NUME

REVIEW ARTICLE

Nutrition-derived bioactive metabolites produced by gut microbiota and their potential impact on human health

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Abstract

The functional role of human gut microbiota has attracted substantial interest and recent research has uncovered various aspects of the interplay between the complex communities of microorganisms colonizing the intestine and their hosts' health. The present review focuses on nutrition-derived bioactive metabolites produced by gut microbiota with potential beneficial effects upon human health. Thereby, the emphasis is on newly generated bacterial metabolites that are not concomitantly present at higher amounts in dietary sources and that have been previously detected in human blood samples. Since a multitude of different substances is generated by gut microbes primarily those metabolites which exert a more pronounced activity than their immediate precursor compound are discussed here. Specifically, the *in vitro* and *in vivo* nutridynamics as well as the nutrikinetics of equol, enterolactone / enterodiol, urolithins, 8-prenylnaringenin, 3,4-dihydroxyphenylacetic acid and 5-(3',4'-dihydroxyphenyl)-γ-valerolactone, the short-chain fatty acids butyrate, propionate and acetate, as well as indole-3-propionic acid are reviewed. Though the metabolites' mechanism of action and the influence of health conditions on metabolite production are not always fully understood yet, there are many reasons to direct the attention to "gut health". It could offer new options for preventing or treating a variety of disease states and nutrition-derived microbial products might inspire future drug development.

Keywords:

INTRODUCTION

Within the past years the functional role of human gut microbiota has attracted substantial interest and recent research has uncovered fascinating aspects of the interplay between the complex communities of microorganisms colonizing the intestine and their hosts' health [1-5]. While it has been known that gut bacteria provide complementary sources of vitamins and contribute to bile acid metabolism [5, 6] current investigations focus on the multifaceted interactions between bacterial communities and human disease states such as colorectal cancer, type II diabetes mellitus, obesity, allergic or inflammatory bowel diseases. The availability of high throughput analytical techniques for DNA, RNA, protein and metabolite profiling linked with bioinformatics facilitated first insights into the complex networks [7-10]. In this context, novel terms describing these latest scientific approaches have been coined (Table 1).

Table 1: Definitions of terms used in the context of nutrient metabolism by gut bacteria.

Term	Definition	References
Microbiota	The complex communities of microorganisms colonizing the (human) body.	[15, 176]
Microbiome	The genome of the ecological community of commensal, symbiotic, and pathogenic microorganisms that share the (human) body space.	[9, 176]
Metagenomics	Science of the gene content and functional and genetic variability of the gut microbial community (microbiome).	[7]
Metatranscript-omics	Science of the transcripts of the active gut microbial community and their functional role for human health.	[7]
Nutrigenetics	Science of the effect of the genetic sequence variation on the responses to dietary compounds and susceptibility to diet-related diseases.	[10, 177]
Nutrigenomics	Science of the role of nutrients and bioactive food components in gene expression.	[10, 177]
Nutrikinetics	Science of how nutrients and bioactive food components are absorbed, distributed, metabolized and eliminated from the human superorganism (communal group of human and microbial cells), including interactions between the host and the gut microbiome.	[9, 26,178]
Nutridynamics	Science of how nutrients and bioactive food components act on the living organism.	[9]
Epigenetics	Science of the processes that regulate DNA and chromatin modifications which influence gene transcriptional activity and persist over cell divisions.	[177, 179]
Epigenomics	Science of the analysis of epigenetic changes in a cell or the entire organism. The epigenome is dynamic and responds to environmental signals.	[177, 179]

Main beneficial roles of the gut microbiota include metabolic, protective and structural / histological functions [1].

These include formation of bioactive metabolites, immune system development, innate and adaptive immunity activation as well as development and preservation of the gut barrier integrity.

Various environmental factors such as the type and composition of the diet, drug use, but also diseases, stress or injury can affect the human microbiome (Figure 1; [1, 4, 5, 11, 12]). On the other side, gut microorganisms influence each other. Symbiotic commensal bacteria prevent growth of pathogenic fecal microorganisms while overgrowth of certain strains, such as Enterobacteriaceae, might support the colonization of pathogens promoting enteric infections [1]. Typically, it is assumed that an individual balance of the microbiome is attained in the healthy stable state [4]. This balance is characterized by a high variety of bacterial species, complex metabolism and resistance to colonization of microbes that are usually abundant in a disturbed gut environment. Interestingly, this

stable microbiome undergoes age-related shifts with different composition and function of the microbiota in distinct phases of life [5]. The gut microbes directly interact with the host organism, e.g. via toll-like receptors [13], and shape immune responses [14-16]. Vice versa, there are indications that the host genome influences the gut flora [17]. The gut microorganisms produce a range of diverse metabolites. These metabolites might influence the growth of certain microbial strains. For example, Bifidobacteria and Lactobacilli were shown to thrive under the influence of urolithins [18]. Bacterial metabolites also exert various local or systemic effects upon the host organism. While some of these microbacterial products play vital roles for the host's health, other metabolites have deleterious effects and are discussed to trigger chronic disorders [1, 5, 19]. The contribution of the microbial metabolic activities on the hosts' blood metabolites can be elucidated using metabolomic techniques. Typically, serum or urinary metabolite profiles of germ-free mammals are compared to conventional controls [8, 20].

Figure 1: Schematic representation of the complex interactions between environment, host and gut microbiome.
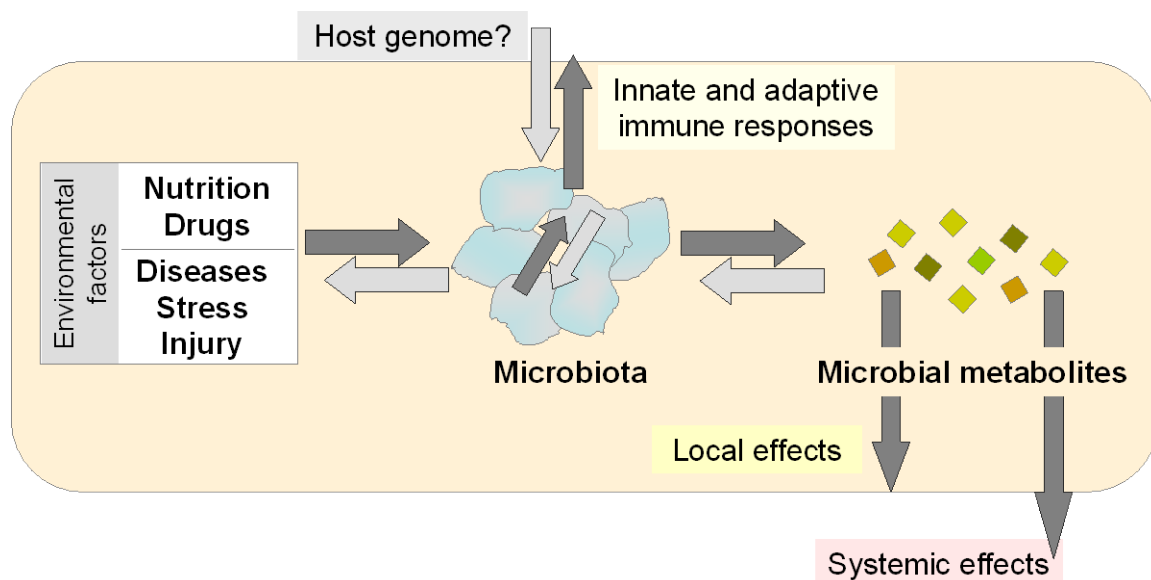
The present review focuses on nutrition-derived bioactive metabolites essentially produced by gut microbiota with potential beneficial effects upon human health. Thereby, the emphasis is on newly generated bacterial metabolites featuring structures that are typically formed by multiple step reactions and that are not concomitantly present at higher amounts in dietary sources. Consequently, a polyphenol metabolite such as protocatechuic acid would be beyond the scope of the present review despite its recently demonstrated *in vivo* and *in vitro* activity [21] since it is also found at higher concentrations in certain food sources [22]. Since a multitude of different metabolites is generated by gut microbes especially from dietary polyphenols [23-27] primarily those metabolites which exert a more pronounced activity than their immediate precursor compound are discussed here. This bioactivation that emerges from the microbial metabolic process is the hallmark of the metabolites discussed here.

NUTRIDYNAMICS OF GUT MICROBIAL METABOLITES

Nutridynamics describes how nutrients and bioactive food components act on the living organism [9]. The bioactivity of individual nutrition-derived microbial metabolites has been primarily investigated using *in vitro* cell culture assays (Table 2). Reflecting these results it should be always considered whether the metabolite concentrations that were required for a particular *in vitro* effect could also be realistically obtained *in vivo*. Few data from human studies with a distinct purified metabolite are available; more frequently investigations with animals have been performed. Typically, more than one effect has been observed with an individual microbial metabolite, in most cases the precise underlying mechanism(s) of action has not been entirely clarified. Generally, the uncovered *in vitro* and *in vivo* effects of microbiota metabolites span a wide range of activities; occasionally, however, results are ambiguous.

Several bioactive metabolites with beneficial health effects have been described for polyphenols [23-25, 28] which might be due to the high abundance and structural diversity of compounds and due to the fact that pronounced research effort has been dedicated to this prominent class of compounds. More recently short-chain fatty acids as bacterial metabolites of complex carbohydrates have attracted attention [29, 30] since they opened a new perspective on obesity and metabolic balance of the host [31, 32]. While some protein fermentation products are regarded as potentially toxic [33] the tryptophan metabolite indole-3-propionic acid was assigned advantageous effects [34, 35]. Bacterial metabolites derived from dietary lipids have been less extensively discussed which might be also related to the estimation that less dietary fat enters the colon compared to carbohydrates or proteins [11]. So far, the analyzed microbiota metabolites of lipids have been discussed to have detrimental effects upon the host's health [19].

ACTIVITIES OF POLYPHENOL-DERIVED MICROBIAL METABOLITES

Equol is an isoflavan metabolite derived from daidzein which is typically found in soy products (Table 2; [36, 38]). Various intestinal bacteria are capable of this biotransformation which exclusively yields S-(-)equol. Another daidzein metabolite, O-desmethylangolensin [39], is less active compared to equol. Numerous biological activities of equol are discussed in the context of its estrogen receptor (ER) binding affinity. Two ER subtypes, α and β, exist and they display varying expressions in different tissues and cell types as well as different regulation of gene classes. There is considerable interest in the development of subtype-selective ERβ activators since they do not stimulate the proliferation of endometrial or breast tissue while they appear to be promising therapeutics for e.g. cardiovascular or malignant neoplastic disorders and Alzheimer's disease [40]. Indeed, it has been shown that S-(-)equol displays a higher binding affinity to the ERβ compared to the ERα [41]. It should be pointed out that R-(+)-equol and (±)-equol display a slightly different binding behaviour to the estrogen receptors. For convenient comparison of the binding affinities of different compounds the relative receptor binding affinity (RBA) is often used. The relative binding affinities of S-(-)equol were determined as RBA= 0.1 (ERα) and RBA= 3 (ERβ) in relation to the binding affinity of the endogenous hormone estradiol (RBA= 100). However, this preferential binding to the ERβ does not translate into a clearly favoured activation of this receptor subtype which would be identified by lower S-(-)equol concentrations being required for ERβ compared to ERα activation.

Table 2: Gut microbial metabolites derived from polyphenols, complex carbohydrates and proteins. All metabolites have been detected in human plasma/serum after ingestion of the respective precursor compound. Examples of dietary food sources and bacteria involved in the metabolite formation are given as well as examples of reported *in vitro* and *in vivo* effects of the isolated compound. For further food source examples see Neveu et al. [22].

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of meta-bolite
Polyphenols				
Daidzein [soybean]	Various bacteria, e.g. Adlercreutzia equolifaciens Slackia equolifaciens Slackia isoflavoniconvertens (*Coriobacteriaceae*) [180-183]	S-(–)Equol	Endocrine effects • Estrogen receptor (ER) ligand (ERβ > ERα) [184] • Antiandrogen effects [47, 48, 185] • Inhibition of osteoclast formation [186] Anticancer activities • Inhibition of cancer cell migration and invasion; induction of apoptosis in cancer cells [187-189] Anti-inflammatory / vasoactive effects • Inhibition of iNOS [190] • Activation of eNOS [191]	Effects in rats • Decrease of prostate weight [46, 47] • Protection against bone mineral density loss [192] • Decrease in body weight, abdominal white adipose tissue and depressive-related behaviour [153] Effects in humans • Alleviation of menopausal related symptoms [50-54]

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of metabolite
Polyphenols				
Lignans [sesame seed, linseed, flaxseed]	Various bacteria, e.g. Bacteriodes sp., Clostridium sp., Eubacterium sp. Eggerthella lenta [57, 135, 193]	Enterolactone Enterodiol	Endocrine effects • Estrogen receptor (ER) ligand [49, 64] • Antiandrogen effects [48] Anticancer activities • Inhibition of cancer cell proliferation and invasion [68, 69, 194, 195] Anti-inflammatory activity • Inhibition of IκB degradation and NF-κB activation [196]	Effects in mice/rats • Inhibition of cancer growth, angiogenesis, and/or metastasis [68-72] • Modulation of estrogen signaling [66, 197]
Isoxanthohumol [hops]	Eubacterium limosum [75]	8-Prenylnaringenin	Endocrine effects • Estrogen receptor (ER) ligand (ERα > ERβ) [76, 78] • Estrogen-like effects on bone cell metabolism [78, 80] Effects on cell proliferation and angiogenesis • Inhibition of angiogenesis and cancer cell growth [81, 82] • Stimulation of angiogenesis and cell proliferation [83] Platelet aggregation effects • Inhibition of platelet aggregation [198]	Effects in rats • Estrogenic activity [199] • Protection against ovariectomy-induced bone loss and hot flushes [79, 200, 201] Effects in humans • Decrease of serum concentrations of luteinizing hormone (LH) [80]

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of metabolite
Polyphenols				
Ellagtannins, ellagic acid [strawberries, raspberries, blackberries, pomgranate, oak-aged wine, walnuts]	Not specified	Urolithin A (3,8-dihydroxy-6H-dibenzopyran-6-one) urolithins B, C, D	**Endocrine effects** • Estrogen receptor (ER) ligand (ERα > ERβ) [87] • Antiproliferative effects on prostate cancer cells and aromatase inhibition [88, 89] **Anti-inflammatory / antioxidant effects** • Downregulation of CCL2 and IL-8, inhibition of PGE$_2$, PAI-1 [91, 92] • Inhibition of NF-κB activation, MAPK, downregulation of COX-2 and microsomal PGE synthase-1 [90] • Antioxidant effects [85] **Anticancer activities** • Inhibition of Wnt signaling [94]	**Effects in mice** • Anti-inflammatory and antioxidant effects [93]

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of metabolite
Polyphenols				
Quercetin [apples, onions] Rutin (Quercetin-glycosid) [fruits, vegatables]	Various bacteria, e.g. Bacteriodes sp., Lactobacillus sp., Bifidobacterium sp. Streptococcus sp. [95]	3,4-Dihydroxyphenyl acetic acid (DOPAC / DHPAA)	Anti-inflammatory effects • Inhibition of LPS-induced cytokine secretion [202] Cardioprotective effects • Inhibition of platelet aggregation [95, 203] • Inhibition of AGE (advanced glycation end products) formation [204] Neuroprotective effects • Protection of neuronal cells against oxidative stress [102] • Induction of mitochondrial dysfunction and apoptosis in neuronal cells [103, 105] Anticancer activities • Cytotoxic activity on cancer cells, antiproliferative activity [95, 100, 103]	Effects in mice • Anxiolytic effects [106]

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of metabolite
Polyphenols				
Procyanidins, catechin, epicatchin, epigallocatechin (-gallate) [maritime pine bark extract, green tea, grape seed extract, cocoa]	Not specified	5-(3',4'-Dihydroxyphenyl)-γ-valerolactone	Anti-inflammatory / antioxidant effects • Inhibition of MMP-1, MMP-2, MMP-9 activity; inhibition of MMP-9 release [205] • Inhibition of iNOS expression and NO release from macrophage cell line [206] • Antioxidant effects [140, 205] Anticancer activities • Antiproliferative effects [207]	Not determined
Procyanidins, epigallocatechin (-gallate) [green tea, wine, berries, nuts]	Not specified	5-(3',4',5'-Trihydroxyphenyl)-γ-valerolactone	Anti-inflammatory / antioxidant effects • Inhibition of arachidonic acid and NO release from macrophage cell line [207] • Antioxidant effects [140] Anticancer activities • Antiproliferative effects [207]	Not determined.

Original Compound(s) [source example(s)]	Bacteria involved in metabolism	Metabolite(s)	Examples of *in vitro* bioactivities of the metabolite	Examples of *in vivo* bioactivities of metabolite
Complex carbohydrates				
Complex carbohydrates [inulin, pectin, resistant starch, dietary fiber]	Various bacteria, e.g. Eubacterium rectale / Roseburia ssp. Clostridium coccoides [208]	Short-chain fatty acids (SCFAs), e.g. butyrate, propionate, and acetate	Multiple intestinal and extraintestinal effects • Anticarcinogenic and chemopreventive activities • Anti-inflammatory effects • Effects on insulin resistance and weight • Cardiovascular effects • Effects on immune system • Effects in inherited disorders (e.g. hemoglobinopathies) • Neuroprotective effects • Effects on stem cells [29, 30, 111, 115, 209, 210]	Effects in mice/rats • Improvement of insulin sensitivity and energy expenditure, protection against diet-induced obesity [120, 122] • Stimulation of neurogenesis [123] • Stimulation of colonic transit time [121] Effects in humans • Improvement of ulcerative colitis [162, 164, 165, 211] • Improvement of congenital chloride diarrhea [212] • Modulation of oxidative stress in the colonic mucosa [213] • Induction of fetal globin gene expression [214]
Proteins				
Tryptophan [various proteins, in e.g. soy beans, nuts]	Clostridium sporogenses [20]	Indole-3-propionic acid	Antioxidant / neuroprotective effects • Antioxidant activity [125, 126] • Neuroprotective properties in cells exposed to Alzheimer β-amyloid [34]	Effects in gerbils • Protection from ischemia-induced neuronal damage [35]

Instead, S-(-)equol induces a similar transcriptional activation of both ERα and ERβ [41-43]. There have been several explanations offered for this discrepancy between receptor binding and activation such as a different interaction with co-regulator proteins [40, 41]. Activation of the receptor requires changes in its conformation and alters the composition of co-regulatory proteins. The complex consisting of ligand, receptor and co-regulator proteins then interacts with the DNA and modulates the gene expression. Besides a cell-type specific gene expression regulation it has been observed that different ligands of the ERβ might influence the transcription of deviating sets of genes [44]. Interestingly, it was reported recently that the ERβ transcription complex can contribute to anti-inflammatory effects by repressing the activity of inflammation-related transcription factors such as AP-1 [45]. Besides interaction with the ER, antiandrogen activities have been described for equol [46, 47]. The antiandrogen effect has been attributed to the complexation of 5α-dihydrotestosterone by equol and thus preventing this highly active hormone from binding to the androgen receptor and induction of biological actions such as prostate growth. Others also determined inhibitory effects of equol on 5α-reductase which converts testosterone to 5α-dihydrotestosterone [48]. The majority of the published *in vitro* and *in vivo* effects of equol (Table 2) are consistent with its estrogenic and antiandrogen activities. It has been pointed out that the risks and benefits of (anti-)estrogenic effects are highly depended on the target tissue as well as on the extent and timing of exposure [49]. Notably, equol is one of the few nutrition-derived microbial metabolites that has been used in human studies in its distinct purified form [50-54]. In that context, effects against various menopausal related symptoms have been described.

Enterolactone and enterodiol are metabolites derived from plant lignans such as pinoresinol [55, 56]. Lignans are found in various food sources such as flaxseed, sesame seed, vegetables or whole grain cereals (Table 2). Various intestinal bacteria have been identified to contribute to the lignan metabolism and formation of enterolactone and enterodiol [57]. While the production of enterodiol dominated in fecal samples [58] higher concentrations of enterolactone were observed in blood samples [59-61]. This discrepancy can be explained by the different elimination kinetics of both compounds [62]. Since enterolactone appears to be the main circulating enterolignan [57, 61, 63] it will be the focus of this discussion. Like for equol, binding to the ER has been observed for enterolactone [55]. Based on reported data [49], the relative binding affinities of enterolactone towards ERα / ERβ were RBA= 0.06 and RBA= 0.01, respectively, of the binding affinity of estradiol (RBA= 100). Thus, there is only a weak and no pronounced preferential binding to one of the ER subtypes. The transactivational potencies and efficacies have been described as not being clearly different towards the ERα / ERβ [49] while others found that enterolactone displays preferential transcription via the ERα *in vitro* and *in vivo* [64]. In contrast to equol which has weak agonistic activity at the ER, enterolactone was characterized as a partial agonist/antagonist [49]. This mixed ligand attributes might contribute to the sometimes divergent results reported in various experimental settings [55]. Other factors adding to this complexity are reports that the simultaneous presence of endogenous estradiol and enterolactone [65, 66] or enterodiol and enterlactone [67] modulates the examined effects. Again, important factors appear to be the target tissue under consideration as well as the extent and timing of exposure with enterolactone. Besides interaction with the ER, antiandrogen activity mediated

by inhibition of 5α-reductase has been found for enterolactone [48]. In addition to those endocrine effects, enterolactone was shown to inhibit cancer cell proliferation and invasion *in vitro* and in rodent studies [68-72]. So far, human studies with purified enterolactone administered as single compound have not been performed.

Another microbial metabolite possessing estrogen-like activities is **8-prenylnaringenin** (Table 2). Although 8-prenylnaringenin is also present at low quantities in beer [22, 73], a major source of this compound appears to be conversion of hops-derived isoxanthohumol by the human intestinal microbia, e.g. by Eubacterium limosum [74, 75]. Both 2S(−) and 2R(+)-8-prenylnaringenin are naturally found [76]. Since 8-prenylnaringenin can also be produced from isoxanthohumol by human hepatic cytochrome P450 enzymes [77] it raises the question to which extent the gut microbial metabolism contributes to the plasma levels in humans. In germ-free rats, no 8-prenylnaringenin production was observed while the administration of Eubacterium limosum increased the metabolite formation [75]. It was reported that 8-prenylnaringenin exhibited a more than twofold higher affinity towards ERα compared to ERβ in receptor binding assays [76]. Thereby, 2S(−)-8-prenylnaringenin displayed a higher affinity to both ERα and ERβ compared to 2R(+)-8-prenylnaringenin. Based on data from a later study [78], relative binding affinities for racemic 8-prenylnaringenin of RBA= 20 (ERα) and RBA= 25 (ERβ) in relation to the binding affinity of estradiol (RBA= 100) were calculated. Thus, compared to equol and enterolactone, a clearly more pronounced binding to both receptor subtypes was determined. Similar to estradiol, 8-prenylnaringenin revealed a stronger absolute binding preference to the ERα in this study though the difference was less than twofold. Since binding to the ER subtypes is not necessarily proportional to the transcriptional activation of genes, the

resulting esterogenic activities have to be considered as well. Like equol, 8-prenylnaringenin is a full agonist [76, 79]. Transactivation analysis uncovered a higher *in vitro* esterogenic activity of 8-prenylnaringenin at ERα compared to ERβ [76]. Animal experiments revealed a tissue-specific action of 8-prenylnaringenin with bone-protective effects comparable to estradiol while the uterotrophic activity was less pronounced in relation to estradiol [80]. Again, the majority of the published *in vitro* and *in vivo* effects of 8-prenylnaringenin (Table 2) are consistent with its estrogenic activity. Results regarding cell growth and apoptosis have been inconsistent [81-83]. It was pointed out that phytoestrogens display dual effects [84]. At low concentrations they often show estrogenic activities, illustrated as e.g. stimulation of breast cell cancer proliferation, while they exhibit antiproliferative effects at higher concentrations. The compound has also been tested in a small human study with postmenopausal women who showed a significant decrease of luteinizing hormone (LH) in response to 8-prenylnaringenin [80].

Urolithins such as urolithin A are ellagic acid metabolites derived from dietary ellagtannins [85] which are found in e.g. raspberries, pomegranate, oak-aged wine, or walnuts ([86]; Table 2). Intestinal bacterial strains that are involved in the generation of urolithins have not been specified yet. Binding to the ER has been observed for urolithins. Based on reported data [87], the relative binding affinities of urolithin A towards ERα / ERβ were RBA= 1.5 and RBA= 0.6, respectively, of the binding affinity of estradiol (RBA= 100). Thus, urolithin A showed a moderate preference for binding to the ERα. Urolithin B displayed a significantly lower affinity to both ER subtypes. Urolithin A exhibited a weak estrogenic and slightly higher antiesterogenic activity in cell culture assays [87]. Consistent with these results antiproliferative effects on prostate cancer cells and aromatase inhibi-

tion have been described for urolithin A [88, 89]. Besides hormonal activities anti-inflammatory and antioxidant effects of urolithins have been extensively investigated *in vitro* [85, 90-92] and *in vivo* [93]. In addition, inhibition of Wnt signaling which plays a key role in colon carcinogenesis, has been found for urolithin A [94].

A microbial metabolite derived from dietary flavonoids such as quercetin or rutin (quercetin-3-O-rutinoside) is 3,4-dihydroxyphenylacetic acid (DOPAC or DHPAA; Table 2). Quercetin is found in e.g. apples and onions; rutin is present in various fruits and vegetables [22]. Miscellaneous intestinal bacteria species have been described to be involved in the flavonoid metabolism to generate phenol derivatives [95]. Traces of 3,4-dihydroxyphenylacetic acid are furthermore present in olives [22]. Notably, 3,4-dihydroxyphenylacetic acid is also the major metabolite of dopamine in the central nervous system [96]. The production and presence of the compound in humans undoubtedly impedes any appraisal of the contribution of the gut microbial metabolism to plasma concentrations and effects of 3,4-dihydroxyphenyl acetic acid. Observed basal concentrations in human plasma varied. For healthy adults 3,4-dihydroxyphenylacetic acid values around 1 ng/mL (≈ 6 nmol/L) [97] or 28 ng/mL (≈ 166 nmol/L) [98] were reported. This is further complicated by the observation of a circadian rhythm of circulating 3,4-dihydroxyphenylacetic acid [99]. Although 3,4-dihydroxyphenylacetic acid was one of the major phenolic acids produced in an *in vitro* model of the colon [100] it is not clear how much is actually absorbed into systemic circulation *in vivo*. After supplementation of volunteers with cocoa powder no significant increase of 3,4-dihydroxyphenylacetic acid (100 nmol/L to 110 nmol/L) was observed in plasma [101]. Though cocoa is not particularly rich in quercetin, the intestinal microbial catabolism of procyanidins or (epi-)catechin has been

described as another potential source of 3,4-dihydroxyphenylacetic acid [25]. The biological *in vitro* activities of 3,4-dihydroxyphenylacetic acid span anti-inflammatory, cardioprotective, and anticancer effects (Table 2). Reported effects on cells serving as model of neurons have been ambiguous. Protection of PC12 cells against oxidative stress was seen at high concentrations of 3,4-dihydroxyphenylacetic acid (25 μM) [102] while others observed induction of mitochondrial dysfunction and apoptosis in these cells at concentrations higher than 0.2 μM [103-105]. The latter was explained by a reaction of 3,4-dihydroxyphenylacetic acid with nitric oxide in mitochondria producing compounds that inhibit oxygen uptake and trigger cell death. The intraperitoneal administration of 3,4-dihydroxyphenylacetic acid exerted anxiolytic effects in mice [106].

Phenylvalerolactones such as 5-(3',4'-dihydroxyphenyl)-γ-valerolactone and 5-(3',4',5'-trihydroxyphenyl)-γ-valerolactone are (epi-)catechin metabolites derived from procyanidins [25] which are found in e.g. pine bark extract, green tea or cocoa (Table 2). Intestinal bacterial strains that are involved in the generation of phenylvalerolactones have not been specified yet, but the formation of these compounds is known to involve multiple steps such as ring opening and ring fission reactions [25]. So far, *in vitro* activities of 5-(3',4'-dihydroxy phenyl)-γ-valerolactone and 5-(3',4',5'-trihydroxy phenyl)-γ-valerolactone include various anti-inflammatory and antiproliferative effects while *in vivo* experiments with the isolated compounds have not been reported yet (Table 2).

ACTIVITIES OF COMPLEX CARBOHYDRATE-DERIVED MICROBIAL METABOLITES

Short-chain fatty acids (SCFA), primary butyrate, propionate and acetate, can be produced by various gut microbial species from dietary complex carbohydrates such as inulin,

resistant starches or dietary fiber (Table 2). SCFA are also present in fermented food products. Besides the intestinal bacterial production, SCFA can originate from endogenous metabolism of fat, carbohydrates and amino acids [107]. This again raises the question of the contribution of the gut microbial metabolism to plasma concentrations measured in humans. A current metabolomic analysis in rats suggested a major role of the gut bacteria in SCFA production [8]. The SCFA concentrations determined in human fecal samples revealed the order acetate > propionate > butyrate [108]. The same order was reported for SCFA plasma concentrations in a human study [107]. SCFA have numerous intestinal and extraintestinal effects ([108-110]; Table 2). Local effects include influence on electrolyte and water absorption [111], colonic blood flow and trophic effects on the healthy intestinal mucosa while suppressing tumorigenic processes [112, 113]. Butyrate is the main energy source of enterocytes [114]. Furthermore, SCFA decrease the colonic pH. This acidification reduces the number of potentially pathogenic bacteria, decreases the solubility of bile salts and ammonia absorption [110]. The potential roles discussed for e.g. butyrate in intestinal and extraintestinal disorders are extensive and cannot be comprehensively reviewed here. Cellular mechanisms identified behind the variety of biological activities include inhibition of histone deacetylase (HDAC) and activation of free fatty acid (FFA) receptors which belong to the family of G-protein coupled receptors (GPCR) [29, 30]. Histone acetylation is involved in epigenetic regulation of gene expression and HDAC inhibitors are considered as future therapeutic options for a range of diseases. Although SCFA are rather weak HDAC inhibitors effective concentrations in the millimolar range might be generated in the gut lumen [108, 115]. Butyrate was found to inhibit HDAC more potently than propionate [116]. SCFA activate FFA2 (GPCR43) and FFA3 receptors

(GPCR41) which are targets of interest in inflammatory and metabolic diseases [117]. The potency of the SCFA was different for the individual receptors with acetate activating preferentially FFA2 / GPCR43 and butyrate preferentially FFA3 / GPCR41 [118, 119]. At both receptors propionate displayed the highest potency. Again, the affinities of SCFA for these receptors appear to be weak and it needs to be clarified how they contribute to the observed effects and whether additional mechanisms might play a role [120]. The effects of single SCFA have been investigated in rodents. Besides influences on gastrointestinal and metabolic functions [120-122] stimulation of neurogenesis was observed [123]. In humans, various intestinal effects of butyrate were described (Table 2) as well as induction of fetal globin expression which is relevant in the context of sickle cell disease.

ACTIVITIES OF PROTEIN-DERIVED MICROBIAL METABOLITES

Indole-3-propionic acid (Table 2) is a tryptophan metabolite produced by human intestinal microbia, e.g. by Clostridium sporogenses [20]. The compound is also present in traces in some food sources, e.g. in bananas, where it functions as a plant hormone [124]. A recent metabolomic analysis revealed that the production of indole-3-propionic acid was completely dependent on the gut microflora [20]. Elucidation of the biological activity uncovered neuroprotective properties of this compound in cells exposed to Alzheimer β-amyloid [34] along with antioxidant efficacy [125, 126]. This *in vitro* observation is consistent with reported protection of gerbils from ischemia-induced neuronal damage [35]. Apparently, at present indole-3-propionic acid is under investigation in humans as a potential therapeutic option for Alzheimer's disease [127, 170].

NUTRIKINETICS OF GUT MICROBIAL METABOLITES

The essential requirement for any of the discussed *in vivo* effects elicited by gut microbial metabolites is a sufficient concentration in the target tissue or cells. With reference to the long established expression "pharmacokinetics" the term "nutrikinetics" has been proposed [9, 128]. Nutrikinetics describe in a quantitative way how nutrients and bioactive food components are absorbed, distributed, metabolized and eliminated from the human superorganism, which is the communal group of human and microbial cells.

METABOLISM I: FORMATION BY GUT BACTERIA

The formation and concentration of the earlier discussed bioactive gut microbial metabolites primarily depend on the presence of sufficient precursor molecules in the relevant dietary sources, on the presence of microbial species that are capable of the respective biotransformation reactions (Table 2; [129]), and on the exposure time of the microbiota with the food components. Of these factors, the most critical aspect appears to be the presence of relevant bacterial colonies in the host's gut. An indication for this is the high variability of microbial metabolite production among different subjects who are exposed to the same dietary components. In a previous extensive study fecal samples of 100 women were incubated with an isoflavone extract from soy germs, a lignan extract from flax and isoxanthohumol to determine the spectrum of microbial metabolites [58]. The observed interindividual variability was high and the study participants were characterized as high, moderate and low metabolite producers of equol, O-desmethylangolensin, enterolactone, enterodiol and 8-prenylnaringenin.

A high interindividual variability of equol production was reported before [130]. About 30–50 % of the adult population do not excrete equol in urine when challenged daily with soy foods [131] and that rate of equol producers is lower in Western countries (25–30 %) compared to an Asian population (50–60 %). Vegetarians were more frequently found to be equol producers [132] while dietary fat intake decreased equol production [133]. A negative association was observed for the production of equol and O-desmethylangolensin which can be explained by the fact that both compounds are daidzein metabolites [58]. Interestingly, equol production was correlated with the presence of sulfate-reducing bacteria whereas O-desmethylangolensin generation was related to the company of methane-producing bacteria.

In a small intervention study with 24 participants the interindividual variation in urine enterolactone excretion was described to be less pronounced compared to equol [133]. A positive correlation was observed between enterolactone and enterodiol production in fecal samples [58] which is congruous with the finding that enterodiol is an intermediate in enterolactone formation [134, 135]. A high abundance of Clostridium coccoides / Eubacterium rectale bacteria was discussed to have a negative influence on the enterodiol production [58].

In agreement with other microbial metabolites, interindividual variations in the production of 8-prenylnaringenin production were described [74, 136]. The microbiota of more than 60 % of 100 participating women converted less than 20 % of isoxanthohumol to 8-prenylnaringenin [58]. Interindividual differences were also reported for the production ellagtannin metabolites [137-139], valerolactones [140] and SCFA [141].
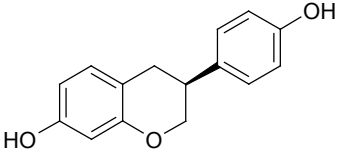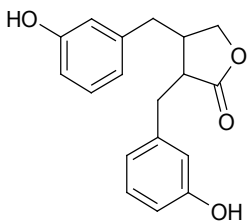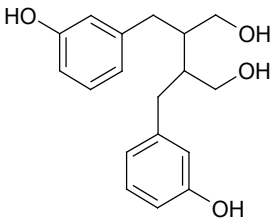
ABSORPTION

A kinetic parameter describing the rate of absorption is the time of maximal plasma concentration, t_{max}. As to be expected for compounds originating from gut bacterial metabolism the t_{max} is typically delayed after
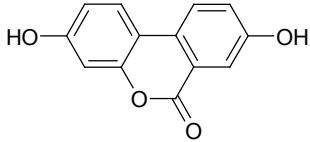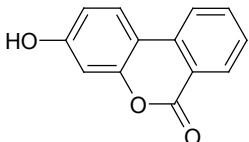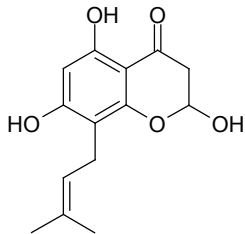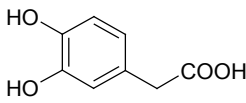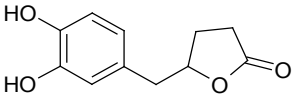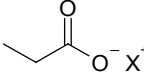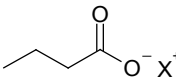
administration of the dietary source of the metabolites (Table 3). This delayed t_{max} can be regarded as the combined result of the longer passage time of the precursor compounds to the colon as compared to the small intestine and the time that the microbiota require to produce the respective metabolite. After ingestion of dietary equol sources t_{max} values of equol in human plasma ranged from 9-24 hours while maximal plasma concentrations were reached significantly faster (1-3 hours) after administration of equol. The t_{max} of 15 hours for enterodiol and t_{max} of 20 hours for enterolactone after ingestion of secoisolariciresinol diglucoside is again consistent with the notion that enterodiol is an intermediate of enterolactone formation [134, 135]. 5-(3',4'-Dihydroxyphenyl) Valerolactone and 5-(3',4',5'-trihydroxyphenyl) valerolactone, which are generated from (epi-)catechin by multiple reaction steps involving ring opening and ring fusion reactions [25], display delayed t_{max} values of up to 12 h. Considerably faster was the formation of SCFA from inulin with t_{max} observed after about 5 hours.
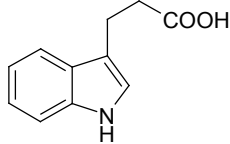
Table 3: Structural formulas and time of maximal plasma or serum concentrations (t_{max}; determined in humans).

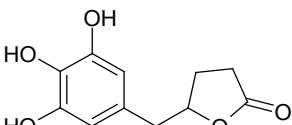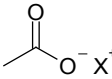| Microbiota metabolite	Structural formula	Human plasma / serum t_{max} after p.o. ingestion of [source]	Reference
S-(-)-Equol		24 h [daidzein] 12 h [daidzein-7-O-glucoside] 9-12 h [baked soybean powder] 1.5-3 h [equol] 1 h [equol]	[215] [216] [144, 217]
Enterolactone		20 h [secoisolariciresinol diglucoside]	[62]
Enterodiol		15 h [secoisolariciresinol diglucoside]	

Microbiota metabolite	Structural formula	Human plasma / serum t_{max} after p.o. ingestion of [source]	Reference
Urolithin A		Detected after 8 and 24 h, t_{max} not determined [pomegranate juice]	[139, 218]
Urolithin B			
8-Prenynaringenin		1-1.5 h [8-prenynaringenin]	[80]
3,4-Dihydroxyphenyl acetic acid			
5-(3',4'-Dihydroxyphenyl)-γ-valerolactone		5-12 h [green tea] 10 h [USP pine bark extract]	[157, 219]
5-(3',4',5'-Trihydroxyphenyl)-γ-valerolactone		5-12 h [green tea]	[219]
Acetate		4.5 h [inulin]	[220]
Propionate		5 h [inulin]	[220]
Butyrate		5 h [inulin] 0.75 h* [sodium butyrate] *measured as $^{13}CO_2$ excretion in breath test	[220] [161]

Microbiota metabolite	Structural formula	Human plasma / serum t_{max} after p.o. ingestion of [source]	Reference
Indole-3-propionic acid			

Besides the rate of absorption the extent of absorption is another key parameter to describe the absolute bioavailability of compounds. However, in case of metabolites generated in the gut by microbiota the absolute bioavailability would be intricate to determine. The pure metabolite would have to be administered into the colon and the resulting blood concentrations would have to be compared to blood levels obtained after intervenous injection. A peroral instead of a colonic administration could be misleading in this case because the absorptive surface area of the small intestine is significantly larger compared to large intestine. Besides simple diffusion processes specialized ways of absorption may play a role such as anion exchange for SCFA [109]. Consequently, there is little information available on the precise extent of absorption of bacterial metabolites from the cecum and colon, though it can be assumed that they are taken up well in healthy humans. The absorption of SCFA from the cecum / colon was described as an efficient process [110, 142, 143]. Within 30 minutes more than 30 % of a combined dose of butyrate, propionate and acetate were absorbed from the human rectum and distal colon [143].

In contrast, it is easier to estimate the extent of absorption if a pure metabolite is administered orally. After oral administration of equol to human volunteers an almost complete absorption was reported [144, 145]. The absorption of 8-prenylnaringenin appeared to be not complete with about 27-31 % of a single peroral dose being excreted via the feces [80].

Interestingly, some gut microbial metabolites reveal two t_{max} peaks in their kinetic profile which is suggestive for an enterohepatic circulation of the compound. This has been observed for enterolactone [62] and 8-prenylnaringenin [80]. Indications for an enterohepatic circulation of equol were less pronounced [144].

DISTRIBUTION

Typical kinetic parameters for the characterization of a compound's distribution *in vivo* are the plasma protein binding and the apparent volume of distribution (Vd) which describes the extent of binding to tissues and organs. A high volume of distribution is typically indicative for a prolonged presence of the compound in the organism. While these parameters are routinely determined for drugs very few data have been published for microbial metabolites.

Moderate to low plasma protein binding has been determined for equol ($\approx$ 50 %) [146] and 5-(3',4'-dihydroxyphenyl)-γ-valerolactone ($\approx$ 35 %) [147]. Urolithin A showed no binding to human serum albumin (HSA) binding sites I and II [148]. In contrast, a very high binding of > 90 % to HSA was reported for indole-3-propionic acid [149].

Though the dimension of the volume of distribution Vd in humans has not been reported for any of the microbial metabolites discussed here, some information is available

about the tissue disposition of some of the compounds. After administration of pomegranate extract or urolithin A to mice an accumulation of the metabolite and its conjugates was observed in prostate, colon, and intestinal tissues in relation to other tissues [88]. In men from China (n= 20), Portugal (n= 22) and UK (n= 17), consistently higher mean concentrations of equol and enterolactone were measured in prostatic fluid as compared to plasma [59]. Among those three groups, men from China had the highest concentrations of equol while men from Portugal exhibited the highest enterolactone levels. In another study Asian men (n= 10) without prostate disease revealed no clearly higher equol concentrations in prostate tissue as compared to plasma while enterolactone levels in prostate tissue exceeded the respective plasma concentrations [60]. After ingestion of a soy-based isoflavone preparation a dose-dependent accumulation of equol was also reported to occur in the breast tissue of women (n= 2) as compared to the plasma concentrations [150].

Interestingly, for various gut microbial metabolites central nervous effects have been observed (Table 2). This implicates that the respective compound was able to cross the blood brain barrier (BBB). The BBB consists of specialized microvascular endothelial cells which strictly limit the access of compounds to the brain [151]. Equol has been detected in rats' brains at concentrations of 126 ng/g [152] which could be related to the observed amelioration of depressive-related behavior in other rodents after exposure to equol [153]. The fact that 8-prenylnaringenin decreased serum concentrations of luteinizing hormone (LH) in postmenopausal women [80] is also suggestive for a passage of the compound through the BBB and a subsequent modulation of the central endocrine regulatory circuit. Likewise, the protection of gerbils by indole-3-propionic acid from ischemia-induced neuronal damage [53] indicates crossing of the BBB.

METABOLISM II: HUMAN METABOLIC INFLUENCES

Gut microbial metabolites derived from polyphenols are typically subjected to conjugation reactions by intestinal or hepatic enzymes to form glucuronated, methylated or sulfated derivatives. In most cases it has not been reported to which degree the respective microbial metabolites undergo conjugation reactions. S-(-)-equol predominately forms glucuronic acid conjugates and to a minor extent sulfuric acid conjugates [38]. Among the lignan metabolites in the urine of human subjects glucuronides prevailed (> 90 %), followed by mono- and disulfates, while unconjugated enterolactone and enterodiol were rare (< 0.1 – 0.9 %) [154]. Glucuronyl and sulfate conjugates of urolithins were the main metabolites detected in human plasma and urine [155]. After administration of 8-prenylnaringenin a higher conjugated than unconjugated percentage of the compound was detected in urine and plasma samples [80]. Glucuronyl and sulfate conjugates of the catechin/epicatechin metabolite 5-(3',4'-dihydroxyphenyl)-γ-valerolactone were discovered in human urine samples [101,156]. No unconjugated 5-(3',4'-dihydroxyphenyl)-γ-valerolactone was identified in human plasma samples [157].

For SCFA three metabolic sites have been described after absorption from the gut [110]. Butyrate is mainly used as energy source of the gut epithelial cells. Colonocytes readily oxidize butyrate to generate acetoacetate and 3-hydroxybutyrate [158]. Propionate, residual butyrate and the major fraction of acetate are metabolized in the liver. Propionate can be utilized for hepatic gluconeogenesis [110, 159]. The residual acetate is metabolized in muscle cells which generate energy by oxidation of this compound.

ELIMINATION

After absorption, the microbial metabolites derived form polyphenols appear to be primarily subjected to renal excretion in their conjugated or unconjugated form. Another way of elimination from the systemic circulation is the biliary secretion which has been observed for enterolactone [62] and 8-prenylnaringenin [80]. After secretion into the gut lumen the compound might be reabsorbed or excreted with the feces. Again, sparse information is available as to which percentage the compound undergoes renal and/or biliary elimination. After oral administration of equol to female volunteers more than 80 % of the dose was excreted in urine [145]. Of single doses of 8-prenylnaringenin about 30 % were recovered within 48 h. The largest dose fraction (22-24 %) was excreted in feces, a smaller fraction (5-6 %) in urine [80]. In contrast to polyphenol metabolites SCFA appear to be completely utilized as energy source.

Kinetic factors characterizing a compound's elimination are the clearance (Cl) and elimination rate constant (ke). The elimination half-live (t½) can be derived from these parameters and it has been described for some of the gut bacterial metabolites in humans. The t½ of equol was determined to be approximately 8 hours [145]. The mean t½ of the lignan metabolites was highly different with 4 hours for enterodiol and 13 hours for enterolactone. The mean residence time (MRT) which describes the average total time substances reside in the body was 21 hours for enterodiol and 36 hours for enterolactone [62]. The longer presence of enterolactone in the body is probably due to the distribution of the compound into tissues and organs besides the fact that it undergoes enterohepatic circulation. Urolithin A has been detected up to 48 hours in urine [139] which also suggests a t½ within a similar range as equol. Although no t½ has been calculated for 8-prenyl-naringenin, the MRT was found to be 9-12 hours [80]. SCFA are rapidly cleared from plasma [160]. After peroral administration of 13C labelled sodium butyrate to human volunteers and subsequent monitoring of exhaled $13CO_2$ the t½ appeared to be less than one hour [161].

MEDICINAL USE OF MICROBIAL METABOLITES

The potentially beneficial effects of selected microbial metabolites and the fact that the formation of those metabolites reveals substantial inter-subject variability based to the composition of the individual microbiome has prompted clinical trials in which the metabolites were administered as single compounds to patients. Prerequisite for such an approach are suitable kinetic properties such as a sufficient stability and half-live of the metabolite.

In randomized, double-blind, controlled trials postmenopausal women (n= 93–134 [50, 51]) received doses of S-(-)equol between 2 mg [51] and 40 mg [53] per day for up to one year [51]. Various menopausal and mood-related symptoms such as depression, fatigue, decrease in bone mineral density, or hot flashes were shown to respond to the equol treatment [50, 51, 53, 54].

Postmenopausal women (n= 8) received 50-750 mg 8-prenylnaringenin in a randomized, double-blind, placebo-controlled pilot study to determine the kinetic profile, safety and endocrine effects [80]. All doses were well tolerated and the highest dose of 8-prenylnaringenin significantly reduced luteinizing hormone (LH) serum concentrations while the levels of follicle-stimulating hormone (FSH) were not significantly altered.

SCFA have attracted lots of attention due to their diverse effects and they have been tested in various clinical trials. In a randomized, single-blind, placebo-controlled study patients with ulcerative colitis (n= 10) received enemas with SCFA. The endoscopic score and degree of inflammation significant-

ly improved [162]. An accelerated healing process was observed in patients with radiation proctitis (n= 19) who received SCFA enemas in a randomized, double-blind, placebo-controlled trial [163]. In a randomized, double-blind, placebo-controlled pilot study patients with ulcerative colitis (n= 30) underwent treatment with oral sodium butyrate (4 g/day) plus oral mesalazine. A significant improvement versus baseline, but not compared to control treatment (mesalazine and placebo), was recorded [164]. In a subsequent multicentre study (n= 51) sodium butyrate was administered locally into the colon in combination with oral mesalazine. In that case the combined treatment with topical butyrate was found to be more effective than mesalazine alone [165]. Though moderate anti-inflammatory effects can be concluded from these studies it also becomes obvious that a major drawback is the fact that high doses of SCFA have to be delivered locally for the discussed medical indications. The fact that SCFA are rapidly cleared hampers their therapeutic utilization and prompted the development of sustained release dosage forms for e.g. butyrate [161] and of butyrate analogs with more favorable kinetic properties [160, 166]. Butyrate derivatives have been tested in studies with the aim of e.g. fetal globin-induction [160], treatment of cystic fibrosis [167], lung cancer [168] or malignant glioma [169].

The tryptophan metabolite indole-3-propionic acid has been suggested to be a potential treatment option for Alzheimer's disease [127]. Obviously, a clinical study (phase I b) is currently performed, but no results are available yet [170]. The compound has also been proposed as a treatment option with orphan drug status for Friedreich's ataxia which is a rare hereditary neurodegenerative disease [171].

OUTLOOK

Diverse nutrition-derived bioactive metabolites produced by gut microbiota have been identified and it can be expected that more of them will be discovered with the availability of new analytical screening and profiling approaches. Some dietary compounds undergo bioactivation by microbial metabolism which is reflected by a higher activity compared to their immediate precursor substance in various functional assays. These metabolites might contribute to the health of the host organism.

Many questions remain to be clarified. The metabolites' mechanism of action is not always fully uncovered and it is unknown whether the identified compounds are actually the active principles or whether they are further modified within the target cells yielding molecules with comparable or altered activity. Recently it was reported that e.g. epigallocatechin-3-gallate undergoes intracellular conjugation to cysteine and that the resulting compound retained biological activity [172]. Similar modifications could occur with the microbial metabolites. Furthermore, it needs to be investigated to which extent the gut microbiota metabolites contribute to human health and how the metabolite production differs in health and disease states.

There are many reasons to direct the attention to "gut health" [2,3,173]. Modification of the gut microflora by pre- or probiotic strategies [1,11,174] could offer new options for preventing or treating a variety of disease states and nutrition-derived microbial products might inspire future drug development [175].

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