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

Annett Braune and Michael Blaut

Department of Gastrointestinal Microbiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

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, flavononols, 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.

KEYWORDS
anaerobic metabolism; flavonoid; gut bacteria; intestinal microbiota; polyphenol

Introduction
The digestive tract of humans and animals is populated by microbial communities that co-evolved with the respective animal species. 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 disorders including metabolic disease, inflammatory bowel disease, colorectal cancer and allergies.

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. It has been proposed to distinguish between a core microbiome and a peripheral microbiome. 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. Similarly, the ability to convert the soy isoflavone daidzein to equol displays a high variability among human individuals, 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
The ingestion of flavonoids by the human host is 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. 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. 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. Flavanols and dihydrochalcones as well as chalcones and aurones 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 isorhamnetin (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 |
| | | *Enterococcus casseliflavus* M1 | | Isoquercetin | 16 |
| | | *Eubacterium ramulus* DSM 16296 | | Quercetin | 16,17 |
| | | *Enterococcus avium* LY1 | | Isoquercetin | 38 |
| | | *Bifidobacterium pseudocatenulatum* B7003, *B. longum* ssp. *infantis* (*B. infantis*) B7377, *B. breve* B7824 | Rutin | Quercetin | 31 |
| | | *Blautia* sp. MRG-PMF1 | Rutin | ND\(^b\) | 36 |
| | | *Bifidobacterium dentium* X13 | Rutin | Isoquercetin, quercetin | 39 |
| | | *Enterococcus avium* EFEL009 | | 3,4-Dihydroxyphenylacetic acid | 86 |
| **C-Ring cleavage** | | *Flavonifractor plautii* (*Clostridium arabinosidis*) strains ATCC 49531, 257, 258 and 264 | | 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 |
| | | | | Taxifolin | \(\alpha,2,3,4,4',6'-\)-Hexahydroxydihydrochalcone | 56 |
| | | | | 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. leichmannii* strain, *Enterococcus faecalis* (*Streptococcus faecalis*) IFO 12964, *Lactococcus lactis* (*Streptococcus lactis*) strain, *Enterobacter cloacae* IAM 12349 | Eriocitrin (eriodyctyol-7-O-rutinoside) | Eriodictyol | 27 |
| | | *Eubacterium ramulus* DSM 16296 Strain CG19-1 | Luteolin-7-O-glucoside | | 17 |
| | | | Luteolin-5-O-glucoside, luteolin-7-O-glucoside, luteolin-3' -O-glucoside | | 37 |

\(^a\) Species/strain names are based on previous reports.

\(^b\) ND: Not determined.
| Flavonoid class | Conversion reaction          | Species/strain (former reported name) | Substrate(s)                                                                 | Product(s)                  | Reference |
|-----------------|-----------------------------|----------------------------------------|------------------------------------------------------------------------------|-----------------------------|-----------|
|                 |                             | Eubacterium cellulosolvens ATCC 43171† | Apigenin-7-O-glucoside (apigetrin) Luteolin-7-O-glucoside, luteolin-5′-O-glucoside Apigenin | Apigenin Luteolin           | 33        |
|                 |                             | Escherichia sp. 4                      | Apigenin-7-O-glucoside                                                        Apigenin                  |                | 58        |
|                 |                             | Blautia sp. MRG-PMF1                   | Diosmetin-7-O-glucoside                                                       Diosmetin                 |                | 36        |
|                 |                             | Bifidobacterium catenulatum ATCC 27539 T, B. breve WC 0422, B. pseudocatenulatum strains WC 0400, WC 0401, WC 0403, WC 0407 and WC 0408 | Apigenin-7-O-glucoside                                                        Apigenin                  |                | 48        |
|                 |                             | Luteolin-6-O-glucoside, luteolin-8-O-glucoside | Apigenin-7-O-glucoside                                                        Apigenin                  |                | 33        |
|                 |                             | Lactobacillus delactobacter sp. 45      | Naringenin-7-O-neohesperidoside (naringin)                                   Naringenin (3-Hydroxyflavone) |                | 40        |
|                 |                             | Eubacterium cellulosolvens ATCC 43171† | Apigenin-6-C-glucoside                                                        Apigenin                  |                | 33        |
|                 |                             | Luteolin-6-C-glucoside                  | Luteolin                                                                      |                | 37        |
|                 |                             | Eubacterium limosum strains DSM 20543† and LMG P23546 | Apigenin-8-C-glucoside (vetexin), apigenin-6-C-glucoside (isovetexin)          | Apigenin                  |                | 50        |
|                 |                             | Blautia sp. MRG-PMF1                   | Luteolin-6-C-glucoside                                                        Luteolin                  |                | 51,52     |
|                 |                             | C-Deglycosylation Strain CG19-1         | Luteolin-6-C-glucoside (homoorientin), luteolin-8-C-glucoside (orientin)      | Luteolin-6-C-glucoside     |                | 33        |
|                 |                             | Eubacterium cellulosolvens ATCC 43171† | Apigenin-6-C-glucoside                                                        Apigenin                  |                | 33        |
|                 |                             | Luteolin-6-C-glucoside                  | Luteolin                                                                      |                | 37        |
|                 |                             | C-O-Demethylation Escherichia sp. 4     | Luteolin, eriodictyol                                                         Luteolin                  |                | 50        |
|                 |                             | Clostridium butyricum IFO 13949†       | Luteolin, eriodictyol                                                         Luteolin                  |                | 51,52     |
|                 |                             | Eubacterium ramulus DSM 16296           | Luteolin, eriodictyol                                                         Luteolin                  |                | 51,52     |
|                 |                             | Flavonifractor plautii (Clostridium arisacidens) 12 | Luteolin, eriodictyol                                                         Luteolin                  |                | 51,52     |
|                 |                             | Strain CG19-1                           | Luteolin                                                                      |                | 50        |
|                 |                             | Eubacterium ramulus DSM 16296           | Apigenin, naringenin                                                          Apigenin                  |                | 37        |
|                 |                             | Dihydrochalcones C-Cleavage             | Luteolin                                                                      |                | 37        |
|                 |                             | Eubacterium ramulus DSM 16296           | Apigenin                                                                      |                | 37        |
|                 |                             | Dihydrochalcones O-Deglycosylation      | Phloretin                                                                     |                | 17        |
| Flavonoid class       | Conversion reaction                    | Species/strain (former reported name) | Substrate(s)                        | Product(s)                                      | Reference |
|-----------------------|----------------------------------------|----------------------------------------|-------------------------------------|-------------------------------------------------|-----------|
|                       |                                        | *Flavonifractor plautii* (*Clostridium orbiscindens*) 12 | Hesperetin dihydrochalcone           | 3-(3-Hydroxy-4-methoxyphenyl)propionic acid      | 34        |
|                       |                                        |                                          | Phloretin                            | 3-(4-Hydroxyphenyl)propionic acid                | 21        |
| Isoflavones / isoflavonones | O-Deglycosylation                    | *E. coli* ATCC BAA-97 (strain HGH21)    | Hesperetin dihydrochalcone           | 3-(3-Hydroxy-4-methoxyphenyl)propionic acid      | 34        |
|                       |                                        | *Eubacterium ramulus* DSM 16296         | Daidzin                             | Daidzein                                        | 87        |
|                       |                                        | *Bifidobacterium animalis* strain, *B. longum* strain, *B. pseudolongum* strain | Genistin                            | Genistein                                        | 35        |
|                       |                                        | *Bifidobacterium pseudocatenulatum*     | Daidzin, acetyldaidzin, malonyldaidzin | Daidzein                                        | 30        |
|                       |                                        | B7003, *B. longum* ssp. *infantis* (*B. infantis*) B7875, *B. catenulatum* B7377, *B. breve* B7824 | Genistin                            | Genistein                                        |           |
|                       |                                        |                                        | Glycitin                            | Glycitein                                        |           |
|                       |                                        |                                        |                                    |                                                 |           |
|                       |                                        | *Bifidobacterium adolescentis* strains | Daidzin                             | Daidzein                                        | 75        |
|                       |                                        | 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 | Genistin                            | Genistein                                        |           |
|                       |                                        | Strain TM-40                           | Daidzin                             | Daidzein                                        | 28        |
|                       |                                        | *Bifidobacterium adolescentis* strains |                                    |                                                 |           |
|                       |                                        |                                        |                                    |                                                 |           |
|                       |                                        | *Eubacterium cellulosolvens* ATCC 43171 | Daidzin                             | Daidzein                                        | 37        |
|                       |                                        |                                          | Genistin                            | Genistein                                        | 33        |
|                       |                                        | *Blautia* sp. MRG-PMF1, *Lactococcus* sp. MRG-IFC-1, *Lactococcus* sp. MRG-IFC-3, *Enterococcus* sp. MRG-IFC-2 | Daidzin                             | Daidzein                                        | 36,40     |
|                       |                                        |                                          | Genistin                            | Genistein                                        |           |
|                       |                                        |                                          | Sissotrin                           | Biochanin A                                      |           |
|                       |                                        |                                          | Ononin                              | Formononetin                                     |           |
|                       |                                        |                                          | Glycitin                            | Glycitein                                        |           |
|                       |                                        |                                        |                                    |                                                 |           |
|                       |                                        | *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\* (former reported name) | Substrate(s) | Product(s) | Reference |
|--------------------------|---------------------------|------------------------------------------|--------------|------------|-----------|
| O-Demethylation          | *Eubacterium limosum* ATCC 8486\(^T\) | Biochanin A                              | Genistein    | 53         |
|                          |                           | Formononetin                             | Daidzein     |            |
|                          |                           | Glycitein                                | 6,7,4'-Trihydroxyisoflavone |            |
|                          | *B. pseudolongum* strain   | Biochanin A                              | Genistein    | 36         |
|                          |                           | Formononetin                             | Daidzein     |            |
|                          |                           | Glycitein                                | 6,7,4'-Trihydroxyisoflavone |            |
| Reduction                | *Bifidobacterium animalis* strain, *B. longum* strain, *B. pseudolongum* strain | Daidzein, dihydrodaidzein               | Equol        | 60         |
|                          |                           | Strain Julong 732                        | Dihydrodaidzein | 76    |
|                          |                           | Strain TM-40                             | Dihydrodaidzein | 75    |
|                          | *Stackia equolifaciens* JCM 1609\(^T\) | Daidzein                                | Equol        | 49,64     |
|                          |                           | Genistein                                | 5-Hydroxy-equol |            |
|                          | *Eggerthella* sp. YY7918  | Daidzein, dihydrodaidzein               | Equol        |            |
|                          |                           | Strain Julong 732                        | Dihydrodaidzein | 67    |
|                          |                           | Strain TM-40                             | Dihydrodaidzein | 67    |
|                          | *Stackia isoflavonionvertens* DSM 22006\(^T\) | Daidzein                                | Equol        |            |
|                          |                           | Genistein                                | 5-Hydroxy-equol |            |
| C-Ring cleavage          | *Lactobacillus garvieae* 20–92 | Daidzein                                | Equol        | 65         |
|                          |                           | *Stackia* sp. NATTS                      | Equol        | 69         |
|                          | *Eubacterium ramulus* DSM 16296 | Daidzein                                | O-Desmethylangolensin | 35        |
|                          |                           | Genistein                                | 6'-Hydroxy-O-Desmethylangolensin | 77        |
|                          | *Eubacterium ramulus* Julong 601 | Daidzein                                | O-Desmethylangolensin | 77        |
|                          |                           | Genistein                                | 2-(4-Hydroxyphenyl)propionic acid |          |
|                          | *Stackia 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             | *Adlercreutzia equolifaciens* JCM 14793\(^T\) | (++)-Epicatechin, (++)-epicatechin       | Resorcinol, 2-(4-hydroxyphenyl)propionic acid | 80        |
|                          |                           | (--)-Epigallocatechin                    | (25:35)-Flavan-3’, 5’, 5”, 7-pentol |          |
|                          |                           | (--)-Gallicatechin                       | (28:33)-Flavan-3’, 3”, 5’, 5”, 7-pentol |          |
|                          | *Eggerthella (Eubacterium)* sp. SDG-2 | (++)-Catechin, (++)-epicatechin          | (2R)-1-(3,4-Dihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol | 56        |
|                          |                           | (--)-Catechin, (--)-epicatechin          | (2S)-1-(3,4,5-Trihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol |          |
|                          |                           | (--)-Gallicatechin, (--)-epigallocatechin | (2S)-1-(3,4-Dihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol |          |
|                          | *Eggerthella lenta* RK3   | (++)-Catechin, (++)-epicatechin          | 1-(3,4-Dihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol | 79        |
|                          | *Eggerthella lenta* CAT-1 | (++)-Catechin                            | (2R)-1-(3,4-Dihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol | 57        |
|                          |                           | (--)-Epicatechin                         | (2S)-1-(3,4,5-Trihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol |          |
|                          | *Lactobacillus plantarum* IFPL935 | (++)-Catechin, (++)-epicatechin          | 1-(3,4-Dihydroxyphenyl)-1-(3,4,6-trihydroxyphenyl)propan-2-ol | 81        |

(continued)
| Flavonoid class | Conversion reaction | Species/strain\(^a\) | Substrate(s) | Product(s) | Reference |
|-----------------|---------------------|---------------------|--------------|------------|-----------|
|                 |                     |                     | (–)-Epicatechin-3-O-gallate | 1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | [includes ester cleavage] |
|                 |                     | *Slackia equolifaciens* JCM 16059\(^T\) | (–)-Epigallocatechin, (–)-gallocatechin | 1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | 80 |
|                 |                     | *Adlercreuztia equolifaciens* JCM 14793\(^T\) | (–)-Gallocatechin | 1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | 80 |
|                 | Dehydroxylation of the C-ring cleavage product | *Eggerthella* (Eubacterium) sp. SDG-2 | (25)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | (2S)-1-(3-Hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | 56 |
|                 |                     | *Eggerthella lenta* CAT-1 | (25)-1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | (2S)-1-(3,5-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | 57 |
|                 |                     | *Adlercreuztia equolifaciens* JCM 14793\(^T\) | (25)-1-(3-Hydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | (2R)-1-(3,4-Dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | 80 |
|                 | Degradation of the C-ring cleavage product | *Flavonifractor plautii* strains DSM 6740 and aK2 | (25)-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    | *Bifidobacterium animalis* ssp. lactis (Bifidobacterium lactis) BB-12, *Lactobacillus casei* LC-01, *L. plantarum* IFPL722 | *Bi* | 1-(3,4,5-Trihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl)propan-2-ol | Malvidin-3-O-glucoside | 29 |

Note. \(^a\) Entries within each reaction type are listed in order of their publication year.
\(^b\) ND, not determined.
casseliavus and Eubacterium ramulus. 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. 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.

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 flavonoids, 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) may result in ATP formation as previously demonstrated for other anaerobes.

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. 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. In contrast, cleavage of C-glycosides 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 anthocyanins (Table 1). The ability to split off the glucose moiety appears to be widely distributed among Bifidobacteriaceae (10 Bifidobacterium species) and prevalent among Lactobacillaceae (5 Lactobacillus species), Lachnospiraceae (4 species) and Enterococcaceae (4 Enterococcus species). 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. 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. Therefore, gut bacteria such as bifidobacteria and lactobacilli 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. Another type of flavonoid O-glycosidase, which consists of 2 proteins, has been identified in Eubacterium cellulosolvens and the Lachnospiraceae strain CG19-1. These enzymes lack similarity to known β-glucosidases and presumably deglycosylation involves an unusual redox-assisted mechanism.

Using a gnotobiotic rat model, 2 species capable of deglycosylation, E. casseliavus and E. ramulus, were additionally demonstrated to cleave isoquercetin in vivo. E. ramulus but not E. casseliavus 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* (former name)                                                                 | Conversion reaction | Flavonoid class(es)                  | Reference |
|--------------------------|-----------------------------------------------------------------------------------------------|---------------------|--------------------------------------|-----------|
| Bifidobacteriaceae       | *Bifidobacterium adolescens* JCM 1275                                                        | O-Deglycosylation   | Flavanones                           | 27        |
|                          | *Bifidobacterium adolescens* strains DSM 18350, DSM 18353, MB 114, MB 237 and MB 243          | O-Deglycosylation   | Flavanones                           | 28        |
|                          | *Bifidobacterium angulatum* MB 223                                                           | O-Deglycosylation   | Isoflavones                          | 28        |
|                          | *Bifidobacterium animalis* ssp. lactis (B. lactis) BB-12                                      | O-Deglycosylation   | Isoflavones                          | 28        |
|                          | *Bifidobacterium animalis* ssp lactis (B.lactis) MB 238                                      | O-Deglycosylation   | Isoflavones                          | 28        |
|                          | *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* brev 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                                                     | O-Deglycosylation   | Flavanones                           | 48        |
|                          | *Bifidobacterium dentium* K12                                                                | O-Deglycosylation   | Flavonols, flavonones                | 32        |
|                          | *Bifidobacterium longum* strains MB 201, MB 217, MB 218 and MB 219                           | O-Deglycosylation   | Isoflavones                          | 28        |
|                          | *Bifidobacterium longum* ssp. infants (B. infantis) MB 208                                   | O-Deglycosylation   | Isoflavones                          | 28        |
|                          | *Bifidobacterium longum* ssp infants (B. infantis) B175                                     | O-Deglycosylation   | Flavonols, isoflavones              | 31        |
|                          | *B. ovatus*                                                                                | Reduction           | Flavonols, isoflavones              | 30        |
|                          | *B. uniformis*                                                                             | Reduction           | Flavonols, isoflavones              | 30        |
|                          | *B. uniformis*                                                                             | Reduction           | Flavonols, flavonones                | 31        |
|                          | *B. uniformis*                                                                             | Reduction           | Flavanones                          | 28        |
|                          | *B. uniformis*                                                                             | Reduction           | Flavanones                          | 48        |
|                          | *B. lenta*                                                                                | Dehydroxylation     | Flavan-3-ols, C-ring cleavage products of flavan-3-ols | 80        |
|                          | *B. lenta*                                                                                | Dehydroxylation     | Flavan-3-ols                         | 67        |
|                          | *B. lenta*                                                                                | Dehydroxylation     | Flavan-3-ols                         | 80        |
|                          | *Eggerthella lenta* CAT-1                                                                   | C-Ring cleavage     | C-Ring cleavage products of flavan-3-ols | 57        |
|                          | *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        |
|                          | *Eggerthella* sp. YY7918 [AB379693] (1469 nt)                                              | C-Ring cleavage     | Flavan-3-ols                         | 66        |
|                          | *Slackia* equilocienisci JCM 16059                                                          | C-Ring cleavage     | Flavan-3-ols, flavanones             | 49,64     |
|                          | *Slackia* isoflavonicvertens DSM 220 06                                                   | C-Ring cleavage     | Flavan-3-ols                         | 80        |
|                          | *Slackia* sp. NATTS [AB505075] (1496 nt), *Slackia isoflavonicvertens* (99%)               | Reduction           | Flavanones                           | 68        |
|                          | *Bacteroides ovatus* ATCC 8483                                                               | O-Deglycosylation   | Flavonols                            | 85        |
|                          | *B. ovatus* strain                                                                        | O-Deglycosylation   | Flavonols                            | 85        |
|                          | *Bacteroides uniformis* ATCC 8492                                                           | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *B. uniformis* strain                                                                       | O-Deglycosylation   | Flavonols                            | 85        |
|                          | *Porphyromonadaceae*                                                                       | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *Parabacteroides distasonis* (Bacteroides distasonis) strain                                | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *Parabacteroides distasonis* (Bacteroides distasonis) JCM 5825                             | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *Lactobacillus acidophilus* strain                                                          | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *Lactobacillus buchneri* strain                                                             | O-Deglycosylation   | Flavonols                            | 27        |
|                          | *Lactobacillus casei* LC-01                                                                 | O-Deglycosylation   | Anthocyanidins                       | 29        |
|                          | *Lactobacillus casei* strain                                                                | O-Deglycosylation   | Flavonols                            | 27        |

(continued)
### Table 2. (Continued)

| Phylum/family | Species/strain$^a$ (former name) | Conversion reaction | Flavonoid class(es) | Reference |
|---------------|----------------------------------|---------------------|--------------------|-----------|
| Lactobacillus leichmanii strain | O-Deglycosylation Flavonones | 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 |
| Enterococcaceae | Enterococcus sp. MRG-IF-3 [KF803553] (1387 nt) | O-Deglycosylation Flavones, isoflavones | 40 |
| Enterococcus avium strains LY1 and EFEL009 | O-Deglycosylation Flavonols | 38,39 |
| Enterococcus casseliflavus M1 | O-Deglycosylation Flavonols | 16 |
| Enterococcus sp. 45 [K417329] (1498 nt) | O-Deglycosylation Flavones | 50 |
| Enterococcus casseliflavus (99%) | O-Deglycosylation Flavonones | 27 |
| Enterococcus faecalis (Streptococcus faecalis) IFO 12964 | O-Deglycosylation Flavones, isoflavones | 40 |
| Enterococcus sp. MRG-IFC-2 [KF803555] (1431 nt), Enterococcus faecium (99%) | O-Deglycosylation Flavones, isoflavones | 40 |
| Clostridiaceae | Clostridium butyricum IFO 13949$^T$ | C-Deglycosylation | Isoflavones | 27 |
| Eubacterium cellulosolvens ATCC 43171$^T$ | O-Deglycosylation Flavones, isoflavones | 33 |
| Flavonifractor plautii DSM 16296 | O-Deglycosylation Flavonols, flavones, dihydrochalcones, isoflavones | 16,17,34,35 |
| Eubacterium ramulus Julong 601 | C-Ring cleavage | Dihydrochalcones, O-desmethylangolensin | 17,34,35 |
| Blautia sp. MRG-PFM1 [KU078647] (1361 nt), Blautia producta (99%) | O-Deglycosylation Flavones, flavones, flavonones, isoflavones | 36 |
| Clostridiaceae | Strain PUE [EU377662] (1346 nt), Dorea longicatena (98%) | O-Demethylation | Flavonones, flavones, isoflavones | 49 |
| Enterococcaceae | Strain CG19-1 [FJ711049] (1454 nt) | C-Deglycosylation | Isoflavones | 49 |
| Lachnospiraceae | Strain SY5819 [AB477431] (1493 nt) | O-Deglycosylation Flavones, flavones, flavonones, isoflavones | 37 |
| Ruminococcaceae | Flavonifractor plautii (Clostridium orbiscindens) strains ATCC 49531, 257, 258 and 264 | O-Deglycosylation Flavones, isoflavones | 37 |
| Flavonifractor plautii strains DSM 6740 and ak2 | C-Ring cleavage | O-Demethylangolensins | 78 |
| Flavonifractor plautii (Clostridium orbiscindens) I2 | C-Ring cleavage | Flavonones | 86 |
| Eubacteriaceae | Eubacterium limosum ATCC B486$^T$ | O-Demethylation | Isoflavones | 53 |
| Eubacterium limosum strains DSM 20543$^T$ and LMG P23546 | O-Demethylation | Flavonones | 51,52 |
| Erysipelotrichaceae | Strain TM-40 [AB249652] (1422 nt) | O-Deglycosylation Reduction | Isoflavones | 75 |
| Proteobacteria | Enterobacter cloaceae IAM 12349 | O-Deglycosylation Flavonones | 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 |
| Coupled flavones and isoflavone glucosides | Flavonone and iso flavonol glucosides | 33,37,40,49,50 |

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 flavon 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.
Strain PUE of the Lachnospiraceae has been affiliated with *Dorea longicatena* (Table 2), a dominant member of the human intestinal microbiota. Systematic screening of *E. cellulosolvens* and strain CG19-1 revealed that the substrate spectrum differs considerably between individual species. In *E. cellulosolvens*, an enzyme system of 5 proteins affords the deglycosylation of *C*-coupled flavone and iso flavone glucosides. 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. 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 (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. In turn, results from the spontaneously occurring cyclization of the hop chalcone xanthohumol, which is observed in vitro and in vivo.

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

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 flavanones and flavanones (Fig. 1), respectively. These metabolites are further converted by fission of the central heterocyclic C-ring. This also applies to dietary flavanols and flavanones. The B-ring of the flavanols 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*. The cleavage of taxifolin by *Eggerthella* (former *Eubacterium*) sp. SDG-2 results in the formation of the corresponding hydroxydihydrochalcone. The ability of *E. ramulus* to degrade quercetin also in vivo was demonstrated in a gnotobiotic rat model. The conversion of flavones and flavanones has also been mainly studied in *E. ramulus* and *F. plautii*. 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/flavanols 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*. Other bacteria capable of flavone or flavanone degradation are strain CG19-1 and *Clostridium butyricum*. 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. The identified bacterial species/strains involved in the conversion of flavonol, flavanone, flavone, flavanonone, 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 $7.0 \times 10^8$ cells per gram of dry feces. *F. plautii* was detected in 80% of individuals at a mean cell count of $4.4 \times 10^8$ per gram of dry feces.

**Conversion of isoflavone aglycones**

Transformation of isoflavone aglycones by human gut bacteria occurs by stepwise reduction to isoflavane 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.](image-url)
Isoflavandiol equol or conversion via O-desmethylangolensin 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 equol49,64-69 (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 isoflavoniconvertens 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 demonstrated in gnotobiotic rats.70 Analysis of the occurrence of S. isoflavoniconvertens strains in Japanese adults revealed a prevalence of 40% and a mean count of 2.5 \times 10^6 cells per gram of wet feces.69

The enzymes involved in the conversion of daidzein and genistein, namely daidzein reductase, dihydrodaidzein racemase, dihydrodaidzein reductase and tetrahydrodaidzein reductase, were identified in Lactococcus garvieae 20-92, S. isoflavoniconvertens DSM 22006T 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 considerable advantage on the recipients.74

Research results concerning the ability of bifidobacteria to form equol from daidzein are contradictory. While strains of Bifidobacterium animalis, B. longum and B. pseudolongum were reported to form equol30 (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 Erysipelotrichaceae strain TM-40 reduces the C2-C3 double 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. ramulus35,77 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 product,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.
which is formed from genistein by the *E. ramulus* strains, is further degraded to 2-(4-hydroxyphenyl)propionic acid (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.

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 (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*, 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. 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*. 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, 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 metabolotypes; 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 metatranscriptomic 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.

**References**

[1] Ley RE, Peterson DA, Gordon JL. Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 2006; 124:837-48; PMID:16497592; http://dx.doi.org/10.1016/j.cell.2006.02.017

[2] Rawls JF, Mahowald MA, Ley RE, Gordon JL. Reciprocal gut microbiota transplants from zebrafish and mice to germ-free recipients reveal host habitat selection. Cell 2006; 127:423-33; PMID:17055441; http://dx.doi.org/10.1016/j.cell.2006.08.043

[3] Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfeld GM, Hold G, Quraishi MN, Kinross J, Smidt H, Tuohy KM, et al. The gut microbiota and host health: a new clinical frontier. Gut 2016; 65:330-9; PMID:26338727; http://dx.doi.org/10.1136/gutjnl-2015-309990

[4] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010; 464:59-65; PMID:20203603; http://dx.doi.org/10.1038/nature08821

[5] Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, Creasy HH, Earl AM, FitzGerald MG, Fulton RS, et al. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486:207-14; PMID:22699609; http://dx.doi.org/10.1038/nature11234

[6] Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JL. The human microbiome project. Nature 2007; 449:806-10; PMID:17943116; http://dx.doi.org/10.1038/nature06244

[7] Hehemann JH, Correc G, Barbeyron T, Helbert W, Czjzek M, Michel G. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature 2010; 464:908-12; PMID:20376150; http://dx.doi.org/10.1038/nature08937

[8] Lampe JW, Karr SC, Hutchins AM, Slavin JL. Urinary equol excretion with a soy challenge: influence of habitual diet. Proc Soc Exp Biol Med 1998; 217:335-9; PMID:9492344; http://dx.doi.org/10.1016/j.1381/00379727-217-42421

[9] Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal 2013; 18:1818-92; PMID:22794138; http://dx.doi.org/10.1089/ars.2012.4581

[10] Rodriguez-Mateos A, Vauzour D, Krueger CG, Shanmugasundaram S, Reed J, Calani L, Mena P, Del Rio D, Crozier A. Bioavailability, bioactivity and impact on health of dietary flavonoids and related compounds: an update. Arch Toxicol 2014; 88:1803-53; PMID:25182418; http://dx.doi.org/10.1007/s00204-014-1330-7

[11] Duenas M, Munoz-Gonzalez I, Cueva C, Jimenez-Giron A, Sanchez-Patan F, Santos-Buelga C, Moreno-Arribas MV, Bartolome B. A survey of modulation of gut microbiota by dietary polyphenols. Biomed Res Int 2015; 2015:850902; PMID:25793210; http://dx.doi.org/10.1155/2015/850902

[12] Moco S, Martin FP, Rezzi S. Metabolomics view on gut microbiome modulation by polyphenol-rich foods. J Proteome Res 2012; 11:4781-90; PMID:22905879; http://dx.doi.org/10.1021/pr300581s

[13] Duda-Chodak A, Tarko T, Satora P, Sroka P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. Eur J Nutr 2015; 54:325-41; PMID:25672526; http://dx.doi.org/10.1007/s00394-015-0852-y

[14] Chiou YS, Wu JC, Huang Q, Shahidi F, Wang YJ, Ho CT, Pan MH. Metabolic and colonic microbiota transformation may enhance the bioactivities of dietary polyphenols. J Funct Foods 2014; 7:3-25; http://dx.doi.org/10.1016/j.jff.2013.08.006
[15] Cook NC, Samman S. Flavonoids - chemistry, metabolism, cardioprotective effects, and dietary sources. J Nutr Biochem 1996; 7:66-76; http://dx.doi.org/10.1016/0955-2863(95)00168-9

[16] Schneider H, Schwertz A, Collins MD, Blaut M. Anaerobic transformation of quercetin-3-glucoside by bacteria from the human intestinal tract. Arch Microbiol 1999; 171:81-91; PMID:9914304; http://dx.doi.org/10.1007/s002030050682

[17] Schneider H, Blaut M. Anaerobic degradation of flavonoids by Eubacterium ramulus. Arch Microbiol 2000; 173:71-5; PMID:10648107; http://dx.doi.org/10.1007/s002030050010

[18] Hidalgo M, Oruna-Concha MJ, Kolida S, Walton GE, Kallithraka S, Spencer JP, de Pascual-Teresa S. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. J Agric Food Chem 2012; 60:3882-90; PMID:22439618; http://dx.doi.org/10.1021/jf3002153

[19] Schröder C, Matthies A, Engst W, Blaut M, Braune A. Identification and expression of genes involved in the conversion of daidzein and genistein by the equal-forming bacterium Slackia isolavoniconvertens. Appl Environ Microbiol 2013; 79:3494-502; PMID:23542626; http://dx.doi.org/10.1128/AEM.03693-12

[20] Braune A, Gütschow M, Engst W, Blaut M. Degradation of quercetin and luteolin by Eubacterium ramulus. Appl Environ Microbiol 2001; 67:5558-67; PMID:11722907; http://dx.doi.org/10.1128/AEM.67.12.5558-5567.2001

[21] Schoefer L, Mohan R, Schwertz A, Braune A, Blaut M. Anaerobic degradation of flavonoids by Clostridium orbiscindens. Appl Environ Microbiol 2003; 69:5849-54; PMID:14532034; http://dx.doi.org/10.1128/AEM.69.10.5849-5854.2003

[22] Brune A, Schink B. Phloroglucinol pathway in the strictly anaerobic Pelobacter acidigallici: fermentation of trihydroxybenzenes to acetate via triacetic acid. Arch Microbiol 1992; 157:417-24; http://dx.doi.org/10.1007/BF00249098

[23] Krumholz LR, Crawford RL, Hemling ME, Bryant MP. Metabolism of gallocate and phloroglucinol in Eubacterium oxidoreducens via 3-hydroxy-5-octohexanoate. J Bacteriol 1987; 169:1886-90; PMID:3571153

[24] Marin I, Miguélez EM, Villar CJ, Lombó F. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. Biomed Res Int 2015; 2015:905215; PMID:25802870; http://dx.doi.org/10.1155/2015/905215

[25] Day AJ, Canada FJ, Diaz JC, Kroon PA, McLauchlan R, Faulds CB, Plumb GW, Morgan MR, Williamson G. Dietary flavonoid and isoflavone glycosides are hydrolysed by the lactase site of lactase phlorizin hydrolase. FEBS Lett 2000; 468:166-70; PMID:10692580; http://dx.doi.org/10.1016/S0014-5793(00)01211-4

[26] Nemeth K, Plumb GW, Berrin JG, Juge N, Jacob R, Naim HY, Williamson G, Swallow DM, Kroon PA. Deglycosylation by small intestinal epithelial cell β-glucosidases is a critical step in the absorption and metabolism of dietary flavonoid glycosides in humans. Eur J Nutr 2003; 42:29-42; PMID:12594539; http://dx.doi.org/10.1007/s00394-003-0397-3

[27] Miyake Y, Yamamoto K, Osawa T. Metabolism of antioxidant in lemon fruit (Citrus limon BURM. f.) by human intestinal bacteria. J Agric Food Chem 1997; 45:3738-42; http://dx.doi.org/10.1021/jf970403r

[28] Raimondi S, Roncaglia L, De Luca M, Amaretti A, Leonard A, Pagnoni UM, Rossi M. Biodconversion of soy isoflavones daidzin and daidzein by Bifidobacterium strains. Appl Microbiol Biotechnol 2009; 81:943-50; PMID:18820905; http://dx.doi.org/10.1007/s00253-008-1719-4

[29] Avila M, Hidalgo M, Sanchez-Moreno G, Pelaez C, Requena T, De Pascual-Teresa S. Bioconversion of anthocyanin glycosides by bifidobacteria and Lactobacillus. Food Res Internat 2009; 42:1453-61; http://dx.doi.org/10.1016/j.foodres.2009.07.026

[30] Tsangalis D, Ashton JF, McGill AEJ, Shah NP. Enzymic transformation of isoflavone phytoestrogens in soymilk by β-glucosidase-producing bifidobacteria. J Food Science 2002; 67:3104-13; http://dx.doi.org/10.1111/j.1365-2621.2002.tb08866.x

[31] Marotti I, Bonetti A, Biavati B, Catizone P, Dinelli G. Bioconversion of common bean (Phaseolus vulgaris L.) flavonoid glycosides by Bifidobacterium species from human intestinal origin. J Agric Food Chem 2007; 55:3913-9; PMID:17439230; http://dx.doi.org/10.1021/jf062997g

[32] Bang SH, Hyun YJ, Shim J, Hong SW, Kim DH. Metabolism of rutin and poncirin by human intestinal microbacteria and cloning of their metabolizing α-L-rhamnosidase from Bifidobacterium dentium. J Microbiol Biotechnol 2015; 25:18-25; PMID:25179902; http://dx.doi.org/10.4014/jmb.1404.04060

[33] Braune A, Blaut M. Intestinal bacteria Eubacterium cellassolvens deglycosylates flavonoid C- and O-glucosides. Appl Environ Microbiol 2012; 78:8151-3; PMID:22961906; http://dx.doi.org/10.1128/AEM.02115-12

[34] Braune A, Engst W, Blaut M. Degradation of neohesperidin dihydrochalcone by human intestinal bacteria. J Agric Food Chem 2005; 53:1782-90; PMID:15740074; http://dx.doi.org/10.1021/jf0484982

[35] Schoefer L, Mohan R, Braune A, Brringer M, Blaut M. Anaerobic C-ring cleavage of genistein and daidzein by Eubacterium ramulus. FEMS Microbiol Lett 2002; 208:197-202; PMID:11959436; http://dx.doi.org/10.1111/j.1365-2004.2010.02352.x

[36] Kim M, Kim N, Han J. Metabolism of Kaempferia parviflora polymethoxylavones by human intestinal bacterium Bifidobacterium sp. MRG-PMF1. J Agric Food Chem 2014; 62:12377-83; PMID:25437273; http://dx.doi.org/10.1021/jf504074n

[37] Braune A, Blaut M. Deglycosylation of puernarin and other aromatic C-glucosides by a newly isolated human intestinal bacterium. Environ Microbiol 2011; 13:482-94; PMID:20946528; http://dx.doi.org/10.1111/j.1462-2920.2010.02352.x
[38] Liu Y, Dai Y, Xun L, Hu M. Enteric disposition and recycling of flavonoids and ginkgo flavonoids. J Altern Complement Med 2003; 9:631-40; PMID:14629841; http://dx.doi.org/10.1089/1075550332524481

[39] Shin NR, Moon JS, Shin SY, Li L, Lee YB, Kim TJ, Han NS. Isolation and characterization of human intestinal Enterococcus avium EFEL009 converting rutin to quercetin. Lett Appl Microbiol 2016; 62:68-74; PMID:26505733; http://dx.doi.org/10.1111/lam.12512

[40] Kim M, Lee J, Han J. Deglycosylation of isoflavone C-glycosides by newly isolated human intestinal bacteria. J Sci Food Agric 2015; 95:1925-31; PMID:25199800; http://dx.doi.org/10.1002/jsfa.6900

[41] Schloissnig S, Arumugam M, Sunagawa S, Mitreva M, Tap J, Zhu A, Waller A, Mende DR, Kultima JR, Martin J, et al. Genomic variation landscape of the human gut microbiome. Nature 2013; 493:45-50; PMID:23222524; http://dx.doi.org/10.1038/nature11711

[42] Kepper K, Humphf HU. Metabolism of anthocyanins and their phenolic degradation products by the intestinal microflora. Bioorg Med Chem 2005; 13:5195-205; PMID:15963727; http://dx.doi.org/10.1016/j.bmc.2005.05.003

[43] Michlmayr H, Kneifel W. β-Glucosidase activities of lactic acid bacteria: mechanisms, impact on fermented food and human health. FEMS Microbiol Lett 2014; 352:1-10; PMID:24330034; http://dx.doi.org/10.1111/j.1574-6968.12348

[44] Braune A, Engst W, Blaut M. Identification and functional expression of genes encoding flavonoid O- and C-glycosidases in intestinal bacteria. Environ Microbiol 2015; PMID:25845411; http://dx.doi.org/10.1111/1462-2920.12864

[45] Schneider H, Simmering R, Hartmann L, Pforte H, Blaut M. Degradation of quercetin-3-glucoside in gnotobiotic rats associated with human intestinal bacteria. J Appl Microbiol 2000; 89:1027-37; PMID:11123476; http://dx.doi.org/10.1046/j.1365-2672.2000.01209.x

[46] Beekwilder J, Marcozzi D, Vecchi S, de Vos R, Janssen P, Francke C, van Hylckama Vlieg J, Hall RD. Characterization of rhamnosidases from Lactobacillus plantarum and Lactobacillus acidophilus. Appl Environ Microbiol 2009; 75:3447-54; PMID:19346347; http://dx.doi.org/10.1128/AEM.02675-08

[47] Avila M, Jaquet M, Moine D, Requena T, Pelaez C, Arigoni F, Jankovic I. Physiological and biochemical characterization of the two α-L-rhamnosidases of Lactobacillus plantarum NCC245. Microbiology 2009; 155:2739-49; PMID:19423635; http://dx.doi.org/10.1099/mic.0.027789-0

[48] Amaretti A, Raimondi S, Leonardi A, Quartieri A, Rossi M. Hydrolysis of the rutinose-conjugates flavonoids rutin and hesperidin by the gut microbiota and bifidobacteria. Nutrients 2015; 7:2788-800; PMID:25875120; http://dx.doi.org/10.3390/nu7042788

[49] Jin JS, Nishihata T, Kakiuchi N, Hattori M. Biotransformation of C-glycosylisoflavone puerarin to estrogenic (3S)-equol in co-culture of two human intestinal bacteria. Biol Pharm Bull 2008; 31:1621-5; PMID:18670101; http://dx.doi.org/10.1248/bpb.31.1621

[50] Xu J, Qian D, Jiang S, Guo J, Shang EX, Duan JA, Yang J. Application of ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry to determine the metabolites of orientin produced by human intestinal bacteria. J Chromatogr B Analyt Technol Biomed Life Sci 2014; 944:123-7; PMID:24316522; http://dx.doi.org/10.1016/j.jchromb.2013.11.002

[51] Possemiers S, Heyerick A, Robbens V, De Keukeleire D, Verstraete W. Activation of prooestrogens from hops (Humulus lupulus L.) by intestinal microbiota; conversion of isoxanthohumol into 8-prenylnaringenin. J Agric Food Chem 2005; 53:6281-8; PMID:16076107; http://dx.doi.org/10.1021/jf0509714

[52] Possemiers S, Rabot S, Espin JC, Bruneau A, Philippe C, Gonzalez-Sarrias A, Heyerick A, Tomas-Barberan FA, De Keukeleire D, Verstraete W. Eubacterium limosum activates isoxanthohumol from hops (Humulus lupulus L.) into the potent phytoestrogen 8-prenylnaringenin in vitro and in rat intestine. J Nutr 2008; 138:1310-6; PMID:18567753

[53] Hur H, Rafii F. Biotransformation of the isoflavonoids biochanin A, formononetin, and glycitein by Eubacterium limosum. FEMS Microbiol Lett 2000; 192:21-5; PMID:11040423; http://dx.doi.org/10.1111/j.1574-6968.2000.tb09355.x

[54] Nikolic D, Li Y, Chadwick LR, Pauli GF, van Breemen RB. Metabolism of xanthohumol and isoxanthohumol, prenylated flavonoids from hops (Humulus lupulus L.), by human liver microsomes. J Mass Spectrom 2005; 40:289-99; PMID:15712367; http://dx.doi.org/10.1002/jms.753

[55] Hanske L, Loh G, Szcesny S, Blaut M, Braune A. Recovery and metabolism of xanthohumol in germ-free and human microbiota-associated rats. Mol Nutr Food Res 2010; 54:1405-13; PMID:20397197; http://dx.doi.org/10.1002/mnfr.200900517

[56] Wang LQ, Meselhy MR, Li Y, Nakamura N, Min BS, Qin GW, Hattori M. The heterocyclic ring fission and dehydroxylation of catechins and related compounds by Eubacterium sp. strain SDG-2, a human intestinal bacterium. Chem Pharm Bull (Tokyo) 2001; 49:1640-3; PMID:11767089; http://dx.doi.org/10.1248/cpb.49.1640

[57] Jin JS, Hattori M. Isolation and characterization of a human intestinal bacterium Eggerthella sp. CAT-1 capable of cleaving the C-ring of (+)-catechin and (−)-epicatechin, followed by p-dehydroxylation of the B-ring. Biol Pharm Bull 2012; 35:2252-6; PMID:23207778; http://dx.doi.org/10.1248/bpb.b12-00726

[58] Zhao M, Du L, Tao J, Qian D, Shang EX, Jiang S, Guo J, Liu P, Su SL, Duan JA. Determination of metabolites of diosmetin-7-O-glucoside by a newly isolated Escherichia coli from human gut using UPLC-Q-TOF/MS. J Agric Food Chem 2014; 62:11441-8; PMID:25382172; http://dx.doi.org/10.1021/jf502676j
[59] Herles C, Braune A, Blaut M. First bacterial chalcone isomerase isolated from *Eubacterium ramulus*. Arch Microbiol 2004; 181:428-34; PMID:15127184; http://dx.doi.org/10.1007/s00203-004-0676-2

[60] Gall M, Thomsen M, Peters C, Pavlidis IV, Jonczyk P, Grunert PP, Beutel S, Schepert T, Gross E, Backes M, et al. Enzymatic conversion of flavonoids using bacterial chalcone isomerase and enoate reductase. Angew Chem Int Ed 2014; 53:1439-42; http://dx.doi.org/10.1002/anie.201306952

[61] Thomsen M, Tuukkanen A, Dickerhoff J, Palm GJ, Kratz H, Svergun DI, Weisz K, Bornscheuer UT, Hinrichs W. Structure and catalytic mechanism of the evolutionarily unique bacterial chalcone isomerase. Acta Crystallogr 2015; D71:907-17

[62] Schoefler L, Braune A, Blaut M. Cloning and expression of a phloretin hydrolase gene from *Eubacterium ramulus* and characterization of the recombinant enzyme. Appl Environ Microbiol 2004; 70:6131-7; PMID:15466559; http://dx.doi.org/10.1128/AEM.70.10.6131-6137.2004

[63] Simmering R, Kleessen B, Blaut M. Quantification of the flavonoid-degrading bacterium *Eubacterium ramulus* in human fecal samples with a species-specific oligonucleotide hybridization probe. Appl Environ Microbiol 1999; 65:3705-9; PMID:10427069

[64] Jin JS, Kitahara M, Sakamoto M, Hattori M, Benno Y. *Slackia equolifaciens* sp. nov., a human intestinal bacterium capable of producing equol. Int J Syst Evol Microbiol 2010; 60:1721-4; PMID:19734283; http://dx.doi.org/10.1099/ijs.0.016774-0

[65] Shimada Y, Yasuda S, Takahashi M, Hayashi T, Miyazawa N, Sato I, Abiru Y, Uchiyama S, Hishigaki H. Cloning and expression of a novel NADP(H)-dependent daidzein reductase, an enzyme involved in the metabolism of daidzein, from equol-producing *Lactococcus* strain 20–92. Appl Environ Microbiol 2010; 76:5892-901; PMID:20639368; http://dx.doi.org/10.1128/AEM.01101-10

[66] Yokoyama S, Suzuki T. Isolation and characterization of a novel equol-producing bacterium from human feces. Biosci Biotechnol Biochem 2008; 72:2660-6; PMID:18838805; http://dx.doi.org/10.1271/bbb.80329

[67] Maruo T, Sakamoto M, Ito C, Toda T, Benno Y. *Adlercreutzia* equolificiens gen. nov., sp. nov., an equol-producing bacterium isolated from human faeces, and emended description of the genus *Eggerthella*. Int J Syst Evol Microbiol 2008; 58:1221-7; PMID:18450717; http://dx.doi.org/10.1099/ijs.0.06540-0

[68] Matthies A, Blaut M, Braune A. Isolation of a human intestinal bacterium capable of daidzein and genistein conversion. Appl Environ Microbiol 2009; 75:1740-4; PMID:19139227; http://dx.doi.org/10.1128/AEM.01795-08

[69] Tsuji H, Moriyama K, Nomoto K, Miyanaga N, Akaza H. Isolation and characterization of the equol-producing bacterium *Slackia* sp. strain NATTS. Arch Microbiol 2010; 192:279-87; PMID:20237913; http://dx.doi.org/10.1007/s00203-010-0546-z

[70] Matthies A, Loh G, Blaut M, Braune A. Daidzein and genistein are converted to equol and 5-hydroxy-equol by human intestinal *Slackia* sp. strain NATTS. Arch Microbiol 2011; 194:49-56; PMID:2113864; http://dx.doi.org/10.1007/s00203-011-0482-4

[71] Shimada Y, Takahashi M, Miyazawa N, Abiru Y, Uchiyama S, Hishigaki H. Identification of a novel dihydrodaidzein racemase, that is essential for equol biosynthesis from daidzein in *Lactococcus* strain 20–92. Appl Environ Microbiol 2012; 78:4902-7; PMID:22582059; http://dx.doi.org/10.1128/AEM.00410-12

[72] Shimada Y, Takahashi M, Miyazawa N, Ohtani T, Abiru Y, Uchiyama S, Hishigaki H. Identification of two novel reductases involved in equol biosynthesis in *Lactococcus* strain 20–92. J Mol Microbiol Biotechnol 2011; 21:160-72; PMID:22286043; http://dx.doi.org/10.1159/000335049

[73] Tsuji H, Moriyama K, Nomoto K, Akaza H. Identification of an enzyme system for daidzein-to-equol conversion in *Slackia* sp. strain NATTS. Appl Environ Microbiol 2012; 78:1228-36; PMID:22179235; http://dx.doi.org/10.1128/AEM.06779-11

[74] Smillie CS, Smith MB, Friedman J, Cordero OX, David LA, Alm EJ. Ecology drives a global network of gene exchange connecting the human microbiome. Nature 2011; 480:241-4; PMID:22037308; http://dx.doi.org/10.1038/nature10571

[75] Tamura M, Tsushida T, Shinohara K. Isolation of an isoflavone-metabolizing, *Clostridium*-like bacterium, strain TM-40, from human faeces. Anaerobe 2007; 13:32-5; PMID:17113326; http://dx.doi.org/10.1016/j.anaerobe.2006.10.001

[76] Wang XL, Hur HG, Lee JH, Kim KT, Kim SI. Enantioselective synthesis of S-equol from dihydrodaidzein by a newly isolated anaerobic human intestinal bacterium. Appl Environ Microbiol 2005; 71:214-9; PMID:15640190; http://dx.doi.org/10.1128/AEM.71.1.214-219.2005

[77] Wang XL, Kim KT, Lee JH, Hur HG, Kim SI. C-ring cleavage of isoflavones daidzein and genistein by a newly-isolated human intestinal bacterium *Eubacterium ramulus* J ulon 601. J Microbiol Biotechnol 2004; 14:766-71

[78] Yokoyama S, Niwa T, Osawa T, Suzuki T. Characterization of an O-desmethylangolensin-producing bacterium isolated from human feces. Arch Microbiol 2010; 192:15-22; PMID:19904524; http://dx.doi.org/10.1007/s00203-009-0524-5

[79] Kutschera M, Engst W, Blaut M, Braune A. Isolation of catechin-converting human intestinal bacteria. J Appl Microbiol 2011; 111:165-75; PMID:21457417; http://dx.doi.org/10.1111/j.1365-2672.2011.05025.x

[80] Takagaki A, Nanjo F. Biotransformation of (−)-epigallocatechin and (−)-gallocatechin by intestinal bacteria involved in isoflavone metabolism. Biol Pharm Bull 2015; 38:325-30; PMID:25747993; http://dx.doi.org/10.1248/bpb.b14-00646
Sanchez-Patan F, Tabasco R, Monagas M, Requena T, Pelaez C, Moreno-Arribas MV, Bartolome B. Capability of *Lactobacillus plantarum* IFPL935 to catabolize flavan-3-ol compounds and complex phenolic extracts. J Agric Food Chem 2012; 60:7142-51; PMID:22646528; http://dx.doi.org/10.1021/jf3006867

Deprez S, Brezillon C, Rabot S, Philippe C, Mila I, Lapierre C, Scalbert A. Polymeric proanthocyanidins are catabolized by human colonic microflora into low-molecular-weight phenolic acids. J Nutr 2000; 130:2733-8; PMID:11053514

Appeldoorn MM, Vincken JP, Aura AM, Hollman PC, Gruppen H. Procyanidin dimers are metabolized by human microbiota with 2-(3,4-dihydroxyphenyl)acetic acid and 5-(3,4-dihydroxyphenyl)-γ-valerolactone as the major metabolites. J Agric Food Chem 2009; 57:1084-92; PMID:19191673; http://dx.doi.org/10.1021/jf803059z

Stoupi S, Williamson G, Drynan JW, Barron D, Clifford MN. A comparison of the in vitro biotransformation of (−)-epicatechin and procyanidin B2 by human faecal microbiota. Mol Nutr Food Res 2010; 54:747-59; PMID:19943260; http://dx.doi.org/10.1002/mnfr.200900123

Bokkenheuser VD, Shackleton CH, Winter J. Hydrolysis of dietary flavonoid glycosides by strains of intestinal *Bacteroides* from humans. Biochem J 1987; 248:953-6; PMID:3435494; http://dx.doi.org/10.1042/bj2480953

Winter J, Popoff MR, Grimont P, Bokkenheuser VD. *Clostridium orbiscindens* sp. nov., a human intestinal bacterium capable of cleaving the flavonoid C-ring. Int J Syst Bacteriol 1991; 41:355-7; PMID:1883711; http://dx.doi.org/10.1099/00207713-41-3-355

Hur HG, Lay JO, Jr, Beger RD, Freeman JP, Rafii F. Isolation of human intestinal bacteria metabolizing the natural isoflavone glycosides daidzin and genistin. Arch Microbiol 2000; 174:422-8; PMID:11195098; http://dx.doi.org/10.1007/s002030000222