

Cite this: *Food Funct.*, 2024, **15**, 2814

## (Poly)phenol-related gut metatypes and human health: an update

 Jiaying Hu,<sup>a</sup> Robin Mesnage,<sup>a,b</sup> Kieran Tuohy,<sup>id c</sup> Christian Heiss<sup>id d</sup> and Ana Rodriguez-Mateos<sup>id \*a</sup>

Dietary (poly)phenols have received great interest due to their potential role in the prevention and management of non-communicable diseases. In recent years, a high inter-individual variability in the biological response to (poly)phenols has been demonstrated, which could be related to the high variability in (poly)phenol gut microbial metabolism existing within individuals. An interplay between (poly)phenols and the gut microbiota exists, with (poly)phenols being metabolised by the gut microbiota and their metabolites modulating gut microbiota diversity and composition. A number of (poly)phenol metabolising phenotypes or metatypes have been proposed, however, potential metatypes for most (poly)phenols have not been investigated, and the relationship between metatypes and human health remains ambiguous. This review presents updated knowledge on the reciprocal interaction between (poly)phenols and the gut microbiome, associated gut metatypes, and subsequent impact on human health.

Received 9th October 2023,  
Accepted 18th February 2024

DOI: 10.1039/d3fo04338j

rsc.li/food-function

### Introduction

Dietary (poly)phenols are plant-derived secondary metabolites that are abundant in many fruits and vegetables, tea, coffee, cocoa, soy products, olive oil, and red wine.<sup>1</sup> Extensive pre-clinical studies have demonstrated promising biological activities of individual (poly)phenols, including anti-inflammatory, antioxidant, and anti-proliferative.<sup>2–7</sup> However, the physiological relevance of such studies, in particular the evidence from *in vitro* studies, has been largely questioned.<sup>8,9</sup> In recent years, increasing evidence from observational studies and randomized controlled trials (RCT) has demonstrated an inverse association between (poly)phenol consumption and the risk of various non-communicable diseases, such as cardiometabolic and neurodegenerative diseases.<sup>10–15</sup> However, inconsistent results also exist and a high inter-individual variability in response to (poly)phenols has been reported.<sup>16,17</sup> In addition to heterogeneous study designs and differences in the physical and genetic make-up of individuals, the widely documented high variability in bioavailability and metabolism of (poly)

phenols is likely to play an important role in explaining the observed variability in response.<sup>18,19</sup>

While a limited amount of the ingested (poly)phenols are absorbed in the small intestine, a large proportion (~95%) reach the colon where they are metabolised by gut microorganisms into smaller phenolic compounds for further uptake.<sup>20,21</sup> These compounds can then undergo phase II metabolism, generating conjugated metabolites that may have very different biological activities from their parent compounds.<sup>22</sup> In this context, genetic differences, such as single nucleotide polymorphisms in transporters and enzymes, may account for some of the individual variability in the absorption and metabolism of (poly)phenols.<sup>23,24</sup> However, the well-known variability in gut microbiota diversity, composition and functionality between individuals, points to the gut microbiota metabolising capacity as a key factor to explain the individual differences on the biological responses to (poly)phenol consumption. (Poly)phenol metabolising phenotypes, or metatypes, have been proposed, with isoflavone and ellagitannin related metatypes being the most widely studied so far.<sup>25,26</sup>

When investigating the effects of dietary (poly)phenols on human health, it is important to consider the two-way interaction between the gut microbiota and (poly)phenols: (poly)phenols are transformed into metabolites *via* the enzymatic activity of gut microbes, and these metabolites may in turn modulate the gut microbial community.<sup>27</sup>

In this review, we summarise the current evidence on inter-individual differences in circulating (poly)phenol gut microbial metabolites, (poly)phenol-related gut metatypes, associated gut microbiota and effects on human health.

<sup>a</sup>Department of Nutritional Sciences, School of Life Course and Population Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK.

E-mail: ana.rodriguez-mateos@kcl.ac.uk

<sup>b</sup>Buchinger Wilhelmi Clinic, Überlingen, Germany

<sup>c</sup>School of Food Science and Nutrition, Faculty of Environment, University of Leeds, Leeds, UK

<sup>d</sup>Department of Clinical and Experimental Medicine, Faculty of Health and Medical Sciences, University of Surrey, Surrey, UK



## Gut microbial metabolism of (poly)phenols

The gut microbiota transforms (poly)phenols into more bioavailable metabolites of lower molecular weight through several catabolic pathways, including hydrolysis, cleavage, and reduction.<sup>28</sup> To date, only a few gut microbial species have been identified to participate in the metabolism of specific (poly)phenols, while most species involved still remain unknown. Moreover, whilst the traditional approach has been tried to identify individual microbial species involved in particular transformations, it is highly likely that the transformation of complex (poly)phenols derives from the concerted action of multiple species working together and also on local pH. Deeper investigation into the composition of multi-species consortia awaits wider application of high-throughput microbiome co-culture or mixed culture methodologies. In Table 1 we summarise the main species that have been identified to date. *Lactobacillus* and *Bifidobacterium* strains have been found to deconjugate flavonoid rhamnoglucosides through rhamnosidase activity, and many species within Bifidobacteriaceae, Bacteroidaceae, Porphyromonadaceae, and Enterococcaceae phyla exert *O*-deglycosylation activity in flavanones, isoflavones and flavan-3-ols.<sup>29</sup> Cleavage of C–C bonds in flavonoids is also a characterised gut microbial activity. For instance, the isoflavone daidzein has two distinct metabolites, a reduction product equol and a ring cleavage product *O*-demethylangolensin.<sup>30</sup> *Eubacterium ramulus* and Strain SY8519 have been reported to catalyse the C-ring cleavage of isoflavones (Table 1).<sup>31,32</sup> *Flavonifractor plautii* also showed similar activity for flavonols.<sup>29</sup> Gut bacteria also catalyse reduction, hydrogenation of double bonds and dehydroxylation reactions of (poly)phenols. In the metabolism of isoflavones, *Eggerthella* sp. YY7918, *Slackia equolifaciens*, *Slackia isoflavoniconvertens*, and *Lactococcus garvieae* have been reported to show reduction activity, thus generating equol (Table 1).<sup>33–36</sup> An example of dehydroxylation is the biotransformation of ellagic acid to urolithins. After hydrolysis and reduction of carboxylic acid, dehydroxylation occurs at the *p*-hydroxy group of a semi-hydroquinone, to form urolithin C and A.<sup>37</sup> *Gordonibacter urolithinifaciens* and *Ellagibacter isourolithinifaciens* are involved in this process (Table 1).<sup>38</sup> They also metabolise catechol dehydroxylation and reduction.<sup>38</sup> Importantly, the gut microbiota can also influence host metabolism. For example, (poly)phenol phase II metabolites that are excreted *via* the bile into the small intestine can be converted back to aglycones in the colon by gut microbes with glucuronidase and sulfatase activity, and re-absorbed.<sup>37</sup> Therefore, the gut microbiota is a key factor affecting (poly)phenol bioavailability and metabolism in multiple ways.

### (Poly)phenols as modulators of the gut microbiota

While dietary (poly)phenols are bio-transformed into absorbable metabolites by the intestinal microbiota, these metabolites are capable of modulating gut microbial communities. Both *in vitro* assays and *in vivo* studies have revealed that (poly)phenols exhibit prebiotic activities through promoting

the growth of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*,<sup>87</sup> and through inhibiting colonies of pathogenic bacteria such as *Escherichia coli*, *Clostridium perfringens* and *Helicobacter pylori*.<sup>88,89</sup> For example, an RCT conducted with 10 healthy male participants showed that 4-week consumption of red wine (poly)phenols significantly enhanced the growth of *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella lenta* and *Blautia coccoides–Eubacterium rectale* groups.<sup>90</sup> Quercetin has been demonstrated to inhibit the growth of *E. coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* in *in vitro* assays.<sup>91,92</sup> It has also been suggested that the altered gut microbial ecology may prevent against metabolic diseases through several physiological actions, including increasing production of short-chain fatty acids (SCFAs), decreasing adipogenesis and lipogenesis, or alleviating systemic inflammation.<sup>93</sup> Zhang *et al.*<sup>94</sup> reported that oolong tea flavan-3-ols are able to promote the growth of *Bifidobacterium* and *Lactobacillus/Enterococcus* groups while inhibiting the growth of *Bacteroides–Prevotella*, *Clostridium histolyticum*, and *Eubacterium–Clostridium* groups *in vitro*, and further increase the concentration of SCFAs. In mouse models, grape (poly)phenols significantly increased *Akkermansia muciniphila* abundance and decreased the *Firmicutes* to *Bacteroidetes* ratio, paralleled with attenuation of high-fat-diet-induced inflammation.<sup>95</sup> An RCT conducted among 22 healthy volunteers found that cocoa flavan-3-ols promoted the beneficial bifidobacterial and lactobacilli populations, and reduced plasma triacylglycerol and C-reactive protein concentrations.<sup>96</sup> However, the evidence from human intervention studies, especially for (poly)phenol extracts or pure (poly)phenol compounds is limited, and the relationship between gut bacteria species, (poly)phenol gut microbial metabolites and health outcomes is still unclear. Some evidence from *in vitro* studies suggest direct biological activities of (poly)phenol gut microbial metabolites, however whether they are the major bioactive compounds responsible for the health benefits or whether they act as biomarkers of a healthy intestinal microbial community remains unknown.<sup>97</sup> The answer to this question is likely to explain at least in part the differential individual biological responses to (poly)phenols observed in clinical trials and their interaction with other putative bioactives in whole plant foods, such as dietary fibre. Nevertheless, what has become clear is that (poly)phenol consumption can modulate gut microbiota diversity, composition and function and this may have important implications for human health.

### Variability in (poly)phenol gut microbial metabolism: the concept of (poly)phenol metabolotypes

The concept of (poly)phenol metabolising phenotypes or metabolotypes was first proposed by Bolca and colleagues as “clusters of gut microbial communities with similar metabolic profiles”.<sup>98</sup> More recently, Espín *et al.*<sup>28</sup> defined gut (poly)phenol metabolotypes as “metabolic phenotypes defined by specific gut microbial metabolites and their associated microbial ecology in terms of composition and functionality”. This is compar-



**Table 1** Bacteria involved in metabolism of (poly)phenols including proposed reactions and corresponding substrate(s). ODMA = O-desmethylangolensin

Phenolic class	Species/strain	Substrate(s)	Reaction	Ref.
Anthocyanins	<i>Bifidobacterium lactis</i>	Anthocyanin	$\beta$ -Glucosidase	39
	<i>Lactobacillus acidophilus</i>	Anthocyanin	$\beta$ -Glucosidase	39
	<i>Lactobacillus casei</i>	Anthocyanin	$\beta$ -Glucosidase	39
Ellagitannins	<i>Lactobacillus plantarum</i>	Anthocyanin	$\beta$ -Glucosidase	39
	<i>Bifidobacterium pseudocatenulatum</i>	Ellagic acid	Metabolise ellagic acid to urolithin A and B	40
	<i>Clostridium coccooides</i> members	Ellagic acid	Metabolise ellagic acid to urolithins	41
	<i>Ellagibacter isourolithinifaciens</i>	Ellagic acid	Metabolise ellagic acid to isourolithin A	42
	<i>Enterococcus faecium</i> FUA027	Ellagic acid	Metabolise ellagic acid to urolithin A	43
	<i>Gordonibacter pamelaee</i>	Ellagic acid	Metabolise ellagic acid to urolithins	44
	<i>Gordonibacter urolithinifaciens</i>	Ellagic acid	Metabolise ellagic acid to urolithins	45
	<i>Lactococcus garvieae</i> FUA009	Ellagic acid	Metabolise ellagic acid to urolithin A	46
Flavanones	<i>Streptococcus thermophilus</i> FUA329	Ellagic acid	Metabolise ellagic acid to urolithin A	47
	<i>Bacteroides distasonis</i>	Eriocitrin	Hydrolysis	48
	<i>Bacteroides uniformis</i>	Eriocitrin	Hydrolysis	48
	<i>Bifidobacterium catenulatum</i>	Hesperidin	Hydrolysis	49
	<i>Bifidobacterium pseudocatenulatum</i>	Hesperidin	Hydrolysis	49
	<i>Clostridium butyricum</i>	Eriocitrin	C-ring cleavage	48
	Flavan-3-ols	<i>Adlercreutzia equolifaciens</i> JCM 14793	(-)-Epigallocatechin, (-)-gallocatechin	Dihydroxylation
<i>Asaccharobacter celatus</i> JCM 14811		(-)-Epigallocatechin, (-)-gallocatechin	C-ring cleavage	50
<i>Eggerthella lenta</i>		(-)-Epicatechin, (+)-catechin	C-ring cleavage	51
<i>Slackia equolifaciens</i> JCM 16059		(-)-Epigallocatechin, (-)-gallocatechin	C-ring cleavage	50
Flavones	<i>Blautia</i> sp. MRG-PMF1	Apigenin	O-Glucose hydrolysis	52
	<i>Eubacterium cellulosolvens</i>	Homoorientin, isovitexin	Deglycosylation of C- and O-glucosides	53
Flavonols	<i>Bacillus subtilis</i>	Quercetin	C-ring cleavage	54
	<i>Bacteroides distasonis</i>	Robinin	Hydrolyse robinin to kaempferol	55
	<i>Bacteroides ovatus</i>	Rutin	$\beta$ -Glucosidase, hydrolyse rutin to quercetin	55
	<i>Bacteroides uniformis</i>	Rutin	$\beta$ -Glucosidase, hydrolyse rutin to quercetin	55
	<i>Bifidobacterium adolescentis</i>	Kaempferol 3-O-glucoside	$\beta$ -Glucosidase	56
	<i>Bifidobacterium bifidum</i>	Kaempferol 3-O-glucoside	$\beta$ -Glucosidase	56
	<i>Bifidobacterium breve</i>	Kaempferol 3-O-glucoside	$\beta$ -Glucosidase	56
	<i>Bifidobacterium catenulatum</i>	Kaempferol 3-O-glucoside	Hydrolysis, $\beta$ -Glucosidase	56
	<i>Bifidobacterium dentium</i>	Rutin, poncirin	Hydrolysis	57
	<i>Bifidobacterium infantis</i>	Kaempferol 3-O-glucoside	$\beta$ -Glucosidase	56
	<i>Bifidobacterium longum</i>	Kaempferol 3-O-glucoside	$\beta$ -Glucosidase	56
	<i>Bifidobacterium pseudocatenulatum</i>	Kaempferol 3-O-glucoside	Hydrolysis, $\beta$ -glucosidase	56
	<i>Blautia</i> sp. MRG-PMF1	Hesperidin, Poylmethoxyflavones	O-Rutinose hydrolysis, demethylation, deglycosylation	52
	<i>Clostridium orbiscindens</i>	Quercetin, taxifolin, luteolin, apigenin, naringenin, phloretin	C-ring cleavage	58
	<i>Enterococcus avium</i>	Rutin	O-Deglycosylation	59,60
	<i>Enterococcus casseliflavus</i>	Quercetin-3-glucoside	Hydrolysis	61
	<i>Eubacterium ramulus</i>	Rutin, quercetin, kaempferol, taxifolin, luteolin, quercetin-3-glucoside	C-ring cleavage	61–63
	<i>Flavonifractor plautii</i>	Quercetin	C-ring cleavage	64
	<i>Lactobacillus acidophilus</i>	Rutin, nicotiflorin, narirutin	$\alpha$ -Rhamnosidase	65
<i>Lactobacillus plantarum</i>	Rutin, nicotiflorin, narirutin	$\alpha$ -Rhamnosidase	65	



Table 1 (Contd.)

Phenolic class	Species/strain	Substrate(s)	Reaction	Ref.
Isoflavones	<i>Adlercreutzia equolifaciens</i>	Daidzein	Bioconversion of daidzein to equol	66
	<i>Asaccharobacter celatus</i>	Daidzein	Bioconversion of daidzein to equol	67
	<i>Bifidobacterium adolescentis</i>	Daidzein	Hydrolysis	68
	<i>Bifidobacterium animalis</i>	Daidzein	Hydrolysis	69
	<i>Bifidobacterium bifidum</i>	Daidzein	Hydrolysis	68
	<i>Bifidobacterium breve</i>	Daidzein	Hydrolysis	68
	<i>Bifidobacterium longum</i>	Daidzein	Hydrolysis	69,70
	<i>Bifidobacterium pseudocatenulatum</i>	Daidzein	Hydrolysis	69,70
	<i>Blautia</i> sp. MRG-PMF1	Daidzein, genistin, glycitin	Hydrolysis, O-glucose & O-methyl hydrolysis	52
	<i>Clostridium</i> strain HGH 136	Daidzein	Bioconversion of daidzein to ODMA	71
	<i>Clostridium</i> strain SY8519	Daidzein	Bioconversion of daidzein to ODMA	32
	<i>Clostridium</i> strain TM-40	Daidzein	Bioconversion of daidzein to dihydrodaidzein	72
	<i>Coriobacteriaceae</i> strain Mt1B8	Daidzein	Bioconversion of daidzein to equol	73
	<i>Eggerthella</i> strain YY7918	Daidzein	Bioconversion of daidzein to equol	74
	<i>Eggerthella</i> sp. Julong 732	Daidzein	Bioconversion of daidzein to equol	75
	<i>Enterococcus</i> sp. MRG-IFC-2	Puerarin	O-Glycosidase	76
	<i>Escherichia coli</i> HGH21	Daidzein, genistin	$\beta$ -Glucosidase	77
	<i>Eubacterium ramulus</i>	Daidzein, genistin	C-ring cleavage	78
	<i>Lachnospiraceae</i> strain CG19-1	Puerarin	Deglycosylation	79
	<i>Lactobacillus</i> sp. Niu-O16	Daidzein	Bioconversion of daidzein to equol	75
	<i>Lactococcus</i> sp. MRG-IFC-1	Puerarin	O-Glycosidase	76
	<i>Lactococcus</i> 20-92	Daidzein	Bioconversion of daidzein to dihydrodaidzein	36
	<i>Slackia isoflavoniconvertens</i>	Daidzein	Bioconversion of daidzein to equol	80
	<i>Slackia</i> sp. strain NATTS	Daidzein	Bioconversion of daidzein to equol	81
Lignans	<i>Bacteroides distasonis</i> DSM 20701 <sup>T</sup>	Secoisolariciresinol (SECO)	Deglycosylation	82
	<i>Bacteroides fragilis</i> DIFe-05	SECO	Deglycosylation	82
	<i>Bacteroides fragilis</i> SDG-Mt85-4C, <i>B. fragilis</i> SDG-Mt85-5B	SECO	Deglycosylation	82
	<i>Bacteroides methylotrophicum</i> DSM 3468 <sup>T</sup>	SECO	Demethylation	82
	<i>Bifidobacterium bifidum</i> INIA P466	SECO	Metabolise SECO to enterodiol	83
	<i>Bifidobacterium catenulatum</i> INIA P732	SECO	Metabolise SECO to enterodiol	83
	<i>Bifidobacterium pseudocatenulatum</i> INIA P946	SDG	Deglycosylation of SDG to SECO	83
	<i>Bifidobacterium pseudolongum</i> INIA P2	SECO	Metabolise SECO to enterodiol	83
	<i>Blautia producta</i> DSM 3507	SECO	Demethylation	84
	<i>Clostridium cocleatum</i>	Secoisolariciresinol diglucoside (SDG)	Deglycosylation	82
	<i>Clostridium ramosum</i>	SDG	Deglycosylation	82
	<i>Eggerthella lenta</i> DSM 2243	Pinoresinol, lariciresinol	Reduction	84
	<i>Eubacterium callanderi</i> DSM 3662 <sup>T</sup>	SECO	Demethylation	82
	<i>Eubacterium limosum</i> DSM 20543 <sup>T</sup>	SECO	Demethylation	82
	<i>Gordonibacter pamelaee</i>	Didemethyl-SECO	dehydroxylation	84
	<i>Lactobacillus gasseri</i> INIA P508,	SECO	Metabolise SECO to enterolignans	83
	<i>Lactobacillus salivarius</i> INIA P183, <i>Lactobacillus salivarius</i> INIA P448	SECO	Metabolise SECO to enterolignans	83
	<i>Lactonifactor longoviformis</i> DSM 17459	Enterodiol	Lactonization, bioconversion of enterodiol to enterolactone	84
	<i>Gordonibacter pamelaee</i>	Didemethyl-SECO	dehydroxylation	84
	<i>Peptostreptococcus productus</i> DSM 2950 <sup>T</sup> , <i>Peptostreptococcus productus</i> DSM 3507	SECO	Demethylation	82



Table 1 (Contd.)

Phenolic class	Species/strain	Substrate(s)	Reaction	Ref.
Stilbenes	<i>Adlercreutzia equolifaciens</i>	Resveratrol	Metabolism resveratrol into dihydroresveratrol	85
	<i>Slackia equolifaciens</i>	Resveratrol	Metabolism resveratrol into dihydroresveratrol	85
Xanthohumol	<i>Eubacterium ramulus</i>	Xanthohumol	Hydrogenation	86
	<i>Eubacterium limosum</i>	Isoxanthohumol	O-Demethylation	86

able to the notion of enterotype, a classification of gut microbiome composition profiles which is proposed to support the development of personalised nutrition strategies.<sup>99</sup>

Currently, there is a lack of consensus regarding whether the concept of (poly)phenol metabolotypes should be used exclusively to differentiate between producers and non-producers of specific (poly)phenol gut microbial metabolites, or in a broader sense to distinguish individuals with different metabolising capacities, such as low vs. high producers (Fig. 1). One of the main arguments proposed by Iglesias-Aguirre *et al.* for the definition of metabolotypes as an exclusive qualitative (*i.e.* presence or absence of unique (poly)phenol gut microbial metabolites) but not quantitative criteria is that the production gradient could be affected by external factors, such as food matrix, sample collection time or diet, and that the cut-off to consider an individual from one or another metabolotype will be arbitrary and will depend on each cohort considered.<sup>97</sup> While we fully agree with these points, we argue that these issues may also apply to the definition of producers vs. non-producers. For example, differences in sensitivity between analytical devices used to determine metabolotypes (typically HPLC-UV or more commonly, LC-MS), could lead to low producers being classified as non-producers in some studies. This can make

comparisons between studies conducted with different instruments and sensitivities difficult. In addition, the cut-off for the definition of non-producers is also arbitrary. For example, for the definition of equol non-producer metabolotype, some researchers have used the Setchell method,<sup>100–102</sup> which is a classification based on a cut-off ( $\log_{10} \geq 1.75$ ) which leads to non-producers and very low producers being classified as non-producers. Other researchers have used different cut-off concentrations, or the limit of detection of their analytical device.<sup>103–105</sup> The type of food matrix, sample collection time, or background diet could also affect this classification in a similar manner. We argue that the definition of metabolotypes does not have to be an absolute criterion but a relative one, and can be used to classify individuals within the same cohort into groups with different (poly)phenol metabolising capacities. The effects of external factors will be minimised, as factors such as food matrix or sample collection time will be homogenous for each defined cohort, therefore unlikely to affect a relative cut-off. For example, tertiles or quintiles of excretion, depending on the sample size of the cohort can be used to classify individuals within the same cohorts into low, medium and high producers, as it has already been done for some (poly)phenols, such as flavanones or lignans.<sup>106,107</sup> Another point to consider is that for some (poly)phenols, individuals classified as non-producers are either non-existent or are present in very low number (*i.e.* 2–10% of the population investigated), which limits the conclusions that can be made and comparisons between groups due to low sample sizes. In some cases therefore, clustering non-producers and low producers in one group may be more accurate than having small groups with not enough power to detect differences in health outcomes or gut microbiome diversity and composition.

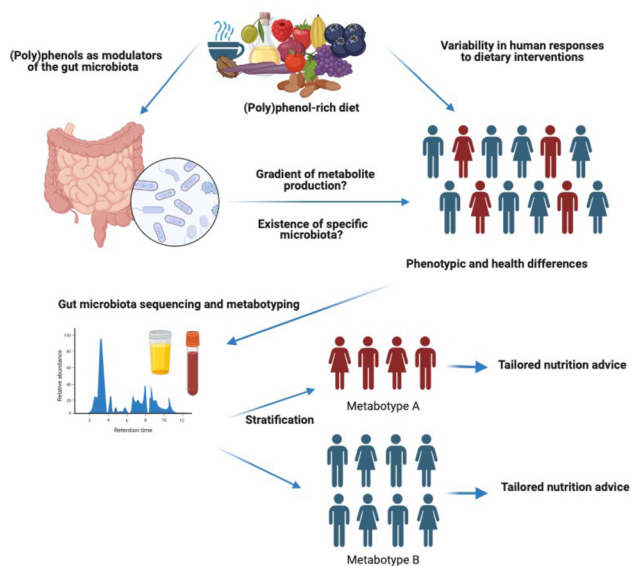


Fig. 1 Inter-individual variability in gut metabolism of (poly)phenols due to distinct gut microbiome composition.

### (Poly)phenol metabolotypes and human health: what we know so far

The most widely studied metabolotypes are the ones related to the gut microbial metabolites of the isoflavone daidzein, equol and ODMA. More recently, ellagitannin and resveratrol related metabolotypes have also been described.<sup>108</sup>

### Equol and ODMA metabolotypes

Isoflavones are a class of phytoestrogens which are found mainly in soy products. They exist as glycoside conjugates in plants.<sup>109</sup> After ingested by humans, isoflavones are hydrolysed



by gut bacteria into bioactive aglycones, including daidzein, genistein and glycitein. Soy consumption is generally high in Asian countries whereas low in Western population.<sup>110–112</sup>

Equol and ODMA are gut microbial metabolites of daidzein (Fig. 2), which have been related to health effects. To date, equol- and ODMA-producer metabolotypes have been identified.<sup>113</sup> It is also suggested that the capacity of an individual to produce equol is not influenced by the capacity to produce ODMA.<sup>114</sup> Several distinct metabolic steps requiring specific intestinal bacteria species exist for the production of equol and ODMA, leading to the stratification of equol- and ODMA-producer metabolotypes. For example, bacteria responsible for the C-ring cleavage is required to transform daidzein to ODMA but not needed for equol production.<sup>113</sup>

There are approximately 30%–50% and 80%–90% of Caucasian population being identified as equol- and ODMA-producers respectively following soy consumption.<sup>115–117</sup> In Asian populations, the prevalence of ODMA-producers is slightly lower than that in Western population, where the prevalence of equol-producers reaches 50%–60%.<sup>117,118</sup> Due to the stability in the long term, metabolotypes are regarded as a biomarker for intestinal ecology and potential disease risks.<sup>116</sup> A number of studies have investigated demographic, anthropometric and dietary factors (*i.e.* race, ethnicity, age, BMI, *etc.*) associated with daidzein-related metabolotypes to describe the features of equol- and ODMA-producers. However, observed results are often inconsistent and no clear associations can be demonstrated.<sup>113,119</sup> One of the reasons could be the inconsistent classification of metabolotypes and arbitrary cut-offs used in different studies, as previously discussed.

The gut bacteria involved in the biotransformation of equol and ODMA are distinct from each other. *Adlercreutzia*, *Asaccharobacter*, *Eggerthella*, *Bifidobacterium* and *Clostridium* are gut bacteria that are associated with the production of equol from daidzein (Table 1).<sup>66–68,72,120</sup> Importantly, the role

of bifidobacterial in the biotransformation of isoflavones in soy milk has been well established.<sup>121–123</sup> However, less is known about the bacteria population responsible for the production of ODMA, except for *Eubacterium ramulus* which is capable of C-ring cleavage activity.<sup>78</sup> *Eubacterium ramulus* also plays a role in the metabolism of other (poly)phenols, such as quercetin, xanthohumol, 8-prenylnaringenin and other flavonoids.<sup>86,124,125</sup> This indicates that the bio-conversion of daidzein into ODMA share some metabolic steps with other (poly)phenols, and most individuals are likely to have the ability to produce ODMA. Further studies are warranted to investigate the gut microbiome composition and biological characteristics of equol- and ODMA-producer metabolotypes, and their relationship with human health.

A 3-day cross-sectional study conducted among 99 Chinese participants found that equol-producers had higher abundance of *Adlercreutzia equolifaciens* and *Bifidobacterium bifidum* compared with non-producers (77.5% vs. 22.5%; 72.0% vs. 28.0%, respectively).<sup>126</sup> The prevalence of dyslipidemia was significantly lower in equol-producers (27% vs. 50%). However, there was no significant difference in microbiome richness between equol-producers and non-producers.<sup>126</sup> In contrast, an US study with 80 healthy females observed that equol-producers had lower gut microbiome diversity and beneficial bacteria taxa, such as *Bacteroides* spp., *Faecalibacterium* spp., and *Butyrivibrium* spp.<sup>127</sup> In non-producers, a higher dominance of *Akkermansia* spp., *Prevotella* 9, and *Megasphaera elsdenii* was presented. The authors also showed that even among individuals with the same metabolotype, the consumption of soy or not would result in different gut microbiota composition.<sup>127</sup> Considering the amount of regular soy intake and distribution of daidzein-related metabolotypes are different between Asian and Western population, it is likely that the inconsistent results are attributable to sociodemographic factors and dietary patterns.



Fig. 2 Metabolic pathways of daidzein and bacteria related to daidzein metabolism.



So far, although studies have suggested that equol-and ODMA producers may have lower cardiometabolic risk than non-producers, mixed results also exist and very few studies have investigated ODMA metabolotypes. Miller *et al.* observed an association between ODMA non-producers and obesity in both *peri*- and post-menopausal women, whereas no significant association was found for equol non-producers.<sup>128</sup> This is in line with the findings by Frankenfeld *et al.*,<sup>129</sup> showing that among 297 adults participants, obesity was associated with being ODMA non-producers (OR: 2.8 [95% CI: 1.2, 6.2]). Cohort studies of Japanese men suggested a lower risk of coronary artery calcification (OR: 0.1 [95% CI: 0.01, 0.90,  $p < 0.04$ ]) in equol-producers compared to equol non-producers.<sup>130,131</sup> On the contrary, Usui *et al.* reported significant improvements in cardiometabolic risk parameters upon 12-week equol supplementation only in female equol non-producers.<sup>132</sup> Interestingly, Hazim *et al.*<sup>100</sup> reported acute benefits on vascular function in equol-producers after isoflavone consumption, and administration of commercially-made equol to non-producers did not cause any change in vascular function despite of increased plasma equol concentrations. Although this study only investigated acute effects and did not test the effect of equol in equol-producers, the study provided an insight that the health benefits might be attributed to the individual capacity of producing equol, *i.e.* the existence of gut microbiome responsible for the biotransformation of daidzein into equol. This would support the idea of the equol metabolotype use as a means of defining microbiome health effects or at least in this case, a microbiome profile associated with improved vascular function. Future studies are therefore needed to link the composition and functionality of metabolotype-related gut microbiota to health effects, and investigate the metabolic reactions for equol. Clear criteria for stratification of equol-producer, ODMA-producer and non-producer is also required. Furthermore, most daidzein-related studies are conducted in Asian population, and more research in Western countries are warranted.

In addition to the classic daidzein equol and ODMA metabolotypes, a recent paper including 60 postmenopausal women investigated novel daidzein and genistein related gut metabolotypes.<sup>133</sup> After 12-week daily consumption of a soy isoflavone extract, the authors defined 5 metabolotypes according to hierarchical cluster analysis. Cluster 1 and 2 shared similar characteristics in terms of high equol production, while cluster 2 showed higher 4-ethylphenol (4EP) production and lower genistein production than cluster 1; cluster 3 produced the highest proportions of 4EP but no or very small proportions of equol; cluster 4, in which most women were included, had the highest proportions of daidzein and genistein; while cluster 5 exhibited high proportions of dihydrodaidzein and dihydrogenistein. This study is unprecedented since the majority of isoflavone studies only include daidzein-related metabolotypes, and highlights the complexity of (poly)phenol metabolism and the need for more research beyond the “classic” metabolotypes.

## Urolithin metabolotypes

Ellagitannins are rich in some berries, such as strawberries and raspberries, other fruits such as pomegranate and nuts, such as walnuts. *In vitro* and *in vivo* studies have demonstrated anti-inflammatory, antioxidant, antimicrobial, and anti-tumour activities of ellagitannins.<sup>134–136</sup> Urolithins, which are dibenzopyran-6-one derivatives metabolised from ellagitannins (Fig. 3), have also shown anti-inflammatory properties.<sup>137,138</sup>

Three urolithin-related metabolotypes (UM) have been described for ellagitannin gut metabolism.<sup>26,139</sup> Urolithin metabolotype A (UMA), which is characterised by the production of urolithin A derivatives; urolithin metabolotype B (UMB), which produces urolithin B and isourolithin A in addition to urolithin A derivatives; and urolithin metabolotype zero (UM0), with no production of urolithin metabolites.<sup>26</sup> The distribution of the three metabolotypes was demonstrated in a relatively large Spanish cohort ( $n = 839$ ) by Cortés-Martín *et al.*<sup>140</sup> Approximately 50–80% of the population were UMA, 10–40% were UMB and 10% were UM0. The authors also suggested that the metabolotype frequency was age-dependent, with the percentage of UMA decreasing and UMB increasing with age, while UM0 prevalence remained constant.<sup>140</sup> However, the stability of urolithin metabolotype over time in a given individual has yet to be measured in longitudinal studies. A recent study in healthy Chinese youth reported the approximate prevalence of 55% UMA, 30% UMB and 15% UM0.<sup>141</sup> However, the sample size was too small ( $n = 35$ ), therefore more studies conducted in Asian countries are required. Studies with large cohorts in different geographic locations are warranted to detect the distribution of metabolotypes in different ethnicities and populations, as most of the evidence currently existing comes from Spanish cohorts.

Few small studies suggest that urolithin metabolotypes can be potential biomarkers for gut microbiome balance and a healthy intestinal ecology. Tomás-Barberán *et al.*<sup>139</sup> reported a higher prevalence of UMB among patients with metabolic syndrome or colorectal cancer. Selma *et al.*<sup>142</sup> also found that UMB prevailed in individuals overweight or with obesity, and UMB metabolites were positively correlated with cardiometabolic disease biomarkers including total cholesterol, LDL, oxidised LDL, VLDL and apolipoprotein B, while urinary urolithin A was positively correlated with HDL and apolipoprotein A-I. However, this study was small ( $n = 69$ ), and the correlation between UM and BMI was not confirmed in the larger cohort of 839 individuals conducted by the same research team.<sup>140</sup> Regarding UM0, a study conducted among 52 Parkinson's disease (PD) patients and 117 healthy participants showed a significant higher proportion of UM0 in PD patients compared with healthy volunteers (27% vs. 9%,  $p = 0.004$ ), and the proportion increased as the disease became more severe.<sup>143</sup> The gut microbiota of UM0 patients displayed an increased pro-inflammatory Enterobacteriaceae and reduced protective butyrate-producing bacteria. This provides an insight that as the research about metabolotype-associated gut microbiota goes





Fig. 3 Metabolic pathways of ellagic acid and bacteria related to urolithin metabolism.

further, disease risks might be predicted based on the features of distinct metabolotypes.

The family Coriobacteriaceae has been found to display a strong correlation with urolithin production.<sup>44,45,144</sup> *Gordonibacter urolithinifaciens* and *Gordonibacter pamelaiae*, which are members of Coriobacteriaceae family, were identified to metabolise ellagitannins into pentahydroxy urolithin M5 and tetrahydroxy urolithins (D, E, and M6) through lactone-ring opening, decarboxylation, and dehydroxylation reactions.<sup>44,45</sup> *Ellagibacter isourolithinifaciens* sp. nov., a member of the family Eggerthellaceae, was isolated from human faeces and found to be capable of producing isourolithin A (Table 1).<sup>42</sup> Romo-Vaquero *et al.*<sup>144</sup> analysed gut microbiome composition from 249 healthy metabolotyped participants. *Olsenella*, *Senegalismassilia*, and *Slackia* were positively correlated with isourolithin A and urolithin B production, while *Gordonibacter* and *Eggerthella* were positively correlated with urolithin A. A recent study by Iglesias-Aguirre *et al.*<sup>145</sup> reported a novel bacterial strain *Enterocloster bolteae* CEBAS S4A9 that could convert Uro-C to Uro-A anaerobically. Very few studies have reported strains involved in the metabolism of ellagic acid to urolithin A, including *Bifidobacterium pseudocatenulatum* INIA P815, *Lactococcus garvieae* FUA009, *Enterococcus faecium* FUA027 and *Streptococcus thermophilus* FUA329.<sup>40,43,46,47</sup> Among three metabolotypes, UM0 showed the lowest diversity and richness of intestinal bacteria, while UMB had the highest richness at phylum and family level.<sup>144</sup> The higher richness of gut microbiome may explain why UMB produces more types of metabolites than UMA. The authors also observed a positive

correlation between *Slackia* and cardiometabolic risk factors, such as total cholesterol, LDL, apolipoprotein B and non-HDL.<sup>144</sup> Overall, the gut bacteria species or consortia responsible for the production of urolithin metabolites and their relationship with disease risk need further investigation.

Very little evidence exists from randomised controlled trials on whether the response to ellagitannin consumption differs between urolithin metabolotypes. A small RCT in healthy men ( $n = 10$ ), which was not stratified into metabolotypes, indicated significant increases in flow-mediated dilation (FMD) at 2 h and 24 h post-consumption of 200 g and 400 g raspberries, and these improvements were correlated with plasma ellagic acid and urolithin A metabolites.<sup>146</sup> An RCT with 49 individuals with overweight or obesity indicated that after consumption of ellagitannins for 24 weeks, only UMB participants had a significant improvement in the blood lipid profile, while no effects were found in UMA individuals.<sup>147</sup> However, it is important to point out that UMB individuals had a less favourable blood lipid profile to start with, so this could be a reason why only this group responded to the intervention. Supporting these findings, a 8-week crossover RCT with 51 older adults reported that a (poly)phenol-rich diet significantly reduced intestinal permeability in UMB but not in UMA individuals.<sup>148</sup> Compared with UMA participants, UMB individuals showed a 2-fold higher improvement in zonulin levels, a marker of intestinal permeability, and an increase in HDL-cholesterol. Fatty acid oxidation was also upregulated in UMB participants after the treatment. Cortés-Martín *et al.*<sup>149</sup> found that changes of gut microbiome and anthropometric metrics of post-partum



mothers differed between UMs. During 1 year after delivery, UMB mothers showed a more robust gut microbial ecology that was resistant to changes, while UMA mothers had altered gut microbiota correlated with decreased waist circumference. The same authors later investigated associations between obesity prevalence and other factors including UM in a cohort of children and adolescents ( $n = 415$ ).<sup>150</sup> The ordinal logistic model showed that the prevalence of overweight-obesity was related to being a UMB or UM0 young boy, low adherence to Mediterranean diet and high contribution of 24 obesity-related single-nucleotide polymorphisms. The potential to modulate UM is therefore worthy to explore. Recently, Iglesias-Aguirre *et al.*<sup>151</sup> conducted an *in vivo* animal study to transfer urolithin-producing bacterial consortia with the aim to convert UM0 to UMA and UMB. Urolithin-producing bacterial strains, *Gordonibacter* and *Ellagibacter*, successfully colonised the rats' gut and replicated the ability to produce urolithins. This provides insights into the potential use of probiotics to convert non-producers into producers to benefit from (poly)phenol consumption. In addition to the investigation into bacterial strains, there are also some studies supporting the benefits of urolithin A supplements without gut metabolites linked.<sup>152–154</sup> To clearly demonstrate the health benefits of different metabolites, larger cohort studies with pre-intervention stratification and balanced focus on the three metabolites should be considered when designing protocols. Pre- and probiotic use to reproduce health-favouring gut ecology is also a novel area waiting further investigation.

### Lunularin metabolites

Resveratrol is a type of stilbenes that are mainly present in grapes, berries, peanuts and wines.<sup>155</sup> Many preclinical studies have shown a wide range of biological properties, including anti-inflammation, anti-obesity, cardioprotective and neuroprotective

effects.<sup>156–161</sup> However, it is important to point out that all the studies showing resveratrol health benefits were conducted using amounts that are not achievable within a normal diet, and the use of resveratrol-enriched foods or supplements is needed.

The research of resveratrol gut metabolites is just at its infancy period. Bode *et al.*<sup>85</sup> in 2013 discovered 2 novel metabolites of resveratrol besides dihydroresveratrol (DHR): 3,4'-dihydroxy-*trans*-stilbene (DHST) and 3,4'-dihydroxybibenzyl (lunularin, LUN) (Fig. 4). Among 9 subjects, only 3 produced LUN. Gut microbiome analysis showed that LUN-producers had higher abundances of *Bacteroidetes*, *Actinobacteria*, *Verrucomicrobia*, *Cyanobacteria*, *Enterobacteriaceae*, and *Coriobacteriaceae*.<sup>85</sup> *Slackia equolifaciens* and *Adlercreutzia equolifaciens*, were identified to be involved in the production of DHR (Table 1). Though only 9 participants were included, this was the first time to identify LUN and DHST.

Recently, Iglesias-Aguirre *et al.*<sup>162</sup> reported a novel dehydroxylated product of LUN at 3-position, 4-hydroxydibenzyl (4HDB). This metabolite was found in urine samples from 41 participants ( $n = 59$ ). The same authors then described the metabolic activities of resveratrol by the human gut microbiome and related metabolites (*i.e.* LUN-producers vs. LUN non-producers).<sup>108</sup> The gut microbiota first converts resveratrol into DHR through hydrogenation,<sup>163</sup> then DHR undergoes two metabolic pathways: the major one in which DHR is dehydroxylated at the 5-position to yield LUN, and LUN then might be transformed into 4HDB *via* dihydroxylation at the 3-position; in the minor pathway, DHR is directly transformed into DHST.<sup>108</sup> The distribution of gut metabolites was also estimated. Among 159 healthy volunteers, there were 74.4% of LUN-producers and 25.6% of LUN non-producers. The distribution varied from geographic locations. Further analysis suggested a significant association between distribution and sex ( $p = 0.037$ ), with more female being LUN non-producers.<sup>108</sup>



Fig. 4 Metabolic pathways of resveratrol and bacteria related to resveratrol metabolism.



This study builds a foundation for future research about resveratrol-related gut metabolites. Large sample size is necessary for the establishment of metabolites and description of distributions, and the association with sex needs further validation.

While no studies investigating the link between resveratrol gut metabolites and health have been conducted, a few pre-clinical studies have investigated the effects of DHR, LUN and DHST on different outcomes. LUN was found to inhibit E-selectin and IL-8 expression *in vitro*,<sup>164</sup> and DHST was found to increase glucose uptake and induce AMPK phosphorylation independently of insulin.<sup>165</sup> Li *et al.*<sup>166</sup> reported that DHR and LUN exerted stronger anti-inflammatory and anti-cancer effects at the concentrations in mouse tissues. However, other studies found that DHR and LUN exhibited lower biological activities than resveratrol in animal models, including caloric restriction mimetics and inhibition of pancreatic oxidative damage.<sup>167,168</sup> Therefore, it is important to conduct more research, including but not limited to *in vitro* and *in vivo* studies, to assess the bioactivity and health-related effects of resveratrol gut metabolites. Besides metabolites, resveratrol gut metabolites, associated gut microbiota, and consequent health benefits also deserve in-depth studies, which will contribute to the understanding of variations in individual responses to resveratrol intake.

### Low vs. high producer metabolites

For many of the (poly)phenols investigated so far, a specific non-producer metabolite has not been reported, but a high inter-individual variability in their gut microbial metabolism. In this context, the variations are indicated by a gradient of metabolite production which stratifies individuals into low or high producers. With the limitations previously discussed regarding how such classification can be standardised, such gradients can be a marker of particular microbial consortia,

and stratification may be useful to explain the high variability in response observed after (poly)phenol consumption. In this section we will discuss some examples of relevant (poly)phenols with very specific and unique gut microbial metabolites. Many other abundant classes of (poly)phenols, such as phenolic acids, anthocyanins or flavonols, have common gut microbial metabolites such as catechol, benzoic acids or hippuric acid derivatives which may come from multiple dietary sources and not exclusively from (poly)phenols, and are therefore not specific enough to stratify individuals into different metabolites easily. However, the circulating levels of those common and abundant metabolites could be used as overall markers of (poly)phenol-rich food consumption and diet quality, and therefore their relationships with health outcomes and gut microbiota diversity, composition, and functionality are of great interest to investigate individual responses and mechanistic aspects.

### Lignans

Lignans are widely studied phenolic compounds that are rich in oilseeds, such as flaxseed, sesame, or sunflower seeds. Whole grains, legumes, fruits, and vegetables also contain low concentrations of lignans.<sup>169</sup> Lignans have a similar structure to 17 $\beta$ -estradiol and are able to bind estrogen receptors, thus activating downstream signalling and exhibiting estrogenic or anti-estrogenic effects.<sup>170</sup> Intervention and epidemiological studies have showed that lignans have a protective effect on cardiovascular diseases,<sup>171</sup> whilst the effects on other chronic diseases, such as breast cancer, have not been unequivocally confirmed.<sup>172</sup> The enterolignans enterodiol (ED) and enterolactone (EL) are the main gut microbial metabolites specific to lignans (Fig. 5). Despite studies suggest that these metabolites are produced by all participants, inter-individual variations in gut microbiome lead to the presence of high vs. low enterolignan excretors.<sup>173,174</sup> Considering lignans undergo extensive



Fig. 5 Metabolic pathways of lignan (secoisolariciresinol diglucoside) and bacteria related to enterolignan metabolism.



phase-II metabolism, both the gut bacteria and phase-II enzymes play roles in varied metabolising capacity of lignans among individuals.

Upon consumption, gut microorganism is responsible for the deglycosylation of lignan secoisolariciresinol diglucoside (SDG), leading to the production of secoisolariciresinol (SECO). Enterodiol is generated by the demethylation and dihydroxylation of SECO, and it then might be transformed into enterolactone through dehydrogenation reactions.<sup>175</sup> Therefore, total of four reactions are involved in the bio-transformation of SDG into EL: deglycosylation, demethylation, dehydroxylation, and dehydrogenation. Clavel *et al.*<sup>176</sup> demonstrated that the genera of *Bacteroides* and *Clostridium* were able to catalyse the first reaction, and *Eubacterium limosum* and *Peptostreptococcus productus* were involved in the demethylation step (Table 1). Peirotn *et al.*<sup>83</sup> reported that some *Bifidobacterium* and *Lactobacillus* strains were capable of produce ED and EL from SECO but not other lignans (*i.e.* matairesinol).

The wide inter-individual variability observed in human studies is likely attributed to the biotransformation from ED to EL. When faecal samples from high and low EL producers were used to ferment flaxseed extract, 200  $\mu\text{M}$  and 20  $\mu\text{M}$  of EL were produced respectively, whereas ED production was similar between samples.<sup>177</sup>

In a prospective cohort study (NHS II) of 121 700 US women, higher urinary lignan metabolites, especially ED (median in the highest quartile, 342.8 nmol  $\text{g}^{-1}$  creatinine; median in the lowest quartile, 16.4 nmol  $\text{g}^{-1}$  creatinine), was associated with less weight gain (95% CI: 0.12, 0.41;  $p < 0.01$ ).<sup>178</sup> Another 10-year cohort study found that urinary EL levels (quartiles of urinary EL ( $\text{ng ml}^{-1}$ ): Q1:  $\leq 127$ ; Q2: 127–420; Q3: 420–979; Q4:  $> 979$ ) were inversely associated with obesity (OR 0.30, 95% CI 0.17, 0.54;  $p < 0.001$ ) and other cardiometabolic risk markers, including triglycerides, fasting glucose concentrations, and fasting insulin levels in men aged 20–60 years old.<sup>179</sup> Two studies also suggested a positive association between plasma and urinary EL levels and diversity of gut microbiota.<sup>180,181</sup> In the Men's Lifestyle Validation Study (MLVS) including 303 male participants, the relative abundance of *Faecalibacterium prausnitzii*, *Alistipes shahii*, *Butyrivibrio crossotus*, and *Methanobrevibacter smithii* was significantly associated with higher plasma EL levels (low EL = 4.4 nM, high EL = 22.9 nM).<sup>181</sup> Among 115 premenopausal US women, EL production was significantly associated with alpha-diversity, and higher EL excretion (mean ( $\mu\text{g mg}^{-1}$  creatinine): 1st tertile = 0.46, 2nd tertile = 1.86, 3rd tertile = 5.66) was associated with gut microbial composition rich in *Moryella* spp., *Acetanaerobacterium* spp., *Fastidiosipila* spp., and *Streptobacillus* spp.<sup>180</sup> The overall evidence favours enterolignan high producers as a beneficial phenotype. However, results from cohort studies should be taken with caution since many factors (diet, lifestyle, smoking habits, health status, drug use, *etc.*) could interfere with the results, and most observational studies did not stratify volunteers into low *vs.* high producers, therefore the associated links with health outcomes

may simply be related to lignan intake rather than the metabolising capacity of the gut microbiota. Therefore, in the absence of stratified randomised controlled trials into low and high EL and ED producers, whether the variability in gut microbial metabolism can explain the variability in response to lignan consumption remains unknown.

### Flavanones

Citrus fruits are rich food sources of flavanones, in which hesperidin (hesperetin-7-*O*-rutinoside) represents a great amount of total flavanones in oranges and orange juices. After consumed by humans, a small fraction of flavanones is absorbed in the small intestine, the rest of hesperidin is cleaved by microorganism in the colon releasing hesperetin, then undergo phase-II metabolism.<sup>182</sup> In this process, gut microbiome, including *Bifidobacterium*, *Clostridium*, *Bacteroides*, *Lactobacillus* and *Eubacterium*, plays a role in the deglycosylation of rhamnoglucoside moiety of hesperidin.<sup>29,183</sup>

A large inter-individual variability has been observed in the metabolism and excretion of flavanones. Tomás-Navarro *et al.*<sup>184</sup> defined high flavanone excretors as those with flavanone excretion values  $>10\%$  of the ingested flavanones; medium excretors as those with excretion values between 5 and 10%, and low excretors those with excretion values  $<5\%$ . Vallejo *et al.*<sup>185</sup> used instead tertiles to stratify producers. Despite the different classification strategies, both studies reported that high hesperetin excretors produced nearly 5–6 times more urinary flavanones than low hesperetin excretors.<sup>184,185</sup> The rhamnosidase activity of the gut microbiome is suggested to be one of the factors accounting for the variations. The urinary metabolites detected were mostly phase-II metabolites, such as hesperetin glucuronides and hesperetin sulfates.<sup>185,186</sup> A cross-over study ( $n = 21$ ) by Nishioka *et al.*<sup>187</sup> was unable to find a significant correlation between excretion gradient and gut microbiome composition at the genus and/or species level. Moreover, the solubility of the food matrix also affects hesperidin metabolism.<sup>188</sup> The gut microbiome associated to flavanone metabolites therefore remains inconclusive. Important to note that flavanones share other common and abundant gut metabolites with other (poly)phenols, including hydroxyphenylacetic, hydroxybenzoic and hydroxyphenylpropionic acids.<sup>189</sup> However, it is challenging to use them as metabolotyping tools, due to their low specificity. This issue also exists for other (poly)phenols, such as flavan-3-ols.

### Flavan-3-ols

Flavan-3-ol monomers (*i.e.* catechin and epicatechin), oligomers and polymers (also known as condensed tannins or proanthocyanidins) are among the most consumed (poly)phenols. In the human diet, the main sources are tea, pome fruits, berries and cocoa products.<sup>190</sup> Phenyl- $\gamma$ -valerolactones (PVL) and phenylvaleric acids (PVA) have been identified as main gut microbial metabolites of flavan-3-ols. The colonic metabolites might be further catabolised by intestinal bacteria into low molecular weight phenolic compounds or conjugated



by phase-II enzymes, then excreted in urine.<sup>191</sup> With respect to the involved gut microbiome, some bacteria capable of carrying out specific actions have been linked to the gut metabolism of flavan-3-ols: *Adlercreutzia equolifaciens* and *Eggerthella lenta* are able to stimulate C-ring cleavage of (*epi*)catechins, and *Eggerthella lenta* also performs 4'-dehydroxylation of ring fission product.<sup>192</sup> *Flavonifractor plautii* has been showed to convert phenyl- $\gamma$ -valerolactones into 3-(phenyl)propionic acids.<sup>51</sup> However, information regarding gut microbiome species involved in the biotransformation of flavan-3-ols into PVL and PVA is still limited.

A large inter-individual variability in flavan-3-ol metabolism has been reported in studies using *in vitro* faecal fermentation and human interventions.<sup>193–197</sup> Mena *et al.*<sup>196,198</sup> described potential gut metabolotypes related with flavan-3-ols: one with high production of tri- and di-hydroxyphenyl- $\gamma$ -valerolactones and a reduced excretion of 3-(hydroxyphenyl)propionic acid; another is characterised by a low production of phenyl- $\gamma$ -valerolactones but high amounts of 3-(hydroxyphenyl)propionic acid. Besides these two metabolotypes, Cortés-Martin *et al.*<sup>199</sup> proposed two additional clusters, one with high excretion of all the PVL and PVA derivatives and the other with low excretion of all of them. Considering that these colonic metabolites are not final products and might be further broken down by bacteria into other common (poly)phenol metabolites, such as phenylpropionic, phenylacetic, and benzoic acids, which are widely abundant in the diet and coming from multiple dietary and non-dietary sources, variations in the amount of metabolite excreted should be taken with caution when defining metabolotypes in these studies. More recently, Tosi *et al.*<sup>200</sup> proposed new additional metabolotypes for cranberry (poly)phenols using data from a 12-week RCT among 60 healthy older adults. Metabolotype 1 was characterized by a higher excretion of 5-(3',4'-dihydroxyphenyl)- $\gamma$ -valerolactones (3',4'-diHPVLs) and 5-(3'-hydroxyphenyl)- $\gamma$ -valerolactones (3'-HPVLs), metabolotype 2 had a higher excretion of 3'-hydroxycinnamic acids (3'-HCAs), 3-(hydroxyphenyl)propanoic acids (HPPAs) and 3-hydroxybenzoic acids (3-HBAs), while metabolotype 3 was characterized by a low excretion of all metabolites. The proposed metabolotypes were not specific to flavan-3-ols, instead, the authors aimed to apply a quali-quantitative approach including various classes of (poly)phenols with different metabolic pathways. Using clustering techniques to establish metabolotypes with multiple gut microbial metabolites is an useful approach, and more research in this area is needed,<sup>201</sup> in particular for non-specific gut microbial metabolites such benzoic, catechol or phenylacetic acid metabolites, which are some of the most abundant (poly)phenol gut microbial metabolites, and the final products for most (poly)phenols.

### Hop prenylflavonoids

Hop-derived prenylflavonoids, including xanthohumol, isoxanthohumol and 8-prenylaringenin (8-PN), are not commonly found in most foods but are present in beer and hop-containing dietary supplements.<sup>202</sup> They have been found to

possess antioxidant, anti-proliferative, anti-inflammatory, estrogenic and immune-regulatory properties.<sup>202–206</sup> *In vitro* and animal studies have shown that isoxanthohumol can be converted into 8-PN by the action of *Eubacterium limosum*.<sup>207</sup> In this regard, inter-individual differences have been observed for the conversion, which is attributed to the biotransformation capacity of the gut bacteria.<sup>208,209</sup> An intervention study with 50 healthy post-menopausal women found a considerable variation in the urinary recovery of 8-PN between low, moderate and high 8-PN producers.<sup>209</sup> The stratification was based on the ratio 8-PN:(8-PN + isoxanthohumol), and the amount of 8-PN excreted in high excretors was nearly 5-fold than that in low excretors. An inverse relationship between antibiotics use and 8-PN production was also reported.<sup>209</sup> These results supports the notion that gut microbiota is involved in the production of 8-PN. However, 8-PN can be further metabolised by liver microsomes, specifically in the prenyl group and the flavanone skeleton.<sup>210</sup> Evidence regarding the metabolite production gradient of prenylflavonoids is limited, leading to the ambiguous demonstration of gut metabolotypes for 8-PN.

### Metabolotype clustering: is there a common metabolotype for multiple (poly)phenol subclasses?

An important question that remains unknown is whether a (poly)phenol “superproducer” metabolotype exist, or if same individuals share the same capacity to produce different (poly)phenol gut microbial metabolites. Very recently, Iglesias-Aguirre *et al.*<sup>211</sup> investigated gut metabolotype clusters (MC) for resveratrol, ellagic acid and daidzein in 127 individuals. To our knowledge, this is the first study investigating (poly)phenol gut metabolotype clusters for different (poly)phenols, which would be more applicable to real life settings since multiple (poly)phenols are consumed together within the same foods and certain gut bacteria species might be involved in the metabolism of more than one (poly)phenol class. A total of 10 metabolotype clusters were proposed, being the 5 more prevalent the following: MC1 (equol-non-producer (ENP) + UMB + LUN-producer (LP)) and MC2 (ENP + UMA + LP) were the most abundant, followed by MC3 (equol-producer (EP) + UMA + LP), MC4 (EP + UMB + LP) and MC5 (ENP + UMA + lunularin-non-producer (LNP)). The association between gut microbiome and metabolotype clusters was explored, and for instance, *Gordonibacter* and *Eggerthella* were positively associated with urolithin A while inversely associated with isourolithin A and urolithin B, indicated by the higher abundance of these two genera in UMA-including MCs (*i.e.* MC2, MC3, and MC5). *Akkermansia* was positively associated with equol, urolithin A and LUN, which was showed by a higher abundance in MC2 and MC3 with UMA and LP prioritized. Although the sample size, participants' ethnicity and intervention duration of this trial were limited, the study provides useful guidance for addressing the complexity of analyzing different classes of (poly)phenol gut metabolites in real-world settings. Considering that different (poly)phenols share some common metabolic pathways and metabolites, future studies could investigate the role of gut bacteria in both specific and com-



bined (poly)phenol metabolism and further confirm the prediction for the models on health outcomes through pre-stratified randomized controlled trials.

## Conclusion

Available evidence demonstrated a two-way interaction between dietary (poly)phenols and human gut microbiota, that is, (poly)phenols consumed are transformed by gut microbiota into smaller absorbable compounds, and these metabolites in turn modulate gut microbial population and subsequent health effects. Current research has noted that variations in gut microbiota and (poly)phenol gut metabolism exist among individuals, which may explain the differences observed in the biological responses to (poly)phenol consumption. We have examples of specific bacterial species mediating key chemical transformations, but much evidence remains correlative and there is an over reliance on the reductionist approach, with few studies examining the relevance of mixed microbial consortia or cooperation between bacterial species in (poly)phenol biotransformation. Therefore, (poly)phenol-related gut metabolites have been proposed as a biomarker for intestinal microbial ecology and individual health status. Based on related scientific evidence, this could contribute to the development of tailored dietary recommendations, especially regarding the consumption of polyphenol-rich diets, which is a critical aspect of personalised nutrition.

Research on (poly)phenol-related gut microbial metabolites is still in its infancy. Many open questions still remain for the most widely investigated metabolites, the daidzein related equol and ODMA producers and non-producers. Mixed results exist for observational studies linking equol and ODMA production with health outcomes, as well as for stratified studies investigating variability in response with metabolites. The main factors driving the prevalence of metabolites among populations are also unclear, but indications suggest age, sex and disease state can impact on metabolites. Whether the background diet, and in particular habitual (poly)phenol consumption is an important factor in metabolite prevalence is unclear, and the lack of reliable and accurate methods for estimating (poly)phenol intake is likely a confounding factor in this matter.

Metabolites could be seen from a microbial point of view as markers of microbiome health. Since microbial metabolic activities are modifiable, then the concentrations of the key microbial metabolites which define metabolites might change with changes in the microbiota *e.g.* induced by age, diet, or disease, with a clear example on the urolithin metabolite being modulated by age. Metabolites then become a marker or readout of microbial activity at a particular time (age) and space (nutritional or dietary space for example), and could be used to define how healthy a given diet: microbiome state is along the scale from healthy to dysbiotic.

The existence of potential metabolites for other (poly)phenols remains ambiguous. In this regard, an integration of

metagenomics and metabolomics could contribute to a better understanding of (poly)phenol metabolism and the role of gut microbiota. Using metabolomics allows determination of functional aspects which is often not captured by gut microbiome composition analyses. Large cohort studies are a suitable means to examine the distribution and determinants of metabolites and also concentration ranges of (poly)phenol unique marker metabolites, but also common metabolites of multiple (poly)phenols. Application of artificial intelligence here would help identify new, less obvious metabolites defined by concentration ranges of common (poly)phenol metabolites. Clinical intervention trials should also be carried out to identify the role of (poly)phenol metabolites in the modulation of health effects. Overall, the relationships between (poly)phenol metabolism, gut microbiota composition, and subsequent health effects deserve further research.

## Author contributions

J. H. and A. R. M. wrote the first draft. All authors improved and critically revised the manuscript, figures, and tables. All authors read and approved the final manuscript.

## Conflicts of interest

There are no conflicts of interest to declare.

## References

- 1 M. Leri, M. Scuto, M. L. Ontario, V. Calabrese, E. J. Calabrese, M. Bucciantini and M. Stefani, Healthy Effects of Plant Polyphenols: Molecular Mechanisms, *Int. J. Mol. Sci.*, 2020, **21**, 1250.
- 2 M. I. Khan, J. H. Shin, T. S. Shin, M. Y. Kim, N. J. Cho and J. D. Kim, Anthocyanins from *Cornus kousa* ethanolic extract attenuate obesity in association with anti-angiogenic activities in 3T3-L1 cells by down-regulating adipogenesis and lipogenesis, *PLoS One*, 2018, **13**, e0208556.
- 3 D. Esposito, A. Chen, M. H. Grace, S. Komarnytsky and M. A. Lila, Inhibitory Effects of Wild Blueberry Anthocyanins and Other Flavonoids on Biomarkers of Acute and Chronic Inflammation in Vitro, *J. Agric. Food Chem.*, 2014, **62**, 7022–7028.
- 4 M. M. Coman, A. M. Oancea, M. C. Verdenelli, C. Cecchini, G. E. Bahrim, C. Orpianesi, A. Cresci and S. Silvi, Polyphenol content and in vitro evaluation of antioxidant, antimicrobial and prebiotic properties of red fruit extracts, *Eur. Food Res. Technol.*, 2018, **244**, 735–745.
- 5 M. Inglés, J. Gambini, M. G. Miguel, V. Bonet-Costa, K. M. Abdelaziz, M. El Alami, J. Viña and C. Borrás, PTEN Mediates the Antioxidant Effect of Resveratrol at Nutritionally Relevant Concentrations, *BioMed Res. Int.*, 2014, **2014**, e580852.



- 6 M. Yousef, I. A. Vlachogiannis and E. Tsiani, Effects of Resveratrol against Lung Cancer: In Vitro and In Vivo Studies, *Nutrients*, 2017, **9**, 1231.
- 7 P. Basu and C. Maier, Phytoestrogens and breast cancer: In vitro anticancer activities of isoflavones, lignans, coumestans, stilbenes and their analogs and derivatives, *Biomed. Pharmacother.*, 2018, **107**, 1648–1666.
- 8 M. Á. Ávila-Gálvez, A. González-Sarrías and J. C. Espín, In Vitro Research on Dietary Polyphenols and Health: A Call of Caution and a Guide on How To Proceed, *J. Agric. Food Chem.*, 2018, **66**, 7857–7858.
- 9 P. Mena and D. Del Rio, Gold Standards for Realistic (Poly)phenol Research, *J. Agric. Food Chem.*, 2018, **66**, 8221–8223.
- 10 A. Tresserra-Rimbau, E. B. Rimm, A. Medina-Remón, M. A. Martínez-González, R. de la Torre, D. Corella, J. Salas-Salvadó, E. Gómez-Gracia, J. Lapetra, F. Arós, M. Fiol, E. Ros, L. Serra-Majem, X. Pintó, G. T. Saez, J. Basora, J. V. Sorlí, J. A. Martínez, E. Vinyoles, V. Ruiz-Gutiérrez, R. Estruch and R. M. Lamuela-Raventós, Inverse association between habitual polyphenol intake and incidence of cardiovascular events in the PREDIMED study, *Nutr., Metab. Cardiovasc. Dis.*, 2014, **24**, 639–647.
- 11 A. A. Fallah, E. Sarmast and T. Jafari, Effect of dietary anthocyanins on biomarkers of glycemic control and glucose metabolism: A systematic review and meta-analysis of randomized clinical trials, *Food Res. Int.*, 2020, **137**, 109379.
- 12 M. Bonaccio, G. Pounis, C. Cerletti, M. B. Donati, L. Iacoviello, G. de Gaetano and on behalf of the M.-S. S. Investigators, Mediterranean diet, dietary polyphenols and low grade inflammation: results from the MOLI-SANI study, *Br. J. Clin. Pharmacol.*, 2017, **83**, 107–113.
- 13 D. J. Lamport, L. Dye, J. D. Wightman and C. L. Lawton, The effects of flavonoid and other polyphenol consumption on cognitive performance: A systematic research review of human experimental and epidemiological studies, *Nutr. Aging*, 2012, **1**, 5–25.
- 14 C. Valls-Pedret, R. M. Lamuela-Raventós, A. Medina-Remón, M. Quintana, D. Corella, X. Pintó, M. Á. Martínez-González, R. Estruch and E. Ros, Polyphenol-Rich Foods in the Mediterranean Diet are Associated with Better Cognitive Function in Elderly Subjects at High Cardiovascular Risk, *J. Alzheimer's Dis.*, 2012, **29**, 773–782.
- 15 L. T. Fike, H. Munro, D. Yu, Q. Dai and M. J. Shrubsole, Dietary polyphenols and the risk of colorectal cancer in the prospective Southern Community Cohort Study, *Am. J. Clin. Nutr.*, 2022, **115**, 1155–1165.
- 16 N. M. Pham, V. V. Do and A. H. Lee, Polyphenol-rich foods and risk of gestational diabetes: a systematic review and meta-analysis, *Eur. J. Clin. Nutr.*, 2019, **73**, 647–656.
- 17 F. Potì, D. Santi, G. Spaggiari, F. Zimetti and I. Zanotti, Polyphenol Health Effects on Cardiovascular and Neurodegenerative Disorders: A Review and Meta-Analysis, *Int. J. Mol. Sci.*, 2019, **20**, 351.
- 18 E. R. Gibney, D. Milenkovic, E. Combet, T. Ruskovska, A. Greyling, A. González-Sarrías, B. de Roos, F. Tomás-Barberán, C. Morand and A. Rodriguez-Mateos, Factors influencing the cardiometabolic response to (poly)phenols and phytosterols: a review of the COST Action POSITIVE activities, *Eur. J. Nutr.*, 2019, **58**, 37–47.
- 19 B. de Roos, A.-M. Aura, M. Bronze, A. Cassidy, M.-T. G. Conesa, E. R. Gibney, A. Greyling, J. Kaput, Z. Kerem, N. Knežević, P. Kroon, R. Landberg, C. Manach, D. Milenkovic, A. Rodriguez-Mateos, F. A. Tomás-Barberán, T. van de Wiele and C. Morand, Targeting the delivery of dietary plant bioactives to those who would benefit most: from science to practical applications, *Eur. J. Nutr.*, 2019, **58**, 65–73.
- 20 L. Chen, H. Cao and J. Xiao, in *Polyphenols: Properties, Recovery, and Applications*, ed. C. M. Galanakis, Woodhead Publishing, 2018, pp. 45–67.
- 21 S. Mithul Aravind, S. Wichienchot, R. Tsao, S. Ramakrishnan and S. Chakkaravarthi, Role of dietary polyphenols on gut microbiota, their metabolites and health benefits, *Food Res Int*, 2021, **142**, 110189.
- 22 A. González-Sarrías, J. A. Giménez-Bastida, M. Á. Núñez-Sánchez, M. Larrosa, M. T. García-Conesa, F. A. Tomás-Barberán and J. C. Espín, Phase-II metabolism limits the antiproliferative activity of urolithins in human colon cancer cells, *Eur. J. Nutr.*, 2014, **53**, 853–864.
- 23 L. Rubio, A. Macia and M.-J. Motilva, Impact of Various Factors on Pharmacokinetics of Bioactive Polyphenols: An Overview, *Curr. Drug Metab.*, 2014, **15**, 62–76.
- 24 T. Rao, Z. Tan, J. Peng, Y. Guo, Y. Chen, H. Zhou and D. Ouyang, The pharmacogenetics of natural products: A pharmacokinetic and pharmacodynamic perspective, *Pharmacol. Res.*, 2019, **146**, 104283.
- 25 C. L. Frankenfeld, O-Desmethylangolensin: The Importance of Equol's Lesser Known Cousin to Human Health, *Adv. Nutr.*, 2011, **2**, 317–324.
- 26 F. A. Tomás-Barberán, A. González-Sarrías, R. García-Villalba, M. A. Núñez-Sánchez, M. V. Selma, M. T. García-Conesa and J. C. Espín, Urolithins, the rescue of “old” metabolites to understand a “new” concept: Metabotypes as a nexus among phenolic metabolism, microbiota dysbiosis, and host health status, *Mol. Nutr. Food Res.*, 2017, **61**, 1500901.
- 27 F. A. Tomás-Barberán, M. V. Selma and J. C. Espín, Interactions of gut microbiota with dietary polyphenols and consequences to human health, *Curr. Opin. Clin. Nutr. Metab. Care*, 2016, **19**, 471–476.
- 28 J. C. Espín, A. González-Sarrías and F. A. Tomás-Barberán, The gut microbiota: A key factor in the therapeutic effects of (poly)phenols, *Biochem. Pharmacol.*, 2017, **139**, 82–93.
- 29 A. Braune and M. Blaut, Bacterial species involved in the conversion of dietary flavonoids in the human gut, *Gut Microbes*, 2016, **7**, 216–234.
- 30 X. Feng, Y. Li, M. Brobbey Oppong and F. Qiu, Insights into the intestinal bacterial metabolism of flavonoids and



- the bioactivities of their microbe-derived ring cleavage metabolites, *Drug Metab. Rev.*, 2018, **50**, 343–356.
- 31 X.-L. Wang, K.-T. Kim, J.-H. Lee, H.-G. Hur and S.-I. Kim, C-Ring Cleavage of Isoflavones Daidzein and Genistein by a Newly-Isolated Human Intestinal Bacterium *Eubacterium ramulus* Julong 601, *J. Microbiol. Biotechnol.*, 2004, **14**, 766–771.
  - 32 S. Yokoyama, T. Niwa, T. Osawa and T. Suzuki, Characterization of an O-desmethylangolensin-producing bacterium isolated from human feces, *Arch. Microbiol.*, 2010, **192**, 15–22.
  - 33 S. Yokoyama and T. Suzuki, Isolation and characterization of a novel equol-producing bacterium from human feces, *Biosci., Biotechnol., Biochem.*, 2008, **72**, 2660–2666.
  - 34 J.-S. Jin, T. Nishihata, N. Kakiuchi and M. Hattori, Biotransformation of C-glucosylisoflavone puerarin to estrogenic (3S)-equol in co-culture of two human intestinal bacteria, *Biol. Pharm. Bull.*, 2008, **31**, 1621–1625.
  - 35 A. Matthies, M. Blaut and A. Braune, Isolation of a Human Intestinal Bacterium Capable of Daidzein and Genistein Conversion, *Appl. Environ. Microbiol.*, 2009, **75**, 1740–1744.
  - 36 Y. Shimada, S. Yasuda, M. Takahashi, T. Hayashi, N. Miyazawa, I. Sato, Y. Abiru, S. Uchiyama and H. Hishigaki, Cloning and Expression of a Novel NADP (H)-Dependent Daidzein Reductase, an Enzyme Involved in the Metabolism of Daidzein, from Equol-Producing *Lactococcus* Strain 20-92, *Appl. Environ. Microbiol.*, 2010, **76**, 5892–5901.
  - 37 J. F. Stevens and C. S. Maier, The chemistry of gut microbial metabolism of polyphenols, *Phytochem. Rev.*, 2016, **15**, 425–444.
  - 38 R. García-Villalba, D. Beltrán, M. D. Frutos, M. V. Selma, J. C. Espín and F. A. Tomás-Barberán, Metabolism of different dietary phenolic compounds by the urolithin-producing human-gut bacteria *Gordonibacter urolithinifaciens* and *Ellagibacter isourolithinifaciens*, *Food Funct.*, 2020, **11**, 7012–7022.
  - 39 M. Ávila, M. Hidalgo, C. Sánchez-Moreno, C. Pelaez, T. Requena and S. de Pascual-Teresa, Bioconversion of anthocyanin glycosides by *Bifidobacteria* and *Lactobacillus*, *Food Res. Int.*, 2009, **42**, 1453–1461.
  - 40 P. Gaya, Á. Peiroten, M. Medina, I. Álvarez and J. M. Landete, *Bifidobacterium pseudocatenulatum* INIA P815: The first bacterium able to produce urolithins A and B from ellagic acid, *J. Funct. Foods*, 2018, **45**, 95–99.
  - 41 R. García-Villalba, D. Beltrán, J. C. Espín, M. V. Selma and F. A. Tomás-Barberán, Time Course Production of Urolithins from Ellagic Acid by Human Gut Microbiota, *J. Agric. Food Chem.*, 2013, **61**, 8797–8806.
  - 42 D. Beltrán, M. Romo-Vaquero, J. C. Espín, F. A. Tomás-Barberán and M. V. Selma, *Ellagibacter isourolithinifaciens* gen. nov., sp. nov., a new member of the family Eggerthellaceae, isolated from human gut, *Int. J. Syst. Evol. Microbiol.*, 2018, **68**, 1707–1712.
  - 43 X. Zhang, Y. Fang, G. Yang, X. Hou, Y. Hai, M. Xia, F. He, Y. Zhao and S. Liu, Isolation and characterization of a novel human intestinal *Enterococcus faecium* FUA027 capable of producing urolithin A from ellagic acid, *Front. Nutr.*, 2022, **9**, 1039697.
  - 44 M. V. Selma, F. A. Tomás-Barberán, D. Beltrán, R. García-Villalba and J. C. Espín, *Gordonibacter urolithinifaciens* sp. nov., a urolithin-producing bacterium isolated from the human gut, *Int. J. Syst. Evol. Microbiol.*, 2014, **64**, 2346–2352.
  - 45 M. V. Selma, D. Beltrán, R. García-Villalba, J. C. Espín and F. A. Tomás-Barberán, Description of urolithin production capacity from ellagic acid of two human intestinal *Gordonibacter* species, *Food Funct.*, 2014, **5**, 1779–1784.
  - 46 H. Mi, S. Liu, Y. Hai, G. Yang, J. Lu, F. He, Y. Zhao, M. Xia, X. Hou and Y. Fang, *Lactococcus garvieae* FUA009, a Novel Intestinal Bacterium Capable of Producing the Bioactive Metabolite Urolithin A from Ellagic Acid, *Foods*, 2022, **11**, 2621.
  - 47 Q. Liu, Y. Bian, S. Mu, M. Chen, S. Liu, G. Yang, Y. Huang, X. Hou and Y. Fang, Genomic and phenotypic-based safety assessment and probiotic properties of *Streptococcus thermophilus* FUA329, a urolithin A-producing bacterium of human milk origin, *Genomics*, 2023, **115**, 110724.
  - 48 Y. Miyake, K. Yamamoto and T. Osawa, Metabolism of Antioxidant in Lemon Fruit (*Citrus limon* BURM. f.) by Human Intestinal Bacteria, *J. Agric. Food Chem.*, 1997, **45**, 3738–3742.
  - 49 A. Amaretti, S. Raimondi, A. Leonardi, A. Quartieri and M. Rossi, Hydrolysis of the Rutinose-Conjugates Flavonoids Rutin and Hesperidin by the Gut Microbiota and *Bifidobacteria*, *Nutrients*, 2015, **7**, 2788–2800.
  - 50 A. Takagaki and F. Nanjo, Biotransformation of (–)-epigallocatechin and (–)-gallocatechin by intestinal bacteria involved in isoflavone metabolism, *Biol. Pharm. Bull.*, 2015, **38**, 325–330.
  - 51 M. Kutschera, W. Engst, M. Blaut and A. Braune, Isolation of catechin-converting human intestinal bacteria, *J. Appl. Microbiol.*, 2011, **111**, 165–175.
  - 52 M. Kim, N. Kim and J. Han, Metabolism of *Kaempferia parviflora* Polymethoxyflavones by Human Intestinal Bacterium *Bautia* sp. MRG-PMF1, *J. Agric. Food Chem.*, 2014, **62**, 12377–12383.
  - 53 A. Braune and M. Blaut, Intestinal Bacterium *Eubacterium cellulosolvens* Deglycosylates Flavonoid C- and O-Glucosides, *Appl. Environ. Microbiol.*, 2012, **78**, 8151–8153.
  - 54 M. R. Schaab, B. M. Barney and W. A. Francisco, Kinetic and spectroscopic studies on the quercetin 2,3-dioxygenase from *Bacillus subtilis*, *Biochemistry*, 2006, **45**, 1009–1016.
  - 55 V. D. Bokkenheuser, C. H. Shackleton and J. Winter, Hydrolysis of dietary flavonoid glycosides by strains of intestinal *Bacteroides* from humans., *Biochem. J.*, 1987, **248**, 953–956.



- 56 I. Marotti, A. Bonetti, B. Biavati, P. Catizone and G. Dinelli, Biotransformation of Common Bean (*Phaseolus vulgaris* L.) Flavonoid Glycosides by Bifidobacterium Species from Human Intestinal Origin, *J. Agric. Food Chem.*, 2007, **55**, 3913–3919.
- 57 S.-H. Bang, Y.-J. Hyun, J. Shim, S.-W. Hong and D.-H. Kim, Metabolism of rutin and poncirin by human intestinal microbiota and cloning of their metabolizing  $\alpha$ -L-rhamnosidase from Bifidobacterium dentium, *J. Microbiol. Biotechnol.*, 2015, **25**, 18–25.
- 58 L. Schoefer, R. Mohan, A. Schwirtz, A. Braune and M. Blaut, Anaerobic Degradation of Flavonoids by Clostridium orbiscindens, *Appl. Environ. Microbiol.*, 2003, **69**, 5849–5854.
- 59 Y. Liu, Y. Liu, Y. Dai, L. Xun and M. Hu, Enteric Disposition and Recycling of Flavonoids and Ginkgo Flavonoids, *J. Altern. Complementary Med.*, 2003, **9**, 631–640.
- 60 N. R. Shin, J. S. Moon, S.-Y. Shin, L. Li, Y. B. Lee, T.-J. Kim and N. S. Han, Isolation and characterization of human intestinal Enterococcus avium EFEL009 converting rutin to quercetin, *Lett. Appl. Microbiol.*, 2016, **62**, 68–74.
- 61 H. Schneider, A. Schwirtz, M. D. Collins and M. Blaut, Anaerobic transformation of quercetin-3-glucoside by bacteria from the human intestinal tract, *Arch. Microbiol.*, 1999, **171**, 81–91.
- 62 H. Schneider and M. Blaut, Anaerobic degradation of flavonoids by Eubacterium ramulus, *Arch. Microbiol.*, 2000, **173**, 71–75.
- 63 A. Braune, M. Gütschow, W. Engst and M. Blaut, Degradation of Quercetin and Luteolin by Eubacterium ramulus, *Appl. Environ. Microbiol.*, 2001, **67**, 5558–5567.
- 64 K. Ulbrich, N. Reichardt, A. Braune, L. W. Kroh, M. Blaut and S. Rohn, The microbial degradation of onion flavonol glucosides and their roasting products by the human gut bacteria Eubacterium ramulus and Flavonifractor plautii, *Food Res. Int.*, 2015, **67**, 349–355.
- 65 J. Beekwilder, D. Marcozzi, S. Vecchi, R. de Vos, P. Janssen, C. Francke, J. van Hylckama Vlieg and R. D. Hall, Characterization of Rhamnosidases from Lactobacillus plantarum and Lactobacillus acidophilus, *Appl. Environ. Microbiol.*, 2009, **75**, 3447–3454.
- 66 T. Maruo, M. Sakamoto, C. Ito, T. Toda and Y. Benno, Adlercreutzia equolifaciens gen. nov., sp. nov., an equol-producing bacterium isolated from human faeces, and emended description of the genus Eggerthella, *Int. J. Syst. Evol. Microbiol.*, 2008, **58**, 1221–1227.
- 67 K. Minamida, K. Ota, M. Nishimukai, M. Tanaka, A. Abe, T. Sone, F. Tomita, H. Hara and K. Asano, Asaccharobacter celatus gen. nov., sp. nov., isolated from rat caecum, *Int. J. Syst. Evol. Microbiol.*, 2008, **58**, 1238–1240.
- 68 S. Raimondi, L. Roncaglia, M. De Lucia, A. Amaretti, A. Leonardi, U. M. Pagnoni and M. Rossi, Bioconversion of soy isoflavones daidzin and daidzein by Bifidobacterium strains, *Appl. Microbiol. Biotechnol.*, 2009, **81**, 943–950.
- 69 D. Tsangalis, J. F. Ashton, A. E. J. McGill and N. P. Shah, Enzymic Transformation of Isoflavone Phytoestrogens in Soymilk by  $\beta$ -Glucosidase-Producing Bifidobacteria, *J. Food Sci.*, 2002, **67**, 3104–3113.
- 70 S. Raimondi, L. Roncaglia, M. De Lucia, A. Amaretti, A. Leonardi, U. M. Pagnoni and M. Rossi, Bioconversion of soy isoflavones daidzin and daidzein by Bifidobacterium strains, *Appl. Microbiol. Biotechnol.*, 2009, **81**, 943–950.
- 71 H.-G. Hur, R. D. Beger, T. M. Heinze, J. O. Lay, J. P. Freeman, J. Dore and F. Ráfii, Isolation of an anaerobic intestinal bacterium capable of cleaving the C-ring of the isoflavonoid daidzein, *Arch. Microbiol.*, 2002, **178**, 8–12.
- 72 M. Tamura, T. Tsushida and K. Shinohara, Isolation of an isoflavone-metabolizing, Clostridium-like bacterium, strain TM-40, from human faeces, *Anaerobe*, 2007, **13**, 32–35.
- 73 A. Matthies, T. Clavel, M. Gütschow, W. Engst, D. Haller, M. Blaut and A. Braune, Conversion of Daidzein and Genistein by an Anaerobic Bacterium Newly Isolated from the Mouse Intestine, *Appl. Environ. Microbiol.*, 2008, **74**, 4847–4852.
- 74 S. Yokoyama, K. Oshima, I. Nomura, M. Hattori and T. Suzuki, Complete Genomic Sequence of the Equol-Producing Bacterium Eggerthella sp. Strain YY7918, Isolated from Adult Human Intestine, *J. Bacteriol.*, 2011, **193**, 5570–5571.
- 75 X.-L. Wang, H.-J. Kim, S.-I. Kang, S.-I. Kim and H.-G. Hur, Production of phytoestrogen S-equol from daidzein in mixed culture of two anaerobic bacteria, *Arch. Microbiol.*, 2007, **187**, 155–160.
- 76 M. Kim, J. Lee and J. Han, Deglycosylation of isoflavone C-glycosides by newly isolated human intestinal bacteria, *J. Sci. Food Agric.*, 2015, **95**, 1925–1931.
- 77 H.-G. Hur, J. O. Lay Jr, R. D. Beger, J. P. Freeman and F. Ráfii, Isolation of human intestinal bacteria metabolizing the natural isoflavone glycosides daidzin and genistin, *Arch. Microbiol.*, 2000, **174**, 422–428.
- 78 L. Schoefer, R. Mohan, A. Braune, M. Birringer and M. Blaut, Anaerobic C-ring cleavage of genistein and daidzein by Eubacterium ramulus, *FEMS Microbiol. Lett.*, 2002, **208**, 197–202.
- 79 A. Braune and M. Blaut, Deglycosylation of puerarin and other aromatic C-glucosides by a newly isolated human intestinal bacterium, *Environ. Microbiol.*, 2011, **13**, 482–494.
- 80 C. Schröder, A. Matthies, W. Engst, M. Blaut and A. Braune, Identification and Expression of Genes Involved in the Conversion of Daidzein and Genistein by the Equol-Forming Bacterium Slackia isoflavoniconvertens, *Appl. Environ. Microbiol.*, 2013, **79**, 3494–3502.
- 81 H. Tsuji, K. Moriyama, K. Nomoto and H. Akaza, Identification of an Enzyme System for Daidzein-to-Equol



- Conversion in *Slackia* sp. Strain NATTS, *Appl. Environ. Microbiol.*, 2012, **78**, 1228–1236.
- 82 T. Clavel, G. Henderson, W. Engst, J. Doré and M. Blaut, Phylogeny of human intestinal bacteria that activate the dietary lignan secoisolariciresinol diglucoside, *FEMS Microbiol. Ecol.*, 2006, **55**, 471–478.
- 83 Á. Peirotén, P. Gaya, I. Álvarez, D. Bravo and J. M. Landete, Influence of different lignan compounds on enterolignan production by *Bifidobacterium* and *Lactobacillus* strains, *Int. J. Food Microbiol.*, 2019, **289**, 17–23.
- 84 E. N. Bess, J. E. Bisanz, F. Yarza, A. Bustion, B. E. Rich, X. Li, S. Kitamura, E. Waligurski, Q. Y. Ang, D. L. Alba, P. Spanogiannopoulos, S. Nayfach, S. K. Koliwad, D. W. Wolan, A. A. Franke and P. J. Turnbaugh, Genetic basis for the cooperative bioactivation of plant lignans by *eggerthella lenta* and other human gut bacteria, *Nat. Microbiol.*, 2020, **5**(1), 56–66.
- 85 L. M. Bode, D. Bunzel, M. Huch, G.-S. Cho, D. Ruhland, M. Bunzel, A. Bub, C. M. Franz and S. E. Kulling, In vivo and in vitro metabolism of trans-resveratrol by human gut microbiota, *Am. J. Clin. Nutr.*, 2013, **97**, 295–309.
- 86 I. L. Paraiso, L. S. Plagmann, L. Yang, R. Zielke, A. F. Gombart, C. S. Maier, A. E. Sikora, P. R. Blakemore and J. F. Stevens, Reductive metabolism of xanthohumol and 8-prenylnaringenin by the intestinal bacterium *Eubacterium ramulus*, *Mol. Nutr. Food Res.*, 2019, **63**, e1800923.
- 87 M. Moorthy, U. Sundralingam and U. D. Palanisamy, Polyphenols as Prebiotics in the Management of High-Fat Diet-Induced Obesity: A Systematic Review of Animal Studies, *Foods*, 2021, **10**, 299.
- 88 H. C. Lee, A. M. Jenner, C. S. Low and Y. K. Lee, Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota, *Res. Microbiol.*, 2006, **157**, 876–884.
- 89 A. Duda-Chodak, T. Tarko, P. Satora and P. Sroka, Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review, *Eur. J. Nutr.*, 2015, **54**, 325–341.
- 90 M. I. Queipo-Ortuño, M. Boto-Ordóñez, M. Murri, J. M. Gomez-Zumaquero, M. Clemente-Postigo, R. Estruch, F. Cardona Diaz, C. Andrés-Lacueva and F. J. Tinahones, Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers, *Am. J. Clin. Nutr.*, 2012, **95**, 1323–1334.
- 91 J.-P. Rauha, S. Remes, M. Heinonen, A. Hopia, M. Kähkönen, T. Kujala, K. Pihlaja, H. Vuorela and P. Vuorela, Antimicrobial effects of Finnish plant extracts containing flavonoids and other phenolic compounds, *Int. J. Food Microbiol.*, 2000, **56**, 3–12.
- 92 M. J. R. Vaquero, M. R. Alberto and M. C. M. de Nadra, Antibacterial effect of phenolic compounds from different wines, *Food Control*, 2007, **18**, 93–101.
- 93 V. Gowd, N. Karim, M. R. I. Shishir, L. Xie and W. Chen, Dietary polyphenols to combat the metabolic diseases via altering gut microbiota, *Trends Food Sci. Technol.*, 2019, **93**, 81–93.
- 94 X. Zhang, X. Zhu, Y. Sun, B. Hu, Y. Sun, S. Jabbar and X. Zeng, Fermentation in vitro of EGCG, GCG and EGCG3"Me isolated from Oolong tea by human intestinal microbiota, *Food Res. Int.*, 2013, **54**, 1589–1595.
- 95 D. E. Roopchand, R. N. Carmody, P. Kuhn, K. Moskal, P. Rojas-Silva, P. J. Turnbaugh and I. Raskin, Dietary Polyphenols Promote Growth of the Gut Bacterium *Akkermansia muciniphila* and Attenuate High-Fat Diet-Induced Metabolic Syndrome, *Diabetes*, 2015, **64**, 2847–2858.
- 96 X. Tzounis, A. Rodriguez-Mateos, J. Vulevic, G. R. Gibson, C. Kwik-Urbe and J. P. E. Spencer, Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study, *Am. J. Clin. Nutr.*, 2011, **93**, 62–72.
- 97 C. E. Iglesias-Aguirre, A. Cortés-Martín, M. Á. Ávila-Gálvez, J. A. Giménez-Bastida, M. V. Selma, A. González-Sarriás and J. C. Espín, Main drivers of (poly)phenol effects on human health: metabolite production and/or gut microbiota-associated metabolites?, *Food Funct.*, 2021, **12**, 10324–10355.
- 98 S. Bolca, T. Van de Wiele and S. Possemiers, Gut metabolites govern health effects of dietary polyphenols, *Curr. Opin. Biotechnol.*, 2013, **24**, 220–225.
- 99 J. Boekhorst, N. Venlet, N. Procházková, M. L. Hansen, C. B. Lieberoth, M. I. Bahl, L. Lauritzen, O. Pedersen, T. R. Licht, M. Kleerebezem and H. M. Roager, Stool energy density is positively correlated to intestinal transit time and related to microbial enterotypes, *Microbiome*, 2022, **10**, 223.
- 100 S. Hazim, P. J. Curtis, M. Y. Schär, L. M. Ostertag, C. D. Kay, A.-M. Miniñane and A. Cassidy, Acute benefits of the microbial-derived isoflavone metabolite equol on arterial stiffness in men prospectively recruited according to equol producer phenotype: a double-blind randomized controlled trial, *Am. J. Clin. Nutr.*, 2016, **103**, 694–702.
- 101 K. D. R. Setchell and S. J. Cole, Method of Defining Equol-Producer Status and Its Frequency among Vegetarians, *J. Nutr.*, 2006, **136**, 2188–2193.
- 102 C. Iino, T. Shimoyama, K. Iino, Y. Yokoyama, D. Chinda, H. Sakuraba, S. Fukuda and S. Nakaji, Daidzein Intake Is Associated with Equol Producing Status through an Increase in the Intestinal Bacteria Responsible for Equol Production, *Nutrients*, 2019, **11**, 433.
- 103 R. Yoshikata, K. Z. Myint, H. Ohta and Y. Ishigaki, Inter-relationship between diet, lifestyle habits, gut microflora, and the equol-producer phenotype: baseline findings from a placebo-controlled intervention trial, *Menopause*, 2019, **26**, 273.
- 104 M. Igase, K. Igase, Y. Tabara, Y. Ohayagi and K. Kohara, Cross-sectional study of equol producer status and cognitive impairment in older adults, *Geriatr. Gerontol. Int.*, 2017, **17**, 2103–2108.
- 105 V. Ahuja, K. Miura, A. Vishnu, A. Fujiyoshi, R. Evans, M. Zaid, N. Miyagawa, T. Hisamatsu, A. Kadota, T. Okamura, H. Ueshima and A. Sekikawa, Significant



- inverse association of equol-producer status with coronary artery calcification but not dietary isoflavones in healthy Japanese men, *Br. J. Nutr.*, 2017, **117**, 260–266.
- 106 J. K. Aschoff, K. M. Riedl, J. L. Cooperstone, J. Högel, A. Bosy-Westphal, S. J. Schwartz, R. Carle and R. M. Schweiggert, Urinary excretion of Citrus flavanones and their major catabolites after consumption of fresh oranges and pasteurized orange juice: A randomized cross-over study, *Mol. Nutr. Food Res.*, 2016, **60**, 2602–2610.
- 107 M. K. Reger, T. W. Zollinger, Z. Liu, J. Jones and J. Zhang, Urinary phytoestrogens and cancer, cardiovascular, and all-cause mortality in the continuous National Health and Nutrition Examination Survey, *Eur. J. Nutr.*, 2016, **55**, 1029–1040.
- 108 C. E. Iglesias-Aguirre, F. Vallejo, D. Beltrán, E. Aguilar-Aguilar, J. Puigerver, M. Alajarín, J. Berná, M. V. Selma and J. C. Espín, Lunularin Producers versus Non-producers: Novel Human Metatypes Associated with the Metabolism of Resveratrol by the Gut Microbiota, *J. Agric. Food Chem.*, 2022, **70**, 10521–10531.
- 109 L. Pilšáková, I. Riečanský and F. Jagla, The physiological actions of isoflavone phytoestrogens, *Physiol. Res.*, 2010, **59**, 651–664.
- 110 Z. Liu, W. Li, J. Sun, C. Liu, Q. Zeng, J. Huang, B. Yu and J. Huo, Intake of soy foods and soy isoflavones by rural adult women in China, *Asia Pac. J. Clin. Nutr.*, 2004, **13**, 204–209.
- 111 S. Oba, C. Nagata, N. Shimizu, H. Shimizu, M. Kametani, N. Takeyama, T. Ohnuma and S. Matsushita, Soy product consumption and the risk of colon cancer: a prospective study in Takayama, Japan, *Nutr. Cancer*, 2007, **57**, 151–157.
- 112 C. L. Frankenfeld, Dairy consumption is a significant correlate of urinary equol concentration in a representative sample of US adults, *Am. J. Clin. Nutr.*, 2011, **93**, 1109–1116.
- 113 C. L. Frankenfeld, Cardiometabolic risk and gut microbial phytoestrogen metabolite phenotypes, *Mol. Nutr. Food Res.*, 2017, **61**, 1500900.
- 114 C. L. Frankenfeld, O-Desmethylangolensin: The Importance of Equol's Lesser Known Cousin to Human Health, *Adv. Nutr.*, 2011, **2**, 317–324.
- 115 C. Atkinson, C. L. Frankenfeld and J. W. Lampe, Gut Bacterial Metabolism of the Soy Isoflavone Daidzein: Exploring the Relevance to Human Health, *Exp. Biol. Med.*, 2005, **230**, 155–170.
- 116 C. L. Frankenfeld, C. Atkinson, W. K. Thomas, A. Gonzalez, T. Jokela, K. Wähälä, S. M. Schwartz, S. S. Li and J. W. Lampe, High concordance of daidzein-metabolizing phenotypes in individuals measured 1 to 3 years apart, *Br. J. Nutr.*, 2005, **94**, 873–876.
- 117 K. B. Song, C. Atkinson, C. L. Frankenfeld, T. Jokela, K. Wähälä, W. K. Thomas and J. W. Lampe, Prevalence of Daidzein-Metabolizing Phenotypes Differs between Caucasian and Korean American Women and Girls, *J. Nutr.*, 2006, **136**, 1347–1351.
- 118 N. Li, X. Wu, W. Zhuang, L. Xia, Y. Chen, R. Zhao, M. Yi, Q. Wan, L. Du and Y. Zhou, Soy and Isoflavone Consumption and Multiple Health Outcomes: Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies and Randomized Trials in Humans, *Mol. Nutr. Food Res.*, 2020, **64**, 1900751.
- 119 C. Atkinson, K. M. Newton, E. J. A. Bowles, M. Yong and J. W. Lampe, Demographic, anthropometric, and lifestyle factors and dietary intakes in relation to daidzein-metabolizing phenotypes among premenopausal women in the United States, *Am. J. Clin. Nutr.*, 2008, **87**, 679–687.
- 120 S. Yokoyama and T. Suzuki, Isolation and characterization of a novel equol-producing bacterium from human feces, *Biosci., Biotechnol., Biochem.*, 2008, **72**, 2660–2666.
- 121 D. Tsangalis, G. Wilcox, N. P. Shah, A. E. J. McGill and L. Stojanovska, Urinary excretion of equol by postmenopausal women consuming soymilk fermented by probiotic bifidobacteria, *Eur. J. Clin. Nutr.*, 2007, **61**, 438–441.
- 122 Q.-K. Wei, T.-R. Chen and J.-T. Chen, Using of Lactobacillus and Bifidobacterium to product the isoflavone aglycones in fermented soymilk, *Int. J. Food Microbiol.*, 2007, **117**, 120–124.
- 123 T. T. Pham and N. P. Shah, Biotransformation of Isoflavone Glycosides by Bifidobacterium animalis in Soymilk Supplemented with Skim Milk Powder, *J. Food Sci.*, 2007, **72**, M316–M324.
- 124 G. P. Rodriguez-Castaño, M. R. Dorris, X. Liu, B. W. Bolling, A. Acosta-Gonzalez and F. E. Rey, Bacteroides thetaiotaomicron Starch Utilization Promotes Quercetin Degradation and Butyrate Production by Eubacterium ramulus, *Front. Microbiol.*, 2019, **10**, 1145.
- 125 A. Braune, W. Engst, P. W. Elsinghorst, N. Furtmann, J. Bajorath, M. Gütschow and M. Blaut, Chalcone Isomerase from Eubacterium ramulus Catalyzes the Ring Contraction of Flavanonols, *J. Bacteriol.*, 2016, **198**, 2965–2974.
- 126 W. Zheng, Y. Ma, A. Zhao, T. He, N. Lyu, Z. Pan, G. Mao, Y. Liu, J. Li, P. Wang, J. Wang, B. Zhu and Y. Zhang, Compositional and functional differences in human gut microbiome with respect to equol production and its association with blood lipid level: a cross-sectional study, *Gut Pathog.*, 2019, **11**, 20.
- 127 M. Y. Lacourt-Ventura, B. Vilanova-Cuevas, D. Rivera-Rodríguez, R. Rosario-Acevedo, C. Miranda, G. Maldonado-Martínez, J. Maysonet, D. Vargas, Y. Ruiz, R. Hunter-Mellado, L. A. Cubano, S. Dharmawardhane, J. W. Lampe, A. Baerga-Ortiz, F. Godoy-Vitorino and M. M. Martínez-Montemayor, Soy and Frequent Dairy Consumption with Subsequent Equol Production Reveals Decreased Gut Health in a Cohort of Healthy Puerto Rican Women, *Int. J. Environ. Res. Public Health*, 2021, **18**, 8254.
- 128 L. M. Miller, J. W. Lampe, K. M. Newton, G. Gundersen, S. Fuller, S. D. Reed and C. L. Frankenfeld, Being overweight or obese is associated with harboring a gut microbial community not capable of metabolizing the soy



- isoflavone daidzein to O-desmethylangolensin in peri- and post-menopausal women, *Maturitas*, 2017, **99**, 37–42.
- 129 C. L. Frankenfeld, C. Atkinson, K. Wähälä and J. W. Lampe, Obesity prevalence in relation to gut microbial environments capable of producing equol or O-desmethylangolensin from the isoflavone daidzein, *Eur. J. Clin. Nutr.*, 2014, **68**, 526–530.
- 130 V. Ahuja, K. Miura, A. Vishnu, A. Fujiyoshi, R. Evans, M. Zaid, N. Miyagawa, T. Hisamatsu, A. Kadota, T. Okamura, H. Ueshima and A. Sekikawa, Significant inverse association of equol-producer status with coronary artery calcification but not dietary isoflavones in healthy Japanese men, *Br. J. Nutr.*, 2017, **117**, 260–266.
- 131 X. Zhang, A. Fujiyoshi, V. Ahuja, A. Vishnu, E. Barinas-Mitchell, A. Kadota, K. Miura, D. Edmundowicz, H. Ueshima and A. Sekikawa, Association of equol producing status with aortic calcification in middle-aged Japanese men: The ERA JUMP study, *Int. J. Cardiol.*, 2022, **352**, 158–164.
- 132 T. Usui, M. Tochiya, Y. Sasaki, K. Muranaka, H. Yamakage, A. Himeno, A. Shimatsu, A. Inaguma, T. Ueno, S. Uchiyama and N. Satoh-Asahara, Effects of natural S-equol supplements on overweight or obesity and metabolic syndrome in the Japanese, based on sex and equol status, *Clin. Endocrinol.*, 2013, **78**, 365–372.
- 133 S. T. Soukup, A. K. Engelbert, B. Watzl, A. Bub and S. E. Kulling, Microbial Metabolism of the Soy Isoflavones Daidzein and Genistein in Postmenopausal Women: Human Intervention Study Reveals New Metabotypes, *Nutrients*, 2023, **15**, 2352.
- 134 M. Shukla, K. Gupta, Z. Rasheed, K. A. Khan and T. M. Haqqi, Consumption of Hydrolyzable Tannins Rich Pomegranate Extract (POMx) Suppresses Inflammation and Joint Damage In Rheumatoid Arthritis, *Nutrition*, 2008, **24**, 733–743.
- 135 E. Barraón-Catalán, S. Fernández-Arroyo, D. Saura, E. Guillén, A. Fernández-Gutiérrez, A. Segura-Carretero and V. Micol, Cistaceae aqueous extracts containing ellagitannins show antioxidant and antimicrobial capacity, and cytotoxic activity against human cancer cells, *Food Chem. Toxicol.*, 2010, **48**, 2273–2282.
- 136 V.-I. Neli, S. Ivo, J. Remi, Q. Stephane and S. G. Angel, Antiviral activities of ellagitannins against bovine herpesvirus-1, suid alphaherpesvirus-1 and caprine herpesvirus-1, *J. Vet. Med. Anim. Health*, 2020, **12**, 139–143.
- 137 A. González-Sarriás, M. Larrosa, F. A. Tomás-Barberán, P. Dolara and J. C. Espín, NF- $\kappa$ B-dependent anti-inflammatory activity of urolithins, gut microbiota ellagic acid-derived metabolites, in human colonic fibroblasts, *Br. J. Nutr.*, 2010, **104**, 503–512.
- 138 J. A. Giménez-Bastida, A. González-Sarriás, M. Larrosa, F. Tomás-Barberán, J. C. Espín and M.-T. García-Conesa, Ellagitannin metabolites, urolithin A glucuronide and its aglycone urolithin A, ameliorate TNF- $\alpha$ -induced inflammation and associated molecular markers in human aortic endothelial cells, *Mol. Nutr. Food Res.*, 2012, **56**, 784–796.
- 139 F. A. Tomás-Barberán, R. García-Villalba, A. González-Sarriás, M. V. Selma and J. C. Espín, Ellagic Acid Metabolism by Human Gut Microbiota: Consistent Observation of Three Urolithin Phenotypes in Intervention Trials, Independent of Food Source, Age, and Health Status, *J. Agric. Food Chem.*, 2014, **62**, 6535–6538.
- 140 A. Cortés-Martín, R. García-Villalba, A. González-Sarriás, M. Romo-Vaquero, V. Loria-Kohen, A. Ramírez-de-Molina, F. A. Tomás-Barberán, M. V. Selma and J. C. Espín, The gut microbiota urolithin metabotypes revisited: the human metabolism of ellagic acid is mainly determined by aging, *Food Funct.*, 2018, **9**, 4100–4106.
- 141 W. Xian, S. Yang, Y. Deng, Y. Yang, C. Chen, W. Li and R. Yang, Distribution of Urolithins Metabotypes in Healthy Chinese Youth: Difference in Gut Microbiota and Predicted Metabolic Pathways, *J. Agric. Food Chem.*, 2021, **69**, 13055–13065.
- 142 M. V. Selma, M. Romo-Vaquero, R. García-Villalba, A. González-Sarriás, F. A. Tomás-Barberán and J. C. Espín, The human gut microbial ecology associated with overweight and obesity determines ellagic acid metabolism, *Food Funct.*, 2016, **7**, 1769–1774.
- 143 M. Romo-Vaquero, E. Fernández-Villalba, A.-L. Gil-Martinez, L. Cuenca-Bermejo, J. C. Espín, M. T. Herrero and M. V. Selma, Urolithins: potential biomarkers of gut dysbiosis and disease stage in Parkinson's patients, *Food Funct.*, 2022, **13**, 6306–6316.
- 144 M. Romo-Vaquero, A. Cortés-Martín, V. Loria-Kohen, A. Ramírez-de-Molina, I. García-Mantrana, M. C. Collado, J. C. Espín and M. V. Selma, Deciphering the Human Gut Microbiome of Urolithin Metabotypes: Association with Enterotypes and Potential Cardiometabolic Health Implications, *Mol. Nutr. Food Res.*, 2019, **63**, 1800958.
- 145 C. E. Iglesias-Aguirre, R. García-Villalba, D. Beltrán, M. D. Frutos-Lisón, J. C. Espín, F. A. Tomás-Barberán and M. V. Selma, Gut Bacteria Involved in Ellagic Acid Metabolism To Yield Human Urolithin Metabotypes Revealed, *J. Agric. Food Chem.*, 2023, **71**, 4029–4035.
- 146 G. Ista, R. P. Feliciano, T. Weber, R. Garcia-Villalba, F. Tomas-Barberan, C. Heiss and A. Rodriguez-Mateos, Plasma urolithin metabolites correlate with improvements in endothelial function after red raspberry consumption: A double-blind randomized controlled trial, *Arch. Biochem. Biophys.*, 2018, **651**, 43–51.
- 147 A. González-Sarriás, R. García-Villalba, M. Romo-Vaquero, C. Alasalvar, A. Örem, P. Zafrilla, F. A. Tomás-Barberán, M. V. Selma and J. C. Espín, Clustering according to urolithin metabotype explains the interindividual variability in the improvement of cardiovascular risk biomarkers in overweight-obese individuals consuming pomegranate: A randomized clinical trial, *Mol. Nutr. Food Res.*, 2017, **61**, 1600830.
- 148 T. Meroño, G. Peron, G. Gargari, R. González-Domínguez, A. Miñarro, E. Vegas-Lozano, N. Hidalgo-Liberona, C. Del



- Bo', S. Bernardi, P. A. Kroon, B. Carrieri, A. Cherubini, P. Riso, S. Guglielmetti and C. Andrés-Lacueva, The relevance of urolithins-based metabotyping for assessing the effects of a polyphenol-rich dietary intervention on intestinal permeability: A post-hoc analysis of the MaPLE trial, *Food Res. Int.*, 2022, **159**, 111632.
- 149 A. Cortés-Martín, M. Romo-Vaquero, I. García-Mantrana, A. Rodríguez-Varela, M. C. Collado, J. C. Espín and M. V. Selma, Urolithin Metabotypes can Anticipate the Different Restoration of the Gut Microbiota and Anthropometric Profiles during the First Year Postpartum, *Nutrients*, 2019, **11**, 2079.
- 150 A. Cortés-Martín, G. Colmenarejo, M. V. Selma and J. C. Espín, Genetic Polymorphisms, Mediterranean Diet and Microbiota-Associated Urolithin Metabotypes can Predict Obesity in Childhood-Adolescence, *Sci. Rep.*, 2020, **10**, 1–13.
- 151 C. E. Iglesias-Aguirre, A. González-Sarriás, A. Cortés-Martín, M. Romo-Vaquero, L. Osuna-Galisteo, J. J. Cerón, J. C. Espín and M. V. Selma, In vivo administration of gut bacterial consortia replicates urolithin metabotypes A and B in a non-urolithin-producing rat model, *Food Funct.*, 2023, **14**, 2657–2667.
- 152 D. D'Amico, P. A. Andreux, P. Valdés, A. Singh, C. Rinsch and J. Auwerx, Impact of the Natural Compound Urolithin A on Health, Disease, and Aging, *Trends Mol. Med.*, 2021, **27**, 687–699.
- 153 D. D'Amico, M. Olmer, A. M. Fouassier, P. Valdés, P. A. Andreux, C. Rinsch and M. Lotz, Urolithin A improves mitochondrial health, reduces cartilage degeneration, and alleviates pain in osteoarthritis, *Aging Cell*, 2022, **21**, e13662.
- 154 S. Liu, D. D'Amico, E. Shankland, S. Bhayana, J. M. Garcia, P. Aebischer, C. Rinsch, A. Singh and D. J. Marcinek, Effect of Urolithin A Supplementation on Muscle Endurance and Mitochondrial Health in Older Adults: A Randomized Clinical Trial, *JAMA Netw. Open*, 2022, **5**, e2144279.
- 155 R. Zamora-Ros, C. Andres-Lacueva, R. M. Lamuela-Raventós, T. Berenguer, P. Jakszyn, C. Martínez, M. J. Sánchez, C. Navarro, M. D. Chirlaque, M.-J. Tormo, J. R. Quirós, P. Amiano, M. Dorronsoro, N. Larrañaga, A. Barricarte, E. Ardanaz and C. A. González, Concentrations of resveratrol and derivatives in foods and estimation of dietary intake in a Spanish population: European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort, *Br. J. Nutr.*, 2008, **100**, 188–196.
- 156 P. Yin, L. Yang, Q. Xue, M. Yu, F. Yao, L. Sun and Y. Liu, Identification and inhibitory activities of ellagic acid- and kaempferol-derivatives from Mongolian oak cups against  $\alpha$ -glucosidase,  $\alpha$ -amylase and protein glycation linked to type II diabetes and its complications and their influence on HepG2 cells' viability, *Arabian J. Chem.*, 2018, **11**, 1247–1259.
- 157 Y. Hou, K. Wang, W. Wan, Y. Cheng, X. Pu and X. Ye, Resveratrol provides neuroprotection by regulating the JAK2/STAT3/PI3K/AKT/mTOR pathway after stroke in rats, *Genes Dis.*, 2018, **5**, 245–255.
- 158 J. K. Bird, D. Raederstorff, P. Weber and R. E. Steinert, Cardiovascular and Antiobesity Effects of Resveratrol Mediated through the Gut Microbiota, *Adv. Nutr.*, 2017, **8**, 839–849.
- 159 B. N. M. Zordoky, I. M. Robertson and J. R. B. Dyck, Preclinical and clinical evidence for the role of resveratrol in the treatment of cardiovascular diseases, *Biochim. Biophys. Acta, Mol. Basis Dis.*, 2015, **1852**, 1155–1177.
- 160 X. Huang, Y. Dai, J. Cai, N. Zhong, H. Xiao, D. J. McClements and K. Hu, Resveratrol encapsulation in core-shell biopolymer nanoparticles: Impact on antioxidant and anticancer activities, *Food Hydrocolloids*, 2017, **64**, 157–165.
- 161 M. Samsami-kor, N. E. Daryani, P. R. Asl and A. Hekmatdoost, Anti-Inflammatory Effects of Resveratrol in Patients with Ulcerative Colitis: A Randomized, Double-Blind, Placebo-controlled Pilot Study, *Arch. Med. Res.*, 2015, **46**, 280–285.
- 162 C. E. Iglesias-Aguirre, F. Vallejo, D. Beltrán, J. Berná, J. Puigcerver, M. Alajarin, M. V. Selma and J. C. Espín, 4-Hydroxydibenzyl: a novel metabolite from the human gut microbiota after consuming resveratrol, *Food Funct.*, 2022, **13**, 7487–7493.
- 163 S. V. Luca, I. Macovei, A. Bujor, A. Miron, K. Skalicka-Woźniak, A. C. Aprotosoai and A. Trifan, Bioactivity of dietary polyphenols: The role of metabolites, *Crit. Rev. Food Sci. Nutr.*, 2020, **60**, 626–659.
- 164 S. Vogl, A. G. Atanasov, M. Binder, M. Bulusu, M. Zehl, N. Fakhrudin, E. H. Heiss, P. Picker, C. Wawrosch, J. Saukel, G. Reznicek, E. Urban, V. Bochkov, V. M. Dirsch and B. Kopp, The Herbal Drug *Melampyrum pratense* L. (Koch): Isolation and Identification of Its Bioactive Compounds Targeting Mediators of Inflammation, *Evid. Based Complement. Alternat. Med.*, 2013, **2013**, 395316.
- 165 T. Ito-Nagahata, C. Kurihara, M. Hasebe, A. Ishii, K. Yamashita, M. Iwabuchi, M. Sonoda, K. Fukuhara, R. Sawada, A. Matsuoka and Y. Fujiwara, Stilbene analogs of resveratrol improve insulin resistance through activation of AMPK, *Biosci., Biotechnol., Biochem.*, 2013, **77**, 1229–1235.
- 166 F. Li, Y. Han, X. Wu, X. Cao, Z. Gao, Y. Sun, M. Wang and H. Xiao, Gut Microbiota-Derived Resveratrol Metabolites, Dihydroresveratrol and Lunularin, Significantly Contribute to the Biological Activities of Resveratrol, *Front. Nutr.*, 2022, **9**, 912591.
- 167 I. Günther, G. Rimbach, C. I. Mack, C. H. Weinert, N. Danylec, K. Lüersen, M. Birringer, F. Bracher, S. T. Soukup, S. E. Kulling and K. Pallauf, The Putative Caloric Restriction Mimetic Resveratrol has Moderate Impact on Insulin Sensitivity, Body Composition, and the Metabolome in Mice, *Mol. Nutr. Food Res.*, 2020, **64**, 1901116.
- 168 S. W. Tsang, Y.-F. Guan, J. Wang, Z.-X. Bian and H.-J. Zhang, Inhibition of pancreatic oxidative damage by



- stilbene derivative dihydro-resveratrol: implication for treatment of acute pancreatitis, *Sci. Rep.*, 2016, **6**, 22859.
- 169 C. Rodríguez-García, C. Sánchez-Quesada, E. Toledo, M. Delgado-Rodríguez and J. J. Gaforio, Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion?, *Molecules*, 2019, **24**, 917.
- 170 R. Kiyama, Biological effects induced by estrogenic activity of lignans, *Trends Food Sci. Technol.*, 2016, **54**, 186–196.
- 171 J. Peterson, J. Dwyer, H. Adlercreutz, A. Scalbert, P. Jacques and M. L. McCullough, Dietary lignans: physiology and potential for cardiovascular disease risk reduction, *Nutr. Rev.*, 2010, **68**, 571–603.
- 172 A. K. Zaineddin, K. Buck, A. Vrieling, J. Heinz, D. Flesch-Janys, J. Linseisen and J. Chang-Claude, The Association Between Dietary Lignans, Phytoestrogen-Rich Foods, and Fiber Intake and Postmenopausal Breast Cancer Risk: A German Case-Control Study, *Nutr. Cancer*, 2012, **64**, 652–665.
- 173 F. L. Miles, S. L. Navarro, Y. Schwarz, H. Gu, D. Djukovic, T. W. Randolph, A. Shojaie, M. Kratz, M. A. J. Hullar, P. D. Lampe, M. L. Neuhouser, D. Raftery and J. W. Lampe, Plasma metabolite abundances are associated with urinary enterolactone excretion in healthy participants on controlled diets, *Food Funct.*, 2017, **8**, 3209–3218.
- 174 J. M. Landete, Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health, *Food Res. Int.*, 2012, **46**, 410–424.
- 175 A. Senizza, G. Rocchetti, J. I. Mosele, V. Patrone, M. L. Callegari, L. Morelli and L. Lucini, Lignans and Gut Microbiota: An Interplay Revealing Potential Health Implications, *Molecules*, 2020, **25**, 5709.
- 176 T. Clavel, J. Doré and M. Blaut, Bioavailability of lignans in human subjects, *Nutr. Res. Rev.*, 2006, **19**, 187–196.
- 177 E. Eeckhaut, K. Struijs, S. Possemiers, J.-P. Vincken, D. D. Keukeleire and W. Verstraete, Metabolism of the Lignan Macromolecule into Enterolignans in the Gastrointestinal Lumen As Determined in the Simulator of the Human Intestinal Microbial Ecosystem, *J. Agric. Food Chem.*, 2008, **56**, 4806–4812.
- 178 Y. Hu, Y. Song, A. A. Franke, F. B. Hu, R. M. van Dam and Q. Sun, A Prospective Investigation of the Association Between Urinary Excretion of Dietary Lignan Metabolites and Weight Change in US Women, *Am. J. Epidemiol.*, 2015, **182**, 503–511.
- 179 C. Xu, Q. Liu, Q. Zhang, A. Gu and Z.-Y. Jiang, Urinary enterolactone is associated with obesity and metabolic alteration in men in the US National Health and Nutrition Examination Survey 2001–10, *Br. J. Nutr.*, 2015, **113**, 683–690.
- 180 M. A. J. Hullar, S. M. Lancaster, F. Li, E. Tseng, K. Beer, C. Atkinson, K. Wähälä, W. K. Copeland, T. W. Randolph, K. M. Newton and J. W. Lampe, Enterolignan-Producing Phenotypes Are Associated with Increased Gut Microbial Diversity and Altered Composition in Premenopausal Women in the United States, *Cancer Epidemiol. Biomarkers Prev.*, 2015, **24**, 546–554.
- 181 Y. Li, F. Wang, J. Li, K. L. Ivey, J. E. Wilkinson, D. D. Wang, R. Li, G. Liu, H. A. Eliassen, A. T. Chan, C. B. Clish, C. Huttenhower, F. B. Hu, Q. Sun and E. B. Rimm, Dietary lignans, plasma enterolactone levels, and metabolic risk in men: exploring the role of the gut microbiome, *BMC Microbiol.*, 2022, **22**, 82.
- 182 W. Mullen, M.-A. Archeveque, C. A. Edwards, H. Matsumoto and A. Crozier, Bioavailability and Metabolism of Orange Juice Flavanones in Humans: Impact of a Full-Fat Yogurt, *J. Agric. Food Chem.*, 2008, **56**, 11157–11164.
- 183 I. Najmanová, M. Vopršalová, L. Saso and P. Mladěnka, The pharmacokinetics of flavanones, *Crit. Rev. Food Sci. Nutr.*, 2020, **60**, 3155–3171.
- 184 M. Tomás-Navarro, F. Vallejo, E. Sentandreu, J. L. Navarro and F. A. Tomás-Barberán, Volunteer Stratification Is More Relevant than Technological Treatment in Orange Juice Flavanone Bioavailability, *J. Agric. Food Chem.*, 2014, **62**, 24–27.
- 185 F. Vallejo, M. Larrosa, E. Escudero, M. P. Zafrilla, B. Cerdá, J. Boza, M. T. García-Conesa, J. C. Espín and F. A. Tomás-Barberán, Concentration and Solubility of Flavanones in Orange Beverages Affect Their Bioavailability in Humans, *J. Agric. Food Chem.*, 2010, **58**, 6516–6524.
- 186 G. Pereira-Caro, G. Borges, J. van der Hooft, M. N. Clifford, D. Del Rio, M. E. Lean, S. A. Roberts, M. B. Kellerhals and A. Crozier, Orange juice (poly) phenols are highly bioavailable in humans, *Am. J. Clin. Nutr.*, 2014, **100**, 1378–1384.
- 187 A. Nishioka, E. de C. Tobaruela, L. N. Fraga, F. A. Tomás-Barberán, F. M. Lajolo and N. M. A. Hassimotto, Stratification of Volunteers According to Flavanone Metabolite Excretion and Phase II Metabolism Profile after Single Doses of ‘Pera’ Orange and ‘Moro’ Blood Orange Juices, *Nutrients*, 2021, **13**, 473.
- 188 M. Á. Ávila-Gálvez, J. A. Giménez-Bastida, A. González-Sarriás and J. C. Espín, New Insights into the Metabolism of the Flavanones Eriocitrin and Hesperidin: A Comparative Human Pharmacokinetic Study, *Antioxidants*, 2021, **10**, 435.
- 189 W. Lin, W. Wang, H. Yang, D. Wang and W. Ling, Influence of Intestinal Microbiota on the Catabolism of Flavonoids in Mice, *J. Food Sci.*, 2016, **81**, H3026–H3034.
- 190 A. Vogiatzoglou, A. A. Mulligan, R. N. Luben, M. A. H. Lentjes, C. Heiss, M. Kelm, M. W. Merx, J. P. E. Spencer, H. Schroeter and G. G. C. Kuhnle, Assessment of the dietary intake of total flavan-3-ols, monomeric flavan-3-ols, proanthocyanidins and theaflavins in the European Union, *Br. J. Nutr.*, 2014, **111**, 1463–1473.
- 191 P. Mena, L. Bresciani, N. Brindani, I. A. Ludwig, G. Pereira-Caro, D. Angelino, R. Llorach, L. Calani, F. Brighenti, M. N. Clifford, C. I. R. Gill, A. Crozier, C. Curti and D. D. Rio, Phenyl- $\gamma$ -valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-



- ols: synthesis, analysis, bioavailability, and bioactivity, *Nat. Prod. Rep.*, 2019, **36**, 714–752.
- 192 A. Takagaki and F. Nanjo, Bioconversion of (–)-Epicatechin, (+)-Epicatechin, (–)-Catechin, and (+)-Catechin by (–)-Epigallocatechin-Metabolizing Bacteria, *Biol. Pharm. Bull.*, 2015, **38**, 789–794.
- 193 S. Wiese, T. Esatbeyoglu, P. Winterhalter, H.-P. Kruse, S. Winkler, A. Bub and S. E. Kulling, Comparative biokinetics and metabolism of pure monomeric, dimeric, and polymeric flavan-3-ols: a randomized cross-over study in humans, *Mol. Nutr. Food Res.*, 2015, **59**, 610–621.
- 194 J. van Duynhoven, J. J. J. van der Hooft, F. A. van Dorsten, S. Peters, M. Foltz, V. Gomez-Roldan, J. Vervoort, R. C. H. de Vos and D. M. Jacobs, Rapid and sustained systemic circulation of conjugated gut microbial catabolites after single-dose black tea extract consumption, *J. Proteome Res.*, 2014, **13**, 2668–2678.
- 195 N. Brindani, P. Mena, L. Calani, I. Benzie, S.-W. Choi, F. Brighenti, F. Zanardi, C. Curti and D. Del Rio, Synthetic and analytical strategies for the quantification of phenyl- $\gamma$ -valerolactone conjugated metabolites in human urine, *Mol. Nutr. Food Res.*, 2017, **61**, 9.
- 196 P. Mena, I. A. Ludwig, V. B. Tomatis, A. Acharjee, L. Calani, A. Rosi, F. Brighenti, S. Ray, J. L. Griffin, L. J. Bluck and D. Del Rio, Inter-individual variability in the production of flavan-3-ol colonic metabolites: preliminary elucidation of urinary metabolotypes, *Eur. J. Nutr.*, 2019, **58**, 1529–1543.
- 197 F. Sánchez-Patán, C. Cueva, M. Monagas, G. E. Walton, G. R. M. Gibson, J. E. Quintanilla-López, R. Lebrón-Aguilar, P. J. Martín-Álvarez, M. V. Moreno-Arribas and B. Bartolomé, In vitro fermentation of a red wine extract by human gut microbiota: changes in microbial groups and formation of phenolic metabolites, *J. Agric. Food Chem.*, 2012, **60**, 2136–2147.
- 198 P. Mena, C. Favari, A. Acharjee, S. Chernbumroong, L. Bresciani, C. Curti, F. Brighenti, C. Heiss, A. Rodriguez-Mateos and D. Del Rio, Metabotypes of flavan-3-ol colonic metabolites after cranberry intake: elucidation and statistical approaches, *Eur. J. Nutr.*, 2022, **61**, 1299–1317.
- 199 A. Cortés-Martín, M. V. Selma, J. C. Espín and R. García-Villalba, The Human Metabolism of Nuts Proanthocyanidins does not Reveal Urinary Metabolites Consistent with Distinctive Gut Microbiota Metabotypes, *Mol. Nutr. Food Res.*, 2019, **63**, 1800819.
- 200 N. Tosi, C. Favari, L. Bresciani, E. Flanagan, M. Hornberger, A. Narbad, D. Del Rio, D. Vauzour and P. Mena, Unravelling phenolic metabotypes in the frame of the COMBAT study, a randomized, controlled trial with cranberry supplementation, *Food Res. Int.*, 2023, **172**, 113187.
- 201 L. Narduzzi, V. Agulló, C. Favari, N. Tosi, C. Mignogna, A. Crozier, D. Del Rio and P. Mena, (Poly)phenolic compounds and gut microbiome: new opportunities for personalized nutrition, *Microbiome Res. Rep.*, 2022, **1**, 16.
- 202 C. Busch, S. Noor, C. Leischner, M. Burkard, U. M. Lauer and S. Venturelli, Anti-proliferative activity of hop-derived prenylflavonoids against human cancer cell lines, *Wien. Med. Wochenschr.*, 2015, **165**, 258–261.
- 203 E. Sommella, G. Verna, M. Liso, E. Salviati, T. Esposito, D. Carbone, C. Pecoraro, M. Chieppa and P. Campiglia, Hop-derived fraction rich in beta acids and prenylflavonoids regulates the inflammatory response in dendritic cells differently from quercetin: unveiling metabolic changes by mass spectrometry-based metabolomics, *Food Funct.*, 2021, **12**, 12800–12811.
- 204 B. Kontek, D. Jedrejek, W. Oleszek and B. Olas, Antiradical and antioxidant activity in vitro of hops-derived extracts rich in bitter acids and xanthohumol, *Ind. Crops Prod.*, 2021, **161**, 113208.
- 205 M. Rad, M. Hümpel, O. Schaefer, R. C. Schoemaker, W.-D. Schleunig, A. F. Cohen and J. Burggraaf, Pharmacokinetics and systemic endocrine effects of the phyto-oestrogen 8-prenylnaringenin after single oral doses to postmenopausal women, *Br. J. Clin. Pharmacol.*, 2006, **62**, 288–296.
- 206 L. A. Calvo-Castro, M. Burkard, N. Sus, G. Scheubeck, C. Leischner, U. M. Lauer, A. Bosy-Westphal, V. Hund, C. Busch, S. Venturelli and J. Frank, The Oral Bioavailability of 8-Prenylnaringenin from Hops (*Humulus Lupulus* L.) in Healthy Women and Men is Significantly Higher than that of its Positional Isomer 6-Prenylnaringenin in a Randomized Crossover Trial, *Mol. Nutr. Food Res.*, 2018, **62**, 1700838.
- 207 S. Possemiers, S. Rabot, J. C. Espín, A. Bruneau, C. Philippe, A. González-Sarriás, A. Heyerick, F. A. Tomás-Barberán, D. De Keukeleire and W. Verstraete, *Eubacterium limosum* activates isoxanthohumol from hops (*Humulus lupulus* L.) into the potent phytoestrogen 8-prenylnaringenin in vitro and in rat intestine, *J. Nutr.*, 2008, **138**, 1310–1316.
- 208 J. Guo, D. Nikolic, L. R. Chadwick, G. F. Pauli and R. B. van Breemen, Identification of Human Hepatic Cytochrome P450 Enzymes Involved in the Metabolism of 8-Prenylnaringenin and Isoxanthohumol from Hops (*humulus Lupulus* L.), *Drug Metab. Dispos.*, 2006, **34**, 1152–1159.
- 209 S. Bolca, S. Possemiers, V. Maervoet, I. Huybrechts, A. Heyerick, S. Vervarcke, H. Depypere, D. D. Keukeleire, M. Bracke, S. D. Henauf, W. Verstraete and T. V. de Wiele, Microbial and dietary factors associated with the 8-prenylnaringenin producer phenotype: a dietary intervention trial with fifty healthy post-menopausal Caucasian women, *Br. J. Nutr.*, 2007, **98**, 950–959.
- 210 D. Nikolic, Y. Li, L. R. Chadwick, S. Grubjesic, P. Schwab, P. Metz and R. B. van Breemen, Metabolism of 8-prenylnaringenin, a potent phytoestrogen from hops (*Humulus lupulus*), by human liver microsomes, *Drug Metab. Dispos.*, 2004, **32**, 272–279.
- 211 C. E. Iglesias-Aguirre, M. V. Selma and J. C. Espín, Unveiling metabotype clustering in resveratrol, daidzein, and ellagic acid metabolism: Prevalence, associated gut microbiomes, and their distinctive microbial networks, *Food Res. Int.*, 2023, **173**, 113470.

