Food & Function

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

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

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

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Received 9th October 2023,
Accepted 18th February 2024

DOI: 10.1039/d3fo04338j

rsc.li/food-function

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 metabotypes have been proposed, however, potential metabotypes for most (poly)phenols have not been investigated, and the relationship between metabotypes and human health remains ambiguous. This review presents updated knowledge on the reciprocal interaction between (poly)phenols and the gut microbiome, associated gut metabotypes, and subsequent impact on human health.

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.[1] Extensive preclinical studies have demonstrated promising biological activities of individual (poly)phenols, including anti-inflammatory, antioxidant, and anti-proliferative.[2–7] However, the physiological relevance of such studies, in particular the evidence from *in vitro* studies, has been largely questioned.[8,9] 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.[10–15] However, inconsistent results also exist and a high inter-individual variability in response to (poly)phenols has been reported.[16,17] In addition to heterogenous 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.[18,19]

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.[20,21] These compounds can then undergo phase II metabolism, generating conjugated metabolites that may have very different biological activities from their parent compounds.[22] 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.[23,24] 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 metabotypes, have been proposed, with isoflavone and ellagitannin related metabotypes being the most widely studied so far.[25,26]

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.[27]

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

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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.[28] 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.[29] 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.[30] *Eubacterium ramulus* and Strain SY8519 have been reported to catalyse the C-ring cleavage of isoflavones (Table 1).[31,32] *Flavonifractor plautii* also showed similar activity for flavonols.[29] 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).[33–36] 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.[37] *Gordonibacter urolithinfaciens* and *Ellagibacter isourolithinifaciens* are involved in this process (Table 1).[38] They also metabolise catechol dehydroxylation and reduction.[38] 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.[37] 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*,[87] and through inhibiting colonies of pathogenic bacteria such as *Escherichia coli*, *Clostridium perfringens* and *Helicobacter pylori*.[88,89] 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.[90] Quercetin has been demonstrated to inhibit the growth of *E. coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* in *in vitro* assays.[91,92] 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.[93] Zhang *et al.*[94] 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.[95] 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.[96] 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.[97] 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 metabotypes

The concept of (poly)phenol metabolising phenotypes or metabotypes was first proposed by Bolca and colleagues as "clusters of gut microbial communities with similar metabolic profiles".[98] More recently, Espín *et al.*[28] defined gut (poly)phenol metabotypes 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	*Bifidobacterium lactis*	Anthocyanin	β-Glucosidase	39
	Lactobacillus acidophilus	Anthocyanin	β-Glucosidase	39
	Lactobacillus casei	Anthocyanin	β-Glucosidase	39
	Lactobacillus.plantarum	Anthocyanin	β-Glucosidase	39
Ellagitannins	*Bifidobacterium pseudocatenulatum*	Ellagic acid	Metabolise ellagic acid to urolithin A and B	40
	Clostridium coccoides members	Ellagic acid	Metabolise ellagic acid to urolithins	41
	Ellagibacter isourolithinifaciens	Ellagic acid	Metabolise ellagic acid to isourolithin A	42
	Enterococcus faecium FUA027	Ellagic acid	Metabolise ellagic acid to urolithin A	43
	Gordonibacter pamelaeae	Ellagic acid	Metabolise ellagic acid to urolithins	44
	Gordonibacter urolithinfaciens	Ellagic acid	Metabolise ellagic acid to urolithins	45
	Lactococcus garvieae FUA009	Ellagic acid	Metabolise ellagic acid to urolithin A	46
	Streptococcus thermophilus FUA329	Ellagic acid	Metabolise ellagic acid to urolithin A	47
Flavanones	*Bacteroides distasonis*	Eriocitrin	Hydrolysis	48
	Bacteroides uniformis	Eriocitrin	Hydrolysis	48
	Bifidobacterium catenulatum	Hesperidin	Hydrolysis	49
	Bifidobacterium pseudocatenultum	Hesperidin	Hydrolysis	49
	Clostridium butyricum	Eriocitrin	C-ring cleavage	48
Flavan-3-ols	*Adlercreutzia equolifaciens* JCM 14793	(−)-Epigallocatechin, (−)-gallocatechin	Dihydroxylation	50
	Asaccharobacter celatus JCM 14811	(−)-Epigallocatechin, (−)-gallocatechin	C-ring cleavage	50
	Eggerthella lenta	(−)-Epicatechin, (+)-catechin	C-ring cleavage	51
	Slackia equolifaciens JCM 16059	(−)-Epigallocatechin, (−)-gallocatechin	C-ring cleavage	50
Flavones	*Blautia* sp. MRG-PMF1	Apigetrin	*O*-Glucose hydrolysis	52
	Eubacterium cellulosolvens	Homoorientin, isovitexin	Deglycosylation of *C*- and *O*-glucosides	53
Flavonols	*Bacillus subtilis*	Quercetin	C-ring cleavage	54
	Bacteroides distasonis	Robinin	Hydrolyse robinin to kaempferol	55
	Bacteroides ovatus	Rutin	β-Glucosidase, hydrolyse rutin to quercetin	55
	Bacteroides uniformis	Rutin	β-Glucosidase, hydrolyse rutin to quercetin	55
	Bifidobacterium adolescentis	Kaempferol 3-*O*-glucoside	β-Glucosidase	56
	Bifidobacterium bifidum	Kaempferol 3-*O*-glucoside	β-Glucosidase	56
	Bifidobacterium breve	Kaempferol 3-*O*-glucoside	β-Glucosidase	56
	Bifidobacterium catenulatum	Kaempferol 3-*O*-glucoside	Hydrolysis, β-Glucosidase	56
	Bifidobacterium dentium	Rutin, poncirin	Hydrolysis	57
	Bifidobacterium infantis	Kaempferol 3-*O*-glucoside	β-Glucosidase	56
	Bifidobacterium longum	Kaempferol 3-*O*-glucoside	β-Glucosidase	56
	Bifidobacterium pseudocatenulatum	Kaempferol 3-*O*-glucoside	Hydrolysis, β-glucosidase	56
	Blautia sp. MRG-PMF1	Hesperidin, Poylmethoxyflavones	*O*-Rutinose hydrolysis, demethylation, degylcosylation	52
	Clostridium orbiscindens	Quercetin, taxifolin, luteolin, apigenin, naringenin, phloretin	C-ring cleavage	58
	Enterococcus avium	Rutin	*O*-Deglycosylation	59,60
	Enterococcus casseliflavus	Quercetin-3-glucoside	Hydrolysis	61
	Eubacterium ramulus	Rutin, quercetin, kaempferol, taxifolin, luteolin, quercetin-3-glucoside	C-ring cleavage	61–63
	Flavonifractor plautii	Quercetin	C-ring cleavage	64
	Lactobacillus acidophilus	Rutin, nicotiflorin, narirutin	α-Rhamnosidase	65
	Lactobacillus plantarum	Rutin, nicotiflorin, narirutin	α-Rhamnosidase	65

Table 1 *(Contd.)*

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

Table 1 *(Contd.)*

Phenolic class	Species/strain	Substrate(s)	Reaction	Ref.
Stilbenes	*Adlercreutzia equolifaciens*	Resveratrol	Metabolism resveratrol into dihydroresveratrol	85
	Slackia equolifaciens	Resveratrol	Metabolism resveratrol into dihydroresveratrol	85
Xanthohumol	*Eubacterium ramulus*	Xanthohumol	Hydrogenation	86
	Eubacterium limosum	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.[99]

Currently, there is a lack of consensus regarding whether the concept of (poly)phenol metabotypes 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 metabotypes 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 metabotype will be arbitrary and will depend on each cohort considered.[97] 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 metabotypes (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 metabotype, some researchers have used the Setchell method,[100–102] 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.[103–105] 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 metabotypes 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.[106,107] 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.

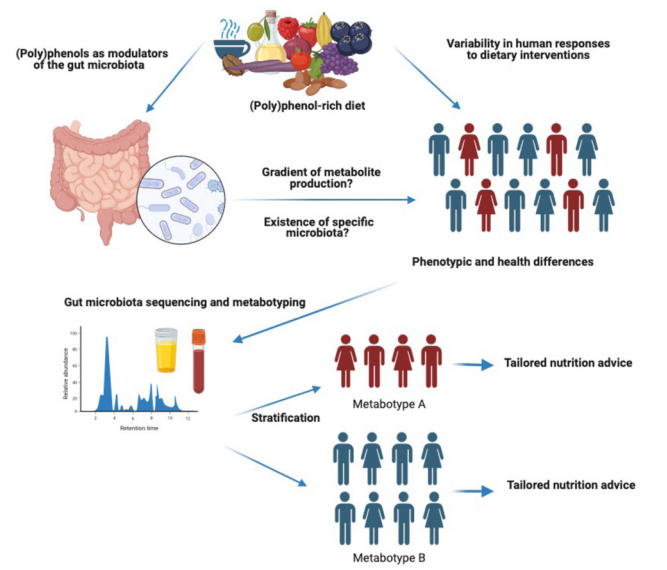

Fig. 1 Inter-individual variability in gut metabolism of (poly)phenols due to distinct gut microbiome composition.

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

The most widely studied metabotypes are the ones related to the gut microbial metabolites of the isoflavone daidzein, equol and ODMA. More recently, ellagitannin and resveratrol related metabotypes have also been described.[108]

Equol and ODMA metabotypes

Isoflavones are a class of phytoestrogens which are found mainly in soy products. They exist as glycoside conjugates in plants.[109] 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.[110–112]

Equol and ODMA are gut microbial metabolites of daidzein (Fig. 2), which have been related to health effects. To date, equol- and ODMA-producer metabotypes have been identified.[113] It is also suggested that the capacity of an individual to produce equol is not influenced by the capacity to produce ODMA.[114] 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 metabotypes. For example, bacteria responsible for the C-ring cleavage is required to transform daidzein to ODMA but not needed for equol production.[113]

There are approximately 30%–50% and 80%–90% of Caucasian population being identified as equol- and ODMA-producers respectively following soy consumption.[115–117] 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%.[117,118] Due to the stability in the long term, metabotypes are regarded as a biomarker for intestinal ecology and potential disease risks.[116] A number of studies have investigated demographic, anthropometric and dietary factors (*i.e.* race, ethnicity, age, BMI, *etc.*) associated with daidzein-related metabotypes to describe the features of equol- and ODMA- producers. However, observed results are often inconsistent and no clear associations can be demonstrated.[113,119] One of the reasons could be the inconsistent classification of metabotypes 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).[66–68,72,120] Importantly, the role of bifidobacterial in the biotransformation of isoflavones in soy milk has been well established.[121–123] 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.[78] *Eubacterium ramulus* also plays a role in the metabolism of other (poly)phenols, such as quercetin, xanthohumol, 8-prenylnaringenin and other flavonoids.[86,124,125] 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 metabotypes, 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).[126] 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.[126] 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.[127] In non-producers, a higher dominance of *Akkermansia* spp., *Prevotella 9*, and *Megasphera elsdenii* was presented. The authors also showed that even among individuals with the same metabotype, the consumption of soy or not would result in different gut microbiota composition.[127] Considering the amount of regular soy intake and distribution of daidzein-related metabotypes are different between Asian and Western population, it is likely that the inconsistent results are attributable to sociodemographic factors and dietary patterns.

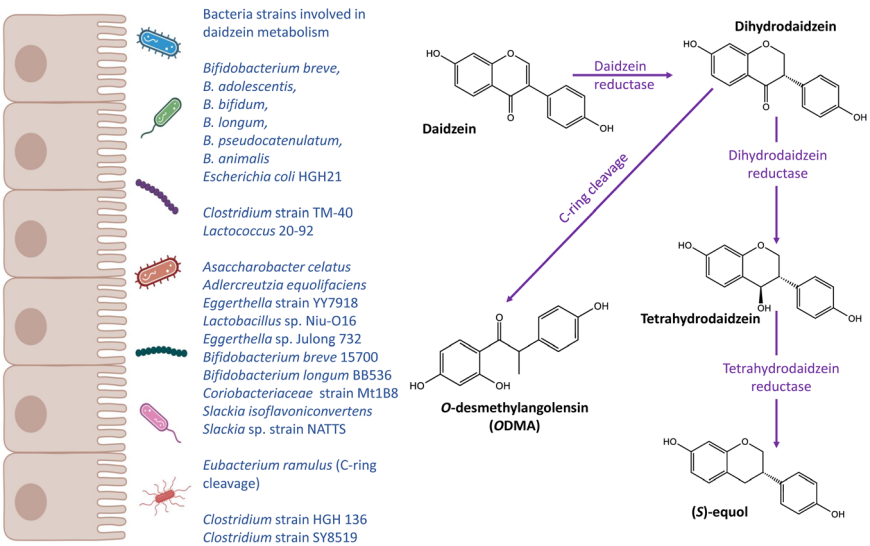

Fig. 2 Metabolic pathways of daidzein and bacteria related to daidzein metabolism.

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 metabotypes. 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.[128] This is in line with the findings by Frankenfeld *et al.*,[129] 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.[130,131] On the contrary, Usui *et al.* reported significant improvements in cardiometabolic risk parameters upon 12-week equol supplementation only in female equol non-producers.[132] Interestingly, Hazim *et al.*[100] 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 metabotype 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 metabotype-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 metabotypes, a recent paper including 60 postmenopausal women investigated novel daidzein and genistein related gut metabotypes.[133] After 12-week daily consumption of a soy isoflavone extract, the authors defined 5 metabotypes 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 metabotypes, and highlights the complexity of (poly)phenol metabolism and the need for more research beyond the "classic" metabotypes.

Urolithin metabotypes

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.[134–136] Urolithins, which are dibenzopyran-6-one derivatives metabolised from ellagitannins (Fig. 3), have also shown anti-inflammatory properties.[137,138]

Three urolithin-related metabotypes (UM) have been described for ellagitannin gut metabolism.[26,139] Urolithin metabotype A (UMA), which is characterised by the production of urolithin A derivatives; urolithin metabotype B (UMB), which produces urolithin B and isourolithin A in addition to urolithin A derivatives; and urolithin metabotype zero (UM0), with no production of urolithin metabolites.[26] The distribution of the three metabotypes was demonstrated in a relatively large Spanish cohort (n = 839) by Cortés-Martín *et al.*[140] Approximately 50–80% of the population were UMA, 10–40% were UMB and 10% were UM0. The authors also suggested that the metabotype frequency was age-dependent, with the percentage of UMA decreasing and UMB increasing with age, while UM0 prevalence remained constant.[140] However, the stability of urolithin metabotype 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.[141] 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 metabotypes in different ethnicities and populations, as most of the evidence currently existing comes from Spanish cohorts.

Few small studies suggest that urolithin metabotypes can be potential biomarkers for gut microbiome balance and a healthy intestinal ecology. Tomás-Barberán *et al.*[139] reported a higher prevalence of UMB among patients with metabolic syndrome or colorectal cancer. Selma *et al.*[142] 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.[140] 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.[143] 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 metabotype-associated gut microbiota goes

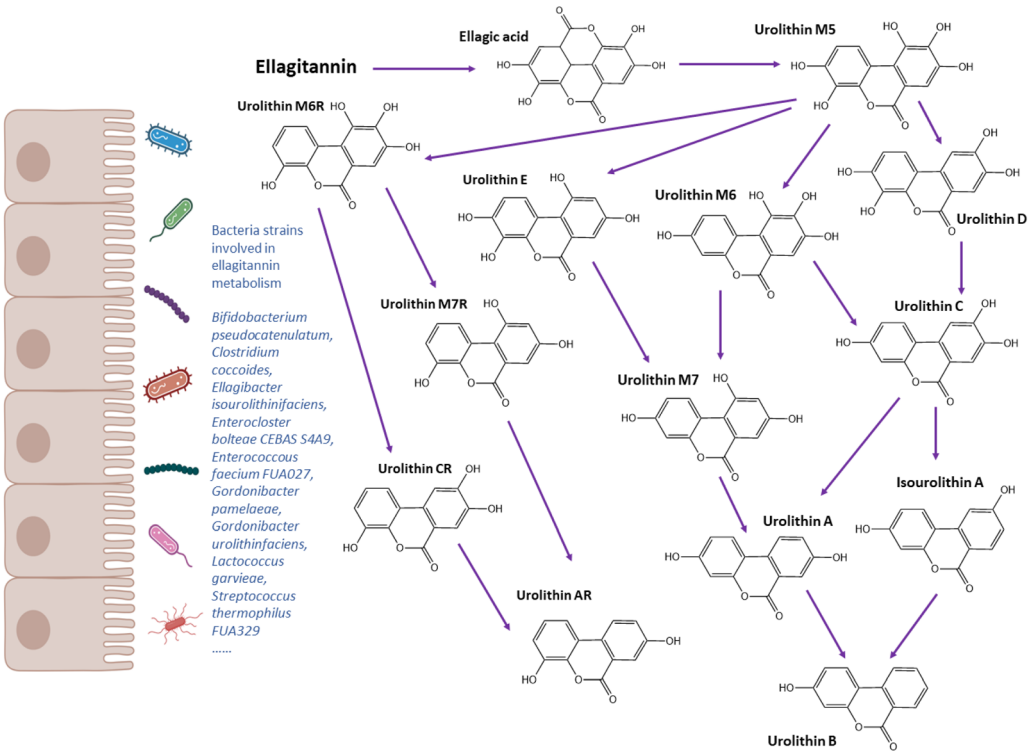

Fig. 3 Metabolic pathways of ellagic acid and bacteria related to urolithin metabolism.

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

The family Coriobacteriaceae has been found to display a strong correlation with urolithin production.[44,45,144] *Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae*, 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.[44,45] *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).[42] Romo-Vaquero *et al.*[144] analysed gut microbiome composition from 249 healthy metabotyped 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.*[145] 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.[40,43,46,47] Among three metabotypes, UM0 showed the lowest diversity and richness of intestinal bacteria, while UMB had the highest richness at phylum and family level.[144] 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.[144] 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 metabotypes. A small RCT in healthy men (n = 10), which was not stratified into metabotypes, 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.[146] 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.[147] 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.[148] 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.*[149] 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).[150] 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.*[151] 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 metabotypes linked.[152–154] To clearly demonstrate the health benefits of different metabotypes, larger cohort studies with pre-intervention stratification and balanced focus on the three metabotypes 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 metabotypes

Resveratrol is a type of stilbenes that are mainly present in grapes, berries, peanuts and wines.[155] Many preclinical studies have shown a wide range of biological properties, including anti-inflammation, anti-obesity, cardioprotective and neuroprotective effects.[156–161] 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 metabotypes is just at its infancy period. Bode *et al.*[85] 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*.[85] *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.*[162] 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 metabotypes (*i.e.* LUN-producers *vs.* LUN non-producers).[108] The gut microbiota first converts resveratrol into DHR through hydrogenation,[163] 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.[108] The distribution of gut metabotypes 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.[108]

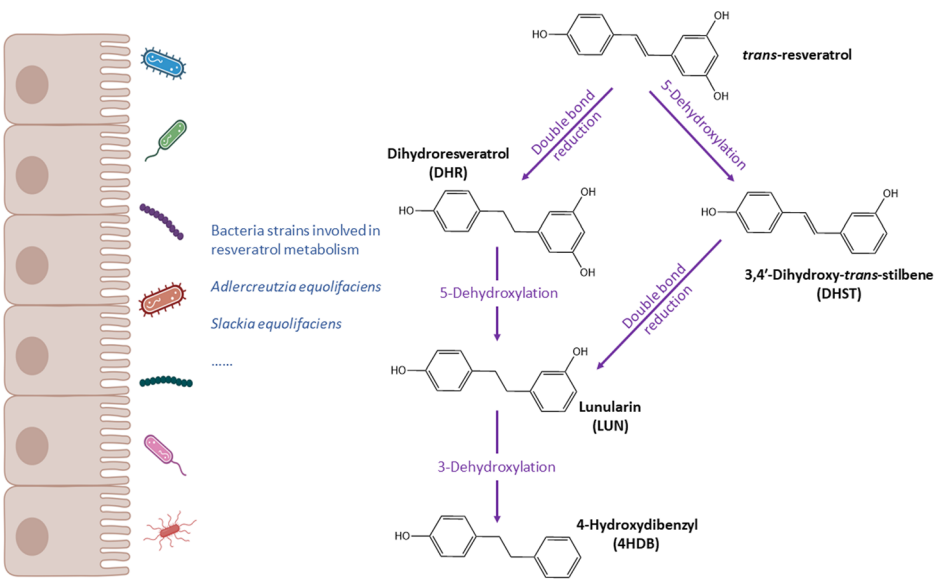

Fig. 4 Metabolic pathways of resveratrol and bacteria related to resveratrol metabolism.

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

While no studies investigating the link between resveratrol gut metabotypes and health have been conducted, a few preclinical 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*,[164] and DHST was found to increase glucose uptake and induce AMPK phosphorylation independently of insulin.[165] Li *et al.*[166] 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.[167,168] 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 metabotypes, 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 metabotypes

For many of the (poly)phenols investigated so far, a specific non-producer metabotype 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 metabotypes 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.[169] Lignans have a similar structure to 17β-estradiol and are able to bind estrogen receptors, thus activating downstream signalling and exhibiting estrogenic or anti-estrogenic effects.[170] Intervention and epidemiological studies have showed that lignans have a protective effect on cardiovascular diseases,[171] whilst the effects on other chronic diseases, such as breast cancer, have not been unequivocally confirmed.[172] 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 excreters.[173,174] Considering lignans undergo extensive

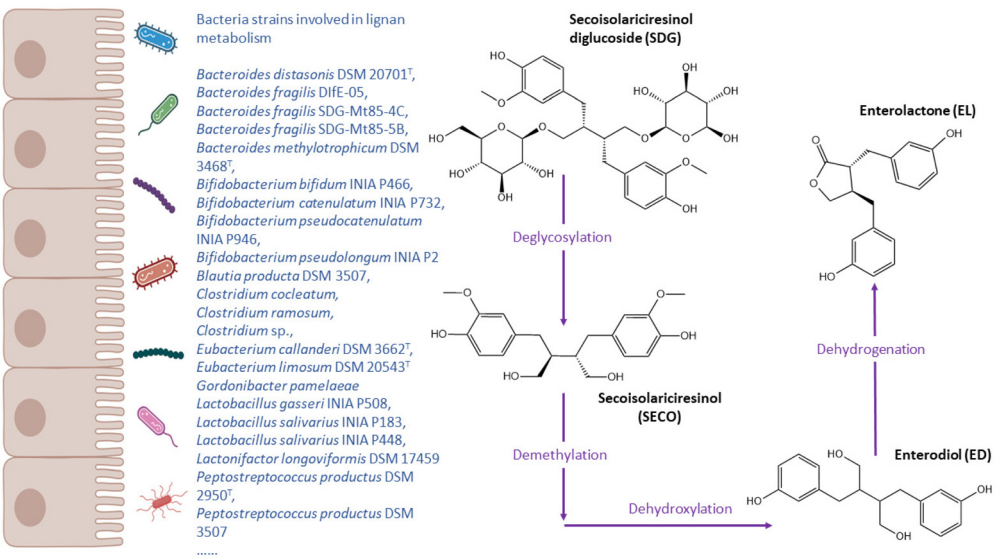

Fig. 5 Metabolic pathways of lignan (secoisolariciresinol diglucoside) and bacteria related to enterolignan metabolism.

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.[175] Therefore, total of four reactions are involved in the bio-transformation of SDG into EL: deglycosylation, demethylation, dehydroxylation, and dehydrogenation. Clavel *et al.*[176] 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). Peirotén *et al.*[83] 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 μM and 20 μM of EL were produced respectively, whereas ED production was similar between samples.[177]

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 g^{-1} creatinine; median in the lowest quartile, 16.4 nmol g^{-1} creatinine), was associated with less weight gain (95% CI: 0.12, 0.41; $p <$ 0.01).[178] Another 10-year cohort study found that urinary EL levels (quartiles of urinary EL (ng ml^{-1}): Q1: ≤ 127; Q2: 127–420; Q3: 420–979; Q4: > 979) were inversely associated with obesity (OR 0.30, 95% CI 0.17, 0.54; $p < 0{\cdot}001$) and other cardiometabolic risk markers, including triglycerides, fasting glucose concentrations, and fasting insulin levels in men aged 20–60 years old.[179] Two studies also suggested a positive association between plasma and urinary EL levels and diversity of gut microbiota.[180,181] 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).[181] Among 115 premenopausal US women, EL production was significantly associated with alpha-diversity, and higher EL excretion (mean (μg 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.[180] 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.[182] In this process, gut microbiome, including *Bifidobacterium*, *Clostridium*, *Bacteroides*, *Lactobacillus* and *Eubacterium*, plays a role in the deglycosylation of rhamnoglucoside moiety of hesperidin.[29,183]

A large inter-individual variability has been observed in the metabolism and excretion of flavanones. Tomás-Navarro *et al.*[184] 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.*[185] 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.[184,185] 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.[185,186] A cross-over study (n = 21) by Nishioka *et al.*[187] 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.[188] The gut microbiome associated to flavanone metabotypes 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.[189] However, it is challenging to use them as metabotyping 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.[190] Phenyl-γ-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.[191] 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 performes 4′-dehydroxylation of ring fission product.[192] *Flavonifractor plautii* has been showed to convert phenyl-γ-valerolactones into 3-(phenyl)propionic acids.[51] 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.[193–197] Mena *et al.*[196,198] described potential gut metabotypes related with flavan-3-ols: one with high production of tri- and di-hydroxyphenyl-γ-valerolactones and a reduced excretion of 3-(hydroxyphenyl)propionic acid; another is characterised by a low production of phenyl-γ-valerolactones but high amounts of 3-(hydroxyphenyl)propionic acid. Besides these two metabotypes, Cortés-Martín *et al.*[199] 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 metabotypes in these studies. More recently, Tosi *et al.*[200] proposed new additional metabotypes for cranberry (poly)phenols using data from a 12-week RCT among 60 healthy older adults. Metabotype 1 was characterized by a higher excretion of 5-(3′,4′-dihydroxyphenyl)-γ-valerolactones (3′,4′-diHPVLs) and 5-(3′-hydroxyphenyl)-γ-valerolactones (3′-HPVLs), metabotype 2 had a higher excretion of 3′-hydroxycinnamic acids (3′-HCAs), 3- (hydroxyphenyl)propanoic acids (HPPAs) and 3-hydroxybenzoic acids (3-HBAs), while metabotype 3 was characterized by a low excretion of all metabolites. The proposed metabotypes 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 metabotypes with multiple gut microbial metabolites is an useful approach, and more research in this area is needed,[201] 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-prenylnaringenin (8-PN), are not commonly found in most foods but are present in beer and hop-containing dietary supplements.[202] They have been found to possess antioxidant, anti-proliferative, anti-inflammatory, estrogenic and immune-regulatory properties.[202–206] *In vitro* and animal studies have shown that isoxanthohumol can be converted into 8-PN by the action of *Eubacterium limosum*.[207] In this regard, inter-individual differenced have been observed for the conversion, which is attributed to the biotransformation capacity of the gut bacteria.[208,209] 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.[209] 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.[209] 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.[210] Evidence regarding the metabolite production gradient of prenylflavonoids is limited, leading to the ambiguous demonstration of gut metabotypes for 8-PN.

Metabotype clustering: is there a common metabotype for multiple (poly)phenol subclasses?

An important question that remains unknown is whether a (poly)phenol "superproducer" metabotype exist, or if same individuals share the same capacity to produce different (poly)phenol gut microbial metabolites. Very recently, Iglesias-Aguirre *et al.*[211] investigated gut metabotype clusters (MC) for resveratrol, ellagic acid and daidzein in 127 individuals. To our knowledge, this is the first study investigating (poly)phenol gut metabotype 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 metabotype 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 metabotype 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 metabotypes 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 metabotypes is still in its infancy. Many open questions still remain for the most widely investigated metabotypes, 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 metabotypes. The main factors driving the prevalence of metabotypes among populations are also unclear, but indications suggest age, sex and disease state can impact on metabotypes. Whether the background diet, and in particular habitual (poly)phenol consumption is an important factor in metabotype prevalence is unclear, and the lack of reliable and accurate methods for estimating (poly)phenol intake is likely a confounding factor in this matter.

Metabotypes 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 metabotypes might change with changes in the microbiota *e.g.* induced by age, diet, or disease, with a clear example on the urolithin metabotype being modulated by age. Metabotypes 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 metabotypes 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 metabotypes 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 metabotypes 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.

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