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PERSPECTIVE

Vaccinating plants

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Abstract – Plant immune systems rely on their ability to recognize enemy molecules, carry out signal transduction, and respond defensively through pathways involving many genes and their products. This Perspective paper aims to explore current views on the vaccination (immunization) of plants against diseases caused by microorganisms and their (macro)molecular components, paying special attention to practical applications. We conclude that the technique of vaccination to control plant disease needs to be further investigated, developed, and considered for wider implementation in plant protection practice.

Keywords – vaccination of plants, plant immunity, disease resistance of plants, systemic acquired resistance, induced systemic resistance, susceptibility, resistance inducers

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1911. "*The writer has seen nothing ... which indicates that plants can be preserved by vaccines*" (Smith, 1911).

1964. "... *it would be worthwhile for a grower who always suffers quality losses from TMV [tobacco mosaic virus] deliberately to inoculate his plants early with a mild strain of the virus*" (Broadbent, 1964).

2017. "*The mixture of attenuated [pepino mosaic virus] isolates ... prevented almost completely the appearance of viral symptoms ... caused by the virulent isolates*" (Vermunt and Kaarsemaker 2017).

INTRODUCTION

The three quotations above span more than a century. They depict the evolution of the concept of plant vaccination from its very beginning until the first successful, large-scale agricultural application of the technology. Here we provide a non-exhaustive review of the potential experimental approaches to exploit the vaccination of plants for practical plant protection and will exemplify the possibilities by citing a limited number of selected papers.

According to the widely accepted definition, vaccines are biological products that are utilized to initiate a reaction that

elicits defense against an existing disease or a subsequent attack by a pathogen (Pollard and Bijker, 2021). In the case of plant vaccination, these biological products are typically pathogenic microorganisms (attenuated or 'mild' variants) or their certain components (oligopeptides, proteins, oligonucleotides, and oligosaccharides).

Vaccination of humans and animals against diseases has been practiced since the Middle Ages (Boylston, 2012). Still, a detailed description of its methods and efficacy was published only at the end of the 18th century by Jenner (Jenner, 1798). The successful implementation of vaccination in combatting diseases of humans and animals was followed by breakthroughs in the elucidation of the mechanisms of the mammalian immune system by the end of the 1800s. The concept of vaccinating plants has been around for more than a century, but until 1911 (Smith, 1911) no paper was published on the subject (probably because of lack of success), and later attempts to find antibodies in plants either failed (Sardina, 1926) or were inconclusive (Kostoff, 1929).

PLANT IMMUNITY

Current knowledge describes the plant immune system as a complex defense network that can be intrinsic (constitutive) or acquired (inducible) (Jones and Dangl, 2006; Pruitt *et al.*, 2021). Resistance of plants against infection and disease

caused by pathogens is based upon a) pre-formed chemicals (antimicrobial peptides, specific metabolites called phytoanticipins and phytoalexins) and b) structural barriers, and c) on a favorable outcome of complex biochemical interactions (these include the recognition of the pathogen and signal transduction processes) between the pathogen and the host (Komives and Kiraly, 2019). As compared to warm-blooded animals, the immune system of plants is not based on circulating cells (Kiraly *et al.*, 2013), rather on a range of sensory receptors that are capable to detect pathogenic microorganisms and initiate a cascade of cellular immune signaling (Yu *et al.*, 2021). For recent, in-depth reviews on plant disease resistance please consult the papers of Nishad *et al.* (2020), Zhou and Zhang, 2020, and Vlot *et al.* (2021).

In this paper we will discuss recent plant vaccinating/immunization (resistance-inducing) techniques, paying special attention to practical applications. Throughout the paper, whenever applicable, the new terminology of De Kesel *et al.* (2021) will be used to discuss observations related to induced disease resistance in plants. It ought to be noted, that vaccination of plants is not yet part of this new terminology.

Levels of disease resistance of plants

The primary immune response (level 1) of a plant is elicited by macromolecular structures characteristic to all microbes (including pathogens) called pathogen-associated molecular pattern (PAMP) or microbe-associated molecular pattern (MAMP). This response of the attacked plant is called pattern-triggered immunity (PTI). The secondary immune response (level 2) is instigated by so-called effectors synthesized by the microorganism to counteract PTI: it is called effector-triggered immunity (ETI) (Jones and Dangl, 2006; Pruitt *et al.*, 2021). PTI is considered as basal immunity that acts in non-host and compatible interactions producing quantitative (incomplete) resistance, while ETI is the source of race-specific, qualitative (complete) resistance (Ke *et al.*, 2017). In addition to protecting the infected tissues, ETI may initiate local immunization around the site of pathogen attack (Ross, 1961A) or a systemic one (called systemic acquired resistance [SAR] (Ross, 1961B)), affecting the whole plant against subsequent attacks by related or even unrelated pathogens (Fu *et al.*, 2009; Vlot *et al.*, 2021). Furthermore, the colonization of plant roots by beneficial, plant growth-promoting rhizosphere bacteria may lead to another form of systemic resistance, called induced systemic resistance (ISR) (Chang *et al.*, 2014; Romera *et al.*, 2019; Vlot *et al.*, 2021).

SAR depends on salicylic acid (SA) (Figure 1) as a signal (actually, the methyl ester of SA [MeSA] is one of the translocated signals [Park *et al.*, 2007]), in addition to pathogenesis-related proteins and other defense genes and gene products. SAR provides long-lasting and effective protection against a broad range of pathogens (Vlot *et al.*, 2021). On the other hand, ISR involves both jasmonic acid and ethylene (Figure 1) signaling (Romera *et al.*, 2019). It has to be noted that neither SAR nor ISR is 100 percent effective.

Plant disease resistance can be efficiently induced by plant hormones and their chemical derivatives, and other small

natural and synthetic molecules. This paper only briefly covers these low-molecular-weight chemicals because 1) they do not conform to the widely accepted definition of vaccination (Pollard and Bijker, 2021), and 2) their chemistry and biological modes of action were thoroughly discussed in recent papers (Tripathi *et al.*, 2019; Zhou and Wang, 2018).

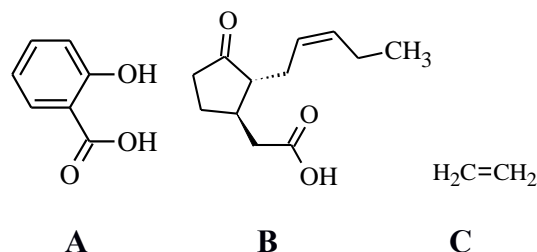


Figure 1. Chemical structures of salicylic acid (A), jasmonic acid (B), and ethylene (C).

As mentioned above, MeSA is a key signaling molecule in the intra-organismal induction of SAR. However, as a volatile compound, it can also serve as an airborne inter-organismal signal that induces resistance in neighboring plants (Liu *et al.*, 2018), thereby contributing to the local ecosystem stability (Singewar *et al.*, 2021). An elegant proof for this activity of MeSA was recently presented by Ninkovic *et al.* (2021), showing that exposure of barley plants to this volatile compound led to the production of systemic resistance factors. It is interesting to note, that the volatile diallyl disulfide metabolite of garlic was also found to induce cucumber resistance to downy mildew (Yang *et al.*, 2021) and green leaf volatiles (oxygenated fatty acids rapidly released by plant leaves upon damage) were shown to increase the protection of potato plants against late blight through enhancing plant immunity (Najdabasi *et al.*, 2021). Further studies are needed to clarify the nature and the scope of the protection mechanisms these volatile chemicals may induce in different plant/pathogen relationships.

Chemical methods of resistance induction for practical uses have been studied by researchers working for the chemical industry for many years and led to the discovery and commercialization of probenazole (Ishiga *et al.*, 2021; Sakata *et al.*, 2020; Wu *et al.*, 2021) and acibenzolar methyl (Figure 2) (Ishiga *et al.*, 2021; Sakata *et al.*, 2020) and their successful introduction in plant protection practice as 'plant activators'. It should be noted that probenazole is a derivative of saccharine (a known plant resistance inducer [Mejri *et al.*, 2021]), while acibenzolar-S-methyl is a synthetic analog of SA (Ishiga *et al.*, 2021; Sakata *et al.*, 2020). Despite certain similarities in their chemical structures, the biochemical modes of action of the two chemicals are not the same, because the expression of resistance genes is induced by them differently (Iwata, 2001) by them, and probenazole acts in the step preceding SA biosynthesis (Ishiga *et al.*, 2021).

Plants can adapt to a pathogen challenge and enhance their defensive potential by transitioning into a 'primed' state, in which their defense response is quicker and more powerful (Ando *et al.*, 2021). The phenomenon of priming (Gong *et al.*,

2019; Westman *et al.*, 2019), *i.e.*, elicitation of long-lasting disease resistance by various treatments using microorganisms and their components to induce SAR and ISR responses (Vlot *et al.*, 2021) makes the efficient vaccination of plants possible.

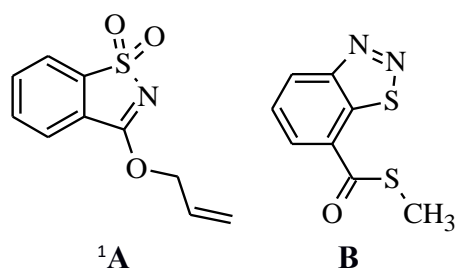


Figure 2. Chemical structures of the plant activators probenazole (A) and acibenzolar S-methyl (B).

BIOLOGICALS INDUCING DISEASE RESISTANCE

Biologicals (also called biologic plant protection agents) are either living microorganisms or their components, such as oligopeptides (including proteins) and oligonucleotides (including RNA and DNA) produced by them. Selected examples of biologicals tested for this purpose are listed in Table 1 (the list in the Table is not intended to be comprehensive).

Virulent (invasive) pathogens

Inducibility of plant disease resistance by virulent pathogens was first described by French scientists (independently from each other) at the turn of the 19th-20th century: they reported that plants may show resistance against a pathogen when infected a second time (Beauverie, 1901; Bernard, 1911; Ray, 1901). Following these studies, numerous promising experiments using virulent and attenuated pathogenic microorganisms of plants as vaccinating agents have been carried out in the laboratory and the field: but, unfortunately, none of them led to successful applications in the field. To mention a few of the milestones: McKinney (1929) observed that infection of tobacco plants with one virus strain may repress the development of disease symptoms when re-inoculated with another strain. Later studies in the UK (Broadbent, 1976) and Hungary (Burgyan and Gaborjanyi, 1984) showed that the inoculation of tomato plants with a fairly severe strain of tomato mosaic virus, while significantly improving the quality of the fruit, failed to keep the plants symptomless during the whole growing season.

Mild (attenuated) strains of pathogens

Failures of experiments to efficiently protect plants from diseases *via* vaccination with virulent pathogens turned the

researchers' attention to mild strains that occurred naturally or could be cost-effectively produced in the laboratory by heat-treatment, UV-light, or other methods (Johnson, 1926) (Chewachong *et al.*, 2015). Early attempts using this approach showed great promise: for example, an almost symptomless mutant (MH-16 of TMV, isolated following the mutagenic treatment with nitrous acid) gave good cross-protection against the virulent pathogen (Rast, 1972). Cross-protection (*i.e.*, homology-dependent resistance based on gene silencing) represents the phenomenon in which a previous infection by a mild isolate prevents attack by the virulent variant (Rast, 1972).

More recent studies were initiated following the outbreak of the disease caused by Pepino mosaic virus (PepMV) in greenhouse tomatoes (*Solanum lycopersicum* L.) in the Netherlands and Belgium in 2000 (and later everywhere in Europe). The rapid spread of the disease led to concentrated research efforts in both countries aiming for the control of the disease by exploiting the cross-protection provided by uniquely mild and stable PepMV isolates of different origins (Schenk *et al.*, 2010). These endeavors resulted in the development of two commercial plant vaccine products ('V10'² by Valto BV, De Lier, the Netherlands and 'PMV-01'³ by DCM, Belgium, respectively) against PepMV in tomatoes (Pechinger *et al.*, 2019; Vermunt and Kaarsemaker, 2017). The new PepMV vaccines are now temporarily registered in Europe and North America.

Similar efforts by researchers in Spain brought forth the creation of another PepMV vaccine that was established on mixed infection by its Sp13 and PS5 mild isolates, resulting in stable and broad-spectrum cross-protection against the virus (Aguero *et al.*, 2018) and the development of a new, PepMV-based antiviral preparation, 'Abioprotect'⁴ (registered for use in Spain in 2021 by Abiopep, Murcia, Spain) (Anastassiadou *et al.*, 2021).

In Japan, 'KYOTOBIKEN' CUBIO ZY-02⁵ (an attenuated Zucchini yellow mosaic virus [ZYMV] preparation) was the first plant vaccine registered as a pesticide by Kyoto Biken Laboratories, Inc., Kyoto, Japan (Ogai *et al.*, 2013; Tomitaka *et al.*, 2018). The same laboratory registered for use an attenuated isolate of Pepper mild mottle virus (PMMoV; designated L3-163), commercialized as 'Green Pepper PM', a biological control agent (Ogai *et al.*, 2013) against PMMoV.

Furthermore, Tamura *et al.* (2013) carried out very promising investigations using apple latent spherical virus (ALSV)-based vectors harboring part of a target viral genome (the authors called these ALSV vector vaccines).

¹ It is worth mentioning that plant activators are registered as pesticides, although they have no antimicrobial activity *in vitro*. On the other hand, herbicide safeners are qualified as "inerts" (Liu *et al.*, 2021; Sivey *et al.*, 2015), although they exhibit significant biological activity *in vitro* and *in planta*.

² valto.nl/en/about-v10/faq (accessed 02.20.2022).

³ pmv-01.com/en/ (accessed 02.20.2022).

⁴ abiopep.com/es/Services/AbioProtect (accessed 02.20.2022).

⁵ kyotobiken.co.jp/en/products/ca.html#forPlant (accessed 02.20.2022).

These vectors were shown to inhibit the multiplication and spread of three challenge viruses (Bean yellow mosaic virus, ZYMV, and Cucumber mosaic virus) *via* homology-dependent resistance. In ZYMV-infected cucumber plants, even a highly unusual curative effect exerted by a plant vaccine was observed: symptoms of the disease symptoms after inocu-

lations with an ALSV vector vaccine (Tamura *et al.*, 2013). It is worth mentioning, that, in contrast to cross-protection, a pre-existing community of microorganisms in the same host may engage in an antagonistic interaction and enhance the impact of the pathogen-induced disease (Walters *et al.*, 2011).

Table 1. Selected biologicals inducing cross-protection / disease resistance in plants

Biological		Plant / Pathogen	Elicitor	Reference
Pathogen	Virulent (invasive)	<i>Nicotinia tabacum</i> L. / Tobacco mosaic virus, Tobacco necrosis virus, Turnip mosaic virus, Tomato ringspot virus	Tobacco mosaic virus	Ross, 1961B
	Attenuated / Mild isolate	<i>Lycopersicon esculentum</i> L.	Pepino mosaic virus	Pechinger <i>et al.</i> , 2019
	Non-host	<i>Triticum aestivum</i> L. / <i>Blumeria graminis</i> f. sp. <i>tritici</i>	<i>Blumeria graminis</i> f. sp. <i>hordei</i>	Ersek, 1973
Beneficial	Biocontrol agent	<i>Raphanus raphanistrum</i> L. / <i>Fusarium oxysporum</i> f.sp. <i>raphani</i>	<i>Pseudomonas fluorescens</i>	Hoffland <i>et al.</i> , 1995
	Commensal	<i>Nicotiana attenuata</i> L. / <i>Fusarium oxysporum</i>	A consortium of <i>Arthrobacter nitroguajacolicus</i> , <i>Bacillus cereus</i> , <i>B. megaterium</i> , <i>B. mojavensis</i> , <i>Pseudomonas azotoformans</i> , <i>P. frederiksbergensis</i>	Santhanam <i>et al.</i> , 2015
	Symbiont	<i>Vitis vinifera</i> L.	<i>Rhizophagus irregularis</i>	Goddard <i>et al.</i> , 2021
Peptide, protein	Harpin	<i>Nicotinia tabacum</i> L. / Tobacco mosaic virus	HpaXpm harpin protein (isolated from <i>Xanthomonas phaseoli</i> pv. <i>manihotis</i>)	Kohl <i>et al.</i> , 2019
	Systemin	<i>Solanum melongena</i> L. and <i>Vitis vinifera</i> L. / <i>Botrytis cinerea</i>	Tomato systemin	Molisso <i>et al.</i> , 2021
	Enzyme	<i>Nicotinia tabacum</i> L. and <i>Solanum lycopersicum</i> L. / <i>Botrytis cinerea</i>	Xylanase	Frias <i>et al.</i> , 2019
	Toxin	<i>Nicotinia tabacum</i> L., <i>Arabidopsis thaliana</i> L.	NEP1-like protein	Kufner <i>et al.</i> , 2009
Oligo-/polynucleotide	Double-stranded RNAs	<i>Nicotiana benthamiana</i> and <i>Solanum lycopersicum</i> L. / Tomato spotted wilt virus	Exogenous application of dsRNAs targeting the nucleocapsid or the movement protein of the virus	Tabein <i>et al.</i> , 2020 Tang <i>et al.</i> , 2021
Oligo-/polysaccharide	Oligopectates, oligochitosans, and chitoooligosaccharides	<i>Arabidopsis thaliana</i> L. / <i>Plectosphaerella cucumerina</i>	Exogenous application of oligosaccharides	Moenne and Gonzalez, 2021

Non-host pathogens

Non-host resistance (NHR) is defined as the immunity of a certain plant species to a wide range of non-adapted pathogen

species (Lee *et al.*, 2016). It can be constitutive or induced (Fonseca and Mysore, 2019; Niks and Marcel, 2009). The mechanisms behind NHR have not been identified yet. Pruitt

et al. (2021) speculated that NHR might be due to the presence of a broad variety of nucleotide-binding domain leucine-rich repeat receptors that recognize non-host pathogens and initiate an ETI-type response, while Lee *et al.* (2016) attribute NHR to PTI that triggers multi-layered basal resistance mechanisms. These two models of non-host resistance may not be mutually exclusive, as the relative contribution of PTI may increase as a function of phylogenetic divergence time between host and non-host plant species (e.g., tobacco and tomato vs. tobacco and barley; Schulze-Lefert and Panstruga, 2011). There are only a few examples of experiments studying the interactions of adapted and non-adapted pathogenic and non-host microorganisms in plants (Barna *et al.* 2022 and references therein). One notable exception is reported by Ersek (1973), who found that the number of mildew colonies from inoculations with *Erysiphe* (current name *Blumeria*) *graminis* f. sp. *tritici* were powerfully reduced by pre-inoculating wheat with the barley form of *E. graminis* (*Erysiphe graminis* f. sp. *hordei*). He also observed that the reduction was due to a local defense reaction by the plant in response to the previous inoculation (Ersek, 1973). In a continuation of this study, Barna *et al.* (2022) showed that defense responses elicited by *Blumeria graminis* f.sp. *hordei* in non-host wheat plants lead to a reduction of infection by the leaf rust *Puccinia triticina*.

Beneficial microorganisms

Beneficial microorganisms (fungi and bacteria) live either inside (endosphere) or outside (episphere: soil, and, in the case of rice, floodwater) of plant tissues (Doni *et al.*, 2022). Typically, in modern agriculture, these microorganisms are used to improve the nutrient uptake of plants and also as plant growth regulators (Orozco-Mosqueda *et al.*, 2021). As an additional advantageous effect, they may be capable of protecting the plants against different diseases by eliciting ISR (Romera *et al.*, 2019). Thus, some beneficial microbes were shown to suppress the outbreak of viral plant diseases (Abo-Zaid *et al.*, 2020) as well as to curb the bacterial blight of anthurium (Nakkeeran *et al.*, 2020). In addition, *Piriformospora indica*, a mycorrhiza-like fungus was shown to induce resistance in barley against powdery mildew and *Fusarium culmorum* (Waller *et al.* 2005).

Precautionary notes: 1) plant pathogens may circumvent the immune system of the plant by targeting and manipulating its microbiome (Snelders *et al.*, 2021) and 2) the ability of certain antifungal biocontrol agents (e.g., *Trichoderma* spp.) to suppress virulent pathogenic fungi involves mycoparasitism and antibiosis, in addition to inducing ISR in plants (Mukhopadhyay and Kumar, 2020).

Proteins

Harpin

In nature, certain bacterial plant pathogens produce proteinaceous inducers (called harpins) influencing the overall plant

growth, vigor, and the plant defense reaction known as the hypersensitive response, therefore they are considered as elicitors (Liu *et al.*, 2020). The first harpin (designated as HrpN) was isolated from *Erwinia amylovora* by Wei *et al.* (1992), and later multiple harpins were identified and characterized.

Today, 'AXIOM' is a marketed harpin product, produced by Rx Green Technologies (Bedford NH, USA)⁶. Other harpin-based commercial products, such as 'ProAct', 'N-Hibit', 'Employ', and 'H2Coplá' (all contain Harpin $\alpha\beta$) were developed and marketed by Plant Health Care plc (Holly Springs NC, USA) and are available worldwide for use in a variety of crops. Noticeably, this company has recently developed its 'PREtec' technology, which is based on the design of new, specific peptides/proteins that elicit disease resistance and increased growth of crop plants. The first product from this pipeline, 'Saori' (also known as 'PHC279'), was registered in Brazil in January 2021. As indicated on the company's website⁷ there are other PREtec products in their pipeline, including 'PHC949' and 'PHC414'.

Natural toxins

Hormesis is a term used in toxicology to describe a biphasic dose-response curve to a toxic compound when a low dose induces a beneficial effect while a high dose leads to toxic symptoms (Vargas-Hernandez *et al.*, 2017). A possible example of such a hormetic effect is the ability of certain NEP1-like protein (NLP) toxins to elicit diverse defense reactions in dicotyledonous plants (Kufner *et al.*, 2009). NLP toxins are general membrane disrupting agents and stimulate plant defenses by interfering with cell integrity. For example, elicitor NLP protein PaNie₂₁₃ (isolated from *Pythium aphanidermatum*) was shown to trigger multiple defense responses in carrot, Arabidopsis, and tobacco, such as programmed cell death and *de novo* formation of 4-hydroxybenzoic acid (Veit *et al.*, 2001).

Oligosaccharides

Oligo- and polysaccharides (derived from the cell walls of plants, fungi, and bacteria during plant-pathogen interactions) are powerful plant resistance inducers (Moenne and Gonzalez, 2021). Recently, several oligosaccharide-based commercial plant protection agents became available, including 'Stemicol', 'Fytosave' and 'Activane' (developed by LIDA Plant Research, Valencia, Spain)⁸ that are effective against fungal diseases and contain mixtures of oligopectates, oligochitosans, and chitooligosaccharides to control fruit rot and downy mildew in different crops.

The glucose polysaccharide laminarin (the main carbohydrate food reserve in brown algae [*Laminaria digitata*]) is a strong elicitor of plant defenses against different fungal diseases (Jamiolkowska, 2020). For example, the laminarin-based formulations 'Vacciplant Plant Defense Stimulant' is available

⁶ rxgreentechnologies.com/product/axiom (accessed 02.25.2022).

⁷ planthealthcare.com/about/strategy (accessed 02.09.2022).

⁸ lidaplantresearch.com/phytovaccines/?lang=en (accessed 02.20.2022)

worldwide from UPL Limited⁹ (Mumbai, India) for boosting plant disease resistance, health, and yields.

Chitosan is a linear polysaccharide consisting of glucosamine and *N*-acetyl glucosamine. Depending on their chemical structure, chitosan molecules may possess plant defense elicitor activity (Suarez-Fernandez *et al.*, 2020). Formulated chitosan products are currently commercialized by several companies, such as Visjon Biologics¹⁰ (Henrietta, Texas, USA) as 'Exceed SAR Plant Defense Booster', 'ARMOUR-Zen' by Botryzen¹¹ (Dunedin, New Zealand), and ChiPro-Plant by ChiPro GmbH, Bremen, Germany¹².

Nucleic acids

Recently, theoretical and practical efforts have intensified to develop RNA-based methods in plant protection (Rank and Koch, 2021). This approach utilizes the phenomenon of RNA interference (RNAi, *i.e.*, RNA-mediated gene silencing), a well-known biochemical mechanism active in eukaryote organisms (Rank and Koch, 2021; Yu *et al.*, 2022). Thus, double-stranded RNA molecules (dsRNAs) can be applied to regulate gene expression by targeting specific endogenous mRNA molecules to influence the expression of genes in the plants, phytopathogenic viruses, and fungi, as well as harmful insects. dsRNAs applied to plants topically can spread locally and systemically within the plants, reaching the pathogens, and may induce RNAi-mediated local and systemic plant resistance. Since this action is highly sequence-specific, the technology promises improved selectivity and safety, far surpassing those of the chemical pesticides (Rank and Koch, 2021; Yu *et al.*, 2022). There are several approaches to exploit the technology, including host-induced gene silencing, spray-induced gene silencing, virus-induced gene silencing, and others, reaching highly impactful protection of plants against pests and diseases (Tang *et al.*, 2021).

Plant extracts

Ethanol extract of giant knotweed (*Reynoutria sachalinensis* F. Schmidt ex Maxim.) protects zucchini against powdery mildew (caused by *Podosphaera xanthii*) via eliciting an SA-dependent defense (Margaritopoulou *et al.*, 2020). The extract is commercialized as 'Regalia Biofungicide' by Marrone Bio Innovations, Inc.¹³ (Davis, California, USA) to boost the defense mechanisms of plants against bacterial and fungal diseases. The active ingredient(s) of the giant knotweed extract have not been identified yet.

Yeast cell wall preparation

Several strains of brewers' yeast (*Saccharomyces cerevisiae*) exhibit antimicrobial properties. *S. cerevisiae* was therefore investigated as a possible biocontrol agent, and cell wall preparations from the fungus were found to show plant resistance eliciting activity (De Miccolis Angelini *et al.*, 2019). The commercial product 'Romeo' developed by

Agrauxine¹⁴ (Beaucouze, France) shows excellent protecting ability against several fungal diseases of different crops.

CONCLUSIONS

At the beginning of the twentieth century, the full potential of chemical plant protection was yet unknown, when Erwin F. Smith (1902) in his brilliant, visionary essay wrote: "Every decade will not be fortunate enough to stumble on a Bordeaux mixture". The discovery of synthetic pesticides was considered as a breakthrough that provided a solid pillar for the Green Revolution, aiming to eradicate famine and poverty in the world (Komives, 2016). The negative impacts of pesticide use on human health and the environment have been discovered only decades later (Szekacs and Komives, 2017). Because of the widespread problems of pesticide-based plant protection, the EU's "Farm-To-Fork" strategy within the European Green Deal¹⁵ targets a 50% reduction of the use of chemical pesticides by 2030. We believe, that plant protection technologies based on plant vaccinations may significantly contribute to these sustainability goals.

On a final note, we would like to add that the technology of plant vaccination is not without risks (e.g., unpredictable side effects, lability of the formulated product, the possibility of genetic recombination in case of RNA, etc.). Therefore, this modern area of agriculture should be approached with caution and considered as a highly research-demanding field.

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