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PLANT SECONDARY METABOLITES AND THEIR DERIVATIVES IN MICROBIOTA – CROSS-KINGDOM INTERACTIONS

MARGOT SCHULZ and PETER DÖRMANN

Institute of Molecular Physiology und Biotechnology of Plants (IMBIO),
University of Bonn, Bonn, Germany

SUMMARY

In this mini-review, we provide a short impression of a few of the plant secondary metabolites that emerged as root-microbiome modifying compounds. We focus on selected metabolite degradation pathways and derivatives occurring during catabolism since these compounds could be crucial for shaping the microbiota. We discuss similarities and differences between some of the known degradation pathways in animals and plants, and highlight cross-bioactivities of a few catabolites in the different kingdoms.

INTRODUCTION

During their evolution, land plants were always associated with microorganisms, i.e. the plant microbiota which, together with the host, is designated as the holobiont. The plant microbiota is composed of microbial communities inhabiting the root (rhizosphere, rhizoplane), the leaf (phyllosphere), or living within tissues as endophytes (endosphere), and of the communities associated with flowers, pollen, fruits and seeds. (*Berg* and *Raaijmakers*, 2018; *Droby* and *Wisniews,* 2018; *Durán* et al., 2018; *Manirajan* et al., 2018; *Shade* et al., 2013; *Compant* et al., 2019*).* The core microbiota represents microbes characteristically associated with a plant species, subspecies or even a cultivar (*Adam* et al., 2018; *Chaluvadi* and *Bennetzen*, 2018). In contrast, the variable part of the microbiota is established by collecting organisms from soil, splash water, air, and it depends on exuded compounds, transfer by vector organisms, for instance insects, and environmental conditions. Plant age and developmental stage influence species diversity of the microbiota (*Aleti* et al., 2017). Domestication of plants seems to alter root specific microbial communities. Indeed, wild plant species have a different microbiota with higher species diversity than domesticated plants (*Wagner* et al., 2016; *Pérez-Jaramillo* et al., 2018). Plants evolutionary divergence had a strong influence on the microbiota composition, with greater effects on the endosphere (*Fitzpatrick* et al., 2018). Recent insights in the interactions between plants and microorganisms unclose new views of co-evolution and ecology with regard to the organisms' interaction and communication dynamics. The coexistence is thought to influence and to modulate all levels of interaction including the genetics of the partners, to strengthen plant health, modulate nitrogen fixation and facilitate mineral uptake. It furthermore triggers adaption to environmental conditions by modifying metabolism, physiology, growth and reproduction.

PLANTS SECONDARY METABOLITES

The rhizosphere seems to be especially suitable for accelerated (horizontal) gene transfer, driving microbial and plant evolution. As hypothesized by *Emiliani* et al., (2009), early during conquering of land, five hundred million years ago, horizontal gene transfer of the phenylalanine ammonia lyase (PAL) gene during symbiosis with soil microorganisms enabled plants to produce phenylpropanoids and lignin, both essential to withstand the altered environmental conditions outside the aquatic habitat. According to *de Vries* et al. (2017), genes for the phenylpropanoid synthesis and lignin precursors were already present in streptophyte algae, where land plant are assumed to have evolved from. However, convergent evolution allows the generation of new enzymes from a shared pool of related enzymes with similar but not identical functions. Anyway, plants acquired new secondary metabolites, which enriched the already existing core set of secondary compounds, such as terpenoids. Additional pathways were established resulting in an enormous manifoldness of secondary metabolites, among them new terpenoids, alkaloids, heterocyclic compounds, simple phenolics, flavonoids, stilbenes, betalains and others. Many of them fulfil diverse functions including communication in new ecological cross-kingdom interactions with animals, plants, fungi, bacteria, other microorganisms, and also with other plants. Many of the compounds are highly toxic, others can be beneficial for the health and survival of target organisms, but effects can be reversed depending on the concentration, on accompanying reactants and on organisms that convert one compound to another with an altered bioactivity. Microorganisms themselves produce thousands of secondary products which can interact and influence the plant and plant secondary metabolite biosynthesis. This aspect however is not addressed further here. Just to mention one example, N-acyl-homoserine lactones, which are bacterial quorum sensing molecules, evoke multiple responses in plants, and often resistance responses are elicited (*Hartmann* et al., 2014).

Endophytes can alter the secondary metabolism of their plant host or establish alliances with the plant to complete the biosynthesis of secondary metabolites that finally accumulate in the plant. The biosynthesis of maytansine by *Maytenus serrata* and its endophytes presents an example for cross-species interaction in secondary metabolite production (*Kursari* et al., 2016). It is hypothesized that qualitative and quantitative variations of pharmaceutically important secondary metabolites of medicinal plants are strongly influenced by the microbiome (*Köberl* et al., 2013; *Schmidt* et al., 2014; *Huang* et al., 2018). The evolution of the chemical diversity of plant secondary metabolites is still in progress (*Moghe* and *Last*, 2015); thus, in evolutionary terms old molecules, to which pathogens might have adapted to, can turn again during co-evolution from an inactive to a bioactive compound by core structure modifications or substituent exchanges. A considerable number of the presently identified 300,000 secondary metabolites are formed by decorating the molecules' core structures with substituents such as sugars or position-specific functional groups that change the reactivity of the molecules dramatically, from almost inactive to highly bioactive compounds.

EXUDATION OF SECONDARY METABOLITES

Root exudation can release up to 20-30% of the carbon fixed by photosynthesis (*Haichar* et al., 2008; *Voges* et al., 2019). The root exudates, composed of primary and secondary metabolites, are essential for the establishment of plant-microbial interactions (*Philippot* et al., 2013; *Haichar* et al., 2014; *Sugiyama*, 2019; *Voges* et al., 2019). Transport proteins of the ABC type are presumed to be involved in secondary metabolite export (*Bertin* et al., 2003; *Yazaki*, 2005; *Sasse* et al., 2018). In contrast to primary metabolites and mucilage, which serve predominantly as nutrients for microorganisms, secondary metabolites are often times specific for certain plant species. Many exudates contain characteristic metabolites, which are found only in certain taxonomic groups of plants, e.g. in families, genera or single species, which can be regarded as a younger event during evolution. Other compounds are widely distributed, such as numerous simple phenolics and flavonoids. As shown by *Zwetsloot* et al. (2018), secondary metabolites can act as nutrients, toxins, interactors with membranes, inhibitors of functional proteins, chelating agents of metals and intercalators with nucleic acids, all depending on the chemical nature of the molecules. Secondary metabolites have therefore the higher potential to modulate microbial communities than any primary metabolite in a plant species dependent manner, especially when acting in concert. The composition of exuded secondary metabolites differs, depending on the developmental stage of the plant, age of the root, root zone, root hairs, abiotic and biotic stress conditions (*Bais* et al., 2006; *Weston* et al., 2012; *Selmar* and *Kleinwächter*, 2013; *Massalha* et al., 2017). In line with this scenario, drought stress alters the microbiota and profiles of secondary metabolite exudation. For instance, the root metabolome of *Quercus ilex* was found to be changed without considerable recovery under severe drought conditions (*Gargallo-Garriga* et al., 2018). The metabolome was then dominated by secondary metabolites, while after mild drought when recovery was possible, a shift to mainly primary metabolites in the exudate was observed. *Edwards* et al. (2018) assessed changes in context with the developmental stage of the plant and concluded that drought stress leads to an immature endosphere microbiota. A similar conclusion was drawn by *Xu* et al. (2018), who report a drought-dependent delay in the formation of the early microbiome of *Sorghum* roots. Drought-dependent shifts in the microbiome species composition favouring the relative abundance of the Actinobacteria together with host-specific changes seem to be a common feature among angiosperms (*Fitzpatrik* et al., 2018; *Naylor* and *Coleman-Derr*, 2018).

DEGRADATION AND DETOXIFICATION OF SECONDARY METABOLITES

Enormous amounts of secondary metabolites are released by living plants and by rotting of dead plant material. Therefore, the degradation of these compounds is important to avoid their accumulation in the environment in toxic concentrations and triggering long-lasting alterations of the soil microbiome. Presently, the effects of the products derived from the original

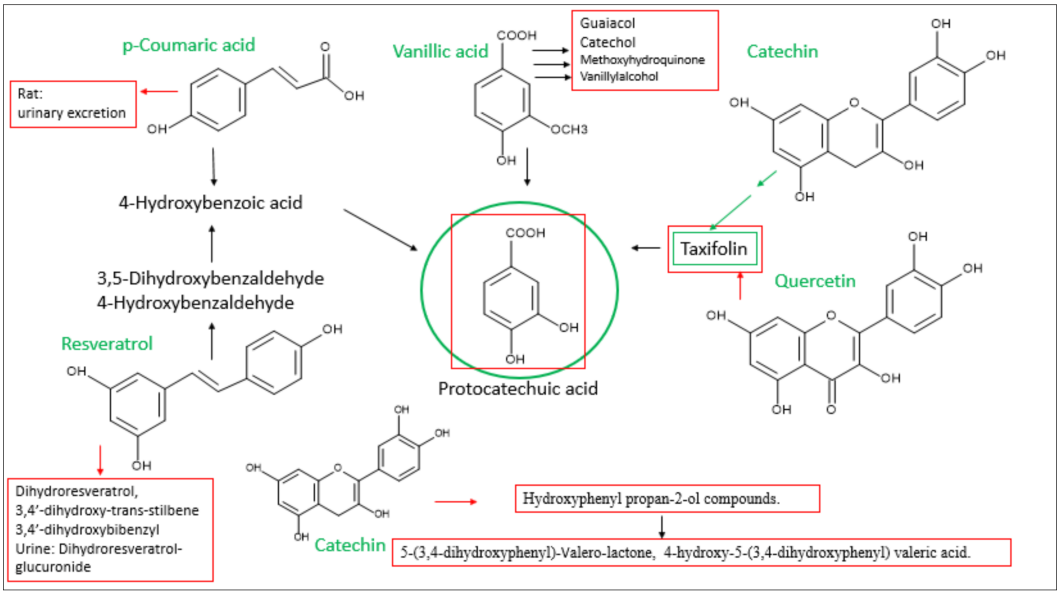

Figure 1: Protocatechuic acid is one of the pivotal catabolites occurring during the degradation of p-coumaric acid (by soil organisms and plant associated bacteria), of vanillic acid (soil bacteria, plant associated bacteria), of resveratrol (*Agrobacterium oleivorans* strain JS678 from peanut rhizosphere), of quercetin (soil bacteria, human gut bacteria) and of catechin (soil bacteria), (simplified scheme). Guaiacol is a catabolite of vanillic acid, formed in the desert locust gut by *Pantoea agglomerans.* Guaiacol is degraded via catechol. Red markers: original compounds found in animals, green markers: in plants.

secondary metabolites by degradation or conversion on plant metabolism and microbiota are poorly understood, although these molecules may have extraordinary properties and special, perhaps unexpected, biological activities. In animals for instance, isovanillic acid 3-*O*-sulfate, a product derived from cyanidin 3-*O*-glucoside degradation by the human gut microbiome, stimulates glucose uptake by muscle cells (*Houghton* et al., 2019). Short-lived, often highly reactive derivatives and catabolic intermediates may be the intrinsic key players, for instance in remodelling microbiota, influencing epigenetics and physiology in target organisms by eliciting signalling cascades that allow adaption to changed environments, or cause death of pro- and eukaryotes. The toxicity is always dose dependent. High concentrations can overexert the degradation and detoxification capacities of organisms. On the other hand, molecules can be per se toxic at very low concentrations by interfering with biomolecules, with signalling pathways, by altering gene expression or enzyme activities. The ability to detoxify and to degrade bioactive and inhibitory molecules is pivotal, since it decides on toxicity or non-toxicity for a given organism. Accumulation of secondary metabolites and relatively stable degradation intermediates in phytotoxic amounts in soil contribute to allelopathic interactions and soil sickness which reduces yields of subsequent crop cultures and soil fertility, sometimes for years.

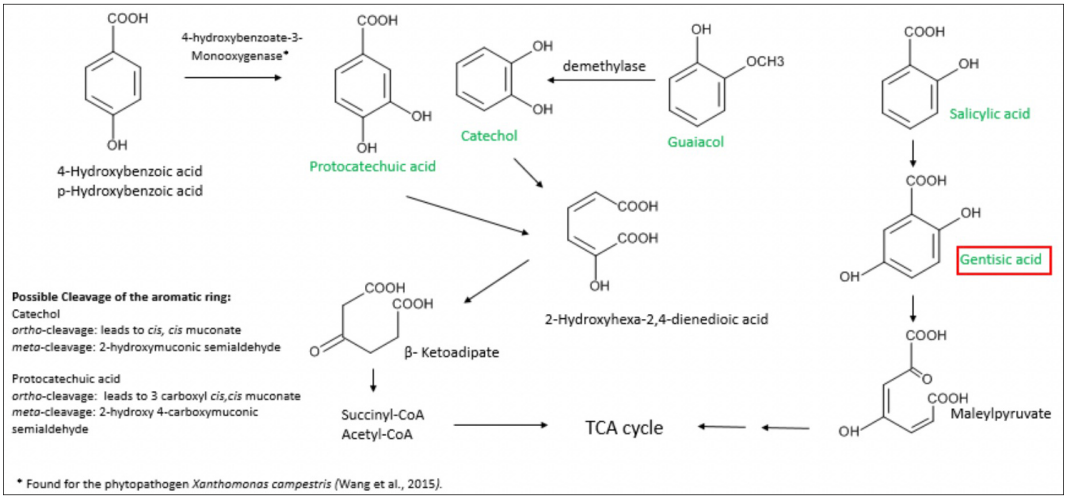

Figure 2: Degradation of the aromatic system of protocatechuic acid, catechol, guaiacol, salicylic acid, gentisic acid and p-hydroxybenzoic acid under aerobic conditions (simplified scheme). *Ortho*-cleavage: aromatic ring fission between carbon atoms with OH substituents; *meta*-cleavage: aromatic ring fission between a carbon atom with OH substituent and unsubstituted carbon-atom. Red markers: Intermediate compounds found in animals, green markers: in plants.

PLANT SECONDARY METABOLITES AS MODIFIERS OF THE MICROBIOTA

Increasing evidence suggests that plant secondary metabolites remodel and shape the species diversity and abundance of the microbiome in favour of microorganisms with beneficial functions for the plant. On the other hand, secondary metabolites released from the plant can act as allelochemicals. By reducing or shifting the microbial species diversity in soil and on root surfaces of neighbouring plants, they influence the microbiota of competitive individuals negatively. Thus, secondary metabolites can modify microbial community structure with different consequences for plants, as exemplified by the following.

p-Coumaric acid

p-Coumaric acid is a constituent in exudates of many species (Figure 1). In higher concentrations, p-coumaric acid is an allelochemical and harmful to the microbiota, for instance of cucumber. It also interferes with the lignin synthesis leading to cell wall stiffening, due to premature lignification (*Lima* et al., 2013; *Zhou* et al., 2018). Both effects result in a reduced growth of the plants. This compound has a negative effect on bacterial community composition of cucumber but promotes the fungal diversity, including phytopathogenic *Fusarium* species. The study of *Zhou* et al. (2018) shows that fungal species able to degrade phenolic compounds have an advantage. In contrast, bacteria with plant growth promoting and pathogen-antagonistic properties were found to be suppressed by p-coumaric acid. Several Gram-positive bacteria (*Bacillus subtilis, Bacillus pumilus*, *Pediococcus pentosaceus*, *Lactobacillus plantarum),* (*Licandro-Seraut* et al., 2013 and references therein) are able to convert p-coumaric acid and other phenolic acids into vinyl phenol derivatives. 4-Vinylphenol derived from

p-coumaric acid showed a stronger inhibitory effect to several *Erwinia*, *Pseudomonas*, and *Enterobacter* species than the parent compound. *Acinetobacter calcoaceticus* strain DSM 586 degrades p-coumaric acid to protocatechuic acid via 4-hydroxybenzoic acid. Following *Egland* et al. (1996), 4-hydroxybenzoate is further degraded to CO_2 by enzymes encoded by a cluster of 24 genes. In bacteria, genes for the *meta*- or *ortho*-pathways for simple phenolics degradation are often clustered into operons (*Suenaga* et al., 2009; see Figure 2). In several bacteria, a gene cluster is responsible for the degradation of protocatechuic acid via the β-ketoadipate pathway, for instance in *Streptomyces* sp. strain 2065; *Acinetobacter* sp. strain ADP1 or in *Agrobacterium tumefaciens* (*Iwagami* et al., 2000). As shown in Figure 1, many aromatic secondary metabolites are degraded via protocatechuic acid. In animals, p-coumaric acid and the precursor ferulic acid are absorbed from the stomach and intestine (*Alam* et al., 2016). Free p-coumaric acid, and especially the conjugated forms, have diverse beneficial effects (*Pei* et al., 2015). Since p-coumaric acid was found in high amounts in urine of rats fed with p-coumaric acid, *Garrait* et al. (2006) hypothesized a low metabolization of the compound.

Vanillic acid

Vanillic acid is a compound derived from the bacterial degradation of exuded ferulic acid, produced via 4-hydroxy-3-methoxyphenyl-hydroxy-propionic acid and vanillin. Vanillic acid alters the cucumber rhizosphere microbial communities and inhibits the growth of the seedlings. 0.2 μmol g^{-1} soil vanillic acid decreased the absolute abundance of *Bacillus* and *Pseudomonas* species, but increased the relative abundances of *Arenimonas, Gemmatimonas, Haliangium, Opitutus, Pseudolabrys, Steroidobacter* and *Rhodanobacter* species, while *Nitrospira spec*. was reduced (*Zhou* and *Wu*, 2018). The authors assumed an increase of species with denitrification capabilities and a decrease of nitrifying bacteria; thus, the nitrogen supply of the plant might be negatively affected. Vanillic acid can be transformed into protocatechuic acid by *O*-methyltransferase which is expressed, for instance, in strains of *Agrobacterium fabrum* (*Campillo* et al., 2014). The basidiomycete *Sporotrichum pulverulentum* decarboxylates vanillic acid to methoxy hydroquinone and reduces vanillin to vanillyl alcohol (*Ander* et al., 1980). When vanillic acid is non-oxidatively decarboxylated, guaiacol is produced. The vanillate decarboxylase enzymatic complex is obviously frequent in bacteria and yeasts, for example in *Bacillus megaterium*, *Streptomyces* strains, *Rhodotorula rubra*, and in *Nocardia* and *Streptomyces* species (*Álvarez-Rodríguez* et al., 2003). Thus, the different degradation pathways for vanillic acid result in a number of bioactive intermediates, such as guaiacol, catechol, protocatechuic acid and vanillin. Thus, protocatechuic acid, presents a catabolite of many secondary metabolites: Flavonoids, p-coumaric acid, resveratrol, vanillic acid and many others. The compound has a very high pharmacological potential (*Kakkar* and *Bais,* 2014).

The microbial degradation of plant derived phenolics with phytotoxic properties have been addressed by *Blum* and *co-workers* in the 1990ies (*Blum*, 1998; *Blum* et al., 2000). They found a reduction of the growth inhibitory effect of phenolic acid mixtures on cucumber seedlings by bacteria isolated from the rhizosphere and bulk soil. The microorganisms produced benzoic acids such as vanillic acid and

p-hydroxybenzoic acid from cinnamic acids, which were subsequently metabolized. Microbial pathways to cleave aromatic compounds are known from simple phenolics and flavonoid degradation pathways (Figure 2).

In mammalian species, vanillic acid seems to have beneficial effects due to its anti-inflammatory properties (*Calixto-Campos* et al., 2015). Studies with isolated rat hearts led to the assumption that vanillic acid may have a cardioprotective effect (*Radmanesh* et al., 2017). *In vitro* experiments with human cell lines point to antimicrobial, anti-inflammatory, anticancer, and liver-protective effects of vanillic acid (*Gong* et al., 2019). One of the catabolites, guaiacol, promotes the aggregation of the desert locust *Schistocerca gregaria*. *Pantoea agglomerans,* a member of the locust gut microbiota, is assumed to be mainly responsible for guaiacol production (*Dillon* et al., 2000). Guaiacol can be transformed into catechol and further degraded to compounds able to enter the TCA cycle.

Salicylic acid

Salicylic acid, commonly found in plants, has functions during the entire life cycle of plants, during seed germination, growth and development, flowering and senescence. Often, salicylate is stored in the form of a precursor, such as salicin in the bark of willow trees (*Salix* species). Salicylic acid (SA) is released into the soil by root exudation and by rotting plant material. In high concentrations, salicylic acid acts as an allelochemical (*Manthe* et al., 1992). In the plant, SA can function as a phytohormone involved in abiotic stress responses. It serves as a signal in local and nonspecific systemic defence against pathogens (*Rivas-San Vicente* and *Plasencia*, 2011). *Lebeis* et al. (2015) described the impact of SA on the species composition of the root microbiota, favouring bacterial strains able to use of SA either as a growth signal or as a carbon source. Interestingly, certain microorganisms of the root microbiota prime the induced systemic resistance in leaves (*Pieterse* et al., 2014). Most of the Gram-negative bacteria, such as *Burkholderia* species, can degrade salicylic acid (*Chowdhury* et al., 2014), (Figure 2). Several plant pathogens have developed methods to eliminate SA signalling in plant defence responses. One strategy is the degradation of SA by salicylate hydrogenase yielding catechol as a catabolic intermediate, or by the Nag pathway via gentisic acid (*Chowdhury* et al., 2014; *Lowe-Power* et al., 2016; *Qi* et al., 2018).

The pharmaceutical effects of salicylic acid and derivatives in animals are well known and are not discussed here. Surprisingly, the effects of acetylsalicylate (aspirin) and salicylic acid on human gut microorganisms are almost completely unknown, except for microbial transformation of aspirin to salicylic acid. In 2018, a clinical trial was started to elucidate effects of aspirin on the human gut microbiota composition and metabolome (ClinicalTrials.gov identifier [NCT number]: NCT03450317). Salicylic acid consumption leads to a number of detoxification products which are excreted. In human urine, salicylurate, glucuronide conjugates and gentisic acid have been identified (*Cham* et al., 1980). Gentisic acid is a bioactive intermediate with anti-inflammatory, antirheumatic and antioxidant properties.

Trans-resveratrol

Trans-resveratrol, the aglycon of *trans*-piceid, is another phytoalexin, which is synthesized by a small number of plant species, for instance, peanut. The active compound is released, similar to all

phytoalexins, only upon severe stress exposure or pathogenic attack. The compound acts anti-pathogenic, possesses antimicrobial activity and is also an allelochemical. The general effects on the rhizobiome are not yet known, but resveratrol might be a good candidate for modulating microbiota, perhaps also indirectly. In wheat cultivars infected with *Blumeria graminis*, resveratrol stimulates the synthesis of phenolic compounds and the efficiency of photosynthesis (*Pociecha* et al., 2014). *Acinetobacter oleivorans* strain JS678, isolated from the peanut rhizosphere, is able to metabolize resveratrol completely via 4-hydroxybenzaldehyde and 3,5-dihydroxybenzaldehyde. Subsequent compounds of the catabolic sequence are 4-hydroxybenzoate and protocatechuic acid. The latter is cleaved by bacterial protochatechuate 3,4-dioxygenase resulting in 3-carboxy-*cis,cis*-muconate (*Kurt* et al., 2018), (Figure 1). The aldehyde intermediates did not only promote growth of strain JS678, but also the growth of all other strains isolated from the rhizosphere which were unable to perform the first degradation steps. In mammals, *trans*-resveratrol is well absorbed in the gut. Most of it is conjugated in the liver with glucuronic acid or sulfate, but the conversions are reversible. Resveratrol was found to modulate the gut microbiota of rats and humans. It might possess positive effects on metabolic syndrome and has many other beneficial effects on human health, but results of such studies are often contradictory (*Salehi* et al., 2018). Human gut bacteria convert resveratrol to dihydroresveratrol, 3,4'-dihydroxy-trans-stilbene and 3,4'-dihydroxybibenzyl (lunularin), but there are differences between individuals (*Chaplin* et al., 2018; *Pallau* et al., 2019). Dihydroresveratrol is also conjugated to glucuronic acid. Since the glucuronide is found in high amounts in urine, the compound seems not be metabolized further.

DEGRADATION OF FLAVONOIDS LEADS TO SIMPLE PHENOLIC INTERMEDIATES

Flavonoids have multiple functions in the rhizosphere and interact with microorganisms (*Hassan* and *Matthesius*, 2012) Flavonoids contribute to microbiota sculpting, also by their degradation products. Microorganisms of the human gut and bacteria isolated from rhizosphere and bulk soil can degrade flavonoids, but the catabolism can differ (Figure 1), and depends on aerobic or anaerobic conditions.

Rhododendron formosanum accumulates catechin in the leaves, which is released from leaf litter and enriched in the soil (*Wang et al*., 2013). In the rhizosphere, *Pseudomonas*, *Herbaspirillum*, and *Burkholderia* species were the dominant genera. *Pseudomonas* used catechin as a carbon source by conversion of (-)-catechin into protocatechuic acid followed by degradation into glycerol. Taxifolin was identified as a first intermediate, thus the introduction of a keto group in position 4 of the C-ring prior to C-ring cleavage is a prerequisite for subsequent catabolic steps. Although not further investigated, ketone formation is most likely catalysed by catechol oxygenase, the key enzyme enabling the β-ketoadipate pathway for catechin degradation. Catechol oxidase was identified in *Acinetobacter calcoaceticus* and in some fungi (*Arunachalam* et al., 2003). Protocatechuic acid is assumed to intensify the phytotoxic effect of catechin dramatically (*Wang*

et al., 2013). Catechin itself acts as a bacteriostatic compound (*Pollock* et al., 2011). In humans however, the compound has several positive properties, including cytoprotective effects, induction of detoxifying enzymes, improvement of cognitive dysfunctions and many others (*Kakkar* and *Bais*, 2014).

At present, it seems that gut microorganisms do not perform the β-ketoadipate pathway for catechin degradation. Instead, intestinal bacteria isolated from human (*Eggerthella lenta* rK3 and *Flavonifractor plautii* aK2) and rat (*Adlercreutzia equolifaciens* MT4s-5 and *Flavonifractor plautii* MT42) performed C-ring cleavage yielding (2R)-1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol. *Flavonifractor plautii* aK2 converts 1-(3,4-dihydroxyphenyl)-3-(2,4,6-trihydroxyphenyl) propan-2-ol subsequently to 5-(3,4-dihydroxyphenyl)-valerolactone and 4-hydroxy-5-(3,4-dihydroxyphenyl) valeric acid. The final degradation products of catechin are phenylpropionic acids, compounds with anti-inflammatory properties (*Kutschera* et al., 2011; *Takagaki* and *Nanjo*, 2016).

The flavanol quercetin is a lipophilic compound which is converted in the liver by *O*-methylation, glucuronidation, and sulphation, yielding quercetin-3-glucuronide, quercetin-3′-sulfate, and isorhamnetin-3-glucuronide (*Suganthy* et al., 2016). Quercetin-3-O-glucuronide and isorhamnetin-3-O-glucuronide (methylquercetin-3-O-glucuronide) are found in the brain, where the compounds are supposed to develop neuroprotective properties. Quercetin and also the conjugates can be attached to or immersed in the lipid bilayer of membranes, but depth of immersion depends highly on charge and hydrophilic substitutions (*Košinová* et al., 2012). The interaction alters fluidity and other properties of the membrane which is thought to be correlated with the radical scavenger function and anti-inflammatory effects of quercetin (*Tsuchiya*, 2015). In plants and microorganisms, membrane interactions of the aglycon are attributed to the antimicrobial and allelopathic effects resulting in membrane leakage, one of the most harmful injuries caused by allelochemicals (*Schulz* et al., 2013).

Many microorganisms are, however, able to degrade quercetin. A fungal pathway starts with C-ring cleavage by quercetin 2,3-dioxygenase, producing 2-protocatechoylphloroglucinol carboxylate. In the anaerobic degradation pathway as performed in the human gut by bacteria, for instance by *Eubacterium ramulus*, quercetin is reduced to taxifolin and then converted to alphitonin. Final products are 3,4-dihydroxyphenylacetic acid and phloroglucinol (*Braune* et al., 2001). 3,4-Dihydroxyphenylacetic acid is also a known metabolite of the neurotransmitter dopamine in animals. A number of soil bacteria degrade quercetin via taxifolin and protocatechuic acid, thus this pathway is widely distributed among bacteria (*Mansuroglu*, *Schütz* and *Schulz*, unpublished).

Terpenoids

In *Arabidopsis thaliana* roots, triterpenes, such as thalianin and arabidin, have an important function in shaping the root microbiome. Several isolated bacterial strains were able to convert these compounds and resulting metabolites have differential influences on the growth of the microorganisms (*Huang* et al., 2019). The authors assume a role of the triterpene biosynthetic network in enriching the rhizosphere especially with Proteobacteria species. *Chen* et al. (2019) report a sesterterpenoid-induced modulation of the root microbiota composition of *Arabidopsis thaliana,*

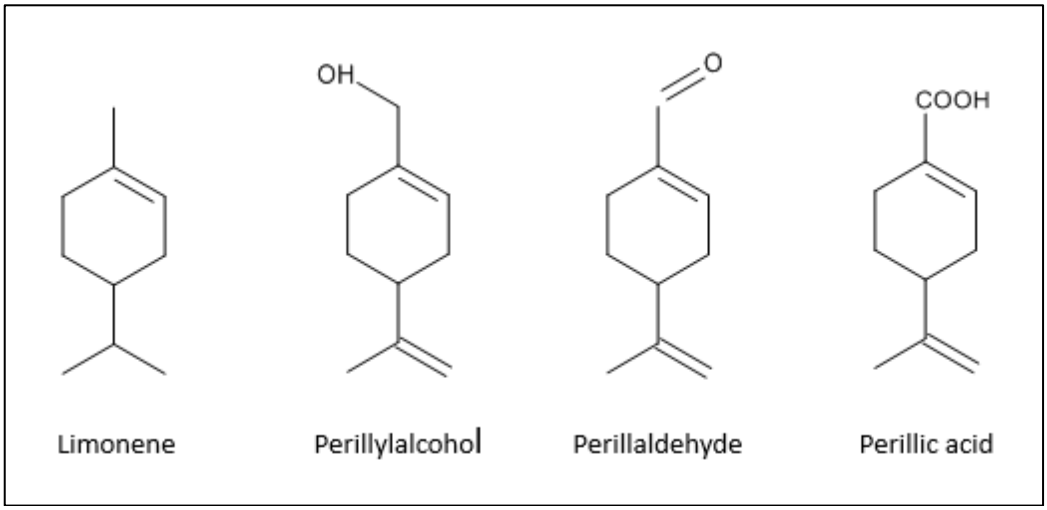

Figure 3: *Fusarium verticillioides, Pseudomonas putida* and some yeasts convert limonene into perillylalcohol, perillaldehyde and perillic acid. Perillic acid is also a secondary metabolite of many plants.

ascertained by the use of loss-of-function mutations in the sesterterpenoid biosynthesis genes. The recently duplicated prenyltransferase-terpene synthase (PT-TPS) gene cluster allows the biosynthesis of these, in evolutionary terms young compounds, due to the late introduction of the prenylation step.

Terpenoids can be converted by microorganisms, leading to hundreds of derivatives (*Marmulla* and *Harder*, 2014; *Parshikov*, 2015), which cannot be considered here. It is presently unclear if plants themselves perform terpenoid degradation, or whether some degradation products and derivatives result intrinsically from activities of endophytes or other members of the microbiota. For instance, the maize pathogen and endophyte *Fusarium verticillioides* converts R-(+)-limonene to R-(+)-perillyl alcohol, which can be oxidized to perillyl aldehyde and perillic acid (Figure 3). This ability is not restricted to *F. verticillioides*. *Pseudomonas putida* and several yeasts perform the same conversions. Perillic acid is found in many plants, sometimes in high amounts. The limonene derivatives are pharmaceutically interesting because of their anticancer and anti-inflammatory properties in humans.

In herbivory animals, the microbiotas are involved in terpenenoid degradation. The mountain pine beetle, *Dendroctonus ponderosae*, feeds on terpene rich conifers without suffering from intoxification, due to its microbiota that take over detoxification and degradation work (*Adams* et al., 2013). Species of the rumen microbiota of goats have capabilities to degrade monoterpene hydrocarbons, oxygenated monoterpenes and the sesquiterpene cedrene, at least in part (*Maleckyl* et al., 2011).

Glucosinolate

Glucosinolate break down products (Figure 4), in particular isothiocyanates (ITCs), are a class of degradation products well known for herbicidal and mostly negative impacts on microorganisms. In agriculture, the compounds are used for biofumigation to suppress weeds and pathogens. These compounds have microbiome modulating properties (*Hu* et al., 2015; *Siebers*

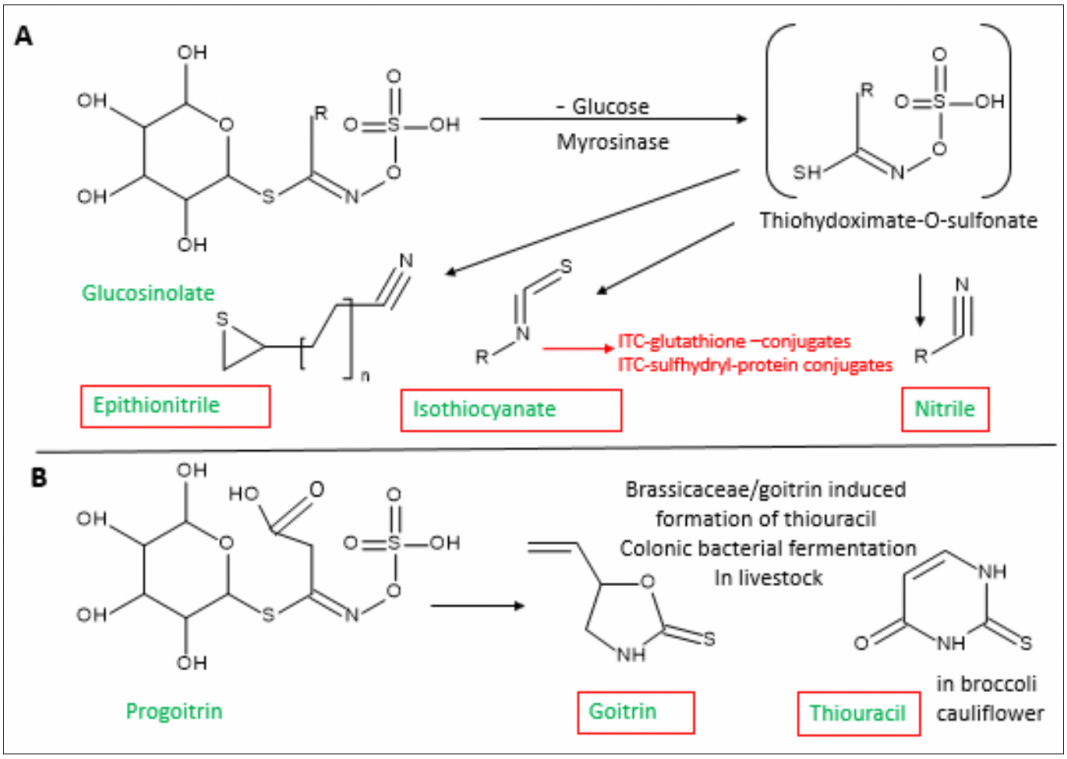

Figure 4: A: Glucosinolate break down is initialized by myrosinase or enzymes possessing similar activities (bacteria). The deglucosylated product is unstable, resulting in the main break down products epithionitriles, isothiocyanates (ITCs) and nitriles. These break down products are found in plants and animals (Angelino et al. 2015; Witzel et al., 2015). In animals, ITC-glutathione- and other sulfhydryl-conjugates can be formed. B: Progoitrin is the precursor of goitrin, which induced thiouracil synthesis in plants and animals. Red markers: Compounds found in animals, green markers: in plants. (Simplified scheme).

et al., 2018). Glucosinolates, typical for Brassicacea and related families, strongly suppress particularly fungi but also many bacteria. Not only pathogenic fungi but also beneficial ones are affected. In agricultural and in natural ecosystems, mycorrhizal fungi can be destroyed with negative long-term effects on several trees and crops (*Lankau*, 2010; *Hilton* et al., 2013; *Hansen* et al., 2019). The findings under field conditions are in agreement with those obtained from exposure of soil samples to mixtures and single glucosinolates and *Brassica* seed extracts. Microorganisms able to cope with glucosinolate break down products are favoured whereas others almost disappeared without recovery. Some cultured bacteria and fungi, isolated from rape seed extract treated soil, eliminated progoitrin derived cyclic ITC goitrin up to 60% within five days (*Siebers* et al., 2018).

The isothiocyanate goitrin has antithyroid effects in mammals by inhibiting the formation of thyroxin, whereas several thiocyanates have a negative influence on iodine uptake. Thiouracil, thought to be derived from goitrin, occurs naturally in some *Brassica* vegetables such as broccoli and cauliflower (*Vanden Bussche* et al., 2011), and is also produced by intestinal bacteria present in the gut of vertebrates. The pathway how thiouracil is synthesized

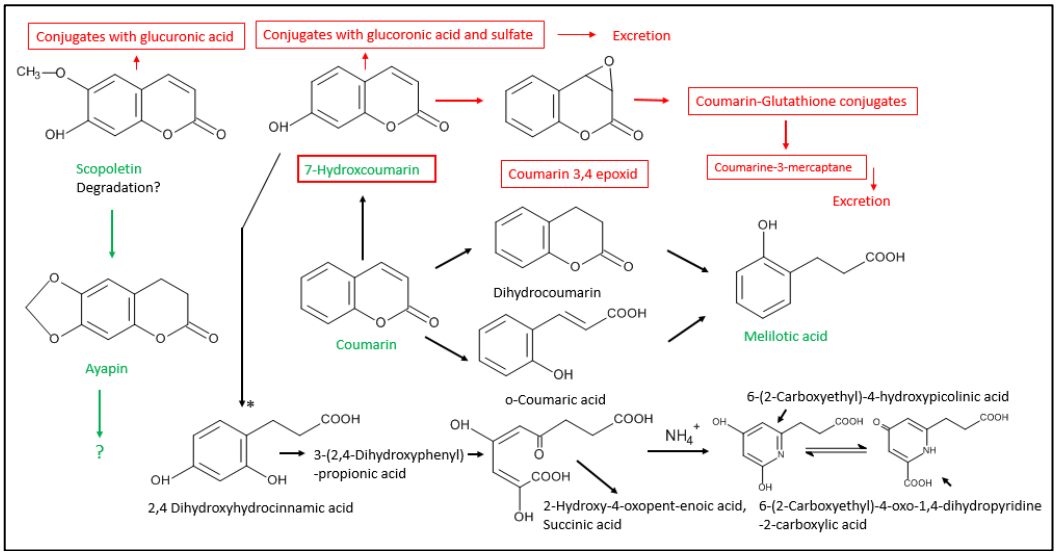

Figure 5: Coumarin degradation and detoxification differs strongly in plants and animals (simplified scheme). Presently only 7-coumarin was identified in animal and plant organisms.
*: Degradation pathway of *Pseudomonas mandelii* 7HK4.

from isothiocyanate is unknown. Thiouracil is a much stronger goitrogen than goitrin (*Kiebooms* et al., 2014). Nitriles, another class of compounds derived from glucosinolate break down, have hepatotoxic effects in cattle. On the other hand, glucosinolate break down products have tumour prevention properties. Benzyl isothiocyanate degradation by *Enterobacter cloacae* led to benzylamine and hydrogen sulphide (*Tang* et al., 1972), but otherwise ITC degradation can occur rather fast and intermediates are hardly identifiable.

Coumarins

The coumarin scopoletin, exuded by roots of the model plant *Arabidopsis thaliana* after inoculation with *Pseudomonas simiae* WCS417, has a modulating effect on the root microbiome. Scopoletin, a compound with antifungal properties, suppressed the pathogens *Fusarium oxysporum* and *Verticillium dahliae*, but was stimulating on ISR-inducing rhizobacteria *Pseudomonas simiae* WCS417 and *Pseudomonas capeferrum* WCS358 (*Stringlis* et al., 2018; 2019). Scopoletin and its 7-β-D-glucoside scopolin are widely distributed in higher plant species (*Gnonlonfin* et al., 2012). It can be speculated therefore that microbiome modulation by scopoletin might be a more general feature. This compound has additional functions, for instance it is a well-known phytoalexin and supports iron uptake. *Voges* et al. (2019) found community shifts in absence of flavonoids and coumarins using a reduced synthetic community (SynCom) of *Arabidopsis thaliana* root-isolated bacteria. *Arabidopsis* f6'h1 mutant lines, unable to synthesize coumarin, showed community shifts under iron deficiency conditions. Application of coumarins causes a partial recovery of the community similar to the wild type.

Ayapin presents a possible degradation product of scopoletin, but the further degradation pathway is not known, whereas the one of coumarin was studied in a few microorganisms: *Arthrobacter* spec., *Bacillus cereus*, *Pseudomonas* spec, *Pseudomonas orientalis*,

various *Saccharomyces cerevisiae* strains and *Fusarium solani* (*Häser* et al., 2006 and references therein). The major pathway in all of them starts with the reduction to dihydrocoumarin and subsequent lactone opening yielding melilotic acid [3-(2-hydroxyphenyl)propionic acid]. In *Arthrobacter,* another pathway yields first o-coumaric acid which is reduced to melilotic acid. In higher plants the same degradation products were found, but the pathways are not sufficiently studied. The further degradation of melilotic acid remains to be elucidated (Figure 5).

The degradation pathway in human and rodents seems to be different, and some of the intermediates could explain the hepatotoxic effects of coumarin in animals. In a first step coumarin is hydroxylated. 7-Hydroxycoumarin (umbelliferone) can be conjugated with glucuronic acid or sulfate in the liver; both conjugates and the hydroxylated coumarin are not toxic. Meanwhile, several degradation pathways and new detoxification products are known (*Leonart* et al., 2017). The most toxic intermediate represents coumarin 3,4-epoxide, which can be conjugated with glutathione. The glutathionylated intermediate is finally converted to coumarin-3-mercapturic acid. The toxicity in animals seems to be species, even individual dependent.

7-Hydroxycoumarin, found in many plants, is toxic for *Ralstonia solanacearum, Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus,* and *Pseudomonas aeruginosa*, but other *Pseudomonas* species and species of *Arthrobacter, Aspergillus, Penicillium*, and *Fusarium* spp. can use it as a C-source. 7-Hydroxycoumarin can be completely degraded by *Pseudomonas mandelii* 7HK4, due to the hcdABC operon (*Krikštaponis* and *Meškys*, 2018; Figure 5). The operon encompasses genes for a flavin-binding hydroxylase (HcdA), an extradiol dioxygenase (HcdB), and a putative hydroxymuconic semialdehyde hydrolase (HcdC).

Benzoxazinones

Benzoxazinones are a special group of secondary products exhibiting a dispersed distribution within the angiosperms. Compounds belonging to this class of heterocycles are present in several wild and domesticated Poaceae and in some dicotyledonous plants (*Sicker* and *Schulz*, 2002; *Schulz* et al., 2013; *Niculaes* et al., 2018). Bezoxazinones have antimicrobial, allelopathic and anti-herbivory functions. They are unstable in the deglucosylated from. Their spontaneous degradation products, the benzoxazolinones BOA (benzoxazolinone) and MBOA (6-methoxybenzoxazolinone) have a modulating activity on the maize root microbiome composition and microorganisms in bulk soil, but different causative mechanisms for the modulation are discussed (*Hu* et al., 2018; *Kudjordjie* et al., 2019). *Cotton* et al. (2019) suggest a function for benzoxazinoids in the control of root flavonoid biosynthesis and a microbiome shaping activity that is also triggered by the root type. In a former study, DIMBOA [2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one], the main benxoxazinone in maize, was found to attract *Pseudomonas putida*. This compound affects the expression of the bacterial genes associated with chemotaxis and benzoate catabolism (*Neal* et al., 2012). Benzoxazinoids can be detoxified by plants and degraded by microorganisms using different pathways which are described in more detail in the following paragraph. In plasma and urine of rats, benzoxazinone [2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one] glucuronides have been identified (*Adhikari* et al., 2012).

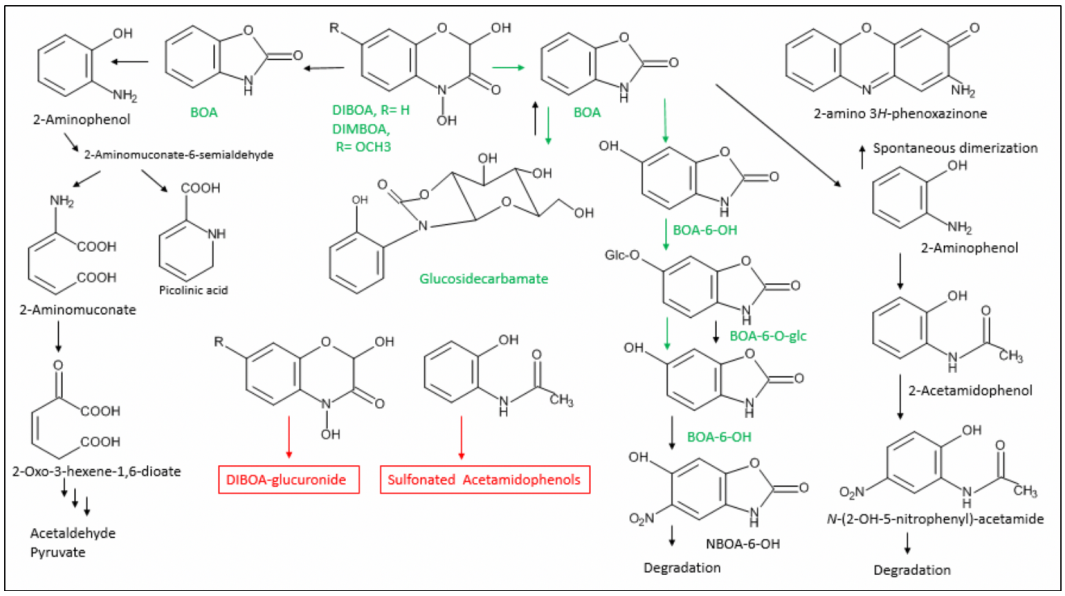

Figure 6: Bacterial pathways for BOA degradation via 2-aminophenol, either by ring cleavage yielding 2-aminomucconate with picolinic acid as a spontaneous byproduct (Arora et al. 2015), or by acetylation of 2-aminophenol /hydroxylation of BOA and subsequent nitration, yielding degradable nitro aromatic compounds (Simplified scheme). Names of plant products are in green. The only detoxification products found in mammals are DIBOA-glucuronide and sulfonated acetamidophenol (red).

PLANT AND MICROBIAL CONVERSIONS OF BENZOXAZOLINONES

Many plants are able to detoxify benzoxazolinones either by hydroxylation or by demethylation of methoxylated benzoxazolinone and subsequent glucosylation (most dicotyledoneous plants). *N*-glucosylation, and rearrangement to glucoside carbamates is more common in wild and cultured Poaceae (Figure 6). The detoxification products are stored in the vacuole, are immobilized in the cell walls or are released by exudation. Deglucosylation of BOA-O-glucosides regenerates the hydroxylated detoxification intermediates BOA-6-OH, BOA-5-OH and the rare BOA-4-OH. Fungal release of the glucose moiety from glucoside carbamate and regeneration of benzoxazolinone is also possible. Thus, these detoxification products meliorate the phytotoxicity of BOA and of the hydroxylated intermediates only temporarily since the compounds are not degraded. As far as investigated, the dominant detoxification product found in maize, glucoside carbamate, promotes the growth of numerous fungi and bacteria (*Schütz* et al., 2019).

A limited number of fungi are able to cleave the benzoxazolinone heterocycle yielding 2-aminophenol, which can be malonylated, probably concomitantly with the cleavage of the heterocycle, to N-(2-hydroxyphenyl) malonamic acid (HPMA), (*Friebe* et al., 1998; *Glenn* et al., 2016). *Acinetobacter calcoaceticus* is presently the only known bacterium able to degrade benzoxazolinone to 2-aminophenol, whereas conversion of 2-aminophenol to acetamidophenol is performed by many fungi and bacteria. In humans, conversion products of acetamidophenol have been found. After consumption of

Figure 7: *Abutilon theophrasti* seedlings (7-day-old) were incubated overnight with 0.5 mM BOA-4-OH without rhamnolipid, 1, 2 und 3mg rhamnolipid in 30ml water (A). B: Roots were heavily covered with a polymer coat (0 mg) but less with increasing amounts of rhamnolipid (left to right side). C. Addition of *Papiliotrema baii* prevent the development of polymer coats almost completely.

benzoxazinoid-rich bread, human postprandial plasma contained two sulfonated acetamidophenols (hydroxy-N-(2-hydroxyphenyl) acetamide and N-(2-hydroxyphenyl) acetamide), (*Hanhineva* et al., 2014). Presently it is unclear whether the gut microbiota is able to degrade benzoxazolinone and how acetamidophenols are generated. While sulphatation and glucuronylation reactions are performed in the liver, *Hanhineva* et al. (2014) assumed that 2-acetamidophenol results from sourdough fermentation since the compound is already present in the bread.

Released 2-aminophenol is otherwise oxidatively dimerized to 2-aminophenoxazinone or degraded, for instance by *Pseudomonas* and *Burkholderia* species (*Arora* et al., 2015). One pathway starts with ring opening to 2-aminomuconic-6-semialdehyde which is further oxidatively degraded to fragments entering the TCA cycle (Figure 6). A spontaneous by-product formed from the semialdehyde is picolinic acid, a bioactive compound with neuroprotective and immuno-modulating properties. In another pathway, presently only found in *Burkholderia* species, 2-aminophenol is hydroxylated via 1,4 benzenediol to 1,2,4 benzenetriol and then cleaved to maleylacetic acid.

2-Aminophenoxazinone has a higher phytotoxicity compared to benzoxazolinones. Phenoxazinone and benzoxazolinones can be extracted from soil after wheat and rye culture. Thus, the compounds are relatively stable and cannot easily eliminated. As a consequence, decontamination of arable soil from benzoxazolinones and phenoxazinones takes several months (*Schulz* et al., 2013 and references therein).

MICROBIAL SUPPORT OF BOA-OH ELIMINATION VIA POLYMERIZATION ON THE ROOT SURFACE

Abutilon theophrasti, a weed found in maize and beet fields, does not accumulate considerable amounts of BOA-6-O-glucoside or glucoside carbamate. Instead, the plant polymerizes hydroxylated BOA in high amounts at the root surface, presenting a completely different way to eliminate toxic compounds. Hydroxylation of benzoxazolinones, a prerequisite for polymerization reactions, is performed by the plant. Root colonizing microorganisms originated from soil, are involved in the process. Depending on the cultivation site,

Abutilon theophrasti can be colonized by a microbial consortium with *Actinomucor elegans* as the dominant species. The fungus is associated with several bacteria, among them *Pantoea ananatis* and *Stenotrophomonas maltophilia*, and the yeast *Papiliotrema baii*. The consortium is a stable microcommunity and the zygomycete cannot be cured from the partners by the addition of antibiotics (*Haghikia* et al., 2014). *Abutilon theophrasti*, inoculated with the *A. elegans* consortium developed dark brown roots within a few hours when incubated with BOA-6-OH or BOA-4-OH. The yeast and *Pantoea ananatis* react with high H_2O_2 production, a substrate for peroxidase catalysed polymerization. Interestingly, polymer coat formation at the root surface can be meliorated or removed by the addition of rhamnolipid (Figure 7, *Schulz* et al., unpublished). The glycolipid with antimicrobial properties is synthesized by many *Pseudomonas, Pantoea, Enterobacter, Burkholderia* species and others. Since *P. baii* not only produces high amounts of H_2O_2 but also the glycolipid 2-O-(β-D-galactopyranosyl-(1->6)-β-D-galacto-pyranosyl) 2S-hydroxynonanoic acid (*Schilasky*, *Siebers*, *Schulz* and *Dörmann*, unpublished), polymer formation and the glycolipid may interact, perhaps in radical scavenging activities. Although speculative, certain microorganisms may use glycolipids to clean roots from polymers.

BACTERIAL NITRATION OF HYDROXYLATED BENZOXAZOLINONE AND ACETAMIDOPHENOL FOR A FAST DEGRADATION

We detected a new compound in the wash liquid obtained from root surfaces of *Abutilon* seedlings inoculated with the *A. elegans* consortium after incubation with BOA-6-OH.

The compound is produced in high amounts by *Pantoea ananatis* and by the complete *A. elegans* consortium when incubated with BOA-6-OH in Czapek medium (Figure 8). It was identified as 6-hydroxy-5-nitro-benzo[*d*]oxazol-2(3*H*)-one (NBOA-6-OH, Figure 6) (*Schulz* et al., 2017, 2018). NBOA-6-OH can be produced by several soil bacteria, but obviously not by fungi. This compound is rapidly degraded without accumulation of identifiable degradation products, also by fungi (*Schütz* et al., 2019). Methoxylated benzoxazolinone (MBOA) is another substrate for nitration by the complete *A. elegans* community, yielding 6-methoxy-4-nitro-benzoxazolin-2(3*H*)-one (NMBOA). Bacterial nitration activates benzoxazolinones for subsequent rapid degradation. Since no intermediates accumulate, it is presently unclear how the degradation pathway is constructed and which enzymes are involved. Several reaction sequences are possible, depending on oxygen availability (*Ju* and *Parales*, 2010).

2-Acetamidophenol can be nitrated by strains of *Paenibacills polymyxa* and *Aminobacter aminovorans* (*Schütz* et al., 2019*)*. The product, *N*-(2-OH-5-nitrophenyl)-acetamide, accumulates in the culture medium, and is also biodegradable. It was described first as a fungal product by *Zikmundova* et al., (2002) derived from acetamindophenol. Nitration may shorten the life time of molecules, as found with BOA-6-OH and 2-acetamidophenol. Nevertheless, nitro aromatic compounds can have fatal effects in animals and are also toxic for numerous microorganisms (*Ju* and *Parales*, 2010). We assume that bacterial nitration of suitable molecules may be more widespread that thought and occurs with different classes of secondary metabolites. For instance,

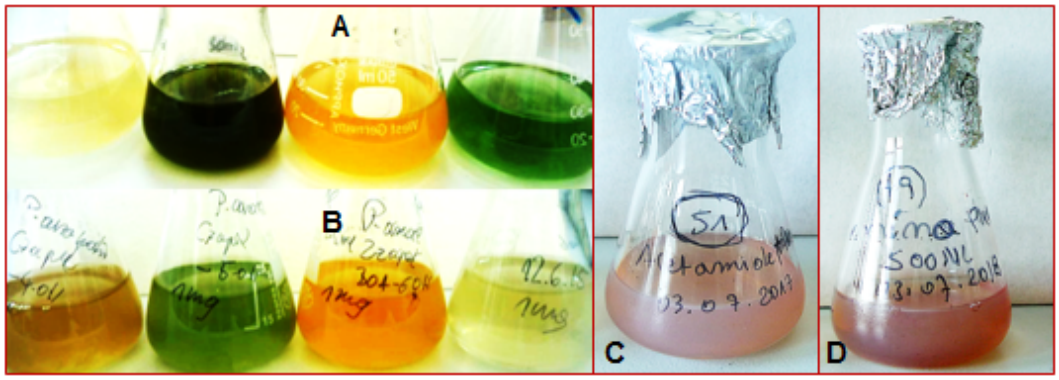

Figure 8: Incubations of the *Actinomucor elegans* consortium in Czapek medium supplemented with 0.5 mM BOA-6-OH lead to yellow compound (A), which is also formed with *Pantoea ananatis*, isolated from the consortium (B). The compound was identified as 6-hydroxy-5-nitrobenzo[*d*]oxazol-2(3*H*)-one. Incubation of *Paenibacills polymyxa* (C) and *Aminobacter aminovorans* (D) with 2-acetamidophenol in Czapek medium for 2 days results in colored cultures containing different products, one of them was identified as *N*-(2-OH-5-nitrophenyl)-acetamide.

nitration of catechin to 6,8-dinitrosocatechin which happens in the stomach, was described by *Veljovic-Jovanovic* et al., (2014). Quercetin partly suppresses the nitration and also prevents further oxidation of 6,8-dinitrosocatechin to the quinone form by nitrous acid. Required nitrite, necessary for nitration, results from the activity of bacteria in the oral cavity of animals including humans, which reduce nitrate present in high concentrations in vegetables.

CONCLUDING REMARKS

Hacquard et al., (2015) ascertained no overlap of the abundant bacterial organisms of mammal and plant root microbiotas. Analyses of the barley, *Arabidopsis,* maize, rice and grapevine microbiotas revealed a high abundance of members of the Chloroflexi, Actinomycetales, Verrucomicrobiota, Bacterioidales, Saprospirales, Burkholderiales, Xanthomonadales, Pseudomonadales, Rhizobiales, and Sphingomonadales. All of them are almost not present in the microbiotas of mammals, including humans. The latter microbiotas are dominated by Bacteriodales, Clostridiales and Lactobacilliales, which are, in turn, not or rarely found in the plant microbiotas. For fungi, a comparable study is presently not available. Nevertheless, pathways for secondary metabolite degradation have sometimes the same catabolic reaction sequences and the same intermediates transiently accumulate, as found for quercetin and some simple phenolics. Others, such as coumarin, differ notably in their detoxification and catabolism by soil, plant and animal microbiotas. For benzoxazinoids, degradation pathways are presently only known from soil and plant associated microorganisms. To cite *Chen* et al. (2019), the plant microbiome acts as intermediary between human and natural microbiomes and opens therefore a possible way of transferring antibiotic resistance. One can speculate that transfer of bacterial genes involved in secondary metabolite degradation and perhaps transfer of entire gene clusters into members of the different microbiotas mirrors co-evolutionary events.

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