yet to be identified. Metatranscriptomics, metaproteomics, and metabolomic advancements will also be crucial to characterize the profile of the human gut microbiome, but these also introduce some noise and thus should be performed by experienced researchers in this area to filter unreliable data and avoid misidentifications (Figure 8).

In the meantime, correlation studies on LMW phenolic metabolites and microbiota composition are likely to expand. We are now increasingly aware of how the microbiota composition changes as a function of (poly)phenol composition of the diet (Boto-Ordóñez et al., 2014; Lordan et al., 2019; Tzounis et al., 2011). However, interindividual variability and metabotype significantly modulate the diet effect (Iglesias-Aguirre et al., 2021). Similar research paths have been pursued in animal studies using (poly)phenol-enriched diets (Gomes et al., 2019), and bacteria isolates from rodent feces have been used to identify putative bacterial strains (Takagaki et al., 2014). Nevertheless, some caution should be made when comparing human metabolism to other mammals. Studies comparing the production of structure-related epicatechin metabolites have shown some significant species-dependent differences between humans and rats and to a lesser extent to mice (Ottaviani et al., 2016). For this reason, validation in human isolates should always be performed (Figure 8).

Even though 137 LMW phenolic metabolites have been quantified in human circulation, many others have been known or predicted but not identified in any of these studies including phase II conjugates such as phenylacetyl glycine or glutamic acid conjugates, acetylcysteine or carnitine conjugates, and phenolic classes such as 2-hydroxy-2-phenylpropanoic acids and 2-phenylpropanoic acids (Djoumbou-Feunang et al., 2019). Furthermore 4-(phenyl)butyric acid has been observed after flavonoid incubation (i.e., epigallocatechin-3-gallate) in human fecal fermentation (Liu et al., 2020), but have not been detected or quantified in any of the intervention studies reported. This phenolic has been extensively used to treat urea cycle disorders, and as such might be of great relevance to understand if it could be significantly present in circulation after ingestion of (poly)phenol rich foods.

Many factors are likely to contribute to this list of phenolic acids not detected in human circulation, including interindividual divergence precluding statistical inference,

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4-hydroxy-5-(phenyl)valeric acids

5-(phenyl)-γ-valerolactones

5-(phenyl)valeric acids

3-hydroxy-3-(phenyl)propanoic acids

Phenylpropanoic acids

Cinnamic acid

4-vinylphenol

2-hydroxy-2-(phenyl)acetic acids

Phenylacetic acids

2-(phenyl)ethanols

4-ethylphenol

2-(phenyl)propanoic acids

Benzaldehydes

Benzoic acids

Benzenes

SCFA ?

CO_2

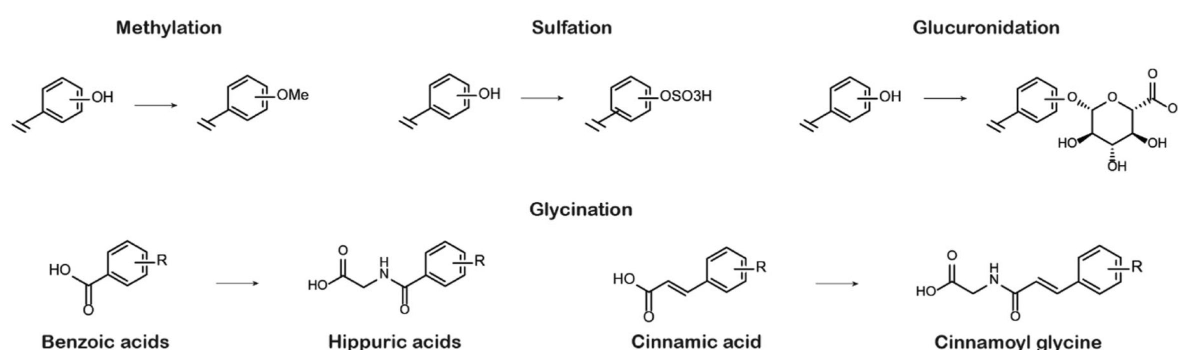

FIGURE 7 Predicted low molecular weight (LMW) phenolic metabolite biotransformation pathway based on the list of identified metabolites, their respective chemical structures, predictable conversions, and pharmacokinetic properties. The pathway culminates in production and release of CO_2, as shown by Czank et al. (2013), possibly via intermediate short chain fatty acids (SCFA) formation. Metabolites with free hydroxyl groups may at any point undergo phase II metabolism (e.g., methylation, sulfation, glycation and glucuronidation) by the human gastrointestinal system

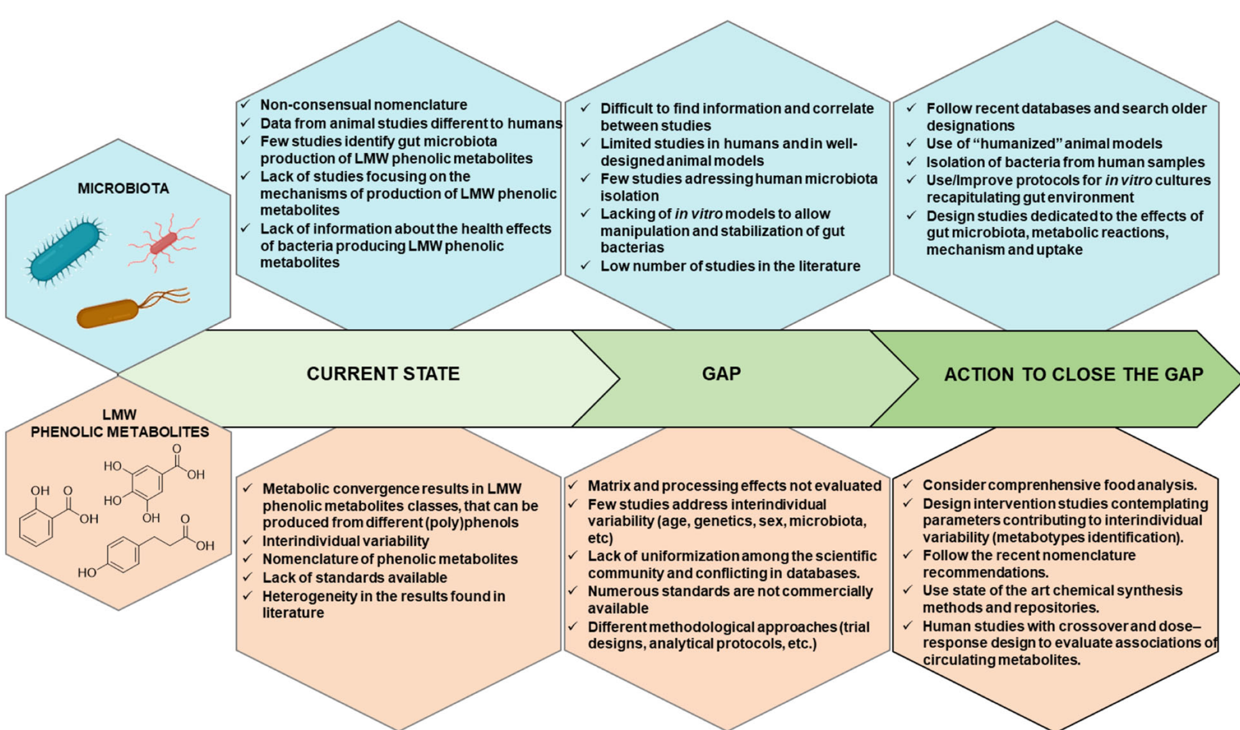

FIGURE 8 Current key limitations and future directions in the field of gut bacteria capable of generating LMW phenolic metabolites identified in human fecal sample isolates. Human intervention studies addressing LMW phenolic metabolites present in systemic circulation and different methodologies employed

rapid excretion rates, suboptimal collection timepoints, fast metabolism by the host cells, and conflicting methodological approaches (Gasperotti et al., 2015). Notably, some LMW phenolic metabolites have been found in urine but not in human plasma (e.g., 5-(phenyl)valeric acids, as reviewed in (Mena et al., 2019)), an observation that may reflect rapid blood clearance and/or renal metabolism or concentrations below the sensitivity of the detection methods. Regarding the circulating metabolites quantified to date, the high interindividual variability observed for all studies underscores the need for monitoring individual parameters, for example, age, sex, health status, genetic background, microbiota composition and functionality, and others, in future intervention studies, which is expected to drive the fields of personalized health and nutrition (Morand et al., 2020).

Animal studies have been critical in the identification and quantification of LMW phenolic metabolites across multiple fluids and tissues (Gasperotti et al., 2015). However, some metabolites identified in animals have failed to be found in humans, for example, 3,5-dimethoxybenzoic acid-4-sulfate (Gomes et al., 2019) and possibly 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate (Angelino et al., 2019). Here, differences at the level of microbiota composition should be considered (Ottaviani et al., 2016).

A wide range of methodologies for metabolite analysis has been used: analyzing plasma versus serum, performing solid phase extraction or liquid–liquid extraction, performing enzymatic hydrolysis of the samples or not doing so, different quantification methodologies, and distinct apparatuses. Divergent methodological choices introduce bias and complicate comparisons of LMW phenolic metabolite quantification due to changes in polarities across different LMW phenolic metabolite classes and to the presence or absence of phase II conjugation products. As such, adopting consensus methodologies for pharmacokinetics studies of LMW phenolic metabolites should be made a priority (Koistinen et al., 2018). Meanwhile, the list of commercially available standards is expanding and methodologies for the chemical synthesis of LMW phenolic metabolites have also increased in the last decade (Almeida et al., 2017; Correia et al., 2020; Gutierrez-Zetina et al., 2019; Manach et al., 2016; Mena et al., 2019; Pimpão et al., 2014). Moreover, collaborative databases for sharing standards (e.g., FoodComEx) are expected to drive the unequivocal identification and quantification of LMW phenolic metabolites (Manach et al., 2016). Adopting the measures reported by Sumner et al. (2007) would also help on the utility, validity, and understanding of metabolomics data (Sumner et al., 2007). Notwithstanding, with or without these improvements (Figure 8), critical analysis by the

researchers should always be performed. Data analysis and curation of the results need to be addressed by a well-trained chemist with experience in this area to avoid miss identification and take full advantage of the data collected.

9 | CONCLUSION

Altogether, this review highlights the LMW phenolic metabolites quantified in human interventions using (poly)phenols or (poly)phenol-rich foods. Furthermore, it addresses the gaps in knowledge regarding the identification of gut bacterial species responsible for the generation of LMW phenolic metabolites. Increasing evidence suggests the potential health benefits of LMW phenolic metabolites, yet it is crucial to produce solid cell-based studies using physiologically relevant concentrations, especially for those dissecting mechanisms of action. Meanwhile, by addressing the pressing issues herein identified, we expect in the future to reach a clear understanding of the potential of the LMW phenolic metabolites and how we can explore personalized nutrition, dietary recommendations, and dietary/microbiota supplementation to fully explore the health benefits of these promising circulating metabolites.

ACKNOWLEDGMENTS

This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under grant agreement No 804229. iNOVA4Health Research Unit (LISBOA-01-0145-FEDER-007344), which is cofunded by Fundação para a Ciência e Tecnologia (FCT) / Ministério da Ciência e do Ensino Superior, through national funds, and by FEDER under the PT2020 Partnership Agreement, is acknowledged. D.B. acknowledges funding by the European Research Council (Starting Grant: FunKeyGut 741623). Authors would like to acknowledge FCT for financial support of D.C. (2020.04630.BD).

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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How to cite this article: Carregosa, D., Pinto, C., Ávila-Gálvez, M. Á., Bastos, P., Berry, D., & dos Santos, C. N. (2022). A look beyond dietary (poly)phenols: The low molecular weight phenolic metabolites and their concentrations in human circulation. *Comprehensive Reviews in Food Science and Food Safety*, 1–32. https://doi.org/10.1111/1541-4337.13006