

REVIEW

Pathogens pulling the strings: Effectors manipulating salicylic acid and phenylpropanoid biosynthesis in plants

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Abstract

During evolution, plants have developed sophisticated ways to cope with different biotic and abiotic stresses. Phytohormones and secondary metabolites are known to play pivotal roles in defence responses against invading pathogens. One of the key hormones involved in plant immunity is salicylic acid (SA), of which the role in plant defence is well established and documented. Plants produce an array of secondary metabolites categorized in different classes, with the phenylpropanoids as major players in plant immunity. Both SA and phenylpropanoids are needed for an effective immune response by the plant. To successfully infect the host, pathogens secrete proteins, called effectors, into the plant tissue to lower defence. Secreted effectors can interfere with several metabolic or signalling pathways in the host to facilitate infection. In this review, we will focus on the different strategies pathogens have developed to affect the levels of SA and phenylpropanoids to increase plant susceptibility.

KEYWORDS

effector, pathogen, phenylpropanoids, salicylic acid

1 | INTRODUCTION

Plants and pathogens have been in a close relationship throughout their evolution. Plant-pathogenic fungi, bacteria, nematodes, and insects try to invade host plants to feed and multiply. Plants, on the other hand, have evolved several methods to ward off their attackers. Next to a rigid cell wall, plants synthesize an array of secondary metabolites like phenylpropanoids and terpenoids as another level of defence. Phenylpropanoids are a large class of secondary metabolites produced from phenylalanine, an aromatic amino acid that is also an intermediate in the salicylic acid (SA) biosynthesis pathway. Phenylpropanoids have been widely studied for their antimicrobial properties and their role in signalling during defence reactions (Yadav et al., 2020). In addition, important plant defence hormones, such as SA, jasmonic acid (JA), and ethylene (ET), can coordinate the defence

response and relay the signal to other parts of the plant. SA is a key component in induced resistance in both local and systemic tissue, and in eliciting the hypersensitive response and cell death (Ding & Ding, 2020). Both SA and phenylpropanoids share some steps in their production process, which is why this review focuses on how pathogens can manipulate the levels of one or both compounds.

On detection of a pathogen, plants start up local defence responses. A first response occurs on recognition of particular pathogen-associated molecular patterns (PAMPs) by plasma membrane-located receptors, triggering PAMP-triggered immunity (PTI). Although in some cases this might be a sufficient defence response, many pathogens have evolved effector proteins that can be secreted in the plant and inhibit PTI. Plants have evolved to recognize specific effectors by resistance proteins, thereby activating the second layer of immunity, called the effector-triggered

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immunity (ETI). The theoretical division of PAMPs and effectors is not justifiable in practice, with a continuum and an interdependency between PTI and ETI (van der Burgh & Joosten, 2019; Ngou et al., 2021; Thomma et al., 2011; Yuan et al., 2021). PTI and ETI are associated with shared responses to fend off invading pathogens, like an accumulation of reactive oxygen species (ROS), phytoalexins, and SA (Jones & Dangl, 2006; Klessig et al., 2018; Pieterse et al., 2009; Thomma et al., 2011). In systemic acquired resistance (SAR), a form of resistance in the whole plant as reaction to a local infection, SA accumulation was also shown to be essential for an adequate immune response (reviewed by Klessig et al., 2018).

The SA pathway has been widely studied in plants and its importance in plant defence against pathogens has already been established in 1979 (White). The biosynthesis pathway consists of two distinct routes, recently reviewed in Lefevere et al. (2020). The first route starts from chorismate, which is metabolized to SA in two steps, with isochorismate as intermediate. This route has recently been completely elucidated in *Arabidopsis thaliana* by the discovery of the enzyme responsible for the conversion of isochorismate to SA (Rekhter et al., 2019; Torrens-Spence et al., 2019). The other route also starts from chorismate and takes multiple steps to produce SA. One of the intermediates is phenylalanine, which is converted to *trans*-cinnamic acid by phenylalanine ammonia-lyase (PAL), hence the name PAL pathway.

Numerous examples with different plants and pathogens show that SA enhances the immune system of the host in both monocots and dicots. Prior exogenous application of SA reduces the infection rate of several pathogens in *Arabidopsis* and soybean (Bawa et al., 2019; Edgar et al., 2006; Ferrari et al., 2003). Exogenous application of SA or its analogue benzothiadiazole (BTH) even increases resistance to pathogens in plants with constitutively high levels of SA, such as rice and potato (Hadi & Balali, 2010; Nahar et al., 2012; Sánchez-Rojo et al., 2011). The importance of SA in plant immunity renders it a proper target for invading pathogens to intervene with. In general, SA is considered to work antagonistically to JA, another key hormone in plant defence. While SA confers resistance against biotrophic pathogens, JA is mostly effective against insects and necrotrophs (Spoel et al., 2007).

In addition to SA, phenylpropanoids can also increase defence against pathogens. Phenylpropanoids are a diverse group that can be roughly divided into five subgroups according to their structure—flavonoids, monolignols, phenolic acids, stilbenes, and coumarins—with each plant having a unique fingerprint of phenylpropanoids (Deng & Lu, 2017; Liu et al., 2015). The initial steps in the phenylpropanoid pathway consist of the three intermediates—cinnamic acid, *p*-coumaric acid, and *p*-coumaroyl CoA—that are consecutively metabolized from phenylalanine. These initial steps are referred to as the general phenylpropanoid pathway (GPP), which then branches out to produce all other phenylpropanoids (Deng & Lu, 2017; Liu et al., 2015). Phenylpropanoids play a role in a variety of different plant processes, ranging from regulating hormonal transport (Brown et al., 2001), providing components to reinforce the secondary cell wall (Boerjan et al., 2003), attracting pollinators (Dudareva et al.,

2013), and aiding in iron uptake from the soil (Fourcroy et al., 2014) to plant defence (Yadav et al., 2020). Activating the phenylpropanoid pathway can increase the resistance of the host to an invading pathogen (Liu et al., 2020; Singh et al., 2019; Xoca-Orozco et al., 2019). The exact mechanism by which phenylpropanoids are able to increase defence is not always clear and different compounds can use different strategies: while some compounds are directly toxic to the invading pathogen, others repel the pathogen before it is able to infect the plant (Ohri & Pannu, 2010).

Pathogens have three possible strategies to minimize the effect of defence hormones like SA. Production can be disrupted through interference with the biosynthesis pathway, accumulation can be prevented by converting SA into an inactive derivative, or signalling can be targeted (Qi et al., 2018). In this review, we will focus on effectors secreted by plant pathogens that target SA or phenylpropanoid biosynthesis or accumulation directly or indirectly to facilitate infection. Although many pathogens are able to interfere in one or both biosynthesis pathways, we have focused on examples where the altered SA or phenylpropanoid concentration has been attributed to a specific effector of the pathogen.

2 | EFFECTORS INTERFERING WITH SA BIOSYNTHESIS

The two best-studied examples of effectors manipulating the SA biosynthesis pathway are chorismate mutase (CM) and isochorismatase (ICM). Both have been identified in several fungi and also in plant-parasitic nematodes (Bauters et al., 2020; Djamei et al., 2011; Liu et al., 2014; Wang et al., 2018). Figure 1 summarizes the action of these and other pathogen effectors affecting SA levels.

Plants also have CM genes and they are present in multiple copies. CM participates in phenylpropanoid and SA biosynthesis through the PAL pathway. The fact that plant-pathogenic organisms secrete CM homologs enables them to affect SA or phenylpropanoid biosynthesis to promote infection. Groundbreaking work was done by Djamei and colleagues (2011) on CM from *Ustilago maydis* (Cmu1). Cmu1 is secreted by *U. maydis* to the plant cytosol and nucleus, interacts with plant CMs, and is needed for full virulence of the pathogen. Infecting plants with a Cmu1 deletion mutant of *U. maydis* resulted in a 10-fold increase of SA compared to infection with the wild type (Djamei et al., 2011). It was proposed that Cmu1 acts in conjunction with a cytosolic plant CM, thereby extracting more chorismate from the plastids, leading to lower substrate availability for plastidic SA biosynthesis. CM has been extensively studied in plants, fungi, and bacteria, but up to 1999 it had not been reported in animals. Lambert et al. (1999) discovered a potentially secreted active CM from the root-knot nematode *Meloidogyne javanica*, but did not make the link with a possible role in plant SA biosynthesis. Since then, CM has been characterized in several other plant-parasitic nematodes (Bekal et al., 2003; Jones et al., 2003; Vanholme et al., 2009) and a possible effect on plant auxin levels was observed (Doyle & Lambert, 2003). Only recently it has been shown that nematode CMs can have

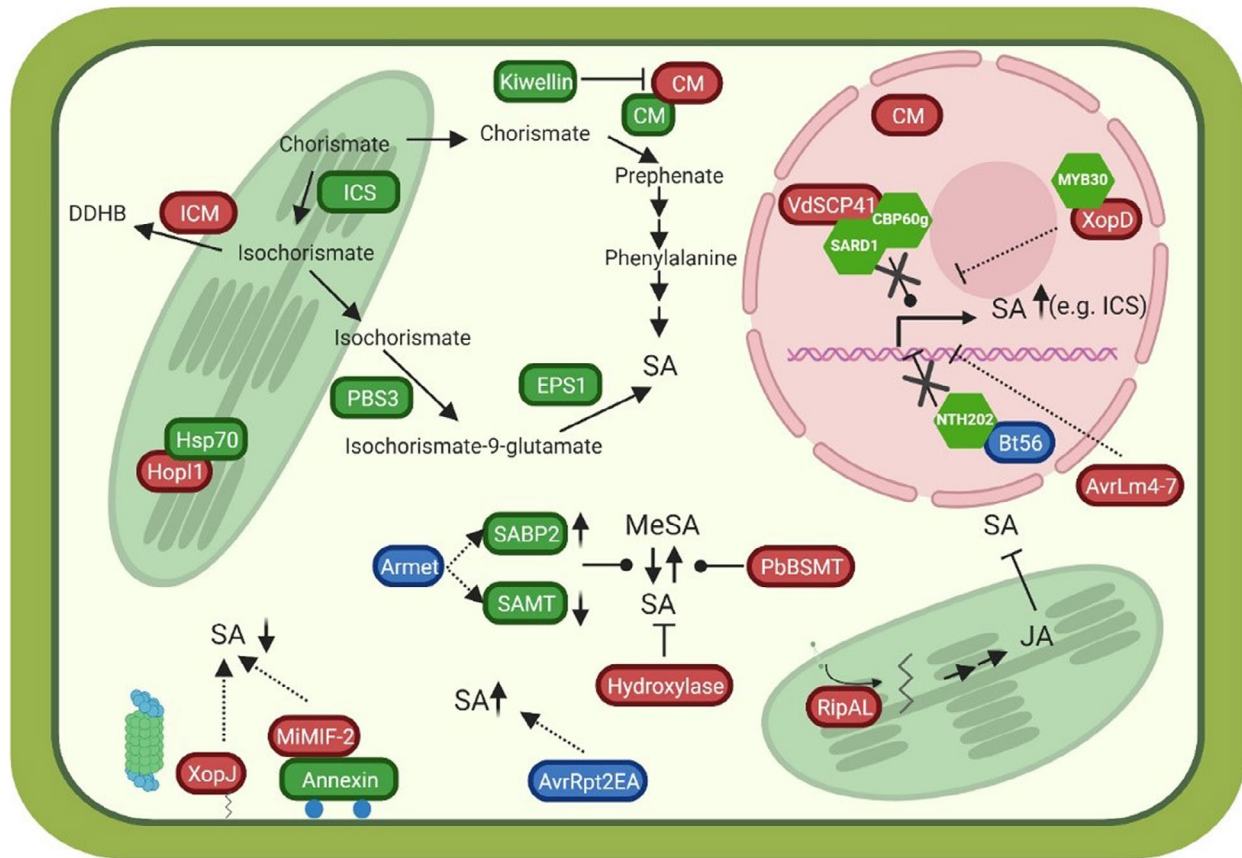


FIGURE 1 Schematic representation illustrating pathogen effectors within a plant cell, having an effect on salicylic acid (SA) content in plants. Plant proteins are indicated in green boxes, plant transcription factors are indicated in green hexagons. Pathogen effectors lowering SA levels are shown in red boxes, while effectors that can increase SA levels to benefit the pathogen are indicated in blue boxes. Arrows with a circular or flat head are indicative for activating or inhibitory effects, respectively. Dashed lines indicate that the exact mechanism/pathway is unknown. JA, jasmonic acid; SA, salicylic acid; MeSA, methylsalicylic acid; ICS, isochorismate synthase; DDHB, 2,3-dihydro-2,3-dihydroxybenzoate; CM, chorismate mutase; ICM, isochorismatase

similar effects on plants as observed by fungal CMs. A CM secreted by *M. incognita* (Mi-CM-3) is directed to the cytosol and nucleus, lowers SA content by half on pathogen infection, and increases the susceptibility of the host (Wang et al., 2018). A potentially secreted CM from the migratory nematode *Hirschmanniella oryzae* increases the susceptibility of rice plants. No effect on SA content could be detected, but there was an effect on the phenylpropanoid pathway. It should be mentioned that SA measurements were performed on unchallenged plants in the latter study, which could explain the discrepancy in results with the two former studies (Bauters et al., 2020; Djamei et al., 2011; Wang et al., 2018). Plants have evolved a way to inhibit the effect of secreted CMs by expressing kiwellins. Kiwellins are present in most plant species, except for Brassicaceae, and are upregulated on infection by fungi and oomycetes (Draffehn et al., 2013; Han et al., 2019; Marcel et al., 2010; Mosquera et al., 2016). A maize kiwellin (ZmKW1) was found to specifically interact with the secreted Cmu1 from *U. maydis*, and not the endogenous CMs, thereby decreasing its CM activity (Han et al., 2019). Although plant-parasitic nematodes secrete CMs as well, reports on increased kiwellin expression on nematode infection are scarce. A nematode-resistant mutant rice line showed a slight, but significant,

upregulation of a kiwellin-encoding gene upon *M. graminicola* infection (Dash et al., 2021).

ICM has been characterized best in the fungus *Verticillium dahliae* (VdIsc1) and the oomycete *Phytophthora sojae* (Pslsc1). Both proteins are secreted in the host and are able to decrease SA content (cotton and soybean) on pathogen infection, thereby inhibiting SA-based defence responses (Liu et al., 2014). Similar results were obtained when using potato as the host of *V. dahliae* (Zhu et al., 2017). It is proposed that ICM catalyses the hydrolysis of isochorismate to 2,3-dihydro-2,3-dihydroxybenzoate (DDHB) to limit the flow of isochorismate into SA biosynthesis. This hypothesis is backed up by the observation that DDHB concentrations are significantly higher in leaves expressing *Pslsc1* or *VdIsc1* (Liu et al., 2014). More recently, an ICM was also characterized (HoICM) from *H. oryzae*. Although rice lines overexpressing this putative effector showed increased susceptibility, no difference in SA content was detected, but it should be noted that data was collected from unchallenged plants (Bauters et al., 2020). It is worth mentioning that the conventional signal peptide that usually guides effector proteins to the secretory pathway is absent for ICMs in fungi and nematodes (Bauters et al., 2020). In fungi, ICM has been shown to be targeted for secretion by an unconventional secretion

system (Liu et al., 2014). In nematodes, several other effectors lacking a signal peptide have been shown to be secreted (Dubreuil et al., 2007; Fioretti et al., 2001; Jaubert et al., 2004; Robertson et al., 2000). Although there is no hard evidence yet that ICM is secreted by nematodes, it is assumed to be secreted because nematodes do not have an endogenous substrate for this enzyme. Isochorismate is metabolized from chorismate, the endproduct of the shikimate pathway, which is only present in plants and microorganisms (Herrmann & Weaver, 1999).

Next to the well-known CM and ICM that directly interfere with SA biosynthesis, there are other effectors that deregulate the SA biosynthesis pathway. The bacterial plant pathogen *Pseudomonas syringae* secretes HopI1, an effector that localizes to the chloroplast where it can remodel thylakoid structure. HopI1 is essential for full virulence and lowers SA content by 50% on ectopic expression in planta (Jelenska et al., 2007). The mechanisms by which HopI1 is able to reduce SA content are unknown, but it was shown to bind with the heat shock protein Hsp70, recruiting it to the chloroplast (Jelenska et al., 2010). Because Hsp70 proteins are needed for an efficient defence response (Jelenska et al., 2010; Kanzaki et al., 2003), HopI1 probably partially suppresses its function in defence, which might lead to a lower SA content. XopD, a bacterial effector secreted by *Xanthomonas campestris*, uses another approach. It localizes to the plant nucleus, has DNA-binding properties, and can cleave small ubiquitin-like modifier (SUMO)-conjugated proteins through its cysteine protease activity (Hotson et al., 2003). XopD is required for maximal growth of *X. campestris* and reduces chlorophyll loss to alleviate disease symptoms. In addition, XopD is responsible for a decrease in SA and ET content in infected plants, promoting infection by the bacterial pathogen (Kim et al., 2008, 2013). XopD interacts with a tomato transcription factor involved in defence (SIERF4) and destabilizes it by desumoylation, which results in decreased immunity by blocked ET signalling (Kim et al., 2013). XopD is able to reduce *ICS1* expression in *A. thaliana*, and it seems the N-terminal region of the effector is indispensable for this action (Canonne et al., 2011). MYB30, a transcription factor positively regulating defence responses in *A. thaliana*, is targeted by XopD, thereby inhibiting transcriptional activation of defence genes, like *ICS1* (Canonne et al., 2011). Interestingly, XopDXcc8004, a shorter version of XopD lacking the N-terminal part, interacts with the transcription factor HFR1 in *Arabidopsis* and not with MYB30 (Canonne et al., 2011; Tan et al., 2015). In addition, the shorter variant increases SA-mediated defence responses, rendering the plant less susceptible to *X. campestris* infection (Tan et al., 2015). XopJ, also secreted by *X. campestris*, is essential for full virulence by delaying tissue degeneration, especially at the onset of infection. One of the effects of XopJ is a reduced SA content during infection (Üstün et al., 2013). XopJ localizes to the plasma membrane in the plant cell, where it is attached with a myristyl group (Thieme et al., 2007). XopJ is a protease and reduces the activity of the 26S proteasome by binding to RPT6 and degrading it. RPT6 is an ATPase that is part of the 19S regulatory particle of the proteasome (Üstün et al., 2013; Üstün & Börnke, 2015). It is not entirely clear how the function of the 26S proteasome correlates with

SA content, but there is data supporting that a functional 26S proteasome is necessary for SA accumulation on pathogen infection due to its involvement in NPR1 turnover. NPR1 is a key regulator of SA-mediated defence responses, but it can also regulate SA biosynthesis (Rayapuram & Baldwin, 2007). It is thought that a decrease in NPR1 turnover by the proteasome lowers SA content in plants. Targeted ubiquitination and degradation of proteins, like transcription factors, by the proteasome make the ubiquitin-proteasome system a preferred target for pathogen effectors that deregulate plant immunity (Adams & Spoel, 2018; Üstün et al., 2016).

V. dahliae is known to manipulate the SA biosynthesis pathway through ICM, but another of its secreted effectors, VdSCP41, is known to contribute to virulence by lowering the SA content as well. VdSCP41 migrates to the plant nucleus, where it binds with the transcription factors CBP60g and SARD1, two master immune regulators that are both able to bind promoters of genes that control SA biosynthesis, like isochorismate synthase (*ICS*) (Qin et al., 2018; Zhang et al., 2010). VdSCP41 was shown to hinder DNA binding properties of CBP60g, thereby inhibiting activation of *ICS* expression and impairing SA biosynthesis, hence lowering plant immunity (Qin et al., 2018). Induction of *ICS* expression is also inhibited by AvrLm4-7, an effector secreted by the fungus *Leptosphaeria maculans*, thereby reducing SA content during initial stages of infection on susceptible plants lacking the corresponding resistance gene. In addition, AvrLm4-7 is able to reduce abscisic acid (ABA), affecting ROS accumulation and SA and ET signalling in the host, but the mechanisms are still unknown (Nováková et al., 2016). It is possible that the observed effects of AvrLm4-7 are indirect because it masks the recognition of the avirulence genes *AvrLm3* and *AvrLm5-9* with their respective resistance proteins (Ghanbarnia et al., 2018; Plissonneau et al., 2016).

Some effectors manipulate SA content in the host by making use of the antagonistic interaction between the SA and JA pathways (Yang et al., 2019a). These effectors elevate JA levels, thereby decreasing SA content. One of the effectors using this approach is RipAL from *Ralstonia solanacearum*. RipAL localizes to the chloroplasts where it targets lipids, and it has a lipase domain sharing homology with the DAD1 protein from *Arabidopsis*, a lipase catalysing the release of linoleic acid, a precursor for JA (Nakano & Mukaiharu, 2018). RipAL induces JA production, probably by acting as DAD1, thereby lowering SA production and increasing virulence of *R. solanacearum* and other pathogens on *Arabidopsis* (Nakano & Mukaiharu, 2018). Some pathogens have evolved to mimic or produce JA to facilitate their infection of the plant (Eng et al., 2021). *Fusarium oxysporum* is known to produce jasmonates to promote JA-induced gene expression (Cole et al., 2014), while *Magnaporthe oryzae* produces 12OH-JA to block JA signalling and disable JA-based host innate immunity (Patkar et al., 2015). The best-studied example of a JA mimic produced by a pathogen is coronatine, produced by *P. syringae*, which also has a clear effect on SA biosynthesis. Coronatine induces the expression of three NAC transcription factors, which are involved in reducing SA biosynthesis, resulting in lower SA levels on *P. syringae*

infection compared with infection with a coronatine-deficient strain of *P. syringae* (Zheng et al., 2012).

Lowering SA content, directly or indirectly, is a good strategy for (hemi)biotrophic pathogens, but the opposite is true for necrotrophic pathogens and insects, which secrete effectors to increase SA production. An example is the AvrRpt2EA effector, a cysteine protease secreted by *Erwinia amylovora*, a necrotrophic bacterial pathogen (Schröpfer et al., 2018). On expression of AvrRpt2EA in apple, PR-1 expression was induced and SA concentration increased, while the JA pathway was not altered (Schröpfer et al., 2018). These results suggest that AvrRpt2EA might be inducing cell death through SA activation. However, this data could not be confirmed by RNA-Seq, where genes involved in SA biosynthesis were not found to be differentially expressed (Schröpfer et al., 2021). Expression of Bt56, a salivary effector from *Bemisia tabaci* (whitefly), increased SA levels in tobacco via interaction with a KNOTTED 1-like homeobox transcription factor (Xu et al., 2019). Plants infected with whitefly indeed have increased SA content, and on infection of plants with Bt56-silenced whiteflies SA content was lower and JA content increased (Xu et al., 2019), resulting in lower insect performance.

Next to manipulating SA biosynthesis, pathogens can also modify SA and its metabolites already present in the plant. Armet, an effector found in saliva of the pea aphid *Acyrtosiphon pisum*, induces a four-fold increase in SA in plants by upregulating expression of salicylic acid-binding protein 2 (SABP2) and downregulating the expression of salicylic acid methyltransferase (SAMT). SABP2 is needed for the conversion of methylsalicylic acid (MeSA) to the biologically active free SA, while SAMT promotes the opposite reaction (Cui et al., 2019). Although Armet does not seem to affect aphid infestation or reproduction, the increased SA content induces resistance against other pathogens like *P. syringae*, making sure the aphids feed on healthy plants. Another example is the putatively secreted protein PbBSMT from *Plasmodiophora brassicae*, which is able to methylate benzoic acid (BA) and SA to the inactive form MeSA (Djavaheri et al., 2019; Ludwig-Müller et al., 2015). On overexpressing PbBSMT in *Arabidopsis*, SA levels dropped by 80% and plants were much more vulnerable to infection with *P. brassicae* and *P. syringae*. Experimental data showed that PbBSMT is more effective in reducing SA content than an endogenous methyltransferase from *Arabidopsis* (Djavaheri et al., 2019). The strategy of actively degrading SA was found in the plant-pathogenic bacterium *R. solanacearum* (Lowe-Power et al. 2016). *R. solanacearum* possesses an SA degradation pathway, metabolizing SA to pyruvate and fumarate, to increase its virulence on plants and to protect itself from SA toxicity. Similarly, an SA hydroxylase from '*Candidatus Liberibacter asiaticus*' degrades plant SA to suppress defence. On expression in transgenic tobacco it can inhibit SA accumulation and the hypersensitive response. In addition, SA hydroxylase from '*Ca. Liberibacter asiaticus*' increases the susceptibility of citrus plants to both pathogenic and nonpathogenic *Xanthomonas citri* strains (Li et al., 2017). In contrast, a functional SA hydroxylase from *Fusarium graminearum*, upregulated on infection, did not affect disease severity (Hao et al., 2019; Rocheleau et al., 2019). Although several functional SA hydroxylases upregulated

during infection were found in *U. maydis*, none seemed to affect virulence, indicating that the main purpose of SA hydroxylase in this pathosystem is to use SA as carbon source rather than subduing SA-orchestrated defence (Rabe et al., 2013). The observation that this enzyme does not appear to be secreted in *U. maydis* strengthens the hypothesis that it is not involved in plant defence suppression (Rabe et al., 2013).

3 | EFFECTORS INTERFERING WITH PHENYLPROPANOID BIOSYNTHESIS

Some of the earliest reports of pathogens manipulating the phenylpropanoid pathway or its derived molecules came from pathogens infecting soybean or pea. An extracellular invertase from the oomycete *Phytophthora megasperma* was found to inhibit glyceollin accumulation on elicitor treatment in soybean. Rather than the enzymatic activity, it was shown that the carbohydrate moiety of this glycoprotein was responsible for the inhibitory effect (Ziegler & Pontzen, 1982). Glyceollin is a phytoalexin from soybean, produced through the phenylpropanoid pathway, that has been shown to rapidly accumulate on infection and to be a central component of the defence system (Lygin et al., 2013). Glyceollin has antifungal, antibacterial, and nematostatic activities (Kaplan et al., 1980; Kim et al., 2010; Parniske et al., 1991). Another phytoalexin produced by the phenylpropanoid pathway is pisatin, from pea, which is also an antifungal compound (Wu & Van Etten, 2004). The fungus *Mycosphaerella pinodes* produces a low molecular weight compound called F5 that is able to reduce pisatin biosynthesis and inhibit the activity of PAL and cinnamate 4-hydroxylase, two key enzymes in the phenylpropanoid pathway (Hiramatsu et al., 1986). In addition, *M. pinodes* also produces two glycopeptides, suppressins A and B, that are able to prevent the induction of the pisatin biosynthesis pathway (Shiraishi et al., 1992). The pisatin produced by the plant can be broken down by a fungal pisatin demethylase, a member of the cytochrome P450 family, and induced in the fungus on sensing pisatin (George & Van Etten, 2001).

Tin2, an effector secreted by *U. maydis*, acts indirectly on the phenylpropanoid pathway. Deleting *Tin2* reduces virulence of *U. maydis* on maize, proving it is an important effector of this pathogen. The typical anthocyanin accumulation in *U. maydis*-infected maize tissue is caused by Tin2 because infection with *Tin2* deletion mutants shows lower expression of anthocyanin biosynthesis genes compared to infection with wildtype *U. maydis* (Brefort et al., 2014). In addition, tissues infected with *Tin2* deletion mutants have an induced lignin biosynthesis pathway compared to those infected by the wildtype fungus, resulting in an increased lignin content. This indicates that Tin2 is responsible for a rewiring of the metabolite flow into the anthocyanin pathway, reducing the amount of defence metabolites produced by the phenylpropanoid pathway (Tanaka et al., 2014). The importance of lignin in the defence against pathogens like *U. maydis* is shown by the hypersusceptibility of a maize mutant affected in lignin biosynthesis (Tanaka et al., 2014). Tin2 binds

and stabilizes a cytoplasmic serine/threonine kinase from maize, ZmTTK1. This kinase most probably phosphorylates the transcription factor ZmR1, which is then imported into the nucleus where it can activate genes involved in the anthocyanin biosynthesis pathway (Tanaka et al., 2014). The function of Tin2 seems to be unique in *U. maydis* because a homolog in *Sporisorium reilianum* binds with paralogous kinases (ZmTTK2 and ZmTTK3) and inhibits their kinase activity instead of stabilizing the protein. While needed for full virulence, the Tin2 protein of *S. reilianum* does not induce accumulation of anthocyanin (Tanaka et al., 2019). The importance of lignin in defence against *U. maydis* is underlined by another effector secreted by this pathogen: Sta1 affects the expression of genes involved in the phenylpropanoid pathway and is essential for efficient colonization of the plant. Compared to wildtype *U. maydis*, Sta1 deletion mutants cause higher expression of 4-coumarate CoA ligase and cinnamyl alcohol dehydrogenase after infection. These results, together with an increase in autofluorescence in plants infected with the deletion mutant, might indicate an increase in lignin content (Tanaka et al., 2020).

Another example of an effector that most probably increases the susceptibility of the host by redirecting carbon flow within the phenylpropanoid pathway is WtsE. WtsE is essential for the plant-pathogenic bacterium *Pantoea stewartii* to successfully infect maize (Frederick et al., 2001). WtsE is able to suppress basal defence in the plant, as it inhibits PR-gene induction and callose formation (Ham et al., 2008). In addition, WtsE causes upregulation of the phenylpropanoid pathway, eliciting the accumulation of coumaroyl tyramine, a compound associated with lignification. Inhibiting PAL enzymes hindered WtsE to promote disease, indicating that the virulence activity of WtsE depends on perturbation of the phenylpropanoid pathway (Asselin et al., 2015). The strategy employed here is probably similar to Tin2: diverting the carbon flow within the phenylpropanoid pathway to one way, limiting the amount of carbon for defence-associated phenylpropanoid-derived metabolites. The specific mechanism has not been elucidated yet, but it is known that WtsE targets the maize protein phosphatase 2A (PP2A) (Jin et al., 2016). PP2A is a crucial negative regulatory component of PTI at the receptor level, affecting secondary metabolism and hormonal signalling (Durian et al., 2016). Furthermore, blocking the enzymatic activity of PP2A completely abolishes the virulence function of WtsE, thereby inhibiting the accumulation of coumaroyl tyramine (Jin et al., 2016).

While for previous examples the plant target of the effector is outside the phenylpropanoid pathway, thereby indirectly affecting it, HopZ1 directly interacts with an enzyme involved in the phenylpropanoid pathway. HopZ1 is a type III effector from *P. syringae* interacting with 2-hydroxyisoflavanone dehydratase (GmHID1) in soybean (Zhou et al., 2011). GmHID1 enzymatically converts 2-hydroxyisoflavones to isoflavones, mainly daidzein and genistein (Akashi et al., 2005). Expression of *GmHID1* increases on infection, but the binding of HopZ1 with the corresponding protein leads to its degradation and ultimately to a lower concentration of daidzein. HopZ1 has two different alleles in *P. syringae* (*HopZ1a* and *HopZ1b*), but only HopZ1b is able to reduce the production of daidzein (Zhou

et al., 2011). Daidzein is a precursor of the phytoalexin glyceollin (Lygin et al., 2013), explaining the strategy behind HopZ1 secretion by *P. syringae*.

CM is best known for its effect on SA biosynthesis, but it also affects the phenylpropanoid pathway. Secreted CM from *U. maydis* (Cmu1) dimerizes with a plant CM, thereby increasing the metabolite flow into the phenylpropanoid pathway, leading to a significantly higher phenylpropanoid and lignin content in the plant (Djamei et al., 2011). These results suggest that Cmu1 increases the virulence of *U. maydis* by directing the metabolite flow into the phenylpropanoid pathway, reducing SA production. In contrast, it was shown that a secreted CM from the nematode *H. oryzae* might lower the phenylpropanoid content of the host, thereby making it more vulnerable to infection (Bauters et al., 2020). These seemingly contradictory results illustrate that different pathosystems can respond in another way, and that thorough research is needed to unravel all mechanisms. In the same pathosystem of rice and *H. oryzae*, there are also indications that ICM affects the phenylpropanoid pathway. An RNA-Seq analysis revealed a downregulation of the phenylpropanoid pathway on ectopic expression of *HoICM* in rice (Bauters et al., 2020).

Necrotrophic pathogens can also interfere with the phenylpropanoid pathway, but rather than subduing the immune system, effectors are secreted to invoke the immune response in some cases. Due to their necrotrophic lifestyle, an immune response leading to cell death at the right time in the development of the pathogen can be beneficial for the invading pathogen (Lorang, 2019). An example of an effector that might serve this purpose is SnTox3, secreted by the necrotrophic fungus *Parastagonospora nodorum* and necessary for disease development in wheat carrying the susceptibility gene *Snn3* (Liu et al., 2009). The expression of several PAL genes is upregulated in leaves infiltrated with SnTox3 and metabolite profiling showed that SnTox3 is responsible for the increased production of the phenylpropanoids chlorogenic acid and feruloylquinic acid (Winterberg et al., 2014). Chlorogenic acid and ferulic acid, which can be released from feruloylquinic acid, play a role in the immune response of plants against bacteria and fungi (Bily et al., 2003; López-Gresa et al., 2011; Sung & Lee, 2010). On the other hand, SnTox3 represses immunity by binding to the wheat pathogenicity-related protein TaPR11 and several other PR1 proteins (Breen et al., 2016). After infection, the C-terminal part of TaPR1 is cleaved off by apoplastic proteases and acts as a signalling peptide inducing plant immune responses, thereby repressing *P. nodorum* infection. The direct interaction of SnTox3 with TaPR1 inhibits its activity by preventing the cleavage of the C-terminal region (Sung et al., 2021).

Two other examples of effectors with an effect on the phenylpropanoid pathway are ToxA and ToxB from the necrotrophic fungus *Pyrenophora tritici-repentis*. ToxA induces necrosis in ToxA-sensitive plants, thereby creating a favourable environment for the necrotrophic pathogen (Manning et al., 2008). Knockout strains not expressing ToxA cause significantly less disease (Moffat et al., 2014). ToxA was shown to interact with the pathogenesis-related protein PR1-5 in wheat, which is necessary to induce necrosis (Lu et al., 2014) and two chloroplastic proteins, ToxABP1 and plastocyanin

(Manning et al., 2007; Tai et al., 2007). The phenylpropanoid pathway is clearly induced in plants on treatment with purified ToxA with significantly higher expression levels of PAL, cinnamate-4-hydroxylase, 4-coumarate:coenzyme A ligase, and chalcone synthase (Adhikari et al., 2009; Pandelova et al., 2009). In contrast,

expression of chalcone isomerase, a key enzyme in the production of flavonoids and phytoalexins, is decreased (Pandelova et al., 2009). The deregulation of the phenylpropanoid pathway almost doubles the phenolic content of ToxA-treated leaves (Pandelova et al., 2012) and also the concentration of two hydroxycinnamic acid

TABLE 1 Summary of effectors interfering with the phenylpropanoid pathway

Effector	Organism	Interaction partner	Effect	Ref.
Invertase	<i>Phytophthora megasperma</i>		Inhibition of accumulation of glyceollin	Ziegler and Pontzen (1982)
F5	<i>Mycosphaerella pinodes</i>		Reduced activity of phenylalanine ammonia-lyase (PAL) and cinnamate 4-hydroxylase	Hiramatsu et al. (1986)
			Reduction of pisatin biosynthesis	
Supprescin A & B	<i>Mycosphaerella pinodes</i>		Reduction of pisatin biosynthesis	Shiraishi et al. (1992)
Tin2	<i>Ustilago maydis</i>	ZmTTK1	Reduction of lignin biosynthesis	Tanaka et al. (2014)
Sta1	<i>Ustilago maydis</i>		Reduced expression of 4-coumarate CoA ligase and cinnamyl alcohol dehydrogenase	Tanaka et al. (2020)
			Possible reduction in lignin biosynthesis	
WtsE	<i>Pantoea stewartii</i>	PP2A	Accumulation of coumaroyl tyramine	Asselin et al. (2015)
HopZ1	<i>Pseudomonas syringae</i>	GmHID1	Reduction of daidzein biosynthesis	Zhou et al. (2011)
CMu1	<i>Ustilago maydis</i>	ZmCm1, ZmCm2	Accumulation of several phenylpropanoids and lignin	Djamei et al. (2011)
HoCM	<i>Hirschmanniella oryzae</i>		Reduced expression of genes involved in the phenylpropanoid pathway	Bauters et al. (2020)
			Reduced synthesis of phenylpropanoids	
HoICM	<i>Hirschmanniella oryzae</i>		Reduced expression of genes involved in the phenylpropanoid pathway	Bauters et al. (2020)
SnTox3	<i>Parastagonospora nodorum</i>	TaPR-1-1	Induced expression of PAL genes	Winterberg et al. (2014)
			Accumulation of chlorogenic acid and feruloylquinic acid	
ToxA	<i>Pyrenophora tritici-repentis</i>	PR1-5, ToxABP1, plastocyanin	Induced expression of PAL, cinnamate-4-hydroxylase, 4-coumarate CoA ligase, and chalcone synthase	Adhikari et al. (2009), Du Fall and Solomon (2013), Pandelova et al. (2009, 2012)
			Reduced expression of chalcone isomerase	
			Induced expression of genes involved in lignification	
			Accumulation of phenolics, coumaroylglutamine, and caffeoylputrescine	
ToxB	<i>Pyrenophora tritici-repentis</i>		Induced expression of PAL, cinnamate-4-hydroxylase, 4-coumarate CoA ligase, caffeoyl-CoA O-methyltransferase, and cinnamyl alcohol dehydrogenase	Pandelova et al. (2012)
			Reduced expression of genes involved in lignification	
			Increase of cell wall-bound phenolics	
Pisatin demethylase	<i>Nectria haematococca</i>		Detoxification of pisatin	George and Van Etten (2001)

amides (coumaroylagmatine and caffeoylputrescine) increased (Du Fall & Solomon, 2013). Expression of genes involved in lignification (caffeoyl-CoA *O*-methyltransferase and cinnamyl alcohol dehydrogenase), downstream in the phenylpropanoid pathway, is upregulated, as well as some peroxidases that contribute to lignin polymer formation (Pandelova et al., 2009). ToxB has a similar effect on the phenylpropanoid pathway, but is slower and less intense. In contrast to ToxA, treatment with purified ToxB tends to downregulate genes involved in lignification processes (Pandelova et al., 2012). The induced phenolic and lignin content might hinder fungal growth and survival if it occurs prior to the rapid cell death. Although ToxA and ToxB are needed for successful infection, *P. tritici-repentis* probably uses other unknown necrotrophic effectors to regulate the infection process. This hypothesis is backed up by recent research by Guo et al. (2018) showing that *toxa toxb* double knockout strains can still infect their host.

Although necrotrophic pathogens seem to invoke a strong immune response, they also create an environment necessary for a necrotrophic pathogen to gather nutrients and thrive within its host. The mechanism by which they are able to survive certain invoked immune responses is largely unknown, but is probably due to a fine-tuned interplay with as yet unknown necrotrophic effectors. A summary of the phenylpropanoid pathway interfering effectors discussed in this paper can be found in Table 1.

4 | CONCLUSION

In this review, we have focused on effectors interfering with the biosynthesis of SA and phenylpropanoids. SA is an important defence hormone working together with other plant hormones, including JA, ET, auxin, and ABA, to form a tightly organized network orchestrating an effective immune response. To successfully infect plants, pathogens have adapted to interfere with the biosynthesis of multiple hormones, not only SA. The SAP11 effector of phytoplasma downregulates lipoxygenase expression, thereby inhibiting JA production (Sugio et al., 2011). AvrXccC₈₀₀₄, an effector secreted by *X. campestris*, elicits expression of *NCED5*, a gene encoding a key enzyme in ABA biosynthesis, leading to higher ABA levels (Ho et al., 2013). *P. sojae* secretes PsAvh238 to suppress ET biosynthesis by blocking 1-aminocyclopropane-1-carboxylate synthase (ACS) activity, an enzyme needed to produce the precursor of ET, 1-aminocyclopropane-1-carboxylic acid (Yang et al., 2019b). Auxin biosynthesis is increased by the *P. syringae* effector AvrRpt2, thereby altering auxin physiology and promoting disease (Chen et al., 2007). These examples show that pathogens have evolved to interfere with the heart of the plant defence system, trying to shut it down or using it for their benefit.

Next to phytohormone biosynthesis pathways, downstream signalling pathways are also targeted by pathogens. For example, *P. syringae* secretes HopI1 to disrupt SA biosynthesis (Jelenska et al., 2007), but it can interfere with downstream signalling as well by secreting the effectors AvrPtoB and coronatine. AvrPto interacts

with NPR1, the master regulator of SA signalling, resulting in its degradation via the host proteasome. Consequently, NPR1-regulated genes are impaired during infection, resulting in a decreased immune response (Chen et al., 2017). Also, papain-like cysteine proteases (PLCPs) are known to play a prominent role in plant immunity by orchestrating SA signalling. Several apoplastic effectors, like AVR2 from *Cladosporium fulvum* (Shabab et al., 2008), EPIC1 from *Phytophthora infestans* (Song et al., 2009), and Pit2 of *U. maydis* (Doehlemann et al., 2011), target these PLCPs to inhibit their activity, thereby disrupting SA signalling.

It is clear that all pathogens, independent of their lifestyle, try to disrupt the defence system of the plant, albeit in different ways. While biotrophic organisms try to remain undetected during infection and feeding, necrotrophic organisms sometimes exploit the defence system to create necrotic patches to feed on. For instance, SnTox3, secreted by *P. nodorum*, or ZtNIP1, secreted by *Zymoseptoria tritici*, induce necrosis in wheat and *Arabidopsis*, respectively (M'Barek et al., 2015; Sung et al., 2021). The opposite is true for biotrophic pathogens, which try to prevent necrosis by secreting effectors. HaCR1, secreted by the biotrophic pathogen *Hyaloperonospora arabidopsidis*, and BEC1011, secreted by *Blumeria graminis*, suppress plant cell death to promote infection in *Arabidopsis* and barley, respectively (Dunker et al., 2021; Pliego et al., 2013). The difference in how to deal with plant cell death is obvious in comparing necrotrophs with biotrophs, but there are other aspects where they differ as well. As described in this review, the lifestyle of the pathogen mainly determines how secreted effectors interfere with the SA pathway. Some necrotrophic pathogens and insects are less affected by SA-dependent defence responses and have evolved a strategy in which they take advantage of the antagonism that exists in some plants between SA and JA by elevating SA content to decrease JA-based defence responses, like Bt56 from *B. tabaci* (Xu et al., 2019). SA-sensitive pathogens may use an opposite tactic by increasing JA content, like RipAL, secreted by *R. solanacearum* (Nakano & Mukaihara, 2018).

It is clear that pathogens try to manipulate biosynthesis of SA to disrupt the defence system of the plant. On the other hand, SA can be directly toxic to pathogens as well. SA is shown to reduce mycelial growth of *Alternaria*, *Verticillium*, *Fusarium*, and *Sclerotinia* (Forchetti et al., 2010; Qi et al., 2012), but at the same time it can act as an allelochemical and stimulate production of toxins and hydrolytic enzymes by the pathogen (Wu et al., 2008). To cope with direct toxic effects of SA, some pathogens have developed ways to degrade SA, like *R. solanacearum* (Lowe-Power et al., 2016).

This review focuses on the effect of single effectors on SA biosynthesis, and it would be interesting to see if different plant species react in a similar or different way to that effector. SA can be produced through the PAL or ICS pathway on infection. Some plants have a dominant pathway to synthesize SA, for instance the ICS pathway in *Arabidopsis* or the PAL pathway in rice, while both pathways contribute equally to SA synthesis in some other plants (Lefevere et al., 2020). Testing the reaction of two plants with different dominant pathways on treatment with the effector could give some interesting views on the mechanism by which it is able

to deregulate SA biosynthesis. Although some effectors are clearly manipulating SA biosynthesis, they might also steer other processes in the plant. One of the best examples is CM. Next to manipulating SA content, it might also have an effect on auxin levels (Doyle & Lambert, 2003), and even terpenoid levels are affected (Bauters et al., 2020). The knowledge that a single effector can affect multiple (unrelated) pathways in plants makes it difficult to elucidate the mode of action of the secreted effector.

A lot of progress has been made in the last decade in the field of plant–pathogen interactions. New effectors have been found and characterized, and their effect on the plant immune system has been mapped. Although interaction partners have been identified in some specific examples, the exact mechanism by which a pathogen effector is able to interfere with plant processes remains elusive in most cases, leaving opportunities for future research.

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DATA AVAILABILITY STATEMENT

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

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