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MINI REVIEW

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Microbial degradation of plant toxins

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Abstract

Plants produce a variety of secondary metabolites in response to biotic and abiotic stresses. Although they have many functions, a subclass of toxic secondary metabolites mainly serve plants as deterring agents against herbivores, insects, or pathogens. Microorganisms present in divergent ecological niches, such as soil, water, or insect and rumen gut systems have been found capable of detoxifying these metabolites. As a result of detoxification, microbes gain growth nutrients and benefit their herbivory host via detoxifying symbiosis. Here, we review current knowledge on microbial degradation of toxic alkaloids, glucosinolates, terpenes, and polyphenols with an emphasis on the genes and enzymes involved in breakdown pathways. We highlight that the insect-associated microbes might find application in biotechnology and become targets for an alternative microbial pest control strategy.

INTRODUCTION

The *Plantae* kingdom includes organisms ranging from minuscule mosses to massive trees. Yet, regardless of their size, all plants produce a variety of low- and high-molecular-weight metabolites. According to their function, they have been classified into three categories: phytohormones (PHs), and phytochemicals, which include plant primary metabolites (PPMs), and specialized molecules or plant secondary metabolites (PSMs). PHs regulate metabolism and integrate internal and external signals to steer effective plant development and defense responses to counteract biotic and abiotic stresses (Aerts et al., 2021; Li et al., 2020; Pieterse et al., 2012). PPMs, namely carbohydrates, proteins, and lipids, are directly required for basic functions, such as photosynthesis, respiration, solute transport, nutrient assimilation, and biosynthesis of metabolic intermediates (Olivoto et al., 2017). Lastly, PSMs are metabolic products and intermediates, which are not essential for plant life or growth. Instead, they navigate the interactions between plants and the surrounding environment (Davies, 2004; Erb & Kliebenstein, 2020; Heitefuss, 2010; Taiz et al., 2015). They are involved in inter-plant communication and the protection against herbivores, insects, and pathogens. They may also attract pollinators, seed dispersers, root nodule bacteria, or influence oviposition, and in plant–plant and plant–microbe interactions act as communication signals (Hartmann, 1996; Wink, 2003). Thus, PSMs are essential in mediating plant adaptations to environmental changes.

PSMs are divided into several classes based on their chemical structure, including alkaloids, glucosinolates, terpenes, polyphenols, cyanogenic glucosides, amines, non-protein amino acids, polyacetylenes and fatty acids, polyketides, and carbohydrates (Wink, 2013). Approximately 200,000 PSMs have been

found and around 100,000 have been experimentally investigated (Hartmann, 2007; Schoonhoven et al., 2005; Willis, 2017). The substantial number of different plant secondary metabolites are likely the results of the biochemical co-evolutionary arms race proposed by Ehrlich and Raven in 1964 (Ehrlich & Raven, 1964). The theory suggests that plant–herbivore interactions in response to herbivore pressure drive plant evolution and diversification in biosynthesis pathways. Originally, PSMs derived from main precursor pathways, that is, acetate, shikimate, mevalonate, and deoxyxylulose, and diversification in these metabolic pathways lead to the generation of various PSMs (Ribera & Zuñiga, 2012).

As a result of constant environmental pressure, plants are genetically predisposed to continually synthesize diverse PSMs. Typically, plant genomes carry multiple gene families coding for enzymes that catalyse compound diversification from common precursors, allowing for a large diversification of PSMs. They benefit from modifying enzymes that can use multiple substrates and hence produce various products out of the same precursors. The structural diversity is even further increased by glycosylation and esterification, and occasionally by the co-modifications with PPMs (Dudareva et al., 2004; Kollner et al., 2004; Negre et al., 2003; Tholl et al., 2005).

Although plants synthesize a tremendous number of PSMs, the majority of PSMs are synthesized from primary metabolism and are accumulated in plant cells. The initial site of synthesis however is typically restricted to an organ, such as leaves, roots, or fruits, and subsequently, PSMs are transported and stored in destined plant tissues (Acamovic & Brooker, 2005). Storage preference differs per tissue or cell and in many plants the concentration of a particular compound varies between plant parts. In annual plants, they tend to concentrate in flowers, fruits, and seeds, whereas in perennial species they typically reach high levels in roots, bulbs, and stems (Guern et al., 1987). Some compounds were shown to be even stored in the epidermis (Wink & Roberts, 1998). The site of storage depends also on the compound's polarity, so hydrophilic compounds such as alkaloids, glucosinolates, and tannins are stored in vacuoles and idioblasts, whereas hydrophobic metabolites such as terpene-based compounds are stored in glandular hairs, trichomes, resin ducts, thylakoid membranes and on the leaf surface (Wiermann, 1981).

Plant secondary metabolites had significant contributions to human life. For centuries, they were used in various ways, especially in medicine as therapeutic painkilling and blood thinning agents (codeine, atropine), yet they also found application as dyes (indigo), flavouring additives (vanillin, mustard oils), fragrances (essential oils), stimulants (caffeine, nicotine), hallucinogens (morphine, cocaine), insecticides (anabasine piperine) and poisons (strychnine) (Heitefuss, 2010). Although PSMs can be toxic to humans and other animals, they are oftentimes eliminated from the environment via natural degradation by microorganisms. Since the emerging trend towards limiting the usage of pesticides in agriculture, PSMs, and their insecticide and herbicide properties have gained more interest. Using PSMs to restore sustainable crop protection could be thus an alternative solution to pesticides, which nowadays are less effective and contribute to pollution (Ahmad et al., 2022; Almeida et al., 2017; Gangola et al., 2022; Itoh et al., 2014; Itoh et al., 2018; Schwarz et al., 2022; Singh & Singh, 2016; van den Bosch & Welte, 2017). Therefore, obtaining more insights into the microbial degradation of PSMs has great value to both agriculture and bioremediation.

In this minireview, we highlight the knowledge gaps in terms of natural plant-derived insecticides and herbicides and their application in resistance breeding (Figure 1). We will summarize the current research in the field of degradation of toxic PSMs, including alkaloids, glucosinolates, terpenes, and polyphenols, with a focus on microbial metabolic pathways and involved enzymes. We will provide evidence that toxin-degrading microorganisms are found in various ecosystems and, we will emphasize that instead of trying to eliminate microbes, we should profit from their degrading capabilities and apply them in biotechnology and bioremediation (Chen et al., 2019; Chitwood-Brown et al., 2021; Wille et al., 2019). We hypothesize, that resistance breeding focused on plant secondary metabolites could greatly benefit sustainable pest control in the future. Ultimately, we will suggest in which direction research regarding increasing the effectiveness of biological pest control could continue to elucidate novel microbial pest control management strategies.

MICROBIAL DEGRADATION OF TOXIC PLANT SECONDARY METABOLITES

Plants produce various plant secondary metabolites (PSMs) in response to biotic and abiotic stresses. Here, we will focus on toxic PSMs and their degradation by environmental microorganisms. The number of toxic PSMs is substantial, which is why in this review, we will divide them into nitrogen-containing and non-nitrogen-containing PSMs.

NITROGEN-CONTAINING PLANT SECONDARY METABOLITES

Alkaloids

Alkaloids are the most diverse heterocyclic nitrogen-containing PSMs. The occurrence of alkaloids was reported to be restricted to higher plants, but their

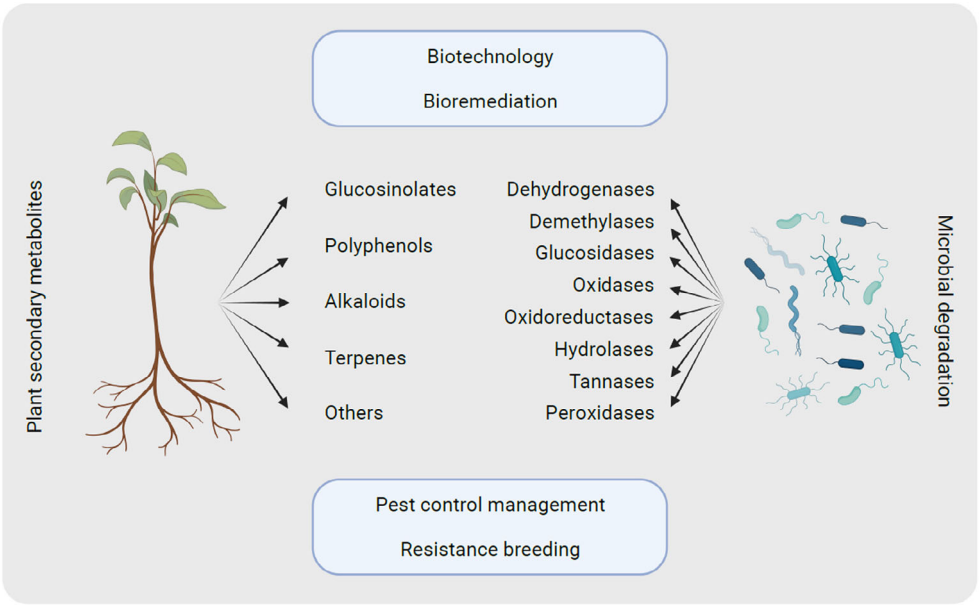

FIGURE 1 An overview showing the summary of microbial degradation of different secondary plant metabolite classes and their applications in agriculture, biotechnology, and bioremediation. Created with BioRender.com.

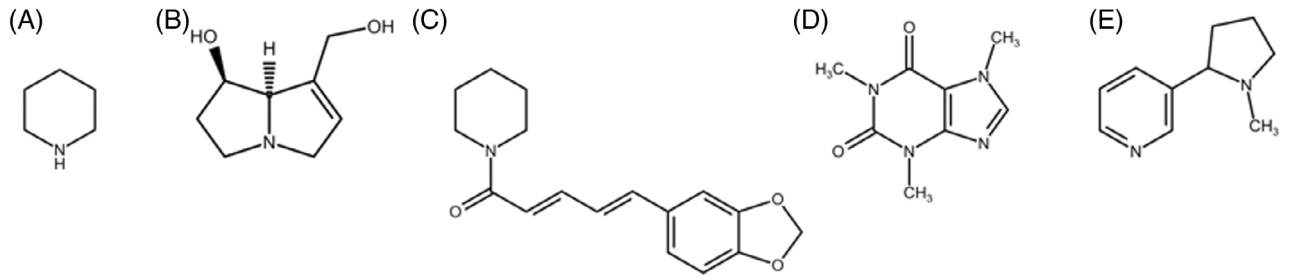

FIGURE 2 Chemical structures of toxic alkaloids and plant genus/species containing these alkaloids: (A) piperidine (black pepper), (B) retronecine (genus *Senecio*), (C) piperine (black pepper), (D) caffeine (coffee bean), (E) nicotine (tobacco).

production has also been confirmed in fungi (Builders, 2019). The chemical reactions catalysed by modifying enzymes, including methylation, glycosylation, oxidation, reduction, hydroxylation, and acylation led to the elucidation of approximately 27,700 different metabolites. The wide chemical diversity of alkaloids contributed to alterations of their physical, chemical, and biological properties and for this reason, there are three classification systems of alkaloids. The first one categorizes them according to their amino acid precursors, that is, phenylalanine, tyrosine, tryptophan, ornithine, lysine, histidine, and anthranilic acid (Wink, 2003). According to their chemical structure, alkaloids are grouped into heterocyclic and non-heterocyclic alkaloids, based on the position of the nitrogen atom in the chemical structure, and in the taxonomic division, alkaloids produced by plant species of the same genus are grouped under one category (Bhambhani et al., 2021). Selected toxic alkaloids are illustrated in Figure 2A–D.

Alkaloids are oftentimes used in the pharmaceutical industry, however, their primary function in the plant is the activity against herbivores, insects, and pathogens and for that reason, anabasine is used as insecticide (Seigler & Seigler, 1998). Microbial transformation and degradation of alkaloids have been reported in various alkaloid classes.

Pyrrolizidine alkaloids (PAs) and PA *N*-oxides are examples of hepatoxic alkaloids identified in over 6000 plants, widely distributed in the Boraginaceae, Asteraceae, and Fabaceae families (Fu et al., 2004). At the moment, more than 660 PAs have been characterized with an estimation that 3% of the world's flowering plants contain PAs (Smith & Culvenor, 1981). Rumen microorganisms from naïve ruminants completely degraded monocrotaline within 48 h in vitro (Aguiar & Wink, 2005), and a mixed culture of ovine ruminal microbes, including strain *Peptostreptococcus heliotrinreducens*, has been shown to degrade macrocyclic PAs from the plant common ragwort (*Senecio*

jacobaea) to 1-methylene-containing compounds (Hovermale & Craig, 2002). The enzymes involved in the degradation pathway, however, remain unknown. Interestingly, it has been hypothesized that there might be a general biodegradation pathway of piperidine alkaloids. A mutant of *Mycobacterium smegmatis* mc2155 degraded for example non-alkaloid metabolites as well as piperidine and pyrrolidine alkaloids which shared similarities in their backbones (Poupin et al., 1999). The reaction was carried out by cytochrome P450 monooxygenase, which likely causes cleavage of the C-N bond and leads to the formation of intermediary amino acids. The reaction is followed by deamination and oxidation to a diacid and ultimately resulting in the complete mineralization of piperidine (Combourieu et al., 2000). In *Pseudomonas* sp. the piperidine alkaloid is first glutamylated and hydroxylated in the second transformation step, which is different than in *Mycobacterium* sp. *Pseudomonas* sp. KU43P converted, for example, piperidine into γ-glutamylpiperidine by a γ-glutamylpiperidine synthase, encoded by the *pip*A gene, which was further transformed by cytochrome P450 monooxygenase, γ-glutamyl-γ-aminovaleral dehyde dehydrogenase, γ-glutamyl peptidase, and γ-aminovalerate transaminase to glutaric acid. The corresponding genes are clustered together in part of the *pip* operon (Yamamoto et al., 2020).

Caffeine is a purine alkaloid and in plants, it serves as a toxic PSM against herbivores (Nathanson, 1984; Wright et al., 2013). Caffeine exhibits a negative effect on insects, arachnids, slugs, and snails and is therefore considered a natural pesticide (Abdelkader et al., 2013; Hollingsworth et al., 2002). Currently, two pathways for bacterial caffeine degradation are known: (1) *N*-demethylation and (2) C-8 oxidation (Figure 3A). The enzymes of the two corresponding pathways share little similarity, which is reflected by substantially different intermediate products. Caffeine degradation via *N*-demethylation was observed by the microbiota of the coffee berry borer *Hypothenemus hampei* which infests coffee plants and shows no signs of intoxication. The pure isolate *Pseudomonas* sp. from the gut of *H. hampei* degraded caffeine in vitro with caffeine demethylase (NdmA; N_1-demethylase specific for N_1-methyl group of caffeine), encoded by *the ndm*A gene. This caffeine-degrading *Pseudomonas* sp. could use caffeine as a sole carbon and nitrogen source (Ceja-Navarro et al., 2015). Strain *Pseudomonas putida* CBB5 additionally harbours the *ndm*B gene which encodes the NdmB N_3-demethylase specific for the N_3-methyl group of theobromine, a first transformation product of caffeine. In the *N*-demethylation pathway, generally, NdmA demethylates caffeine to theobromine, and subsequently, NdmB demethylates it to 7-methylxanthine. Ultimately, the pathway yields glyoxylic acid and urea (Summers et al., 2012). On the contrary, caffeine degradation via the C-8 oxidation pathway has been demonstrated in *Pseudomonas putida* and *Serratia marcescens* isolated from a coffee plantation soil, and coculture of *Klebsiella* sp. with *Rhodococcus* sp. In *Alcaligenes* sp. isolated from lake water, caffeine was degraded with a serine-type metallo-caffeine oxidase (Dash & Gummadi, 2010; Madyastha & Sridhar, 1998; Mohapatra et al., 2006). The study by Mohanty et al. (2012) revealed that *Pseudomonas* sp. strain CBB1 detoxified caffeine with a novel trimeric caffeine dehydrogenase (Cdh), encoded by the *cdh*ABC operon, and was capable of growth on caffeine as the sole carbon, nitrogen, and energy source. In C-8 oxidation, caffeine is oxidized at the C-8 position to form 1,3,7-trimethyluric acid (TMU), which is then transformed into glyoxylic acid, dimethylurea, and monomethylurea. Although two pathways have been described for caffeine degradation, little is known about the enzymes involved in caffeine transformation. More questions are to be addressed regarding the possibility of C-8 oxidation of *N*-demethylated metabolites and the distribution of caffeine-degrading genes among bacteria. Here, we performed a phylogenetic analysis of the genes encoding NdmA, NdmB, and Cdh which are involved in two distinct degradation pathways of caffeine (Figure 3B). The analysis revealed that NdmA and NdmB share a high degree of similarity and are clustered closely, whereas Cdh forms a separate branch, showing dissimilarity between enzymes involved in *N*-demethylation and C-8 oxidation pathways of caffeine. Likewise, the similarities of the *Pseudomonas* spp. enzymes NdmA, NdmB, and Cdh were found in several other bacterial species, suggesting potentially widespread occurrence of caffeine detoxification among bacteria.

Nicotine is a toxic PSM produced by tobacco (*Nicotiana*) plants. Due to the processing of tobacco products, nicotine accumulates in soil, freshwater, and the plant rhizosphere, and contributes to the pollution of the environment (Jimenez et al., 2002). Although nicotine has toxic properties, nicotine-degrading microbes have been characterized. Oftentimes these microorganisms are applied in bioremediation to reduce nicotine pollution, for example, *Arthrobacter* sp. follows a pyridine pathway, which attacks the nicotine pyridine ring during the degradation (Briški et al., 2003; Meher et al., 1995). *P. putida* S16, in contrast, degrades nicotine via an alternative pyrrolidine pathway. A key enzyme in this pathway is nicotine oxidoreductase NicA2 which converts nicotine to *N*-methylmyosmine. In subsequent degradation steps, the intermediate products are transformed ultimately yielding fumaric acid as the end product. In fungi, however, a demethylation pathway is used instead, which demethylates the pyrrolidine ring of the nicotine. Interestingly, in *Agrobacterium tumefaciens* strain S33 a novel pathway of pyridine and pyrrolidine degradation was found. *A. tumefaciens* transform nicotine via the pyridine

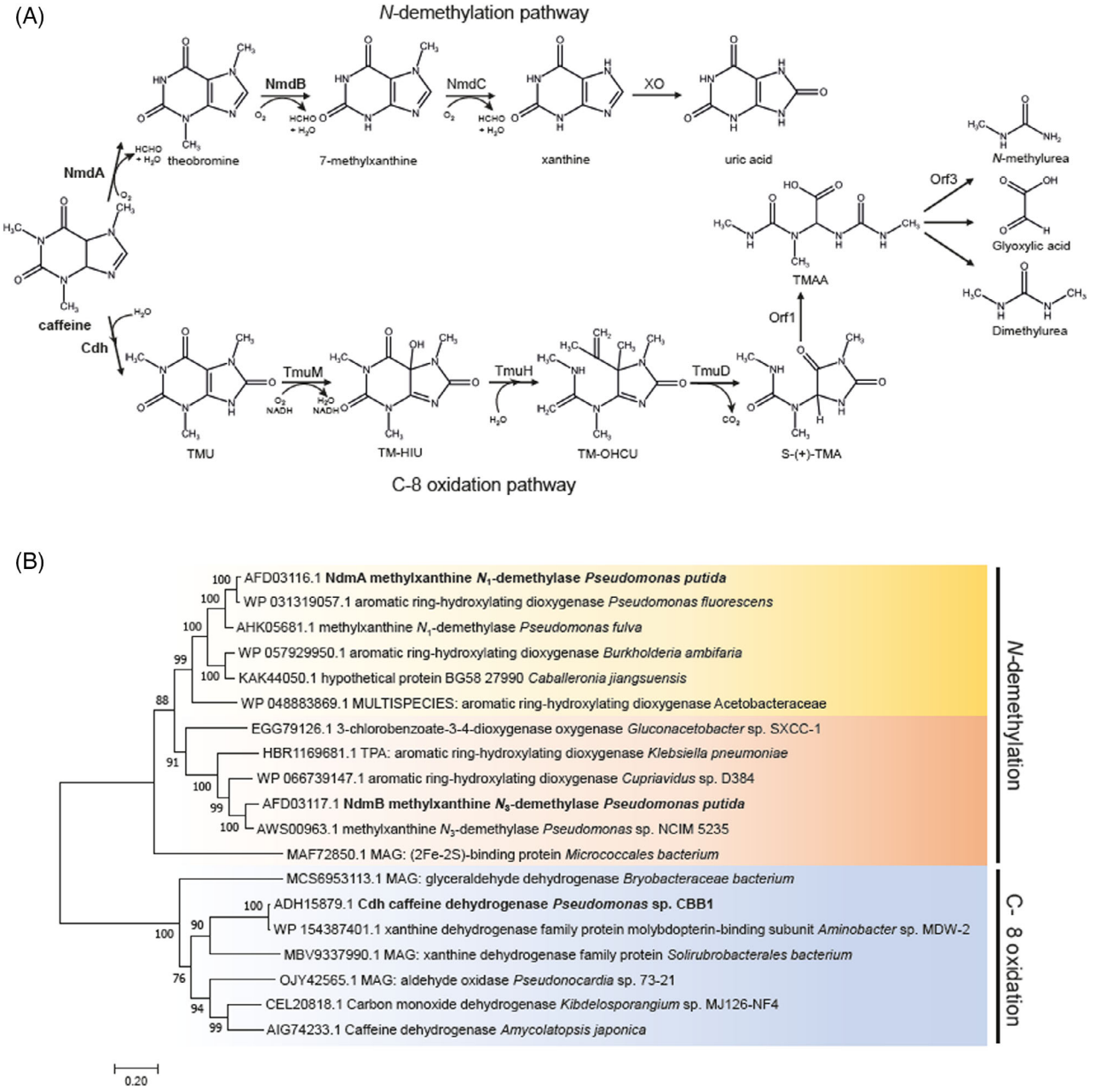

FIGURE 3 Comparison of the *N*-demethylation and C-8 oxidation pathway of caffeine biodegradation and phylogenetic analysis of the key enzymes involved in the breakdown pathway. (A) Two alternative degradation pathways of caffeine. (i) In the *N*-demethylation pathway caffeine degradation begins with demethylation at the N_1 position by methylxanthine N_1-demethylase (NdmA) forming theobromine. Subsequently, methylxanthine N_3-demethylase (NdmB) catalyses the removal of a methyl group at the N_3 position of theobromine, yielding 7-methylxanthine, which is further transformed to xanthine with N_7-specific *N*-demethylase (NmdC). Lastly, xanthine is metabolised to uric acid with xanthine oxidase (XO). (ii) In the C-8 oxidation pathway, caffeine dehydrogenase (Cdh) oxidises caffeine to 1,3,7-trimethyluric acid (TMU), which is then further oxidized to 1,3,7-trimethyl-5-hydroxyisourate (TMU-HUI) by trimethyluric acid monooxygenase (TmuM). TMU-HUI is metabolized to 3,6,8-trimethyl-2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline (TM-OHCU) by 1,3,7-trimethyl-5-hydroxyisourate hydrolase (TmuH) and subsequently to 3,6,8-trimethylallontoin (S-(+)-TMA) via 3,6,8-trimethyl-2-oxo-4-hydroxy-4-carcoxy-5-ureidoimidazoline decarboxylase (TmuD) and 1,6,8-trimethylallantoic acid (TMAA) via a putative trimethylallantoinase (Orf1). Lastly, TMAA is cleaved to dimethylurea, glyoxylic acid, and monomethyl urea by acetylornithine deacetylase (Orf3). Degradation pathways are reconstructed based on the proposed caffeine-degrading pathways of *Pseudomonas putida* CBB5 and *Pseudomonas* sp. CBB1 (Mohanty et al., 2012; Summers et al., 2012). (B) Phylogenetic tree of *N*-demethylases and caffeine dehydrogenases. Multiple sequence alignment was constructed based on the protein sequence of the corresponding genes using Blastp search with default settings. The clustering of tree branches depicts differences in the proteins belonging to the *N*-demethylation and C-8 oxidation breakdown pathways of caffeine. The evolutionary history was inferred using the Neighbor-Joining method (Saitou & Nei, 1987). The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (500 replicates) is shown next to the branches. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the Poisson correction method and are in the units of the number of amino acid substitutions per site. Evolutionary analyses were conducted in MEGA7 (Kumar et al., 2016).

pathway to 6-hydroxy-pseudomooxynicotine, through 6-hydroxy-L-nicotine and 6-hydroxy-N-methylmyosmide, and then via the pyrrolidine pathway to 6-hydroxy-3-succinoylpyridine and 2,5-dihydroxypyridine (Wang et al., 2012). Interestingly, the nicotine-degrading enzymes were encoded both in the genome and in plasmids which hinders the possible horizontal gene transfer of genes required for nicotine biodegradation to evolutionary distinct non-degrading microbes (Gurusamy & Natarajan, 2013; Tang et al., 2013; Uchida et al., 1983; Wang et al., 2009; Wang et al., 2012).

In potatoes (*Solanum tuberosum*) all parts of the plant produce two steroidal glycoalkaloids, *α*-chaconine and *α*-solanine (Figure 4A,B) which are toxic to humans, snails, insects, and fungi (Fewell & Roddick, 1993; McKee, 1959; Morris, 1984; Smith et al., 2001). Similar to nicotine, these toxic glycoalkaloids may leach into the groundwater after the decomposition of dead plants, causing a danger of acute poisoning in aquatic organisms. Jensen, Jacobsen, et al. (2009) found that groundwater microorganisms were capable of degrading glycoalkaloids *α*-chaconine and *α*-solanine to the corresponding *β*- and *γ*-structures and ultimately solanidine via stepwise removal of monosaccharides from the side chain. Similar intermediary product formation was found in two fungal potato pathogens from the genus *Gibberella* (Weltring et al., 1997). *Arthrobacter* sp. S41 isolated from potato field soil was able to degrade *α*-chaconine and *α*-solanine similarly via enzymatic activity of *β*-galactosidase, *β*-glucosidase, and *α*-rhamnosidase. This study showed that these genes form a gene cluster encoded in the genome that harboured novel enzymes for the deglycosylation of potato glycoalkaloids (Hennessy et al., 2020). Overall, it seems that *α*-chaconine and *α*-solanine in both fungi and bacteria are degraded in the same 3-step breakdown pathway, generating *β*- and *γ*-structures of toxic glycoalkaloids, yielding in the final step solanidine. Whether a complete degradation of these toxic glycoalkaloids, namely further metabolism of solanidine is possible, remains however unclear.

Glucosinolates

Glucosinolates (GSLs) are nitrogen-containing *β*-thioglucoside-*N*-hydroxysulfates with a side chain and a sulphur-linked *β*-D-glucopyranose moiety. They are PSMs of the Brassicaceae, Capparaceae, and Caricaceae families, and currently, account for approximately 130 known PSMs (Fahey et al., 2001). Glucosinolates are present mainly in cruciferous vegetable crops, such as broccoli, cabbage, cauliflower, and turnip, and in non-cruciferous crops such as rapeseed (Bischoff, 2016; Wink, 2003). GSLs *per se* are not toxic and they do not exhibit biological activity, however, upon hydrolysis carried out by the myrosinase enzyme (*β*-thioglucosidase), they are converted to pungent and toxic isothiocyanates (ITC), thiocyanates and nitriles. This phenomenon is commonly referred to as the *mustard oil bomb* (Lüthy & Matile, 1984; Wittstock et al., 2004). Normally, GSLs and myrosinase are physically separated in plants but upon tissue damage, myrosinase comes in contact with GSLs, causing their rapid hydrolysis (Koroleva et al., 2000). The produced

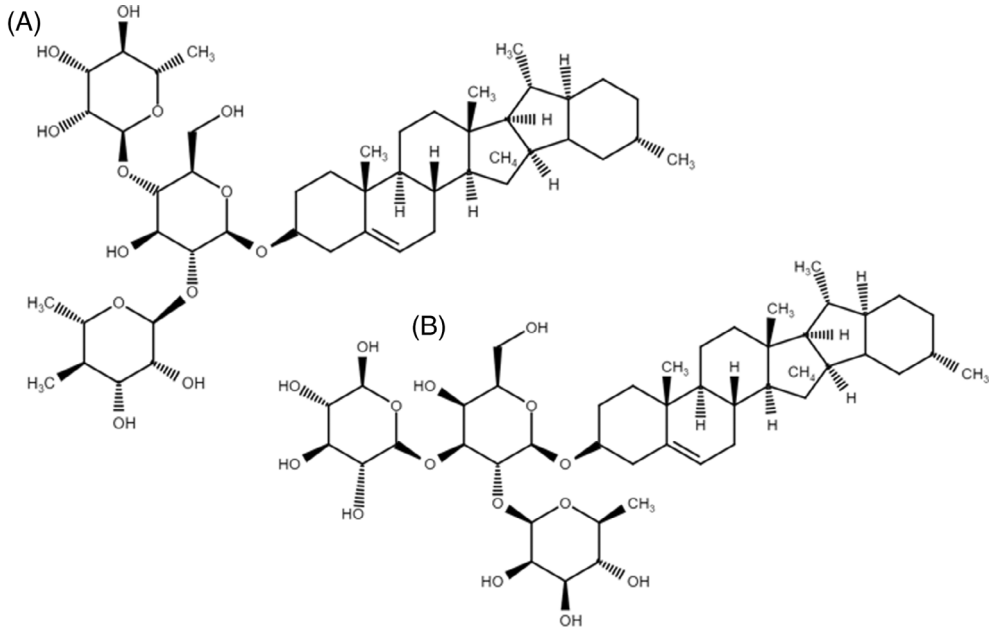

FIGURE 4 Chemical structures of toxic potato alkaloids: (A) *α*-chaconine, (B) *α*-solanine.

glucosinolates hydrolysis products (GHPs) possess bactericidal, fungicidal, nematocidal, and allelopathic properties, making them natural pesticides. Several bacterial species found in various ecosystems were capable of GHPs degradation, including ITC, one of the most bioactive and toxic GHPs.

Pest insects feeding on Brassicaceae family plants encounter toxic ITC but show no adverse effect, implying their ability to either resist or degrade ITC to non-toxic products. Recently, it became apparent that insects benefit from acquiring microorganisms that mediate toxic degradation, enabling insects to infest various crops (Sato et al., 2021). One detoxifying symbiosis was shown in the cabbage root fly larvae *Delia radicum*, which is a notorious pest feeding on roots and stems of rapeseed and cabbage. It was demonstrated that *Serratia* sp., *Pectobacterium* sp., *Acinetobacter* sp., *Providencia* sp., and *Pectobacterium* sp. were able to break down 2-phenylethyl isothiocyanate (2-PI; Figure 5) in vitro. Likewise, strains carrying the Drgb3 plasmids encoded SaxA, an isothiocyanate hydrolase, that catalyses the conversion of 2-PI (van den Bosch et al., 2018; van den Bosch et al., 2020; Welte et al., 2016). Phylogenetic analysis showed that plasmid-encoded *sax*A genes were present in diverse bacterial species, showing that detoxifying genes are frequently transmitted between bacteria (Itoh et al., 2018). Another pest of rapeseed, the cabbage stem flea beetle *Psylliodes chrysocephala*, harboured *Pantoea* sp. in the gut which rapidly degraded ITC in vitro (Shukla & Beran, 2020). The antibiotic treatment resulted in a decreased abundance of microbes and loss of capability to detoxify ITC. The authors demonstrated that in vivo, insects could restore ITC degradation when the microbiota was re-established after treating beetles with antibiotics. The results indicate the wide distribution of ITC degrading capabilities in insect-associated microorganisms and the significance of the bacterial symbionts in the detoxification of toxic PSMs.

Toxic ITC usually confers broad resistance against pathogens and herbivorous insects. Nevertheless, a fungal pathogen, the necrotrophic white mold *Sclerotinia sclerotiorum* was able to infect glucosinolate-producing-plants and eventually degrade ITC via either conjugation to glutathione or hydrolysis to amines (Chen et al., 2020). The importance of ITC-degrading microbes was also demonstrated in forest and nursery soils, where microbial degradation accounted for >60% reduction in the concentration of methyl-ITC (Zhang et al., 2005).

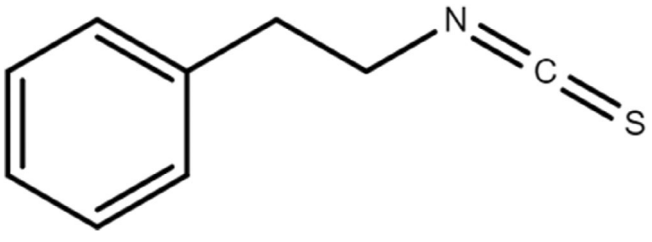

FIGURE 5 Chemical structure of 2-phenylethyl isothiocyanate which is widely present in cruciferous crops, such as broccoli, cabbage, and turnip.

OTHER NITROGEN-CONTAINING PLANT SECONDARY METABOLITES

Alkaloids and glucosinolates are the two biggest classes of nitrogen-containing plant secondary metabolites; however, some nitrogen-containing metabolites do not belong to either class and therefore form a separate group. In this section, other nitrogen-containing PSMs are described.

Amygdalin (Figure 6A) is a cyanogenic glycoside that is typically found in honey bee-pollinated almond trees and microbe-mediated detoxification of amygdalin has been demonstrated in bees (*Apis* sp.). Among several amygdalin-degrading bacteria found in the bee's gut, *Bifidobacterium* wkB204 was capable of complete degradation to first prunasin and ultimately hydrogen cyanide via the activity of carbohydrate-degrading enzymes belonging to glycoside hydrolase family 3 (GH3). The amygdalin-degrading properties of GH3 were later confirmed by the expression of GH3 in *E. coli*, which resulted in the degradation of amygdalin to prunasin (Motta et al., 2022).

Another nitrogen-containing secondary plant metabolite, glycoside 3-nitropropionic acid (NPA; Figure 6B), is a toxic PSM produced by leguminous plants. NPA irreversibly inhibits succinate dehydrogenase in the TCA cycle, causing toxicity in eukaryotes. Microbial detoxification of NPA has been shown by soil microbes and gut-associated bacteria isolated from rumen and insects, like the Southern green shield bug *Nezara viridula* (Anderson et al., 1993; Nishino et al., 2010; Rogowska-van der Molen et al., 2022). Detoxification of NPA is carried out by either nitronate monooxygenase (NMO), encoded by *nmo*A or *pnm*R (putative nitronate monooxygenase [reductase]), or by propionate-3-nitronate monooxygenase (PnoA), encoded by *pno*A. Although three enzymes were identified to metabolize NPA, all transform it to a non-toxic intermediate 3-oxopropanoate with subsequent release of nitrate and nitrite. The reaction ultimately yields carbon dioxide and acetyl-CoA which enters the TCA cycle and thus serves bacteria as a carbon source (Rogowska-van der Molen et al., 2022). The phylogenetic analysis of genome-encoded *pnm*R revealed the widespread distribution of the gene in diverse bacterial classes, suggesting that potentially many NPA-degrading microorganisms remain yet uncharacterized (Rogowska-van der Molen et al., 2022).

NON-NITROGEN-CONTAINING PLANT SECONDARY METABOLITES

Terpenes

With more than 80,000 known compounds (Christianson, 2017), terpenes constitute the most chemically, structurally, and functionally diverse family of non-nitrogen-containing PSMs described to date (Christianson, 2017; Connolly & Hill, 1991). While these compounds can be synthesized by most organisms, they are particularly abundant and diverse in plants, being an essential component of tree resin and essential oils (Pichersky & Raguso, 2018). Terpenes consist of hydrocarbon chains (or rings) built from linked isoprene units that can subsequently be decorated with functional groups leading to the biosynthesis of terpenoids. Terpenoids are classified according to the isoprene units that contain either two, three, or four isoprene units, that is, monoterpenes, sesquiterpenes, and diterpenes, respectively (Figure 7A–C), and act as both primary and secondary metabolites.

For instance, pigments involved in photosynthesis or in maintaining membrane integrity such as carotenoids or sterols, are of terpenoid nature (Cazzonelli & Pogson, 2010; Dufourc, 2008). Most terpenes, however, serve plants as PSMs and increase fitness under abiotic or biotic stresses. Isoprenoids are known to mediate ecological interactions between plants and other organisms underlying attraction of pollinators, and most importantly, defence against pathogenic microbes and herbivores, particularly insects (Bakkali et al., 2008; Gershenzon & Dudareva, 2007). Terpenoids thus contribute to both direct as well as indirect plant chemical defences. Direct defences frequently act as deterrents and can be toxic to herbivores through a

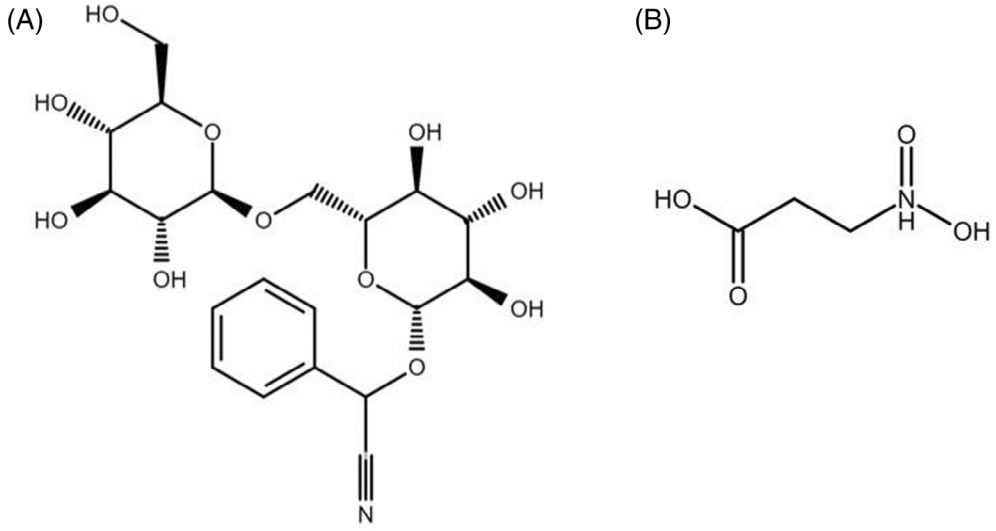

FIGURE 6 Chemical structures of (A) amygdalin present in the almond tree and (B) 3-nitropropionic acid (NPA) found in crown vetch.

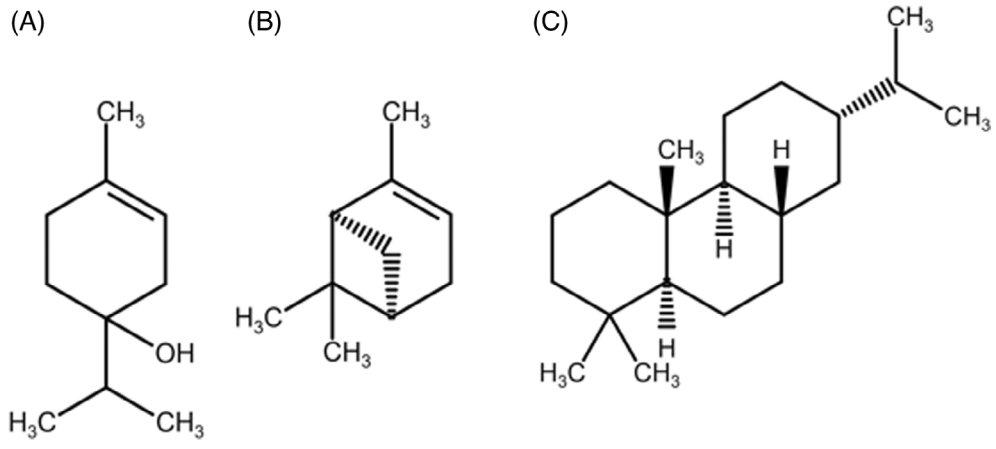

FIGURE 7 Chemical structures of terpenes present in pine tree: (A) terpinene-4-ol, (B) *α*-pinene, (C) abietane.

variety of detrimental effects, hampering the normal functioning of herbivore metabolism. Indirect chemical defences, on the other hand, are used to attract herbivores' natural enemies such as predators or parasitoids (Delphia et al., 2007).

Although the exact mode of action of terpenoids remains unknown, some of their toxic properties derive from their lipophilic nature (Gershenzon & Dudareva, 2007). It has been determined, that by integrating between the acyl chains of phospholipids, terpenes damage cell membranes causing leakage of ions and metabolites (Keeling & Bohlmann, 2006; Lambert et al., 2001).

Given their protective role against natural enemies, many organisms have evolved mechanisms to cope with terpenes. Herbivores contend with isoprenoids in a variety of ways often involving behavioural strategies, for example, avoiding exposure by ingesting low amounts of these chemical defenses. For instance, bark beetle larvae feed gregariously in one continuous front, presumably outrunning tree-induced and terpene-rich resin (Deneubourg et al., 1990; Gregoire et al., 1981).

Microbes possess a variety of detoxification responses to terpenes (Marmulla & Harder, 2014). These strategies include (i) excretion of terpenes through efflux pumps (Papadopoulos et al., 2008; Wang et al., 2013), (ii) enzymatic detoxification of terpenes through glycosylation or oxidation (Wang et al., 2014), and, (iii) utilization of terpenes as carbon sources for nutrition (Wang et al., 2014). The tea tree (*Melaleuca alternifolia*) has been used in traditional Australian medicine because it produces essential oils that are rich in monoterpenes with antimicrobial activity (e.g., terpinene-4-ol, 1,8-cineole, and α-terpineol). The bacterium *Pseudomonas aeruginosa* harbours an efflux system called MexAB-OprM that not only mediates its resistance against these compounds but is also responsible for its resistance to other antibiotics with clinical importance (Papadopoulos et al., 2008). On the other hand, *Pseudomonas putida* strain ATCC 17453 degrades the monoterpene camphor through a series of reactions, in which the first step is catalysed by a cytochrome P450 monooxygenase. The catabolic pathway results in the production of isobutanoyl-CoA and acetyl-CoA. The enzymes involved in these reactions are encoded by the operon *cam*ABCDEFG and are located in a plasmid. Lastly, free-living microbes isolated from pulp mill wastewater and forest soil, such as *Pseudomonas abietaniphila* BKME-9 and *Burkholderia xenovorans* LB400, grow on a variety of diterpenes like abietane, a diterpene that commonly occurs on coniferous trees. These microbes harbour in their genomes a *dit* gene cluster, a group of 20 genes (as described in *P. abietaniphila* BKME-9) that are involved in diterpene catabolism. Not all genes within the cluster are required for diterpene mineralization, but at least three (*dit*I, *dit*H, and *dit*F) are essential (Martin & Mohn, 2000; Smith et al., 2004; Smith et al., 2007). Deleting *dit*R from the genome does not arrest the growth of *P. abietaniphila* BKME-9 on diterpene-rich media (Martin & Mohn, 2000); however, deleting *dit*Q impairs the growth of *P. abietaniphila* BKME-9 on dehydroabietic acid but not on abiotic acid (Smith et al., 2004). Not only can *P. abietaniphila* BKME-9 and *B. xenovorans* degrade diterpenes, they are also able to utilize them as their sole carbon source (Morgan & Wyndham, 2002; Smith et al., 2004; Smith et al., 2007).

Mutualistic terpene-degrading bacteria often live in a close relationship with insects (Itoh et al., 2018; van den Bosch & Welte, 2017). Herbivorous beetles feeding on coniferous trees profit from their gut microbiota, which detoxifies terpenes. Conifers are prolific producers of resin rich in mono- and diterpenes that are highly toxic to insects and have antibacterial properties (Bakkali et al., 2008). Nevertheless, many insects such as bark beetles and pine weevils are conifer specialists. Terpenoid catabolism by symbiotic microbes has been previously described for bacteria isolated from the gut of several bark beetles in vitro (Adams et al., 2013; Berasategui et al., 2017; Boone et al., 2013; Deneubourg et al., 1990; Xu et al., 2016).

The bark beetle *Dendroctonus valens* feeds on *Pinus tabuliformis* trees, whose resin is rich in α-pinene. Two yeasts and three bacterial strains isolated from the digestive system of this beetle can degrade pinene, lowering in vitro its concentration by half (Xu et al., 2016). Likewise, the mountain pine beetle *Dendroctonus ponderosae* hosts a bacterial gut microbiome dominated by *Pseudomonas* sp., *Rahnella* sp., *Serratia* sp., *Brevundimonas* sp., and *Burkholderia* sp. that harbour terpene-degrading genes (Adams et al., 2013). While *Serratia* sp. can reduce the concentration of all monoterpenes—except for α-pinene—by 80%, *Rahnella* sp. degrades up to 45% of the available α-pinene (Boone et al., 2013). Furthermore, both *Serratia* sp. and *Brevundimonas* sp. eliminate the diterpene abietic acid when it was present at low concentrations in the diet (Boone et al., 2013). While the mechanisms of monoterpene degradation in bark beetles remain undescribed, compelling evidence suggested that diterpene mineralization in the mountain pine beetle is catalysed by microbes that harbour the *dit* gene cluster. Likewise, the bacterial gut metagenome in *D. ponderosae* is enriched in *dit* genes compared with that of other herbivores, suggesting these microbes may be benefiting the host through the detoxification of conifer defences (Adams et al., 2013). Further evidence of beetles benefiting from microbial degradation of terpenes comes from the large pine weevil (*Hylobius abietis*). The gut microbiome of this weevil is very similar to that of bark beetles, despite being phylogenetically more related to weevils such as the red palm weevil (*Rhynchophorus ferrugineus*) or the vine weevil

(*Otiorhynchus salicicola*), specializing in palm trees and vines, respectively (Berasategui et al., 2016). A metagenomic survey of *H. abietis'* gut microbial community indicated that the microbiome of this insect harbours several *dit* genes (Berasategui et al., 2017). Genomic binning and subsequent phylogenetic analysis revealed that, as in other bark beetles, these genes are encoded in the genomes of members of Enterobacteriaceae strains (Berasategui et al., 2017). Consequently, the microbiome of the pine weevils can degrade diterpene both in vivo and in vitro. Thus, it is essential to further explore beetle-symbiont interactions, since it could provide insights in general understanding of role of detoxifying microbes in pest management.

Polyphenols

Polyphenols form one of the biggest and most complex classes of non-nitrogen-containing plant secondary metabolites of over 10,000 structurally different compounds that contain a hydroxyl functional group in the aromatic ring (Figure 8A–E) (Li et al., 2014). Polyphenols derive from the shikimate and malonic acid biosynthesis pathways, and are divided into four subgroups: phenols, phenolic acids, flavonoids, and tannins (Chiocchio et al., 2021; Olivoto et al., 2017; Teoh , 2015). Polyphenols are present in all plant organs but individual groups have a storage preference. Phenolic acids, for example, are most often found in seeds, leaves, roots, and stems, flavonoids in aerial parts of plants, whereas tannins are often present in roots, bark, and seeds (Robbins, 2003; Tuominen et al., 2013). Polyphenols vary in size and structure, and can be either a single benzenic ring compound linked to a hydroxyl group (simple phenols) or benzoic acid derivatives (phenolic acids). More complex polyphenols, flavonoids, are composed of two benzene rings (A and B) linked by a three-carbon backbone (C_6-C_3-C_6; ring C), and an oxygen atom that forms a heterocyclic ring (Wang et al., 2022). Flavonoids are further classified into subgroups depending on the degree of saturation in the heterocyclic ring and can be either saturated (flavanones, dihydroflavonols, flavan-3-ols) or unsaturated (anthocyanidins, flavones, flavonols, isoflavones) (Cesco et al., 2012; Gahlawat et al., 2017; Panche et al., 2016). Luteolin, tangeretin, quercetin, kaempferol, genistein and daidzein are one of the most known PSMs among flavonoids. Tannins, on the other hand, are high molecular weight PSMs, which are polymers constituted by flavonoid units or esterified monosaccharides with one or more molecules of phenolic acids (Bravo, 1998). They represent the fourth most abundant plant component, after cellulose, hemicellulose, and lignin (Lonsane, 1997). Tannins are subdivided into two major groups based on their structures and properties: hydrolysable and condensed tannins. Condensed tannins are polymers composed of monomeric flavonoid units (flavan 3-ol or flavan 3,4-diol), which consist of two aromatic rings that are connected via C_4-C_8 bonds, as well as C_4-C_6 linkages in a three-carbon backbone chain but do not contain a carbohydrate core. Polymers of flavonol units are the most common type of tannins found in forage and browse legumes (Smith et al., 2005). Hydrolysable tannins, however, do not contain flavonoid units but are comprised of a polyol carbohydrate core, usually glucose, esterified to phenolic acids, such as gallic or ellagic acids, forming gallotannins and ellagitannins, respectively (Bule et al., 2020; Li et al., 2006).

Polyphenols perform various functions in plants. Flavonoids, for instance, participate in floral pigmentation designed to attract pollinators. Flavonoids are additionally involved in UV filtration and can act as chemical messengers, physiological regulators, and cell cycle inhibitors. In host–microbe interaction, they can initialize the symbiotic relationship between Rhizobia and legumes (Galeotti et al., 2008; Kabera et al., 2014). Besides, polyphenols were proposed to serve as stabilizers of carbon in anoxic soils, according to the *enzyme latch* hypothesis (McGivern et al., 2021). Polyphenols that accumulate in anoxic soil are toxic to soil microorganisms which leads to the inactivation of their extracellular enzymes and ability to bind substrates, hence depriving microbes of nutrients and minimizing their microbial activity. This reduces the rate of soil organic matter decomposition (Fenner & Freeman, 2020; Freeman et al., 2001). Depending on the concentration of polyphenols in animal feed, they might be either beneficial or toxic. Low to moderate concentrations of tannins (≤4%) prevented bloating in ruminants, whereas high (>5%) concentrations inhibited ruminal gut microbiota and resulted in a reduction of nutrient digestibility (Smith et al., 2005). In addition, tannins showed a negative effect on insects (Goldstein & Swain, 1965), and high doses of quercetin (2%–4%) led to chronic nephropathy in rats (Dunnick & Hailey, 1992). Hydrolysable tannins and condensed tannins were shown to have antinutritional and toxic properties when ingested by animals (Acamovic & Brooker, 2005). Furthermore, tannins are known to have antimicrobial properties and they are therefore resistant to microbial attack and degradation (Sallam et al., 2021). The structure of condensed tannins confers a higher resistance to attack than hydrolysable tannins and thus, condensed tannins are more toxic to microorganisms (Pagliarulo et al., 2016). However, there are a significant number of bacteria and fungi that are resistant to these compounds and can degrade them to use them as a sole carbon source. Tannic acid is a high-molecular-weight polyphenol present in the seeds of *Camellia oleifera*. The camellia weevil *Curculio chinensis* is capable of overcoming plant chemical

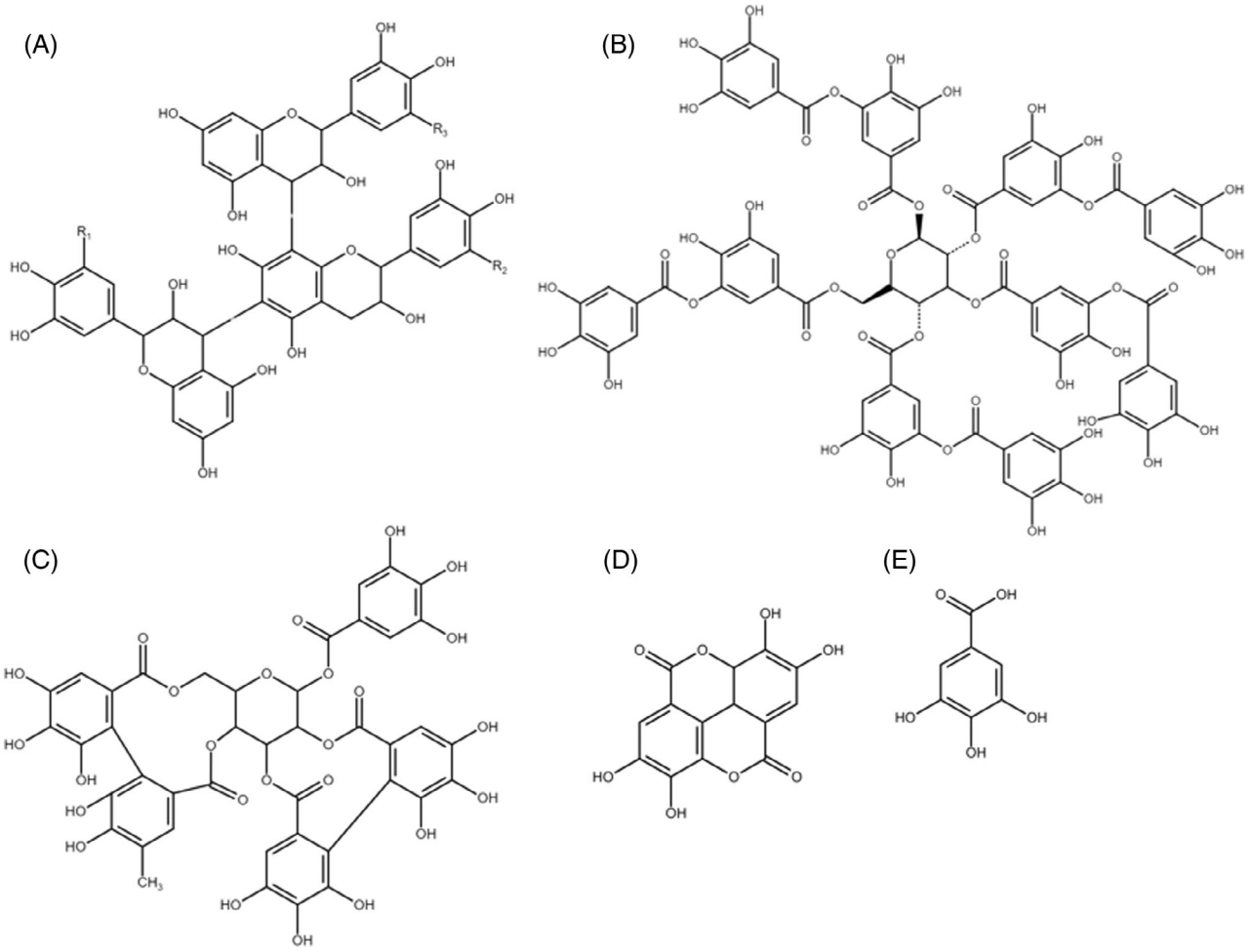

FIGURE 8 Chemical structures of selected polyphenols: (A) condensed tannins, (B) casuricitin (ellagitannin), (C) gallotannin, (D) ellagic acid, (E) gallic acid.

defences and degrading toxic tannic acid (Zhang et al., 2020). Zhang et al. (2020) showed that bacteria from the phyla Proteobacteria, Firmicutes, Fusobacteria, and Cyanobacteria were dominant degraders of tannic acid; however, the microbial enzymes involved in the degradation remain unknown. Likewise, the symbiotic yeast of the cigarette beetle *Lasioderma serricorne* was capable of tannic acid detoxification to gallic acid (GA) (Dowd, 1989). Furthermore, the rumen microbiota has been shown to harbour tannin-degrading microbes and the introduction of a tannin-adapted inoculum to Ethiopian Highland sheep prevented the adverse effect after feeding from *Acacia angustissima* which is rich in condensed tannins. The widespread tannin resistance in rumen microbiota protects ruminant animals from antinutritional effects and is an example of a symbiotic relationship (Odenyo et al., 2001). Moreover, the introduction of tannin-degrading *Escherichia coli*, *Bacillus subtilis*, and *Enterococcus faecalis* bacteria from the desert woodrat to laboratory rats resulted in a higher body mass than control animals when exposed to tannins (Kohl et al., 2016).

The analysis of the degradation pathways of hydrolysable and condensed tannins showed that both subclasses do not share a common breakdown pathway. Hydrolysable tannins were found to be more easily hydrolysed than condensed tannins, due to the presence of ester bonds of gallic (gallotannins) or ellagic (ellagitannins) acids. Gallotannins and ellagitannins are considered the simplest forms of hydrolysable tannins, and upon hydrolysis, they yield gallic acid (GA), ellagic acid (EA), respectively, and glucose (Bhat et al., 1998). Ellagitannins are highly abundant in many plant species, and they occur in monomeric, dimeric, oligomeric, and C-glycosidic forms (Sallam et al., 2021). Although tannins are one of the most diverse classes of PSMs, hydrolysable tannins were found to be degraded by one ubiquitous enzyme, tannin acyl hydrolase, commonly known as tannase (EC 3.1.1.20). Tannase is present in various bacteria, fungi, and yeasts and catalyses the hydrolysis of ester and depside bonds (>2 monocyclic aromatic units linked by an ester group) in gallotannins, GA esters, epigallocatechin gallate, and epicatechin gallate, releasing GA and glucose

(Aguilar & Gutiérrez-Sánchez, 2001; Bhat et al., 1998; de Las Rivas et al., 2019). Bacterial, yeast and fungal tannases share a common pentapeptide active site motif Gly-X-Ser-X-Gly, which is a common feature of the superfamily of esterases (Jimenez et al., 2014; Ren et al., 2013). Tannase is present in a diverse group of microorganisms that occupy different environments, such as rumen gut, soil, and wastewater. Bacteria that exhibited tannase activity are part of many genera, for example, *Actinobacillus* sp., *Campylobacter* sp., *Corynebacterium* sp., *Lactobacillus* sp., *Methanobrevibacter* sp., *Staphylococcus* sp., *Streptococcus* sp., *Streptomyces* sp. (de Las Rivas et al., 2019). Hydrolysable tannins, gallotannins, and ellagitannins are metabolised by tannase either under oxic or anoxic conditions, and the GA which is released upon tannase hydrolysis is further transformed into various metabolites. Under oxic conditions, *Pseudomonas putida* KR2440 metabolises GA as a sole carbon source via a ring-cleavage reaction, followed by hydration and final cleavage to pyruvic and oxaloacetic acid (Nogales et al., 2011). The authors found that enzymes involved in the degradation of GA are part of the *gal* gene cluster. On the contrary, anaerobic degradation of GA in *Lactobacillus plantarum* WCFS1 was carried out by the oxygen-sensitive gallate decarboxylase forming pyrogallol as the intermediary product (Jimenez et al., 2013; Jimenez et al., 2014).

Even though hydrolysable tannins are a large group of polyphenols, their degradation is similar in many microorganisms, since the initial step relies on tannases. Tannases exhibit substantial differences in their molecular structures and amino acid sequences which likely is the adaptation to the complex structures of tannins. Moreover, tannase action is independent of oxygen availability and the differences in the formation of end-products from tannin degradation are restricted to the activity of the subsequent enzymes. The structural differences between hydrolysable and condensed tannins mean that the breakdown pathway of condensed tannins is not initiated by tannases. Below we discuss the current knowledge on the microbial metabolism of flavonoids and condensed tannins, which are polymers of flavonoid units and therefore share similarities in their breakdown pathways.

The gut microbiota of various animal species is well-adapted to the toxicity of condensed tannins and thus is capable of their degradation. The unique structure of flavonoid units (Figure 9A–C), which consists of A, B, and C rings, provides the chemical stability of condensed tannins and flavonoids. Their degradation mediated by microorganisms includes carbon-carbon cleavage reactions involving C- and A-rings, dehydroxylation, and hydrogenation and results in the formation of different compounds under oxic and anoxic conditions. The aerobic breakdown of flavonoid units is carried out via two alternative pathways and yields either quercetin or catechin. Quercetin is one of the most abundant flavonoids, predominantly present in fruits and vegetables in the form of *O*-glucosides (Anand David et al., 2016). Quercetin is converted by *Bacillus subtilis* 168 to 2-protocatechuoyl-phloroglucinol carboxylic acid and carbon monoxide by novel Fe-containing quercetin 2,3-dioxygenase encoded by the *qdo*I gene (Bowater et al., 2004). It is the first described prokaryotic carbon monoxide-forming enzyme that can utilize flavonol. On the other hand, the catechin breakdown

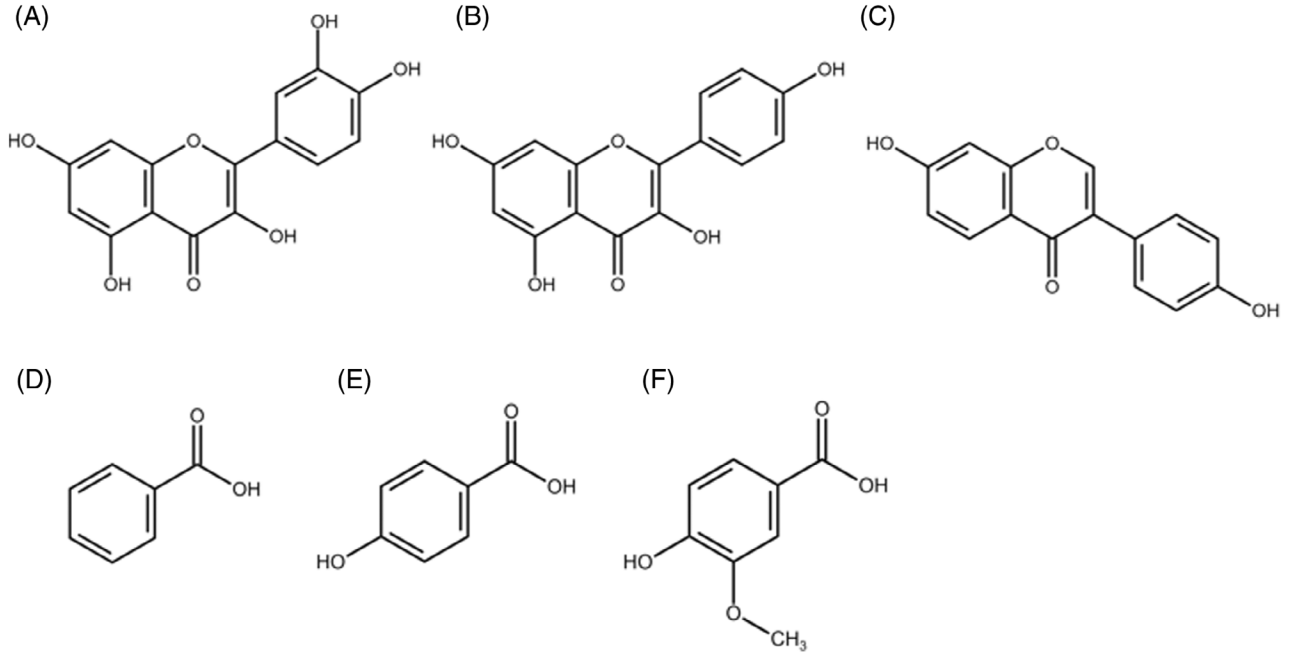

FIGURE 9 Chemical structures of flavonoids and phenolic acids and their occurrence in plants: (A) quercetin (citrus fruits), (B) kaempferol (kale), (C) daidzein (soybeans), (D) benzoic acid (cinnamon), (E) 4-hydroxybenzoic acid (coconut), (F) vanillic acid (*Angelica sinensis*).

pathway relies on the cleavage of the heterocyclic ring of catechin, a flavan-3-ol to phloroglucinol carboxylic acid and protocatechuic acid (Leisinger, 1981; William et al., 1986). The anaerobic conversion of catechin on the other hand yields diarylpropanol as a first degradation product, whereas quercetin is broken down into phloroglucinol and phenylacetate derivatives. Ultimately the anaerobic digestion of catechin and quercetin yields acetate and butyrate and depending on the microbial activity, acetate might either enter the TCA cycle, or along with butyrate be used in methanogenesis via syntrophic ruminal microbes to form methane and CO_2 (Bhat et al., 1998; Field & Lettinga, 1992). *Bradyrhizobium japonicum* (Alphaproteobacteria) uses catechin as a sole carbon source (Hopper & Mahadevan, 1997) and it was found that condensed tannins are depolymerized to monomers, epicatechin, and catechin (McGivern et al., 2021). Another way to degrade flavonoids is a dehydroxylation reaction which is based on the removal of the *p*-hydroxy group from the aromatic ring. Human gut microbiota was shown to dehydroxylate ellagic acid into urolithins via sequential removal of hydroxyl groups (Espín et al., 2013). Hydrogenation of daidzein is the third way of flavonoid degradation and although daidzein is not toxic, its conversion is the model for understanding hydrogenation mechanisms of flavonoid units. Human gut bacterium *Slackia isoflavoniconvertens* (Coriobacteriia) converts soybean isoflavones daidzein and genistein via dihydrodaidzein and dihydrogenistein, respectively in subsequent hydrogenation reactions to equol and 5-hydroxy-equol (Schroder et al., 2013).

Phenolic acids and phenolic acid esters (Figure 9D–F) are the simplest and the last group of polyphenols. They are found to be the most toxic compounds in the polyphenolic class. Coumaric acid, benzoic acid, 4-hydroxybenzoic acid (4-HBA), vanillic acid, and 4-hydroxybenzaldehyde are among the best-known simple toxic phenolics. 4-HBA is commonly used in manufacturing processes (e.g., processing petroleum) which resulted in the accumulation of the compound in the environment. It is harmful to humans and the accumulation of 4-HBA in the soil causes deficiency of nutrients and inhibits the growth of plants. Two strains isolated from marine sediments, *Acinetobacter johnsonii* FZ-5 and *Klebsiella oxytoca* FZ-8 were able to degrade 4-HBA under anoxic conditions (Lu et al., 2022). Fungi *Phomopsis liquidambari* isolated from *Bischofia polycarpa*, degraded 4-HBA using three enzymes: 4-HBA hydroxylase, 3,4-dihydroxybenzoic acid decarboxylase and catechol 1,2-dioxygenase to *cis*,*cis*-muconic acid TCA cycle (Chen et al., 2011). Furthermore, rumen gut microbiota and fungus *Aspergillus niger* degraded toxic ferulic acid, caffeic acid, and coumaric acid, and multiple bacterial strains, including *Bacillus* sp., *Brucella* sp., and *Enterobacter* sp., isolated from tobacco cropping soil degraded in vitro eleven phenolic compounds (Chang et al., 2022; Kim et al., 2021; Lubbers et al., 2021). Likewise, the degradation potential for toxic phenolic compounds has been determined in the gut microbiota of the diamondback moth *Plutella xylostella*. The metagenomic analysis of *Enterobacter asburiae* and *Enterobacter cloacae* showed that these two species might aerobically degrade catechol. The authors identified eight genes encoding for catechol 1,2-dioxygenase, muconate cycloisomerase, muconolactone D-isomerase, 3-oxoa dipate enol-lactonase, 3-oxoadipate CoA-transferase,-acetyl-CoA acyltransferase, 3-oxoadipyl-CoA thiolase, and 3-oxoadipate enol-lactose/4-carboxymucono lactone decarboxylase (Xia et al., 2017). The in vitro experiment showed that gut bacteria of *P. xylostella* degraded phenol within 24 h. This is in line with findings from Kohl et al. (2014), establishing that the gut microbes of the desert woodrat *Neotoma lepida* are responsible for the detoxification of phenolic-rich resin from the leaves of creosote bush *Larrea tridentata* and antibiotic removal of microbiota resulting in woodrat susceptibility to toxic compounds.

OTHER NON-NITROGEN-CONTAINING PLANT SECONDARY METABOLITES

Terpenes and polyphenols constitute the majority of non-nitrogen PSMs, and all other metabolites, that do not fit within either class and grouped separately. One such compound is oxalate, which is a hydrocarbon commonly present in higher plants. The calcium salt of oxalate (Figure 10) serves plants as a defensive agent against herbivores (Franceschi & Nakata, 2005). Genomic analysis of the endosymbiotic bacterium *Ishikawaella capsulata* isolated from the plataspid shield bug *Megacopta punctatissima* showed that *I. capsulata* carries an *ode* gene on its plasmid the coding for an oxalate decarboxylase and therefore could have a detoxifying role in insects.

DEGRADING MICROBES IN BIOTECHNOLOGY AND BIOREMEDIATION

We have discussed the metabolic potential of microorganisms to degrade toxic PSMs. Microorganisms that

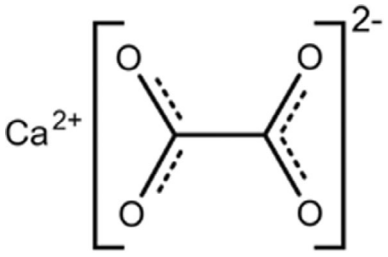

FIGURE 10 Chemical structure of calcium oxalate. It is accumulated in various plants, such as rhubarb or turmeric.

exhibit toxin-degrading abilities may be applied in various industries, such as agriculture, biotechnology, and bioremediation. The identification of novel genes and determination of breakdown pathways allows understanding and optimization of the degradation processes. Moreover, these microbes might contribute to the removal of toxic PSMs from soil, aquatic sediments, and ground waters and similarly to the removal of pharmaceuticals, they might aid in the removal of plant toxins from wastewater.

Due to the increased usage of tobacco products, the industry generates solid and liquid tobacco wastes, which contain high concentrations of nicotine. The improper post-production handling of tobacco wastes causes nicotine to dissolve in water, which leads to the contamination of soil and groundwater. The microbial removal of nicotine from contaminated sources can be an effective way to decrease nicotine pollution in the environment (Gurusamy & Natarajan, 2013). A similar approach could be applied in handling tannery waste. Tannins are agricultural waste that exhibits antinutritional properties. They can bind proteins, making them unavailable for living organisms. Microorganisms were observed to grow and degrade tannins and therefore could be applied in waste management. Thus, tannin-degrading microbes could contribute to decreasing tannin deposition in the ecosystem (Farias et al., 1994). Furthermore, several bacteria species were isolated from conifer pulp mill wastewater, which is rich in resin terpenes and their removal could prevent terpenes from leaching into the soil (Smith et al., 2008). On the other hand, moving towards sustainable waste management by recycling plant wastes using microbes seems to be crucial for a circular economy. Industrial plant wastes could be subjected to microbial valorisation since they are enriched in highly nutritious compounds. It was suggested that toxin-degrading microbes might contribute to the caffeine removal from coffee pulp and husk (Dash & Gummadi, 2006). These by-products are rich in carbohydrates and proteins after decontamination and could be further used as animal feed (Pandey et al., 2000). Moreover, the removal of α-chaconine and α-solanine from potato juice could result in the production of potentially high-value food ingredients due to the high protein concentration of potato juice (Hennessy et al., 2018). Also, via microbial decontamination, products containing nitrotoxins, such as NPA or 3-nitropropanol (NPOH) could be pre-treated with detoxifying bacteria or bacterial extracts (Rogowska-van der Molen et al., 2022).

Resistance breeding

As sessile organisms, plants developed well-adapted defences, such as the biosynthesis of PSMs that allow them to cope with environmental stressors like herbivores, insects, and pathogens. However, domesticated crops have lost many of their natural adaptive responses due to selective breeding directed towards favourable traits such as taste and appearance (Ku et al., 2020; Wink, 1988). To better protect commercial crops, plant breeders have started to reintroduce natural adaptive responses that are well embedded into the genetics of wild crop relatives and can be mined for plant breeding purposes (Huang & Han, 2014). Currently, natural genetic variation is explored using either wild plants, backcrosses, or inbred populations in large-scale genome-wide association studies and using quantitative trait loci mapping (Coolen et al., 2019; Coolen et al., 2023; Davila Olivas et al., 2017; Kloth et al., 2016; Proietti et al., 2018; Thoen et al., 2017). Ultimately, these studies contribute to reintroducing lost plant defence mechanisms against pests.

Plant defences are regulated by plant hormones (PHs) such as salicylic acid, jasmonic acid, ethylene, abscisic acid, and a complex network of intertwined signalling cascades regulated by transcription factors (Frick et al., 2017; Pieterse et al., 2012). Eventually, such defence cascades lead to the production of either constitutive or stress-induced PSMs. Some of these metabolites are healthy for humans, while others may be toxic to either humans or other animals, including pest insects, and pathogens. Examples of such secondary metabolites are quinolizidine-alkaloids that are abundant in lupins, making them thereby bitter and toxic to humans and insects, yet via cross-breeding sweet lupins were devoid of alkaloids, making them highly susceptible to insect herbivores (Wink, 1988; Wink et al., 1995). Since alkaloids are toxic, plant breeding is directed towards further reducing their content, thereby making plants more susceptible to insect herbivores.

Similarly, commercial tomato plants have lost their resistance to many insect herbivores, including virus-transmitting whiteflies. Wild tomato plants (i.e., *Solanum habrochaites*) produce sesquiterpene 7-epizingiberene, which is toxic to spider mites, and repels whiteflies (Bleeker et al., 2011; Bleeker et al., 2012). Introgressing the sesquiterpene biosynthetic pathway of wild tomato into a cultivated tomato, resulted in improved plant resistance to several insect herbivores (Bleeker et al., 2011; Bleeker et al., 2012). Moreover, it also conferred resistance to several plant pathogens, including bacteria, fungi, and oomycete pathogens, showing the potential of PSMs in resistance to both insects and pathogens (Zabel et al., 2021). Incidentally, spontaneous mutations can lead to increased resistance against pathogens. In cotton, the flavonoid level was enriched and led to the red coloration of flowers and increased resistance to wilting caused by *Verticillium dahlia*, a major threat to cotton production (Long et al., 2019).

In grapevine, resistance to the powdery mildew pathogen *Erysiphe nectator* was associated with both plant primary and secondary metabolites (Ciubotaru et al., 2023). Metabolic profiles of susceptible and

resistant plants pointed towards the involvement of many different compounds in plant resistance, including primary compounds, volatile organic compounds, and phenolic compounds. Complementary omics approaches will be necessary to reveal underlying genetics that can be used for resistance breeding. On the other hand, plants face the challenge of encountering multiple stress factors in the field that induce defense mechanisms that may counteract each other and therefore complicate breeding strategies (Coolen et al., 2022; Thoen et al., 2017). For these reasons, multi-stress and multi-omics approaches are of great value to further improve resistance breeding. Finding the ultimate combination of plant metabolites, with a focus on plant secondary metabolites, that confer resistance to major threats while at the same time maintaining the crop's flavour and digestibility will hopefully support sustainable plant-based production in the future.

MICROBIAL PEST CONTROL STRATEGIES

The ability to overcome plant defences and degrade toxic PSMs is the evolutionary achievement of microorganisms. Via detoxifying symbiosis, microbes protect insects against the adverse effects of toxins. Insect-associated microbes show the ability to degrade toxic metabolites belonging to every class of secondary metabolites synthesized by plants. Their close relationship with the host contributes to the insects' widespread infestation of multiple plant species and poses a threat to the far-reaching spread of resistance to toxic compounds. The increase in the abundance of toxin-degrading microbes in the environment could lead to the overpopulation of pest insects, which could drastically reduce crop yields (Itoh et al., 2018; Rupawate et al., 2023). The Food and Agriculture Organization of the United States (FAO) estimated that approximately 40% of the world's total crops are lost due to the intervention of pest insects. Nowadays, the use of chemical pesticides has started to discontinue, and biological pest control strategies are time-consuming and oftentimes do not yield satisfactory results. Moreover, to secure the supply in the face of an increasing food demand an effective pest control strategy is needed. Manipulation of insect microbiota by targeting toxin-degrading microbes could become one of the approaches to fighting pests. Here, we emphasize that the Microbial Pest Control strategy (MPC) could become a sustainable and effective alternative to traditional pest management techniques.

Development of an alternative pest control strategy towards widely used chemical insecticides comes with challenges; however, microbes were already shown to be an effective tool in that field. One of the current MPC approaches relies on employing bacterial species as natural enemies against pests. The spores of an entomopathogen *Bacillus thuringiensis* (*Bt*) enhanced with bacterial culture broth suppressed the immune response of beet armyworm *Spodoptera exigua* (Hrithik et al., 2022). Further, *Photorhadbys luminescens* EGAP3 was found an effective biocontrol agent against the African migratory locust *Locusta migratoria migratorioides* (Muhammad et al., 2022).

Another MCP strategy specializes in targeting insect microbiota, which was shown to be essential for insects. Antibiotic removal of microbiota or egg surface sterilization has negative effects on insects since they impair insects' development and fecundity (Goane et al., 2022; Kafil et al., 2013). Currently, one of the popular MPC strategies is the incompatible insect technique (IIT), which has been proven to be an effective approach in pest management and is used to manipulate insect microbiota, through which male insects are made incompatible for reproduction. These techniques are now widely used in *Drosophila* and mosquitos (Pagendam et al., 2020; Ridley et al., 2013). On the other hand, applying paratransgenesis, as the MPC technique, allows for the genetic modification of the insect gut microbes. The genetically modified microbes that are no longer capable of the synthesis of essential nutrients the insects cause a reduction in the insect population (Taracena et al., 2015). Targeting gut symbionts via CRISPR-Cas9 mechanisms is another novel MPC strategy, since it allows deleting of detoxifying genes and hence decreases the spread of resistance phenotype among insects (Sander & Joung, 2014; Selle & Barrangou, 2015; Zhao et al., 2020). Although several MPC approaches emerged, they often suffer from technical difficulties, such as population size in IIT, or high costs and limiting their use. More research needs to be done to tackle these obstacles and deliver sustainable and affordable means to fight pests and insects.

Over the past decades, several alternative approaches focusing on exploiting microbes as MPC strategy have been described, yet only recently have they started to gain popularity. The manipulation of gut microbiota via IIT, paratransgenesis, CRISPR-Cas9, and their application in pest control are considered historic breakthroughs, and more research should be conducted in that direction. The development of novel MPS techniques could lead to securing future food demand and guaranteeing environmental safety.

CONCLUSIONS

Plants rely on the interdependent function of plant hormones, primary metabolites, and secondary metabolites. Although plant hormones and primary metabolites are essential for plants, their life depends on their capacity to interact with the environment and is largely facilitated by secondary metabolites. One of their main roles is providing defence against the harmful attackers

such as herbivores, insects, and pathogens. This defence depends on the biosynthesis of toxic compounds, which have been classified into nitrogen-containing and non-nitrogen-containing PSMs. The most-studied PSMs belong to the classes of alkaloids, glucosinolates, terpenes, and polyphenols, and even though they exhibit toxic properties, many microorganisms have the capabilities to detoxify or biotransform them into non-toxic compounds. Often, these toxins even serve microbes as nitrogen and/or carbon source. Toxin-degrading microbes were isolated from various ecological niches, such as soil, water, human, rumen, and insect gut systems, showing widespread detoxifying capabilities. The far-reaching distribution of toxin biodegradation by microbes poses a threat to ever-growing food demand and measures need to be taken to prevent further crop losses (Dwivedi et al., 2021). Studying these microorganisms might inform future crop protection approaches.

Microbes degrade compounds belonging to all major classes of PSMs, and often they rely on the same enzymes that detoxify different compounds. For instance, cytochrome P450 was shown to be involved in the degradation of both alkaloids and terpenes, and is commonly considered to be involved in the detoxification of various compounds in both eukaryotes and prokaryotes (Kelly & Kelly, 2013). On the other hand, some microbes harbour unique genes in their genomes and plasmids, and might even exhibit multiple detoxification pathways of the same metabolites. For example, bacteria belonging to the genera *Pseudomonas* sp. degrade toxic alkaloid caffeine via either *N*-demethylation or C-8 oxidation using breakdown pathways that showed little to no similarity, implying a divergent origin. Likewise, differences in the metabolic pathways are frequently dependent on the presence or absence of oxygen; the biotransformation of gallic acid yields different products under oxic and anoxic conditions. Even though the degradation of particular compounds may depend on many factors, the adaptive capabilities of microbes to degrade toxic plant secondary metabolites in the development of alternative microbial pest control and industry, have only recently gained more interest.

Many toxin-degrading microbes live in a close relationship with insects, and via detoxifying symbiosis, they provide them with protection against the adverse effect of toxic PSMs and insecticides (Itoh et al., 2018; van den Bosch & Welte, 2017). Henceforth, microbes contribute to the spread of insect resistance to natural plant defences. One of the trends in current pest control management is applying the breeding of domesticated plants with wild species to restore the lost potential of plants to defend themselves against insects and pathogens (Ku et al., 2020). Although challenging, focusing on the optimization of resistance breeding and choosing the right combination of metabolites might bring a functional solution to current problems in pest control. Alternatively, targeting detoxifying microbes that live in a symbiosis with insects, is yet another example of benefiting from their evolutionary achievements. Recent scientific advances allowed for such techniques as incompatible insect techniques, paratransgenesis, and CRISPR-Cas9 to target specific microbes and therefore modulate the insect's microbiome (Rupawate et al., 2023). Ultimately, detoxifying microbes might be applied in biotechnology and bioremediation to pre-treat contaminated feed and remove toxic compounds from soil and wastewater (Jensen, Strobel, et al., 2009; Rogowska-van der Molen et al., 2022).

AUTHOR CONTRIBUTIONS

Magda Rogowska-van der Molen: Conceptualization (lead); investigation (lead); writing – original draft (lead); writing – review and editing (lead). **Aileen Berasategui-Lopez:** Conceptualization (supporting); investigation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (supporting). **Silvia Coolen:** Conceptualization (supporting); investigation (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Robert S. Jansen:** Conceptualization (supporting); project administration (supporting); supervision (equal); writing – original draft (supporting); writing – review and editing (supporting). **Cornelia Welte:** Conceptualization (equal); funding acquisition (lead); project administration (lead); supervision (lead); writing – original draft (supporting); writing – review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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