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Review

Revisiting the bioavailability of flavan-3-ols in humans: A systematic review and comprehensive data analysis

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ABSTRACT

This systematic review summarizes findings from human studies investigating the different routes of absorption, metabolism, distribution and excretion (ADME) of dietary flavan-3-ols and their circulating metabolites in healthy subjects. Literature searches were performed in PubMed, Scopus and the Web of Science. Human intervention studies using single and/or multiple intake of flavan-3-ols from food, extracts, and pure compounds were included. Forty-nine human intervention studies met inclusion criteria. Up to 180 metabolites were quantified from blood and urine samples following intake of flavan-3-ols, mainly as phase 2 conjugates of microbial catabolites ($n = 97$), with phenyl-γ-valerolactones being the most representative ones ($n = 34$). Phase 2 conjugates of monomers and phenyl-γ-valerolactones, the main compounds in both plasma and urine, reached two peak plasma concentrations (C_{max}) of 260 and 88 nmol/L at 1.8 and 5.3 h (T_{max}) after flavan-3-ol intake. They contributed to the bioavailability of flavan-3-ols for over 20%. Mean bioavailability for flavan-3-ols was moderate (31 ± 23%, n bioavailability values = 20), and it seems to be scarcely affected by the amount of ingested compounds. While intra- and inter-source differences in flavan-3-ol bioavailability emerged, mean flavan-3-ol bioavailability was 82% (n = 1) and 63% (n = 2) after (−)-epicatechin and nut (hazelnuts, almonds) intake, respectively, followed by 25% after consumption of tea (n = 7), cocoa (n = 5), apples (n = 3) and grape (n = 2). This highlights the need to better clarify the metabolic yield with which monomer flavan-3-ols and proanthocyanidins are metabolized in humans. This work clarified in a comprehensive way for the first time the ADME of a (poly)phenol family, highlighting the pool of circulating compounds that might be determinants of the putative beneficial effects linked to flavan-3-ol intake. Lastly, methodological inputs for implementing well-designed human and experimental model studies were provided.

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1. Introduction

A high adherence to plant-based dietary patterns has been strongly associated with a reduced risk of developing cardiometabolic diseases, type 2 diabetes, and certain cancers, the leading causes of mortality worldwide (FAO/WHO, 2004; Hemler and Hu, 2019; Qiao et al., 2022). The health benefits associated with a high plant-based food intake are attributed to the nutritional profile and the content of a multitude of bioactive compounds synthesized *in planta* in response to various environmental inputs (Crozier et al., 2007). Dietary bioactive compounds include thousands of phytochemicals belonging to different families, among which phenolic compounds (aka (poly)phenols) are the most important ones (Del Rio et al., 2013; Rodriguez-Mateos et al., 2014). (Poly)phenols, classified as flavonoids and non-flavonoids, have been identified as potential key mediators of the health benefits of plant-based diets (Manach et al., 2004; Williamson, 2017; Ulaszewska et al., 2020). Flavan-3-ols represent the most complex subclass of flavonoids, ranging from simple monomers to oligomeric and polymeric proanthocyanidins, also known as condensed tannins (Del Rio et al., 2013; Rodriguez-Mateos et al., 2014). The daily intake of flavan-3-ols varies from 200 to 1000 mg, representing together with hydroxycinnamic acids the main contributor of (poly)phenols in Western diet across all age groups, with main sources being tea, cocoa products, red wine, fruits (i.e. apples, pears, berries), and nuts (Vogiatzoglou et al., 2014, 2015; Ziauddeen et al., 2018).

Various investigations have pinpointed the capacity of flavan-3-ols to positively affect platelet and endothelial function (Ostertag et al., 2013; Heiss et al., 2015; Rodriguez-Mateos et al., 2015b; Sansone et al., 2015; Saarenhovi et al., 2017; Gröne et al., 2019). The European Food Safety Authority (EFSA) approved a health claim related to cocoa flavan-3-ols and maintenance of normal endothelium-dependent vasodilation (Agostoni et al., 2012). Flavan-3-ol consumption has been associated with significantly lower systolic blood pressure in the EPIC Norfolk cohort (Ottaviani et al., 2020) and with improvements in some biomarkers related to metabolic syndrome development (Yang et al., 2012). Recently, cocoa flavan-3-ol supplementation has been found reducing cardiovascular disease death by 27% in the COSMOS trial (Sesso et al., 2022).

After their consumption, only a small fraction of flavan-3-ols is absorbed along the upper gastrointestinal (GI) tract (Monagas et al., 2010). Over 70% of ingested flavan-3-ols reach intact the large bowel (Kahle et al., 2005, 2007; Hagl et al., 2011; Borges et al., 2013) where they are catabolized by gut microbiota into smaller phenolic compounds, which can be further metabolized by phase-2 conjugation reactions occurring in colonocytes or in the liver (Monagas et al., 2010; Mena et al., 2019a). Whereas it is well known that the ingested native compound seldom is the active compound reaching and interacting with organs and tissues but its metabolites (Velderrain-Rodríguez et al., 2014), it becomes clear that metabolites and catabolites of flavan-3-ols may directly drive the bioactivity recognised to these phytochemicals (Campos et al., 2019; Roager and Dragsted, 2019; Márquez Campos et al., 2020). However, to date, comprehensive data on the absorption, metabolism, distribution and excretion (ADME) of these dietary phytochemicals is scarce, and it appears to be largely influenced by the experimental design of the study, target population characteristics, and flavan-3-ol sources (Neilson and Ferruzzi, 2011; Velderrain-Rodríguez et al., 2014). To the best of our knowledge, no systematic and updated data is available on the nutrikinetic features for a comprehensive set of metabolites produced after flavan-3-ol intake. Thus, this systematic review aims to (i) summarize findings from existing human studies evaluating the ADME of flavan-3-ols in healthy volunteers, (ii) perform a comprehensive data analysis of their circulating metabolites and associated nutrikinetic parameters including urinary recovery, (iii) establish an estimation of flavan-3-ol bioavailability based on published data.

2. Methods

2.1. Search strategy and study selection

This systematic review was reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines (Moher et al., 2009; Page et al., 2021). The systematic literature search was conducted using PubMed, Scopus, and the Web of Science databases in May 2021 and updated in January 2022, using the syntaxes reported in Supplemental Table 1. Any temporal or spatial filters were applied to the search. Studies were included in the present systematic review provided (i) they were human studies investigating the ADME of flavan-3-ols in healthy subjects, (ii) volunteers consumed single or repeated (multiple) dose(s) of flavan-3-ols through a dietary source, an extract or a pure compound, (iii) they provided a quantitative characterization of the total content of ingested flavan-3-ols, (iv) native flavan-3-ols and their derived metabolites were quantified in plasma, serum, and/or urine samples without applying a hydrolysis step to remove phase-2 conjugating moieties, and (v) at least one nutrikinetic parameter is reported, namely peak plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the curve (AUC), apparent elimination half-life ($t_{½}$), total cumulative urinary excretion, or urinary excretion (expressed as % of intake), for native flavan-3-ols and their circulating metabolites. Exclusion criteria included (i) the consumption of flavan-3-ols through a mixture of different flavan-3-ol sources, and (ii) studies reported in a non-European languages. No restrictions for the characteristics of study participants for age, sex and ethnicity were applied.

2.2. Data extraction

Two author-pairs independently assessed the studies for their inclusion. Disagreement between authors was resolved through consultation with a third author. Data were extracted from each identified study using a standardized form and the following information was collected: name of the first author; year of publication; type of study (intervention or observational); chemical name, molecular weight, and PhytoHub ID (https://phytohub.eu/) of the circulating compound; type of biofluid(s) (i.e. plasma, serum, urine) in which circulating compounds were quantified; origin of flavan-3-ol metabolite [*unchanged* (when the native flavan-3-ol did not undergo any metabolic step following its ingestion), *host metabolism* (when the compound derived from a biotranformation by small intestine, hepatic or renal phase 1 or phase 2 enzyme), *gut microbiota metabolism* (when the compound derived from flavan-3-ol metabolism through gut microbiota activity), *host and gut microbiota metabolism* (when the compound derived from flavan-3-ol metabolism through gut microbiota activity and further conjugation by a phase 2 enzyme); chemical name of the precursor compound(s) of the metabolite [as i) *single compound* belonging to the flavan-3-ol class when it was clearly a precursor of that metabolite, or ii) *class* (i.e. flavan-3-ols) when various compounds belonging to the flavan-3-ol class were putative precursors of the same metabolite]; classification (i.e. food, pure compound, extract) and description of the ingested flavan-3-ol source; type of ingested dose(s) (i.e. single or repeated (multiple)); intervention duration (for studies in which multiple doses were ingested); ingested amount (μmol) of total flavan-3-ols (for multiple dose studies, the total daily dose was provided); description of the study population (i.e. number of subjects, sex, age, body mass index (BMI), and ethnicity, if available); and published values (i.e. mean, concentration unit, dispersion parameter type, dispersion parameter value, and time covered for AUC) for nutrikinetic parameters (i.e. T_{max}, C_{max}, AUC, and $t_{1/2}$) and urinary excretion data (expressed as cumulative excreted amount and/or % of intake) of the circulating compounds. Data on circulating compounds presented as mean and/or sum of metabolites belonging to different chemical species but grouped based on their chemical structure were excluded. On the other hand, data on simple

phenolic acids that were not strictly related to flavan-3-ol intake, due to their putative production through the metabolism of other dietary compounds (Del Rio et al., 2013; Rodriguez-Mateos et al., 2014; Selma et al., 2009), were not collected. Finally, only data related to phase-2 conjugates of flavan-3-ols and their specific colonic metabolites, namely phenyl-γ-valerolactones and phenylvaleric acids (Mena et al., 2019a), were collected.

2.3. Data analysis

Chemical names of circulating metabolites were standardized according to Kay et al. (2020). When isomer identification for flavan-3-ol metabolites was not clearly stated in the manuscript, their identification was carried out considering the retention time of unknown isomers in comparison to other metabolites reported in the manuscript and, when possible, the main isomers found in blood fractions following flavan-3-ol intake by previous literature (Männistö and Kaakkola, 199 Stalmach et al., 2009; Actis-Goretta et al., 2012; Ottaviani et al., 2012, 2016; Van Der Hooft et al., 2012; Liang et al., 2014; Van Duynhoven et al., 2014; Rodriguez-Mateos et al., 2015a; Brindani et al., 2017; Pereira-Caro et al., 2017, 2018; Borges et al., 2018; Gómez-Juaristi et al., 2019; Mayorga-Gross and Esquivel, 2019; Favari et al., 2020). If the total amount (μmol) of ingested flavan-3-ols was not reported in the manuscript, the total ingested flavan-3-ol content (including both monomers and oligomer/polymeric forms) was calculated by summing the ingested μmol of individual flavan-3-ols (calculated considering the amount and the molecular weight for each ingested compound), ignoring native compounds which accounted for less than 5% of the total consumed flavan-3-ols.

Nutrikinetic parameters and urinary excretion data for each metabolite were processed to obtain the following parameters (using harmonized units): (i) C_{max} (nmol/L); (ii) T_{max} (h) (values of $T_{max} \leq 2$ h for phenyl-γ-valerolactones and phenylvaleric acids were excluded due to their lack of physiological meaning (Borges et al., 2018; Mena et al., 2019a)); (iii) AUC (nmol/L*h); (iv) $t_{1/2}$ (h); (v) urinary excretion expressed as cumulative excreted amount (μmol), calculated by summing the excreted amounts over different time intervals when it was not reported; (vi) % of intake, calculated as the ratio between the cumulative urinary excretion (μmol) of the metabolite and the total intake (μmol) of ingested flavan-3-ols when no directly reported (urinary excretion data (expressed as % of intake) > 100%, possibly due to underestimations of the ingested dose of flavan-3-ols or to overestimations of the excreted amount occurring when metabolites were quantified without the proper reference standards (Ottaviani et al., 2018b), were excluded); and (vii) average concentration (C_{avg}) (nmol/L) as the ratio between AUC $(nmol/L*h)_{(0\text{-}t)}$ and the total number of hours considered for AUC calculation (Mena et al., 2021) (when the time interval employed for AUC calculation was equal to 0-inf, it was considered as 24 h).

When a circulating compound in a publication had a C_{avg} value exceeding its C_{max} value, C_{avg} value was excluded due to its low physiological relevance. C_{max}, AUC and C_{avg} values for each circulating compound were also normalized by dividing their value by the dose (μmol) of ingested flavan-3-ols (Mullen et al., 2009); in the case of multiple-dose studies, values of C_{max}, AUC and C_{avg} were normalized by using the total daily amount (μmol) of consumed flavan-3-ols. Normalized C_{max} values [C_{max} (nmol/L)/ingested μmol of flavan-3-ols] were used for comparisons among studies to determine the main circulating metabolites of flavan-3-ols. This approach avoided any confounding factors related to the putative dose-response relationship existing in the production of phenolic metabolites (Rodriguez-Mateos et al., 2016a, 2016b; Feliciano et al., 2017; Favari et al., 2020). Mean normalized C_{max} values ≥ 1 nmol/L (for unchanged monomer and dimer flavan-3-ols and host metabolites) and ≥0.3 nmol/L (for gut microbiota and host-gut microbiota metabolites) were selected as threshold values to define the main circulating forms of flavan-3-ol metabolites; they were established by ranking the metabolites according to their normalized C_{max} values and taking into account C_{max} values reached in the context of habitual flavan-3-ol dietary intake (Ottaviani et al., 2012a, 2012b, 2016; Urpi-Sarda et al., 2009; Borges et al., 2018; Vogiatzoglou et al., 2014, 2015; Zanotti et al., 2015; Ziauddeen et al., 2018). Finally, to ensure data robustness, the main circulating metabolites of flavan-3-ols were selected when their mean normalized C_{max} values were calculated using at least three biological replicates deriving from at least two manuscripts.

When data on flavan-3-ol bioavailability (%) was not reported in the manuscript, it was calculated by computing the ratio between the total flavan-3-ol metabolite urinary excretion (μmol) and the total intake (μmol) of parent flavan-3-ols (both monomers and oligomers/polymers) for each ingested source. Values for flavan-3-ol bioavailability (published and/or estimated) deriving from each study were averaged to provide a mean bioavailability value as accurate as possible, while excluding bioavailability data if they were i) < 1 and/or >100%, or ii) calculated by not taking into account a complete and appropriate metabolic pathway in terms of metabolites produced following flavan-3-ol intake (i.e. excluding phase 2 conjugates and/or not considering an exhaustive array of colonic metabolites produced after flavan-3-ol intake).

Data on plasma and urinary circulating compounds and on the bioavailability of flavan-3-ols were expressed as mean ± standard deviation (SD) and median (25th-75th percentile).

3. Results

3.1. Study selection

The study selection process is shown in Supplemental Fig. 1. A total of 5517 records were identified through the database search. After removing 1822 duplicates, up to 3695 studies were screened, of which 3458 were excluded based on the title or abstract. A total of 237 eligible records went under the full-text screening process, after which 188 records were excluded. Forty-nine publications met eligibility criteria and were included in the data analysis.

3.2. Characteristics of the included studies

The main characteristics of the studies that met all inclusion criteria are reported in Supplemental Table 2. Out of the 49 included intervention studies (total sample size $n = 653$), 39 investigated the ADME of flavan-3-ols following a single dose intake. Five publications investigated the ADME of flavan-3-ols following a multiple-dose (1–30 days) intake, while the remaining five publications showed an experimental setting having both single and multiple doses. No observational study met inclusion criteria. Tea (both green and black tea) was the most commonly consumed source of flavan-3-ols in the studies that investigated flavan-3-ol ADME, followed by cocoa and its derived products, then by pure compounds (Supplemental Table 2). The administered doses (μmol) of total flavan-3-ols ranged from 4 to almost 10000 μmol [677.1 (215.6–1335.9) μmol (median (25th-75th percentile))] (Supplemental Table 2 and Supplemental Fig. 2).

3.3. Circulating compounds after flavan-3-ol intake by healthy subjects

Up to 180 quantified metabolites in blood and urine fractions were reported following intake of flavan-3-ols by healthy subjects (Table 1). This included 97 host-gut microbiota metabolites [among which phenyl-γ-valerolactones were the main representatives ($n = 34$), followed by phenylvaleric acids (19), benzoic acids (12), phenylacetic acids (8), phenylpropanoic acids (7), catechols (7), cinnamates (6), and hippuric acids (4)], 49 host metabolites [phase 2 conjugates of (−)-epicatechin ($n = 22$), (epi)gallocatechin (7), (−)-epigallocatechin (6), (+)-epicatechin (6), (epi)catechin-3-*O*-gallate (4), (epi)gallocatechin-3-*O*-gallate (2),

Table 1
Metabolites of flavan-3-ols quantified at circulating level following flavan-3-ol intake by healthy humans. Metabolites are classified according to their metabolic origin: (I) *unchanged compounds*: indicates when the native flavan-3-ol did not undergo any metabolic step following its ingestion, (II) *host metabolism*: when the compound derived from a biotranformation by small intestine, hepatic or renal phase 1 or phase 2 enzymes, (III) *gut microbiota metabolism*: when the compound derived from flavan-3-ol metabolism through gut microbiota activity, (IV) *host and gut microbiota metabolism*: when the compound derived from flavan-3-ol metabolism through gut microbiota activity and further conjugation by a phase 2 enzyme. Metabolites are named according to Kay et al. (2020).

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Unchanged compounds					
Monomer flavan-3-ols					
(+)-Catechin ((+)-C)	290	PHUB000261	P, U	GT (+)-C; RW (+)-C	(Donovan et al., 2002; Hodgson et al., 2014; Mena et al., 2019b)
(−)-Epicatechin ((−)-EC)	290	PHUB000262	P, U	pure (−)-EC; GT (−)-EC; CHOC (−)-EC; CC (−)-EC	(Barnett et al., 2015; Chow et al., 2001; Hodgson et al., 2014; Mukai et al., 2021; Ottaviani et al., 2012; Yang et al., 2000)
(Epi)catechin[†] ((Epi)C)	290	PHUB001241	S, U	CC f-3-ols[§]	Vitaglione et al. (2013)
(−)-Catechin ((−)-C)	290	PHUB002190	U	GT (−)-C	Yang et al. (2000)
(+)-Epicatechin ((+)-EC)	290	PHUB002207	P	pure (+)-EC	Moreno-Ulloa et al. (2018)
(−)-Epigallocatechin ((−)-EGC)	306	PHUB000264	P, U	GT (−)-EGC	(Chow et al., 2001; Hodgson et al., 2014; Mukai et al., 2021; Yang et al., 2000)
(+)-Gallocatechin ((+)-GC)	306	PHUB000268	P	GT (+)-GC	Hodgson et al. (2014)
(−)-Gallocatechin ((−)-GC)	306	PHUB002189	U	GT (−)-GC	Yang et al. (2000)
Galloyl flavan-3-ols					
(−)-Epicatechin-3-*O*-gallate ((−)-ECG)	442	PHUB000263	P	GT (−)-ECG	(Mukai et al., 2021; Stalmach et al., 2009)
(Epi)catechin-3-*O*-gallate[†] ((Epi)CG)	442	PHUB002265	P	BT f-3-ols[§]	Van Duynhoven et al. (2014)
(−)-Epigallocatechin-3-*O*-gallate ((−)-EGCG)	458	PHUB000265	P	pure (−)-EGCG; GT (−)-EGCG;	(Abe et al., 2018; Chow et al., 2001, 2003; Del Rio et al., 2010b; Fernández et al., 2020; Gawande et al., 2008; Hodgson et al., 2014; Mukai et al., 2021; Nakagawa et al., 2009; Naumovski et al., 2015; Pietta et al., 1998; Stalmach et al., 2009; Ullmann et al., 2003, 2004)
(+)-Gallocatechin-3-*O*-gallate ((+)-GCG)	458	PHUB000269	P	GT (+)-GCG	Hodgson et al. (2014)
(Epi)gallocatechin-3-*O*-gallate[#] ((Epi)GCG)	458	PHUB002256	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
Dimer flavan-3-ols					
Procyanidin B2 (Proc B2)	572	PHUB000277	U	CC proc B2	Vitaglione et al. (2013)
Host metabolism					
Phase 2 conjugates of (+)-catechin					
with methyl group(s)					
3′-Methoxy-(+)-catechin* (3′-Me-(+)-C)	304	PHUB002215	U	RW (+)-C	Donovan et al. (2002)
Phase 2 conjugates of (−)-epicatechin					
with sulfate group(s)					
(−)-Epicatechin-3′-sulfate ((−)-EC-3′-S)	370	PHUB001030	P, U	CC f-3-ols[§]; pure (−)-EC; CHOC (−)-EC; CC (−)-EC	(Actis-Goretta et al., 2012; Barnett et al., 2015; Gómez-Juaristi et al., 2019; Ottaviani et al., 2011, 2012, 2016; Rodriguez-Mateos et al., 2015a)
(−)-Epicatechin-4′-sulfate ((−)-EC-4′-S)	370	PHUB001032	P, U	CHOC (−)-EC	Actis-Goretta et al. (2012)
(−)-Epicatechin-5-sulfate ((−)-EC-5-S)	370	PHUB001033	P, U	pure (−)-EC; CHOC (−)-EC; CC (−)-EC	(Actis-Goretta et al., 2012; Javier I. Ottaviani et al., 2012; Ottaviani et al., 2016, 2011)
(−)-Epicatechin-7-sulfate ((−)-EC-7-S)	370	PHUB002147	P	pure (−)-EC; CC (−)-EC	(Ottaviani et al., 2012, 2016)
(−)-Epicatechin-sulfate* ((−)-EC-S)	370	PHUB002150	P, U	CC f-3-ols[§]; GT f-3-ols[§]	(Del Rio et al., 2010b; Roura et al., 2008)
(−)-Epicatechin-sulfate*[‡] ((−)-EC-S)	370	–	U	BT f-3-ols[§]	(Del Rio et al., 2010c; Pereira-Caro et al., 2017)
with methyl and sulfate group(s)					
3′-Methoxy-(−)-epicatechin-4′-sulfate (3′-Me-(−)-EC-4′-S)	384	PHUB001049	P, U	pure (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Ottaviani et al., 2016)
3′-Methoxy-(−)-epicatechin-5-sulfate (3′-Me-(−)-EC-5-S)	384	PHUB001050	P, U	CC f-3-ols[§]; pure (−)-EC; CC (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Mullen et al., 2009; Ottaviani et al., 2016; Rodriguez-Mateos et al., 2015a)
3′-Methoxy-(−)-epicatechin-7-sulfate (3′-Me-(−)-EC-7-S)	384	PHUB001051	P, U	CC f-3-ols[§]; pure (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Ottaviani et al., 2016; Rodriguez-Mateos et al., 2015a)
4′-Methoxy-(−)-epicatechin-5-sulfate (4′-Me-(−)-EC-5-S)	384	PHUB001054	P, U	pure (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Ottaviani et al., 2016)
4′-Methoxy-(−)-epicatechin-7-sulfate (4′-Me-(−)-EC-7-S)	384	PHUB001055	P, U	pure (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Ottaviani et al., 2016)
Methoxy-(−)-epicatechin-sulfate* (Me-(−)-EC-S)	384	PHUB002236	P, U	GT f-3-ols[§]; pure (−)-EC; CC (−)-EC;	(Barnett et al., 2015; Del Rio et al., 2010b; Gómez-Juaristi et al., 2019)
Methoxy-(−)-epicatechin-sulfate*[‡] (Me-(−)-EC-S)	384	–	U	BT f-3-ols[§]	(Del Rio et al., 2010c; Pereira-Caro et al., 2017)
with glucuronic acid					
	466	PHUB001029	P, U		

(*continued on next page*)

Table 1 (*continued*)

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
(−)-Epicatechin-3′-glucuronide ((−)-EC-3′-GlcUA)				CC f-3-ols[§]; pure (−)-EC; CC (−)-EC; CHOC (−)-EC; GT f-3-ols[§]	(Actis-Goretta et al., 2012; Barnett et al., 2015; Gómez-Juaristi et al., 2019; Mullen et al., 2009; Ottaviani et al., 2011, 2012, 2016; Rodriguez-Mateos et al., 2015a; Roura et al., 2008; Stalmach et al., 2009)
(−)-Epicatechin-4′-glucuronide ((−)-EC-4′-GlcUA)	466	PHUB001031	P, U	CHOC (−)-EC	Actis-Goretta et al. (2012)
(−)-Epicatechin-7-glucuronide ((−)-EC-7-GlcUA)	466	PHUB001034	P	pure (−)-EC; CHOC (−)-EC	(Actis-Goretta et al., 2012; Ottaviani et al., 2016)
(−)-Epicatechin-glucuronide* ((−)-EC-GlcUA)	466	PHUB001035	P, U	GT f-3-ols[§]; BT f-3-ols[§]	(Del Rio et al., 2010b, 2010c; Pereira-Caro et al., 2017)
with methyl(s) and glucuronic acid					
4′-Methoxy-(−)-epicatechin-glucuronide* (4′-Me-(−)-EC-GlcUA)	480	PHUB001056	U	CHOC (−)-EC	Actis-Goretta et al. (2012)
3′-Methoxy-(−)-epicatechin-7-glucuronide (3′-Me-(−)-EC-7-GlcUA)	480	PHUB002148	P	pure (−)-EC	Ottaviani et al. (2016)
Methoxy-(−)-epicatechin-glucuronide* (Me-(−)-EC-GlcUA)	480	PHUB002153	P, U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
3′-Methoxy-(−)-epicatechin-glucuronide* (3′-Me-(−)-EC-GlcUA)	480	PHUB002232	U	CHOC (−)-EC	Actis-Goretta et al. (2012)
3′-Methoxy-(−)-epicatechin-5-glucuronide (3′-Me-(−)-EC-5-GlcUA)	480	PHUB002266	P, U	pure (−)-EC; CC (−)-EC	(Gómez-Juaristi et al., 2019; Ottaviani et al., 2016)
4′-methoxy-(−)-epicatechin-7-glucuronide (4′-Me-(−)-EC-7-GlcUA)	480	PHUB002310	P	CC (−)-EC	(JOttaviani et al., 2012)
with sulfate and glucuronic acid					
(−)-Epicatechin-sulfate-glucuronide* ((−)-EC-S-GlcUA)	546	PHUB001037	U	GT f-3-ols[§]	Del Rio et al. (2010b)
Phase 2 conjugates of (+)-epicatechin					
with sulfate group(s)					
(+)-Epicatechin-sulfate* ((+)-EC-S)	370	PHUB002210	P	pure (+)-EC	Moreno-Ulloa et al. (2018)
(+)-Epicatechin-5-sulfate ((+)-EC-5-S)	370	PHUB002312	P	CC (+)-EC	Ottaviani et al. (2011)
(+)-Epicatechin-3′-sulfate ((+)-EC-3′-S)	370	PHUB002313	P	CC (+)-EC	Ottaviani et al. (2011)
with methyl and sulfate group(s)					
Methoxy-(+)-epicatechin-sulfate* (Me-(+)-EC-S)	384	PHUB002209	P	pure (+)-EC	Moreno-Ulloa et al. (2018)
with glucuronic acid					
(+)-Epicatechin-glucuronide* ((+)-EC-GlcUA)	466	PHUB002208	P	pure (+)-EC	Moreno-Ulloa et al. (2018)
(+)-Epicatechin-3′-glucuronide ((+)-EC-3′-GlcUA)	466	PHUB002311	P	CC (+)-EC	Ottaviani et al. (2011)
Phase 2 conjugates of (epi) catechin[†]					
with sulfate group(s)					
(Epi)catechin-sulfate*[†] ((Epi)C–S)	370	PHUB001040	P, U	CC f-3-ols[§]; GT f-3-ols[§]; RGP f-3-ols[§]; A f-3-ols[§]; HZT f-3-ols[§]; ALM f-3-ols[§]; BT f-3-ols[§]; RW f-3-ols[§]	(Bartolomé et al., 2010; Castello et al., 2018; Clarke et al., 2014; Garrido et al., 2010; Hollands et al., 2020; Mena et al., 2019b; Mocciaro et al., 2019; Motilva et al., 2016; Mullen et al., 2009; Van Duynhoven et al., 2014)
(Epi)catechin-sulfate*,‡,†[†] ((Epi)C–S)	370	–	P, U	GT f-3-ols[§]; G f-3-ols[§]	(Calani et al., 2012b; Stalmach et al., 2009, 2012)
(Epi)catechin-disulfate*[†] ((Epi) C–S–S)	450	PHUB002239	U	A f-3-ols[§]; HZT f-3-ols[§]	(Hollands et al., 2020; Mocciaro et al., 2019)
with methyl and sulfate group(s)					
Methoxy-(epi)catechin-sulfate*[†] (Me-(epi)C–S)	384	PHUB002164	P, U	GT f-3-ols[§]; RGP f-3-ols[§]; A f-3-ols[§]; HZT f-3-ols[§]; ALM f-3-ols[§]; BT f-3-ols[§]; CC f-3-ols[§]; RW f-3-ols[§]	(Castello et al., 2018; Clarke et al., 2014; Garrido et al., 2010; Hollands et al., 2020; Mena et al., 2021, 2019b; Mocciaro et al., 2019; Motilva et al., 2016; Van Duynhoven et al., 2014)
Methoxy-(epi)catechin-sulfate*,‡,†[†] (Me-(epi)C–S)	384	–	P, U	GT f-3-ols[§]; G f-3-ols[§]	(Calani et al., 2012b; Stalmach et al., 2009, 2012)
with glucuronic acid					
(Epi)catechin-glucuronide*,†[†] ((Epi)C-GlcUA)	466	PHUB002205	P, U	GT f-3-ols[§]; RGP f-3-ols[§]; A f-3-ols[§]; ALM f-3-ols[§]; G f-3-ols[§]; CC f-3-ols[§]; RW f-3-ols[§]	(Calani et al., 2012b; Castello et al., 2018; Clarke et al., 2014; Garrido et al., 2010; Hollands et al., 2020; Mena et al., 2019b, 2021; Motilva et al., 2016; Stalmach et al., 2012)
with methyl(s) and glucuronic acid					

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Table 1 (*continued*)

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Methoxy-(epi)catechin-glucuronide*,† (Me-(epi)C-GlcUA)	480	PHUB002206	U	GT f-3-ols§; HZT f-3-ols§; ALM f-3-ols§; G f-3-ols§; RW f-3-ols§; RGP f-3-ols§	(Garrido et al., 2010; Mena et al., 2019b; Mocciaro et al., 2019; Motilva et al., 2016; Stalmach et al., 2012)
with sulfate and glucuronic acid					
(Epi)catechin-sulfate-glucuronide*,† ((Epi)C–S-GlcUA)	546	PHUB002188	P, U	RGP f-3-ols§; A f-3-ols§; GT f-3-ols§; HZT f-3-ols§; CC f-3-ols§	(Castello et al., 2018; Hollands et al., 2020; Mena et al., 2019b, 2021; Mocciaro et al., 2019)
(Epi)catechin-sulfate-glucuronide*,‡,† ((Epi)C–S-GlcUA)	546	–	U	GT f-3-ols§	Calani et al. (2012b)
Phase 2 conjugates of (−)-epigallocatechin					
with methyl group(s)					
Methoxy-(−)-epigallocatechin*,‡ (Me-(−)-EGC)	320	–	U	BT f-3-ols§	Del Rio et al. (2010c)
with sulfate group(s)					
(−)-Epigallocatechin-sulfate* ((−)-EGC-S)	386	PHUB002166	U	GT f-3-ols§	(Clarke et al., 2014; Del Rio et al., 2010b)
(−)-Epigallocatechin-sulfate*,‡ ((−)-EGC-S)	386	–	U	BT f-3-ols§	Del Rio et al. (2010c)
with methyl and sulfate group(s)					
Methoxy-(−)-epigallocatechin-sulfate* (Me-(−)-EGC-S)	400	PHUB002168	P, U	GT f-3-ols§; BT f-3-ols§	(Clarke et al., 2014; Del Rio et al., 2010b, 2010c)
with glucuronic acid					
(−)-Epigallocatechin-glucuronide* ((−)-EGC-GlcUA)	482	PHUB002165	P, U	GT f-3-ols§; BT f-3-ols§	(Clarke et al., 2014; Del Rio et al., 2010b, 2010c)
with methyl(s) and glucuronic acid					
Methoxy-(−)-epigallocatechin-glucuronide* (Me-(−)-EGC-GlcUA)	496	PHUB002167	P, U	GT f-3-ols§	(Clarke et al., 2014; Del Rio et al., 2010b)
Methoxy-(−)-epigallocatechin-glucuronide*,‡ (Me-(−)-EGC-GlcUA)	496	–	U	BT f-3-ols§	Del Rio et al. (2010c)
with methyl, sulfate and glucuronic acid					
Methoxy-(−)-epigallocatechin-sulfate-glucuronide* (Me-(−)-EGC-S-GlcUA)	576	PHUB002181	U	GT f-3-ols§	Del Rio et al. (2010b)
Phase 2 conjugates of (epi)gallocatechin#					
with sulfate group(s)					
(Epi)gallocatechin-sulfate*,# ((Epi)GC-S)	386	PHUB002246	U	HZT f-3-ols§	Mocciaro et al. (2019)
(Epi)gallocatechin-sulfate*,‡,# ((Epi)GC-S)	386	–	U	GT f-3-ols§	(Calani et al., 2012b; Stalmach et al., 2009)
with methyl and sulfate group(s)					
Methoxy-(epi)gallocatechin-sulfate*,# (Me-(epi)GC-S)	400	PHUB002203	P, U	BT f-3-ols§; G f-3-ols§	(Stalmach et al., 2012; Van Duynhoven et al., 2014)
4′-Methoxy-(epi)gallocatechin-sulfate*,‡,# (4′-Me-(epi)GC-S)	400	–	P, U	GT f-3-ols§	Stalmach et al. (2009)
Methoxy-(epi)gallocatechin-sulfate*,‡,# (Me-(epi)GC-S)	400	–	U	GT f-3-ols§	Calani et al. (2012b)
Dimethoxy-(epi)gallocatechin-sulfate*,# (Di-me-(epi)GC-S)	414	PHUB002204	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
with glucuronic acid					
(Epi)gallocatechin-glucuronide*,# ((Epi)GC-GlcUA)	482	PHUB001041	P, U	GT f-3-ols§; HZT f-3-ols§	(Calani et al., 2012b; Mena et al., 2019b; Mocciaro et al., 2019; Stalmach et al., 2009)
with methyl(s) and glucuronic acid					
4′-Methoxy-(epi)gallocatechin-glucuronide*,# (4′-Me-(epi)GC-GlcUA)	496	PHUB001058	P, U	GT f-3-ols§	Stalmach et al. (2009)
Methoxy-(epi)gallocatechin-glucuronide*,# (Me-(epi)GC-GlcUA)	496	PHUB002158	U	GT f-3-ols§	(Calani et al., 2012b; Mena et al., 2019b)
with methyl, sulfate and glucuronic acid					
Methoxy-(epi)gallocatechin-sulfate-glucuronide*,# (Me-(epi)GC-S-GlcUA)	576	PHUB002241	U	GT f-3-ols§	Mena et al. (2019b)
Methoxy-(epi)gallocatechin-sulfate-glucuronide*,‡,# (Me-(epi)GC-S-GlcUA)	576	–	U	GT f-3-ols§	Calani et al. (2012b)
Phase 2 conjugates of (epi)catechin-3-*O*-gallate†					
with sulfate group(s)					
(Epi)catechin-3-*O*-gallate-sulfate*,† ((Epi)CG-S)	522	PHUB002254	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
with methyl and sulfate group(s)					
	536	PHUB002252	P	BT f-3-ols§	(Van Duynhoven et al., 2014)

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Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Methoxy-(epi)catechin-3-*O*-gallate-sulfate*,† (Me-(epi)CG-S)					
with sulfate and glucuronic acid					
(Epi)catechin-3-*O*-gallate-sulfate-glucuronide*,† ((Epi)CG-S-GlcUA)	698	PHUB002255	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
with methyl, sulfate and glucuronic acid					
Methoxy-(epi)catechin-3-*O*-gallate-sulfate-glucuronide*,† (Me-(epi) CG-S-GlcUA)	712	PHUB002253	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
Phase 2 conjugates of (epi)gallocatechin-3-*O*-gallate#					
with sulfate group(s)					
(Epi)gallocatechin-3-*O*-gallate-sulfate*,# ((Epi)GCG-S)	538	PHUB001043	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
with methyl and sulfate group(s)					
Methoxy-(epi)gallocatechin-3-*O*-gallate-sulfate*,# (Me-(epi)GCG-S)	552	PHUB002257	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
Phase 2 conjugates of Procyanidin B-type					
with sulfate group(s)					
Procyanidin B-type sulfate* (Proc B2–S)	658	PHUB002245	U	HZT f-3-ols§	Mocciaro et al. (2019)
Gut microbiota metabolism					
Phenyl-γ-valerolactones					
5-(3′-Hydroxyphenyl)-γ-valerolactone (3′–OH–VL)	192	PHUB001249	U	CC f-3-ols§	(Gómez-Juaristi et al., 2019)
5-(4′-Hydroxyphenyl)-γ-valerolactone (4′–OH–VL)	192	PHUB001834	U	GT f-3-ols§	Mena et al. (2019b)
5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone (3′,4′-diOH-VL)	208	PHUB001993	P, S, U	RW f-3-ols§; CC f-3-ols§; CR f-3-ols§; RGP f-3-ols§; A f-3-ols§; GT f-3-ols§	(Castello et al., 2018; Favari et al., 2020; Gómez-Juaristi et al., 2019; Hodgson et al., 2014; Hollands et al., 2020; Mena et al., 2019b; Motilva et al., 2016; Vitaglione et al., 2013)
5-(3′,5′-Dihydroxyphenyl)-γ-valerolactone (3′,5′-diOH-VL)	208	PHUB002235	U	RGP f-3-ols§	Castello et al. (2018)
5-(3′,4′,5′-Trihydroxyphenyl)-γ-valerolactone (3′,4′,5′-triOH-VL)	224	PHUB001833	U	GT f-3-ols§	Roowi et al. (2010)
Phenylvaleric acids					
4-Hydroxy-5-(3′,4′-dihydroxyphenyl)valeric acid (4-OH-(3′,4′-diOH-VA))	226	PHUB001987	U	BT f-3-ols§	Pereira-Caro et al. (2017)
Phenylpropanoic acids					
3-(4′-Hydroxyphenyl)propanoic acid (4′–OH–PPA)	166	PHUB000605	U	BT f-3-ols§	Pereira-Caro et al. (2017)
3-(3′-Hydroxyphenyl)propanoic acid (3′–OH–PPA)	166	PHUB001047	U	CC f-3-ols§	(Gómez-Juaristi et al., 2019)
3-(3′,4′-Dihydroxyphenyl)propanoic acid (3′,4′-diOH-PPA)	182	PHUB000604	U	CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
3-Hydroxy-3-(3′-hydroxyphenyl) propanoic acid (3-OH-(3′–OH–PPA))	182	PHUB001331	U	GT f-3-ols§; pure (−)-EC	(Ottaviani et al., 2016; Roowi et al., 2010)
Phenylacetic acids					
Phenylacetic acid (PAA)	136	PHUB001068	U	BT f-3-ols§	Pereira-Caro et al. (2017)
4′-Hydroxyphenylacetic acid (4′–OH–PAA)	152	PHUB000543	U	GT f-3-ols§; BT f-3-ols§	(Pereira-Caro et al., 2017; Roowi et al., 2010)
3′-Hydroxyphenylacetic acid (3′–OH–PAA)	152	PHUB001048	U	CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
3′,4′-Dihydroxyphenylacetic acid (3′,4′-diOH-PAA)	168	PHUB000527	U	CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
2-Hydroxy-2-(4′-hydroxyphenyl) acetic acid (2-OH-(4′–OH–PAA))	168	PHUB001584	U	BT f-3-ols§	Pereira-Caro et al. (2017)
Benzoic acids					
3-Hydroxybenzoic acid (3-OH-BA)	138	PHUB000294	U	CC f-3-ols§; BT f-3-ols§; GT f-3-ols§	(Clarke et al., 2014; Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
4-Hydroxybenzoic acid (4-OH-BA)	138	PHUB000295	U	BT f-3-ols§; GT f-3-ols§	(Pereira-Caro et al., 2017; Roowi et al., 2010)
3,4-Dihydroxybenzoic acid (3,4-diOH-BA)	154	PHUB000310	U	CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
3,4,5-Trihydroxybenzoic acid (3,4,5-triOH-BA)	170	PHUB000303	U	BT f-3-ols§	Pereira-Caro et al. (2017)
Catechols					
Benzene-1,2-diol (BE-1,2-diol)	110	PHUB000583	U	GT f-3-ols§; BT f-3-ols§	(Pereira-Caro et al., 2017; Roowi et al., 2010)
Benzene-1,2,3-triol (BE-1,2,3-triol)	126	PHUB000632	U	GT f-3-ols§; BT f-3-ols§	(Pereira-Caro et al., 2017; Roowi et al., 2010)

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Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Benzene-1,3,5-triol (BE-1,3,5-triol)	126	PHUB001126	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
Host and gut microbiota metabolism					
Phenyl-γ-valerolactones					
Phase 2 conjugates of 5-(hydroxyphenyl)-γ-valerolactone					
with sulfate group(s)					
5-(Phenyl)-γ-valerolactone-3′-sulfate (VL-3′-S)	272	PHUB001751	P, U	CR f-3-ols[§]; RGP f-3-ols[§]; CC f-3-ols[§]; A f-3-ols[§]; BT f-3-ols[§]; GT f-3-ols[§]; pure (−)-EC; HZT f-3-ols[§]	(Anesi et al., 2019; Castello et al., 2018; Favari et al., 2020; Gómez-Juaristi et al., 2019; Mena et al., 2019b, 2021; Mocciaro et al., 2019; Ottaviani et al., 2016; Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
5-(Phenyl)-γ-valerolactone-4′-sulfate (VL-4′-S)	272	PHUB002182	P	CR f-3-ols[§]	Favari et al. (2020)
5-(Phenyl)-γ-valerolactone-sulfate* (VL-S)	272	PHUB002267	U	GT f-3-ols[§]	Calani et al. (2012b)
with glucuronic acid					
5-(Phenyl)-γ-valerolactone-glucuronide* (VL-GlcUA)	368	PHUB002159	P, U	GT f-3-ols[§]; A f-3-ols[§]	(Calani et al., 2012b; Yuste et al., 2018)
5-(Phenyl)-γ-valerolactone-3′-glucuronide (VL-3′-GlcUA)	368	PHUB002183	P, U	CR f-3-ols[§]; RGP f-3-ols[§]; CC f-3-ols[§]; GT f-3-ols[§]; BT f-3-ols[§]	(Anesi et al., 2019; Castello et al., 2018; Favari et al., 2020; Gómez-Juaristi et al., 2019; Mena et al., 2021, 2019b; Van Duynhoven et al., 2014)
5-(Phenyl)-γ-valerolactone-4′-glucuronide (VL-4′-GlcUA)	368	PHUB002247	P, U	CR f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]	(Favari et al., 2020; Mocciaro et al., 2019; Van Duynhoven et al., 2014)
Phase 2 conjugates of 5-(dihydroxyphenyl)-γ-valerolactone					
with methyl group(s)					
5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-methoxy (4′–OH–VL-3′-Me)	222	PHUB002145	P	GT f-3-ols[§]	Hodgson et al. (2014)
with sulfate group(s)					
5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-sulfate (4′–OH–VL-3′-S)	288	PHUB001755	P, U	pure (−)-EC; A f-3-ols[§]; ALM f-3-ols[§]; BT f-3-ols[§]	(Garrido et al., 2010; Hollands et al., 2020; Ottaviani et al., 2016; Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
5-(3′-Hydroxyphenyl)-γ-valerolactone-4′-sulfate (3′–OH–VL-4′-S)	288	PHUB001995	P, U	CR f-3-ols[§]; CC f-3-ols[§]; A f-3-ols[§]; RS (−)-EC; BT f-3-ols[§]	(Anesi et al., 2019; Feliciano et al., 2017, 2016; Gómez-Juaristi et al., 2019; Istas et al., 2018; Pereira-Caro et al., 2017)
5-(Hydroxyphenyl)-γ-valerolactone-sulfate* (OH-VL-S)	288	PHUB002179	P, U	GT f-3-ols[§]; CC f-3-ols[§]	(Clarke et al., 2014; Del Rio et al., 2010b; Mena et al., 2019b, 2021)
5-(5′-Hydroxyphenyl)-γ-valerolactone-3′-sulfate (5′–OH–VL-3′-S)	288	PHUB002185	P, U	CR f-3-ols[§]; RGP f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]	(Castello et al., 2018; Favari et al., 2020; Mocciaro et al., 2019; Van Duynhoven et al., 2014)
5-(Hydroxyphenyl)-γ-valerolactone-sulfate*[‡] (OH-VL-S)	288	–	P, U	CR f-3-ols[§]; RGP f-3-ols[§]; HZT f-3-ols[§]	(Castello et al., 2018; Favari et al., 2020; Mocciaro et al., 2019)
5-(Phenyl)-γ-valerolactone-3′,5′-disulfate (VL-3′,5′-di-S)	368	PHUB002161	U	GT f-3-ols[§]	Calani et al. (2012b)
5-(Phenyl)-γ-valerolactone-4′,5′-disulfate (VL-4′,5′-di-S)	368	PHUB002162	U	GT f-3-ols[§]	Calani et al. (2012b)
with methyl and sulfate group(s)					
5-(Phenyl)-γ-valerolactone-methoxy-sulfate* (VL-Me-S)	302	PHUB002180	P, U	GT f-3-ols[§]; RGP f-3-ols[§]; CC f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]	(Castello et al., 2018; Clarke et al., 2014; Gómez-Juaristi et al., 2019; Mocciaro et al., 2019; Van Duynhoven et al., 2014)
5-(Phenyl)-γ-valerolactone-4′-methoxy-3′-sulfate (VL-4′-Me-3′-S)	302	PHUB002187	P, U	CR f-3-ols[§]; A f-3-ols[§]; ALM f-3-ols[§]	(Anesi et al., 2019; Favari et al., 2020; Garrido et al., 2010)
5-(Phenyl)-γ-valerolactone-3′-methoxy-4′-sulfate (VL-3′-Me-4′-S)	302	PHUB002216	P, U	CR f-3-ols[§]; A f-3-ols[§]; ALM f-3-ols[§]	(Anesi et al., 2019; Bartolomé et al., 2010; Favari et al., 2020)
with glucuronic acid					
5-(4′-Hydroxyphenyl)-γ-valerolactone-3′-glucuronide (4′–OH–VL-3′-GlcUA)	384	PHUB002146	P, U	pure (−)-EC; CR f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]; RGP f-3-ols[§]; CC f-3-ols[§]; A f-3-ols[§]; ALM f-3-ols[§]	(Castello et al., 2018; Favari et al., 2020; Garrido et al., 2010; Gómez-Juaristi et al., 2019; Hollands et al., 2020; Mena et al., 2021; Mocciaro et al., 2019; Ottaviani et al., 2016; Van Duynhoven et al., 2014)
5-(Hydroxyphenyl)-γ-valerolactone-glucuronide* (OH-VL-GlcUA)	384	PHUB002160	U	GT f-3-ols[§]; BT f-3-ols[§]	(Clarke et al., 2014; Del Rio et al., 2010b; Pereira-Caro et al., 2017)
5-(5′-Hydroxyphenyl)-γ-valerolactone-3′-glucuronide (5′–OH–VL-3′-GlcUA)	384	PHUB002186	P, U	GT f-3-ols[§]; BT f-3-ols[§]; CR f-3-ols[§]	(Calani et al., 2012b; Favari et al., 2020; Van Duynhoven et al., 2014)
5-(3′-Hydroxyphenyl)-γ-valerolactone-4′-glucuronide (3′–OH–VL-4′-GlcUA)	384	PHUB002234	P, U	CR f-3-ols[§]; RGP f-3-ols[§]; CC f-3-ols[§]; A f-3-ols[§]; ALM f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]	(Castello et al., 2018; Favari et al., 2020; Garrido et al., 2010; Gómez-Juaristi et al., 2019; Hollands et al., 2020; Mena et al., 2021; Mocciaro et al., 2019; Van Duynhoven et al., 2014)
5-(Hydroxyphenyl)-γ-valerolactone-glucuronide*[‡] (OH-VL-GlcUA)	384	–	U	GT f-3-ols[§]; A f-3-ols[§]	(Anesi et al., 2019; Calani et al., 2012b)
with methyl(s) and glucuronic acid					
	398	PHUB002163	P, U		

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Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
5-(Phenyl)-γ-valerolactone-methoxy-glucuronide* (VL-Me-GlcUA)				GT f-3-ols[§]; CR f-3-ols[§]; CC f-3-ols[§]; A f-3-ols[§]	(Anesi et al., 2019; Calani et al., 2012b; Favari et al., 2020; Gómez-Juaristi et al., 2019)
5-(Phenyl)-γ-valerolactone-5′-methoxy-3′-glucuronide (VL-5′-Me-3′-GlcUA)	398	PHUB002191	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
5-(Phenyl)-γ-valerolactone-3′-methoxy-4′-glucuronide (VL-3′-Me-4′-GlcUA)	398	PHUB002212	U	ALM f-3-ols[§]	Garrido et al. (2010)
5-(Phenyl)-γ-valerolactone-4′-methoxy-3′-glucuronide (VL-4′-Me-3′-GlcUA)	398	PHUB002213	U	ALM f-3-ols[§]	Garrido et al. (2010)
with sulfate and glucuronic acid					
5-(Phenyl)-γ-valerolactone-sulfate-glucuronide* (VL-S-GlcUA)	464	PHUB002156	P, U	pure (−)-EC; GT f-3-ols[§]; CR f-3-ols[§]; RGP f-3-ols[§]; A f-3-ols[§]; BT f-3-ols[§]; HZT f-3-ols[§]; CC f-3-ols[§]	(Anesi et al., 2019; Calani et al., 2012b; Castello et al., 2018; Del Rio et al., 2010b; Favari et al., 2020; Mena et al., 2021, 2019b; Mocciaro et al., 2019; Ottaviani et al., 2016; Van Duynhoven et al., 2014)
Phase 2 conjugates of 5-(trihydroxyphenyl)-γ-valerolactone					
with sulfate group(s)					
5-(Dihydroxyphenyl)-γ-valerolactone-sulfate* (DiOH-VL-S)	304	PHUB002177	U	GT f-3-ols[§]	(Clarke et al., 2014; Del Rio et al., 2010b)
5-(4′,5′-Dihydroxyphenyl)-γ-valerolactone-3′-sulfate (4′,5′-DiOH-VL-3′-S)	304	PHUB002199	P, U	BT f-3-ols[§]	(Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
5-(3′,5′-Dihydroxyphenyl)-γ-valerolactone-4′-sulfate (3′,5′-DiOH-VL-4′-S)	304	PHUB002218	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
5-(Dihydroxyphenyl)-γ-valerolactone-sulfate*[‡] (DiOH-VL-S)	304	–	U	GT f-3-ols[§]	Calani et al. (2012b)
with methyl and sulfate group(s)					
5-(Hydroxyphenyl)-γ-valerolactone-methoxy-sulfate* (OH-VL-Me-S)	318	PHUB002178	P, U	GT f-3-ols[§]; BT f-3-ols[§]	(Clarke et al., 2014; Del Rio et al., 2010b; Mena et al., 2019b; Van Duynhoven et al., 2014)
5-(Hydroxyphenyl)-γ-valerolactone-methoxy-sulfate*[‡] (OH-VL-Me-S)	318	–	U	GT f-3-ols[§]	Calani et al. (2012b)
with glucuronic acid					
5-(Dihydroxyphenyl)-γ-valerolactone-glucuronide* (DiOH-VL-GlcUA)	400	PHUB002176	U	GT f-3-ols[§]	(Clarke et al., 2014; Del Rio et al., 2010b; Mena et al., 2019b)
5-(4′,5′-Dihydroxyphenyl)-γ-valerolactone-3′-glucuronide (4′,5′-DiOH-VL-3′-GlcUA)	400	PHUB002197	P, U	BT f-3-ols[§]	(Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
5-(3′,5′-Dihydroxyphenyl)-γ-valerolactone-4′-glucuronide (3′,5′-DiOH-VL-4′-GlcUA)	400	PHUB002198	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
5-(Dihydroxyphenyl)-γ-valerolactone-glucuronide*[,‡] (DiOH-VL-GlcUA)	400	–	U	GT f-3-ols[§]	Calani et al. (2012b)
with methyl(s) and glucuronic acid					
5-(Hydroxyphenyl)-γ-valerolactone-methoxy-glucuronide* (OH-VL-Me-GlcUA)	414	PHUB002200	P, U	GT f-3-ols[§]; BT f-3-ols[§]	(Clarke et al., 2014; Van Duynhoven et al., 2014)
5-(Hydroxyphenyl)-γ-valerolactone-methoxy-glucuronide*[,‡] (OH-VL-Me-GlcUA)	414	–	U	GT f-3-ols[§]	Calani et al. (2012b)
with sulfate and glucuronic acid					
5-(Hydroxyphenyl)-γ-valerolactone-sulfate-glucuronide* (OH-VL-S-GlcUA)	480	PHUB002201	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
Phenylvaleric acids					
Phase 2 conjugates of 5-(hydroxyphenyl)valeric acid					
with sulfate group(s)					
5-(Phenyl)valeric acid-sulfate* (PVA-S)	274	PHUB002225	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
5-(Phenyl)valeric acid-3′-sulfate (PVA-3′-S)	274	PHUB002264	U	HZT f-3-ols[§]	Mocciaro et al. (2019)
with glucuronic acid					
5-(Phenyl)valeric acid-glucuronide* (PVA-GlcUA)	370	PHUB002226	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
5-(Phenyl)valeric acid-3′-glucuronide (PVA-3′-GlcUA)	370	PHUB002262	U	HZT f-3-ols[§]	Mocciaro et al. (2019)

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Table 1 (*continued*)

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Phase 2 conjugates of 5-(dihydroxyphenyl)valeric acid					
with sulfate group(s)					
5-(4′-Hydroxyphenyl)-valeric acid-3′-sulfate (4′–OH–PVA-3′-S)	290	PHUB002263	U	HZT f-3-ols[§]	Mocciaro et al. (2019)
with methyl and sulfate group(s)					
5-(Phenyl)valeric acid-methoxy-sulfate* (PVA-Me-S)	304	PHUB002251	P, U	BT f-3-ols[§]; HZT f-3-ols[§]	(Mocciaro et al., 2019; Van Duynhoven et al., 2014)
with glucuronic acid					
5-(4′-Hydroxyphenyl)valeric acid-3′-glucuronide (4′–OH–PVA-3′-GlcUA)	386	PHUB002222	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
5-(3′-Hydroxyphenyl)valeric acid-4′-glucuronide (3′–OH–PVA-4′-GlcUA)	386	PHUB002223	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with sulfate and glucuronic acid					
5-(Phenyl)-valeric acid-sulfate-glucuronide* (PVA-S-GlcUA)	466	PHUB002242	P, U	RGP f-3-ols[§]	Castello et al. (2018)
Phase 2 conjugates of 4-hydroxy-5-(hydroxyphenyl)valeric acid					
with sulfate group(s)					
4-Hydroxy-5-(phenyl)valeric acid-3′-sulfate (4-OH-(PVA)-3′-S)	290	PHUB002220	P, U	pure (−)-EC; BT f-3-ols[§]	(Ottaviani et al., 2016; Pereira-Caro et al., 2017)
4-Hydroxy-5-(phenyl)valeric acid-4′-sulfate (4-OH-(PVA)-4′-S)	290	PHUB002221	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
Phase 2 conjugates of 4-hydroxy-5-(dihydroxyphenyl)valeric acid					
with sulfate group(s)					
4-Hydroxy-5-(4′-hydroxyphenyl) valeric acid-3′-sulfate (4-OH-(4′–OH–PVA)-3′-S)	306	PHUB001989	P, U	CC f-3-ols[§]; A f-3-ols[§]; pure (−)-EC	(Anesi et al., 2019; Gómez-Juaristi et al., 2019; Ottaviani et al., 2016)
4-Hydroxy-5-(hydroxyphenyl)valeric acid-sulfate* (4-OH–(OH–PVA)-S)	306	PHUB002224	P, U	BT f-3-ols[§]	(Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
with methyl and sulfate group(s)					
4-Hydroxy-5-(phenyl)valeric acid-methoxy-sulfate* (4-OH-(PVA)-Me-S)	320	PHUB002258	P, U	BT f-3-ols[§]; A f-3-ols[§]	(Anesi et al., 2019; Van Duynhoven et al., 2014)
with glucuronic acid					
4-Hydroxy-5-(3′-hydroxyphenyl) valeric acid-4′-glucuronide (4-OH-(3′–OH–PVA)-4′-GlcUA)	402	PHUB001745	P, U	pure (−)-EC	Ottaviani et al. (2016)
4-Hydroxy-5-(4′-hydroxyphenyl) valeric acid-3′-glucuronide (4-OH-(4′–OH–PVA)-3′-GlcUA)	402	PHUB002238	U	CC f-3-ols[§]; A f-3-ols[§]	(Anesi et al., 2019; Gómez-Juaristi et al., 2019)
4-Hydroxy-5-(hydroxyphenyl)valeric acid-glucuronide* (4-OH–(OH–PVA)-GlcUA)	402	PHUB002259	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
4-Hydroxy-5-(hydroxyphenyl)valeric acid-glucuronide*[,†] (4-OH–(OH–PVA)-GlcUA)	402	–	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl(s) and glucuronic acid					
4-Hydroxy-5-(phenyl)valeric acid-methoxy-glucuronide* (4-OH-(PVA)-Me-GlcUA)	416	PHUB002260	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
Phase 2 conjugates of 4-hydroxy-5-(trihydroxyphenyl)valeric acid					
with methyl(s) and glucuronic acid					
4-Hydroxy-5-(hydroxyphenyl)valeric acid-methoxy-glucuronide* (4-OH–(OH–PVA)-Me-GlcUA)	432	PHUB002261	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
Phase 2 conjugates of cinnamates					
with methyl group(s)					
4′-Hydroxy-3′-methoxycinnamic acid (4′–OH–3′-Me-CA)	194	PHUB000608	U	CC f-3-ols[§]; BT f-3-ols[§]	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
3′-Hydroxy-4′-methoxycinnamic acid (3′–OH–4′-Me-CA)	194	PHUB000622	U	CC f-3-ols[§]; BT f-3-ols[§]	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017)
with sulfate group(s)					
4′-Hydroxycinnamic acid-3′-sulfate (4′–OH–CA-3′-S)	260	PHUB001594	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl and sulfate group(s)					
3′-Methoxycinnamic acid-4′-sulfate (3′-Me-CA-4′-S)	274	PHUB001171	U	BT f-3-ols[§]; HZT f-3-ols[§]	(Mocciaro et al., 2019; Pereira-Caro et al., 2017)
with methyl(s) and glucuronic acid					
3′-Methoxycinnamic acid-4′-glucuronide (3′-Me-CA-4′-GlcUA)	370	PHUB001170	U	BT f-3-ols[§]; HZT f-3-ols[§]	(Mocciaro et al., 2019; Pereira-Caro et al., 2017)

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Table 1 (*continued*)

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
4′-Methoxycinnamic acid-3′-glucuronide (4′-Me-CA-3′-GlcUA)	370	PHUB001432	U	HZT f-3-ols[§]	Mocciaro et al. (2019)
Phase 2 conjugates of phenylpropanoic acids					
with methyl group(s)					
3-(3′-Methoxy-4′-hydroxyphenyl) propanoic acid (3′-Me-4′–OH–PPA)	196	PHUB001168	U	CC f-3-ols[§]	(Gómez-Juaristi et al., 2019)
with sulfate group(s)					
3-(Phenyl)propanoic acid-4′-sulfate (PPA-4′-S)	246	PHUB002227	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
3-(3′-Hydroxyphenyl)propanoic acid-4′-sulfate (3′–OH–PPA-4′-S)	262	PHUB001206	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
3-(4′-Hydroxyphenyl)propanoic acid-3′-sulfate (4′–OH–PPA-3′-S)	262	PHUB001588	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl and sulfate group(s)					
3-(3′-Methoxyphenyl)propanoic acid-4′-sulfate (3′-Me-PPA-4′-S)	276	PHUB001436	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with glucuronic acid					
3-(4′-Hydroxyphenyl)propanoic acid-3′-glucuronide (4′–OH–PPA-3′-GlcUA)	358	PHUB001204	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl(s) and glucuronic acid					
3-(3′-Methoxyphenyl)propanoic acid-4′-glucuronide (3′-Me-PPA-4′-GlcUA)	372	PHUB001435	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
Phase 2 conjugates of phenylacetic acids					
with methyl group(s)					
4′-Hydroxy-3′-methoxyphenylacetic acid (4′–OH–3′-Me-PAA)	182	PHUB000617	U	GT f-3-ols[§]; CC f-3-ols[§]	(Gómez-Juaristi et al., 2019; Roowi et al., 2010)
3′-Methoxy-4′-hydroxyphenylacetic acid (3′-Me-4′–OH–PAA)	182	PHUB001920	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
2-Hydroxy-2-(4′-hydroxy-3′-methoxyphenyl)acetic acid (2-OH-(4′–OH–3′-Me-PAA))	198	PHUB001585	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with sulfate group(s)					
Dihydroxyphenylacetic acid-sulfate* (Di–OH–PAA-S)	248	PHUB002157	U	pure (−)-EC	Ottaviani et al. (2016)
with methyl and sulfate group(s)					
Methoxy-phenylacetic acid-sulfate* (Me-PAA-S)	262	PHUB001375	P	BT f-3-ols[§]	(Van Duynhoven et al., 2014)
3′-Methoxyphenylacetic acid-4′-sulfate (3′-Me-PAA-4′-S)	262	PHUB002228	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
4′-Methoxyphenylacetic acid-3′-sulfate (4′-Me-PAA-3′-S)	262	PHUB002229	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl(s) and glucuronic acid					
Methoxyphenylacetic acid-glucuronide* (Me-PAA-GlcUA)	358	PHUB002230	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
Phase 2 conjugates of benzoic acids					
with methyl group(s)					
4-Methoxy-trihydroxybenzoic acid (4-Me-triOH-BA)	184	PHUB001861	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
3-Methoxy-trihydroxybenzoic acid (3-Me-triOH-BA)	184	PHUB002269	U	GT f-3-ols[§]; BT f-3-ols[§]	(Clarke et al., 2014; Pereira-Caro et al., 2017)
Methoxy-trihydroxybenzoic acid*[‡] (Me-triOH-BA)	184	–	P	GT f-3-ols[§]	Hodgson et al. (2014)
with sulfate group(s)					
Benzoic acid-sulfate* (BA-S)	202	PHUB002173	U	GT f-3-ols[§]	Clarke et al. (2014)
Benzoic acid-4-sulfate (BA-4-S)	218	PHUB001583	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
Benzoic acid-3-sulfate (BA-3-S)	218	PHUB002231	U	BT f-3-ols[§]; GT f-3-ols[§]	(Clarke et al., 2014; Pereira-Caro et al., 2017)
4-Hydroxybenzoic acid-3-sulfate (4-OH-BA-3-S)	234	PHUB001289	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
3-Hydroxybenzoic acid-4-sulfate (3-OH-BA-4-S)	234	PHUB001921	U	BT f-3-ols[§]	Pereira-Caro et al. (2017)
with methyl and sulfate group(s)					
Methoxy-dihydroxybenzoic acid-sulfate* (Me-diOH-BA-S)	264	PHUB002270	U	GT f-3-ols[§]	Clarke et al. (2014)
3,5-Dimethoxy-hydroxybenzoic acid-4-sulfate (3,5-DiMe–OH–BA-4-S)	278	PHUB002174	U	GT f-3-ols[§]	Clarke et al. (2014)
with glucuronic acid					
Trihydroxybenzoic acid-glucuronide* (TriOH-BA-GlcUA)	346	PHUB002271	U	GT f-3-ols[§]	Clarke et al. (2014)
with methyl(s) and glucuronic acid					

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Table 1 (*continued*)

Systematic name of metabolite (Abbreviation)	MW (Da) of metabolite	PhytoHub ID of metabolite	Biofluid(s) where metabolite was quantified	Dietary source and precursor(s) of metabolite	Ref.
Methoxy-dihydroxybenzoic acid-glucuronide* (Me-diOH-BA-GlcUA)	360	PHUB002272	U	GT f-3-ols§	Clarke et al. (2014)
3,5-Dimethoxy-hydroxybenzoic acid-4-glucuronide (3,5-DiMe–OH–BA-4-GlcUA)	374	PHUB001443	U	GT f-3-ols§	Clarke et al. (2014)
Hippuric acids					
Hippuric acid (HA)	179	PHUB001174	P, U	pure (−)-EC; CHOC f-3-ols§; GT f-3-ols§; BT f-3-ols§	(Clarke et al., 2014; Ottaviani et al., 2016; Rios et al., 2003; Roowi et al., 2010; Van Duynhoven et al., 2014)
3′-Hydroxyhippuric acid (3′–OH–HA)	195	PHUB001161	P, U	pure (−)-EC; CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Ottaviani et al., 2016; Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
4′-Hydroxyhippuric acid (4′–OH–HA)	195	PHUB001334	U	CHOC f-3-ols§; CC f-3-ols§; BT f-3-ols§	(Gómez-Juaristi et al., 2019; Pereira-Caro et al., 2017; Rios et al., 2003)
with sulfate group(s)					
Hippuric acid-sulfate* (HA-S)	259	PHUB002175	U	GT f-3-ols§	Clarke et al. (2014)
Phase 2 conjugates of catechols					
with sulfate group(s)					
Hydroxy-benzene-sulfate* (OH-BE-S)	190	PHUB002196	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
Benzene-2,3-diol-1-sulfate (BE-2,3-diol-1-S)	206	PHUB001967	U	BT f-3-ols§	Pereira-Caro et al. (2017)
Benzene-1,3-diol-2-sulfate (BE-1,3-diol-2-S)	206	PHUB002268	P, U	BT f-3-ols§	(Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)
with methyl and sulfate group(s)					
1-methoxy-benzene-2-sulfate (1-Me-BE-2-S)	204	PHUB002193	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
2-methoxy-benzene-1-sulfate (2-Me-BE-1-S)	204	PHUB002194	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
with glucuronic acid					
Hydroxy-benzene-glucuronide* (OH-BE-GlcUA)	286	PHUB002195	P	BT f-3-ols§	(Van Duynhoven et al., 2014)
Benzene-1,3-diol-2-glucuronide (BE-1,3-diol-2-GlcUA)	302	PHUB002192	P, U	BT f-3-ols§	(Pereira-Caro et al., 2017; Van Duynhoven et al., 2014)

P: plasma, U: urine; S: serum; BT: black tea; GT: green tea; CR: cranberry; RW: red wine; CHOC: chocolate; CC: cocoa; A: apple; RGP: red grape pomace; HZT: hazelnut; ALM: almond; G: grape; RS: raspberry.

* symbol: when the position of the conjugation is unknown.

‡ symbol: this compound is reported as the sum of isomers (in this case, no PhytoHub ID was created).

† symbol: when the compound corresponds to (−/+)-epicatechin or (−/+)-catechin.

symbol: when the compound corresponds to (−/+)-epigallocatechin or (−/+)-gallocatechin.

§ when various native flavan-3-ols are possible precursors of the same metabolite.

(+)-catechin (1), and procyanidin dimer B2 (1)], 22 gut microbiota metabolites comprising 6 5C-ring fission catabolites (5 phenyl-γ-valerolactones and 1 phenylvaleric acid), 5 phenylacetic acids, 4 phenylpropanoic acids, 4 benzoic acids and 3 catechols) and 12 unchanged among monomer and dimer flavan-3-ols. The correct name and identifier in the database PhytoHub (www.phytohub.eu), where more chemical data can be found, are provided for each metabolite in Table 1. Grouping all the flavan-3-ol metabolites based on their metabolic pathway and chemical structure, up to 11 different classes of circulating compounds related strictly to flavan-3-ol intake, namely unchanged monomer and dimer flavan-3-ols, phase 2 conjugates of monomeric and dimeric flavan-3-ols (P2MD), phase 2 conjugates of galloylated flavan-3-ols, phenyl-γ-valerolactones, phenylvaleric acids, cinnamates, phenylpropanoic acids, phenylacetic acids, benzoic acids, hippuric acids, and catechols, were identified in blood and urine fractions following flavan-3-ol intake.

Unchanged monomer and dimer flavan-3-ol class was mostly represented by (+/−)-epigallocatechin-*O*-gallate and (+/−)-gallocatechin-*O*-gallate, whereas the main representatives for P2MD class were monomeric flavan-3-ols conjugated with methoxy and sulfate moieties (Supplemental Fig. 3). Phase 2 conjugates of 5-(dihydroxyphenyl)-γ-valerolactone and 4-hydroxy-5-(dihydroxyphenyl)valeric acid appeared in biofluids most frequently compared to their aglycones and other hydroxylated forms (Supplemental Fig. 4). Out of the 180 quantified metabolites following intake of flavan-3-ols, 88 of them were recovery only in urine samples, followed by those detected in both plasma/serum and urine (n = 56), and only in plasma/serum (n = 36) (Supplemental Fig. 5).

The intake of tea flavan-3-ols provided the most heterogeneous set of circulating metabolites (n = 134), mainly in the form of phenyl-γ-valerolactones (31), P2MD (18), and phenylvaleric acids (13), followed by cocoa and its derived products (48), pure compounds (30), nuts or oily fruits (hazelnuts, almonds) (28), grape and its derived products (19), apple (19), and berries (14) (Fig. 1).

3.4. Nutrikinetics and urinary excretion of flavan-3-ol metabolites in biological samples

3.4.1. Nutrikinetic parameters of the different classes of flavan-3-ol metabolites

The nutrikinetic data for flavan-3-ol metabolites, grouped by classes, are presented in Fig. 2 and Table 2. Except for nutrikinetic parameters that were independent of dose-response with native compounds consumed, such as T_{max} and $t_{1/2}$, an important intra-class variability emerged, as shown from the SD values obtained for C_{max}, AUC and C_{avg} (Table 2).

Unchanged monomer and dimer flavan-3-ols reached a C_{max} of 565 ± 1112 (mean ± SD) and 271 (36–597) nmol/L (median (25th-75th

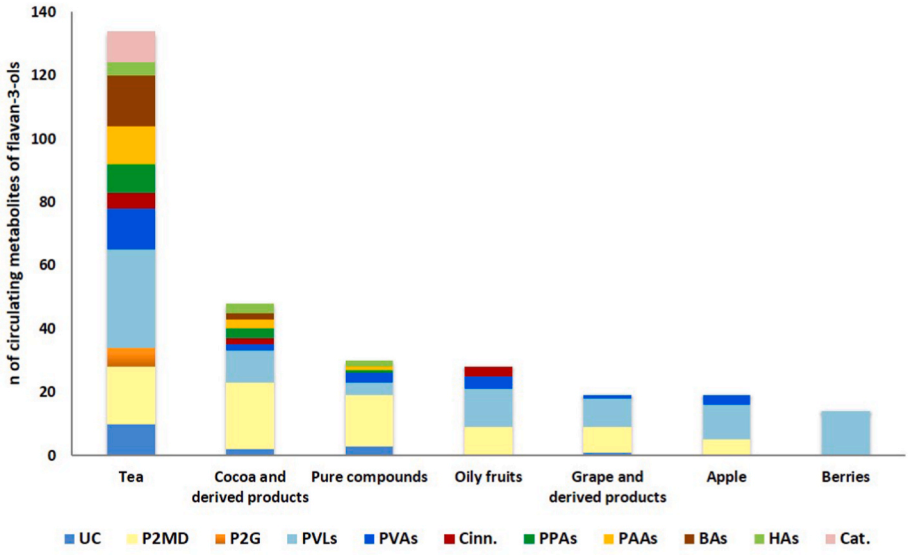

Fig. 1. Number of metabolites of flavan-3-ols, grouped by classes based on their metabolic pathway and chemical structure, quantified at circulating level following intake of the different flavan-3-ol sources by healthy humans. Unchanged monomer and dimer flavan-3-ols (UC), phase 2 conjugates of monomer and dimer flavan-3-ols (P2MD), phase 2 conjugates of galloyl flavan-3-ols (P2G), phenyl-γ-valerolactones (PVLs), phenylvaleric acids (PVAs), cinnamates (Cinn.), phenylpropanoic acids (PPAs), phenylacetic acids (PAAs), benzoic acids (BAs), hippuric acids (HAs), catechols (Cat.). For food sources containing other classes of (poly)phenols yielding also small phenolic metabolites, only P2MD, P2G, PVLs, and PVA were taken into account (i.e. apple, grape and derived products, and berries).

percentile) at T_{max} 1.9 ± 1.0 and 1.6 (1.4–2.0) h. P2MD and phenyl-γ-valerolactones, which are the most specific metabolite classes of flavan-3-ols quantified in plasma, reached a C_{max} of 260 ± 483 and 77 (31–256) nmol/L, and 89 ± 211 and 7 (1–59) nmol/L for P2MD and phenyl-γ-valerolactones, respectively. Phase 2 conjugates of galloylated flavan-3-ols reached a T_{max} greater than 2.5 h. Unchanged monomer and dimer flavan-3-ols showed a C_{avg} of 143 ± 181 and 81 (11–221) nmol/L, followed by P2MD (111 ± 235 and 20 (4–99) nmol/L), and phenyl-γ-valerolactones (20 ± 49 and 1 (0–9) nmol/L) (Fig. 2 and Table 2). Phenyl-γ-valerolactones and phenylvaleric acids had higher values of $t_{1/2}$ compared to unchanged monomer and dimer flavan-3-ols and P2MD (10.4 ± 11.4 and 6.4 (4.8–11.0) h for phenyl-γ-valerolactones; 16.7 ± 16.7 and 7.6 (7.1–21.8) h for phenylvaleric acids). Although analyses of plasma samples did not reveal in a clear, robust and comprehensive manner the nutrikinetic profile of low molecular weight phenolic compounds upon flavan-3-ol intake (Fig. 2 and Table 2), we found that both hippuric acids and catechols reached C_{max} values exceeding 1000 nmol/L over 6 h (T_{max}), followed by benzoic acids (about 111 nmol/L). Normalized values for C_{max}, AUC and C_{avg}, calculated for the different classes of flavan-3-ol metabolites, are reported in Supplemental Fig. 6 and Table 2. This normalization approach highlighted the higher contribution of P2MD to the plasma concentration of flavan-3-ol metabolites with respect to unchanged monomer and dimer flavan-3-ols. Despite normalization, a large within-class variability was found.

3.4.2. Nutrikinetics of the main circulating flavan-3-ol metabolites

Based on the 68 normalized C_{max} mean values calculated for all the metabolites quantified in blood fractions (serum/plasma) (Supplemental Fig. 7A), nine compounds were established as the most abundant circulating metabolites of flavan-3-ols: one unchanged monomer flavan-3-ol, namely (−)-epigallocatechin-3-*O*-gallate [(−)-EGCG], five P2MD [(−)-epicatechin-3′-sulfate, methoxy-(−)-epicatechin-sulfate, (−)-epicatechin-3′-glucuronide, (epi)catechin-sulfate, (epi)catechin-glucuronide], and three phenyl-γ-valerolactones (5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate, 5-(hydroxyphenyl)-γ-valerolactone-sulfate and 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide). The nutrikinetic data for these main flavan-3-ol metabolites are presented in Fig. 3 and Supplemental Table 3, while normalized data is presented in Supplemental Fig. 8 and Supplemental Table 3. (−)-EGCG, representing the main unchanged monomer flavan-3-ol recovered at circulating level following flavan-3-ol consumption, reached a C_{max} of 868 ± 1327 and 476 (272–771) nmol/L (mean ± SD; median (25th-75th percentile) at 2.2 ± 0.9 and 2.0(1.5–2.7) h (T_{max}). Among host metabolites, phase 2 conjugates of (−)-epicatechin showed the highest C_{max} values, ranging from 393 ± 464 and 256 (51–448) nmol/L to 656 ± 878 and 328 (191–649) nmol/L for methoxy-(−)-epicatechin-sulfate and (−)-epicatechin-3′-sulfate, respectively. Overall, the T_{max} of the five phase-2 conjugates of flavan-3-ol monomers was 1.6 ± 0.2 and 1.7 (1.5–1.7) h. Considering the main phenyl-γ-valerolactones found at circulating level after flavan-3-ol intake, 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate presented the highest C_{max} values (368 ± 156 and 332 (305–383) nmol/L, mean ± SD; median (25th-75th percentile), reached at 5.2 ± 1.2 and 5.3 (5.2–6.1) h (T_{max}) (Fig. 3 and Supplemental Table 3). (−)-Epicatechin-3′-sulfate showed the highest C_{avg} values among phase 2 conjugates of flavan-3-ol monomers (318 ± 481 and 114 (42–439) nmol/L).

The C_{avg} of the three main circulating phenyl-γ-valerolactones was 75 ± 20 and 63 (61–83) nmol/L. While (−)-EGCG and the five main phase-2 conjugates of flavan-3-ol monomers showed a mean $t_{½} \approx 2$ h, the $t_{½}$ of the main phenyl-γ-valerolactones appeared to be higher (≈6.3 h) (Fig. 3 and Supplemental Table 3).

3.4.3. Urinary excretion of flavan-3-ol metabolites

Total excretion (μmol) of the different classes of flavan-3-ol metabolites in relation to the ingested amount (μmol) of flavan-3-ols for each study are reported in Supplemental Fig. 9. They were highly variable considering both the same or different sources of flavan-3-ols consumed. Overall, and mainly after tea intake, P2MD and phenyl-γ-valerolactones were excreted in higher amounts than the other classes of metabolites (Supplemental Fig. 9 B/C).

As previously observed for other nutrikinetic parameters, a large within-class variability in the urinary excretion of flavan-3-ol metabolites was found (Table 2). Catechols showed the highest mean value of urinary excretion (≈10% of the ingested dose), followed by P2MD and phenyl-γ-valerolactones (≈4%). A similar trend was also observed when median values were considered [9.0 (2.0–11.5) %, 0.7 (0.2–3.8) %, and 0.3 (0.0–2.1) %, median (25th-75th percentile)] for catechols, P2MD and phenyl-γ-valerolactones, respectively (Fig. 4A). Even if the urinary excretion, expressed as % of intake, varied widely within the same class of flavan-3-ol metabolites (Fig. 4B), robust data distribution for P2MD and phenyl-γ-valerolactones suggested that both classes were extensively excreted in urine after native flavan-3-ol intake.

To unravel the contribution of each metabolite class to the overall bioavailability of flavan-3-ols, for each study and for each ingested source of flavan-3-ols, the bioavailability (%) of the 10 classes of flavan-3-ol metabolites was calculated by computing the ratio between the total

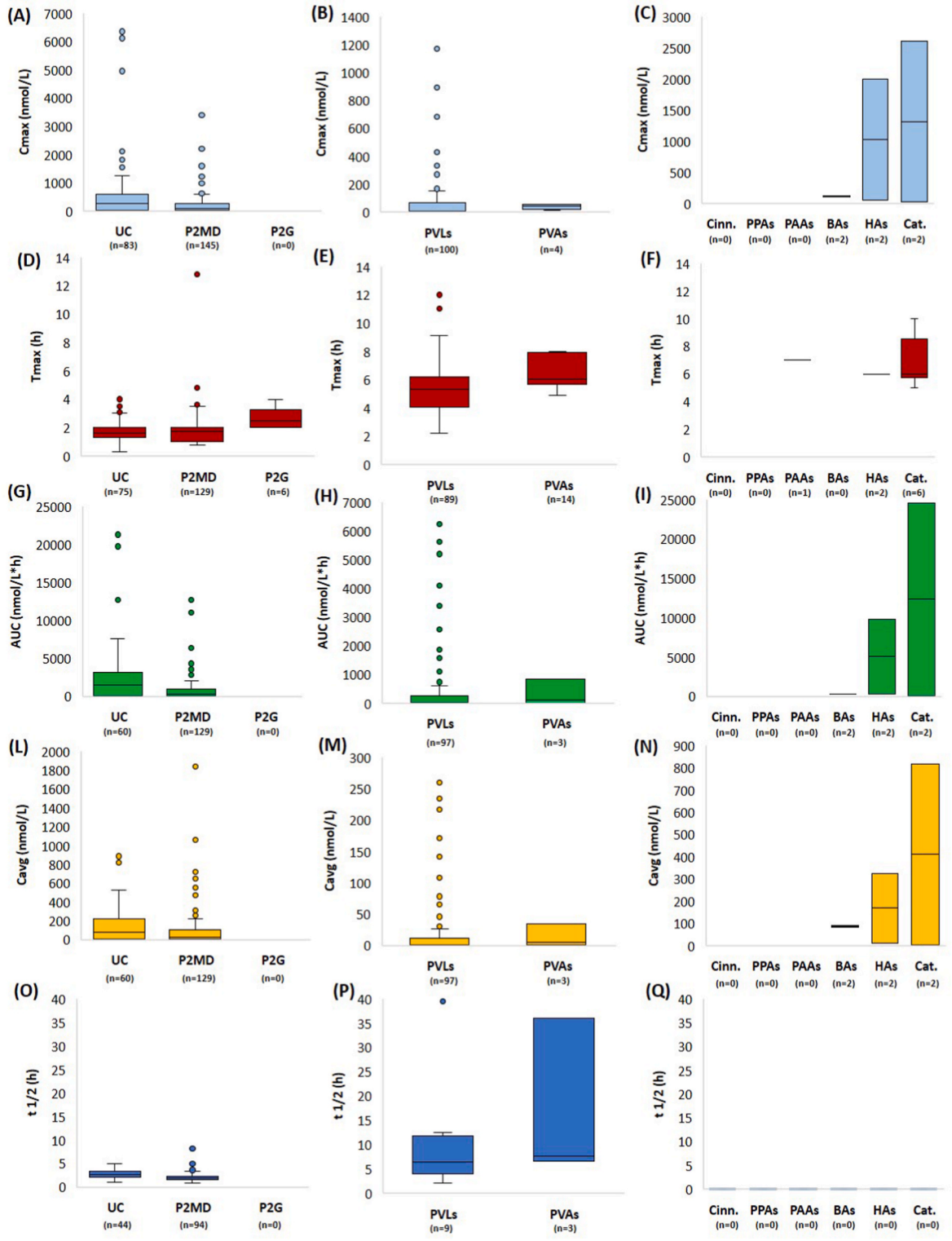

Fig. 2. Box plot for C_{max} (nmol/L) (**A**, **B**, **C**), T_{max} (h) (**D**, **E**, **F**), AUC (nmol/L*h) (**G**, **H**, **I**), C_{avg} (nmol/L) (**L**, **M**, **N**), $t_{1/2}$ (h) (**O**, **P**, **Q**) of unchanged monomer and dimer flavan-3-ols (UC), phase 2 conjugates of monomer and dimer flavan-3-ols (P2MD), phase 2 conjugates of galloyl flavan-3-ols (P2G), phenyl-γ-valerolactones (PVLs), phenylvaleric acids (PVAs), cinnamates (Cinn.), phenylpropanoic acids (PPAs), phenylacetic acids (PAAs), benzoic acids (BAs), hippuric acids (HAs), catechols (Cat.). Apart for UC, classes of flavan-3-ol metabolites include data derived from both aglycones and their phase 2 conjugates. Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the curve (AUC), average concentration (C_{avg}), apparent half elimination time ($t_{½}$), n indicates the number of biological replicates collected for the same class of flavan-3-ol metabolites and for the same nutrikinetic parameter. No data was available to build panel Q, related to $t_{1/2}$.

Table 2
Nutrikinetic parameters and urinary excretion data for metabolites of flavan-3-ols, grouped by classes based on their metabolic pathway and chemical structure, quantified at circulating level following flavan-3-ol intake by healthy humans. Data are reported as mean ± SD (*n* indicates the number of biological values collected from literature for each parameter for the flavan-3-ol class).

Classes of flavan-3-ol metabolites	C_{max} (nmol/L)	C_{max} normalized ((nmol/L)/total μmol of ingested flavan-3-ols)	T_{max} (h)	AUC (nmol/L*h)	AUC normalized ((nmol/L*h)/total μmol of ingested flavan-3-ols)	C_{avg} ((nmol/L*h)/n hours)	C_{avg} normalized ((nmol/L*h)/total μmol of ingested flavan-3-ols/n hours)	$t_{1/2}$ (h)	Urinary excretion (% of intake)
Unchanged monomer and dimer flavan-3-ols	565.2 ± 1111.5 (*n* = 83)	0.7 ± 0.9 (*n* = 83)	1.9 ± 1.0 (*n* = 75)	2606.5 ± 4118.8 (*n* = 60)	2.8 ± 3.6 (*n* = 60)	143.3 ± 181.3 (*n* = 60)	0.2 ± 0.3 (*n* = 60)	2.8 ± 0.9 (*n* = 44)	1.1 ± 2.0 (*n* = 11)
Phase 2 conjugates of monomer and dimer flavan-3-ols*	259.8 ± 482.5 (*n* = 145)	1.1 ± 1.8 (*n* = 145)	1.8 ± 1.2 (*n* = 129)	892.0 ± 1763.4 (*n* = 129)	4.4 ± 9.0 (*n* = 129)	110.5 ± 234.8 (*n* = 129)	0.4 ± 0.7 (*n* = 129)	2.2 ± 1.1 (*n* = 94)	4.3 ± 10.4 (*n* = 189)
Phase 2 conjugates of galloylated flavan-3-ols*	–	–	2.7 ± 0.8 (*n* = 6)	–	–	–	–	–	–
Phenyl-γ-valerolactones*	88.5 ± 210.5 (*n* = 100)	0.6 ± 3.7 (*n* = 100)	5.3 ± 1.8 (*n* = 89)	479.2 ± 1174.4 (*n* = 97)	0.7 ± 3.2 (*n* = 97)	20.0 ± 48.9 (*n* = 97)	0.0 ± 0.1 (*n* = 97)	10.4 ± 11.4 (*n* = 9)	3.9 ± 10.4 (*n* = 196)
Phenylvaleric acids*	39.5 ± 20.8 (*n* = 4)	0.2 ± 0.1 (*n* = 4)	6.4 ± 1.1 (*n* = 14)	314.7 ± 453.6 (*n* = 3)	1.4 ± 2.3 (*n* = 3)	13.2 ± 18.8 (*n* = 3)	0.1 ± 0.1 (*n* = 3)	16.7 ± 16.7 (*n* = 3)	1.4 ± 2.3 (n = 22)
Cinnamates*	–	–	–	–	–	–	–	–	0.8 ± 1.5 (*n* = 12)
Phenylpropanoic acids*	–	–	–	–	–	–	–	–	2.1 ± 4.4 (*n* = 16)
Phenylacetic acids*	–	–	7 (*n* = 1)	–	–	–	–	–	1.1 ± 1.8 (*n* = 18)
Benzoic acids*	111.4 ± 11.5 (*n* = 2)	0.0 ± 0.0 (*n* = 2)	–	261.9 ± 17.2 (*n* = 2)	0.1 ± 0.0 (*n* = 2)	87.3 ± 5.7 (*n* = 2)	0.0 ± 0.0 (*n* = 2)	–	3.2 ± 5.6 (*n* = 42)
Hippuric acids*	1023.0 ± 1381.7 (*n* = 2)	4.4 ± 6.0 (*n* = 2)	6.0 ± 0.0 (*n* = 2)	5031.0 ± 6679.3 (*n* = 2)	21.9 ± 29.0 (*n* = 2)	167.7 ± 222.6 (*n* = 2)	0.7 ± 1.0 (*n* = 2)	–	2.5 ± 4.0 (*n* = 13)
Catechols*	1309.5 ± 1825.0 (*n* = 2)	5.7 ± 7.9 (*n* = 2)	6.8 ± 1.8 (*n* = 6)	12309.0 ± 17280.3 (*n* = 2)	53.5 ± 75.1 (*n* = 2)	410.3 ± 576.0 (*n* = 2)	1.8 ± 2.5 (*n* = 2)	–	10.3 ± 16.2 (*n* = 8)

C_{max}: maximum plasma concentration; T_{max}: time to reach C_{max}; AUC: area under the curve; C_{avg}: average concentration; $t_{1/2}$: apparent half elimination time; *symbol: when the class includes data derived from both aglycones and their phase 2 conjugates; - means any data was collected for that nutrikinetic parameter.

excreted μmol of each metabolite class and the ingested μmol of flavan-3-ols and thus bioavailability values for each metabolite class were averaged (Supplemental Fig. 10). P2MD and phenyl-γ-valerolactones contributed to the bioavailability of flavan-3-ols for about 26 and 24% for P2MD and phenyl-γ-valerolactones, respectively, followed by phenylvaleric acids and unchanged monomer and dimer flavan-3-ols (2%). Instead, comparing the classes of flavan-3-ol metabolites related to a delayed biotransformation pathway, catechols contributed to flavan-3-ol bioavailability for about 41%, followed by benzoic acids (19%), phenylpropanoic acids (7%), phenylacetic acids and hippuric acids (4%), and cinnamates (2%).

Regarding individual main metabolites, while (−)-EGCG was not recovered in urine (Fig. 5A/C), (epi)catechin-sulfate was excreted at higher amounts (12.6 ± 21.3 and 3.8 (1.0–11.8), mean ± S D; median (25th-75th percentile)) than the other main host metabolites (Fig. 5A/C and Supplemental Table 3). Among the main phenyl-γ-valerolactones, 22.0 ± 26.5 and 15.8 (0.5–38.9) % (mean ± SD; median(25th-75th percentile) of the ingested dose of flavan-3-ols was excreted as 5-(hydroxyphenyl)-γ-valerolactone-sulfate (3',4' isomers) (Fig. 5B/D and Supplemental Table 3). Values of urinary excretion, expressed as a percentage of intake, for circulating metabolites were pooled according to the same source of ingested flavan-3-ols from which they were derived and are reported in Fig. 6, while the single values of urinary excretion of metabolites produced from each flavan-3-ol source are shown in Fig. 6B. Flavan-3-ols consumed from grape and derived products were excreted in amounts equal to 8.8 ± 16.2 and 2.7 (0.2–9.3) % of their intake, followed by oily fruits (5.2 ± 12.4 and 1.0 (0.1–4.2) %), pure compounds (4.3 ± 5.0 and 1.8 (0.7–6.5) %) and tea (4.0 ± 10.1 and 0.6 (0.1–3.0) %). Flavan-3-ols ingested from cocoa, apples and berries were excreted in urine to a lesser extent.

3.5. Bioavailability of flavan-3-ols

The mean bioavailability of flavan-3-ols, calculated from the 20 studies which met inclusion criteria for calculating flavan-3-ol bioavailability (see 2.3. section, Supplemental Table 4), was 31 ± 23% [median 25th-75th percentile: 35 (13–40)] (Fig. 7). Differences in these values were associated with the type of study considered, which somehow is related to the period when each article was published (Fig. 7).

The 20 bioavailability values were compared source by source with the ingested amount (μmol) of total flavan-3-ols deriving from each study (Fig. 8A). They were pooled to estimate the mean bioavailability of flavan-3-ols for each source employed in the analysed studies. The bioavailability of flavan-3-ols was 82% (number -n- of flavan-3-ol bioavailability values collected/estimated for each source = 1) and 63% (n = 2) after pure compound (i.e. (−)-epicatechin) and oily fruit (i.e. almond, hazelnut) intake, respectively, followed by 25% after consumption of tea (n = 7), cocoa and derived products (n = 5), apple (n = 3), and grape and derived products (n = 2) (Fig. 8B).

4. Discussion

This is the first work that systematically investigated the nutrikinetics of up to 180 flavan-3-ol derived compounds following their intake by healthy subjects, and estimated the bioavailability of flavan-3-ols. All collected data on the identified metabolites and nutrikinetics data have been made available in the database PhytoHub (www.phytohub.eu) to

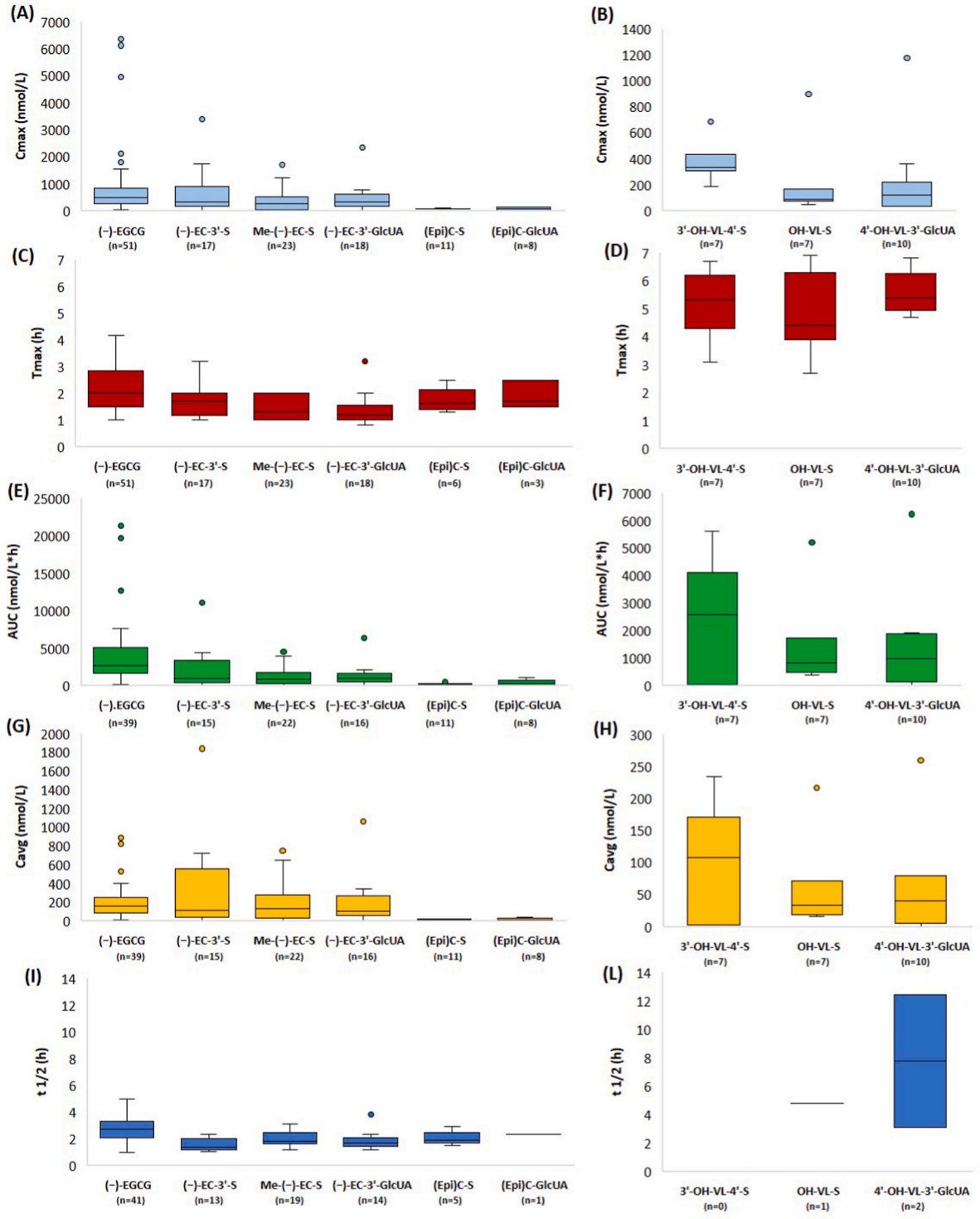

Fig. 3. Box plot for C_{max} (nmol/L) (**A**, **B**), T_{max} (h) (**C**, **D**), AUC (nmol/L*h) (**E**, **F**), C_{avg} (nmol/L) (**G**, **H**), $t_{1/2}$ (h) (**I**, **L**) of (−)-epigallocatechin-3-*O*-gallate ((−)-EGCG), (−)-epicatechin-3′-sulfate ((−)-EC-3′-S), methoxy-(−)-epicatechin-sulfate (Me-(−)-EC-S), (−)-epicatechin-3′-glucuronide ((−)-EC-3′-GlcUA), (epi)catechin-sulfate ((Epi)C–S), (epi)catechin-glucuronide ((Epi)C-GlcUA), 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate (3′–OH–VL-4′-S), 5-(hydroxyphenyl)-γ-valerolactone-sulfate (OH-VL-S), 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide (4′–OH–VL-3′-GlcUA). (Epi)C–S and (epi)C-GlcUA values include all the (−/+)-epicatechin and (−/+)-catechin isomers quantified at circulating level following flavan-3-ol intake. Me-(−)-EC-S and OH-VL-S values include data derived from both individual and sum of unknown isomers quantified at circulating level following flavan-3-ol intake. Maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the curve (AUC), average concentration (C_{avg}), apparent half elimination time ($t_{½}$). Metabolites are named according to (Kay et al., 2020). n indicates the number of biological replicates collected for the same flavan-3-ol metabolite and for the same nutrikinetic parameter.

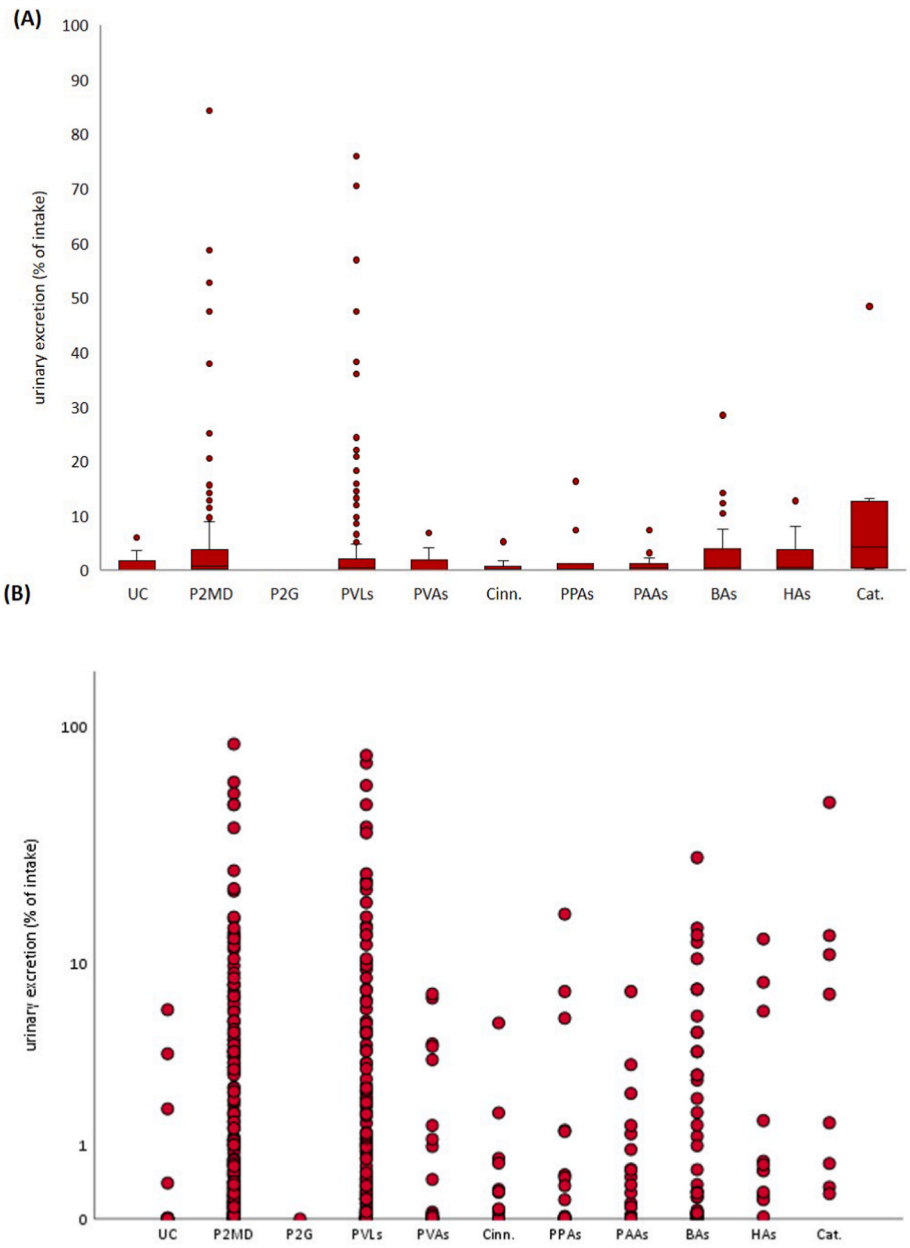

Fig. 4. (**A**) Box plot and single values (**B**) of urinary excretion (% of intake) for metabolites of flavan-3-ols, grouped by classes based on their metabolic pathway and chemical structure, quantified at circulating level following flavan-3-ol intake by healthy humans. Classes of flavan-3-ol metabolites include data derived from both aglycones and their phase 2 conjugates. Unchanged monomer and dimer flavan-3-ols (UC), phase 2 conjugates of flavan-3-ol monomers and dimers (P2MD), phase 2 conjugates of galloylated flavan-3-ols (P2G), phenyl-γ-valerolactones (PVLs), phenylvaleric acids (PVAs), cinnamates (Cinn.), phenylpropanoic acids (PPAs), phenylacetic acids (PAAs), benzoic acids (BAs), hippuric acids (HAs), and catechols (Cat.).

extend the impact of the work.

Tea intake leads the largest number of metabolites (Fig. 1). Although (−)-EGCG is the main unmetabolized compound found at circulating level following tea consumption (Clifford et al., 2013), galloylated flavan-3-ols are easily available to a myriad of metabolic pathways by colonic microflora and mammalian phase 2 enzymes (Calani et al., 2012a, 2012b; Roowi et al., 2010; Stalmach et al., 2009). Flavan-3-ol intake from cocoa elicited a higher increase in circulating compounds (n = 48), prevalently as P2MD (21), and in the appearance of simple phenolic metabolites (Table 1 and Fig. 1), compared to other ingested sources of procyanidins, such as nuts, grape, wine, apple, and berries. These differences might be attributable to the high amount of flavan-3-ol monomers in cocoa (Sorrenti et al., 2020), more prone to gut microbiota metabolism (Crozier et al., 2010; Monagas et al., 2010; Borges et al., 2018; Di Pede et al., 2022). Indeed, the low number of metabolites recovered after berry intake was probably attributable to their richness in highly polymerized procyanidins (Nile and Park, 2014), which are less susceptible to catabolism by gut microbiota (Mena et al., 2015; Di Pede et al., 2022). On the other hand, it should be noted that when flavan-3-ols were consumed together with other flavonoids (i.e. anthocyanins, flavonols), considered precursors of various late-products of microbial metabolism, data on simple C_6–C_3, C_6–C_2, C_6–C_1 phenolic acids were not collected. Indeed, berries, apples, oily fruits, grapes and wine contain a huge variety of putative precursors of simple phenolic acids other than flavan-3-ols (Selma et al., 2009; Del Rio et al., 2010a; Teixeira et al., 2014; Trošt et al., 2018; Alasalvar et al., 2020), which may hinder a clear assessment of the bioavailability of flavan-3-ols coming from these dietary sources. But, beyond this aspect related to the co-presence of other precursors of low molecular weight metabolites, the variability in the number of studies collected for each dietary source (Supplementary Table 2) and in the number of metabolites quantified within each study, as well as metabolites coming from the dietary background of volunteers, should be taken into account in the interpretation of these findings. To have a clear and more realistic scenario on the ability of the different dietary sources of flavan-3-ols in producing metabolites, a large intervention study should be conducted to compare the dietary sources provided at the same dose, with quantification of all produced metabolites using a large-coverage analytical

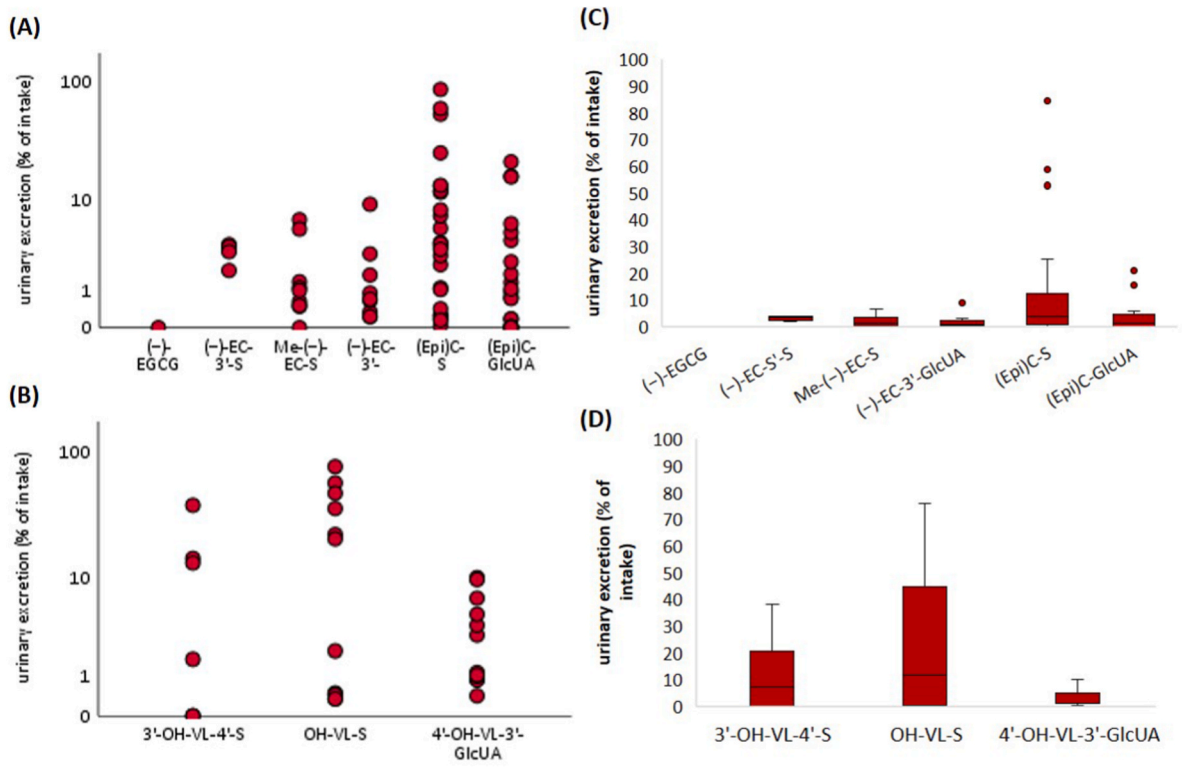

Fig. 5. Single values of urinary excretion (% of intake) (**A**, **B**) and box plot (**C**, **D**) of urinary excretion (% of intake) for the main flavan-3-ol metabolites quantified following flavan-3-ol intake by healthy humans. (−)-Epigallocatechin-3-*O*-gallate ((−)-EGCG), (−)-epicatechin-3′-sulfate ((−)-EC-3′-S), methoxy-(−)-epicatechin-sulfate (Me-(−)-EC-S), (−)-epicatechin-3′-glucuronide ((−)-EC-3′-GlcUA), (epi)catechin-sulfate ((Epi)C–S), (epi)catechin-glucuronide ((Epi)C-GlcUA), 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-sulfate (3′–OH–VL-4′-S), 5-(hydroxyphenyl)-γ-valerolactone-sulfate (OH-VL-S), 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-glucuronide (4′–OH–VL-3′-GlcUA). (Epi)C–S and (epi)C-GlcUA values include all the (−/+)-epicatechin and (−/+)-catechin isomers quantified at circulating level following flavan-3-ol intake. Me-(−)-EC-S and OH-VL-S values include data derived from both individual and sum of unknown isomers quantified at circulating level following flavan-3-ol intake. Metabolites are named according to (Kay et al., 2020).

method.

Analyses of data arising from plasma samples proved that unchanged monomer and dimer flavan-3-ols were mainly represented by (−)-EGCG in feeding studies with green/black tea (Fig. 3 and Supplemental Table 3). Tea trials highlighted that unchanged (−)-EGCG circulates at the highest concentration when all the other parent flavan-3-ols and their phase 2 metabolites are taken into account (Stalmach et al., 2009; Del Rio et al., 2010b). The metabolic fate of (−)-EGCG remains to be further investigated, as it is quickly removed from the circulatory system (low $t_{1/2}$ value) but, surprisingly, it is not recovered in urine (Fig. 3 and Supplemental Table 3). It is possible that the galloyl moiety may impact the absorption and subsequent phase 2 conjugation mechanisms of galloylated flavan-3-ols (Henning et al., 2008). With this work, we have supported the large body of evidence (Crozier et al., 2009; Borges et al., 2018) indicating that flavan-3-ol monomers and dimers are prevalently absorbed in the small intestine, even if some differences in the metabolic yield after ingestion of monomeric, dimeric and oligomeric flavan-3-ols were highlighted (Wiese et al., 2015).

The phase 2 conjugates of parent compounds (P2MD), mainly monomers, reached plasma concentration peaks (C_{max} ≈ 260 nmol/L) at 1.8 h (T_{max}) after flavan-3-ol intake, to rapidly disappear from the circulatory system, as demonstrated from their $t_{1/2}$ values (≈2 h post-consumption) (Fig. 2 and Table 2). It has been shown that (−)-epicatechin-3′-sulfate, methoxy-(−)-epicatechin-sulfate, (−)-epicatechin-3′-glucuronide, (epi)catechin-sulfate and (epi)catechin-glucuronide are the most abundant phase 2 conjugates of flavan-3-ol monomers in plasma, even if some quantitative differences in their nutrikinetic profiles were highlighted (Fig. 3 and Supplemental Table 3). Data clearly indicates that the stereochemistry may impact phase 2 sulfation, glucuronidation and methylation of flavan-3-ol monomers, since the three conjugates of (−)-epicatechin attained the highest C_{max} (≈500 nmol/L) compared to the other host metabolites (Fig. 3 and Supplemental Table 3). This is not surprising since it has been widely demonstrated that (−)-epicatechin is more bioavailable than (+)-epicatechin and (−/+)-catechin (Ottaviani et al., 2011; Clifford et al., 2013; Borges et al., 2018). This robust data is further supported by the huge efforts in synthesizing pure analytical standards of phase 2 conjugates enabling a more accurate assessment of the circulating levels of (−)-epicatechin metabolites (Sharma et al., 2010; Mull et al., 2012; Ottaviani et al., 2012; Zhang et al., 2013a, 2013b).

Although 3′-methoxy-(−)-epicatechin-5-sulfate, methoxy-(epi)catechin-sulfate, methoxy-(epi)catechin-glucuronide, and methoxy-(−)-epigallocatechin-sulfate were not selected as main plasma metabolites of flavan-3-ols, they were excreted in urine in amounts equal to 4, 10, 2 and 7% of the ingested dose, respectively (Supplemental Excel file), indicating the importance of assessing both blood and urine samples when evaluating the bioavailability of flavan-3-ols. On the other hand, (−)-epicatechin was present in the systemic circulation predominantly as sulfate and glucuronide conjugates at the 3′ position (Borges et al., 2018; Ottaviani et al., 2016), proving that phase 2 conjugation mechanisms of flavan-3-ol monomers are stereochemically-dependent. Indeed, Ottaviani et al. (2012) demonstrated that sulfation of (+)-epicatechin took place at 5 position. Nevertheless, the identity of methoxy-(−)-epicatechin-sulfate, as well as that of the two (epi)catechin conjugates [(epi)catechin-sulfate and (epi)catechin-glucuronide] remain unknown for most of the publications. This should encourage further identification initiatives for a complete assessment of the host metabolites occurring in circulation. A point to keep in mind is that the C_{max} values for these (epi)catechin conjugates might suffer from misquantification, commonly occurring in the absence of reference

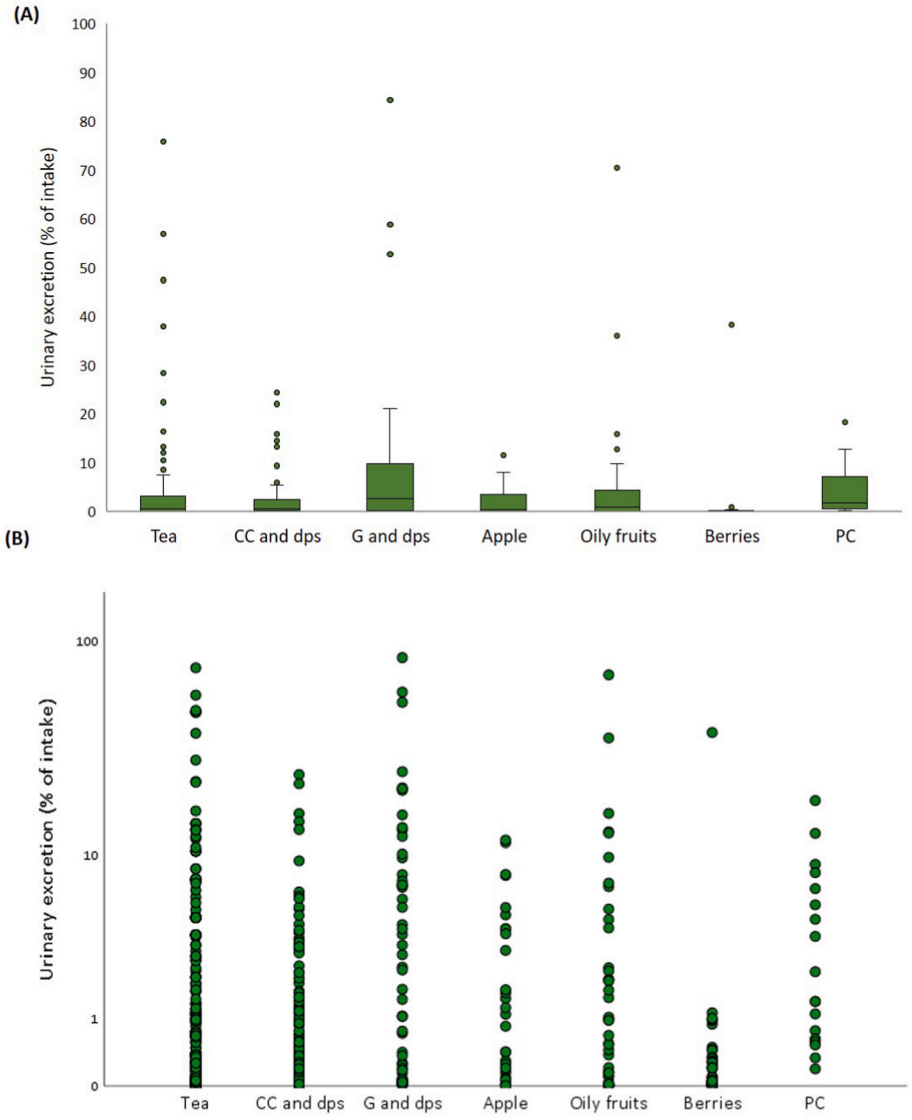

Fig. 6. (**A**) Box plot and single values (**B**) of urinary excretion (% of intake) for all the metabolites quantified following intake of the different sources of flavan-3-ols. Cocoa and derived products (CC and dps), G and dps (grape and derived products), and pure compounds (PC). Flavan-3-ol source (n of biological replicates): tea (210), CC and dps (104), G and dps (50), apple (37), oily fruits (41), berries (67), PC (18).

standards (Ottaviani et al., 2018b), or the presence of low bioavailable flavan-3-ol stereoisomers (Donovan et al., 2006; Ottaviani et al., 2011), since nutrikinetic values for these metabolites included all the (−/+)-epicatechin and (−/+)-catechin isomers quantified at circulating level following flavan-3-ol intake (Fig. 3 and Supplemental Table 3).

Flavan-3-ols circulate principally as phase 2 conjugates of colonic catabolites, as up to 97 host-gut microbiota metabolites were found (Table 1), mainly represented by specific ring fission catabolites of flavan-3-ols as phenyl-γ-valerolactones and phenylvaleric acids (Mena et al., 2019a). Unmetabolized flavan-3-ols that reach the colon undergo microbiota-induced transformations, yielding phenyl-γ-valerolactones which may be further converted to phenylvaleric acids (Mena et al., 2019a; Stevens and Maier, 2016), as demonstrated from the T_{max} values obtained for phenyl-γ-valerolactones and phenylvaleric acids (5.3 and 6.4 h, respectively) (Fig. 2 and Table 2). Of note, phenyl--γ-valerolactones were quantified after intake of all the dietary sources of flavan-3-ols. Up to 31 phenyl-γ-valerolactones were recovered after tea intake, followed by berries ($n = 14$), oily fruits (12), apple (11), cocoa and its derived products (10), grape and its derived products (9), and pure compounds (4) (Fig. 1). These findings support the potential role of phenyl-γ-valerolactones in being considered valuable biomarkers of dietary consumption of flavan-3-ols monomers and procyanidins, although they still require proper validation for that use (Urpi-Sarda et al., 2009; Duynhoven et al., 2011; Ottaviani et al., 2016, 2018a).

Phenyl-γ-valerolactones were present in the systemic circulation at a higher concentration than phenylvaleric acids. Moreover, regardless of the conjugation position, phase 2 conjugates of 5-(dihydroxyphenyl)-γ-valerolactones had a higher C_{max} compared to those of 5-(hydroxyphenyl)-γ-valerolactones (≈107 and 56 nmol/L, respectively) (Supplemental Excel file), both had a T_{max} of 5 h (T_{max}). Residual aglycones of phenyl-γ-valerolactones had very low C_{max} levels (≈19 nmol/L) with a 6 h T_{max}, as a result of the extensive phase II metabolism of these catabolites (Mena et al., 2019a). High $t_{1/2}$ values for phenyl--γ-valerolactones and phenylvaleric acids indicated that these gut microbiota metabolites remain in the systemic circulation for a relatively long time. The exact identity of 5-(hydroxyphenyl)-γ-valerolactone-sulfate, one of the main plasma phenyl-γ-valerolactones identified following flavan-3-ol intake, remains unclear in many reports (Fig. 3 and Supplemental Table 3). This can be due to the difficulties in fully identifying these catabolites, although big

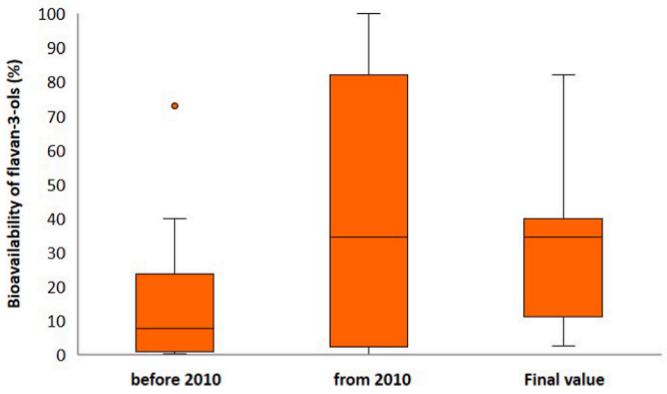

Fig. 7. Box plot for bioavailability (%) of flavan-3-ols calculated taking into account all the values for flavan-3-ol bioavailability collected from literature and/or estimated from urinary excretion data derived from studies published before 2010 ($n = 14$), from studies published from 2010 onwards ($n = 31$), from studies which met inclusion criteria [bioavailability values that were <1 and/or >100%, or were calculated by not taking into account a complete and appropriate metabolic pathway in terms of metabolites produced following flavan-3-ol intake were excluded] for calculating the final value of flavan-3-ol bioavailability (%) ($n = 20$). Details on flavan-3-ol bioavailability (%) values employed to calculate the final value for bioavailability of flavan-3-ols are reported in Supplemental Table 5.

advances have been made in the synthesis of their aglycones and phase II conjugates (Sánchez-Patán et al., 2011; Curti et al., 2015; Brindani et al., 2017). Nevertheless, it seems likely that most of the work with dihydroxylated flavan-3-ols refer to 3',4' isomers, 5-(4'-hydroxyphenyl)-γ-valerolactone-3'-sulfate being the most representative isomer (Ottaviani et al., 2016). In this respect, 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-sulfate was excreted in urine in amounts higher than 15% of the ingested dose.

Additional specific 5C-ring fission catabolites were also excreted in urine in amounts representing over 2% of flavan-3-ol intake, including 5-(phenyl)-γ-valerolactone-methoxy-sulfate [2.8 ± 5.8 and 0.9 (0.1–1.4) %] [mean ± SD; median (25th-75th percentile)], 5-(hydroxyphenyl)-γ-valerolactone-glucuronide (final values include data derived from both individual and sum of unknown isomers) [3.3 ± 2.8 and 2.2 (1.7–4.9) %], 5-(3′-hydroxyphenyl)-γ-valerolactone-4′-glucuronide [2.5 ± 6.3 and 0.4 (0.3–1.7) %], 5-(phenyl)-γ-valerolactone-sulfate-glucuronide [2.1 ± 6.0 and 0.3 (0.2–0.8) %] and one phenylvaleric acid, 4-hydroxy-5-(4′-hydroxyphenyl)valeric acid-3′-sulfate [2.5 ± 2.1 and 3.4 (1.8–3.7) %](Supplemental Excel file). Phase II conjugates of phenyl-γ-valerolactones, derived from flavan-3-ol monomers, were excreted in urine prevalently as sulfate conjugates. Different profiles between plasma and urine in the appearance and accumulation of some metabolites might suggest that the kidneys may represent a key organs for the metabolism of some compounds, beyond the phase 2 conjugation mechanisms occurring at small intestine and/or hepatic levels.

Comparing the mean value of ingested flavan-3-ols (≈1308 μmol) with the mean cumulative urinary excretion of phenyl-γ-valerolactones (≈217 μmol) indicates that the ingestion of about 5 μmol of flavan-3-ols would potentially result in excretion of 1 μmol of phenyl-γ-valerolactones. This observation is in line with stoichiometry in the production of these C_5–C_6 colonic metabolites from flavan-3-ol monomers and B-type dimers (Di Pede et al., 2022). Likewise, when comparing the mean cumulative urinary excretion of phenylvaleric acids (≈4 μmol) with the mean ingested amount of flavan-3-ols obtained from studies that quantified these catabolites (≈1190 μmol), we calculated that 303 μmol of flavan-3-ols would be needed to reach 1 μmol of urinary phenylvaleric acids.

Although plasma sample analyses did not fully reveal robust kinetic profiles of low molecular weight phenolic acids in the systemic circulation (Fig. 2 and Table 2), urine analyses showed that these "late-products" of flavan-3-ol metabolism were excreted in average amounts ranging from ≈1% up to 10% of the ingested flavan-3-ol dose for cinnamates and catechols, respectively, values somewhat comparable to that obtained for P2MD and phenyl-γ-valerolactones (≈4%). Additionally, the contribution of simple phenolic acids to flavan-3-ol bioavailability is underlined by values calculated for their bioavailability (Supplemental Fig. 10). A radiolabel study investigating the ADME of [2–^{14}C](−)-epicatechin in healthy humans (Ottaviani et al., 2016) found that about 57 μmol of C_6–C_3, C_6–C_2, and C_6–C_1 metabolites were excreted in urine, representing 28% of parent compound intake. Our data suggests that low molecular weight phenolic metabolites should be considered as relevant contributor of the ADME of flavan-3-ols. Indeed, although data on C_6–C_3, C_6–C_2, and C_6–C_1 derivatives were collected if they were related to the ingestion of dietary sources providing only flavan-3-ols (Table 1), it is well known that these metabolites have unspecific dietary origin and precursor compounds (Del Rio et al., 2013;

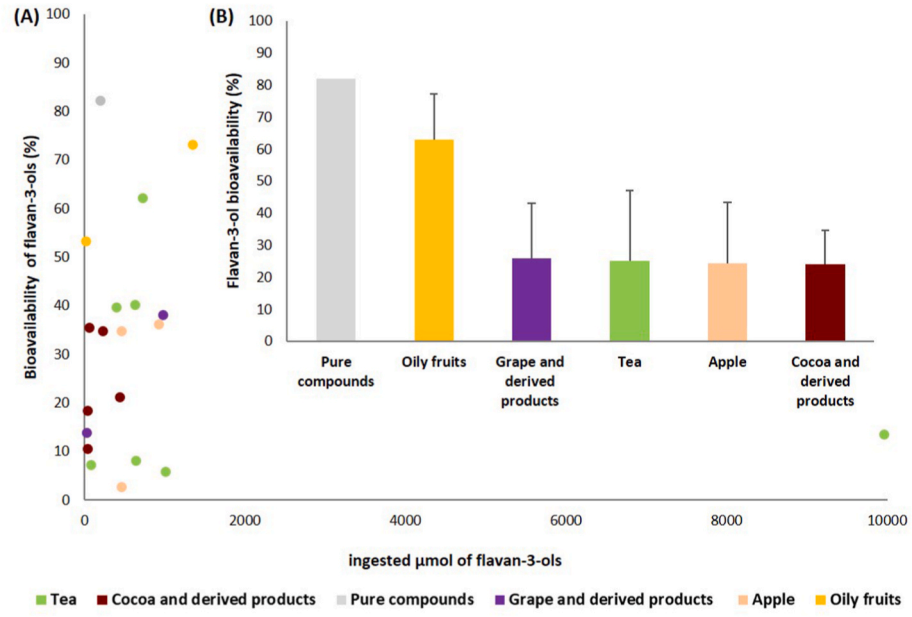

Fig. 8. (**A**) Values of bioavailability (%) for flavan-3-ols, collected from literature and/or estimated from urinary excretion data, and ingested μmol of the different flavan-3-ol sources. Each bullet indicates the bioavailability (%) value for flavan-3-ols, obtained for every single study, and related to each dose of consumed flavan-3-ols in the study. (**B**) Bioavailability of flavan-3-ols calculated for the different food sources employed in the human studies that underwent data analyses. Data are expressed as mean and SD. Flavan-3-ol source (n of values of flavan-3-ol bioavailability (%)): pure compounds (1), oily fruits (2), grape and derived products (2), tea (7), apple (3), cocoa and derived products (5).

Rodriguez-Mateos et al., 2014; Mena et al., 2019a; Carregosa et al., 2022) and their blood and urine profiles might be partially influenced by volunteers' diet.

The mean bioavailability of flavan-3-ols was 31%, which accounts for the moderate bioavailability of dietary flavan-3-ols. Nevertheless, when the mean bioavailability was calculated from studies published before 2010, it was 16% (Fig. 7). This time cutoff was selected since it coincides with the early development of methods for the synthesis of flavan-3-ol metabolites, allowing proper identification, quantification, and a better knowledge of their metabolic pathways (Borges et al., 2018). As expected, the bioavailability of flavan-3-ols resulted in a higher 38% when studies published from 2010 onwards were considered, providing a clear indication of the impact that the use of reference standards has on the accuracy in the identification and quantification of flavan-3-ols and their whole set of metabolites (Ottaviani et al., 2018b).

In accordance with various human trials (Feliciano et al., 2017; Trošt et al., 2018; Gómez-Juaristi et al., 2019; Favari et al., 2020), this systematic review suggested that bioavailability of flavan-3-ols seems to be scarcely affected by the amount of ingested compounds, since 19 out of 20 values considered for assessing the final bioavailability values ranged from 3 up to 82%, without exceeding 1500 μmol of flavan-3-ol intake (Fig. 8A).

In this context, when the source of flavan-3-ols is taken into account, it should be noted that:

- considering individual bioavailability values, intra- and inter-source differences in flavan-3-ol bioavailability exist and could be explained by the study designs (i.e. degree of processing of the source, period for blood and urine collection), population characteristics, analytical methods used, and the set of metabolites targeted, among other factors;
- pooling bioavailability values for each source employed along the studies analysed, it is possible to observe that principal, flavan-3-ol monomer, (−)-epicatechin, was more bioavailable compared to ingested sources of proanthocyanidins (Crozier et al., 2010; Del Rio et al., 2013), suggesting a role of the structure of ingested flavan-3-ol in affecting the metabolic efficiency in their biotransformation.

Further human studies employing other pure monomer flavan-3-ols are required, also paying attention to the bioavailability of proanthocyanidins from different plant-based foods. Indeed, a trend pointing out a higher bioavailability of flavan-3-ols from almond/hazelnut compared to grapes, apple, tea and cocoa, whose values appear to be entirely comparable, was observed (Fig. 8B). This should be considered a trend, since the mean bioavailability value calculated for each ingested source derived from a highly variable number of replicates, affecting the power of results. In addition, discriminating blood and urinary profiles of circulating metabolites coming from monomers or proanthocyanidins would be an excellent future turning point to better unravel the ADME of this important class of (poly)phenols and understand differences among food sources. The identification of metabolites strictly related to flavan-3-ol intake (Table 1), their occurrence in the different biofluids where they are detected (Supplemental Fig. 5), and the stoichiometric balances calculated in the production of phenyl-γ-valerolactones and phenylvaleric acids may be valuable tools to potentially support the implementation of i) well-designed human intervention studies and ii) target MS/MS methods able to cover a comprehensive panel of flavan-3-ol metabolites, derived from specific food sources. While plasma analyses provide data on the occurrence, presence, and clearance of the circulating metabolites, urinary excretion gives a more realistic assessment of the uptake and metabolic yield of flavan-3-ols along their biotransformation pathway. Another point worth mentioning is that the C_{max} and C_{avg} values calculated herein may support the design of cell studies firmly in line with more realistic physiological conditions.

Finally, this work further support the vital need to use authentic reference compounds to i) fully identify the circulating flavan-3-ol metabolites, ii) improve the accuracy in assessing concentration levels/excreted amounts and so the bioavailability of these phytochemicals, and iii) conduct proper cell or *in vivo* assays, as different isomers may lead to different biological effects (Mele et al., 2017; Mena et al., 2017; Montagnana et al., 2018; Luca et al., 2019; Ruotolo et al., 2020; Cecarini et al., 2021). This systematic review approach, commonly used for health-related observations, has never been previously used to assess the pharmacokinetics of (poly)phenols, as far as we know. The workflow reported herein may support the scientific community in further gathering evidence on bioactive phenolic metabolites and (poly)phenol bioavailability by using robust methodological approaches related to study design, data processing and result presentation. The presence of data on publicly accessible repositories may also facilitate data processing and harmonization. Applying this systematic approach to other classes of secondary dietary compounds to gain further evidence on their metabolism and bioavailability may pave the way for a better understanding of their bioactivity and the development of sound dietary recommendations. Last but not least, although this work evaluated the ADME of flavan-3-ols starting from a very huge number of studies, our knowledge on dose-response effects, bioavailability of the different flavan-3-ol sources, and how inter-individual variation may affect kinetic profiles and concentration levels of metabolites produced after flavan-3-ol intake remains still incomplete. Understanding how these aspects may condition the health effects attributed to flavan-3-ols is also fully needed. Further research efforts on these aspects are guaranteed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mam.2022.101146.

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