The Chemical Ecology of Benzoxazinoids

Christelle Aurélie Maud Robert* and Pierre Mateo

Abstract: Benzoxazinoids are specialized metabolites that modulate plant physiology and plant interactions with their environment. In this review, we synthesize their multiple functions and ecological relevance. We first provide an overview of benzoxazinoid biosynthesis and highlight known regulatory elements involved in modulating their production. We then outline the role of benzoxazinoids in plant nutrition, vegetative and reproductive growth, and defense. We further summarize how plants modulate benzoxazinoid production in response to environmental factors such as temperature, drought, CO_2, light, or nutrient levels. We emphasize the potential role of benzoxazinoids in conferring plant tolerance to abiotic stresses. Finally, we argue that benzoxazinoids act as a strong selective force on different trophic levels by shaping the plant interactions with microbes, insect herbivores, and competitor plants. Understanding the pivotal role of benzoxazinoids in plant biology is crucial to apprehend their impact on (agro)ecosystem functioning and diversity.

Keywords: Benzoxazinoids · Plant–environment interactions · Plant–herbivore interactions · Plant–microbe interactions · Plant–plant interactions

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1. Introduction

Benzoxazinoids are indole-derived compounds comprising benzoxazinones (1,4-benzoxazin-3-one skeleton) and benzoxazolinones (1,3-benzoxazol-2-one core structure) (Table 1). Benzoxazinones can further be classified as lactams, hydroxamic acids and methyl hydroxamates. Benzoxazinoids are widespread in Poaceae (grasses such as maize, rye, and wheat)[1] and can additionally be found in some dicotyledon species of Acanthaceae, Lamiacae, Ranunculaceae, and Plantaginaceae.[2,3]

The benzoxazinoid synthesis pathway has been extensively studied in maize (Fig. 1), although its regulation remains unclear. Multiple mutants, exhibiting mutations at different steps of the

benzoxazinoid pathway, have been isolated from natural maize populations or engineered.[4–6] These advanced genetic background and tools offer the ideal ground to further characterize benzoxazinoid chemistry and biology.

The pivotal role of benzoxazinoids in plant physiology and plant interactions with their environment is becoming increasingly evident.[7–10] Benzoxazinoids are important modulators of plant nutrition and development, defenses, and reproduction.

This multifunctionality demonstrates that the classical trichotomy of plant low molecular weight compounds in hormones, primary or secondary metabolites is not as sharp as initially thought.[11] While studies on non-defensive roles of benzoxazinoids remain scarce, they will be key to understand the evolutive and (agro)ecological impact of benzoxazinoids in ecosystem functioning. Here we aim at summarizing the current knowledge on the multiple roles of benzoxazinoids in plant physiology and interactions with abiotic and biotic factors.
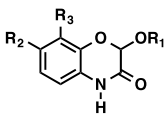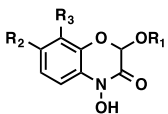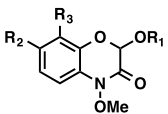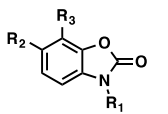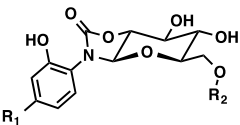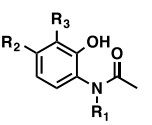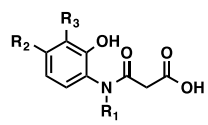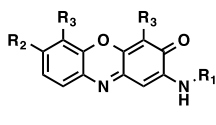
2. Benzoxazinoid Biosynthesis and Distribution

2.1 *Biosynthesis*

The biosynthesis of benzoxazinoids has essentially been characterized in maize, *Zea mays*[2,5,12–14] and was recently reviewed in depth.[8,9,15,16] Benzoxazinoids are derived from the shikimic acid pathway. The first step of their biosynthesis is the conversion of indole-3-glycerol phosphate (IGP), also precursor of tryptophan biosynthesis, into indole. This transformation occurs in the chloroplast and is operated *via* the indole-3-glycerol phosphate lyase activity of benzoxazinless1 (BX1) enzyme.[2,12] DIMBOA levels correlate with *BX1* expression in maize,[17] but may also mirror other processes such as storage and recycling.[17–19] In maize, the conversion of IGP into indole can also be mediated by an indole-3-glycerol phosphate lyase1 IGL1 and by the tryptophan synthase alpha subunit1 TSA1, albeit at lower rates.[20,21] It is generally accepted that indole is then converted into the lactam HBOA and oxidized to form the hydroxamic acid DIBOA, through a series of transformations that happen in the endoplasmic reticulum membrane.[12,22] This conversion includes four consecutive oxidations by the cytochrome P450 enzymes BX2, BX3, BX4 and BX5.[12,23] DIBOA is glucosylated by one of the UDP-glucosyltransferases BX8 or BX9 in the cytoplasm of the plant cell.[24] Noteworthy, an alternative pathway has recently been proposed discussing the

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Table 1. Overview of benzoxazinoid structures, their major metabolites and the corresponding commonly accepted acronyms.

Benzoxazinone, lactams

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	HBOA
R_1=Glc	R_2=H	R_3=H	HBOA-Glc
R_1=H	R_2=OCH$_3$	R_3=H	HMBOA
R_1=Glc	R_2=OCH$_3$	R_3=H	HMBOA-Glc
R1=Glc-Hex	R_2=OCH$_3$	R_3=H	HMBOA-2Hex
R_1=H	R_2=OCH$_3$	R_3=OCH$_3$	HM$_2$BOA
R_1=Glc	R_2=OCH$_3$	R_3=OCH$_3$	HM$_2$BOA-Glc
R_1=Glc	R_2=OH	R_3=H	DHBOA-Glc

Benzoxazinone, hydroxamic acids

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	DIBOA
R_1=Glc	R_2=H	R_3=H	DIBOA-Glc
R_1=H	R_2=OCH$_3$	R_3=H	DIMBOA
R_1=Glc	R_2=OCH$_3$	R_3=H	DIMBOA-Glc
R_1=Glc-Hex	R_2=OCH$_3$	R_3=H	DIMBOA-2Hex
R_1=Glc-Hex-Hex	R_2=OCH$_3$	R_3=H	DIMBOA-3Hex
R_1=H	R_2=OCH$_3$	R_3=OCH$_3$	DIM$_2$BOA
R_1=H	R_2=OCH$_3$	R_3=OCH$_3$	DIM$_2$BOA-Glc
R_1=Glc	R_2=OH	R_3=H	TRIBOA-Glc
R_1=Glc	R_2=OH	R_3=OCH$_3$	TRIMBOA-Glc

Benzoxazinone, methyl hydroxamates

R_1	R_2	R_3	
R_1=H	R_2=OCH$_3$	R_3=H	HDMBOA
R_1=Glc	R_2=OCH$_3$	R_3=H	HDMBOA-Glc
R_1=H	R_2=OCH$_3$	R_3=OCH$_3$	HDM$_2$BOA
R_1=Glc	R_2=OCH$_3$	R_3=OCH$_3$	HDM$_2$BOA-Glc

Benzoxazolinones

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	BOA
R_1=H	R_2=OCH$_3$	R_3=H	MBOA
R_1=Glc	R_2=OCH$_3$	R_3=H	MBOA-Glc
R_1=H	R_2=OGlc	R_3=H	BOA-6-O-Glc

Glucoside carbamates

R_1	R_2	
R_1=H	R_2=OC(O)CH$_2$CO$_2$H	HMPGC
R_1=OCH$_3$	R_2=H	HPMGC

N-(2-Hydroxyphenyl)acetamides

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	HPAA
R_1=H	R_2=OCH$_3$	R_3=H	HMPAA

N-(2-Hydroxyphenyl)malonamic acids

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	HPMA
R_1=H	R_2=OCH$_3$	R_3=H	HMPMA

2-Aminophenoxazin-3-ones

R_1	R_2	R_3	
R_1=H	R_2=H	R_3=H	APO
R_1=C(O)CH$_3$	R_2=H	R_3=H	AAPO
R_1=H	R_2=OCH$_3$	R_3=H	AMPO
R_1=C(O)CH$_3$	R_2=OCH$_3$	R_3=H	AAMPO

possibility of an inversion between the glucosylation and oxidation steps. In this case, HBOA would be first glucosylated and then oxidized to give DIBOA-Glc.[9] DIBOA-Glc hydroxylation and subsequent methylation at the 7-position on the aromatic ring, by respectively BX6 and BX7, yield the hydroxamic acid DIMBOA-Glc.[13] The latter undergoes further methylation at the 4-hydroxy groups by O-methyltransferases, BX10, BX11, BX12, and BX14, to form the methyl hydroxamate HDMBOA-Glc.[5] Interestingly, while the O-methyltransferases BX12 and BX14 are constitutively expressed, BX10 and BX11 are only induced upon herbivory.[5,25] DIMBOA-Glc can further be oxidized and methylated by BX13 and BX7, leading to the introduction of a second methoxy group at the position 8 on the aromatic ring of the benzoxazinones.[6] The resulting DIM$_2$BOA-Glc is used as a substrate by BX14 and converted into the corresponding methyl hydroxamate, HDM$_2$BOA-Glc. Glucosylated benzoxazinones ((2R)-2-β-D-glucosides) are highly stable[26] and stored in the cell vacuole.[27] Storage in the vacuole prevents their hydrolysis by β-glucosidases from the cytosol, plastids, and cell walls.[13,28] Analogues of the sugar derivatives where the saccharide moiety consists of a di- or a trisaccharide have also been detected in rye and wheat.[29] Nevertheless, their full characterization, biosynthesis and biological role remain to be established.

2.2 Reactivity

Upon cell damage (*e.g.* damage by an herbivore), the compartmentalization of benzoxazinone glucosides and β-glucosidases is disrupted, leading to the formation of reactive aglycones and their spontaneous degradation products, benzoxazolinones. The formed aglycones are in equilibrium with their corresponding open forms. These α-oxo-aldehydes are electrophiles and react with primary amines and thiols.[30,31] Ishizaki *et al.* proposed an alternative mode of action, *via* the formation of a nitrenium ion resulting from the elimination of the nitrogen substituents of hydroxamic acids and methyl hydroxamates.[32] The resulting electrophiles can then react with various nucleophiles, the regioselectivity being governed by the nature of the latter (oxygen-, nitrogen- or sulfur-centered nucleophiles).[33,34] Another reactivity worth mentioning is the chelation of metal cations by the hydroxamic acid members of the benzoxazinoid family.[35–39]

2.3 Regulation

The elucidation of the regulatory networks modulating benzoxazinoid production is still in its infancy, but the ongoing considerable effort will likely further shed light on these mechanisms in the coming decade.

BX genes are distributed in clusters that likely originated from gene duplication and chromosomal translocation.[40] In maize, *ZmBX1-BX5* and *BX8* form a 'BX core cluster' at the tip region (within 264 kB) of chromosome 4.[2,12] The genes *ZmBX6* and *ZmBX7* are located 1.7 Mb up- and 15 Mb downstream of the core cluster.[17] Benzoxazinoid-related genes are also grouped in clusters in barnyard grass, and in subclusters in wheat and rye.[41,42] Clustering may facilitate co-heritance and regulation of gene expression through chromatin modification.[43,44]

Cis-regulatory elements were identified as modulators of benzoxazinoid biosynthesis. *Cis*-regulatory elements are typically non-coding DNA containing binding sites for regulatory molecules (*e.g.* transcription factors) required to activate and sustain transcription.[45] In wheat, *TaBX3* and *TaBX4* share 75% sequence identity, but no similarity in their promoter sequences.[43] Additionally, homologous *BX* genes (*BX1* through *BX5*) in wheat, and their orthologs in their ancestors, share a similar transcription dynamic,[46] suggesting a unified regulatory mechanism. Three putative *cis*-regulatory elements, including an MBS, a G-box, and a GAG-motif, were identified as potential regulators of *TaBX3* and *TaBX4* homologs and orthologs in wheat and maize.[43] The function of the three *cis*-regulatory elements in benzoxazinoid synthesis remains though to be further confirmed. In maize, a *cis*-element called DICE (distal *cis*-element), located 140 kbp upstream of *ZmBX1*, is required for the late transcription of *ZmBX1*, but not of *ZmBX2* nor *ZmBX8*.[17]

Several transcriptions factors (TFs) have been associated with benzoxazinoid biosynthesis regulation. TFs transmit stress signals to the nucleus and regulate gene expression of specific genes by interacting with their promoters. In maize, the expression of four TF genes, *ZmWRKY75*, *ZmMYB61*, *ZmNAC35*, and *ZmGRAS37,* correlates with *ZmBX1* expression patterns and mirrors benzoxazinoid concentrations upon infestation by the aphid *Rhopalosiphum padi*.[47] Additionally, the TFs *ZmbHLH57* (Basic
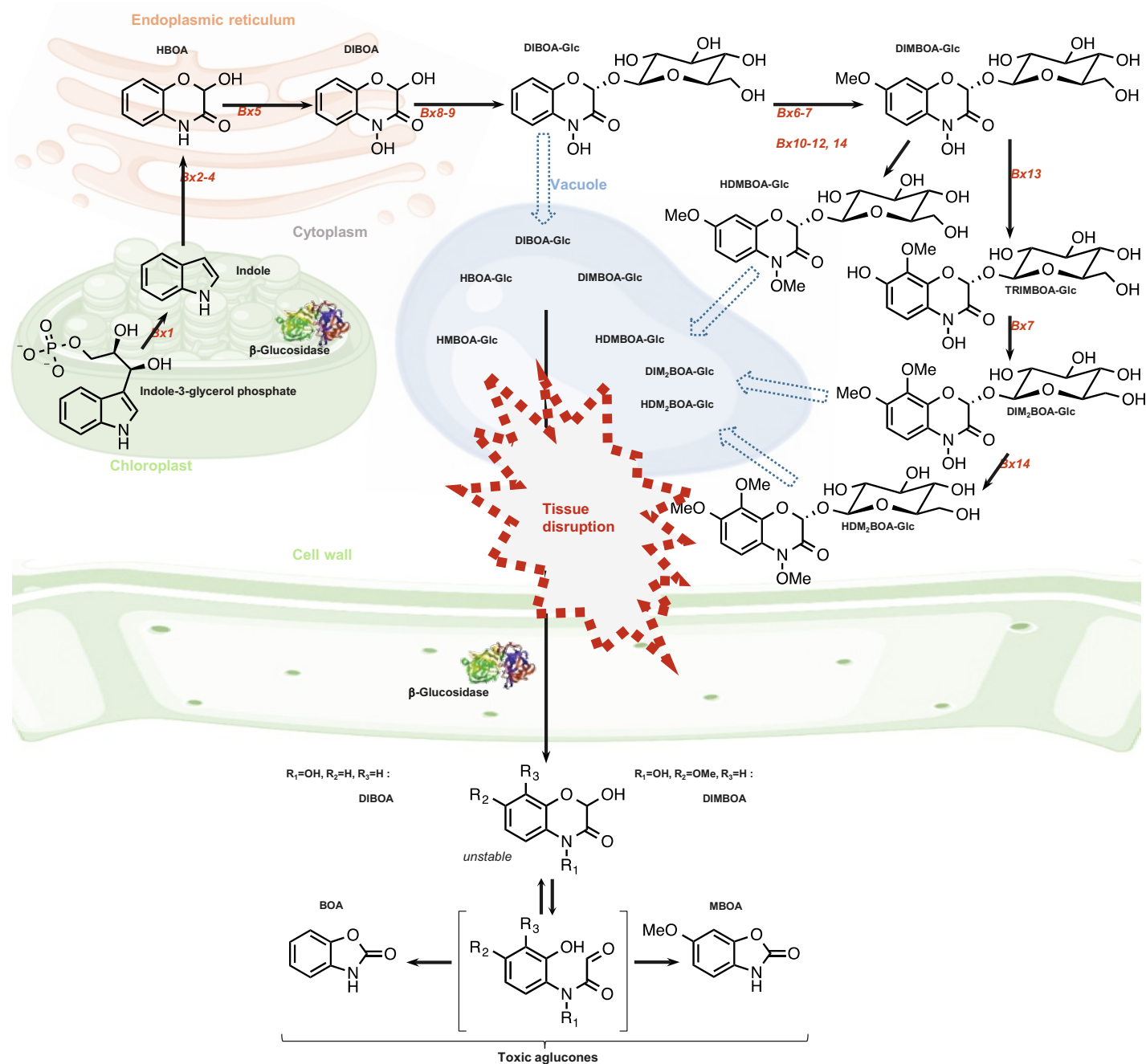
Fig. 1. Known pathways involved in benzoxazinoid biosynthesis. Pictures modified from AdobeStock (95039831; 211095371; 382683055; 216243678).

helix-loop-helix protein) and *ZmWRKY34* gene expression correlates with this of benzoxazinoid biosynthesis genes in systemic leaves of plants infested with oriental armyworm, the *Mythimna separata*.[48] Further analyses predict that *ZmbHLH57* binds to the *ZmBX2* promoter, while *ZmWRKY34* may bind to the *ZmBX6*, *ZmBX10* and *ZmBX11* promoters.[48] Multiple gene regulatory network analyses identified four TFs *ZmMYB112*, *ZmNAC21*, *dwarf plant 8* (GRAS family), and *golden plant 2* (G2-like family) that may be involved in benzoxazinoid regulation in maize.[49] The functional characterization of *ZmbHLH20* and *ZmbHLH76* in a protoplast transfection system revealed that the two TFs modulates, directly or indirectly, the expression of *ZmBX1*, *ZmBX4*, *ZmBX6*, *ZmBX8*, *ZmBX9*, and *ZmBX10/11*.[50] While *ZmbHLH20* regulates DIMBOA, DIMBOA-Glc, DIM_2BOA-Glc, M_2BOA, and HM_2BOA-Glc levels, *ZmbHLH76* modulates DIMBOA, DIMBOA-Glc, DIM_2BOA-Glc, HDMBOA-Glc, M_2BOA, HMBOA-Glc, HM_2BOA-Glc accumulation.[50] The expression of the two TFs modulates, directly or indirectly, the expression of *ZmBX1*, *ZmBX4*, *ZmBX6*, *ZmBX8*, *ZmBX9*, and *ZmBX10/11*.[50] Recently, manipulative assays in the tetraploid wheat, *Triticum turgidum*, demonstrated that the TF gene *TaMYB31* regulates benzoxazinoid biosynthesis by binding to the *BX1* and *BX4* gene promoters, and modulates plant benzoxazinoid levels and resistance towards aphid-, spider mite-, and caterpillar herbivory.[51]

Peptides can regulate the plant immunity. Pep1, encoded by *ZmPROPEP1*, is a maize peptide induced by fungal infection. The peptide elicits a rapid *de novo* production of plant hormones (jasmonic acid (JA) and ethylene), triggers the overexpression of *ZmBX1*, and the accumulation of HDMBOA-Glc in leaves.[52] Whether Pep1 regulates the benzoxazinoid production through a direct interaction with the *BX* genes or through hormonal signaling remains to be tested.

Phytohormones, such as JA, methyl-jasmonate (MeJA), JA–isoleucine conjugate (JA-Ile), *cis*-jasmone, methyl-salicylate (MeSA), and ethylene, and abscisic acid (ABA), can elicit the accumulation of benzoxazinoids in maize and wheat

seedlings.[19,53–59] Importantly, the hormone treatment triggers tissue- and gene-specific responses.[19] For instance, treating wheat seedlings with JA induces *TaBX6*, but not *TaBX8*, and results in varying increases in benzoxazinoid concentrations in different leaf tissues of wheat.[19] How plant hormones regulate the benzoxazinoid biosynthesis pathway remains to be elucidated. Yet, it should be noted that phytohormone independent pathways have also been suggested in controlling benzoxazinoid levels.[48]

Some evidence suggests that some plant specialized metabolites, such as anthocyanins, may regulate the benzoxazinoid pathway: in maize, two W22 lines, that only differ in gene insertions for anthocyanins, exhibit different levels of benzoxazinoids.[60] Further investigations should thus be conducted to characterize the interaction between anthocyanins and benzoxazinoids.

2.4 *Distribution in Plants*
Benzoxazinoids can be found in all the different parts of the plant.[1] Yet, no generalization can be made about the nature and the quantities of compounds in the different plant tissues as they vary greatly between species[5,6,61] and developmental stages.[62–65] Whereas benzoxazinoids can be found in wheat and rye grain,[66] dry maize seeds do not contain any.[62] Upon germination, maize kernels show a fast production increase that reaches a maximum after a couple of weeks.[62,63] Then, after the vegetative phase, a gradual decrease is observed in the late phenological stages for all three major benzoxazinoid-producing Poaceae (maize, rye and wheat).[62,64,67] Benzoxazinoid transport is not yet well understood, but the possibility of long-distance translocation has been suggested.[68]

2.5 *Release in the Rhizosphere*
Benzoxazinoids are released from the roots into the rhizosphere through exudation or cell debris. The transport mechanisms enabling benzoxazinoid exudation remain unclear but is suspected to involve active mechanisms. The exuded benzoxazinoid profiles is qualitatively and quantitatively species-, and even cultivar-specific.[1,69-72] The exudation patterns are dynamic and influenced by environmental factors, such as nutrient conditions, and by biotic interactions.[73,74] DI(M)BOA glucosides are generally exuded and readily hydrolyzed by glucosidases, whose origin (plant or microbe derived) remains unknown. DI(M)BOA aglycones spontaneously degrade and form the more stable (M)BOA (Fig. 2).[75] The further degradation of (M)BOA requires microbial activity.[76] The first step of the process includes a conversion of (M)BOA to the corresponding aminophenol.[77,78] In a second step, aminophenols are converted into aminophenoxazinones (A(M)PO, can occur through oxidation by air), acetamides (H(M)PAA), or malonamic acids (H(M)PMA, Fig. 2).[64,76,78–80] The aminophenoxazinones can further be acetylated to form AA(M)PO.[78,81] In soil, (M)BOA is stable for a few days but the corresponding 2-aminophenoxazin-3-ones can be detected at a stable concentration for months.[75]

3. Benzoxazinoids as Regulators of the Plant Metabolism

3.1 *Plant Mineral Nutrition*
The hydroxamic acid benzoxazinoids DIMBOA-Glc and DIMBOA are involved in nutrient acquisition by plants. DIMBOA-Glc is released by maize roots into the rhizosphere and readily hydrolyzed into DIMBOA. DIMBOA acts as a strong chelator of micronutrients such as iron (Fe), aluminum (Al) and molybdenum (Mo).[35–39] DIMBOA reacts preferentially with iron,[39] with whom it forms complexes of one Fe molecule with two or three DIMBOA ligands, referred to as $Fe(III)(DIMBOA)_2$ and $Fe(III)(DIMBOA)_3$ respectively.[38] The formed Fe-DIMBOA complexes are taken up by the plants and transported to the shoot.[74,82] By combining mutant plants and complementation assays, Hu *et al.* demonstrated that the Fe-DIMBOA complex in the root vicinity enhances chlorophyll contents and promotes plant performance in maize.[38] The mechanisms involved in the transport of Fe-DIMBOA from the soil to the plants remain unknown. Interestingly, although rice and oat do not produce benzoxazinoids, both species are able to take up the metal complex for their iron nutrition.[83]

3.2 *Plant Growth*
Benzoxazinoids regulate shoot and root development by modulating hormonal signaling. To date, benzoxazinoids were suggested to modulate the auxin, cytokinin, and gibberellin signaling pathways.

DIMBOA and MBOA alter growth patterns in oat, timothy grass, amaranth, and pea by lowering auxin binding affinity.[84–87] DIBOA and BOA inhibit the binding of 1-naphthylacetic acid (NAA) to auxin receptors, as well as auxin-induced coleoptile growth in maize.[84] Through their effect as auxin inhibitors, DI(M)BOA and (M)BOA are further suspected to be involved in cases of phototropism occurring in absence of an auxin gradient.[88,89]

Benzoxazinoids may further regulate stem elongation through the modulation of the gibberellin pathway. The 'quick development' mutant (*qd*), identified in wheat, has a transiently quicker stem elongation rate than that of wild type plants.[90] The dynamics of endogenous gibberellin (GA) biosynthesis and the transiently higher GA accumulation in *qd* plants coincides with the observed transient phenotype.[90] A transcriptomic KEGG analysis revealed that the benzoxazinoid biosynthesis pathway is the only pathway to be enriched in *qd* plants.[91] In particular, *BX3*, *BX4*, *BX5*, and *BX8-9* are down-regulated in *qd* plants.[91] Because benzoxazinoids were previously reported to inhibit gibberellin-induced α-amylase activity,[92] they may regulate GA signaling, and thereafter, stem elongation in plants. Yet, this hypothesis should be further investigated to shed light on the interactions between gibberellins and benzoxazinoids.

Finally, benzoxazinoids might shape the plant development *via* the modulation of the cytokinin homeostasis. DIMBOA-Glc can be used as an electron acceptor by a maize cytokinin oxidase/dehydrogenase, CKX1, an enzyme responsible for the irreversible degradation of aromatic cytokinins.[93,94] In Arabidopsis, the expression of *CKX1* is associated with a decline in cytokinin and auxin contents.[95] The constitutive expression of the enzyme leads to tissue-specific responses. In Arabidopsis shoots, *AtCKX1* expression is responsible for a slower formation of the primordia (meristem), a delayed (and in some cases an arrestment of) rosette growth and leaf expansion, a delayed flowering, and fewer flowers per inflorescence.[95] In roots, *AtCKX1* expression is associated with an increase in root growth rate, size, and number of lateral and adventitious roots.[95] It is thus tempting to speculate that DIMBOA-Glc can shape the plant vegetative growth through the activation of cytokinin degrading enzymes.

3.3 *Plant Defenses*
Benzoxazinoids, themselves specialized metabolites involved in plant defenses (See Section 5.2 'Plant-Herbivore Interactions'), also function as regulators of other defensive processes, such as callose deposition and ferulic acid production. The benzoxazinoid-deficient BX1 maize mutant is no longer able to mount callose deposition in response to aphids or pathogens, an effect that can be rescued by complementing the plants with DIMBOA or DIMBOA-Glc, but not with HDMBOA-Glc.[5,68] Consistently, BX12 activity, responsible for the methylation of DIMBOA-Glc to HDMBOA-Glc, decreases callose deposition upon aphid infestation in maize and wheat.[5] Yet its expression in Arabidopsis does not elicit such a response, suggesting a highly specific mechanism which remains unknown.[96] Wheat lines overexpressing the
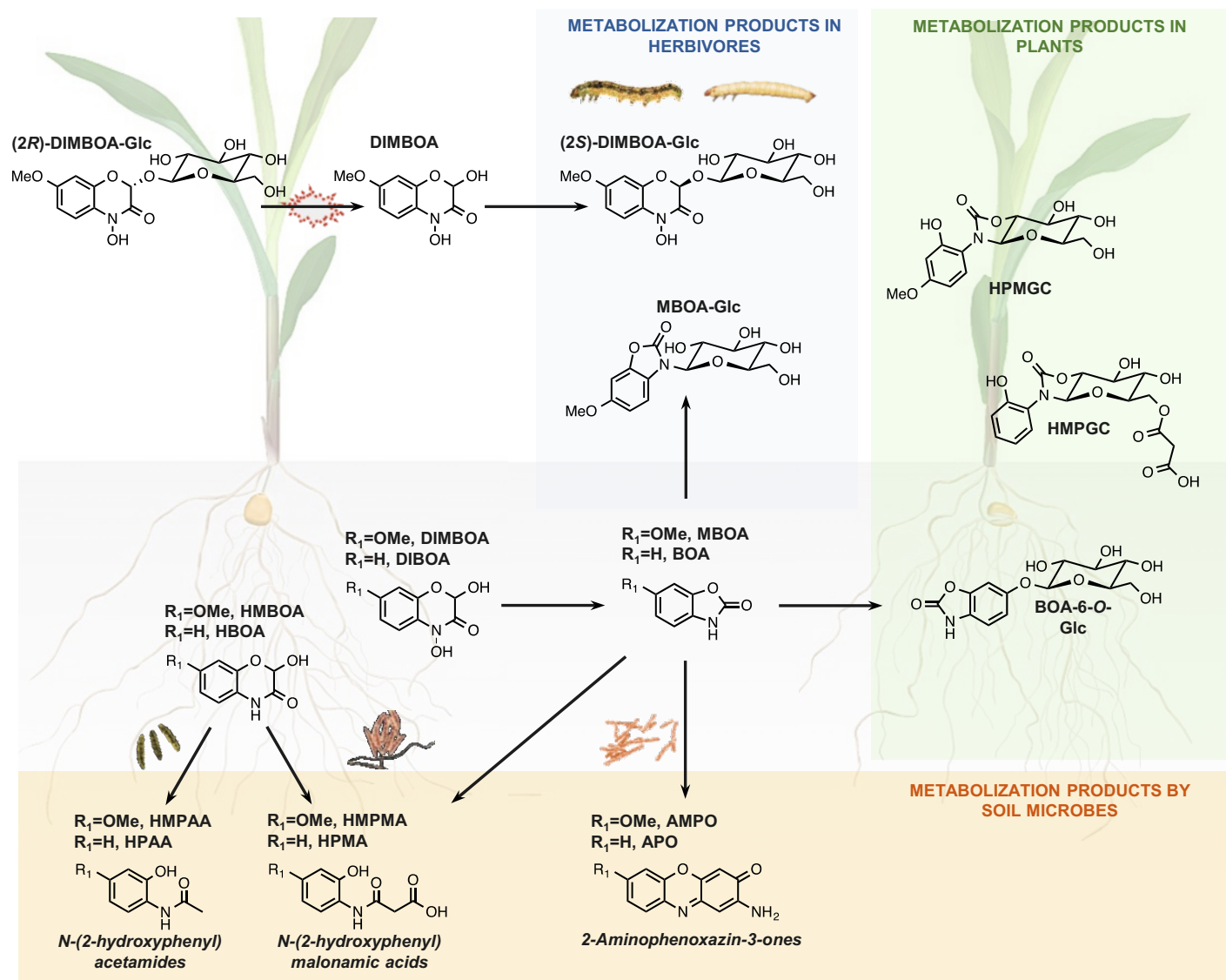
Fig. 2. Benzoxazinoid activation, degradation and metabolization by plants, herbivores, and soil microbes. Drawings of maize and *Diabrotica virgifera* larvae by Thomas Degen.

maize *ZmBX12* further exhibit higher concentrations of the phenylpropanoid ferulic acid, albeit no alteration in pools of amino acid precursors.[96] Ferulic acid is a component of lignocelluloses and confers rigidity to cell walls by linking lignins to polysaccharides.[97] It can thus be suggested that ferulic acid acts as a physical defense against infection by pathogens or piercing-sucking herbivores. Yet, the involved mechanisms and interactions between the benzoxazinoid and phenylpropanoid pathways await to be elucidated.

3.4 *Plant Reproduction*

Benzoxazinoids may also control flowering. In maize, the *BX12* locus affects both male and female flowering time.[98] The role of benzoxazinoids in flowering may, for instance, rely on enhanced iron nutrition, itself regulating flowering time,[99] or on a reconfiguration of the hormonal network.[100] Interestingly, the inactivation of BX12 was selected in maize as its cultivation moved northward.[8] The fact that flowering time and photoperiod sensitivity are traits that were under strong selection during maize adaptation to temperate climates[101] supports a role for *BX12* in flowering, although other hypotheses, such as resistance to herbivory, cannot be excluded.[8]

4. Benzoxazinoid Response to Environmental Conditions

Constitutive and/or induced benzoxazinoid levels depend on abiotic factors such as temperature, precipitation, CO_2, photoperiod, light intensity, UV radiation, and nutrients in maize, wheat, and rye (Table 2). However, the very limited number of studies, together with their differences in characterizing the benzoxazinoid profiles, and species and cultivar-specific effects,[1,114] render comparisons and generalizations premature. For instance, warmer temperatures were associated with lower levels of DIMBOA-Glc, DIMBOA, HDMBOA-Glc, and DIM_2BOA-Glc in maize,[103] and of MBOA in wheat.[104] These results are however not contradictory, as the first study did not report MBOA levels, while the second only focused on MBOA.[103,104] The impact of environmental factors on benzoxazinoids often focused on DIMBOA-Glc and its aglycone (Table 2). Elevated temperature, CO_2 levels, nitrogen availability, light intensity, and UV all lead to a decrease in the metabolite concentration in maize and wheat (Table 2).[103,104,109,111,112,115,116] Iron and drought promote the accumulation of DIMBOA-Glc and DIMBOA respectively (Table 2).[74,103,108] Importantly, interactions between different abiotic factors should be considered, as individual factors can have additive or interactive (synergistic or antagonistic) effects. For instance, and while elevated temperature and CO_2 levels applied

individually decrease DIMBOA-Glc concentrations in maize, their interaction results in antagonistic effects and annihilates the DIMBOA-Glc response.[103] Further investigations are critically required to characterize the role of environmental factors as determinants of benzoxazinoid profiles in plants.

The abiotic-mediated modulation of benzoxazinoid concentrations can be explained by changes in precursor availability, in plant physiology, or by a role of benzoxazinoid in plant tolerance to environmental stresses. For instance, the production of benzoxazinoids directly depends on nitrogen availability in soil and their accumulation is developmentally regulated.[62] In maize, benzoxazinoid levels are the highest at the seedling stage (two leaves) and decline continuously afterwards.[62] The production of the specialized metabolites further depends on environmental factors, such as temperature.[117,118] Identifying the factors leading to variations in benzoxazinoid profiles can thus be challenging. For instance, the lower levels of benzoxazinoids observed under elevated temperatures may be the direct result of temperature or an indirect consequence of temperature due to an accelerated development.[118] Finally, benzoxazinoids may provide an adaptive advantage to plants under abiotic stresses. Although such examples were not yet clearly demonstrated, preliminary and indirect evidence suggests that benzoxazinoids may enhance plant tolerance to drought and to nutrient toxicity. The transcription factor TaMYB31 that regulates the benzoxazinoid biosynthetic pathway in the tetraploid wheat, *Triticum turgidum*,[51] is associated with a higher ABA sensitivity and drought tolerance in Arabidopsis

through the induction of wax biosynthesis genes and drought-responsive genes.[119,120] DIMBOA may protect maize plants from Al toxicity, as the addition of the compound in the growing medium of an Al-susceptible maize line is sufficient to confer protection from Al adverse effects.[121] The role of benzoxazinoids in Al tolerance remains a matter of debate, as no correlation between benzoxazinoids and Al tolerance was observed in other maize lines.[122,123] Yet, the release of benzoxazinoids from the roots into the rhizosphere may have underestimated effects on the soil physical (*e.g.* aggregates) and chemical properties (*e.g.* pH, nutrient availability).[39,124,125]

Understanding the mechanisms underlying abiotic-mediated changes in benzoxazinoids and their adaptive value in stress tolerance will be crucial to develop sustainable strategies to cope with imminent challenges in agriculture, such as climate change or depleted soil fertility.[72,103,126]

5. Benzoxazinoids as Modulators of Plant Biotic Interactions

5.1 *Plant–Microbe Interactions*

Benzoxazinoids are important drivers of plant–microbe interactions above- and below-ground.[1] While benzoxazinoids do not correlate with leaf bacterial and fungal alpha diversity, they are sufficient to suppress pathogens.[60] For instance, benzoxazinoids such as DIMBOA-Glc, HDMBOA-Glc, HMBOA-Glc, HMBOA, DIBOA-Glc, HBOA-Glc, and/or DIM_2BOA-Glc are associated

Table 2. Plants modulate benzoxazinoid production in response to environmental factors. Hypocot.: Hypocotyle; Ref.: Reference. In brackets are aglycones.

	Species	Tissue	DIBOA-Glc (DIBOA)	DIMBOA-Glc (DIMBOA)	HDMBOA-Glc (HDMBOA)	DIM_2BOA-Glc (DIM_2BOA)	(MBOA)	(BOA)	Total	Ref.
	Maize	Shoot							↑	[102]
	Maize	Roots	↓ (↓)		↓	↓				[103]
Temperature	Wheat	Hypoc.					(↓)			[104]
	Wheat	Shoot	↓ (−)		-	-				[51]
[CO_2]	Maize	Roots	↓ (−)		-	↓				[103]
	Maize	Roots	− (−)		− (−)	↑				[103]
Drought	Maize	Shoots, Roots	(↑)							[105]
	Wheat	Shoot	↑ (↑)		-	-				[51]
	Maize	Stem	↓		↓					[106]
Drought x [CO_2]	Maize	Roots	− (−)		-	-				[103]
Temperature x [CO_2]	Maize	Roots	− (−)		-	-				[103]
Drought x Temperature	Maize	Roots	− (−)		-	-				[103]
Drought x [CO_2] x Temperature	Maize	Roots	− (−)		-	-				[103]
Photoperiod	Wheat	Hypoc., Roots					(↓)			[104]
Fertility regime	Rye	Shoot	(↓)					(↓)		[72]
Salt	Rye	Shoot							↑	[107]
	Wheat	Shoot	↑	↑ (−)	-	-				[51]
Iron	Maize	Exudates		↑						[74,108]
Nitrogen	Maize	Shoot		(↑)						[109]
Light intensity	Maize	Shoot		(↓)						[110]
	Wheat	Shoot		↓						[111]
Darkness	Wheat	Shoot		↑						[19]
UV	Maize	Shoot		(↓)						[112]
	Maize	Leaves		(↓)						[113]

with a higher resistance against the Fusarium Head Blight (FHB, fungal infection by *Fusarium* spp.,) in wheat[127–129] and against *Setosphaeria turtica* and *Exserohilum turcicum* in maize.[68,130]

In soil, the presence of benzoxazinoids is associated with lower fungal, but not bacterial, alpha diversity at the root surface,[60,131–133] an effect that may be explained by the fungicidal properties of the compounds.[127,134–142] The clustering of fungal and bacterial communities in the rhizosphere of benzoxazinoid producing- and benzoxazinoid mutant plants was more pronounced at later growth stages, a phenomenon which may be attributed to a lag-phase between benzoxazinoid accumulation and shifts in microbial communities.[143–145] The impact of benzoxazinoids on fungi and bacteria is OTU-specific.[131,146] For instance, DIMBOA triggers chemotaxis (chemically-mediated attraction) of the plant beneficial *Pseudomonas putida*.[147,148] On the other hand, the HDMBOA natural degradation product, an o-imidoquinone intermediate, (3Z)-2,2-dihydroxy-*N*-(4-methoxy-6-oxocyclohexa-2,4-dienylidene)acetamide, inhibits the expression of genes encoding virulence factors in *Agrobacterium tumefaciens*.[149]

Benzoxazinoids and their degradation products are suspected to interact with histone deacetylase (HDAC)-like proteins, suppress anaerobic growth of cellulolytic bacteria, and may inhibit their metal metabolism through direct metal-chelating properties.[32,150,151] Some microbes have evolved the ability to detoxify the plant specialized metabolites into aminophenoxazinones (A(M)PO), acetamides, or malonamic acids (H(M)PMA, Fig. 2).[64,78–80,152,153]

For example, the fungus *F. verticillioides* and the bacteria *Pigmentiphaga* sp. strain DL-8 convert BOA to 2-aminophenol *via* a metallo-β-lactamase (MBL1) and a hydrolase (CbaA) respectively.[142] The fungi *F. moniliforme* and *F. subglutinans* can catabolize BOA and MBOA into *N*-(2-hydroxyphenyl) and *N*-(2-hydroxy-4-methoxyphenyl) malonamic acids respectively.[81,154–156] The fungi *Fusarium* spp. possess an arylamine N-acetyltransferase (NAT1) that converts 2-aminophenol (2-AP) into the nontoxic malonamic acid, N-(2-hydroxyphenyl) malonamic acid (HPMA).[157–160] Some strains of the fungus *Gaeumannomyces graminis* are further able to additionally catabolize BOA into 2-aminophenoxazin-3-one.[81] Importantly, the different benzoxazinoid catabolization pathways existing in soil microbes should be integrated when investigating benzoxazinoid-mediated shifts in microbial community. For instance, while the fungus *F. verticillioides* can metabolize BOA to a less toxic form, it is unable to cope with the presence of the even more toxic APO.[161] The simultaneous presence of microbes that can catalyze the conversion of BOA to APO, such as the bacteria *Bacillus mojavensis*, disrupts the growth of the pathogenic fungus.[161] The growth response to benzoxazinoids of isolated microbial strains grown under laboratory conditions may thus not reflect the response of the same strains growing in community.[162]

Overall, benzoxazinoids, in particular the stable degradation product MBOA, are consistently associated to an increase in abundance of some proteobacteria, and to a decrease in abundance of some *Chloroflexi* bacteria in soil.[60,131,146] Benzoxazinoid-mediated changes in the soil microbial community assemblage are long lasting (over several months) and result in plant soil feedback.[131,163] For example, plants growing in soil previously conditioned by benzoxazinoid-producing maize lines will experience decrease in growth, but enhanced jasmonate-dependent defenses, and increased herbivore resistance.[131] The potential of benzoxazinoids in shaping microbial community assemblages is thus a promising avenue to control pests in agriculture.

5.2 *Plant–Herbivore Interactions*

Leaf herbivory by chewing herbivores locally induces benzoxazinoid biosynthesis and reconfigures their metabolic profile, mostly in favor of HDMBOA-Glc.[1,8,25,27,55,63,164–167] In maize, 24 h feeding by the chewing caterpillar *S. exigua* elicits the rapid

(1 h) overexpression of BX10, BX11, and BX13*,* followed by a transient (4–6 h) induction of BX4, BX5, BX7*,* BX8, and BX9, and a long-lasting (several days) overexpression of BX1, BX2, BX3, and BX6.[25] The increased levels of HDMBOA-Glc can persist after removal of the herbivore.[165] Leaf herbivory by piercing sucking herbivores, such as aphids, elicits a strong induction of DIMBOA-Glc and DIMBOA, and to a lesser extent, of HDMBOA-Glc in the leaf apoplast.[68] Although HDMBOA-Glc is more toxic than DIMBOA-Glc for aphids such as *Rhipalosiphum padi in-vitro*, elevated levels of DIMBOA-Glc confers a higher resistance to the insect *in-planta*.[5] This observation may be explained by the role of DIMBOA-Glc and DIMBOA in regulating other defensive traits, such as callose deposition, which in turn reduce the insect performance.[47] Trade-offs between defenses against chewing and piercing sucking herbivores were observed.[164] For example, feeding by the chewing herbivore *S. exigua* reduces the plant resistance to the aphid *R. maidi*.[164] Root herbivory does not trigger the induction of the benzoxazinoid pathway in roots.[168,169]

Benzoxazinoid glucosides and their activated aglycones have anti-feeding, anti-digestive, or toxic activity on a broad range of generalist herbivores (for a comprehensive review see ref. [27]), although the effects can be dose-dependent,[170–172] species-, and instar-specific.[173,174] DI(M)BOA and HDMBOA-Glc deter and reduce food consumption by caterpillars, such as *S. littoralis*, *S. graminum*, *S. exigua*, and aphids, such as *R. padi*.[167,170,175–177] DIMBOA-Glc, DIMBOA, and MBOA reduce the digestibility and absorption of the consumed food in caterpillars and aphids.[4,170,171,178] The reduced digestibility can be attributed either to the detrimental interaction of benzoxazinoids with digestive enzymes, such as trypsin and chymotrypsin, or with nutrients.[179,180] DI(M)BOA and MBOA reduce growth, and increase developmental time and mortality of chewing and piercing sucking herbivores.[165,166,181–185] The mode of action underlying benzoxazinoid toxicity remains unclear but may be attributed to their mutagenic and neurological effects, as well as to the disruption of important metabolic pathways.[179,186–188]

The adverse effects conferred by benzoxazinoids can lead to avoidance strategies by some herbivores. For instance, the aphid *Sitobion fragariae* can learn and adapts its feeding strategy by reducing probing time and cell punctures when feeding on high-benzoxazinoid wheat varieties.[189] Some herbivores, mostly specialist insects feeding on a narrower range of plant species than generalists, have evolved counter-adaptations to cope with-, and even highjack, benzoxazinoids.[27] Counteradaptations to plant defenses include resistance and tolerance strategies.[190] While tolerance refers to adaptations that prevents from damage (*e.g.* target insensitivity), resistance refers to the active transport and/ or biotransformation of the plant defensive compound.[190] To date, resistance strategies to benzoxazinoids were mostly investigated and include the isomerization of (2*R*)DIMBOA-Glc to (2*S*)-DIMBOA-Glc by *Spodoptera frugiperda*,[191] MBOA *N*-glycosylation by *S. frugiperda* and *Diabrotica virgifera*,[4,192] and detoxification through cytochrome P450 and glutathione *S*-transferase.[188] The root herbivore, *D. virgifera*, further sequesters HDMBOA-Glc and MBOA-Glc in its hemolymph and uses them for its own protection from entomopathogenic nematodes.[192,193] The transfer of benzoxazinoids in food webs further shapes the evolution of higher trophic levels.[193]

5.3 *Plant–Plant Interactions*

The exudation of chemicals in soil may affect the growth, development, and distribution of neighboring plants.[10,64] The process by which root-exuded chemicals elicit detrimental effects on neighboring plants is termed 'allelopathy'.[194] Benzoxazinoids, released from the roots into the rhizosphere, play a critical role in allelopathy in maize, rye, and wheat interactions with neighboring plants.[10,69,73,77,162,195,196] For example, exposure to BOA

suppresses weed germination and growth and is sufficient to kill sensitive species.[64] These allelopathic effects can be direct or indirect. Indirect effects can be mediated through a reconfiguration of the soil microbiome (See Section 5.1 Plant–Microbe Interactions) or of nutrient availability (See Section 3.1 Plant Mineral Nutrition).[10,162] Direct effects include binding with amino acids, nucleic acids, or metal cations.[33–35,38,39] For instance, BOA exposure triggers the production of reactive oxygen species (ROS), lipid peroxidation and protein oxidation in bean.[197] A(M)PO inhibit HDAC activity in *Arabidopsis thaliana* and thus modulate gene expression on a genome-wide scale.[187] Interestingly, some plants have evolved the ability to detoxify benzoxazinoids.[64,198–201] For instance, some Poales species can metabolize BOA into malonyl glucoside carbamate.[201] Benzoxazinoid detoxification is a costly process that may be partially responsible for the observed slowed growth responses. Allelopathy should be distinguished from general resource competition (also known as exploitive competition), a phenomenon in which plants have a competitive advantage over their neighbors due to a more efficient uptake of limited resources, thereafter constraining the growth of other plants.[202] Yet, because benzoxazinoids are directly involved in plant mineral nutrition and shape the rhizosphere microbiome, it is likely that their exudation in soil feeds back in general resource competition by influencing the plant ability to acquire nutrients.[162]

6. Conclusions

Through their multiple functions, benzoxazinoids are pivotal drivers of the plant success. It is thus not surprising that these specialized metabolites have been under positive selection during crop domestication.[40,203,204] By shaping the plant interactions with other living organisms, benzoxazinoids shape the evolution of trophic interactions and ecosystem functioning.[192,193,205–207] Harnessing their power in modulating the plant physiology (*e.g.* tolerance to stress, reproduction) and its environment (*e.g.* soil feedback effects, allelopathy) will strongly facilitate the development of novel, and sustainable, strategies for food production.

Yet, many questions remain open: What is the structure and function of benzoxazinoid double/triple hexoses? How are benzoxazinoid contents regulated and recycled? How do the specialized metabolites modulate the plant vegetative and reproductive growth? How do they contribute to plant tolerance to abiotic stresses? How can the benefits and costs of benzoxazinoids be exploited and balanced to optimize crop breeding strategies? How do they shape ecosystems at the community level? How does their transfer along the food chain affect human health? Benzoxazinoids are promising chemicals for a broad range of applications and their proper use may contribute to facing and solving current societal challenges.

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