



## The Practical Role of Induced Resistance for Crop Protection

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### Abstract

Plants have evolved a highly sophisticated immune system to resist pathogen attack comprising both preformed and inducible mechanisms. Over the last 50 years, various biological and chemical inducers have been used to artificially trigger the defense response in plants, thereby promoting an induced resistance (IR) to subsequent pathogen attack. IR has proven effective for disease control in laboratory and glasshouse conditions but has seldom equalled the level of protection offered by synthetic pesticides in the field. However, renewed interest in IR for crop protection is being driven by legislation to reduce the use of synthetic chemicals in agriculture. Inducers can contribute to integrated crop management strategies when used in combination with fungicides, bactericides, and with other biological control options. Integrating inducers in this way can reduce chemical inputs without loss of efficacy. Moreover, advances in our understanding of plant defense are informing the development of new inducers and guiding new strategies for their implementation in sustainable crop protection. This review will discuss the use of IR in selected cropping systems and describe opportunities for optimizing its potential, including the development of more effective inducers and their integration with conventional and cultural control options.

**Keywords:** disease resistance, plant immune responses

### Historical Perspective

The phenomenon of induced resistance (IR), where plants develop an increased resistance to pathogen attack following localized pathogen infection, has been recognized for over 100 years. In a review of the early literature, Chester (1933) cited several examples where plants developed an acquired physiological immunity to pathogen attack following recovery from earlier infection and speculated that it may play a role in reducing the spread of natural disease outbreaks. Since then, the discovery of biological and chemical inducers and advances in our understanding of plant defense has paved the way for IR implementation in crop protection (Fig. 1). The first empirical evidence for biological activation of IR was presented by Ross (1961) who demonstrated that localized inoculation of tobacco leaves with tobacco mosaic virus (TMV) resulted in the development of resistance to TMV in distal noninoculated leaves. Ross coined the phrase systemic acquired resistance (SAR) to describe the response. Subsequently, SAR was demonstrated in a range of plant species following localized inoculation with viral, fungal, and bacterial pathogens, so prompting interest in

the potential of IR for plant protection (Hammerschmidt and Kuc 1995; Kuc 1987).

The first report of chemical-IR was reported by Kuc et al. (1959) who showed that infiltration of apple leaves with D-phenylalanine, D-alanine, and amino-isobutyric acid promoted systemic resistance to apple scab, caused by the fungal pathogen *Venturia inaequalis*. In a landmark study 20 years later, evidence that salicylic acid (SA) played a role in defense activation was obtained when White (1979) showed that infiltration of tobacco leaves with SA induced the synthesis of pathogenesis-related (PR) proteins and the development of systemic resistance to TMV. Subsequently it was confirmed that endogenous accumulation of SA and the expression of PR genes were prerequisites for establishment of SAR (Delaney et al. 1994; Métraux et al. 1991). Furthermore, topical application of SA was shown to induce SAR in a broad range of plant species and to activate the same set of SAR genes as biological induction (Kessmann et al. 1994; Ward et al. 1991). However, SA was considered unsuitable as a crop protectant because of the narrow margin that separated rates of SA that were efficacious with those that were phytotoxic (Kessmann et al. 1994). Nevertheless, together the above studies laid the foundations for inducer screening programs that identified highly effective SA functional analogues such as 2,6-dichloroisonicotinic acid (INA) (Métraux et al. 1991) and acibenzolar-S-methyl (ASM) (Görlach et al. 1996; Kunz et al. 1997). ASM was commercialized as Bion® and Actigard® in Europe and the United States, respectively. Subsequently, other synthetic

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inducer compounds have been identified and commercialized including tiadinil (Nihon Nohyaku, Tokyo, Japan) and isotianil (Bayer AG and Sumitomo Chemicals, Tokyo, Japan) (Bektas and Eulgem 2015).

Concurrent with the studies on SAR in the 1990s, various groups reported a form of systemic resistance that was associated with root colonization by plant growth-promoting rhizobacteria (PGPR), notably *Pseudomonas* spp. and *Bacillus* spp. (Pieterse et al. 1996; van Loon et al. 1998; Wei et al. 1996). This was called induced systemic resistance (ISR) but differed from SAR in that it depended on the jasmonic acid (JA) and ethylene (ET) responsive pathways and was independent of SA accumulation and PR expression (van Loon et al. 1998). Subsequently, ISR has been shown to be promoted by various beneficial fungi, most notably *Trichoderma* spp., and some arbuscular mycorrhizae (Cameron et al. 2013; Nawrocka and Malolepsza 2013). The potential for beneficial microbes to promote plant growth and to enhance health, not solely through ISR, has led to the development of commercial bioinoculants and biofertilizers (Meena et al. 2020).

In the last 30 years, SAR and ISR have become established in the literature as the two main forms of induced resistance. They are differentiated mainly according to their underlying signaling pathways and on evidence that SAR is predominantly effective against biotrophic pathogens whereas ISR is more effective against necrotrophic pathogens (Pieterse et al. 2014). However, the SAR:ISR dichotomy has been challenged because components of their signaling networks are sometimes shared and SA/JA crosstalk can sometimes mediate immunity against both biotrophic and necrotrophic pathogens (Aerts et al. 2021; Pieterse et al. 2014). Moreover, a feature that is common to SAR and ISR is the phenomenon called priming, whereby defense mechanisms are not strongly activated by the initial treatment, but plants are conditioned for an amplified response upon subsequent pathogen attack (Conrath et al. 2015). The use of different acronyms to describe essentially the same phenotype has potential to cause confusion and so in this review we refer to IR (induced resistance), thus making no assertion as to underlying mechanisms. Similarly, multiple terms have been used to describe the triggers of IR including elicitor, activator, booster, enhancer, and stimulant. In this review, we will name the agent in question or use the terms inducer or inducing agent.

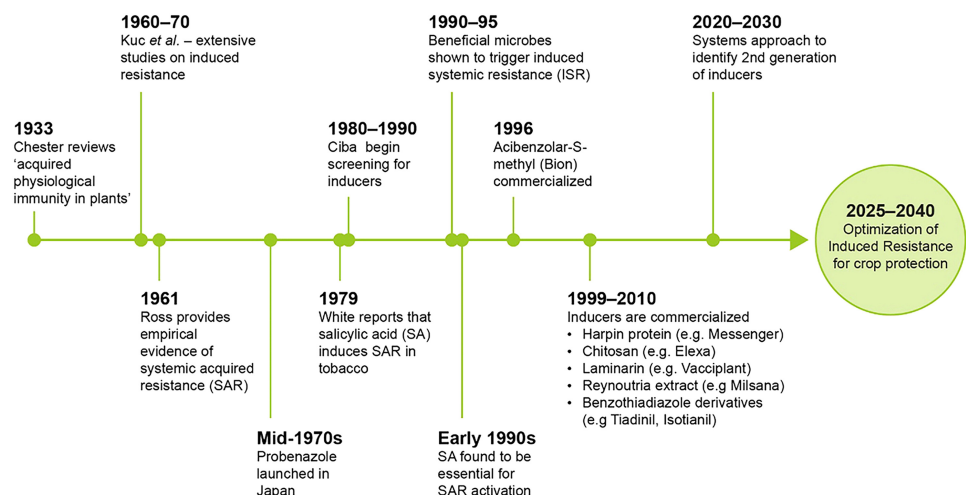
## Practical Implementation of Inducers

Numerous biotic and abiotic inducers of plant defense have been identified (Bektas and Eulgem 2015; Lyon 2014). Biotic inducers include molecules of microbial origin (e.g., flagellin, glucan, chitin, and lipopolysaccharides), referred to as microbe- and

pathogen-associated molecular patterns (MAMP and PAMPs) and host-derived molecules known as damage-associated molecular patterns (DAMPs) that are released during pest and pathogen attack (Boutrot and Zipfel 2017). Upon recognition of these molecules by pattern recognition receptors (PRRs) in the plant plasma membrane, a complex biochemical signaling cascade is triggered that activates transcriptional reprogramming and the expression of plant defense mechanisms. The phytohormones SA and JA play central roles in regulating the defense response with synergistic and/or antagonistic interactions between SA and JA responsive pathways fine-tuning the transcriptional response according to the original molecular trigger (Berens et al. 2017). Exogenous applications of SA and JA can similarly modulate the plant defense responses (Pieterse et al. 2012). Moreover, functional analogues of SA, such as ASM and INA, operate downstream of SA accumulation but induce similar transcriptional changes in plants as SA (Tripathi et al. 2019). Ultimately, transcriptional reprogramming leads to the activation of a range of inducible defense responses including stomatal closure, generation of toxic reactive oxygen species (ROS), cell-wall fortification, synthesis of PR proteins, and the production and secretion of antimicrobial phytoalexins (Li et al. 2020). The temporal dynamics of IR are complex with some responses occurring within minutes of inducer recognition (e.g., ROS) and other taking hours or even days (e.g., PR expression). Moreover, defenses may be directly induced following inducer application and/or may be “primed” for more rapid expression upon subsequent pathogenic attack (Conrath et al. 2015). The resulting IR may afford broad-spectrum protection against pathogens which generally persists for between 2 to 4 weeks after treatment (Walters et al. 2013).

The efficacy achieved with IR under controlled conditions has seldom been repeated in the field and this has hindered the commercialization and widespread use of inducers (Desmedt et al. 2021; Walters et al. 2013). Nevertheless, IR has been identified by the European Parliament as a future strategy for crop protection (Riemens 2021) and there is renewed interest in inducers and their implementation as crop protectants within integrated management systems (Yassin et al. 2021). In this review, we discuss the practical implementation of inducers in different cropping systems and the contribution of IR to disease management. We focus on the performance of commercially available chemical products that function primarily as inducers (Table 1). Beneficial microbes that affect plant health via direct and indirect modes of action will only be discussed in brief. We describe the incorporation of inducers into existing disease management programs and discuss limitations of IR and constraints to commercial implementation. We also look ahead and speculate how advances in our understanding of plant defence may facilitate the development of more efficacious inducing agents and

**FIGURE 1**  
Timeline for discovery and implementation of inducers as crop protectants.



optimize the implementation of IR for crop protection. The literature on IR has grown considerably during the last 20 years, and this review is not intended to be comprehensive but rather presents selected examples to demonstrate the current and future potential of IR as a crop protection strategy.

### Arable production

In arable crops, one of the first resistance inducers to be used extensively was the benzothiazole compound, probenazole (3-allyloxy-1,2-benzisothiazole-1,1-oxide, Oryzemat<sup>®</sup>, Meiji Seika Kaisha Ltd., Tokyo, Japan). This product has been used extensively in rice production since the 1970s when it was first reported to control rice blast disease (caused by *Pyricularia oryzae*) (Watanabe

et al. 1977). Probenazole is applied either to the paddy field or as a presowing treatment to the seedling box and provides control of the pathogen for 40 to 70 days (Iwata 2001). Detailed studies of the effect of probenazole on rice indicated a change in host metabolism signal transduction that resulted in the formation of lignoid membranes, which impair the ability of the fungus to infect the host plant (Iwata et al. 1980). Probenazole became a mainstay of rice protection programs with more than 50% of the seedling boxes treated with the IR agent (Ishii 2008). Probenazole was the sixth most used fungicide in rice production in 2015 at which time the fungicide market for rice was worth \$1.03 billion (Philips-McDougall 2017). More recently, granule formulations containing probenazole with different insecticides (e.g., fipronil and chlorantraniliprole) have been

**TABLE 1**  
**Commercially available inducers mentioned in this review (nonexhaustive)**

Inducer	Chemical-biological group	Commercial product(s)	Company (country)	Pathogen (selected reference)
Acibenzolar-S-methyl	Benzothiadiazole	Actigard <sup>®</sup> Bion <sup>®</sup>	Syngenta, U.S.A. Syngenta, Europe	<i>Fusarium graminearum sensu stricto</i> (Shude et al. 2022) <i>Pseudomonas syringae</i> pv. <i>tomato</i> (Louws et al. 2001) <i>Pseudomonas syringae</i> pv. <i>actinidiae</i> (de Jong et al. 2019) <i>Erwinia amylovora</i> (Johnson and Temple 2017) <i>Elsinoe fawcettii</i> (Agostini et al. 2003) ' <i>Candidatus Liberibacter asiaticus</i> ' (Li et al. 2016)
<i>Bacillus</i> spp.	Plant growth promoting bacteria	Bioyield <sup>™</sup> flowable	Gustafson, U.S.A.	<i>Botrytis cinerea</i> (Sarosh et al. 2009)
Chitosan	Polysaccharide	ChitoPlant <sup>®</sup> ARMOUR-Zen <sup>®</sup> Kendal Cops <sup>®</sup>	ChiPro GmbH, Germany BotryZen 2010 Ltd., NZ Valagro, Italy	<i>Plasmopara viticola</i> (Dagostin et al. 2011) <i>Erysiphe necator</i> (Iriti et al. 2011)
COS-OGA	Polysaccharide	Fytosave <sup>®</sup>	FytoFend Isnes, Belgium	<i>Erysiphe necator</i> (Calderone et al. 2022; van Aubel et al. 2014)
Harpin	Harpin $\alpha\beta$ protein	Messenger Gold <sup>®</sup>	Plant Health Care, U.K.	<i>Venturia inaequalis</i> and <i>V. nashicola</i> (Percival et al. 2009)
Laminarin	Polysaccharide	Vacciplant <sup>®</sup> Iodus <sup>®</sup> 40 HMO 736 Frontiere	Arysta LifeScience, France Laboratoires Goëmar, France BioAtlantis, Ireland	<i>Blumeria graminis</i> f. sp. <i>tritici</i> (Renard-Melier et al. 2007) <i>Plasmopara viticoli</i> (Romanazzi et al. 2016, 2021) <i>Zymoseptoria tritici</i> (de Borba et al. 2022)
Phosphorous acid salts	Phosphonates	Phospho-jet <sup>®</sup> Phoenix <sup>®</sup>	Arborjet, U.S.A. Orion Future Technology, U.K.	<i>Erwinia amylovora</i> (Aćimović et al. 2015) ' <i>Candidatus Liberibacter asiaticus</i> ' (Hu et al. 2018) <i>Alternaria alternata</i> (Agostini et al. 2003)
Fosetyl-Al		Aliette <sup>®</sup>	Bayer Crop Science, U.S.A.	<i>Elsinoe fawcettii</i> (Agostini et al. 2003)
Probenazole	Benzisothiazole	Oryzemat <sup>®</sup>	Meiji Seika Kaisha Ltd., Japan	<i>Pyricularia oryzae</i> (Watanabe et al. 1977) <i>Cochliobolus heterostrophus</i> (Yang et al. 2011)
Pro-C	Prohexadione	Apogee <sup>®</sup>	BASF, U.S.A.	<i>Erwinia amylovora</i> (Aćimović et al. 2021)
ReZist	Mineral nutrients	ReZist <sup>®</sup>	Stoller Enterprises Inc., U.S.A.	<i>Alternaria alternata</i> (Agostini et al. 2003) <i>Elsinoe fawcettii</i> (Agostini et al. 2003)
<i>Reyonouria sacchalinensis</i> extract	Plant extract	Milsana <sup>®</sup> Regalia <sup>®</sup> Regalia Maxx <sup>®</sup> Sakaliaa <sup>®</sup>	Biofa, Germany Marrone Bio Innovations, U.S.A. Syngenta Nordics, Denmark	<i>Leveillula taurica</i> (Konstantinidou-Doltsinis et al. 2006) <i>Podosphaera xanthii</i> (Rur et al. 2018)
<i>Saccharomyces</i> spp. extract	Yeast extract	Oomisine <sup>®</sup>	Kalosgate, Italy	<i>Plasmopara viticola</i> (Romanazzi et al. 2016, 2021)
Salicylic acid	Salicylic acid	Rigel-G	Orion, Future Technology, U.K.	' <i>Candidatus Liberibacter asiaticus</i> ' (Hu et al. 2018) <i>Venturia inaequalis</i> and <i>V. nashicola</i> (Percival et al. 2009)

commercialized in Japan for control of rice blast and a variety of pests (Hokko 2019). Probenazole has also demonstrated activity against southern corn leaf blight, caused by *Cochliobolus heterostrophus*, in both controlled and field conditions (Yang et al. 2011). Although control was slightly inferior to the commercial fungicide (maneb), the authors suggested that integration of probenazole into a program would help to reduce the environmental impact of maize production.

ASM (Bion<sup>®</sup>, Actigard<sup>®</sup>, Syngenta) was introduced into the market nearly 20 years ago after demonstrating high levels of disease control in a range of plant species (Oostendorp et al. 2001). Initial field trials on tobacco suggested control levels of approximately 90% or more against tobacco wildfire (*Pseudomonas syringae* pv. *tabaci*), leaf spot (*Cercospora nicotianae*), and brown spot (*Alternaria alternata*) (Cole 1999; Perez et al. 2003). The application of ASM to wheat at the two-node stage was reported to give season-long protection against powdery mildew (*Blumeria graminis* f. sp. *tritici*) (Görlach et al. 1996). However, a recent study suggested the activity of ASM against wheat foliar pathogens could be limited to a period of only 20 days postapplication (Ducatti et al. 2022). ASM has recently been shown to reduce Fusarium head blight (*Fusarium graminearum sensu stricto*) in wheat (Shude et al. 2022). Application at anthesis gave the most significant control of disease and reductions in seed infection. ASM control of barley diseases has been less convincing. Despite over 60% control of barley scald (*Rhynchosporium graminicola*) in controlled conditions on susceptible varieties ('Optic' and 'Cellar'), field trials were less encouraging (Walters et al. 2014). ASM on its own, or in combination with  $\beta$ -amino butyric acid (BABA) and cis-jasmone, induced variable control of foliar disease (Walters et al. 2014). Overall, most effective disease control and yield response in the barley trials was obtained when inducers were integrated into programs with synthetic fungicides. It was suggested that the optimization of inducers would require additional research to evaluate the effect of cultivar on the induced response.

The effect of inducer application on powdery mildew populations in barley was investigated in small scale field trials over two seasons (Newton et al. 1998). Two spray applications of an unformulated yeast-derived inducer reduced mildew infection by 78% in year one and by 24% in year two but did not exert selection on the mildew population. Similarly, a glasshouse study on the evolution of disease resistance in *B. graminis* in barley showed that ASM did not exert a selection pressure on the pathogen over ten generations (Bousset and Pons-Kuhnemann 2003). However, mildew population diversity was lower in barley plants treated with a combination of ASM with the fungicide (ethirimol) than with the fungicide alone, suggesting that inducers have potential to contribute to selection pressure (Bousset and Pons-Kuhnemann 2003). Wiese et al. (2003) conducted four independent experiments to investigate the effect of soil properties on ASM-induced resistance against powdery mildew in barley. Induction of resistance by ASM was not affected by nitrogen, phosphorus, or potassium content but was affected by soil organic matter, based on total carbon content. A significant level of resistance against barley powdery mildew was induced by ASM in low organic matter soils, compared with untreated controls, but not in plants grown in a high organic matter soil. However, the barley in the high organic matter soil showed greater constitutive resistance to powdery mildew than the ASM-treated plants grown in low organic matter soil. It was suggested that the elevated disease resistance in high organic matter soils may be associated with higher microbial activity and that there may be a maximum level of resistance that cannot be further increased (Wiese et al. 2003).

In field trials conducted over two seasons, ASM in combination with BABA and cis-jasmone (CJ) was also shown to give significant control of light leaf spot (*Pyrenopeziza brassicae*) in winter oilseed rape (*Brassica napus*) (Oxley and Walters 2012). Indeed, in one season the inducers outperformed the conventional fungicides

by giving complete control of disease in the susceptible cultivar Castille. Earlier glasshouse studies indicated that this combination had potential to activate SA-dependent (ASM) and SA-independent (BABA, CJ) pathways with the subsequent expression of a broader array of PR genes than with individual treatments (Walters et al. 2011). ASM, applied as a seed soak, has also been shown to have activity against the soilborne pathogen, *Plasmodiophora brassicae*, the causal agent of club root in brassicaceae (McGrann et al. 2016). The symptoms of club root were reduced by over 50% and gall weight was reduced by 63% compared with the control. *P. brassicae* is an increasing problem in arable cropping systems with brassicas in a short rotation.

Laminarin is a brown seaweed extract, containing polysaccharides, which was introduced in the market by Arysta LifeScience (Paris, France) as Vacciplant<sup>®</sup>. It remains the only algal polysaccharide registered for control of cereal crop diseases in Europe. Early glasshouse studies indicated activity of a laminarin formulation (Iodus<sup>®</sup>40, Goëmar, Saint-Malo, France) against *B. graminis* f. sp. *tritici*, the causal agent of wheat powdery mildew (Renard-Merlier et al. 2007). On the susceptible cultivar Orvantis, a single spray application gave 55% control compared with the untreated, while a double application increased efficacy to 60%.

More recently, de Borba et al. (2022) found that laminarin demonstrated efficacy against Septoria leaf spot (*Zymoseptoria tritici*) in wheat and that disease control depended on direct antifungal activity in combination with defense induction. In field trials on the susceptible cultivar Alixan, Septoria leaf spot symptoms were reduced by 42% and pycnidium density by 45% compared with untreated controls. Carrageenans are sulphated marine polysaccharides extracted from red seaweed with the potential to elicit the primary and secondary metabolisms of plants (Shukla et al. 2016). In Brazil, a carrageenan-based biostimulant, Algomel PUSH<sup>®</sup> (Olmix Plant Care), was evaluated for its potential to control fungal diseases in wheat (Ducatti et al. 2022). In field trials a spray application of 1.2 liter/ha gave control of the foliar diseases powdery mildew (*B. graminis*), spot blotch (*Bipolaris sorokiniana*), tan spot (*Drechslera tritici-repentis*), and leaf rust (*Puccinia triticina*) for approximately 20 days. The level of disease control was statistically similar to that obtained with ASM. However, there was no control of Fusarium head blight and no effect on grain yield or quality.

## Tomatoes

The inducer ASM has good potential to protect tomatoes against bacterial pathogens. Glasshouse and field trials in the north-eastern United States showed that foliar applied ASM reduced the severity of bacterial spot (*Xanthomonas* spp.) and bacterial speck (*Pseudomonas syringae* pv. *tomato*) as well or better than the standard copper-based control program (Louws et al. 2001). Soil applied ASM reduced bacterial spot disease severity in 'Florida 47' and 'SecuriTY 28' under controlled conditions and in the field (Huang and Vallad 2018). Soil application of ASM outperformed the foliar application under controlled conditions and had comparable efficacy in the field. It was also suggested that rainfall and irrigation may have caused leaching of ASM in the field thus affecting efficacy. The authors proposed that combining ASM soil treatment with PGPR and/or other inducers could improve efficacy (Huang and Vallad 2018). The integrated use of ASM spray with fungicides to control bacterial spot was evaluated in 10 trials over a 6-year period (Roberts et al. 2008). These showed that the use of ASM, alternated with copper and mancozeb, achieved the same level of control of bacterial spot as the fungicide alone, thus demonstrating potential to reduce copper-mancozeb applications by 50% (Roberts et al. 2008). ASM has also been tested in combination with other biologically based controls. Applications of ASM in combination with a bacteriophage formulation (Agriphage<sup>™</sup>, OmniLytics, Inc., Sandy, UT, U.S.A.) provided similar or better disease control of tomato bacterial spot than copper-mancozeb treatments in the field

and glasshouse (Obradovic et al. 2004). In glasshouse tomatoes, ASM combined with *Bacillus subtilis* GB03 and *Bacillus amyloliquefaciens* IN937a (Bioyield™ flowable, Gustafson, TX, U.S.A.) provided greater control of bacterial wilt (*Ralstonia solanacearum*) than the individual treatments (Anith et al. 2004). Moreover, the same combination treatment provided control of bacterial speck that was similar or better than ASM alone (Herman et al. 2008).

IR has also been investigated as a control option for fungal diseases on tomato. In glasshouse studies, soil application of ASM to tomato 'ACE55' suppressed *Fusarium* crown and root rot (*Fusarium oxysporum* f. sp. *radicis-lycopersici*) when used in combination with *Bacillus* spp. PGPR strains (*B. subtilis* GB03 and FZB24, *B. amyloliquefaciens* IN937a, and *B. pumilus* SE34) but not when used alone (Myresiotis et al. 2012). A formulated plant extract from *R. sachalinensis* (Milsana®, Biofa, Münsingen, Germany) reduced powdery mildew infection (*Leveillula taurica*) on 'Manthos' tomato leaves by up to 64% in glasshouse conditions and was as effective as sulfur (Konstantinidou-Doltsinis et al. 2006). Similarly, an investigation of alternatives for organic production found that foliar applications of Milsana and chitosan (Chitoplant®, ChiPro GmbH, Bremen, Germany) was as effective against powdery mildew on glasshouse 'Belladonna' tomato as sulfur (Ribas-Agusti et al. 2013). In efficacy trials under commercial glasshouse conditions in Mexico, foliar applications of *R. sachalinensis* extract (Regalia Maxx®, FMC, Philadelphia, PA, U.S.A.) and harpin  $\alpha\beta$  proteins (Messenger Gold®, Plant Health Care, Holly Springs, NC, U.S.A.) used in combination with soil application of *Bacillus*-containing products (PHC Colonize® or Fungifree AB®) were as effective as a conventional fungicide program against tomato diseases (Esquivel-Cervantes et al. 2022). Suppression of root disease by the soil treatment was complemented by control of foliar diseases by the inducers. Regalia Maxx was effective against powdery mildew and *Botrytis* gray mold whilst Messenger Gold was effective against late blight (*Phytophthora infestans*). However, none of the inducers affected bacterial canker (*Clavibacter michiganensis*) or pith necrosis (*Pseudomonas corrugata*). Overall, it was concluded that the integration of inducers with cultural and chemical alternatives can reduce chemical applications and contribute to more sustainable disease management in glasshouse tomato production.

### Cucurbits

The use of inducing agents, alone and in combination with fungicides, was investigated for control of powdery mildew (*Podosphaera fuliginea*) in cucurbits. In field trials, three applications of ASM, at 2-week intervals, significantly reduced powdery mildew severity in cucumber ('Ushuaia' F1 hybrid) plants to 8 to 10% compared with 37 to 46% in untreated controls (Awad et al. 2012). The inducers, ASM, Milsana, and ReZist® (SA/potassium silicate formulation, Stoller Enterprises, Houston, TX, U.S.A.) were compared with fungicide for the control of powdery mildew in 'Sultana' cucumber in a commercial polytunnel (Bokshi et al. 2008). All treatments controlled powdery mildew for 4 weeks, but only ASM remained effective for 6 weeks. The same study compared the inducers alone and in paired combinations, applied 1 week apart, for control of powdery mildew on 'Austin' cucumber. A single application of ASM was more effective than two applications of ReZist or Milsana. The most effective treatments, ASM applied twice and a Milsana-ASM combination, provided almost complete control of powdery mildew but there was a greater yield penalty associated with the ASM treatment than with the Milsana-ASM combination. Milsana was directly inhibitory to the pathogen but was a relatively weak inducer (based on chitinase induction) and so this may explain its lesser effect on yield.

A formulation containing *R. sachalinensis* extract (Sakaliaa®, Syngenta Nordics A/S, Denmark) was assessed for control of powdery mildew in semicommercial cucumber trials in Sweden (Rur et al. 2018). Weekly applications of Sakaliaa significantly reduced

the severity of powdery mildew compared with untreated controls, however, the treatment resulted in brown residues on cucumber plants and fruits. When Sakaliaa was combined with Yuccah® (extract from *Yucca schidigera*; Plant Health Cure B.V., Oosterwijk, Netherlands) to act as a wetting agent, the leaf residues were less visible and disease severity was significantly reduced in susceptible ('Euphoria') and partially resistant ('Proloog') cultivars compared with untreated and standard fungicide treatments (Rur et al. 2018). Field trials assessed the potential of controlling powdery mildew in squash using *R. sachalinensis* extract (Regalia) and the laminarin product (HMO 736, Laboratoires Goëmar, Saint-Jouan-des-Guéréts, France) (Zhang et al. 2016). The results with individual inducers on different cultivars (summer squash 'HMX 5703' F1 hybrid or squash 'Medallion') were inconsistent. However, combining the inducing agents with the fungicide Procure 480SC (triflumizole) resulted in significantly greater disease control (Zhang et al. 2016).

### Apples and pears

During the last 20 years several research groups have investigated defense inducers as alternatives or supplements to copper and bactericides in apples and pears (Aćimović et al. 2015, 2021; Johnson and Temple 2016, 2017; Johnson et al. 2016; Maxson-Stein et al. 2002). Fire blight, caused by *Erwinia amylovora*, is one of the most important bacterial diseases of apple and pear worldwide. Management of fire blight traditionally relies on cultural practices and application of copper and antibiotics. Weekly spray applications of ASM induced a dose-dependent resistance against fire blight in mature 'Jonathan' apple trees that resulted in fewer flower infections and a reduction in shoot canker extension (Maxson-Stein et al. 2002). Whilst ASM was not as effective as streptomycin, it demonstrated potential to supplement the bactericide. It was suggested that using streptomycin at critical periods during bloom, combined with weekly ASM applications, would provide effective management of fire blight and decrease the risk of streptomycin-resistance development.

The application of ASM as a root drench or a trunk paint was shown to suppress fire blight canker extension in potted apple (M9/'Cameo' and M26/'Gala') trees (Johnson and Temple 2016). Two ASM applications by either method, at 1 and 2 months before inoculation with *E. amylovora*, resulted in a 78 to 92% reduction in canker size compared with non-ASM controls. Orchard evaluation of the paint method was conducted in 3- to 14-year-old 'Bosc' pear and 'Gala' apple trees as an aid to restore health in fire blight-diseased plantings (Johnson and Temple 2017). ASM was generally applied immediately after pruning by painting 30 to 45 cm of branch length below each pruning cut. Over a 5-year period, the treatment was shown to reduce both tree mortality and the proportion of pruning cuts where fire blight (re)developed. The potential of the ASM paint treatment was particularly effective in young trees during early orchard establishment (ages 2 to 10 years). The label for ASM in the United States was recently extended to include its use as a trunk paint treatment following canker removal.

Trunk injection offers a more targeted approach than spraying and is sometimes used for the delivery of agrochemicals such as phosphonate in tree crops and forestry (Berger and Laurent 2019; Dann and McLeod 2021). Phosphonate fungicides were originally developed for the management of oomycete pathogens but have also demonstrated inducer activity (Dann and McLeod 2021). Phosphonate is highly mobile and is translocated according to physiological sink strengths to the most actively growing tissues. Trunk injection of mature 'Gala' apple trees with either streptomycin, ASM, or phosphonate (Phospho-jet, Arborjet, Inc., Woburn, MA, U.S.A.) resulted in a significant reduction in blossom and shoot blight incidence (Aćimović et al. 2015). Each treatment significantly reduced disease incidence compared with the untreated control; however, streptomycin and phosphonate were more effective than ASM. In general, the suppression of fire blight on shoots was greater than

on flowers and this was attributed to faster accumulation of the injected compounds in the shoots. Trunk injection with prohexadione (Pro-C, Apogee®, BASF, Triangle Park, NC, U.S.A.) reduced blossom blight infection in 'White Transparent' and 'Gala' trees to a level that was comparable to that achieved with streptomycin spray (Duker and Kubiak 2011). Pro-C is a growth regulator that inhibits gibberellin synthesis but there is evidence that it activates apple SA-pathway defence genes (de Bernonville et al. 2014). Spray application of Pro-C, 2 to 3 days after inoculation with *E. amylovora*, followed by three applications of Pro-C + ASM at 12- to 16-day intervals, reduced canker development by up to 83% compared with untreated controls on mature 'Royal Court' apple trees (Aćimović et al. 2021). It was suggested that these programs may suppress tree deaths in apple orchards where no protective antibiotic has been applied. Previously, Spinelli et al. (2007) reported that a single spray application of Pro-C before flower opening reduced blossom blight incidence by up to 50% in 'Golden Delicious' trees. Efficacy was increased when a preflowering Pro-C spray was followed by an application of a suspension of *Pantoea agglomerans* P10c at full bloom (Spinelli et al. 2012). In commercial orchard trials conducted over 2 years, the efficacy of ASM, Pro-C, Fosetyl-Al, and phosphonate against blossom and shoot blight in 'Coscia' pear was increased when the inducers were used in combination with commercial formulations of *Bacillus subtilis* QST713 (Serenade optimum, Bayer CropScience, St. Louis, MO, U.S.A.) and *P. agglomerans* P10c (BLOSSOM BLESS, Agrifutur, Alfianello, Italy) (Bahadou et al. 2017). The greatest protective effects were achieved when the bio-control agents were combined with ASM or Pro-C and this was attributed to the complementary actions of competition, antibiosis and IR.

Defense inducers have also demonstrated potential for the control of fungal disease in apple and pear (Gur et al. 2021; Marolleau et al. 2017; Nakao et al. 2021; Percival and Graham 2021; Percival et al. 2009). Three commercial formulations containing harpin (Messenger®), potassium phosphite (Phoenix®, Orion Future Technology Ltd., Ashford, U.K.), and salicylic acid derivative (Rigel-G®, Orion Future Technology Ltd.) were tested for efficacy against apple scab (*Venturia inaequalis*) and pear scab (*V. nashicola*) under field conditions (Percival et al. 2009). The inducers were efficacious against leaf and fruit scab when applied at three growth stages between budburst and early fruitlet but were less effective than the fungicide penconazole. Moreover, it was suggested that inducers could complement fungicide use between bud break and fruitlet formation. Two of the products (Messenger and Rigel-G) and a commercial chitosan product (Chitosan, Viresco Ltd., Thirsk, U.K.) were tested individually and combined with fungicide for the control of fungal diseases in container-grown apple plants (Percival and Graham 2021). A total of nine experiments conducted over five seasons showed that the combined use of an inducer with reduced rates of fungicide was as efficacious as the full-strength fungicide against apple scab (*V. inaequalis*) and leaf blotch (*Phyllosticta paviae*). These results hold promise for fungal disease management in container nurseries.

In orchard studies on 'Golden Reindeers' apple trees, weekly applications of ASM enhanced the efficacy of a light fungicide program (three sprays) against apple scab (Marolleau et al. 2017). The integrated program, however, was less effective against than a conventional program comprising 12 fungicides and further studies were recommended to establish the relative economic viability of the integrated strategy for apple scab control. In Japan, a series of orchard trials either during the growing season in spring or after fruit harvest were conducted on Asian pear to compare the efficacy of ASM sprays against pear scab (Nakao et al. 2021). Three field applications with ASM, at 10-day-intervals after fruit harvest, reduced scab lesion development on leaves and shoots of 'Nuitaka' trees by over 80% compared with controls and inhibited pseudothecium formation, thus decreasing the primary inoculum source for

infection the following spring. During the growing season, regular ASM applications, commencing at bud scale detachment, showed strong efficacy against pear scab on leaves of 'Kousui' and 'Housui' trees; 6 weekly applications and three fortnightly applications reduced scab incidence by 84 and 98%, respectively, compared with untreated controls (Nakao et al. 2021).

### Citrus

Citrus are cultivated throughout the tropical and temperate regions across the globe and are affected by a broad range of fungal and bacterial diseases. A range of commercially available inducers were evaluated in glasshouse experiments for their potential to control citrus scab (*Elsinoe fawcettii*) on rough lemon, melanose (*Diaporthe citri*) on 'Duncan' grapefruit and Alternaria brown spot (*A. alternata*) on 'Dancy' tangerine (Agostini et al. 2003). Of the inducers tested ASM, ReZist and fosetyl-Al (Aliette®, Bayer CropScience) were the most effective, however, the level and consistency of control did not match that of the standard fungicides. In Australia, ASM was evaluated in citrus orchards for its potential to augment fungicide activity as part of an anti-resistance strategy (Miles et al. 2005). ASM alone reduced the incidence of citrus black spot (*Phyllosticta citricarpa*) on 'Imperial' mandarin (50% reduction) and 'Navel' orange (20% reduction compared with the untreated control). However, ASM did not enhance the activities of copper/mancozeb or strobilurin fungicides when tank-mixed. Conversely, on 'Murcott' mandarins ASM alone was not effective against Alternaria brown spot but it did increase the efficacy of azoxystrobin when the two were tank-mixed (Miles et al. 2005).

Citrus canker (*Xanthomonas axonopodis* pv. *citri*) is one of the most destructive bacterial diseases and causes significant economic losses (Graham et al. 2004). Copper-based bactericides are commonly applied during the spring and summer months for control of citrus canker when immature plant tissue is abundant and climatic conditions are most favourable to the pathogen. Application of ASM has been considered as a potential control agent for citrus canker and as a replacement/supplement for copper (Francis et al. 2009; Graham and Myers 2011, 2013, 2016; de Mello et al. 2020). In glasshouse trials on potted citrumelo plants, a single soil application of INA, ASM, and the neonicotinoid insecticide imidacloprid (IMID) reduced foliar canker lesions by up to 70% (Francis et al. 2009). Moreover, soil-drench application of ASM provided more sustained protection against canker (up to 24 weeks) than foliar-applied ASM (4 weeks). It was proposed that the sustained activity of the soil drench may be due to slower uptake by roots and translocation into actively growing shoots. In field studies in the United States (Graham and Myers 2011, 2013) and Brazil (de Mello et al. 2020) soil drenches with ASM in combination with copper sprays have shown potential to provide more effective control of canker than copper spray alone. In Florida, the reduction in citrus canker lesions in leaves of 'Ray Ruby' grapefruit trees (Graham and Myers 2011, 2013) and 'Vernia' orange trees (Graham and Myers 2013) with four soil drenches of ASM was comparable to 11 sprays with copper and streptomycin. The incidence of canker lesions on 'Red Ruby' grapefruit was significantly reduced by ASM soil drench alone, and ASM in rotation with neonicotinoid insecticides (Graham and Myers 2016). One of the most effective treatments, ASM soil drench integrated with foliar copper sprays, provided significantly greater control of canker on 'Red Ruby' fruit than copper spray alone (Graham and Myers 2016). This integrated approach can enable reduction in the rate and frequency of copper sprays and alleviate adverse environmental effects and selection pressure for copper resistance development.

Chemical inducers have also been considered for the control of citrus huanglongbing (HLB), also called citrus greening disease (Hu et al. 2018; Li et al. 2016, 2021). HLB is caused by the psyllid-transmitted bacterium '*Candidatus Liberibacter asiaticus*' (CLAs) and is considered one of the most destructive citrus diseases

worldwide. Management of HLB has primarily relied upon cultural practice and control of the insect vector responsible for transmission. The inducers BABA, INA, and ASM were evaluated over four growing seasons on orange and mandarin in Florida (Li et al. 2016). Spray application with BABA, INA, and ASM reduced HLB disease severity by 15 to 30% and suppressed CLAs populations in leaves. Inducers have also proven effective against HLB in orange trees when applied by trunk injection (Hu et al. 2018). Four injections at 3-month intervals with ASM, SA, oxalic acid, and potassium phosphonate significantly suppressed CLAs populations in leaves and disease progress of HLB (Hu et al. 2018). Trunk injections were conducted when new flush was present and were applied at approximately 3-month intervals. More recently, Li et al. (2021) conducted studies in ‘Hamlin’ oranges over 3 years to compare the efficacy of four inducers, ASM, IMI, INA, and SA, applied either by trunk injection, foliar spray or soil drench. All trunk injection treatments at 0.25 g active ingredient (a.i.)/tree and foliar sprays of INA or SA (but not ASM or IMI) at 0.5 g a.i./tree significantly reduced HLB severity and CLAs population and increased fruit yield. Moreover, only three trunk injections were required per year compared with six foliar sprays. None of the inducers were effective when applied to the soil.

### Grapes

Downy mildew (*Plasmopara viticola*), powdery mildew (*Erysiphe necator*), and gray mold (*Botrytis cinerea*) are globally significant grapevine diseases that adversely affect the yield and quality of table and wine grapes. Disease control in conventional vineyards relies on a broad range of synthetic fungicides whilst in organic vineyards only copper and sulfur compounds are permitted. Inducers have demonstrated the potential to activate grapevine defense and to reduce these diseases under controlled conditions, but relatively few have shown efficacy in the vineyard (Delaunois et al. 2014).

Formulations containing copper are often used for disease management in organic viticulture (La Torre et al. 2019). However, concerns over copper toxicity have led to increasing restrictions on its use by the European Commission (Commission Implementing Regulation (EU) 2018/1981), thereby prompting an urgent need for alternatives (La Torre et al. 2019). A range of organically acceptable control agents, including defence inducers, were field evaluated for downy mildew control on ‘Cabernet Sauvignon’ in Italy and ‘Chasselas’ and ‘Riesling-Sylvaner’ in Switzerland between 2004 and 2007 (Dagostin et al. 2011). Of these, a chitosan product (ChitoPlant<sup>®</sup>, ChiPro GmbH, Bremen, Germany) was found to be as effective as copper hydroxide (CuOH) and reduced downy mildew on bunches by up to 89% compared with the control. Subsequently, the chitosan product was compared with laminarin, a soluble  $\beta$ -glucan-based inducer (Frontiere, BioAtlantis, Tralee, Ireland), laminarin with reduced rate copper, and laminarin with a *Saccharomyces* spp. extract (Oomisine<sup>®</sup>, Kalos, Codroipo, Italy) in vineyard trials in ‘Montepulciano’ and ‘Verdicchio’ grapes (Romanazzi et al. 2016, 2021). These studies, spanning over 6 years, concluded that chitosan was a viable alternative or supplement to copper formulations and provided good control of downy mildew even under high disease pressure. The integrated CuOH/chitosan strategies were as effective as CuOH alone regardless of whether the treatments were alternated on a weekly basis or split by early/late season. It was proposed that the use of copper during the first half of the season followed thereafter by chitosan would control downy mildew and avoid the negative impact of copper accumulation in grapes. Laminarin was generally not effective on its own, whilst laminarin + *Saccharomyces* extract afforded moderate control of downy mildew but only under low disease pressure.

In vineyard trials, applications of laminarin every 8 to 10 days reduced leaf powdery mildew incidence on ‘Moscato’ grapes by approximately 30 to 55% compared with untreated controls (Pugliese

et al. 2018). The laminarin was not as effective as sulfur but demonstrated sufficient activity to merit further investigation as part of an integrated management program. A chitosan-based inducer (Kendal Cops<sup>®</sup>, Valagro, Atessa, Italy) applied weekly on its own, or alternated with fungicides (penconazole and methylidnocal), significantly reduced the incidence and severity of powdery mildew on leaves and bunches in ‘Montepulciano d’Abruzzo’ grapevines (Iriti et al. 2011). It should be noted that the chitosan formulation contained low concentrations of 1.5% copper and 0.5% manganese which may have contributed direct antifungal activity. A complex containing chitosan and pectate fragments (COS-OGA) and formulated as a liquid concentrate (Fytosave<sup>®</sup>, FytoFend S.A., Gembloux, Belgium) exhibited a dose-dependent efficacy against powdery mildew on ‘Carignan’ and ‘Moscato’ grapevines (van Aubel et al. 2014). In both cultivars, it was shown that six sprays of COS-OGA at 14-day intervals reduced powdery mildew on bunches by over 70% compared with the control. This was achieved under high disease pressure and the level of control was comparable with a commercial sulfur treatment. Efficacy of COS-OGA against powdery mildew was confirmed in a more recent study on organically grown ‘Nero d’Avola’ and ‘Inzola’ grapes in Sicily (Calderone et al. 2022). Moreover, the COS-OGA demonstrated efficacy against gray mold and sour rot, caused by bacterial and yeast complexes, that was comparable with the copper-sulfur control. COS-OGA is approved as a low-risk active substance on the EU Pesticides database ([https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database\\_en](https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en)) and may have potential for organic producers.

### Factors Affecting the Efficacy of IR

IR requires a strong plant defense response to be effective and this can depend on plant genotype, tissue, timing and environment (Marolleau et al. 2017; Reglinski et al. 2014). In glasshouse and field-grown tomatoes, the efficacy of ASM against *R. solanacearum* was greater in tomato cultivars with moderate resistance (‘Neptune’, ‘BHN 466’, and ‘FL 7514’) than in susceptible cultivars (‘Equinox’ and ‘FL 47’) (Pradhanang et al. 2005), thus demonstrating the importance of understanding genotype–inducer interactions. Breeding programs should include responsiveness as a selection criterion. In annual crops, the use of cultivar and multiline mixtures to facilitate natural priming of host defenses and cross-protection may complement the inducer response (Clin et al. 2022). Environmental stress can suppress IR because of antagonism between stress-response and defense-response signaling networks (Kusajima et al. 2017). Therefore, IR is likely to be most effective in controlled intensive production systems, such as glasshouses and nurseries, where environmental and cultural variables can be managed and where inducers can be used as seed treatments and applied via hydroponics, fertigation systems, and/or overhead misting. In the field, ecologically sensitive cultural practices (e.g., soil management and nutrition) that favor plant health and minimize environmental stress are critical.

Soil properties can affect general plant health and therefore the ability of the plant to respond to inducer treatment (Verly et al. 2020; Wiese et al. 2003). Nitrogen (N) is an essential plant nutrient for plant growth but can have contrasting effects on plant defense and plant disease resistance depending on N source and concentration (Mur et al. 2016). In general, physical defenses and phytoalexin synthesis are negatively regulated by N, whereas defense-related enzymes and proteins are positively regulated (Sun et al. 2020). The effects of N fertilization on basal resistance can vary depending on the pathosystem, with high N associated with increased susceptibility to biotrophic pathogens but reduced susceptibility to necrotrophs (Mur et al. 2016). The availability of N also influences IR as it is necessary for the formation of nitric oxide (NO), an important defense signal. Moreover, the modulation of plant defense

by N has been shown to involve an interaction with the SA defense pathway (Ding et al. 2021). Verly et al. (2020) showed that ASM, a functional SA mimic, was effective against *P. syringae* pv. *tomato* DC3000 in arabidopsis plants under low soil nitrate levels but was ineffective when applied to plants supplied with high nitrate. Associated molecular analyses indicated that the N-mediated response depended on a functional NPR1 protein, a key modulator of the SA defense pathway. Similarly, tomato immunity to *P. syringae* pv. *tomato* DC3000 and *R. solanacearum* was greater under low N and was associated with increased SA accumulation (Ding et al. 2021). Clearly, N-mediated modulation of plant immunity is complex and involves interactions between defense signaling pathways and metabolic pathways (Verly et al. 2020). Further research is required to better understand interactions between nutrient availability and inducer efficacy in different cropping systems and the implications for IR and growth/yield.

Differences in soil organic matter content affected the efficacy of ASM against powdery mildew in barley (Wiese et al. 2003). It was suggested that high organic matter soil had greater microbial activity that enhanced resistance to such an extent that further increase by ASM was not significant. Crop type and cultural practices such as tillage have also been shown to affect microbial community structure in soils in cereal cropping systems (Choudhary et al. 2020). It is well established that beneficial soil microbes can suppress plant disease directly through pathogen suppression and indirectly through stimulation of IR (Pieterse et al. 2014). Moreover, PGPR, *Trichoderma* spp., and arbuscular mycorrhizal fungi (AMF) bring added benefits of plant growth promotion and improved stress tolerance by enhancing nutrient acquisition and water uptake (Pozo et al. 2021). Understanding how the microbiome affects plant immunity, and vice versa, can facilitate the development of microbial consortia with complementary modes of action that can be tailored to different cropping systems (Pozo et al. 2021; Teixeira et al. 2019; Trivedi et al. 2020). This may involve the use of synthetic microbial communities (SynComs) to enable functional understanding of plant–microbiome–environment interactions and facilitate the design of SynComs to enhance nutrient acquisition and disease resistance (Shayanthan et al. 2022). For example, a SynCom comprising four rhizobacterial strains induced greater resistance against bacterial wilt (*R. solanacearum*) in tomato than each individual strain (Lee et al. 2021). Unravelling the complexities of how microbial communities directly influence IR and affect plant responses to chemical inducers has potential to transform the integrated use of microbial and chemical inducers for crop protection.

## Current and Future Role of IR in Crop Protection

Over the past 20 years, European legislation (European Parliament, Council of the European Union 2009, Regulation (EC) No. 1107/2009) has resulted in some plant protectants being listed as “candidates for substitution” to be replaced with “more environmentally friendly” alternatives where possible. Inducers offer one option but typically lack eradicant activity and are unlikely to provide comparable efficacy, particularly in conditions of high disease pressure. Indeed, inducer efficacy has been reported to range from 20 to 85% (Walters et al. 2013). There is good evidence, however, that inducers, when combined or alternated with pesticides, biological control agents and antimicrobial natural products can be effective components of integrated crop management (ICM) strategies (Yassin et al. 2021). A recent study commissioned by the European Parliament identified IR as a component of future crop protection strategies in Europe (Riemens 2021). The implementation of inducers in multi-component programs will enable complementary modes of action to operate in different ecological niches thereby offering additive or even synergistic activity (Fig. 2). This holistic approach will integrate different interventions to target specific components of the disease cycle based on an intimate knowledge of the pathosystem.

Alternating inducers with conventional chemistry can enable reductions in chemical use without loss of efficacy or yield and thus may serve as part of a resistance management strategy. This is in accord with anti-resistance strategies recommended by the Fungicide Resistance Action Committee (FRAC) to prolong the effectiveness of “at risk” fungicides (<https://www.frac.info/>). Fungicide resistance has increased since the introduction of single-site fungicides and the time interval between introduction and resistance development can be surprisingly short (Lamberth et al. 2021). The FRAC Code list is based on biochemical mode of action and host plant defence inducers are listed in their own grouping (Group P) (FRAC Code List 2022). Because inducers control disease primarily via the activation of multiple plant defences they are considered at less risk for pathogen resistance development. Probenazole is sometimes cited as an example of inducer longevity because it has been used against rice blast (*Pyricularia grisea*) since 1975 without evidence of pathogen resistance development (Iwata 2001; Walters et al. 2013). However, Bousset and Pons-Kuhnemann (2003) reported that whilst ASM alone did not affect powdery mildew population composition, the combined use of ASM plus the fungicide ethirimol exerted a greater effect on the pathogen population than ethirimol alone. The authors cautioned against “wide and careless use” of inducers until the effects of IR on pathogen population was better understood.

The complementary actions of chemical inducers and beneficial microbes has potential to increase the efficacy and reduce the variability of IR. For example, a tank mix containing ASM plus *Aureobasidium pullulans* CG163 (Aureo®Gold, UPL, Auckland, NZ) had greater efficacy against *Pseudomonas syringae* pv. *actinidiae* in kiwifruit leaves than either treatment alone (de Jong et al. 2019). Moreover, the enhanced efficacy correlated with stronger amplification of defence gene expression in the combination treatment. Preflowering applications of ASM (Actigard®) are used in approximately 68% of kiwifruit orchards in New Zealand to control *P. syringae* pv. *actinidiae* (Melanie Walker, *personal communication*, Orchard Quality Services Manager, Zespri International Limited). Tank-mixing of Actigard® with Aureo®Gold is now recommended during the preflowering period (Kiwifruit Spray Guide 2022). Similarly, the efficacy of ASM and *B. subtilis* QST713 against blossom and shoot blight (*E. amylovora*) in a commercial pear orchard was greater when combined than when each were used alone (Bahadou et al. 2017). The uptake and systemic translocation of soil applied ASM was reportedly higher in tomato plants treated with the PGPR strains *B. subtilis* GB03 and *B. pumilus* SE34 than in control plants receiving no PGPR (Myresiotis et al. 2014). The authors proposed that the enhanced uptake of ASM may be attributable to greater root biomass in the PGPR-treated plants. The elucidation of the molecular and physiological mechanisms that underpin these additive benefits can help to inform the development of smarter ICM strategies. Caution is warranted, however, because the induction of plant defence can result in yield penalties (Pontes et al. 2016) the potential trade-offs associated with IR (Walters et al. 2013) should be considered when developing integrated programs that involve more than one inducer and/or induce stronger defence upregulation.

## New Inducers

Legislation enforcing restrictions in pesticide use will be a major driver for inducer discovery and the implementation of IR in ICM strategies. For example, the European Green Deal promotes a more ecologically sensitive approach with a 50% reduction in chemical pesticides by 2030 (Helepciuc and Todor 2022). Because of this, the future growth of defence inducers and biological control agents is predicted to exceed the growth of synthetic chemical pesticides (Maienfisch and Mangelinckx 2021) with the global market for inducers forecast to reach \$880 million by 2026 (Market Data Forecast 2022). The search for inducers represents a rapidly devel-

oping field of research in China (Dewen et al. 2017), with particular interest in protein-based elicitors. For example, a new inducer product ATaiLing (Arysta LifeScience), which contains a protein from *A. alternata*, was the top-selling crop protection product in China in 2015 with sales over U.S. \$10 million (Dewen et al. 2017). In the United States, Plant Health Care (PHC) Inc., has launched a new platform PREtec (plant response elicitor technology) which is based on the use of bacterial harpin-based proteins. Harpin was the active ingredient in one of the earliest protein-based inducers, Messenger® (Eden BioScience, Bothell, WA, U.S.A.), that was registered in the United States in 2000. In 2007, PHC released EMPLOY® H&T (Employ® Hort and Turf) which contained modified formulations of the harpin  $\alpha\beta$  protein. The first product to emerge from the PREtec platform, Saori™, was registered in Brazil in 2021 for the control of Asian soybean rust (de Paula et al. 2021). There is increasing interest in the potential of nanotechnology to enhance stability and delivery of crop protectants. A recent study of Nadendla et al. (2018) demonstrated the advantages of a harpin (Pss) encapsulation into chitosan nanoparticles to improve its bioavailability and increase the IR response in tomato plants.

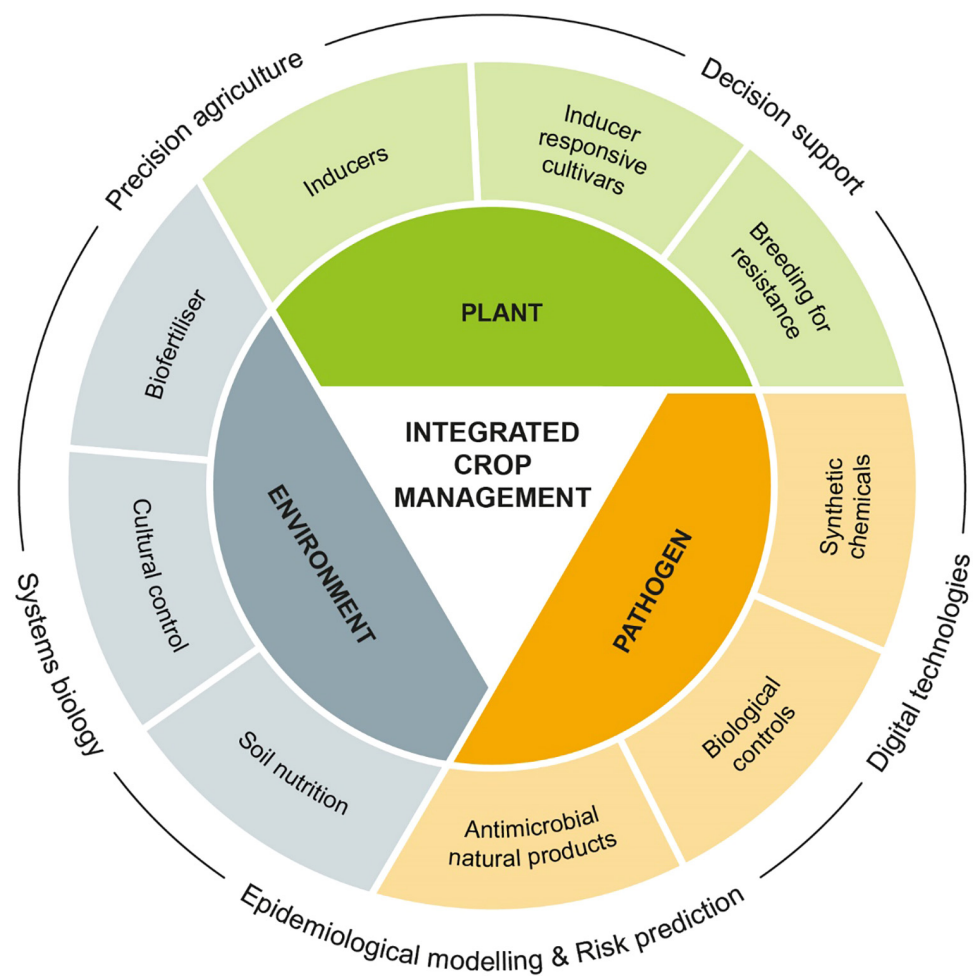
New derivatives of the benzothiadiazole inducer ASM have been developed with greater solubility than the parent compound with comparable or even greater inducer activity (Smiglak et al. 2017). The search for other synthetic inducers remains an active area of research with several new chemistries emerging including, methiadinil and various thiadiazole/isothiazole carboxamide analogs (Qi et al. 2022). In some cases these inducer compounds also exhibit fungicidal activity similar to existing products such as probenazole and phosphonate. Systems biology approaches with high-throughput analytical technologies have potential to accel-

erate inducer identification and their in planta targets (Zhou and Wang 2018). The latter may also serve as breeding markers for the selection of genotypes with enhanced capacity to respond to inducers.

Replacing synthetic pesticides with synthetic inducers may be a short-term strategy and does not necessarily address the environmental impact of synthetic chemicals. For example, ASM is classified as hazardous to the aquatic environment and there are maximum residues levels for treated produce. Ultimately the development of effective organically acceptable biologically based inducers is highly desirable. Carbohydrate-based inducers obtained from plants and fungi including various oligosaccharides and oligogalacturonides are considered safer for the environment and have the potential to become broadly applicable in future crop protection, including organic agriculture (Zheng et al. 2020). For example, chitosan is a versatile polymer that offers potential dual benefits of direct antimicrobial activity and IR (Riseh et al. 2022). Polysaccharide-based inducers mimic the action of naturally occurring PAMPs and DAMPS and are recognised by PRRs in the plant plasma membrane, so triggering pattern triggered immunity (PTI), an important component of IR (Boutrot and Zipfel 2017). Greater understanding of PAMPs/DAMPs structure-activity relationships and their perception by PRRs can guide inducer design and development (Rebaque et al. 2021). This extends beyond carbohydrates and includes proteins, peptides and lipids that trigger plant immunity. Moreover, it has been suggested that PRRs may be used as a criterion in plant breeding programs or engineered to improve inducer recognition (Boutrot and Zipfel 2017). Beneficial microbes modulate plant immunity via the secretion of low-molecular-weight metabolites including acyl-homoserine lactones, cyclic lipopep-

**FIGURE 2**

Components of integrated crop management. The outer circle lists factors that guide the implementation of different interventions (second layer) that may be integrated to promote plant and environmental health and to suppress the pathogen.



tides, rhamnolipids, and N-alkylated benzylamine derivatives (Pršić and Ongena 2020). Depending on production methods, these compounds may also be acceptable in organic systems.

Advances in production and formulation technologies may enable the development of more effective inducers with more sustained and consistent activity. Moreover, the use of low volume sprayers or application via irrigation lines or seed treatments can enable more targeted and efficient use of inducers. Precision agriculture uses digital technologies to gather massive data sets that are used to inform crop management decisions (Duncan et al. 2021). Novel sensors and analytical tool are emerging that can monitor plant health (Ang and Lew 2022) and the environment (Kim and Lee 2022) in real time. This information, together with mathematical models for IR (Abdul Latif et al. 2014) and disease risk prediction (Newlands 2018), can provide a decision support tool to guide inducer application. Moreover, the integration of these models may facilitate the development of algorithms for virtual cropping systems (“digital twins”) that can be used to optimize IR and to design smarter ICM strategies.

## Conclusions

During the last 50 years our understanding of IR has advanced considerably, leading to the commercialisation of a range of inducer products. The scepticism associated with the notion that IR could contribute to disease management has been replaced by an acceptance that inducers may at last be coming of age as crop protectants. There is good evidence that inducers can make a practicable contribution to disease control, particularly in integrated management programs. The use of inducers in rotation with pesticides and/or in combination with BCAs can reduce chemical inputs and so address environmental and ecological concerns associated with pesticide use. Systems biology approaches will facilitate development of the next generation of inducers that are based on an ever-increasing understanding of plant recognition receptors and defence signaling pathways. This, together with the selection of inducer responsive cultivars, more efficient application methods, and new digital decision support tools to enable early intervention, can optimize inducer efficacy and establish IR as a central component of crop protection management.

## Literature Cited

- Abdul Latif, S., N., Wake, G. C., Reglinski, T., and Elmer, P. A. 2014. Modelling induced resistance to plant diseases. *J. Theor. Biol.* 347:144-150.
- Ćimović, S. G., Meredith, C. L., Santander, R. D., and Khodadadi, F. 2021. Proof of concept for shoot blight and fire blight canker management with postinfection spray applications of prohexadione-calcium and acibenzolar-S-methyl in apple. *Plant Dis.* 105:4095-4105.
- Ćimović, S. G., Zeng, Q., McGhee, G. C., Sundin, G. W., and Wise, J. C. 2015. Control of fire blight (*Erwinia amylovora*) on apple trees with trunk-injected plant resistance inducers and antibiotics and assessment of induction of pathogenesis-related protein genes. *Front. Plant Sci.* 6:16-26.
- Aerts, N., Pereira Mendes, M., and Van Wees, S. C. 2021. Multiple levels of crosstalk in hormone networks regulating plant defense. *Plant J.* 105:489-504.
- Agostini, J. P., Bushong, P., and Timmer, L. W. 2003. Greenhouse evaluation of products that induce host resistance for control of scab, melanose, and *Alternaria* brown spot of citrus. *Plant Dis.* 87:69-74.
- Ang, M. C.-Y., and Lew, T. T. S. 2022. Non-destructive technologies for plant health diagnosis. *Front. Plant Sci.* 13:884454.
- Anith, K. N., Momol, M. T., Kloepper, J. W., Marois, J. J., Olson, S. M., and Jones, J. B. 2004. Efficacy of plant growth-promoting rhizobacteria, acibenzolar-S-methyl, and soil amendment for integrated management of bacterial wilt on tomato. *Plant Dis.* 88:669-673.
- Awad, M. E.-M., Abo-Elyousr, K. A., and Abdel-Monaim, M. F. 2012. Management of cucumber powdery mildew by certain biological control agents (BCAs) and resistance inducing chemicals (RICs). *Arch. Phytopathol. Plant Prot.* 45:652-659.
- Bahadou, S. A., Oujija, A., Boukhari, M. A., and Tahiri, A. 2017. Development of field strategies for fire blight control integrating biocontrol agents and plant defense activators in Morocco. *J. Plant Pathol.* 99:51-58.
- Bektas, Y., and Eulgem, T. 2015. Synthetic plant defense elicitors. *Front. Plant Sci.* 6:804.
- Berens, M. L., Berry, H. M., Mine, A., Argueso, C. T., and Tsuda, K. 2017. Evolution of hormone signaling networks in plant defense. *Annu. Rev. Phytopathol.* 55:401-425.
- Berger, C., and Laurent, F. 2019. Trunk injection of plant protection products to protect trees from pests and diseases. *Crop Prot.* 124:104831.p1-9.
- Bokshi, A. I., Jobling, J., and McConchie, R. 2008. A single application of Milsana (R) followed by Bion (R) assists in the control of powdery mildew in cucumber and helps overcome yield losses. *J. Hortic. Sci. Biotechnol.* 83:701-706.
- Bousset, L., and Pons-Kuhnemann, J. 2003. Effects of acibenzolar-S-methyl and ethirimol on the composition of a laboratory population of barley powdery mildew. *Phytopathology* 93:305-315.
- Boutrot, F., and Zipfel, C. 2017. Function, discovery, and exploitation of plant pattern recognition receptors for broad-spectrum disease resistance. *Annu. Rev. Phytopathol.* 55:257-286.
- Calderone, F., Vitale, A., Panebianco, S., Lombardo, M. F., and Cirvilleri, G. 2022. COS-OGA applications in organic vineyard manage major airborne diseases and maintain postharvest quality of wine grapes. *Plants (Basel)* 11:1763.
- Cameron, D. D., Neal, A. L., van Wees, S. C., and Ton, J. 2013. Mycorrhiza-induced resistance: More than the sum of its parts? *Trends Plant Sci.* 18: 539-545.
- Chester, K. S. 1933. The problem of acquired physiological immunity in plants. *Quart. Rev. Biol.* 8:275-324.
- Choudhary, M., Jat, H. S., Datta, A., Sharma, P. C., Rajashekar, B., and Jat, M. L. 2020. Topsoil bacterial community changes and nutrient dynamics under cereal based climate-smart agri-food systems. *Front. Microbiol.* 11:1812.
- Clin, P., Grognaud, F., Andrivon, D., Mailleret, L., and Hamelin, F. M. 2022. Host mixtures for plant disease control: Benefits from pathogen selection and immune priming. *Evol. Appl.* 15:967-975.
- Cole, D. L. 1999. The efficacy of acibenzolar-S-methyl, an inducer of systemic acquired resistance, against bacterial and fungal diseases of tobacco. *Crop Prot.* 18:267-273.
- Conrath, U., Beckers, G. J., Langenbach, C. J., and Jaskiewicz, M. R. 2015. Priming for enhanced defense. *Annu. Rev. Phytopathol.* 53:97-119.
- Dagostin, S., Scharer, H. J., Pertot, I., and Tamm, L. 2011. Are there alternatives to copper for controlling grapevine downy mildew in organic viticulture? *Crop Prot.* 30:776-788.
- Dann, E., and McLeod, A. 2021. Phosphonic acid: A long-standing and versatile crop protectant. *Pest Manag. Sci.* 77:2197-2208.
- de Bernonville, T. D., Marolleau, B., Staub, J., Gaucher, M., and Brisset, M. N. 2014. Using molecular tools to decipher the complex world of plant resistance inducers: An apple case study. *J. Agric. Food Chem.* 62: 11403-11411.
- de Borba, M. C., Velho, A. C., de Freitas, M. B., Holvoet, M., Maia-Grondard, A., Baltenweck, R., Magnin-Robert, M., Randoux, B., Hilbert, J. L., Reignault, P., Huguency, P., Siah, A., and Stadnik, M. J. 2022. A laminarin-based formulation protects wheat against *Zymoseptoria tritici* via direct antifungal activity and elicitation of host defense-related genes. *Plant Dis.* 106: 1408-1418.
- de Jong, H., Reglinski, T., Elmer, P. A., Wurms, K., Vanneste, J. L., Guo, L. F., and Alavi, M. 2019. Integrated use of *Aureobasidium pullulans* strain CG163 and acibenzolar-S-methyl for management of bacterial canker in kiwifruit. *Plants* 8:287.
- Delaney, T. P., Uknes, S., Vernooij, B., Friedrich, L., Weymann, K., Negrotto, D., Gaffney, T., Gutrella, M., Kessmann, H., Ward, E., and Ryals, J. 1994. A central role of salicylic-acid in plant-disease resistance. *Science* 266: 1247-1250.
- Delaunais, B., Farace, G., Jeandet, P., Clément, C., Baillieux, F., Dorey, S., and Cordelier, S. 2014. Elicitors as alternative strategy to pesticides in grapevine? Current knowledge on their mode of action from controlled conditions to vineyard. *Environ. Sci. Pollut. Res.* 21:4837-4846.
- de Mello, F. E., Zaniboni, C., Barreto, T., da Silva, M. R. L., and Leite, R. P. 2020. Soil application of acibenzolar-s-methyl and thiamethoxam for the management of citrus canker under subtropical conditions. *Tropic Plant Pathol.* 45:684-690.
- de Paula, S., Holz, S., Souza, D. H. G., and Pascholati, S. F. 2021. Potential of resistance inducers for soybean rust management. *Can. J. Plant Pathol.* 43:S298-S307.
- Desmedt, W., Vanholme, B., and Kyndt, T. 2021. Chapter 5-Plant defense priming in the field: A review. Pages 87-124 in: *Recent Highlights in the Discovery and Optimization of Crop Protection Products*. P. Maienfisch and S. Mangelinckx, eds. Academic Press, Cambridge, MA.
- Dewen, Q., Yijie, D., Yi, Z., Shupeng, L., and Fachao, S. 2017. Plant immunity inducer development and application. *Mol. Plant-Microbe Interact.* 30: 355-360.

- Ding, S., Shao, X., Li, J., Ahammed, G. J., Yao, Y., Ding, J., Hu, Z., Yu, J., and Shi, K. 2021. Nitrogen forms and metabolism affect plant defence to foliar and root pathogens in tomato. *Plant Cell Environ.* 44:1596-1610.
- Ducatti, R. D. B., Tironi, S. P., Filho, J. A. W., and Mazaro, S. M. 2022. Carrageenan as an elicitor of wheat's mechanisms of defense. *Agron. Sci. Biotech.* 8:1-11.
- Duker, A., and Kubiak, R. 2011. Stem injection of prohexadione carboxylic acid to protect blossoms of apple trees from fire blight infection (*Erwinia amylovora*). *J Plant Dis. Prot.* 118:156-160.
- Duncan, E., Glaros, A., Ross, D. Z., and Nost, E. 2021. New but for whom? Discourses of innovation in precision agriculture. *Agric. Human Values* 38:1181-1199.
- Esquivel-Cervantes, L. F., Tlapal-Bolaños, B., Tovar-Pedraza, J. M., Pérez-Hernández, O., Leyva-Mir, S. G., and Camacho-Tapia, M. 2022. Efficacy of biorational products for managing diseases of tomato in greenhouse production. *Plants* 11:1638.
- European Parliament, Council of the European Union. 2009. REGULATION (EC) No. 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. *Off. J. Eur. Union L(309):1-50*.
- Francis, M. I., Redondo, A., Burns, J. K., and Graham, J. H. 2009. Soil application of imidacloprid and related SAR-inducing compounds produces effective and persistent control of citrus canker. *Eur. J. Plant Pathol.* 124:283-292.
- Fungicide Resistance Action Committee. 2022. FRAC code list 2022. Fungal control agents sorted by cross-resistance pattern and mode of action. <https://www.frac.info/knowledge-database/downloads>
- Görlach, J., Volrath, S., Knauf-Beiter, G., Hengy, G., Beckhove, U., Kogel, K.-H., Oostendorp, M., Staub, T., Ward, E., and Kessmann, H. 1996. Benzothiadiazole, a novel class of inducers of systemic acquired resistance, activates gene expression and disease resistance in wheat. *Plant Cell* 8:629-643.
- Graham, J. H., Gottwald, T. R., Cubero, J., and Achor, D. S. 2004. *Xanthomonas axonopodis* pv. *citri*: Factors affecting successful eradication of citrus canker. *Mol. Plant Pathol.* 5:1-15.
- Graham, J. H., and Myers, M. E. 2011. Soil Application of SAR inducers imidacloprid, thiamethoxam, and acibenzolar-S-methyl for citrus canker control in young grapefruit trees. *Plant Dis.* 95:725-728.
- Graham, J. H., and Myers, M. E. 2013. Integration of soil applied neonicotinoid insecticides and acibenzolar-S-methyl for systemic acquired resistance (SAR) control of citrus canker on young citrus trees. *Crop Prot.* 54:239-243.
- Graham, J. H., and Myers, M. E. 2016. Evaluation of soil applied systemic acquired resistance inducers integrated with copper bactericide sprays for control of citrus canker on bearing grapefruit trees. *Crop Prot.* 90:157-162.
- Gur, L., Reuveni, M., and Cohen, Y. 2021.  $\beta$ -Aminobutyric acid induced resistance against *Alternaria* fruit rot in apple fruits. *J. Fungi* 7:564-577.
- Hammerschmidt, R., and Kuc, J. 1995. Induced resistance to disease in plants. Kluwer Academic Publishers, Dordrecht, The Netherlands.
- Helepciuc, F.-E., and Todor, A. 2022. Improving the authorization of microbial biological control products (MBCP) in the European Union within the EU green deal framework. *Agronomy* 12:1218-1226.
- Herman, M., Davidson, J., and Smart, C. 2008. Induction of plant defense gene expression by plant activators and *Pseudomonas syringae* pv. *tomato* in greenhouse-grown tomatoes. *Phytopathology* 98:1226-1232.
- Hokko. 2019. Company information and market report of agrochemicals in Japan. <https://www.hokkochem.co.jp/wp-content/uploads/2019.pdf>
- Hu, J., Jiang, J., and Wang, N. 2018. Control of citrus huanglongbing via trunk injection of plant defense activators and antibiotics. *Phytopathology* 108:186-195.
- Huang, C.-H., and Vallad, G. E. 2018. Soil applications of acibenzolar-S-methyl induce defense gene expression in tomato plants against bacterial spot. *Eur. J. Plant Pathol.* 150:971-981.
- Iriti, M., Vitalini, S., Di Tommaso, G., D'Amico, S., Borgo, M., and Faoro, F. 2011. New chitosan formulation prevents grapevine powdery mildew infection and improves polyphenol content and free radical scavenging activity of grape and wine. *Aust. J. Grape Wine Res.* 17:263-269.
- Ishii, H. 2008. Fungicide research in Japan—An overview. Pages 11-17 in: *Modern fungicides and antifungal compounds V: 15th International Reinhardtbrunn Symposium*, Friedrichroda, Germany. Deutsche Phytomedizinische Gesellschaft eV Verlag.
- Iwata, M. 2001. Probenazole—A plant defence activator. *Pestic. Outlook* 12:28-31.
- Iwata, M., Suzuki, Y., Watanabe, T., Mase, S., and Sekizawa, Y. 1980. Effect of probenazole on the activities of enzymes related to the resistant reaction in rice plant. *Japan J. Phytopathol.* 46:297-306.
- Johnson, K. B., Smith, T. J., Temple, T. N., Gutierrez, E., Elkins, R. B., and Castagnoli, S. P. 2016. Integration of acibenzolar-S-methyl with antibiotics for protection of pear and apple from fire blight caused by *Erwinia amylovora*. *Crop Prot.* 88:149-154.
- Johnson, K. B., and Temple, T. N. 2016. Comparison of methods of acibenzolar-S-methyl application for post-infection fire blight suppression in pear and apple. *Plant Dis.* 100:1125-1131.
- Johnson, K. B., and Temple, T. N. 2017. Induction of systemic acquired resistance aids restoration of tree health in field-grown pear and apple diseased with fire blight. *Plant Dis.* 101:1263-1268.
- Kessmann, H., Staub, T., Hofmann, C., Maetzke, T., Herzog, J., Ward, E., Uknes, S., and Ryals, J. 1994. Induction of systemic acquired disease resistance in plants by chemicals. *Annu. Rev. Phytopathol.* 32:439-459.
- Kim, M. Y., and Lee, K. H. 2022. Electrochemical sensors for sustainable precision agriculture—A review. *Front. Chem.* 10:848320.
- Kiwifruit Spray Guide. 2022. Spring 2022 Spray Guide: Conventional – all varieties. <https://trevelyan.co.nz/wp-content/uploads/2022/09/2022-Conventional-Kiwifruit-Spray-Guide-web.pdf>
- Konstantinidou-Doltsinis, S., Markellou, E., Kasselaki, A.-M., Fanouraki, M., Koumaki, C., Schmitt, A., Liopa-Tsakalidis, A., and Malathrakis, N. 2006. Efficacy of Milsana®, a formulated plant extract from *Reynoutria sachalinensis*, against powdery mildew of tomato (*Leveillula taurica*). *Biocontrol* 51:375-392.
- Kuc, J. 1987. Plant immunization and its applicability for disease control. Pages 255-274 in: *Innovative Approaches to Plant Disease*. I. Chet, ed. John Wiley, New York.
- Kuc, J., Barnes, E., Daftsios, A., and Williams, E. 1959. The effect of amino acids on susceptibility of apple varieties to scab. *Phytopathology* 49:313-315.
- Kunz, W., Schurter, R., and Maetzke, T. 1997. The chemistry of benzothiadiazole plant activators. *Pestic. Sci.* 50:275-282.
- Kusajima, M., Okumura, Y., Fujita, M., and Nakashita, H. 2017. Abscisic acid modulates salicylic acid biosynthesis for systemic acquired resistance in tomato. *Biosci. Biotech. Biochem.* 81:1850-1853.
- La Torre, A., Righi, L., Iovino, V., and Battaglia, V. 2019. Evaluation of copper alternative products to control grape downy mildew in organic farming. *J. Plant Pathol.* 101:1005-1012.
- Lamberth, C., Rendine, S., and Sulzer-Mosse, S. 2021. Agrochemical disease control: The story so far. Pages 65-85 in: *Recent Highlights in the Discovery and Optimization of Crop Protection Products*. Elsevier.
- Lee, S.-M., Kong, H. G., Song, G. C., and Ryu, C.-M. 2021. Disruption of Firmicutes and Actinobacteria abundance in tomato rhizosphere causes the incidence of bacterial wilt disease. *ISME J.* 15:330-347.
- Li, J., Kolbasov, V. G., Pang, Z., Duan, S., Lee, D., Huang, Y., Xu, J., Teper, D., Lamichhane, T., and Wang, N. 2021. Evaluation of the control effect of SAR inducers against citrus Huanglongbing applied by foliar spray, soil drench or trunk injection. *Phytopathol. Res.* 3:1-15.
- Li, J. Y., Trivedi, P., and Wang, N. 2016. Field evaluation of plant defense inducers for the control of citrus huanglongbing. *Phytopathology* 106:37-46.
- Li, P., Lu, Y. J., Chen, H., and Day, B. 2020. The Lifecycle of the Plant Immune System. *Crit. Rev. Plant Sci.* 39:72-100.
- Louws, F., Wilson, M., Campbell, H., Cuppels, D., Jones, J., Shoemaker, P., Sahin, F., and Miller, S. 2001. Field control of bacterial spot and bacterial speck of tomato using a plant activator. *Plant Dis.* 85:481-488.
- Lyon, G. D. 2014. Agents that can elicit induced resistance. Pages 11-40 in: *Induced Resistance for Plant Defence: A Sustainable Approach to Crop Protection*, 2nd ed. John Wiley and Sons, New York.
- Maienfisch, P., and Mangelinckx, S. 2021. Chapter 1 - Recent innovation in crop protection research. Pages 1-23 in: *Recent Highlights in the Discovery and Optimization of Crop Protection Products*. P. Maienfisch and S. Mangelinckx, eds. Academic Press, Cambridge, MA.
- Market Data Forecast. 2022. Plant activators market. <https://www.marketdataforecast.com/market-reports/plant-activators-market>
- Marolleau, B., Gaucher, M., Heintz, C., Degrave, A., Warneys, R., Orain, G., Lemarquand, A., and Briset, M.-N. 2017. When a plant resistance inducer leaves the lab for the field: Integrating ASM into routine apple protection practices. *Front. Plant Sci.* 8:1938.
- Maxson-Stein, K., He, S. Y., Hammerschmidt, R., and Jones, A. L. 2002. Effect of treating apple trees with acibenzolar-S-methyl on fire blight and expression of pathogenesis-related protein genes. *Plant Dis.* 86:785-790.
- McGrann, G. R. D., Gladders, P., Smith, J. A., and Burnett, F. 2016. Control of clubroot (*Plasmodiophora brassicae*) in oilseed rape using varietal resistance and soil amendments. *Field Crops Res.* 186:146-156.
- Meena, M., Swapnil, P., Divyanshu, K., Kumar, S., Harish, Tripathi, Y. N., Zehra, A., Marwal, A., and Upadhyay, R. S. 2020. PGPR-mediated induction of systemic resistance and physiochemical alterations in plants against the pathogens: Current perspectives. *J. Basic Microbiol.* 60:828-861.
- Métraux, J., Ahlgoy, P., Staub, T., Speich, J., Steinemann, A., Ryals, J., and Ward, E. 1991. Induced systemic resistance in cucumber in response to 2,6-dichloro-isonicotinic acid and pathogens. Pages 432-439 in: *Advances in*

- Molecular Genetics of Plant-Microbe Interactions, Vol. 1. Kluwer Academic Publishers, Dordrecht, the Netherlands.
- Miles, A. K., Willingham, S. L., and Cooke, A. W. 2005. Field evaluation of a plant activator, captan, chlorothalonil, copper hydroxide, iprodione, mancozeb and strobilurins for the control of citrus brown spot of mandarin. *Australas. Plant Pathol.* 34:63-71.
- Mur, L. A. J., Simpson, C., Kumari, A., Gupta, A. K., and Gupta, K. J. 2016. Moving nitrogen to the centre of plant defence against pathogens. *Ann. Bot.* 119:703-709.
- Myresiotis, C. K., Karaoglaniadis, G. S., Vryzas, Z., and Papadopoulou-Mourkidou, E. 2012. Evaluation of plant-growth-promoting rhizobacteria, acibenzolar-S-methyl and hymexazol for integrated control of *Fusarium* crown and root rot on tomato. *Pest Manag. Sci.* 68:404-411.
- Myresiotis, C. K., Vryzas, Z., and Papadopoulou-Mourkidou, E. 2014. Enhanced root uptake of acibenzolar-S-methyl (ASM) by tomato plants inoculated with selected *Bacillus* plant growth-promoting rhizobacteria (PGPR). *Appl. Soil Ecol.* 77:26-33.
- Nadendla, S. R., Rani, T. S., Vaikuntapu, P. R., Maddu, R. R., and Podile, A. R. 2018. HarpinPss encapsulation in chitosan nanoparticles for improved bioavailability and disease resistance in tomato. *Carbohydr. Polym.* 199: 11-19.
- Nakao, S., Watanabe, H., Yano, T., Yamaoka, Y., and Ishii, H. 2021. Control efficacy of the systemic acquired resistance (SAR) inducer acibenzolar-S-methyl against *Venturia nashicola* in Japanese pear orchards. *J. Gen. Plant Pathol.* 87:307-315.
- Nawrocka, J., and Małolepsza, U. 2013. Diversity in plant systemic resistance induced by *Trichoderma*. *Biol. Control* 67:149-156.
- Newlands, N. K. 2018. Model-based forecasting of agricultural crop disease risk at the regional scale, integrating airborne inoculum, environmental, and satellite-based monitoring data. *Front. Environ. Sci.* 6:63.
- Newton, A. C., Hackett, C. A., and Guy, D. C. 1998. Diversity and complexity of *Erysiphe graminis* f. sp. *hordei* collected from barley cultivar mixtures or barley plots treated with a resistance elicitor. *Eur. J. Plant Pathol.* 104: 925-931.
- Obradovic, A., Jones, J. B., Momol, M. T., Balogh, B., and Olson, S. M. 2004. Management of tomato bacterial spot in the field by foliar applications of bacteriophages and SAR inducers. *Plant Dis.* 88:736-740.
- Oostendorp, M., Kunz, W., Dietrich, B., and Staub, T. 2001. Induced disease resistance in plants by chemicals. *Eur. J. Plant Pathol.* 107:19-28.
- Oxley, S. J. P., and Walters, D. R. 2012. Control of light leaf spot (*Pyrenopeziza brassicae*) on winter oilseed rape (*Brassica napus*) with resistance elicitors. *Crop Prot.* 40:59-62.
- Percival, G. C., and Graham, S. 2021. The potential of resistance inducers and synthetic fungicide combinations for management of foliar diseases of nursery stock. *Crop Protect* 145:105636.
- Percival, G. C., Noviss, K., and Haynes, I. 2009. Field evaluation of systemic inducing resistance chemicals at different growth stages for the control of apple (*Venturia inaequalis*) and pear (*Venturia pirina*) scab. *Crop Prot.* 28:629-633.
- Perez, L., Rodriguez, M. E., Rodriguez, F., and Roson, C. 2003. Efficacy of acibenzolar-S-methyl, an inducer of systemic acquired resistance against tobacco blue mould caused by *Peronospora hyoscyami* f. sp. *tabacina*. *Crop Prot.* 22:405-413.
- Philips-McDougall. 2017. The Global Agrochemical Market Trends by Crop. 11th China International Forum on Development of Pesticide Industry, Shanghai. <http://www.cac-conference.com/Uploads/Editor/2017-03-07/58be2c387de29.pdf>
- Pieterse, C. M. J., Van der Does, D., Zamioudis, C., Leon-Reyes, A., and Van Wees, S. C. M. 2012. Hormonal modulation of plant immunity. *Annu. Rev. Cell. Dev. Biol.* 28:489-521.
- Pieterse, C. M. J., van Wees, S. C. M., Hoffland, E., van Pelt, J. A., and van Loon, L. C. 1996. Systemic resistance in *Arabidopsis* induced by biocontrol bacteria is independent of salicylic acid accumulation and pathogenesis-related gene expression. *Plant Cell* 8:1225-1237.
- Pieterse, C. M. J., Zamioudis, C., Berendsen, R. L., Weller, D. M., Van Wees, S. C. M., and Bakker, P. 2014. Induced systemic resistance by beneficial microbes. *Annu. Rev. Phytopathol.* 52:347-375.
- Pontes, N. D., Nascimento, A. D., Golynski, A., Mania, A., de Oliveira, J. R., and Quezado-Duval, A. M. 2016. Intervals and number of applications of acibenzolar-S-methyl for the control of bacterial spot on processing tomato. *Plant Dis.* 100:2126-2133.
- Pozo, M. J., Zabalgozeazcoa, I., Vazquez de Aldana, B. R., and Martinez-Medina, A. 2021. Untapping the potential of plant mycobiomes for applications in agriculture. *Curr. Opin. Plant Biol.* 60:102034.
- Pradhanang, P., Ji, P., Momol, M., Olson, S., Mayfield, J., and Jones, J. 2005. Application of acibenzolar-S-methyl enhances host resistance in tomato against *Ralstonia solanacearum*. *Plant Dis.* 89:989-993.
- Pršić, J., and Ongena, M. 2020. Elicitors of plant immunity triggered by beneficial bacteria. *Front. Plant Sci.* 11:594530.
- Pugliese, M., Monchiero, M., Gullino, M. L., and Garibaldi, A. 2018. Application of laminarin and calcium oxide for the control of grape powdery mildew on *Vitis vinifera* cv. Moscato. *J. Plant Dis. Prot.* 125:477-482.
- Qi, X., Li, K., Chen, L., Zhang, Y., Zhang, N., Gao, W., Li, Y., Liu, X., and Fan, Z. 2022. Plant defense responses to a novel plant elicitor candidate LY5-24-2. *Int. J. Mol. Sci.* 23:5348.
- Rebaque, D., del Hierro, I., López, G., Bacete, L., Vilaplana, F., Dallabernardina, P., Pfrengle, F., Jordá, L., Sánchez-Vallet, A., Pérez, R., Brunner, F., Molina, A., and Mérida, H. 2021. Cell wall-derived mixed-linked  $\beta$ -1,3/1,4-glucans trigger immune responses and disease resistance in plants. *Plant J.* 106: 601-615.
- Reglinski, T., Dann, E., and Deverall, B. 2014. Implementation of induced resistance for crop protection. Pages 249-299 in: *Induced Resistance for Plant Defense*. John Wiley & Sons, Oxford, U.K.
- Renard-Merlier, D., Randoux, B., Nowak, E., Farcy, F., Durand, R., and Reignault, P. 2007. Iodine 40, salicylic acid, heptanoyl salicylic acid and trehalose exhibit different efficacies and defence targets during a wheat/powdery mildew interaction. *Phytochemistry* 68:1156-1164.
- Ribas-Agusti, A., Bouchagier, P., Skotti, E., Erba, D., Casiraghi, C., Sarraga, C., and Castellari, M. 2013. Effects of different organic anti-fungal treatments on tomato plant productivity and selected nutritional components of tomato fruit. *J. Hortic. Sci. Biotechnol.* 88:67-72.
- Riemens, M. 2021. The future of crop protection in Europe, EPRS: European Parliamentary Research Service. Belgium. <https://policycommons.net/artifacts/1426473/the-future-of-crop-protection-in-europe/2040898/>
- Riseh, R. S., Hassanisaadi, M., Vatankhah, M., Babaki, S. A., and Barka, E. A. 2022. Chitosan as a potential natural compound to manage plant diseases. *Int. J. Biol. Macromol.* 220:998-1009.
- Roberts, P. D., Momol, M. T., Ritchie, L., Olson, S. M., Jones, J. B., and Balogh, B. 2008. Evaluation of spray programs containing famoxadone plus cymoxanil, acibenzolar-S-methyl, and *Bacillus subtilis* compared to copper sprays for management of bacterial spot on tomato. *Crop Prot.* 27: 1519-1526.
- Romanazzi, G., Mancini, V., Feliziani, E., Servili, A., Endeshaw, S., and Neri, D. 2016. Impact of alternative fungicides on grape downy mildew control and vine growth and development. *Plant Dis.* 100:739-748.
- Romanazzi, G., Mancini, V., Foglia, R., Marcolini, D., Kavari, M., and Piancatelli, S. 2021. Use of chitosan and other natural compounds alone or in different strategies with copper hydroxide for control of grapevine downy mildew. *Plant Dis.* 105:3261-3268.
- Ross, A. F. 1961. Localized acquired resistance to plant virus infection in hypersensitive hosts. *Virology* 14:329-339.
- Rur, M., Rämert, B., Hökeberg, M., Vetukuri, R. R., Grenville-Briggs, L., and Liljeroth, E. 2018. Screening of alternative products for integrated pest management of cucurbit powdery mildew in Sweden. *Eur. J. Plant Pathol.* 150:127-138.
- Sarosh, B. R., Danielsson, J., and Meijer, J. 2009. Transcript profiling of oilseed rape (*Brassica napus*) primed for biocontrol differentiate genes involved in microbial interactions with beneficial *Bacillus amyloliquefaciens* from pathogenic *Botrytis cinerea*. *Plant Mol. Biol.* 70:31-45.
- Shayanthan, A., Ordoñez, P. A. C., and Oresnik, I. J. 2022. The role of synthetic microbial communities (syncom) in sustainable agriculture. *Front. Agron.* 4:896307.
- Shude, S. P., Mbili, N. C., and Yobo, K. S. 2022. The efficacy of acibenzolar-S-methyl (ASM) in inducing resistance against *Fusarium graminearum* sensu stricto in wheat (*Triticum aestivum* L.). *Plant Sci. Today* 9:183-190.
- Shukla, P. S., Borza, T., Critchley, A. T., and Prithiviraj, B. 2016. Carrageenans from red seaweeds as promoters of growth and elicitors of defense response in plants. *Front. Marine Sci.* 3:81.
- Smiglak, M., Lewandowski, P., Kukawka, R., Budziszewska, M., Krawczyk, K., Obrępańska-Stepłowska, A., and Pospieszny, H. 2017. Dual functional salts of benz[1.2.3]thiadiazole-7-carboxylates as a highly efficient weapon against viral plant diseases. *ACS Sustain. Chem. Eng.* 5:4197-4204.
- Spinelli, F., Vanneste, J., Ciampolini, F., Cresti, M., Rademacher, W., Geider, K., and Costa, G. 2007. Potential and limits of acylcyclohexanediones for the control of blossom blight in apple and pear caused by *Erwinia amylovora*. *Plant Pathol.* 56:702-710.
- Spinelli, F., Vanneste, J. L., and Costa, G. 2012. Acylcyclohexanediones and biological control agents: Combining complementary modes of action to control fire blight. *Trees* 26:247-257.
- Sun, Y., Wang, M., Mur, L. A. J., Shen, Q., and Guo, S. 2020. Unravelling the roles of nitrogen nutrition in plant disease defences. *Int. J. Mol. Sci.* 21:572.
- Teixeira, P. J. P., Colaïanni, N. R., Fitzpatrick, C. R., and Dangi, J. L. 2019. Beyond pathogens: Microbiota interactions with the plant immune system. *Curr. Opin. Microbiol.* 49:7-17.
- Tripathi, D., Raikhy, G., and Kumar, D. 2019. Chemical elicitors of systemic acquired resistance-Salicylic acid and its functional analogs. *Curr. Plant Biol.* 17:48-59.

- Trivedi, P., Leach, J. E., Tringe, S. G., Sa, T., and Singh, B. K. 2020. Plant-microbiome interactions: From community assembly to plant health. *Nat. Rev. Microbiol.* 18:607-621.
- van Aubel, G., Buonatesta, R., and Van Cutsem, P. 2014. COS-OGA: A novel oligosaccharidic elicitor that protects grapes and cucumbers against powdery mildew. *Crop Prot.* 65:129-137.
- van Loon, L. C., Bakker, P. A. H. M., and Pieterse, C. M. J. 1998. Systemic resistance induced by rhizosphere bacteria. *Annu. Rev. Phytopathol.* 36:453-483.
- Verly, C., Djoman, A. C. R., Rigault, M., Giraud, F., Rajjou, L., Saint-Macary, M.-E., and Dellagi, A. 2020. Plant defense stimulator mediated defense activation is affected by nitrate fertilization and developmental stage in *Arabidopsis thaliana*. *Front. Plant Sci.* 11:583-583.
- Walters, D. R., Havis, N. D., Paterson, L., Taylor, J., Walsh, D. J., and Sablou, C. 2014. Control of foliar pathogens of spring barley using a combination of resistance elicitors. *Front. Plant Sci.* 5:241.
- Walters, D. R., Paterson, L., Sablou, C., and Walsh, D. J. 2011. Existing infection with *Rhynchosporium secalis* compromises the ability of barley to express induced resistance. *Eur. J. Plant Pathol.* 130:73-82.
- Walters, D. R., Ratsep, J., and Havis, N. D. 2013. Controlling crop diseases using induced resistance: Challenges for the future. *J. Exp. Bot.* 64:1263-1280.
- Ward, E. R., Uknes, S. J., Williams, S. C., Dincher, S. S., Wiederhold, D. L., Alexander, D. C., Ahlgoy, P., Metraux, J. P., and Ryals, J. A. 1991. Coordinate gene activity in response to agents that induce systemic acquired resistance. *Plant Cell* 3:1085-1094.
- Watanabe, T., Igarashi, H., Matsumoto, K., Seki, S., Mase, S., and Sekizawa, Y. 1977. Studies on rice blast controlling agent of benzothiazole analogs. 1. Characteristics of probenazole (Oryzemat) for control of rice blast. *J. Pestic. Sci.* 2:291-296.
- Wei, G., Kloepper, J. W., and Tuzun, S. 1996. Induced systemic resistance to cucumber diseases and increased plant growth by plant growth-promoting rhizobacteria under field conditions. *Phytopathology* 86:211-244.
- White, R. F. 1979. Acetylsalicylic acid (aspirin) induces resistance to tobacco mosaic virus in tobacco. *Virology* 99:410-412.
- Wiese, J., Bagy, M. M. K., and Schubert, S. 2003. Soil properties, but not plant nutrients (N, P, K) interact with chemically induced resistance against powdery mildew in barley. *J. Plant Nutr. Soil Sci.* 166:379-384.
- Yang, K. H., Huang, C. J., Liu, Y. H., and Chen, C. Y. 2011. Efficacy of probenazole for control of southern corn leaf blight. *J. Pestic. Sci.* 36:235-239.
- Yassin, M., Ton, J., Rolfe, S. A., Valentine, T. A., Cromey, M., Holden, N., and Newton, A. C. 2021. The rise, fall and resurrection of chemical-induced resistance agents. *Pest Manag. Sci.* 77:3900-3909.
- Zhang, S., Mersha, Z., Vallad, G. E., and Huang, C. H. 2016. Management of powdery mildew in squash by plant and alga extract biopesticides. *Plant Pathol. J.* 32:528-536.
- Zheng, F., Chen, L., Zhang, P., Zhou, J., Lu, X., and Tian, W. 2020. Carbohydrate polymers exhibit great potential as effective elicitors in organic agriculture: A review. *Carbohydr. Polym.* 230:115637.
- Zhou, M., and Wang, W. 2018. Recent advances in synthetic chemical inducers of plant immunity. *Front. Plant Sci.* 9:1613.