



# **Sustainable Management of Diseases in Horticulture: Conventional and New Options**

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**Citation:** Scortichini, M. Sustainable Management of Diseases in Horticulture: Conventional and New Options. *Horticulturae* **2022**, *8*, 517. https://doi.org/10.3390/ horticulturae8060517

Academic Editors: Hillary Righini, Roberta Roberti, Stefania Galletti and Harald Scherm

Received: 11 April 2022 Accepted: 8 June 2022 Published: 13 June 2022

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**Abstract**: To reduce the impact of chemical pesticides on the environment, there are relevant efforts to enhance the possibility of controlling plant diseases using environmentally friendly biocontrol agents or natural products that show pathogen control capacity. The European Union, FAO, and the United Nations largely promote and finance projects and programs in order to introduce crop protection principles that can attain sustainable agriculture. Preventive measures related to the choice of cultivars, soil fertility, integrated pest management (IPM), and organic farming strategies are still the basis for obtaining satisfactory crop yields and reducing classical pesticide utilisation through the application of commercially available and ecofriendly control agents. Effective pathogen detection at borders to avoid quarantine pathogens is mandatory to reduce the risk of future epidemics. New technical support for the development of sustainable pathogen control is currently being provided by forecasting models, precision farming, nanotechnology, and endotherapy. New biocontrol agents and natural products, disease management through plant nutrition, systemic resistance inducers, and gene-silencing technology will provide solutions for obtaining satisfactory disease control in horticulture. The "multi-stakeholder partnership" strategy can promote the implementation of sustainable crop protection.

**Keywords:** Green Deal; integrated pest management; biocontrol agents; natural products; models; precision agriculture; nanotechnology; endotherapy; systemic resistance inducers; gene silencing

# 1. Introduction

The concepts that illustrate sustainable agriculture have been posed and defined decades ago and can be summarised by the principles and approaches described by F.A.O. "Building a common vision for sustainable food and agriculture" (https://www.fao.org/ 3/i3940e/i3940e.pdf, accessed on 22 May 2022) as "an integrated system of plant and animal production practices having a site-specific application that over the long-term will: (a) satisfy human food and fiber needs; (b) enhance environmental quality and the natural resources; (c) make the most efficient use of nonrenewable resources and on-farm resources and integrate natural biological cycles and control; (d) sustain the economic viability of farm operations; (e) enhance the quality of life for farmers and society as a whole".

Considering that the complete achievement of all such goals still requires a relevant effort [1], the success of sustainable agriculture mainly depends on the acceptance of these principles by the farmers, which should actively identify strategies for maintaining, enhancing, and developing their on-site resources (i.e., soil, water, air, biodiversity, and landscape) for future generations [2]. The successful application of such goals can be assessed by indicators that measure the percentage of the agricultural area which satisfies the specified criteria of sustainability regarding water, soil, and biodiversity, and achieving a specific level of productivity [3]. However, the need for a continuously widespread application of sustainability criteria in agriculture with less impact on the environment is also necessary in a world where food demand is increasing.

For the European Union, sustainable agriculture, through the "Farm to Fork" strategy, is one of the main objectives of the European Green Deal (Annex to the European Green

Deal, 2019). The aim of agriculture before the year 2030 should be: (a) at least 25% of agriculture in Europe being organic; (b) reduction by 50% of chemical pesticide utilisation; (c) reduction by 50% of more hazardous pesticide utilisation; (d) reduction by 20% of fertiliser utilisation; (e) reduction of soil nutrient losses by at least 50%. In addition, to diminish the utilisation of copper in agriculture, the executive regulation 2018/1981 of the European Commission reduced the maximum limit of usable copper to 4 kg per hectare, and a maximum of 28 kg per hectare in seven years to minimise the potential accumulation of copper in soil and the exposure of non-target organisms. Similarly, the United Nations 2030 agenda promotes sustainability in agriculture through Sustainable Development Goals (SDG) (https://sdgs.un.org/goals, accessed on 22 May 2022). Within this scenario, there are already examples of communities that, upon a referendum, decided to ban the use of chemical pesticides to protect the local environment and obtain pesticide-free food [4].

It should be noted that the use of traditional pesticides showed a 2% decrease per year owing to the application of regulatory restriction laws, compared to the 15% increase per year in favour of biopesticide utilisation [5]. Within this context, the future of agriculture will be based on environmentally friendly agronomical techniques that, at the same time, can assure a profit to the farmer and the sustainability of the farm itself [6].

The success of obtaining satisfactory pathogen management according to sustainable agriculture principles requires parallel actions to prevent the spread of phytopathogens. From this perspective, effective quarantine measures are necessary to avoid the introduction of destructive plant pathogens into new areas of cultivation. Currently, this aspect is particularly relevant because of the extensive global circulation of plant materials and climate change [7]. Modern diagnostic tools should be implemented at the points of plant material circulation (i.e., airports and ports) and the local entry points (i.e., regional phytosanitary services) [8]. Local quarantine agencies can be assisted by climate-matching tools and geographical information systems that can predict the possibility of pathogen spread in a new area [9].

Many reviews have been published on the different aspects of sustainable agriculture, including basic knowledge on the control of phytopathogens [10–14]. The principles that rule out agro-ecology and organic farming are not discussed. This review attempts to provide a broad overview of sustainable agriculture and integrated pest management (IPM) principles applied to achieve pesticide reduction, with a focus on disease management under the regulatory framework of the European Union. There is a focus on the main strategies based on the utilisation of well-known and new biocontrol agents and products or compounds with a low impact on the environment that are already developed or undergoing achievements regarding the control of some diseases of woody and herbaceous crops. New technologies to augment the efficacy of disease control in sustainable agriculture are also presented and discussed.

A synoptic panel of current control strategies in relation to sustainability principles and policies is shown in Figure 1.



**Figure 1.** Synoptic panel that shows the current strategies and policies related to the achievement of sustainable disease control in horticulture.

#### 2. The Basis for a Sustainable Disease Control: The Preventive Measures

#### 2.1. Suitability and Selection of the Site and Cultivars

In addition to the economic aspects and infrastructural facilities, the climatic factors characterising an area must be considered for the choice of the crop to be cultivated. At present, this issue is relevant because of climatic changes that affect most areas of the world. Climate change can result in the adoption of different pathogen control strategies and agronomical techniques, owing to the possible adaptation of new pathogens to the new climatic scenario. For example, many areas with a Mediterranean climate that are traditionally free from freezing events either in winter or early spring have recently faced relevant frost damage during such periods, which seriously threatens the economic profit of crops [15,16]. In addition, for other areas such as Central and Eastern Asia, Central–North America, Northern India, Australia, and the Mediterranean Basin, the occurrence of "hot spots" (i.e., temperature > 40 °C for many consecutive days, accompanied by the absence of rainfall) during summer pose a risk to wheat cultivation [17] and can cause severe damage to heat-tolerant crops such as olive [18]. Edaphic (i.e., soil fertility, texture, and porosity) and biotic (i.e., occurrence of bees, pests, and pathogens) factors must also be considered to avoid future problems due to climate change.

In addition to area suitability, the right choice of cultivars is another basic element that can allow the success of the crop according to sustainability criteria. For woody species, the choice is of basic importance and, according to soil characteristics, should also consider the choice of rootstock. The right choice is even more critical, particularly when the crop reaches a new cultivation area [19]. The cultivar choice for herbaceous crops is also important in the context of climate change, as shown by an extensive survey performed in Germany with cereal producers. Farmers judged eco-stability, grain yield performance, and steadiness as being the most important cultivar requirements [20].

#### 2.2. Healthy Seeds and Plant Material

The healthy phytosanitary status of seeds, tubers, plantlets, potted plants, and propagative material is a fundamental prerequisite for initiating cultural cycles. At present, this aspect is particularly important considering the extensive global circulation of these commodities. In recent years, the relevant increase in global plant circulation regarding the agricultural and forest trade has dramatically increased the possibility of pests and pathogens to rapidly reach new countries and, consequently, to colonise and infect new crops and the same crops cultivated on another continent [21]. Once introduced in a new area, phytopathogens can become part of the new environment(s) depending on a series of factors, such as the number of introduction events, the transmission rate of the pathogen, the density and spatial variation of the susceptible host, the favourability of the climatic conditions, the synchronicity between host susceptibility, and the pathogen life cycle [22]. An efficient surveillance system at the border should be developed in each country to rapidly intercept new threats before they can be established in a new territory. This issue is particularly important for countries that have not yet developed a phytosanitary regulation system based on quarantine principles. In contrast, seed companies and plant nurseries should efficiently implement all preventive measures that can reduce the colonisation of plant material (i.e., effective pathogen control strategies during plant growth and disinfection of plant material before shipping). In addition, farmers should carefully monitor crops, particularly during the first phases of growth, to observe and eliminate potential diseases.

# 2.3. Optimal Soil Fertility and Agronomical Techniques

One of the pillars of the European Common Agricultural Policy (CAP) is the maintenance and enhancement of soil fertility; correct soil management is one of the fundamental prerequisites for sustainability in agriculture [23]. According to agroecological principles, some effective practices can be applied to herbaceous and woody crops to maintain and augment soil fertility. Crop rotation with leguminous species and the planting of cover crops between tree rows are methods that can ensure, over a long-term period, the maintenance of natural soil fertility [24,25]. Crop rotation can also result in a better control of some soil-borne diseases, such as in potatoes affected by Rhizoctonia solani and *Streptomyces scabies* [26]. In addition, the application of plant growth-promoting rhizobacteria (PGPR), biofertilisers, composts, mycorrhiza, biochars, and humic and fulvic acids can augment nutrient acquisition and assimilation, improve soil texture and plant growth, and induce systemic resistance to biotic and abiotic stresses [26-32]. For example, the distribution to the soil of a biofertiliser that contained a mixed fungal and bacterial microflora induced conferred protection against Fusarium wilt of banana caused by Fusarium oxysporum f. sp. cubense after three years [33]. Paecilomyces variotii, a fungus obtained from agro-industrial compost, showed efficacy in the control of Fusarium wilt of melon caused by Fusarium oxysporum f. sp. melonis [34]. However, care should be given to the correct choice of compounds released into the soil to increase their overall fertility. In some circumstances, organic matter, particularly animal manure, can release antibiotics that can perturb native microflora, causing adverse effects on the crop [35]. It should be noted that balanced crop nutrition is an essential component of any integrative program for crop protection [36].

Given that the application of compounds for crop protection aims to deposit the highest amount of the active ingredient on the target plant part (i.e., buds, leaves, and canopy) in which the pathogen resides, an effective and desirable reduction of the spread of any compound in the environment can be achieved by the appropriate calibration of the sprayers. At present, it is possible to adjust the sprayer nozzles to achieve the intended target (i.e., the plant part that shows symptoms of disease), which also reduces water utilisation [37]. Soil solarisation is a well-known technique that, when properly applied, can effectively control important soil-borne pathogens. However, the utilisation of plastic covers poses a relevant concern for their subsequent removal and disposal [38]. Organic

farming largely benefits from such preventive measures to obtain effective pathogen control, particularly soilborne pathogens [39].

#### 3. Sustainable Agriculture and Pathogen Control

#### 3.1. The Basis for an Effective Sustainable Pathogen Control

Knowledge of the genomic structure, virulence factors, and epidemiology of pathogens is the basis for developing fine-tuned strategies for the effective control of biotic diseases in crops. Selected biocontrol agents or compounds with potential curative effects should be tested against different strains of pathogens that represent the entire population structure. In addition, the disease cycle of the target pathogen should be fully understood to precisely apply the biocontrol agent/compound before and during plant colonisation or the internal multiplication of the microorganism. Some examples of the basic studies that link crop and pathogen epidemiology to the selection of biocontrol agents and fine-tune the spread of active ingredients for disease control are as follows [40-46]. Knowledge of the pathogen cycle of diseases is also the basis for the development and implementation of disease forecasting [47,48]. Moreover, the sustainability of modern pathogen control should be considered in addition to crop productivity, the ecological function of the crop, and the social acceptance of the strategy [49]. A report that concerns either the effectiveness or the social impact of different strategies to control fire blight of apple, caused by *Erwinia amylovora*, in Switzerland has been prepared. A thorough investigation performed by interviewing experts and a literature data search revealed that biological control performed with Aureobasidium pullulans is either effective or widely accepted in rural areas because of its feasibility, durability, low impact on animals, biodiversity, soil and water habitation, low cost, and acceptance by consumers [50]. In this case, the majority of the inhabitants of an area are aware of the importance and efficacy of sustainable agriculture for the maintenance and improvement of their lifestyle and environmental safety.

#### 3.2. Current Control Strategies

Integrated pest management (IPM) is the current strategy that allows for the effective control of many plant pathogens in many cases. According to the European Union Framework Directive on the sustainable use of pesticides (Directive 2009/128/EC), IPM "means careful consideration of all available plant protection methods and subsequent integration of appropriate measures that discourage the development of populations of harmful organisms and keep the use of plant protection products and other forms of intervention to levels that are economically and ecologically justified and reduce or minimise risks to human health and the environment. IPM emphasises the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms". In addition, the FAO IPM programme involves three large areas located in Asia, the Near East, and West Africa to improve farming skills, raise the awareness of smallholder farmers of the risks posed by traditional agrochemicals, and promote sustainable agriculture (https://www.fao.org/agriculture/crops/core-themes/theme/pests/ipm/en/, accessed on 22 May 2022).

However, given the diversity and complexity of agricultural scenarios, IPM can differ significantly among countries, and each crop of a definite area of cultivation should apply the IPM criteria according to the local reality and a holistic approach; thus, the combination of control tactics into a planned strategy can provide more effective and sustainable results than the single-tactic approach [51,52]. The development and utilisation of ad hoc web-based platforms illustrating control thresholds, cultural practices that can influence disease attack, pathogen virulence, and fungicide efficacy can help farmers, advisors, and researchers to better plan the control strategy according to a real-time assessment of the environmental conditions of the area [53].

The application of the IPM strategy on a large scale would benefit from ad hoc studies that provide updated information on the current control strategies applied to any crop in an area in order to identify the lack of knowledge in the field, to be resolved through future studies. These systematic maps of knowledge have proven useful in applying IPM to arable crops (i.e., wheat, barley, oat, potato, sugar beet, and oilseed rape) cultivated in large areas in Sweden [54]. A refined IPM strategy which combines all the validated methods for monitoring and reducing the impact of the diseases would allow researchers to control apple scab and apple powdery mildew, caused by *Venturia inaequalis* and *Podosphaera leucotricha*, respectively. This strategy includes disease monitoring and forecasting, ecofriendly fungicides, adequate orchard sanitation, biological control, and insect control through mating disruption. It is comparable with the results obtained by conventional pest management methods [55]. IPM is also the basis for a transition from a chemical to a biological control strategy in Canada regarding greenhouse vegetable crops [56].

In addition, IPM strategies largely benefit from the cultivation of resistant/tolerant cultivars, as observed for the more effective application of biocontrol agents such as *Bacillus mycoides* to a sugar beet cultivar that is more tolerant to *Cercospora beticola*, or *Bacillus subtilis* towards chickpeas infected by *Fusarium oxysporum* f. sp. *ciceris* [57]. In the Netherlands and Ireland, the utilisation of novel potato cultivars resistant to late blight, caused by *Phytophthora infestans*, in combination with real-time pathogen population monitoring and checking of its genetic structure allowed for a reduction of 80–90% of fungicide use (https://www.wur.nl/en/newsarticle/more-sustainable-potato-production-through-extended-ipm-for-late-blight.htm, accessed on 22 May 2022). The protection of crops starting from the seed is another relevant option for better management of diseases. *Trichoderma gamsii*, applied to maize kernels, has been proven effective in reducing pink ear rot caused by *Fusarium verticillioides* and root infection [58].

Despite the higher incidence of pathogens in the crop, the application of organic farming principles for some years can also support, in many circumstances, the effective biological control of pathogens [59]. The observed increase in ecological intensifications of the agro-ecosystem promotes a higher occurrence of beneficial microorganisms in the crop [59]. The synergism between IPM strategies and organic farming principles in relation to pathogen control could provide benefits for improving environmental quality, farm economic viability, and soil and human health [60].

At present, the success of IPM and organic farming in relation to pathogen control is based on three research sectors that are closely related to each other: disease forecasting models, biological control, and environmentally friendly natural products or compounds.

#### 3.2.1. Disease-Forecasting Models

Disease forecasting is based on mechanical models designed with the input of climatic data and the pathogen cycle of disease to alert the grower on whether, when, and how to apply an agrochemical or a biocontrol agent to protect crops. Such models are dynamic because they analyse the changes in the components of an epidemic over time according to external variables (i.e., climatic data, pathogen multiplication, and plant growth stage in relation to disease development) [47] (Figure 2). An effective example of a forecasting model that allows a relevant reduction in pesticide distribution in the environment is vite.net<sup>®</sup> [61]. Based on a decision support system that calculates vineyard parameters (i.e., air, soil, plant, pathogen, and disease development) and a web-based tool that analyses such data, vite.net<sup>®</sup> provides information for *Plasmopara viticola* management in the vineyard. The system is flexible and can be tailored to a single vineyard or an area characterised by high similarity. This tool was largely utilised by grape growers on more than 17,000 h in 2017 in Italy, Spain, Portugal, Greece, Romania, and the United Kingdom and allowed for a reduction of approximately 50% in pesticide utilisation [47,61].

Another effective and used disease-forecasting model is Brassica<sub>spot</sub><sup>TM</sup> that is applied to manage *Albugo candida*, a causal agent of white blister of *Brassica* crops (i.e., radish and broccoli) in Australia [62]. The application of the model allowed for a reduction of more than 80% of the disease and reduced the number of pesticide sprays from fourteen to one or two per year. In addition, the introduction of a resistant cultivar and the simple change in the time of irrigation from 2000 h to 4000 h also decreased disease incidence [62].

Similarly, in Florida, the Strawberry Advisory System (SAS) based on local weather data allows growers to reduce the use of chemical sprays for controlling anthracnose, caused by *Colletotrichum* spp., and grey mould, caused by *Botrytis cinerea* [63], by 50%. In South Korea, the EPIRICE model was developed to assess the daily risk for the occurrence of rice blast caused by *Magnaporthe oryzae* [48]. The model utilises some climatic data linked to fungus multiplication, such as air relative humidity, temperature, and precipitation, and can be used to predict the risk of disease at an early stage [48].



Figure 2. Scheme of a modern decision support system based on a forecasting model for plant disease management. Information about crop-specific characteristics (A1), environmental conditions (A2), crop and plant status (A3), and agricultural operations (A4) flows from the crop to a remote server (B1), and it is stored in database (B2). This information is then used as an input for running mathematical models and decision algorithms (B3), which generate decision supports and alerts to the grower for deciding when and how apply a protective agent (C1). (Reproduced from [47]).

# 3.2.2. Biological Control

Biological control agents for plant diseases are defined as naturally occurring microorganisms capable of suppressing the growth and proliferation of a target pathogen by different mechanisms of action (i.e., competition for space and nutrients, antibiosis, predation, induced host resistance, and lytic enzymes). In addition to living microorganisms, they sometimes utilise metabolite(s) that can be sprayed directly onto crops [64]. Beneficial microorganisms are registered as plant protection products, and they are usually applied to crops at a high density once or several times during the growing season. In the United States and Canada, government agencies are responsible for confirming the biosafety of the biocontrol agents (i.e., the Environmental Protection Agency (EPA) in the United States, and the Pest Management Regulatory Agency (ARLA) in Canada). In Europe, according to Regulation 1107/2009 for plant protection products, the authorisation for commercialising biocontrol agents is obtained through some related steps: (a) the bioactive microorganism should be approved at the European level by the European Food Safety Authority (EFSA) according to the physiochemical properties of the substance, its risk profile for human health, and its risk profile for the environment; (b) formulated products should be authorised at the member state level; (c) further scrutiny with regard to organic agriculture requirements. In addition, the Directorate General for Health and Food Safety (DG SANTE), the Standing Committee on Plants, Animal, Food, and Feed (PAFF Committee), and the Rapporteur Member State are involved in the decision according to Directive 91/414, which states that any active substance should be included in an approved EU list (Annex 1), and its further application must be authorised by member states. These procedures take a long time, thus creating an overall slowness for final approval [65].

The causal agents of plant diseases can have either a worldwide occurrence in specific crops or local distribution. For the first case, the application of the Nagoya protocol of October 2014, for the "Access and the Fair and Equitable Benefit-sharing of Genetic Resources" that restricts the international exchange of biological material, can result in a limitation on the circulation and use of biological control agents that are selected in a different geographical area [66]. Consequently, given the increase in organic food demand and the current Green Deal policy, the selection of native local biocontrol agents is of paramount importance [11]. It should be noted that this selection largely depends on the specific pathosystem under study. Two approaches illustrate how it is possible to proceed: (a) selection through consecutive screenings for testing the effectiveness of the biocontrol agent (i.e., in vitro assays for antibiosis, lytic enzymes, and antimicrobial metabolites, in planta assays for colonisation, control performance, and induced resistance); (b) selection through the assistance of genetic/genomic studies (i.e., the use of genetic markers for finding single biocontrol traits, genome-wide DNA markers for selecting complex traits) [11,67]. The durability of biocontrol agents is another important prerequisite for their long-standing efficacy. Indeed, there are documented reports of a significant reduction in the control effectiveness of Botrytis cinerea in Astilbe hybrids, as shown by Pseudomonas chlororaphis after eight treatments [68].

In some circumstances, natural selection yields biocontrol agents that are capable of displaying long-term positive effects on some diseases, such as for soybean root rot caused by *Fusarium* spp., *Pythium* spp., and *Rhizoctonia solani* in Northeast China. In this case, a naturally occurring suppressive soil was analysed, and *Trichoderma harzianum*, *Pochonia clamydosporia*, *Paecilomyces lilacinus*, and *Pseudomonas fluorescens* strains have been found to inhibit the fungal pathogens of soybean roots [69]. Another well-known example is the natural occurrence of mycoviruses of the family *Hypoviridae*, which infect *Cryphonectria parasitica*, the causal agent of chestnut blight. Upon infection, the virus incites hypovirulence in the fungus by reducing its parasitic growth and sporulation capacity. The virus can be isolated from chestnut cankers and utilised as a biocontrol agent to cure trees by inhibiting further canker development. In addition, the virus is capable of spreading naturally in the forest and reaching other infected trees [70].

Fungi, bacteria, and yeast are the most widely used biocontrol agents. The following species are among the most versatile: Trichoderma harzianum, Trichoderma viride, Bacillus subtilis, and Pseudomonas fluorescens. All of them, indeed, have shown control activity towards some common fungal pathogens such as Botrytis cinerea, Monilinia fructicola, Plasmopara viticola, Puccinia graminis, and Erisiphe spp. [71]. Rhizobium (Agrobacterium) radiobacter strain K84 is among the most known biocontrol agents used for many years to control crown gall caused by Agrobacterium tumefaciens [72]. A stand-alone effective biocontrol agent has been also selected for apple scab caused by *Venturia inaequalis*, namely *Cladosporium cladosporioides* H39, that, over a wide range of environment, showed a high control level and appears effective even when applied after some days from the infection event [73]. Similarly, Bacillus amyloliquefaciens strains are capable of effectively controlling Fusarium equiseti in broad bean cultivation [74]. In some circumstances, a single biocontrol agent is capable of effectively reducing two diseases caused by distantly related microorganisms, as was seen for *Paecilomyces variotii*, which showed control activity towards both the bacterium Xanthomonas vesicatoria, the causal agent of bacterial spot of tomato, and *Fusarium oxysporum* f. sp. *melonis*, the causal agent of Fusarium wilt of melon [34].

*Trichoderma* spp. are among the most studied biocontrol agents in agriculture. Through different metabolic pathways, the induction of systemic resistance to the plant, multiple adaptive mechanisms, antimicrobial molecules, and antagonistic behaviour, *Trichoderma* strains can either promote plant growth or act as effective biocontrol agents against fungal species under numerous agricultural conditions, including in greenhouses and nurseries [75,76]. These strains account for the greatest proportion of fungal biocontrol agents against the phytopathogenic microorganisms investigated, and many commercial formulations that contain a single *Trichoderma* strain or a mixture of different *Trichoderma* strains

are available [75,77]. A series of common and widespread phytopathogenic fungi, such as *Rhizoctonia solani*, *Fusarium oxysporum*, *Botrytis cinerea*, *Pythium* spp., *Sclerotinia* spp., *Verticillium* spp., *Phytophthora* spp., and *Alternaria* spp. can be controlled by generalist *Trichoderma* spp. strains [75,78]. Other fungal genera that also show antagonistic activity toward phytopathogenic fungi are *Alternaria*, *Aspergillus*, *Penicillium*, *Pichia*, *Candida*, *Talaromyces*, and nonpathogenic *Fusarium*, *Pythium*, and *Verticillium* [79]. *Pichia anomala* is effective in controlling postharvest crown rot of banana caused by *Colletotrichum musae*, *Fusarium verticillioides*, and *Lasidiodiplodia theobromae* [80]. In addition, *Ampelomyces quisqualis* is commercially available for the preventive control of powdery mildew fungi in different crops, such as eggplant, cucumber, tomato, and strawberry.

Pseudomonad strains provide a very large amount of potential biocontrol agents that can be found within the following species and species complexes: *Pseudomonas fluorescens*, *P. chlororaphis*, *P. putida*, *P. syringae*, *P. aureofaciens*, *P. protegens*, *P. mandelii*, *P. corrugata*, *P. koreensis*, and *P. gessardii* [81]. However, very few commercially available products are currently available: *P. fluorescens* for *Erwinia amylovora*; nonpathogenic *Pseudomonas syringae* for postharvest disease of fruits, potato, and sweet potato; *Pseudomonas chlororaphis* for fungal diseases of ornamental crops and turf grass; *Pseudomonas aureofaciens* for lawn and grass management against soil-borne fungi. Genetic instability and poor shelf life are among the main causes of the limited registration of pseudomonads as biocontrol agents [81]. *Bacillus* species have a higher shelf life due to their possibility to form endospores, and have many potential biocontrol agents, stemming from their ample antagonism mechanisms (i.e., antibiosis, enzymes, lipopeptides, competition for space, and nutrients), are also present in this genus, with *Bacillus subtilis*, *B. amyloliquefaciens*, and *B. polymixa* being the richest in providing biocontrol effectiveness [82].

Among the yeasts, five species are most widely used as biocontrol agents, namely *Candida oleophila, Metschnikowia fructicola, Cryptococcus albidus, Saccharomyces cerevisiae*, and the yeast-like fungus *Aureobasidium pullulans*. The low production of toxic secondary metabolites by yeast is an important prerequisite that raises fewer biosafety concerns and increases their possibility of utilisation [83]. *Candida oleophila* is utilised as a postharvest biocontrol agent for banana, apple, and citrus, towards *Colletotrichum musae*, *Botrytis cinerea*, and *Penicillium* spp., whereas *Aureobasidium pullulans* is utilised as a biocontrol agent towards fire blight of apple and pear, caused by *Erwinia amylovora*, and for apple postharvest diseases [84]. Moreover, a satisfactory control has been also achieved in strawberry cultivated in greenhouses towards *Phytophthtora cactorum* and *Botrytis cinerea*, the causal agents of crown and root rot and grey mould, respectively [85].

In some cases, a combination of more biocontrol agents provides better control than the application of a single agent. The sprays of *Bacillus mycoides* and the yeast *Pichia guillermondii* on strawberry leaves provided a better performance for controlling *Botrytis cinerea* than the application of a single biocontrol agent [86]. In addition, to induce stimuli for the plant growth, plant growth-promoting rhizobacteria (i.e., *Bacillus subtilis* and *Curtobacterium flaccumfaciens*) can also act as effective biocontrol agents as the case of a multiple effectiveness against three cucumber pathogens, namely *Colletotrichum orbiculare*, *Pseudomonas syringae* pv. *Lachrymans*, and *Erwinia tracheiphila* [87]. However, the compatibility between different control agents should always be assessed because there are also cases of reduced control activity when two agents are applied without a prior compatibility assessment [88,89]. In the case of proven compatibility, the two biocontrol agents can provide satisfactory disease control activity through a multitrophic approach [90]. The addition of specific substances that promote the growth of biocontrol agents on the plant's surface can also enhance the performance of the biocontrol agents, as in the case of lactic acid, which is used as a biocontrol agent for *Erwinia amylovora* [91].

#### 3.2.3. Natural Products and Compounds

A natural product with a potential use for controlling plant diseases can be defined as a physiologically active chemical that is synthesised by plants, microorganisms, or

10 of 31

animals. These products can act as antimicrobials or inducers of systemic resistance, are usually easily biodegradable, and do not persist in the environment [92]. Some of them can act as templates for chemical pesticides (i.e., synthetic analogues), such as the fungicide strobilurin, which was named with reference to *Strobilurus tenacellus*, a woodrotting mushroom. Chitosan and its derivatives, alkaloids, flavonoids, terpenes, proteins, and phenolic compounds are the most widely studied and used dried materials [93]. These products are the result of their coevolution with the biotic environment; thus, many of them are defence compounds toward other organisms and can possess potent bioactivities and selectivity [94]. Within this category could be included also antibiotics. However, in many countries, these products are banned for their utilisation in agriculture as protectants because of the possibility of transmission of genetic traits from bacterial phytopathogens to microbes of human and animal importance, which could confer resistance to a single or multiple antibiotics [95,96]. However, these are not discussed in this paper.

Harpin, a proteinaceous elicitor of the self-protective hypersensitivity reaction in plants against pathogens, obtained from the pathogen Erwinia amylovora [97], was among the first natural products to be commercially utilised in plant protection. Protection obtained through harpin was observed for harvested apples infected by blue mould, which is caused by Penicillium expansum [98]. Currently, it is included among the biostimulants. Another well-known natural fungicide was obtained from *Reynoutria sachalinensis* to control powdery mildew of cucumber and tomato in glasshouse cultivations, as well as downy mildew of grapevine [99,100]. The extract induces plant defence responses such as callose papillae and an increase in salicylic acid and caffeic acid [101]. Chitosan is a derivative polymer of chitin, the primary component of the cell wall of fungi and the exoskeleton of insects and crustaceans, and is usually extracted from shrimp shells, mud crabs, and fungi for utilisation in medical and chemical science, as well as in agriculture. Chitosanbased compounds are traditionally utilised postharvest to protect fruit decay [102]. Due to the very high economic losses in crops caused by phytopathogens that show pesticide resistance [103], the discovery, validation, and registration of new natural products that are characterised by different and novel modes of action are required, and DNA sequence technologies can help in identifying gene(s) or clusters of genes of potential interest for pathogen control [94].

# 4. Developing Control Strategies

A synoptic panel concerning developing control strategies is shown in Figure 3.



Figure 3. Synoptic panel that illustrates the developing disease control strategies for sustainable agriculture.

#### 4.1. Technical Support

## 4.1.1. Precise Timing Decision for Pathogen Control

Modern forecasting models for plant disease should be characterised by (a) flexibility and accuracy; (b) differential interactions between the analysed data and statistical representation; (c) different thresholds of infection risks in relationships with possible mixed infections and changes in crop susceptibility during the season; (d) modelling the disease dynamics, taking into account the long-distance interactions of biological parameters (e.g., spore dispersal through wind and deposition via rainfall events); (e) defining the precise timing for applying biopesticides, taking into account the different scales of climatic and epidemiological data [104]. Knowledge of the pathogenic genetic structure is also important for including such variability into the model according to a fine-tuned pathogen disease cycle. In addition, the assessment of field infection over consecutive years can also be used to calibrate and compare the current-year prediction range [104]. Because some models of the past are hindered by sparse spatial data and a limited use of field monitoring technology, predictive models for pathogen infection based on weather forecasting can now largely benefit from recent advances in the large-scale monitoring of the space provided by satellites [104]. Consequently, a further improvement could be obtained by incorporating data besides the meteorological parameters, obtained by using remote sensing, into the model, such as the leaf reflectance of the red band obtained during the crop growing season [105]. In some circumstances, remote sensing analyses allow for the detection of pre-symptomatic outbreaks and distinguish symptoms caused by different causal agents, such as *Phytophthora infestans* and *Alternaria solani* [106]. The final validation of the models in the field and their utilisation by farmers is considered a mandatory step for including the model in an effective IPM strategy [12], and the direct involvement of farmers (i.e., the end-users) in developing such tools is important [107].

Climate change projections should also be considered, so that modern forecasting models also aim to predict possible scenarios of pathogen outbreaks and provide a finetuned timing for applying preventive and curative biocontrol agents, or natural products, for plant protection [108]. Through different global circulation models, it is now possible to generate climatic projections of diseases in different geographical areas. Several key plant pathogens, including *Fusarium* spp., *Puccinia recondita, Pyrenophora teres, Magnaporthe oryzae, Plasmopara viticola, Phytophthora infestans,* and *Xanthomonas oryzae* pv. *oryzae* have been assessed for their potential impact on climate change [108]. These models can also predict the impact of a pathogen outbreak at the landscape level when introducing a new crop adapted to the changing climate or in the case of a widely distributed crop facing a new pathogen introduced from abroad [108].

#### 4.1.2. Precision Farming and Pathogen Control

Strictly connected with the forecasting models, precision farming can provide methods that can be utilised at a single-farm level in order to predict pathogen outbreaks in realtime and site-specifically. The geographical information system (GIS), in combination with on-site monitoring platforms for continuously assessing pedo-climatic data, are the basis for providing alerts to the farmers in relation to the pathogen outbreak [109]. A so-called phenomic approach can assist to establish the precise time for performing the preventive or curative treatment to the crop. The measurements of crop traits such as growth and performance during the season obtained through noninvasive techniques can detect pre-symptomatic events of disease-related changes in the crop that are not visually apparent [110]. In these cases, the "Internet-of-Things" monitoring platform utilises an artificial intelligence algorithm for emulating the decision-making ability of humans regarding the choice of the precise timing for controlling the pathogen [111]. An agro-weather station is installed in the field for measuring many climatic data and additional data such as leaf wetness, soil temperature and water content, and solar radiation in order to detect the early stages of the pathogen infection and to provide an alert to the farmer for applying control measures [111]. Another advantage of precision farming for

pathogen control is the management of the disease according to its possible occurrence only in some area of the farm, this resulting in a reduction of pesticide distribution. The monitoring platforms can also detect soilborne diseases by recording the changes in the foliage characteristics [109]. An on-going application for monitoring disease spread both on a large scale and at the single-farm level is the agricultural research outcomes system (AgCROS), developed in Florida to manage the citrus greening disease of citrus crops, caused by the non-cultivable bacterium Candidatus *Liberibacter asiaticus*. AgCROS is a GIS-based monitoring platform for sharing research data between farmers and researchers and to provide decisions for a better management of the disease [112]. One of the most important outcomes of the platform is the early detection of trees infected by the pathogen. This result can be achieved by analysing, in each farm, some plant physiological indexes such as NDVI and NDRE, shown by the trees during the season and captured by remote sensing through unmanned aerial vehicles (UAV) [112]. Moreover, to reduce the cost of the analyses for large areas, data obtained from satellite can be also utilised [112].

Another application of precision farming coupled with remote sensing data analyses is currently performed to control cotton root rot, caused by the soilborne fungus *Phymatotrichopsis omnivora*, in Texas [113]. Field multispectral images are acquired though satellite sensors, and field maps are created to monitor the crop. A classification map distinguishes infected field parts from the healthy ones based on different colors pointing out the diseased plants. Consequently, different rates of fungicides and fertilisers are applied to any single farm according to the precise occurrence of diseased plants in a specific area, thus allowing for a relevant reduction of pesticide spread [113].

#### 4.1.3. Nanotechnology

Nanomaterials released within a plant through nanotechnology can provide a relevant contribution to the reduction of agrochemicals spread in the environment. However, we must first assess the interactions of the nanoparticles with the plant tissue [114], as well as the bioavailability and durability of nanoparticles [115], their potential ecotoxicological risks and accumulation in food [116], and the relative costs for their application [116]. In addition, nano-biopesticides should have refined technical properties such as a high solubility of low-solubility active ingredients, a slow targeted release, and the non-premature degradation of active ingredients [117]. Additionally, some traditional pesticides have been re-formulated by developing nanoparticles to reduce the dispersal of the active ingredients in the environment [116]. Among the preventive measures for pathogen control to be applied in sustainable agriculture, copper and zinc-based nanoparticles could be used as seed coating substances or in foliar applications to improve the overall growth of plantlets [118]. The nanomaterials that show potential for application as nanopesticides include silver, copper, zinc, carbon, magnesium, manganese, silicon, calcium carbonate, and chitosan [114]. Bioactive products can also be encapsulated within biodegradable nanomaterials or, alternatively, loaded with plant extracts possessing antimicrobial activities. These nanocarriers can release the active product selectively to the plant. Among these nanocarriers, chitosan oligomers and methacrylated lignin could be effectively utilised [119]. PGPR strains could also be utilised as nano-fertilisers and/or inducers of systemic resistance to phytopathogens [120].

Greenhouse studies have shown the relevant activity of copper-based nanoparticles towards *Fusarium oxysporum* f. sp. *niveum*, the causal agent of watermelon root rot [121]. Similarly, sprayed copper-based nanoparticles showed relevant antifungal activities in eggplant grown in a glasshouse on a soilless medium and infected with *Verticillium dahliae*, whereas copper, zinc, and manganese nanoparticles significantly reduced the pathogenic activity of *Fusarium oxysporum* f. sp. *lycopersici* in tomato grown on a soilless medium [122]. Nanoparticles obtained from crude extracts of *Chaetomium cochlioides*, a fungus that possesses antimicrobial compounds, reduced the severity of rice blast caused by *Magnaporthe oryzae* by 60% [123]. It should be stressed that, to date, most applications of nanoparticles have been restricted to basic laboratory studies and some field applications [114]. Due to the low degradability of nanoparticles in the natural environment [49], the full development of this sector still requires in-depth studies on the impacts of the different active ingredients used as nanoparticles to determine the long-term effects of nanoparticles on the environment and their residual content in food. The field applications of silver nanoparticles retained as effective antimicrobials are the most striking example of this cautious approach [124]. The need to formulate precise guidelines for nanoparticle utilisation in the field is also required [114,125]. Notably, however, chitosan-derived nanoparticles offer a good avenue for assessing the biosafety risks, since these nanoparticles are created from biodegradable bioactive polymers, are not toxic to humans and animals, and offer good antimicrobial activity towards both fungi and bacteria [117,126].

Antimicrobial peptides obtained from natural compounds or that are designed and synthetically obtained de novo are small peptides that show the potential capacity for controlling plant diseases, as replacements for traditional pesticides once we have verified their impacts on the ecosystem (i.e., the epiphytic microbiota of leaves and fruit) [127]. A current limitation of the wide utilisation of such peptides is the high cost of field treatments. These peptides offer the possibility to control plant diseases by either inactivating the pathogenicity of the target phytopathogen or inciting plant defense mechanisms in a multitarget approach. This possibility was verified by applying a bifunctional synthetic peptide to tomato plants and observing its control capacity towards *Pseudomonas syringae* pv. *tomato*, the causal agent of tomato bacterial speck; *Xanthomonas campestris* pv. *vesicatoria*, the causal agent of tomato bacterial spot; *Botrytis cinerea*, the causal agent of tomato grey mould [128].

#### 4.1.4. Endotherapy

The release of specific products within the xylem tissue of trees through trunk injection or trunk infusion is another technique that could allow for a notable reduction of agrochemical dispersal in the environment, reduce the risk of toxicity for farmers, and possibly reduce the overall cost of the protective treatment [129]. The products to be released through endotherapy should be preliminarily verified for their suitability in apoplastic transport within the plant, for the absence of phytotoxic effects [130], and to determine the most suitable plant port for effective injection [131]. There is also a need to reduce the trunk wounds that are caused by devices utilised for the injection [132-134]. Apple trees infected with Erwinia amylovora, the causal agent of fire blight, and injected with products that incite the induction of systemic acquired resistance, such as acibenzolar-S-methyl and potassium phosphite, were found to significantly reduce both blossom and shoot blight. This injection also induced the expression of some proteins related to plant defense [133]. Similarly, a study in Apulia (Italy) on evaluating the possibility of controlling *Xylella fastidiosa* subsp. *pauca*, the causal agent of olive quick decline syndrome, showed that the trunk injection of a curative biocomplex containing zinc, copper, and citric acid incited an increase in some plant defense-related metabolites, such as oleuropein and polyphenols, as well as a simultaneous decrease in other metabolites related to the disease, such as quinic acid and mannitol [135]. Endotherapy performed with glutaraldehyde on grapevine cuttings provided a satisfactory control of *Phaeoacremonium minimum*, one of the fungi involved in the esca disease complex [136]. In addition, endotherapy performed on grapevine plants showing symptoms of esca disease complex using chitosan oligomers as nanocarriers loaded with the extracts of some plants offering antimicrobial properties, such as Rubia tinctorum, Equisetum arvensis, Urtica dioica, and Silybum marianum, yielded a significant reduction of foliar symptoms [119].

#### 4.2. New Bioproducts and Sustainability

#### 4.2.1. Biocontrol Agents

The potential use of biocontrol agents in sustainable plant protection is currently limited by factors such as the fragmentation of biocontrol sub-disciplines and crop site-specific factors; unwieldy regulatory processes; increasingly bureaucratic barriers to access biocontrol agents; insufficient engagement and communication with the public, stakeholders, growers, and politicians in regards to the considerable economic benefits of biocontrol; relatively high costs [137,138]. For biosafety reasons, any microorganism released into the environment should be carefully assessed via the post-release field monitoring of putative negative environmental impacts, and well-designed ecological monitoring programs will provide data that can help regulators [139]. The cost-efficiency of the product plays a relevant role in farmer choice, and considerable attention should be devoted by the selling companies to the methods of formulation, storage, and delivery [32]. Additionally, the cost of registration for the biocontrol agents is very high, and some companies register their bioproducts as biofertilisers [140].

Apart from bureaucratic and regulatory barriers, some technical aspects for identifying potential biocontrol agents could also be improved, and the need for new high-throughput screening systems was previously suggested [141]. In particular, marker-based screening that can test, in vitro, many enzymes and/or metabolites linked to the antagonistic activity of the microorganism(s) and perform genomic-based searches for genetic traits that show antagonistic activity should be applied to reveal potential beneficial strains to be further assessed through in planta tests [11,141].

One branch of development for obtaining biocontrol agents is based on bacteriophages and phages, the viruses of bacteria. Apart from their stability in the environment [142], one of the most critical points for the utilisation of biocontrol agents is the definition of their host range. This aspect is critical since the potential dispersal of such agents into the environment should not create problems for beneficial bacterial microflora [143,144]. Moreover, phages should not interfere with the genetic material of the target plant by r eleasing traits through transduction that could be incorporated into the plant cell [143]. There are many studies demonstrating the in vitro effectiveness of phages and phage cocktails in infecting and killing plant pathogenic bacteria, even though relatively few strains have reached the commercial phase [142–144]. This lack of commercial applications could be due to the intrinsic difficulty in establishing a direct correlation between laboratory and field conditions [145].

In the U.S.A., *Xanthomonas vesicatoria*, the causal agent of bacterial spot of tomato and pepper, *Pseudomonas syringae* pv. *tomato*, the causal agent of bacterial speck of tomato, *Erwinia amylovora*, the causal agent of fire blight of apple and pear, and *Xylella fastidiosa* subsp. *fastidiosa*, the causal agent of Pierce's disease of grapevine are examples of bacterial pathogens that can be controlled or mitigated using commercially available products based on phages. In Europe, *Enterobacteriaceae (Pectobacterium, Dickeya)*, which affects potato during post-harvest, and *Erwinia amylovora*, which is under strict regulation during spring, are the sole pathogens for which commercially distributed phages are allowed [143,144]. Soil-borne pathogens and seeds are other targets for biocontrol through phage utilisation [143,144]. In addition, phage-derived proteins, such as endolysin for Gram-positive species, can be exploited as potential antimicrobial agents [146]. In the future, precision farming through sensor-based technology could effectively assist and improve upon the field utilisation of phages. The detection of early stages of the disease coupled with the best time to avoid leaf desiccation and U.V. stress could facilitate the success of phage activity in the field [144].

Usually, the rhizosphere and phyllosphere are the most commonly exploited resources for isolating potential bacterial strains for biological control. Plant-growth-promoting rhizobacteria are well-known active agents that enhance the plant defense system, thus conferring a general healthy status to the crop. *Acinetobacter, Arthrobacter, Azospirillum, Bacillus, Bradyrhizobium, Rhizobium, Sphingomonas, Serratia,* and the nonpathogenic *Agrobacterium, Burkholderia,* and *Pseudomonas* are the most common isolated genera that show growth-promoting activities [147]. *Bacillus* spp. and *Pseudomonas* spp. isolated from the rhizosphere and/or soil are among the bacterial genera most widely utilized as biocontrol agents for soil-borne fungal and bacterial phytopathogens, whereas the genus *Streptomyces* yielded a relevant number of strains with potential as biocontrol agents, especially towards fungal species [148]. In the phyllosphere, *Pseudomonas, Bacillus,* and *Pantoea* are the predominant

genera that can be isolated as potential biocontrol agents [149]. Preliminary screening to reveal the occurrence of antimicrobial compounds and antagonistic activities (e.g., hydrolytic enzymes, ammonia, and antibiosis) related to phytopathogen biocontrol and the promotion of plant growth should be performed on a large collection of isolates to highlight the most promising strains [150]. Other important features of successful biocontrol agents include niche-adaptability, competition for nutrients, and colonisation ability [151,152]. Moreover, some commercial products based on strains of the aforementioned bacterial genera are currently used as biocontrol agents for crop protection, including soil-borne diseases.

For example, *Pantoea vagans* and *Pseudomonas fluorescens* provide many strains with antagonistic activities to both phytopathogenic bacterial and fungal species. Some strains of both species show control capacity for *Erwinia amylovora*, the causal agent of fire blight of apple and pear [153]. Additionally, commercial compounds have been developed as potential substitutes for streptomycin application in disease control. *Pseudomonas fluorescens* is among the most versatile bacterial species and can act as either a plant-growth-promoting or biocontrol agent for plant diseases, especially soil-borne diseases [154]. Similarly, *Pseudomonas chlororaphis* strains have been registered in commercial formulations to control leaf blight and grey mould in tomato, which are caused by *Alternaria alternata* and *Botrytis cinerea*, respectively [155].

*Bacillus subtilis, Bacillus amyloliquefaciens,* and *Bacillus pumilus* are largely employed as biocontrol agents for citrus diseases both in the field and during storage—namely, *Colletothricum acutatum* and *Colletothricum gloeosporioides,* the causal agents of anthracnose; *Alternaria citri,* the causal agent of black rot; *Phytophthora citrophthora,* the causal agent of root rot; *Plenodomus thacheiphilus,* the causal agent of mal secco; *Penicillium digitatum, Penicillium italicum,* and *Geotrichum candidum,* which are involved in fruit decay during storage [156,157]. To improve the effectiveness of these biocontrol agents during fruit storage, additional compounds or physical treatments (i.e., copper hydroxide, sodium carbonate, tea saponins, and hot water) are applied to provide more integrated and effective management [156]. The salt-tolerant *Bacillus velezensis* showed significant biocontrol activity towards Verticillium wilt of olive [158] (Figure 4).



# Diseased non-treated control

# Diseased B. velezensis XT1-treated

**Figure 4.** Olive Verticillium wilt, caused by *Verticillim dahliae*, treated with *Bacillus velezensis*: olive trees in the field experiment before and after the treatment with *B. velezensis* strain XT1. (Reproduced from [158]).

*Bacillus* strains could also be effectively used in mixed compounds to exploit the synergistic effects of their diverse antagonistic modes of action towards target pathogenic bacteria and fungi [159]. Potato is another crop that largely benefits from the utilisation of biocontrol agents to prevent tuber soft rotting caused by *Pectobacterium* spp., *Dickeya* spp., and *Clostridium* spp. [160]. The overall strategy includes soaking potato tubers prior to sowing in a solution containing *Pseudomonas fluorescens* strains to prevent future colonisation by pathogens. Similarly, the soil can also be inoculated with antagonistic bacteria such as *Bacillus*, *Pantoea*, *Pseudomonas*, and *Streptomyces* to colonize the root zone where phytopathogens usually start plant colonisation.

Finally, cocktails of biocontrol agents in the form of a solution or powder are used to protect harvested tubers during storage. In this case, the tubers are soaked in the solution prior to storage [160]. A significant reduction in economic losses caused by rice blast incited by *Magnaporthe oryzae* is expected to be obtained through the application of *Streptomyces* strains as biocontrol agents [161,162]. Some lactic acid bacteria, which are usually used as bioprotective agents for foodborne pathogens and spoilage microorganisms, have also shown good potential to act as biocontrol agents for plant pathogens. Due to its antimicrobial metabolites, *Lactobacillus plantarum* shows broad-spectrum antagonism towards some bacterial phytopathogens such as *Pseudomonas syringae* pv. *actinidiae*, the causal agent of kiwifruit bacterial canker; *Xanthomonas arboricola* pv. *pruni*, the causal agent of strawberry [163] (Figure 5). A consortium of endophytic lactobacilli composed of *Weissella cibaria* and *Lactococcus lactis* enabled the control of papaya dieback caused by *Erwinia mallotivora* [164].



**Figure 5.** Effect of the treatments with lactobacilli strains (grey bars) on *Pseudomonas syringae* pv. *actinidiae, Xanthomonas arboricola* pv. *pruni,* and *Xanthomonas fragariae* infections in kiwifruit, Prunus, and strawberry plants, respectively, under greenhouse conditions. The effect of strains on disease incidence (%) was compared with streptomycin (white bars) and a non-treated control (black bars). Different letters indicate statistical significance (Reproduced from [163]).

The versatile behavior of *Trichoderma* spp. can also be exploited to provide effective control through the colonisation of additional niches besides those that are usually targeted, such as in the case of *T. gamsii*, which is commonly utilised to protect wheat spikes from *Fusarium graminearum*, the causal agent of Fusarium head blight of wheat. The addition of fungus in the soil or during sowing can enhance the overall biocontrol activity [165]. Similarly, the addition of *Trichoderma polysporum* spores to seeds in combination with liquid compost rich in organic matter supplied in fertigation during plant growth enhanced overall bioactivity towards melon wilt caused by *Fusarium oxysporum* f. sp. *melonis* under semiarid conditions [166]. A combination of *Trichoderma* strains with nanoparticles could also provide augmented control effectiveness [167].

The search for new beneficial traits within *Trichoderma* spp. can now be assisted through genomic prediction tools that reveal the occurrence of a single gene or cluster of genes that produce bioactive product(s) either *per se* or under some stimuli [168,169]. Several predicted terpenes and phytotoxins with potential bioactive behavior have been found in the genome by genomically screening publicly available *Trichoderma* genomes [169]. A reduction in production costs is also an important issue to resolve for this important sector of biocontrol agents, and new types of formulations exploiting low-cost substrates for producing pure fungal spores should be implemented [75].

Consortia of bacteria and fungi, so-called multi-strain biological control agents, or microbial synthetic communities, can also be utilised for the management of soil-borne diseases caused by bacteria, fungi, and oomyctes [170] or key fruit pathogens, such Botrytis cinerea, by developing niche-specific microbial interactions [171]. A microbial consortium based on Trichoderma atroviride, Aureobasidium pullulans, and Bacillus subtilis that colonises different ecological niches of the bunch during the season was proven to be effective in significantly reducing the activity of *B. cinerea*, the causal agent of grey mould of grapevine [171]. According to this strategy, Trichoderma atroviride, a good coloniser of dead plant tissue, provides protection at the bunch closure stage. Additionally, Aureobasidium pullulans can compete for sugar utilisation, with the fungus occurring on cracks in berries, whereas Bacillus subtilis, which produces antagonistic metabolites, should be sprayed close to harvest time [171]. Commercially available formulations contain Trichoderma strains and other bioactive species such as Pseudomonas fluorescens, Pseudomonas aureofaciens, Bacillus spp., and Streptomyces spp. [75]. Consortia of different Streptomyces strains showed the potential capability to reduce the severity of some diseases caused by *Fusarium oxysporum* in vegetables [172].

Non-harmful endophytic microorganisms are another source of potential biocontrol agents currently being exploited. Generally, these microbes live within plant tissues and provide useful metabolites for plant growth and tolerance to stress, including plant pathogens [13,173]. Volatile organic compounds could also be used to control plant diseases [174]. The genus *Trichoderma* also includes endophytic species that can be exploited as mycoparasites, as in the case of coffee leaf rust caused by *Hemileia vastatrix* [175]. Other fungal genera that have shown potential beneficial activities towards fungal phytopathogens include *Heteroconium; Ramularia; Xylaria; Candida;* and nonpathogenic strains of *Fusarium oxysporum, Cladosporium, Colletotrichum, Alternaria, Phoma, Pestalotiopsis,* and *Botryosphaeria* [13,173]. The genus *Streptomyces* is another source of beneficial endophytes that show antagonistic activities towards soilborne fungi such as *Fusarium, Pythium, Verticillium, Rhizoctonia,* and *Phytophthora* (directly to the phytopathogens or mediated through their metabolites). Some commercial products are also available [176]. *Bacillus, Paenibacillus* spp., and *Rhodococcus* are other good candidates for obtaining biocontrol agents [177].

## 4.2.2. Natural Products

Natural products that show biocidal activities are commonly obtained from plant or animal extracts or microbial metabolites. Essential oils, chitosan, some plant extracts (i.e., *Yucca schidigera*, *Equisetum arvense*, *Punica granatum*, *Allium cepa*, *Urtica dioica*, and Camellia sinenis), alkaloids, and bacterial lipopeptides are currently being studied, and some are already available as commercial biopesticides [178]. Seaweeds represent another potential source for obtaining biopesticides [179], especially when utilised in a well-planned IPM strategy [180]. Essential oils (i.e., mixtures of terpenes hydrocarbons, alcohols, and phenols) extracted from many plant species have been studied in detail as products with potential biocidal activities towards phytopathogenic fungi, oomycetes, and bacteria, without inciting pathogen resistance [181,182]. However, the stability and persistence of essential oils in the environment, as well as their high cost of authorisation and regulatory barriers, remain obstacles for their wide utilisation in sustainable agriculture [181,182]. Essential oils obtained from Mentha arvensis, Mentha spicata, Juniperus mexicana, Citrus x sinensis, Persicaria odorata, Piper nigrum, Canarium commune, Cinnamomum zeylanicum, Boswellia carterii, Cymbopogon flexuosus, Litsea cubeba, Artemisia alba, Cistus ladaniferus, Copaifera tree, Ferula galbaniflua, Citrus aurantium, and Schinus terebinthifolius are registered in Europe by the European Chemical Agency (Homepage-ECHA (europa.eu)) as being suitable for use in agriculture, with some approved for their biocidal activities. In addition, when applied as seed protectants against cabbage black rot caused by Xanthomonas campestris pv. campestris, essential oils obtained from Zataria multiflora yielded a significant reduction in the further occurrence of disease in the field [183], whereas clove oil obtained from Eugenia caryophyllata was observed to control pomegranate bacterial blight caused by Xanthomonas axonopodis pv. punicae [184]. Essential oils obtained from cumin, basil, and geranium, applied either as seed protectants or directly in the soil, showed effectiveness towards cumin root rot caused by Fusarium spp. [185]. New techniques such as emulsion and the encapsulation of essential oils are currently being studied to enhance the stability and persistence of such oils in the environment [181].

Chitosan is currently being studied both as a plant defense inducer and for its direct involvement in disease control [186,187]. One of chitosan's properties is its film-forming abilities, which can be exploited to protect the surface of plants, thus avoiding colonization by pathogens. This feature can protect fruits and vegetables under postharvest conditions, and many crops benefit from treatments for controlling fungi involved in decay. These crops include table grapes, strawberry, pear, apple, citrus, peach, sweet cherry, plum, and mango [188]. The film formed by chitosan can also reduce both the incidence and severity of Pseudomonas syringae pv. actinidiae, the causal agent of kiwifruit bacterial canker [189]. Significant activity was also observed in rice infected with bacterial leaf blight caused by Xanthomonas oryzae pv. oryzae [190]. Seed dressing is another potential application of chitosan to reduce disease [191]. Interestingly, chitosan showed a synergistic effect with some biocontrol agents such as Trichoderma spp., indicating both castor seed protection [192] and a increased reduction in the pathogenicity of Cercospora beticola and *Fusarium oxysporum* [193]. Chitosan should also be added to the soil to reduce the severity of tomato crown and root rot caused by Fusarium oxysporum f. sp. radicis lycopersici [194]. Similarly, chitosan should be applied together with essential oils to reduce the volatility of such oils and to enhance their effectiveness in the control of Aspergillus flavus on dates [195].

In a previous study, *Yucca schidigera* extract protected sorghum seeds through the pathogenic activity of *Phoma sorghina*, *Curvularia lunata*, *Cladosporium* spp., and *Fusarium* spp. [196]. The macerate of *Equisetum arvense* (common horsetail) presented control activities that were very similar to those of different copper compounds towards *Phytophthora infestans*, the causal agent of tomato late blight; *Puccinia triticina*, the causal agent of durum wheat brown rust; *Fusarium graminearum*, the causal agent of Fusarium head blight of durum wheat [197]. Pomegranate (*Punica granatum*) peel extract is another natural product that shows potential activities for the control of phytopathogens. Pomegranate fruit peel extract showed a significant reduction in the severity and incidence of disease for *Pseudomonas syringae* pv. *tomato*, the causal agent of tomato bacterial speck, and tomato damping-off caused by *Fusarium oxysporum* f. sp. *lycopersici* [198,199]. Pomegranate (*Punica granatum*) fruit peel extract also showed interesting activities for the postharvest control of *Botrytis cinerea*, *Penicillium expansum*, and *Penicillium digitatum* on sweet cherry and citrus

fruits [200]. *Camellia sinensis* extracts presented antibacterial activities towards *Pseudomonas syringae* pv. *actinidiae*, the causal agent of kiwifruit bacterial canker [201].

Tetrahydro-β-carboline alkaloids, which naturally occur in fruits, showed potential inhibitory activities towards some emergent and dangerous phytopathogenic bacteria such as *Xanthomonas axonopodis* pv. *citri*, the causal agent of Asiatic citrus canker; *Xanthomonas oryzae* pv. *oryzae*, the causal agent of rice bacterial blight; *Pseudomonas syringae* pv. *actinidiae*, the causal agent of kiwifruit bacterial canker [202].

#### 4.2.3. Nutrition Management

Apart from playing fundamental roles in plant growth and development, nutrients are also involved in plant pathogenesis and disease control [203]. Moreover, for pathogen control in sustainable agriculture, preventive balanced nutrition coupled with rational agronomical techniques may be more cost effective and environmentally friendly than the application of any pesticide [36,204]. However, each pathosystem (i.e., the interaction between one single pathogen and one single crop in a certain environment) has its own peculiarities that should be investigated in order to verify the relationships between the contents of each nutrient within the plant and the development of disease over the season [36]. Among the various macronutrients, nitrogen can have either a beneficial or negative effect when applied to a crop to contain disease. These differing behaviors seem to be influenced by the overall characteristics of the pathogen (i.e., an increase in disease severity with obligate pathogens and a decrease in disease severity with facultative pathogens) [205].

The role of phosphorus in crop protection appears to be inconsistent and unpredictable. Relatively high potassium content generally has positive effects in reducing disease severity [202]. In particular, potassium phosphate was found to significantly reduce the severity of barley powdery mildew [206]. After establishing that a specific dose does not reach the limit imposed for the maximum residue level of phosphites, potassium phosphite can also contribute to disease reduction, as in the case of *Alternaria solani* on potato and *Alternaria alternata* on citrus fruit [207,208]. Calcium appears to be especially effective for post-harvest treatments against gray mould caused by *Botrytis cinerea* [209,210], whereas magnesium showed inconsistent results in controlling diseases [211]. Further ad hoc studies should be performed to determine the potential beneficial effects [212].

Among the various micronutrients, copper has been widely used as a fungicide and bactericide for a long period of time, although its excessive utilisation can result in the accumulation of copper in the soil, which poses risks for the microbial microflora [213]. Zinc and manganese are microelements that show clear beneficial activities against plant diseases [205]. Applying a supply of manure rich in zinc prior to planting winter wheat was found to significantly reduce the severity of spring blight caused by *Rhizoctonia cerealis* [211]. Moreover, the higher uptake of manganese in paddy-grown rice when compared to the low uptake in upland rice cultivations yielded a greater resistance to *Magnaporthe oryzae*, the causal agent of rice blast [214]. The wheat root rot disease caused by *Gaeumannomyces graminis* can be effectively managed through the nutrition of the host plant, especially through the supply of manganese [205]. Iron can also enhance the virulence of bacteria and fungi, and soilborne pathogens can be limited by adding rhizosphere-beneficial microorganisms that, through the activation of siderophores, reduce the iron content in the soil [36].

An in-depth study to determine which nutrients can impede the multiplication of pathogens showed that the direct supply of nutrients can help directly manage disease in some circumstances [215]. Another study explored the application of a biocomplex fertiliser containing low doses of zinc, copper, and citric acid to the crowns of infected trees, providing a striking example of the importance of plant nutrition as a strategy for significantly reducing infection in olive groves with symptoms of olive quick decline syndrome caused by *Xylella fastidiosa* subsp. *pauca* [216,217] (Figure 6). In this case, zinc and copper ions, which also showed direct bactericidal activities [215], increased in olive trees grown in soils that were characterised by low contents of such ions [218]. The increases in zinc and copper content within the plant that were caused by supplying this biocomplex over a



few years allowed the severely infected trees to achieve good yields [214]. Additionally, supplying some nutrients as a foliar spray—in this case, calcium and boron—enabled the better control of gray mould in strawberry, caused by *Botrytis cinerea* [219].

**Figure 6.** Two olive groves in Nardò (Lecce province, Apulia, Italy): the trees on the right were abandoned upon the infection by *Xylella fastidiosa* subsp. *pauca*, whereas the trees on the left were treated with the zinc–copper–citric acid biocomplex described in [216,217]. The treated trees continue to yield despite the occurrence of the pathogen in the surrounding areas.

#### 4.2.4. Systemic Resistance Inducers

The inducers of plant systemic resistance to pathogens show potential applications in IPM strategies. Such resistance can be mediated via (a) salicylic acid or its precursors, which incite systemic acquired resistance (SAR), or by (b) PGPR, which incites induced systemic resistance (ISR) by modulating the jasmonate and ethylene pathways [220]. Such inducers activate signals related to the plant defense mechanisms that are able to counteract pathogen colonisation. Acibenzolar-S-methyl, harpin, chitosan, and extracts of Reynoutria sachalinensis and Saccharomyces cerevisiae are commercially available inducers of resistance, whereas  $\beta$ -aminobutyric acid (BABA), probenazole, saccharin, phosphites, biochar, mycorrizhal fungi, endophytes, and algal extracts are among the most commonly studied future candidates for new commercial products [220]. Acibenzolar-S-methyl is able to induce resistance towards different kinds of pathogens in different crops, including the postharvest decay fungi of mango species such as *Colletotrichum gloeosporioides* [221]. Moreover, fava bean was found to be protected from Uromyces viciae-fabae and Ascochyta rabiei after acibenzolar-S-methyl treatments [222]. Within an IPM strategy, acibenzolar-S-methyl, in combination with copper treatments, reduced the severity of kiwifruit bacterial canker caused by *Pseudomonas syringae* pv. actinidiae [223].

Besides plant growth, PGPR mixtures showed the ability to protect crops, as in the case of pepper infected with *Xanthomonas vesicatoria*, the causal agent of bacterial spot [224]. Similarly, *Azospirillum brasilense* protected strawberry infected with *Colletotrichum acutatum*, the causal agent of anthracnose fruit rot [225]. Preventive BABA treatments protected lettuce and grapevine from downy mildew caused by *Bremia lactucae* and *Plasmopora viticola*, respectively [226,227]. As an inducer, biochar (i.e., a product of biomass pyrolysis obtained in the absence of oxygen) showed broad-spectrum activities when applied to the soil as an amendment, yielding protection against *Botrytis cinerea*, *Colletotrichum acutatum*, and

*Podosphaera aphanis* in strawberry [228]. This product, obtained from olive pruning, also showed inhibitory activities towards tomato spotted wilt virus, a systemic viral agent, without negatively affecting beneficial soil biocontrol agents such as *Bacillus* spp. and *Trichoderma* spp. [229]. Marine algae also showed potential broad-spectrum activities towards plant pathogens. Extracts from *Ulva fasciata* reduced the activities of *Colletotrichum lindemuthianum*, the causal agent of anthracnose of bean [230]. Additionally, extracts of *Ulva armoricana* showed activities towards the powdery mildew of grapevine, bean, and cucumber [231].

# 4.2.5. Gene Silencing

Using RNA interference technology to achieve host-induced silencing of the pathogen gene(s) involved in mechanisms of pathogenicity and virulence is another strategy that is currently being studied to provide sustainable tools for plant disease control, including the control of viruses [232–234]. Gene silencing through RNA interference is a common plant strategy aimed at blocking the activities of pathogens. Phytopathogens attempt to overcome this measure through anti-silencing mechanisms aimed at inactivating the host plant's RNA interference machinery to start the infection [232]. This technology is based on establishing small interfering host-induced (or more recently, exogenous (i.e., sprayed)) non-coding RNAs that, upon their uptake into the plant, can silence genes that are fundamental for the pathogen life cycle and/or infection (i.e., cross-kingdom RNA interference) [232–234]. The pathogen target genes used in developing the gene-silencing approach are numerous [234]. However, the success of this strategy largely depends on the efficiency of the pathogen in RNA uptake [235]. Some difficulties in the application of gene silencing include the degradation and uptake of RNA into the plant due to physical or biological interference, the lack of transformability among various crops, and the potential absence of genetic stability among silencing traits [236,237].

The pathogenicity of *Fusarium graminearum* was significantly reduced on barley leaves by using a spray that released double-stranded RNA, targeting the *FgAGO* and *FgDCL* genes in the RNA interference machinery of the fungus [238]. The pathogenic activity of *Phytophthora infestans*, the causal agent of potato late blight, was significantly reduced by gene-silencing targeting of the *hp*-*PiGPB1* gene, coding for the G protein  $\beta$ -subunit [239]. *Botrytis cinerea*, the causal agent of grey mould on many crops, is potentially manageable using gene-silencing technology. Spraying fruits, foliage, and flowers with exogenous RNAs targeted to the *DCL1* and *DCL2* genes, coding for the fungus' effectors involved in pathogenicity, can obtain a significant reduction of the disease on tomato, lettuce, onion, strawberry, and grapevine [240]. In addition, spray-induced gene silencing has been effectively applied to reduce the virulence of the fungus on grapevine, both on potted plants and on harvested bunches, by targeting the *erg11* gene of the cytochrome P450 monooxygenase. Double-stranded RNA was sprayed under high pressure on the leaves, absorbed by the petiole, and sprayed on the bunch at postharvest [241].

#### 5. Concluding Remarks and Perspectives

The successful control of plant diseases in horticulture has long been a pillar of both food production and the conservation of agroecosystems. At present, these two goals are becoming increasingly urgent due to the rapid increase in human population and the threats posed by climate change [242]. The global circulation of plant material, with the potential introduction in new areas of dangerous phytopathogens, poses additional risks to safeguarding crop longevity and, in some circumstances, concerns the whole landscape of a territory. Within this context, high levels of crop productivity, conservation, and improvements to agroecosystem fertility should not be viewed as contradictory, and the development and utilisation of effective environmentally sustainable strategies should be applied more consistently to integrate and substitute for chemical pesticides in the near future [243]. Achieving good quality fruits and vegetables during the postharvest period is a complementary and relevant goal to achieve [244]. This scenario is largely

22 of 31

fostered by supranational policies that are supporting projects and developing strategies to increase either the achievement of scientific and technical results or the wide acceptance of a "greener" agriculture. Many scientists involved in various aspects of sustainable agriculture complain about delays in achieving the regulation and commercial utilisation of known and novel biopesticides and/or products that can control phytopathogens. The safety and quality checks of these formulations are compulsory, but more frequent and initiative-taking activities among regulatory institutions are required to promote the spread of new active ingredients.

The conservation of agroecosystems according to sustainability principles greatly depends on the development and application of environmentally friendly strategies on a large scale. The "multi-stakeholder partnership" is an interesting strategy that could support the spread and acceptance of sustainable agriculture. This concept highlights the possibility that diverse groups in the agro-food chain can have common problems or aspirations despite having different interests [245]. A striking example of such a strategy for sustainable agriculture came from the agreement between Barilla, a well-known Italian brand of pasta, and some private companies that produce and supply ingredients such as tomato, sugar beet, and cereals; these organisations had no previous contact. These partners, including the farmers of each single company, share mutual and diversified interests in supporting their planned activities. The network also includes agronomists, research centers, and universities. Single farms are directed to adopt crop rotation, nitrogen fixer crops or green manure, and IPM in their agronomical practices. However, these practices are ruled out in most common methods of production. Farms receive a supply contract from Barilla with some guarantees concerning the price and quantity of the product over many years [246]. These initiatives appear to be positive for improving the circulation of sustainable principles in agriculture and should be expanded to promote sustainable agriculture.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

**Conflicts of Interest:** The author declares no conflict of interest.

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