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REVIEW

Bacterial species involved in the conversion of dietary flavonoids in the human gut

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ABSTRACT

The gut microbiota plays a crucial role in the conversion of dietary flavonoids and thereby affects their health-promoting effects in the human host. The identification of the bacteria involved in intestinal flavonoid conversion has gained increasing interest. This review summarizes available information on the so far identified human intestinal flavonoid-converting bacterial species and strains as well as their enzymes catalyzing the underlying reactions. The majority of described species involved in flavonoid transformation are capable of carrying out the *O*-deglycosylation of flavonoids. Other bacteria cleave the less common flavonoid-*C*-glucosides and/or further degrade the aglycones of flavonols, flavanonols, flavones, flavanones, dihydrochalcones, isoflavones and monomeric flavan-3-ols. To increase the currently limited knowledge in this field, identification of flavonoid-converting bacteria should be continued using culture-dependent screening or isolation procedures and molecular approaches based on sequence information of the involved enzymes.

Introduction

The digestive tract of humans and animals is populated by microbial communities that co-evolved with the respective animal species.[1,2] It has been recognized that the gut microbiota fulfills important functions such as the fermentation of non-digestible carbohydrates (dietary fiber) to short-chain fatty acids, the priming and shaping of the immune system and the provision of colonization resistance against pathogens. The gut microbiota has also been implicated in host energy metabolism and the onset of various disordes including metabolic disease, inflammatory bowel disease, colorectal cancer and allergies.[3]

The intestinal microbiota is mainly composed of representatives of 5 dominant phyla, Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia with the first 2 accounting for more than 90% of the bacteria.[4,5] It has been proposed to distinguish between a core microbiome and a peripheral microbiome.[6] According to this concept, intestinal bacterial genes present in almost every human would represent the core microbiome while those activities that are present in some, but not all individuals would be attributed to the peripheral microbiome. In this sense, the functions of the intestinal microbiota mentioned above would represent core activities, while the conversion of rare carbohydrates or non-nutritive ingredients would be considered peripheral activities. For example, an intestinal bacterium (*Bacteroides plebeius*) capable of degrading the sulfated algal polysaccharide porphyran has only been found in Japanese subjects.[7] Similarly, the ability to convert the soy isoflavone daidzein to equol displays a high variability among human individuals,[8] which therefore may be attributable to the peripheral gut microbiome. Based on the lower occurrence of such bacterial activities in humans, there is considerably less insight into the conversion of non-nutritive secondary plant compounds by intestinal bacteria than in pathways involved in the breakdown of carbohydrates or proteins. In particular, knowledge about the responsible bacterial species and their involved enzymes is fragmentary even though there is a considerable interest in several of these compounds owing to reports about their health-promoting effects on the host.

Flavonoids are a major class of secondary plant compounds, which are ingested by humans when foods of plant origin are consumed. Accumulating

evidence from epidemiological, preclinical and clinical studies supports a role of these polyphenols in the prevention of cancer, cardiovascular disease, type 2 diabetes, and cognitive dysfunction, whose incidence in the Western population has been increasing.[9,10] However, the ingested flavonoids are poorly absorbed in the small intestine and substantial quantities may reach the colon. In addition, flavonoid conjugates formed by the human host are excreted back into the intestine via the enterohepatic circulation. In the intestine, the flavonoids may affect the composition of the microbiota, which represents one possible mode of action of these compounds.[11-13] By promoting beneficial bacteria and inhibiting potentially pathogenic species, flavonoids could therapeutically target the intestinal microbiome. Flavonoids may also be metabolized by the resident microbiota and the resulting products may have bioactivity, which differs from that of the parent compounds. The bacterial conversion may have potential health consequences for the human host.[14] Inter-individual differences in intestinal microbiota composition may result in different profiles of flavonoid metabolites. Thus, the current aim is to link specific gut bacteria to certain metabolic phenotypes associated with beneficial health effects. Since the crucial role of gut bacteria in flavonoid metabolism has been increasingly recognized, the knowledge on species involved has been growing in recent years but is far from complete.

This review gives an overview of the so far identified human intestinal bacteria involved in the conversion of flavonoids. We included all bacterial species or strains, for which a proper taxonomic description or at least 16S rRNA sequences are available. Such information is missing for some of the reported flavonoid-metabolizing bacterial strains. The collected data are included in 2 tables, one being arranged according to the flavonoid classes and catalyzed reactions (Table 1) and the other according to taxonomic ranks (phylum, family) of the bacteria (Table 2). Wherever data are available, information on bacterial enzymes involved in flavonoid conversion is also reported.

Metabolism of flavonoids by intestinal bacteria: Reactions and benefits

The flavonoids exhibit a basic phenyl chroman (flavan) structure consisting of 2 phenyl rings (A and B) and an oxygen-containing heterocyclic ring (C)

(Fig. 1). The more than 8000 different flavonoid compounds known so far have been grouped into several classes. Flavonoids present in the diet can be assigned to 6 main classes: flavonols, flavones, flavanones, isoflavones, flavan-3-ols and anthocyanidins.[15] Flavanonols and dihydrochalcones as well as chalcones and auronols represent minor classes. The flavonoid classes most relevant for this review are depicted in Figure 1. The basic structure of the individual compounds is modified by hydroxy, methoxy and alkyl groups attached to the A- and B-ring. The majority of flavonoids in plants and, thus, in foods occur as glycosides. These are mainly O-glycosides, in which coupling of the sugar moiety to the aglycone occurs via a hydroxy group. However, C-coupled flavonoid glycosides are also widely distributed among plants. Exceptions to this are the flavan-3-ols, which are not conjugated but may form oligomeric and polymeric structures, the proanthocyanidins.

Based on its enormous gene pool, the intestinal microbiota has a large metabolic potential and therefore many reactions taking place in the intestinal tract are catalyzed by the gut microbiota. In contrast to the hepatic metabolism of xenobiotics, bacterial metabolism of xenobiotics in the intestine does not involve oxygen but rather reductions and hydrolyses resulting in the formation of nonpolar low molecular weight products. This also applies to the conversion of flavonoids in the gut. The following reactions are catalyzed by intestinal bacteria in the course of flavonoid conversion: O- and C-deglycosylation, demethylation, dehydroxylation, ester cleavage, reduction of carbon-carbon double bonds, isomerization, ring fission, extension and truncation of the aliphatic carbon chain and decarboxylation. Bacterial species or strains reported to catalyze these reactions are listed in Table 1 and Table 2 and will be discussed in the following chapters with respect to the relevant flavonoid classes. The ensuing transformation of monophenolic metabolites resulting from flavonoid degradation is only included if catalyzed by the same species responsible for conversion of the basic flavonoid structure.

Obligate or facultative anaerobic bacteria may utilize flavonoids entering the intestine as additional growth substrates. Glycosylated flavonoids can serve as sole carbon and energy source, with the attached sugar moieties being preferentially fermented. For example, growth on isoquercetin (quercetin-3-O-glucoside) has been demonstrated for *Enterococcus*

Table 1. Flavonoid classes, bacterial conversion reactions, active human gut bacteria, their flavonoid substrates and resulting products.

Flavonoid class	Conversion reaction	Species/strain[a] (former reported name)	Substrate(s)	Product(s)	Reference
Flavonols / flavanonols	O-Deglycosylation	Bacteroides uniformis ATCC 8492[T], B. uniformis strain	Rutin (quercetin-3-O-glucorhamnoside)	Quercetin	85
		Bacteroides ovatus ATCC 8483[T], B. ovatus strain	Rutin	Quercetin	85
		Parabacteroides distasonis (Bacteroides distasonis) strain	Rutin	Quercetin-3-O-glucoside	85
			Robinin (kaempferol-3-O-robinoside-7-O-rhamnoside)	Kaempferol	
		Enterococcus casseliflavus M1	Isoquercetin (quercetin-3-O-glucoside)	Quercetin	16
		Eubacterium ramulus DSM 16296	Isoquercetin	Quercetin	16,17
		Enterococcus avium LY1	Rutin	3,4-Dihydroxyphenylacetic acid	38
		Bifidobacterium pseudocatenulatum B7003, B. longum ssp. infantis (B. infantis) B7875, B. catenulatum B7377, B. breve B7824	Rutin Kaempferol-3-O-glucoside	Quercetin Kaempferol	31
		Blautia sp. MRG-PMF1	Rutin	Quercetin	36
		Bifidobacterium dentium K13	Rutin	ND[b]	32
		Enterococcus avium EFEL009	Rutin	Isoquercetin, quercetin	39
	C-Ring cleavage	Flavonifractor plautii (Clostridium orbiscindens) strains ATCC 49531, 257, 258 and 264	Quercetin	3,4-Dihydroxyphenylacetic acid	86
		Eubacterium ramulus DSM 16296	Quercetin	Taxifolin, alphitonin, 3,4-dihydroxyphenylacetic acid, phloroglucinol, acetate, butyrate	16,17,20
			Taxifolin	3,4-Dihydroxyphenylacetic acid	
			Kaempferol	4-Hydroxyphenylacetic acid	
		Eggerthella (Eubacterium) sp. SDG-2	Taxifolin	α,2′,3,4,4′,6′-Hexahydroxydihydrochalcone	56
		Flavonifractor plautii (Clostridium orbiscindens) l2	Quercetin, taxifolin	3,4-Dihydroxyphenylacetic acid	21
Flavones / flavanones	O-Deglycosylation	Parabacteroides distasonis (Bacteroides distasonis) JCM 5825[T], Bacteroides uniformis JCM 5828, Bifidobacterium adolescentis JCM 1275, B. bifidum IFO 14252, Lactobacillus plantarum IAM 12477, L. acidophilus strain, L. buchneri strain, L. casei strain, L. leichmanii strain, Enterococcus faecalis (Streptococcus faecalis) IFO 12964, Lactococcus lactis (Streptococcus lactis) strain, Enterobacter cloacae IAM 12349	Eriocitrin (eriodictyol-7-O-rutinoside)	Eriodictyol	27
		Eubacterium ramulus DSM 16296	Luteolin-7-O-glucoside	3-(3,4-Dihydroxyphenyl)propionic acid	17
		Strain CG19-1	Luteolin-5-O-glucoside, luteolin-7-O-glucoside, luteolin-3′-O-glucoside	Luteolin	37

Table 1. (Continued)

Flavonoid class	Conversion reaction	Species/strain[a] (former reported name)	Substrate(s)	Product(s)	Reference
		Eubacterium cellulosolvens ATCC 43171[T]	Apigenin-7-O-glucoside (apigetrin), Luteolin-7-O-glucoside, luteolin-3'-O-glucoside	Apigenin, Luteolin	33
		Escherichia sp. 4	Apigenin-7-O-glucoside, Diosmetin-7-O-glucoside	Apigenin, Diosmetin	58
		Blautia sp. MRG-PMF1	Apigenin-7-O-glucoside, Hesperetin-7-O-rutinoside (hesperidin)	Apigenin, Hesperetin	36
		Bifidobacterium catenulatum ATCC 27539[T], B. breve WC 0422, B. pseudocatenulatum strains WC 0400, WC 0401, WC 0403, WC 0407 and WC 0408	Hesperetin-7-O-rutinoside	Hesperetin	48
		Bifidobacterium dentium K13	Isosakuranetin-7-O-neohesperidoside (poncirin), Naringenin-7-O-neohesperidoside (naringin)	ND, ND	32
		Lactococcus sp MRG-IFC-1, Enterococcus sp. MRG-IFC-2, Lactococcus sp. MRG-IF-3	Apigenin-7-O-glucoside	Apigenin	40
	C-Deglycosylation	Strain CG19-1	Luteolin-6-C-glucoside (homoorientin), luteolin-8-C-glucoside (orientin), Apigenin-8-C-glucoside (vitexin), apigenin-6-C-glucoside (isovitexin)	Luteolin, Apigenin	37
		Eubacterium cellulosolvens ATCC 43171[T]	Luteolin-6-C-glucoside	Luteolin	33
		Enterococcus sp. 45	Apigenin-6-C-glucoside, Luteolin-8-C-glucoside	Apigenin, Luteolin	50
	O-Demethylation	Eubacterium limosum strains DSM 20543[T] and LMG P23546	Isoxanthohumol	8-Prenylnaringenin	51,52
		Blautia sp. MRG-PMF1	Hesperetin, 5,7-Dimethoxyflavone, 5,7,4'-Trimethoxyflavone	Eriodictyol, 5,7-Dihydroxyflavone (chrysin), 5,7,4'-Trihydroxyflavone (apigenin)	36
	Dehydroxylation	Escherichia sp. 4	Diosmetin	Acacetin	58
	C-Ring cleavage	Clostridium butyricum IFO 13949[T]	Eriodictyol	3-(3,4-Dihydroxyphenyl)propionic acid	27
		Eubacterium ramulus DSM 16296	Luteolin, eriodictyol, Naringenin	3-(3,4-Dihydroxyphenyl)propionic acid, 3-(4-Hydroxyphenyl)propionic acid	17,20
		Flavonifractor plautii (Clostridium orbiscindens) I2	Luteolin, eriodictyol	3-(3,4-Dihydroxyphenyl)propionic acid	21
		Strain CG19-1	Apigenin, naringenin, Luteolin, Apigenin	3-(4-Hydroxyphenyl)propionic acid, 3-(3,4-Dihydroxyphenyl)propionic acid, 3-(4-Hydroxyphenyl)propionic acid	37
Dihydrochalcones	O-Deglycosylation	Eubacterium ramulus DSM 16296	Hesperetin dihydrochalcone-4'-O-glucoside	Hesperetin dihydrochalcone	34
	Cleavage	Eubacterium ramulus DSM 16296	Phloretin	3-(4-Hydroxyphenyl)propionic acid	17

(continued)

Table 1. (Continued)

Flavonoid class	Conversion reaction	Species/strain[a] (former reported name)	Substrate(s)	Product(s)	Reference
		Flavonifractor plautii (Clostridium orbiscindens) l2	Hesperetin dihydrochalcone Phloretin	3-(3-Hydroxy-4-methoxyphenyl)propionic acid 3-(4-Hydroxyphenyl)propionic acid	34 21
Isoflavones / isoflavanones	O-Deglycosylation	E. coli ATCC BAA-97 (strain HGH21)	Hesperetin dihydrochalcone Daidzin Genistin	3-(3-Hydroxy-4-methoxyphenyl)propionic acid Daidzein Genistein	34 87
		Eubacterium ramulus DSM 16296	Genistin	Genistein	35
		Bifidobacterium animalis strain, B. longum strain, B. pseudolongum strain	Daidzin, acetyldaidzin, malonyldaidzin	Daidzein	30
		Bifidobacterium pseudocatenulatum B7003, B. longum ssp. infantis (B. infantis) B7875, B. catenulatum B7377, B. breve B7824	Daidzin Genistin Glycitin	Daidzein Genistein Glycitein	31
		Strain TM-40	Daidzin	Daidzein	75
		Bifidobacterium adolescentis strains DSM 18350, DSM 18353, MB 114, MB 237 and MB 243, B. bifidum strains MB 110 and 254, B. breve strains DSM 18352, MB 113, MB 234 and MB 235, B. longum ssp. infantis (B. infantis) MB 208, B. animalis ssp. lactis (B. lactis) MB 238, B. longum strains MB 201, MB 207, MB 217, MB 218 and MB 219, B. pseudocatenulatum MB 264, B. angulatum MB 223	Daidzin	Daidzein	28
		Strain CG19-1	Daidzin Genistin	Daidzein Genistein	37
		Eubacterium cellulosolvens ATCC 43171[T]	Daidzin Genistin	Daidzein Genistein	33
		Blautia sp. MRG-PMF1, Lactococcus sp. MRG-IFC-1, Lactococcus sp. MRG-IF-3, Enterococcus sp. MRG-IFC-2	Daidzin Genistin Sissotrin Ononin Glycitin	Daidzein Genistein Biochanin A Formononetin Glycitein	36,40
	C-Deglycosylation	Strain PUE	Puerarin	Daidzein	49
		Strain CG19-1	Puerarin	Daidzein	37
		Lactococcus sp. MRG-IFC-1, Enterococcus sp. MRG-IFC-2	Puerarin	Daidzein	40

Table 1. (*Continued*)

Flavonoid class	Conversion reaction	Species/strain[a] (former reported name)	Substrate(s)	Product(s)	Reference
	O-Demethylation	Eubacterium limosum ATCC 8486[T]	Biochanin A Formononetin Glycitein	Genistein Daidzein 6,7,4′-Trihydroxyisoflavone	53
		Blautia sp. MRG-PMF1	Biochanin A Formononetin Glycitein	Genistein Daidzein 6,7,4′-Trihydroxyisoflavone	36
	Reduction	Bifidobacterium animalis strain, B. longum strain, B, pseudolongum strain	Daidzein	Equol	30
		Strain Julong 732	Dihydrodaidzein	Equol	76
		Strain TM-40	Daidzein	Dihydrodaidzein	75
		Slackia equolifaciens JCM 16059[T]	Daidzein Genistein	Equol 5-Hydroxy-equol	49,64
		Eggerthella sp. YY7918	Daidzein, dihydrodaidzein	Equol	66
		Adlercreutzia equolifaciens JCM 14793[T]	Daidzein	Equol	67
		Slackia isoflavoniconvertens DSM 22006[T]	Daidzein	Equol	68
		Lactococcus garvieae 20–92	Genistein	5-Hydroxy-equol	65
		Slackia sp. NATTS	Daidzein	Equol	69
	C-Ring cleavage	Eubacterium ramulus DSM 16296	Daidzein Genistein	O-Desmethylangolensin 6′-Hydroxy-O-desmethylangolensin	35
		Eubacterium ramulus Julong 601	Daidzein Genistein	O-Desmethylangolensin 2-(4-Hydroxyphenyl)propionic acid	77
		Strain SY8519	Daidzein	O-Desmethylangolensin	78
	O-Desmethylangolensin cleavage	Eubacterium ramulus DSM 16296	6′-Hydroxy-O-desmethylangolensin	Phloroglucinol, 2-(4-hydroxyphenyl)propionic acid	35
		Strain CG19-1	6′-Hydroxy-O-desmethylangolensin	Phloroglucinol, 2-(4-hydroxyphenyl)propionic acid	37
Flavan-3-ols	Dehydroxylation	Adlercreutzia equolifaciens JCM 14793[T]	O-Desmethylangolensin	Resorcinol, 2-(4-hydroxyphenyl)propionic acid	80
	C-Ring cleavage	Eggerthella (Eubacterium) sp. SDG-2	(−)-Epigallocatechin (−)-Gallocatechin	(2S,3S)-Flavan-3,3′,5,5′,7-pentol (2R,3S)-Flavan-3,3′,5,5′,7-pentol	56
			(+)-Catechin, (+)-epicatechin	(2R)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	
			(−)-Catechin, (−)-epicatechin	(2S)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	
			(−)-Gallocatechin, (−)-epigallocatechin	(2S)-1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	
		Eggerthella lenta rK3	(+)-Catechin, (−)-epicatechin	1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	79
		Eggerthella lenta CAT-1	(+)-Catechin	(2R)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	57
			(−)-Epicatechin	(2S)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	
		Lactobacillus plantarum IFPL935	(+)-Catechin, (−)-epicatechin	1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	81

(*continued*)

Table 1. (*Continued*)

Flavonoid class	Conversion reaction	Species/strain[a] (former reported name)	Substrate(s)	Product(s)	Reference
		Slackia equolifaciens JCM 16059^T	(−)-Epicatechin-3-O-gallate	1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol [includes ester cleavage]	80
		Adlercreutzia equolifaciens JCM 14793^T	(−)-Epigallocatechin, (−)-gallocatechin	1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	80
	Dehydroxylation of the C-ring cleavage product	*Adlercreutzia equolifaciens* JCM 14793^T	(−)-Gallocatechin	1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	80
		Eggerthella (*Eubacterium*) sp. SDG-2	(2S)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (2S)-1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	(2S)-1-(3-Hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (2S)-1-(3,5-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	56
		Eggerthella lenta CAT-1	(2S)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (2R)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	(2S)-1-(3-Hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol (2R)-1-(3-Hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	57
		Adlercreutzia equolifaciens JCM 14793^T	1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	1-(3,5-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	80
	Degradation of the C-ring cleavage product	*Flavonifractor plautii* strains DSM 6740 and aK2	1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol	5-(3,4-Dihydroxyphenyl)-γ-valerolactone, 4-hydroxy-5-(3,4-dihydroxyphenyl)valeric acid	79
Anthocyanins	O-Deglycosylation	*Bifidobacterium animalis* ssp. *lactis* (*Bifidobacterium lactis*) BB-12, *Lactobacillus casei* LC-01, *L. plantarum* IFPL722	Malvidin-3-O-glucoside	Gallic acid, homogentisic acid, syringic acid	29

Note. [a] Entries within each reaction type are listed in order of their publication year.
[b] ND, not determined.

casseliflavus and *Eubacterium ramulus*.[16,17] Prebiotic effects of flavonoid glycosides observed for certain bacterial groups of the human intestinal microbiota may also be explained by utilization of the attached sugar moieties. The growth enhancement of *Bifidobacterium, Lactobacillus* and *Enterococcus* species by anthocyanins may serve as an example.[18] Furthermore, flavonoids may serve as electron acceptors enabling the re-oxidation of electron or hydrogen carriers. This is accompanied by cleavage of the heterocyclic C-ring or modifications of ring substituents. Analysis of gene sequences of bacterial isoflavone-reducing enzymes suggests that the corresponding genes were acquired by horizontal gene transfer from other bacteria indicating that they confer a considerable advantage on the recipients.[19]

Complete degradation of flavonoids by gut bacteria including cleavage of the aromatic A- and B-ring metabolites is usually not observed. However, phloroglucinol, which originates from the A-ring of certain flavonols, flavones and isoflavones, is subject to keto/enol tautomerism. The latter weakens the aromatic character of phloroglucinol and thereby facilitates its reduction with NAD(P)H. The degradation of phloroglucinol into short-chain fatty acids by flavonoid-degrading bacteria such as *E. ramulus* and *Flavonifractor plautii* (former *Clostridium orbiscindens*)[20,21] may result in ATP formation as previously demonstrated for other anaerobes.[22,23]

Beside their growth-promoting effects, flavonoids have antibacterial properties, which among others may be due to disturbance of membrane function or enzyme inhibition. This may result in the modulation of microbiota composition.[11,13,24] The conversion of flavonoids with bacteriostatic or bactericidal effects to inactive metabolites could be regarded as a means to detoxify these xenobiotics promoting the survival and growth of intestinal bacteria that are sensitive to flavonoids.

Deglycosylation of flavonoids

The majority of flavonoids in plants except of the flavan-3-ols are present as *O*- or *C*-glycosides. The glycosides usually undergo deglycosylation prior to their absorption and/or further conversion. In general, *C*-glycosides are more resistant toward acid, alkaline and enzymatic treatment than the corresponding *O*-glycosides. *O*-Coupled flavonoid glucosides may also be hydrolyzed by human glycosidases such as lactase-phlorizin hydrolase and cytosolic β-glucosidase.[25,26] In contrast, cleavage of *C*-glucosides in the human gut appears to be restricted to bacteria. Bacteria are also required for cleaving off sugar moieties other than glucose from flavonoid glycosides.

O-Deglycosylation by specific human gut bacteria has been reported for glycosides of flavonols, flavones, flavanones, dihydrochalcones, isoflavones and anthocyanidins (Table 1). The ability to split off the glucose moiety appears to be widely distributed among Bifidobacteriaceae (10 *Bifidobacterium* species)[27-32] and prevalent among Lactobacillaceae (5 *Lactobacillus* species),[27,29] Lachnospiraceae (4 species)[16,17,33-37] and Enterococcaceae (4 *Enterococcus* species).[16,27,38-40] Several bacteria with β-glucosidase activity are dominant members of the human intestinal microbiota, namely *Bifidobacterium adolescentis, Bifidobacterium longum, Enterococcus faecalis, Bacteroides ovatus, Bacteroides uniformis, Parabacteroides distasonis* and *Escherichia coli*.[4,41] Studies involving *B. longum, B. ovatus, B. uniformis* and *Enterococcus avium* indicated that the deglycosylating ability is not restricted to single strains of any of these species.

O-Deglycosylation of anthocyanins leads to aglycones, which are more or less unstable, in particular at neutral pH, and undergo spontaneous cleavage of the C-ring resulting in phenolic acids and aldehydes.[42] Therefore, gut bacteria such as bifidobacteria and lactobacilli[29] are assumed to only initiate anthocyanin degradation by catalyzing the first deglycosylation step, which is then followed by bacteria-independent decomposition.

Flavonoid-hydrolyzing β-glucosidases identified in bifidobacteria and lactobacilli belong to the glycosyl hydrolase family 1.[43] Another type of flavonoid *O*-glycosidase, which consists of 2 proteins, has been identified in *Eubacterium cellulosolvens* and the Lachnospiraceae strain CG19-1.[44] These enzymes lack similarity to known β-glycosidases and presumably deglycosylation involves an unusual redox-assisted mechanism.

Using a gnotobiotic rat model, 2 species capable of deglycosylation, *E. casseliflavus* and *E. ramulus*, were additionally demonstrated to cleave isoquercetin in vivo.[45] *E. ramulus* but not *E. casseliflavus* degraded the aglycone quercetin further.

Some dietary flavonoids carry sugar moieties other than glucose. For example, gut bacteria

Table 2. Flavonoid-converting human gut bacteria listed according to their taxonomic classification including catalyzed conversion reactions with respect to the corresponding flavonoid classes.

Phylum/family	Species/strain[a] (former name)	Conversion reaction	Flavonoid class(es)	Reference
Bifidobacteriaceae	*Bifidobacterium adolescentis* JCM 1275	*O*-Deglycosylation	Flavanones	27
	Bifidobacterium adolescentis strains DSM 18350, DSM 18353, MB 114, MB 237 and MB 243	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium angulatum MB 223	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium animalis ssp. *lactis* (*B. lactis*) BB-12	*O*-Deglycosylation	Anthocyanidins	29
	Bifidobacterium animalis ssp *lactis* (*B.lactis*) MB 238	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium animalis strain	*O*-Deglycosylation	Isoflavones	30
		Reduction	Isoflavones	
	Bifidobacterium bifidum IFO 14252	*O*-Deglycosylation	Flavanones	27
	Bifidobacterium bifidum strains MB 110 and 254	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium breve B7824	*O*-Deglycosylation	Flavonols, isoflavones	31
	Bifidobacterium breve strains DSM 18352, MB 113, MB 234 and MB 235	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium breve WC 0422	*O*-Deglycosylation	Flavanones	48
	Bifidobacterium catenulatum B7377	*O*-Deglycosylation	Flavonols, isoflavones	31
	Bifidobacterium catenulatum ATCC 27539[T]	*O*-Deglycosylation	Flavanones	48
	Bifidobacterium dentium K13	*O*-Deglycosylation	Flavonols, flavanones	32
	Bifidobacterium longum strains MB 201, MB 207, MB 217, MB 218 and MB 219	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium longum ssp. *infantis* (*B. infantis*) MB 208	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium longum ssp *infantis* (*B. infantis*) B7875	*O*-Deglycosylation	Flavonols, isoflavones	31
	Bifidobacterium longum strain	*O*-Deglycosylation	Isoflavones	30
		Reduction	Isoflavones	
	Bifidobacterium pseudocatenulatum B7003	*O*-Deglycosylation	Flavonols, flavanones	31
	Bifidobacterium pseudocatenulatum MB 264	*O*-Deglycosylation	Isoflavones	28
	Bifidobacterium pseudocatenulatum strains WC 0400, WC 0401, WC 0403, WC 0407 and WC 0408	*O*-Deglycosylation	Flavanones	48
	Bifidobacterium pseudolongum strain	*O*-Deglycosylation	Isoflavones	30
		Reduction	Isoflavones	
Coriobacteriaceae	*Adlercreutzia equolifaciens* JCM 14793[T]	Dehydroxylation	Flavan-3-ols, C-ring cleavage products of flavan-3-ols	80
		Reduction	Isoflavones	67
		C-Ring cleavage	Flavan-3-ols	80
	Strain Julong 732 [AY310748] (1429 nt), *Adlercreutzia equolifaciens* (99%)	Reduction	Isoflavanones	76
	Eggerthella lenta CAT-1	Dehydroxylation	C-Ring cleavage products of flavan-3-ols	57
		C-Ring cleavage	Flavan-3-ols	
	Eggerthella lenta rK3	C-Ring cleavage	Flavan-3-ols	79
	Eggerthella (*Eubacterium*) sp. SDG-2 [EF413638] (1306 nt) *Eggerthella lenta* (99%)	Dehydroxylation	Flavan-3-ols, C-ring cleavage products of flavan-3-ols	56
		C-Ring cleavage	Flavanonols, flavan-3-ols	
	Eggerthella sp. YY7918 [AB379693] (1469 nt)	Reduction	Isoflavones	66
	Slackia equolifaciens JCM 16059[T]	Reduction	Isoflavones	49,64
		C-Ring cleavage	Flavan-3-ols	80
	Slackia isoflavoniconvertens DSM 220 06[T]	Reduction	Isoflavones	68
	Slackia sp. NATTS [AB505075] (1496 nt), *Slackia isoflavoniconvertens* (99%)	Reduction	Isoflavones	69
Bacteroidetes				
Bacteroidaceae	*Bacteroides ovatus* ATCC 8483[T], *B. ovatus* strain	*O*-Deglycosylation	Flavonols	85
	Bacteroides uniformis ATCC 8492[T], *B. uniformis* strain	*O*-Deglycosylation	Flavonols	85
	Bacteroides uniformis JCM 5828	*O*-Deglycosylation	Flavanones	27
Porphyromonadaceae	*Parabacteroides distasonis* (*Bacteroides distasonis*) strain	*O*-Deglycosylation	Flavonols	85
	Parabacteroides distasonis (*Bacteroides distasonis*) JCM 5825[T]	*O*-Deglycosylation	Flavanones	27
Firmicutes				
Lactobacillaceae	*Lactobacillus acidophilus* strain	*O*-Deglycosylation	Flavanones	27
	Lactobacillus buchneri strain	*O*-Deglycosylation	Flavanones	27
	Lactobacillus casei LC-01	*O*-Deglycosylation	Anthocyanidins	29
	Lactobacillus casei strain	*O*-Deglycosylation	Flavanones	27

(*continued*)

Table 2. (Continued)

Phylum/family	Species/strain[a] (former name)	Conversion reaction	Flavonoid class(es)	Reference
	Lactobacillus leichmanii strain	O-Deglycosylation	Flavanones	27
	Lactobacillus plantarum IFPL722	O-Deglycosylation	Anthocyanidins	29
	Lactobacillus plantarum IAM 12477	O-Deglycosylation	Flavanones	27
	Lactobacillus *plantarum* IFPL935	C-Ring cleavage	Flavan-3-ols	81
Streptococcaceae	*Lactococcus garvieae* 20–92	Reduction	Isoflavones	65
	Lactococcus lactis (*Streptococcus lactis*) strain	O-Deglycosylation	Flavanones	27
	Lactococcus sp. MRG-IFC-1 [KF803554] (1423 nt), *Lactococcus lactis* (99%)	O-Deglycosylation	Flavones, isoflavones	40
		C-Deglycosylation	Isoflavones	
	Lactococcus sp. MRG-IF-3 [KF803553] (1387 nt)	O-Deglycosylation	Flavones, isoflavones	40
Enterococcaceae	*Enterococcus avium* strains LY1 and EFEL009	O-Deglycosylation	Flavonols	38,39
	Enterococcus casseliflavus M1	O-Deglycosylation	Flavonols	16
	Enterococcus sp. 45 [KC417329] (1498 nt), *Enterococcus casseliflavus* (99%)	C-Deglycosylation	Flavones	50
	Enterococcus faecalis (*Streptococcus faecalis*) IFO 12964	O-Deglycosylation	Flavanones	27
	Enterococcus sp. MRG-IFC-2 [KF803555] (1431 nt), *Enterococcus faecium* (99%)	O-Deglycosylation	Flavones, isoflavones	40
		C-Deglycosylation	Isoflavones	
Clostridiaceae	*Clostridium butyricum* IFO 13949[T]	C-Ring cleavage	Flavanones	27
Lachnospiraceae	*Eubacterium cellulosolvens* ATCC 43171[T]	O-Deglycosylation	Flavones, isoflavones	33
		C-Deglycosylation	Flavones, isoflavones	
	Eubacterium ramulus DSM 16296	O-Deglycosylation	Flavonols, flavones, dihydrochalcones, isoflavones	16,17,34,35
		C-Ring cleavage	Flavonols/flavanonols, flavones/flavanones, isoflavones	16,17,20,35
		Cleavage	Dihydrochalcones, O-desmethylangolensin	17,34,35
	Eubacterium ramulus Julong 601	C-Ring cleavage	Isoflavones	77
	Blautia sp. MRG-PMF1 [KJ078647] (1361 nt), *Blautia producta* (99%)	O-Deglycosylation	Flavonols, flavones, flavanones, isoflavones	36
		O-Demethylation	Flavones, flavanones, isoflavones	
	Strain PUE [EU377662] (1346 nt), *Dorea longicatena* (98%)	C-Deglycosylation	Isoflavones	49
	Strain CG19-1 [FJ711049] (1454 nt)	O-Deglycosylation	Flavones, isoflavones	37
		C-Deglycosylation	Flavones, isoflavones	
		C-Ring cleavage	Flavones	
		Cleavage	O-Desmethylangolensins	
	Strain SY8519 [AB477431] (1493 nt)	C-Ring cleavage	Isoflavones	78
Ruminococcaceae	*Flavonifractor plautii* (*Clostridium orbiscindens*) strains ATCC 49531, 257, 258 and 264	C-Ring cleavage	Flavonols	86
	Flavonifractor plautii strains DSM 6740 and aK2	Degradation	C-Ring cleavage products of flavan-3-ols	79
	Flavonifractor plautii (*Clostridium orbiscindens*) I2	C-Ring cleavage	Flavonols/flavanonols, flavones/flavanones	21
		Cleavage	Dihydrochalcones	34
Eubacteriaceae	*Eubacterium limosum* ATCC 8486[T]	O-Demethylation	Isoflavones	53
	Eubacterium limosum strains DSM 20543[T] and LMG P23546	O-Demethylation	Flavanones	51,52
Erysipelotrichaceae	Strain TM-40 [AB249652] (1422 nt)	O-Deglycosylation	Isoflavones	75
		Reduction	Isoflavones	
Proteobacteria				
Enterobacteriaceae	*Enterobacter cloacae* IAM 12349	O-Deglycosylation	Flavanones	27
	Escherichia coli ATCC BAA-97 (strain HGH21)	O-Deglycosylation	Isoflavones	87
	Escherichia sp. 4 [KC819112] (1298 nt), *Eschericha fergusonii* (99%)	O-Deglycosylation	Flavones	58
		Dehydroxylation	Flavones	

Note. [a] For strains not assigned to species, accession numbers of the 16S rRNA sequence in squared brackets (length in nucleotides, nt) and most closely related species with > 97% sequence identity to the corresponding type strain (sequence identity in percent) are included.

hydrolyze certain flavonol and flavanone disaccharides, including the most abundant rutinoside (6-β-L-rhamnosyl-D-glucose) or neohesperidoside (2-β-L-rhamnosyl-D-glucose). Bacteria acting on these flavonoids possess in addition to β-glucosidases α-rhamnosidases. α-L-Rhamnosidases involved in deglycosylation of flavonoids have been characterized from strains of *Lactobacillus acidophilus*, *Lactobacillus*

plantarum and *Bifidobacterium dentium*.[32,46,47] Screening approaches revealed that the rhamnosidase activity may be strain specific.[47,48]

The deglycosylation of flavonoid *C*-glycosides is less prevalent and has so far been scarcely investigated. Some members of the Lachnospiraceae, Enterococcaceae and Streptococcaceae were reported to cleave *C*-coupled flavone and isoflavone glucosides[33,37,40,49,50]
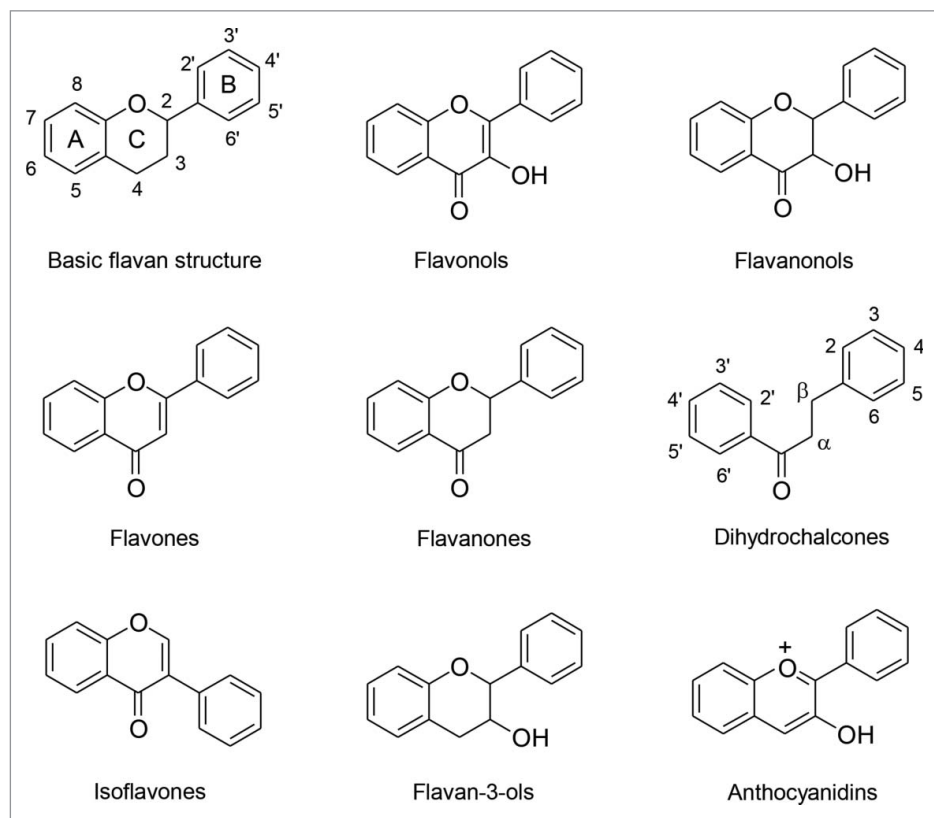
Figure 1. Basic flavan structure and flavonoid classes discussed in more detail in this review.

(Table 1). Strain PUE of the Lachnospiraceae has been affiliated with *Dorea longicatena* (Table 2), a dominant member of the human intestinal microbiota.[4,41] Systematic screening of *E. cellulosolvens* and strain CG19-1 revealed that the substrate spectrum differs considerably between individual species.[33,37] In *E. cellulosolvens*, an enzyme system of 5 proteins affords the deglycosylation of *C*-coupled flavone and isoflavone glucosides.[44] Two of these 5 proteins are sufficient to catalyze the unusual deglycosylation of corresponding flavonoid *O*-glucosides mentioned above. The majority of the identified *C*-glucoside-cleaving bacteria also act on the corresponding *O*-coupled glucosides.[33,37,40]

Demethylation and dehydroxylation of flavonoids

The phenolic A- and B-rings of flavonoids usually carry hydroxy and/or methoxy groups. *Eubacterium limosum* and *Blautia* sp. MRG-PMF1 are able to *O*-demethylate flavones, isoflavones or prenylated flavanones[36,51-53] (Table 1). The *O*-demethylation may occur at the A- or B-ring. By cleaving off the only methyl group of isoxanthohumol, which is attached to

the hydroxy group at C5 of the A-ring, *E. limosum* activates this prenylated flavanone in vitro and in vivo to 8-prenylnaringenin.[51,52] Isoxanthohumol, in turn, results from the spontaneously occurring cyclization of the hop chalcone xanthohumol, which is observed in vitro and in vivo.[51,54,55]

Other bacteria catalyze the dehydroxylation of flavonoids or their metabolites (Table 1). *Eggerthella lenta* and *Adlercreutzia equolifaciens*, both of which are members of the Coriobacteriaceae, dehydroxylate flavan-3-ols and their C-ring cleavage products at the B-ring.[56,57] In addition, an *Escherichia* strain catalyzes the dehydroxylation of a flavone at the B-ring.[58]

Conversion of flavonol, flavanonol, flavone, flavanone and dihydrochalcone aglycones

The bacterial degradation of flavonols and flavones (Fig. 1) starts with the reduction of the C2-C3 double bond yielding the corresponding flavanonols and flavanones (Fig. 1), respectively. These metabolites are further converted by fission of the central heterocyclic C-ring. This also applies to dietary flavanonols and flavanones. The B-ring of the flavanonols is finally

transformed to hydroxyphenylacetic acids, whereas the phenolic products arising from the A-ring may be completely degraded to short-chain fatty acids. The degradation of the best known flavonol quercetin involves the formation of the intermediates taxifolin and alphitonin (Fig. 2A) as shown for *E. ramulus* and *F. plautii*.[20,21] The cleavage of taxifolin by *Eggerthella* (former *Eubacterium*) sp. SDG-2 results in the formation of the corresponding hydroxydihydrochalcone.[56] The ability of E. ramulus to degrade quercetin also in vivo was demonstrated in a gnotobiotic rat model.[45]

The conversion of flavones and flavanones has also been mainly studied in *E. ramulus* and *F. plautii*.[20,21] C-ring cleavage of the flavanones results in the formation of chalcones, which are further reduced to dihydrochalcones, whose hydrolysis yields hydroxyphenylpropionic acids arising from the B-ring. The A-ring metabolites are identical to those resulting from the degradation of corresponding flavonols/flavanonols and may be degraded further to non-aromatic metabolites as described above. This pathway is exemplified in Figure 2B for the flavone apigenin, whose degradation involves the transient formation of naringenin and phloretin. The enzymes catalyzing the isomerization of flavanones (chalcone isomerase), the reduction of chalcones (enoate reductase) and the cleavage of dihydrochalcones (phloretin hydrolase) have been identified in *E. ramulus*.[59-62] Other bacteria capable of flavone or flavanone degradation are strain CG19-1 and *Clostridium butyricum*.[27,37]

Dihydrochalcones are not only intermediates in flavone/flavanone degradation, but also occur in their glycosidic forms in plant-derived foods. To date, only *E. ramulus* and *F. plautii* are known to convert dihydrochalcone aglycones. Besides the already mentioned phloretin, hesperetin dihydrochalcone is cleaved by both species.[17,21,34]

The identified bacterial species/strains involved in the conversion of flavonol, flavanonol, flavone, flavanone, and dihydrochalcone aglycones are members of different families within the Firmicutes, except *Eggerthella* sp. SDG-2, which belongs to the Actinobacteria (Table 2). The two particularly active *E. ramulus* and *F. plautii* are highly prevalent in humans. *E. ramulus* was found to be present in each of the tested human subjects, amounting to a mean count of 7.0×10^8 cells per gram of dry feces.[63] *F. plautii* was detected in 80% of individuals at a mean cell count of 4.4×10^8 per gram of dry feces.[21]

Conversion of isoflavone aglycones

Transformation of isoflavone aglycones by human gut bacteria occurs by stepwise reduction to isoflavan structures or by C-ring fission resulting in *O*-desmethylangolensins, which may be cleaved further into smaller phenolic products. Most studies investigating the conversion of isoflavones used the soy-derived daidzein. Daidzein may undergo bioactivation to the
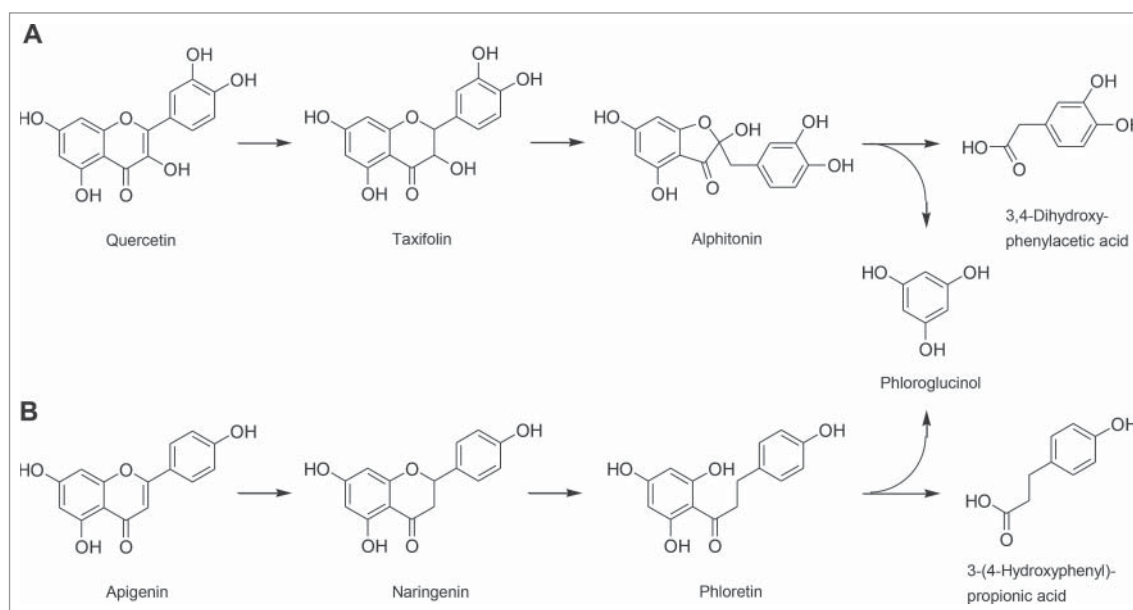
Figure 2. Pathways of the conversion of (A) flavonols using the example of quercetin and (B) flavones using the example of apigenin by human intestinal bacteria.

isoflavandiol equol or conversion via *O*-desmethylan-golensin to the A-ring metabolite resorcinol and the B-ring product 2-(4-hydroxyphenyl)propionic acid (Fig. 3). Genistein, another soy isoflavone, carries an additional hydroxy group at C5 of the A-ring and is converted in an analogous fashion. (Fig. 3)

To date 6 human intestinal bacterial strains have been isolated that catalyze the complete reduction of daidzein to equol[49,64-69] (Table 1). The conversion of genistein to 5-hydroxy-equol has been shown for 2 of these bacteria.[49,68] The isolates represent 5 rather than 6 species since one of them, *Slackia* sp. NATTS, based on its 16S rRNA sequence, is a *Slackia isoflavonicon-vertens* strain (Table 2). All but one species are members of the Coriobacteriaceae. The in vivo conversion of daidzein and genistein by *S. isoflavoniconvertens* to equol and 5-hydroxy-equol, respectively, was demon-strated in gnotobiotic rats.[70] Analysis of the occur-rence of *S. isoflavoniconvertens* strains in Japanese adults revealed a prevalence of 40% and a mean count of 2.5×10^6 cells per gram of wet feces.[69]

The enzymes involved in the conversion of daidzein and genistein, namely daidzein reductase, dihydro-daidzein racemase, dihydrodaidzein reductase and tet-rahydrodaidzein reductase, were identified in *Lactococcus garvieae* 20-92, *S. isoflavoniconvertens* DSM 22006[T] and *Slackia* sp. NATTS, and further characterized.[19,65,71-73] Interestingly, the expression of the genes encoding these enzymes needs to be induced by their isoflavone substrates. Sequence analysis of the genes encoding the isoflavone-converting reductases in *Lactococcus garvieae* 20–92 and *Eggerthella* sp.

YY7918 suggests that these genes were acquired by horizontal gene transfer from other bacteria: The genes of the 2 phylogenetically unrelated bacteria show complete identity and their GC content deviates from the mean GC content of the genome of each organism.[19] Horizontal gene transfer is a frequent event within the human intestinal microbiome and indicates that the corresponding genes confer a con-siderable advantage on the recipients.[74]

Research results concerning the ability of bifidobac-teria to form equol from daidzein are contradictory. While strains of *Bifidobacterium animalis*, *B. longum* and *B. pseudolongum* were reported to form equol[30] (Table 1), 22 bifidobacteria tested in another study including strains of *B. animalis* and *B. longum* did not show any equol-forming activity.[28]

Two other bacterial isolates only catalyze some reactions of the equol formation pathway: The Erysi-pelotrichaceae strain TM-40 reduces the C2-C3 dou-ble bond of daidzein to dihydrodaidzein,[75] while strain Julong 732 transforms dihydrodaidzein but not daidzein to equol.[76] Julong 732 is presumably another strain of *Adlercreutzia equolifaciens* (Table 2), but differs in its isoflavone-converting activity compared to the corresponding type strain, which is capable of converting daidzein to equol.[67]

Fission of the heterocyclic C-ring of isoflavones was found to be catalyzed by 2 strains of *E. ramulus*[35,77] and by strain SY8519,[78] all of which are members of the Lachnospiraceae (Table 2). Cleavage of daidzein by these bacteria yields *O*-desmethylangolensin as the final prod-uct,[35,77,78] whereas 6′-hydroxy-*O*-desmethylangolensin,
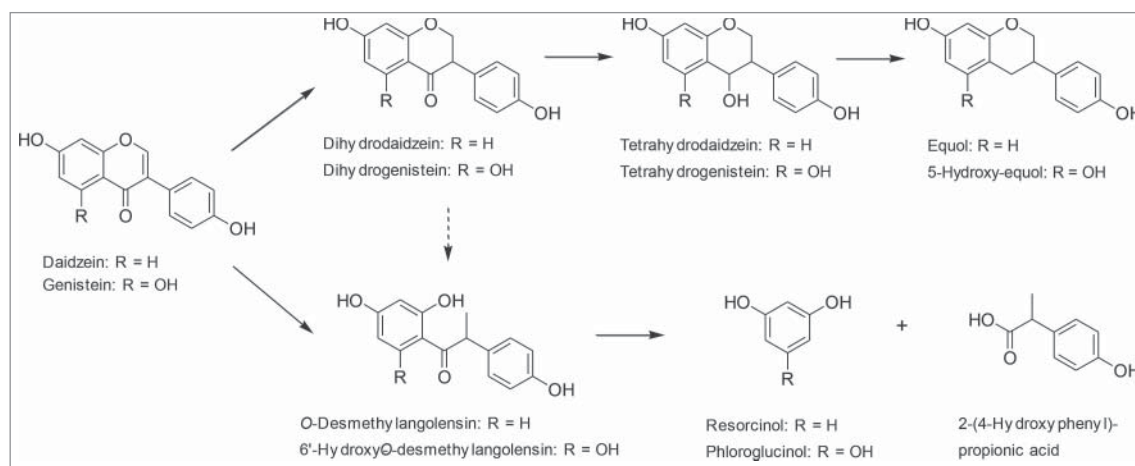
Figure 3. Pathways of the conversion of isoflavones using the examples of daidzein and genistein by human intestinal bacteria. The dashed arrow indicates a controversially discussed reaction.
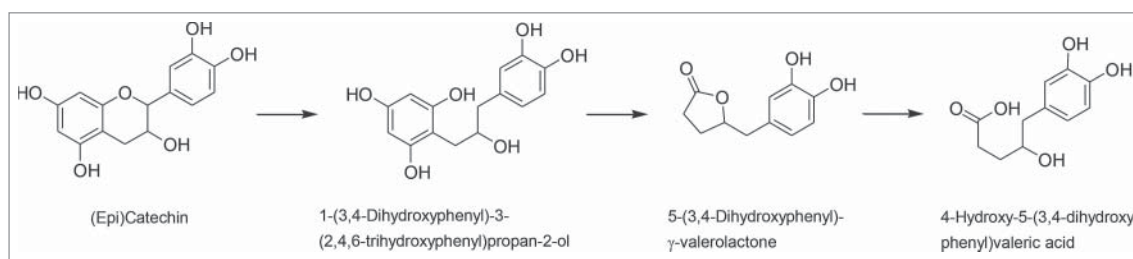
Figure 4. Pathway of the conversion of flavan-3-ols using the example of (epi)catechin.

which is formed from genistein by the *E. ramulus* strains, is further degraded to 2-(4-hydroxyphenyl)propionic acid[35,77] (Fig. 3). The expected A-ring metabolite phloroglucinol was not detected, which may be explained by its further degradation as described above. It remains to be clarified, whether the reduction of the C2-C3 double bond of isoflavones is imperative before the ring fission can occur. Dihydrodaidzein and dihydrogenistein have not been detected as intermediates and cells or cell-free extracts of *E. ramulus* DSM 16296 did not convert dihydrogenistein to 6′-hydroxy-*O*-desmethylangolensin.[35]

In contrast to *E. ramulus*, strain CG19-1 is capable of cleaving both 6′-hydroxy-*O*-desmethylangolensin and *O*-desmethylangolensin to phloroglucinol and resorcinol, respectively; 2-(4-hydroxyphenyl)propionic acid is additionally formed from the 2 desmethylangolensins[37] (Fig. 3). As mentioned above, strain CG19-1 deglycosylates isoflavones, but does not degrade the resulting aglycones any further.

Conversion of flavan-3-ols

Flavan-3-ols are predominantly not glycosylated and occur in dietary plants in form of monomers (catechins) or oligomers and polymers (proanthocyanidins). The flavan-3-ol structure (Fig. 1) is characterized by 2 chiral centers at C2 and C3, so that 4 stereoisomers exist. The most studied flavan-3-ol monomers are catechin, epicatechin, gallocatechin, epigallocatechin and their corresponding gallate esters. Bacterial conversion of these compounds in the human intestine includes the hydrolysis of ester bonds, the reductive cleavage of the C-ring and further conversion of the resulting 1,3-diphenylpropan-2-ols (Fig. 4) in addition to a dehydroxylation, which was already discussed above. Several bacteria responsible for the conversion of catechins have been described (Table 1). The C-ring fission is catalyzed by strains of

E. lenta, *S. equolifaciens* and *A. equolifaciens*,[56,57,79,80] all of which are members of the Coriobacteriaceae (Table 2). In addition, cleavage of the C-ring and an esterase activity were reported for a *Lactobacillus plantarum* strain.[81] Further degradation of the C-ring cleavage product 1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol to the corresponding valerolactone and valeric acid (Fig. 4) was demonstrated for 2 strains of *F. plautii*.[79] Although proanthocyanidins are also known to be metabolized by the human intestinal microbiota and to result in a variety of aromatic compounds including phenolic acids,[82-84] none of the involved bacterial species has been identified yet.

Concluding remarks

A number of human intestinal bacteria responsible for the conversion of flavonoids have been identified. Some strains catalyze only single steps of a known transformation pathway, while others catalyze complete conversion to the typical degradation products. The majority of described species, among them a few dominant human gut bacteria, are capable of carrying out the *O*-deglycosylation of flavonoids. Further degradation of the aglycones appears to be catalyzed by less prevalent bacteria, which may result in individually different host metabotypes; the formation of equol or 8-prenylnaringenin may serve as examples. The flavonoid-converting bacteria are distributed among the dominant phyla of the human intestine: Actinobacteria, Bacteroidetes and Firmicutes, except 3 strains that belong to the Proteobacteria. In particular, members of the Lachnospiraceae stand out in their ability to *O*- and/or *C*-deglycosylate and cleave the basic structure of flavonoids from various classes. Several Coriobacteriaceae strains are involved in the transformation of unglycosylated isoflavones and flavan-3-ols. The two well-studied *E. ramulus* and *F. plautii* are

particularly active in flavonoid conversion. Both species are not described as dominant species, but found to be highly prevalent in humans.

However, we assume that the current knowledge is far from complete, since systematic screenings of bacterial groups or flavonoid classes are missing. The selection of bacterial species included in flavonoid-conversion tests has been arbitrary and which new strains were isolated depended on the chosen cultivation conditions. Which flavonoids were selected has been governed by their occurrence in dietary plants and commercial availability.

The identification and characterization of the bacterial enzymes catalyzing flavonoid-transforming reactions have only started in recent years but nevertheless provide a good basis for the future identification of other flavonoid-converting species by searching genome sequences of human gut bacteria for genes encoding flavonoid-transforming enzymes. Moreover, conserved enzyme sequences may be used to quantify the encoding genes and their expression in individual gut microbiomes by targeted metagenomic and meta-transcriptomic analyses. This approach would enable to evaluate the flavonoid-converting potential of a given microbiome beyond profiling gut bacterial species.

The identification of flavonoid-converting bacteria should also be continued by screening previously isolated species or by isolating new strains from human intestinal contents. Although laborious and time-consuming, classical isolation procedures are essential to discover novel bacteria and enzymes.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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