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Data collection on antibiotics for control of plant pathogenic bacteria

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Abstract

There are neither guidance nor methodology proposed to systematically collect data on antibiotics used as plant protection products, antimicrobial resistance of plant pathogenic bacteria or alternative and innovative treatments for the control of phytopathogenic bacteria, at the worldwide scale level. This is the final report of the project on data collection on antibiotics for control of plant pathogenic bacteria, with the view of reducing risk assessment uncertainties. The project collected and reviewed scientific, grey and patent literature information. This analysis highlighted the lack of publicly easily accessible data on antibiotics as plant protection products. On a worldwide scale, up to 39 countries have been found using antibiotics such as kasugamycin, gentamicin, streptomycin, oxolinic acid, oxytetracycline, validamycin or zhongshengmycin. This analysis also pointed out i) the change of use over time and scale, dependent on practice and legislation changes and ii) the question about the risk for animal and human health lying with antibiotics used in plant production and the possibility to select for complex antibiotic resistance gene vectors. Streptomycin is the antibiotic to which plant pathogenic bacteria are the most often reported as resistant, via several ways of counteracting the effect of this antibiotic. Streptomycin resistance in plant pathogenic bacteria was reported in 18 countries. Globally antibiotic resistance reports arose mainly from the USA, South America and Asia. The report also highlighted alternative control measures, with a few already commercially available and sometimes providing efficient control of the plant pathogenic bacteria, but mostly with a lot under research and development. Data gaps, uncertainties and research needs to improve antibiotic use and resistance risk assessment were also highlighted. Finally, the project stressed the need to raise awareness on the risk of improper use of antibiotics as plant protection products, with an emphasis on capacity building and communication.

Key words: Antimicrobial, Antibiotic resistome, Antimicrobial resistance, control measures, horizontal gene transfer, Plant pathogenic bacteria, Phage

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Summary

The call "Reduce risk assessment uncertainties: data collection on antibiotics for control of plant pathogenic bacteria" is based on EFSA's 2020-2022 draft Work Programme for grants and operational procurements as presented in Annex IX of the Programming Document 2020 – 2022, available on the EFSA's website.

Currently, there are neither guidance nor methodology in place to systematically account for data collection on antibiotics for control of plant pathogenic bacteria, or antimicrobial resistance of plant pathogenic bacteria or data collection on alternative and innovative treatments for the control of systemic plant pathogenic bacteria. Here we report on collecting and reviewing data and information on: i) the use of antibiotics for the control of plant pathogenic bacteria, ii) the resistance to antibiotics in plant pathogenic bacteria and iii) alternative and innovative control measures.

For assessing the use of antibiotics in agriculture as a control measure against plant pathogenic bacteria, a systematic review of the scientific literature has been conducted, targeting publications highlighting the current use of antibiotics as plant protection products. This approach allows identification of countries or regions where antibiotics are authorized as plant protection products targeting plant pathogenic bacteria. Reports on the use of antibiotics in plant protection from the scientific literature are time-dependent. Information published, for example, early in this century, might be outdated in 2023. Data on antibiotics used as plant protection products and quantitative data on the use of antibiotics as plant protection products are not easily accessible. Therefore, a dedicated grey literature search was organized, at first using known pesticide-orientated databases, exploring the agricultural antibiotic-producing companies to finally target the national plant protection organizations to collect officially available information. This approach was found to be the most efficient, highlighting the current use of antibiotic as plant protection products in up to 39 different countries in Africa, America, Asia and Australia continents. Antibiotics such as kasugamycin, gentamicin, ningnanmycin, streptomycin, oxolinic acid, tetracycline or oxytetracycline or validamycin or zhongshengmycin have been recorded. The information collected allowed an analysis of i) the change over time and scale of use, dependent on constant legislation changes and ii) the question about the risk for human health lying with antibiotics only used in plant production.

Resistance reports often coincided with antibiotic use in the same country or region. Streptomycin is the antibiotic to which plant pathogenic bacteria are most often reported as resistant with reports of resistance in plant pathogenic bacteria in 18 countries. Up to 82% of resistance cases were reported in countries where it is used as a plant protection product. The remaining 18% are reported in countries where the use of streptomycin is not authorized currently. Bacteria have numerous ways of counteracting the effect of this antibiotic: i) a point mutation of the *rpsL* gene and ii) the acquisition of the *strA-strB* or *aadA* genes. Moreover, streptomycin resistance genes *strA-strB* are quite widespread, even among human pathogens, and often found on mobile genetic elements (e.g. transposon), which means that the spreading potential for these genes is high. Attention should be paid to the possible transfers of resistance genes between bacterial species. In particular, the transposon Tn*5393* is the only well-documented example of ARGs vector in PPB. It carries streptomycin resistance genes and numerous highly similar variants of the transposon are found among various bacterial species, including PPB but also human pathogenic bacteria (*Salmonella* or *Klebsiella*). Its presence outside PPB might be concerning, notably because its structure has evolved into complex associations with other ARGs and MGEs, which illustrates its potential to also become more complex in PPB. As for the other antibiotics used in crop protection, tetracycline resistance genes are also prevalent among many bacterial species. The emergence of a transmissible kasugamycin resistance gene constitutes a considerable threat; oxolinic acid seems less worrying at the moment; and finally the gentamicin resistance gene was also found on a mobile

genetic element. Globally, antibiotic resistance reports arose mainly from the USA and South America, as well as some Asian countries. However, the lack of studies in Europe and other parts of the world might introduce a bias about the actual presence or absence of antibiotic resistant plant pathogenic bacteria. More studies are needed to better evaluate the current situation in Europe.

The management of PPB requires a comprehensive approach beyond traditional synthetic chemicals through implementation of integrated PPB management strategies. The search for alternative to antibiotic’s use in crop protection highlights the versatility of strategies used or that could be used to minimize PPB incidence and severity. There are distributed among three main approaches aiming at: directly controlling PPB, controlling their vectors (when applicable) and enhancing host resistance.

These approaches are structured around five primary strategies, which involve the use of biocontrol agents (BCA), both synthetic or organic chemicals, employing physical methods, implementing new breeding techniques, and adjusting farming practices.

Biocontrol agents (BCA) are a popular alternative studied extensively both in the scientific and industrial communities. These include various macro- and microorganisms such as insect parasitoids and predators, bacteriophages from *Inoviridae*, *Myoviridae*, *Podoviridae* and *Siphoviridae* families and of course bacteria and fungi. Bacterial BCA mainly belong to *Bacillus*, *Pseudomonas*, *Streptomyces*, and *Pantoea* species. *Bacillus* species like *B. amyloliquefaciens* and *B. subtilis* are well represented and noted for their antimicrobial and plant growth-promoting properties. Fungal biocontrol agents, including *Trichoderma* sp., are also well covered, along with entomopathogenic fungi from *Isaria*, *Hirsutella*, *Metarhizium*, *Beauveria* and *Cordyceps* species used as biological mean for managing vectors of plant pathogenic bacteria. Entomopathogen fungi

Chemicals, whether synthetic or organic-based, constitute the second most widely studied alternative within the scientific and industrial communities; half of the identified active substances originate synthetically, while a quarter are derived from plants, with other sources including microorganisms, insects, animals and categorized according to their use—ranging from antimicrobial delivery systems, behavior-impairing agents, insecticides, plant defense inducers, and growth promoters to substances interfering at the RNA level; antimicrobial substances predominate, amounting to about two thirds of the identified active substances.

Most retrieved patents favor antibiotic-like approaches relying on direct PPB control strategy (70%), very few claims on enhancing of plant resistance either through defense stimulation or breeding programs. Breeding plant cultivars with resistance to PPB has been a longstanding approach. It is still widely used and now combined with cutting-edge technologies such as gene-editing speeding up the process of resistant cultivars development.

Delivering all these new solutions for PPB management contribute to multifaceted approaches that offer efficient solutions when incorporated with sounded and integrated farming practices along with quarantine regulations, early and efficient diagnosis and all measures ensuring the use of healthy plant material.

The project outcome has been communicated via a satellite online and in-person meeting organized back-to-back with the ONE conference held in Brussels (Belgium) in June 2022 as well as in a concurrent session of the International Congress of Plant Pathology in Lyon (France) in August 2023.

A concept note was prepared to present the ongoing project at the International Plant Protection Convention (IPPC) - Convention on Phytosanitory Meeting (CPM) (March 2022). This triggered the proposition of a IPPC-CPM parallel session on antibiotic use and resistance in Plant Health, held in Rome in March 2023.

The outcome of the project has also been communicated at the 26th Belgian Society for Food Microbiology Conference in Brussels, October 2022 (Poster presentation, see Annex D).

A video presentation was also prepared and proposed at the High-Level meeting on Antimicrobial resistance, held in Stockholm on March 6 and 7, 2023, under the Swedish Presidency of the European Union.

Antimicrobial use and resistance is a cross-cutting topic at EFSA but also with other agencies. Possible convergence and cooperation between EFSA and FAO in plant health have been identified, highlighting possible future co-operation.

Finally, recommendations are provided for further improving the risk assessment on antibiotic use and resistance in plant health, with the need to cross-link this specific field of research with animal and human health issues, in a ONE health perspective.

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1. Introduction

From an historical point of view, following the discovery of penicillin, a wide range of different antibiotics have been found in soil- and plant-associated microorganisms (Raaijmakers and Mazzola, 2012). Plant-associated bacteria are considered as a major source of antimicrobials. Thousands of different metabolites have been evidenced from *Streptomyces* sp. (Genilloud et al., 2011). Bacteria proposed as biocontrol agents (*Agrobacterium*, *Bacillus*, *Pseudomonas*, *Stenotrophomonas* and *Streptomyces*) display a wide range of antimicrobial compounds (Caulier et al., 2019), some of which exhibiting a broad-spectrum of activities: besides antibacterial, antifungal, anthelminthic or phytotoxic activities, plant growth promotion, drought tolerance, induction of systemic resistance to plant pathogens, acquisition of trace elements or role in motility as surfactants.

It is quite common to find bacteria producing antibiotics to target other microorganisms including bacteria. This also occurs for plant pathogenic bacteria (PPB), although less frequently. For example, *Xanthomonas albilineans*, agent of the sugar cane leaf scald, is producing a potent antibiotic called albicidin, used by the bacteria for competition with other bacteria (Pieretti et al., 2015). *Pseudomonas syringae* has been long known for the production of phytotoxic and antimicrobial cyclic lipopeptides (Girard et al., 2020), also evidenced in different pseudomonads including non-pathogenic ones.

Plant diseases caused by bacteria are of growing concern because of their rapid spread and devastating impacts on agriculture and the environment. For example, the bacterium *Xylella fastidiosa* affects olive groves, vineyards, citrus and almond plantations and *Candidatus Liberibacter* spp. (also called Huanglongbing, HLB or citrus greening) infests citrus plants resulting in severe yield losses and leading ultimately to the death of infected trees. Antibiotics are used against some bacterial plant pathogens. Oxytetracycline is permitted on crops in the USA, Mexico, and Central America. Oxolinic acid (a quinolone antibiotic) is used in Japan and Israel on rice and pome fruits, respectively. Gentamicin is used in Mexico and Central America and kasugamycin is registered in Canada (Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges, 2018). Streptomycin is registered for the control of fire blight of pear and apple, caused by *Erwinia amylovora* in North America, New Zealand (Stockwell and Duffy, 2012). Antibiotics are not commercialised in Europe for plant protection except tightly regulated emergency uses against fire blight (*E. amylovora*) in some countries. Generally, only a limited number of antibiotics are authorized for plant protection, from a limited number of classes of antibiotics, such as tetracyclines, aminoglycosides and quinolones. A recent study from an international database of agronomic advice to farmers' shows, however, that antibiotics may be recommended far more frequently and on a much greater variety of crops than previously thought (Taylor and Reeder, 2020).

Antibiotic resistance is recognised as a major crisis in relation to human health (Ventola, 2015) and strategies are developed in order not to lose antibiotics as an efficient treatment of human and animal diseases (WHO, 2001; Smith and Coast, 2002). The European Commission has developed an action plan against antimicrobial resistance in the context of a one-health initiative with the aim to make the EU a best practice region, boosting research, development and innovation and shaping the global agenda (https://ec.europa.eu/health/amr/antimicrobial-resistance_en). The use of antibiotics in plant protection is one of the potential causes of an increase in antimicrobial resistance genes in the environment. An increased use of antimicrobial substances as pesticides could undermine the efficiency of antibiotic therapy in humans (Curutiu et al., 2017). Streptomycin resistant strains of *E. amylovora* were found in pear orchards where streptomycin was applied (Loper et al., 1991). In addition to *E. amylovora*, streptomycin resistance genes were also found in *P. syringae* and *Xanthomonas campestris* (Sundin and Wang, 2018). Other studies did not find a significant increase of resistance genes after antibiotic treatments in orchards (Duffy et al., 2014).

The efficiency and potential risks resulting from the use of antibiotics in plant protection are under scientific debate. A recent example is the emergency applications of tetracyclines and streptomycin against Citrus greening in the USA (McKenna, 2019). Some studies conclude that antibiotics are essential for treatment of some plant diseases and that antibiotics decline rapidly on the treated plants, that there are no changes in the microbial communities and that there are no adverse effects on human health or persistent impacts on the environment (Stockwell and Duffy, 2012; Stockwell, 2014). While other researchers question the efficacy of antibiotic treatments (Vidaver, 2002) and observed long persistence of antibiotics, e.g. after trunk treatments in citrus trees (Hu and Wang, 2016).

Alternatives to antibiotic treatments in plant protection are being researched and are under evaluation (e.g. see: Johnson and Temple, 2013; EFSA PLH Panel et al., 2019) and some of the alternative treatments, e.g. copper, may lead to cross-resistance to antibiotics (Scheck et al., 1996). Strategies such as integrated pest and disease management (IPM), planting resistant cultivars, pathogen exclusion, crop rotation and soil improvement are suggested to reduce or eliminate the need to use antimicrobials in plant protection (Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges, 2018).

Given the new global emergency of highly destructive bacterial plant pests (e.g. *Xylella*, HLB), the EFSA Plant Health Panel has considered the conduct of a comprehensive analysis of the efficacy of and on the risk of development of antimicrobial resistance in plant pathogens among the future challenges and priorities for plant health risk assessment.

1.1. Background and terms of reference as provided by the requestor

This contract/grant was awarded by EFSA to:

Contractor/Beneficiary: UCLouvain

Contract/Grant title: Data collection on antibiotics for control of plant pathogenic bacteria

Contract/Grant number: GP/EFSA/ALPHA/2020/02

1.2. Interpretation of the Terms of Reference (if appropriate)

The project here will focus on collection of data and information on the use of antibiotics as plant protection products against plant pathogenic bacteria, on resistance to antibiotics in plant pathogenic bacteria and on alternative control measures to antibiotics.

The project as been organized into five different workpackages, with WP0 devoted to coordination, WP1 for the collection of data on the use of antibiotics as plant protection products for controlling plant pathogenic bacteria, WP2 dealing with the search of antibiotic resistance in plant pathogenic bacteria, WP3 reviewing the alternative control measures for management of plant pathogenic bacteria, WP4 devoted to communication and WP5 axed on cross-cutting initiatives within EFSA.

Each WP was organized in tasks and deliverables as illustrated below (Table 1).

Table 1: Work packages and tasks associated.

Work package	Tasks
WP0: Coordination	**T0.1:** Kick-off meeting organized (foreseen location – Parma, Italy) **T0.2:** Tele-meeting scheduled, organized **T0.3:** Data collected for the Interim report, data sets collected (for objective 1 and 2) and checked **T0.4:** Mid-term meeting organized (foreseen location – Brussels, Belgium) **T0.5:** Tele-meeting scheduled and organized **T0.6:** Data collected for draft final report **T0.7:** Final meeting organized, datasets collected, report sections checked (methods, results, discussion, overall summary, conclusions and general discussion) (foreseen location – Parma, Italy) **T0.8:** Project results are disseminated and communicated **T0.9:** Final report and databases delivered
WP1: Reviewing data and information on the use of antibiotics for the control of plant pathogenic bacteria	**T1.1:** Review of scientific literature for information and data on the use of antibiotics for the control of plant pathogenic bacteria **T1.2:** Review of the technical and grey literature **T1.3:** Collect patent information on antibiotic for PPB control **T1.4:** Scientific report for WP1
WP2: Collection and review of data and information on resistance to antibiotics in plant pathogenic bacteria	**T2.1:** Review of scientific literature for information and data on resistance to antibiotics in PPB **T2.2:** Review of the technical and grey literature **T2.3:** Review of databases for AMR of plant pathogenic bacteria **T2.4:** Review of patents linked to AMR of plant pathogenic bacteria **T2.5:** Collect information available from several surveillance programs of antibiotic use and antibiotic resistance **T2.6:** *In silico* search for AMR for plant pathogenic bacteria **T2.7:** Scientific report for WP2
WP3: Collection and review of data and information on alternative and innovative treatments for the control of systemic plant pathogenic bacteria	**T3.1:** Review of scientific literature for information and data on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases **T3.2:** Review of the technical and grey literature on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases **T3.3:** Collection of patent information on alternative and innovative treatments for the control (including also prophylactic use) of systemic bacterial plant diseases **T3.4:** Scientific report for WP3

WP4: Communication and dissemination of project results	**T4.1:** Organization of a Kick-off meeting, Mid-term meeting and Final meeting **T4.2:** Mid-term report and final report **T4.3:** Website dedicated to the use of antibiotic for the control of PPB and AMR, alternative and innovative control measures
WP5: Cross-cutting issues within EFSA	/

Since the term 'antibiotic' is sometimes defined very widely, the project was focused on antibiotics, which are:

a) reported to be used as plant protection products,

b) possibly registered as a fungicide, or also used as plant protection products against fungal diseases, provided they also display antibacterial activities.

To remain as exhaustive as possible, the report here will stick to the general definition for antibiotic: a substance produced by a microorganism used to inhibit or kill another microorganism (Webster's English dictionary). Nevertheless, a distinction will be made between substances used only in agriculture as plant protection products, from those commonly also used as medicine in both animal and human health.

Concerning the antimicrobial resistance, the project focuses only on plant pathogenic bacteria, without searching resistance associated with non-pathogenic bacteria associated with their host plants, or present in the soil or water, as well as from manure, fertilizers, irrigation water.

2. Methodologies

2.1. Methodologies

2.1.1.Work Package 1 - collect and review data and information on the use of antibiotics for the control of plant pathogenic bacteria

2.1.1.1. Review of scientific literature for information and data on the use of antibiotics for the control of plant pathogenic bacteria (task 1.1.)

The review of scientific literature will be organized according to the EFSA critical appraisal tool for assessing quality of extensive literature searches (ELS CAT) (EFSA, 2015). The methodology was tailored to the current grant request, and depending on the search section, in the context that here the extensive literature search sometimes aim at an inventory of items (e.g. antibiotics used as control measures in plant protection).

With regards to the review of the use of antibiotics for the control of plant pathogenic bacteria (PPB), key elements and search concepts identified are antibiotics and plant protection as control measure for PPB. A pilot study was conducted to obtain a first list of antibiotics used as plant protection production, based on data extracted from databases and reports from international organization (FAO, EC, EPA, FDA, BCPC, BPDB) and scientific literature using two simple search strings 'Antibiotic AND Plant pathogenic Bacteria' AND Control – and 'Antibiotic AND Plant disease AND Control'.

Following this approach, a systematic search was conducted based on generic searches using the list of antibiotics and PPB compiled in the first search. The relevance of the records for providing the related information was assessed by screening the title, keywords and the abstract (based on the knowledge of the grant experts and the report of antibiotics as (potential) PPP as inclusion criteria, and taking into consideration as exclusion criteria the absence of reference to antibiotics as control measure (Table 2). Another expert then reviews the selected publications. In case of disagreement between experts, the opinion of a third independent expert is used to support the decision process.

Table 2: Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Research question		
Population	Studies on crops, Legislation	Studies on animals
Concept	Use of antibiotic as PPP	Absence of reference to antibiotic as control measures
Context	Report on authorized use	
Study		
Study design	All primary research	
Study type	Scientific literature	
Publication year	2000-2022	
Language	English (abstract)	
Microbes	Plant pathogenic bacteria	
Antimicrobials	Antibiotic used as PPP	

The number of scientific literature publication collected at first amount at 5030, reduced to 845 following the exclusion criteria application, then to 81 publications following abstract screening.

The systematic search was organized to collect information on the use of antibiotics for the control of PPB. The search used EBSCO CAB Abstract, Nature Online, Science Direct bibliographic databases, using organized simple string search mentioned above combined with the list of antibiotics obtained previously – i.e. Amikacin, Amoxicillin, Carbenicillin, Cefadroxil, Ceftriaxone, Cephalexin hydrate, Cephaloglycin, Cephaloridine, Cephalotium sodium salt, Chloramphenicol, Cycloserine, Doxycycline, Nalidixic acid, Neomycin, Gentamicin, Kanamycin, Kasugamycin, Ningnanmycin, Nitrapyrin, Novobiocin, Oxolinic acid, Oxytetracycline, Penicillin, Polymyxin, Rifampicin, Spiramycin, Streptomycin, Techloftalam, Tetracycline, Tobramycin, Tyrothricin, Vancomycin, Zhongshengmycin - targeted on plant pathogenic bacteria genera in combination with the term antibiotic or synonyms, e.g. ‘Plant pathogenic bacteria AND Control AND Antibiotic’, ‘Plant disease AND Control AND Antibiotic’, ‘Phytoplasma AND Control and Antibiotic’, ‘Acidovorax, OR Agrobacterium OR Brenneria OR Burkholderia OR Clavibacter OR Corynebacterium OR Curtobacterium OR Clavibacter OR Dickeya OR Enterobacter OR Erwinia OR Enterobacter OR Leifsonia OR Pantoea OR Pectobacterium OR Pseudomonas OR Ralstonia OR Rathayibacter OR Rhizobacter OR Rhizobium OR Rhodococcus OR Samsonia OR Spiroplasma OR Streptomyces OR Xanthomonas OR Xylella AND Antibiotic. Alternative or combined additional searches will be used to refine the search, knowing that such searches will deliver a high number of publications not always dealing exactly with what is searched for.

Special attention has also been given to the use of different terms linked to the definition of antibiotic, after clarification with EFSA, like antimicrobials, antibacterial, bactericide, biocide, nonantibiotic antiseptic, and additional terms.

Data to be extracted from the publications are antibiotic used as plant protection products or screened for potential use as plant protection products. Additionally, data on the plant pathogenic bacteria targeted, the crop on which the antibiotic is used, and about the mode and type of application on the crop have also been collected. This information is summarized in tables or lists. Key identified publications have also been listed.

A targeted search has also been done on “antibiotics” dedicated primarily to fungi control, e.g. aureofungin, sasugamycin, polyoxin B or validamycin, and on different classes of interest, including aminoglycosides, carbapenems, cephalosporins, cycloserine, fluoroquinolones, glycopeptides and lipoglycopeptides, macrolides, penicillins (aminopenicillins, antipseudomonal penicillins), polypeptides, polymyxins, rifamycins, sulfonamide, tetracyclines and vancomycins.

2.1.1.2. Review of technical and grey literature

The search over technical and grey literature was organized following two approaches, using key elements and search concepts identified to assess where antibiotics are used as control measure against PPB.

The first one focused on National Plant Protection Organization (NPPO) dedicated to plant protection products (PPP) or via a network of scientists, via a systematic search. Established organizations (e.g. US EPA-Environmental Protection Agency, US FDA (https://www.fda.gov), the EU pesticide database (https://ec.europa.eu/food/ plant/pesticides/eu-pesticides-database) or targeted databases like the FAOSTAT (http://www.fao.org/faostat/en/), the online pesticide or biopesticide manual (British Crop Production Council) have also been systematically consulted, with the constitution of a websites database.

US EPA (https://www.epa.gov/) or more general searching engines like WorldWideScience.org, allowing searches in different languages, have also been used to provide additional data or to cross check data previously collected.

Table 3: Database searched for the use of antibiotics as plant protection products.

	Web link	
Database		
Pesticide manual online	http://www.bcpc.org	Online database for pesticide, proposed by the British Crop Protection Council, with the aim to provide independent information
Manual of biocontrol agents	http://www.bcpc.org	Online database for biocontrol agents, proposed by the British Crop Protection Council, with the aim to provide independent information
Pesticide Info	https://www.pesticideinfo.org/	Interactive, searchable database of every chemical and product related to pesticide use

		and application set up by the Pesticide Action Network (PAN)
Compendium of Pesticide Common Names	https://pesticidecompendium.bcpc.org/	Compendium of pesticide common names provided by BCPC, allows for the search of synonyms and names of pesticides
FAO Food and agriculture data	http://www.fao.org/faostat/en/	Open access database provided by FAO
EU pesticide database	https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en	The EU Pesticides Database allows users to search for information on active substances used in plant protection products, Maximum Residue Levels (MRLs) in food products, and emergency authorisations of plant protection products in Member States.
US Environmental Protection Agency	https://www.epa.gov/pesticide-registration	Provide information on pesticide registration in the U.S.A.
US Food and Drug Agency	https://www.fda.gov/food/chemicals-metals-pesticides-food/pesticides	Provide information on pesticide (e.g. residue monitoring and data)
Biopesticide Database	http://sitem.herts.ac.uk/aeru/bpdb/index.htm	An international database for pesticide risk assessments and management (Lewis et al., 2016)

The second approach was organized according to the commercial names of branded antibiotics, known to be used for controlling PPB (e.g. Atackin (Nippon Soda), Agrept (Meiji Seika), AS-50 (Nufarm America), Bac-Master (Amvac), Blamycin (Farm Hannong, Firewall (UPI), Flame out (UPI), Mepatar, Mycoject (Mauget), Mycoshield (Nufarm Americas), Kasugamin (Dong Ban), Kasumin (Hokko), Kasuran (CPC), Plantomycin (Aries), Starner (Sumimoto Chemical), Sheatmar (Dhanuka), Streptrol (Nufarm America), Cuprimicin (Adama Mexico)) including products commercialized as mixtures. Product datasheets proposed by companies have also been collected and translated.

2.1.1.3. Collection of Patent Information for Plant Pathogenic Bacteria Control

Patents issued for antibiotics currently used as plant protection products have been collected via PubMed and Patentscope (see appendix I). Additional searches for collecting patent information on antibiotics for PPB control will be organized via known sources, like the European patent office (https://www.epo.org) or the world intellectual property organization (www.wipo.int/patents/) and patent scope, Google patent or via databases currently available like https://worldwide.espacenet.com/patent or https://patentscope.wipo.int/search/en/search.jsf in the frame of WP3.

2.1.2. Work Package 2 – Collection and review of data and information on resistance to antibiotics in plant pathogenic bacteria

2.1.2.1. Review of scientific literature for information and data on resistance to antibiotics in plant pathogenic bacteria (Task 2.1.)

The review of scientific literature was organized according to an extended approach based on the search, study extraction and data extraction proposed for *X. fastidiosa* in EFSA PLH Panel (Bragard et al., 2019) and the PICO-PECO conceptual model (EFSA, 2010; Jaspers et al., 2018). Systematic literature review was conducted to search and collect information on resistance to antibiotics in plant pathogenic bacteria (PPB), ensuring transparency and minimizing bias in the process. The adopted methodology can be divided in several steps: (i) gathering of key reviews (ii) searching for publications (iii) selecting relevant publications (iv) assessment of the reliability, (v) extracting the data, and (vi) summarizing.

In the initial step, a search aimed at gathering key reviews was conducted. From these key reviews, uncertainties linked to the risks of antibiotic use in plant agriculture could be identified and the scope of the review could be determined. Additionally, several relevant articles that were referenced by these reviews were retrieved. This first step was useful to determine the search terms that should be used in the search for the scientific literature. Indeed, using the appropriate vocabulary is essential to ensure the quality of the search. These key reviews should be retrieved by most search strings used later on in order to assess their relevancy.

The second step consisted in the search for scientific publications. Publications could be obtained in three different ways. The first source of publications was obtained through the use of PICO-PECO questions in search engines and databases. The PICO-PECO conceptual model is a tool designed to efficiently retrieve relevant information to a problematic, by formulating a question that comprises four elements: Population, Intervention/Exposure, Comparison, Outcome. Each element of the question is then translated into search terms.

PICO or PO questions were established and translated into search terms. For a single PICO question, several approaches can be used. For each element of the question, synonyms were used to broaden the scope of the search while keeping the same relevancy. If different spellings or common misspellings exist, they should be included (for details see Table 4). To broaden the search, the “C” comparator was not always used, or it was used implicitly (for example, the question a) in the Table 4).

Several information sources (ISI Web of Science, EBSCO CAB Abstract, Nature Online, Science Direct, PubMed Central) were screened in order to select the most appropriate for the project and they yielded various levels of quality. After discussion, CAB abstract and PubMed Central were first selected but CAB abstract was the database that showed the best results with the keywords chosen (see Tables 4 and 5). The same main publications were retrieved when doing the search with PubMed Central but the numbers of results was always higher, probably showing a lower effectiveness of our chosen key words in that database. Finally, it was concluded that CAB Abstract was the most adequate database to cover as much as possible the scientific evidence of antibiotic resistance in agriculture. CAB abstract is a database containing documents relating to agriculture and veterinary medicine.

The quality of a search was evaluated on different levels. After several iterations, search strings which yielded an optimal balance between specificity and sensitivity were selected. If too many articles were yielded by the search, it was deemed not specific enough. Inversely, if the number of articles was too low, the search was deemed too restrictive. Additionally, key reviews should be retrieved with the search string to indicate its accuracy. The “advanced search” option was used directly on the CAB Abstract and PubMed Central websites.

The second source of publications was additional searches that did not follow the PICO-PECO model. These searches aimed at more specific subjects, or questions that did not fit the PICO-PECO structure.

The final source of publications was through referenced articles by the publications retrieved through the searches. For various reasons, some articles can be ignored by our search even though they are relevant to the subject.

The third step is the selection of relevant articles, based on their title and abstract. Inclusion and exclusion criteria were identified to only select relevant publications. For each PICO element, an inclusion criterion was attributed and described in the table below (Table 4).

The fourth step was the assessment of the reliability of the selected publications. In order to make sure that the articles retrieved could be trusted, the quality of the journals in which they were published was evaluated. Two approaches were used in this regard. First, Scimago was used to retrieve the h-index score associated with the journal, as well as the quartile in which it was found regarding its overall score. The h-index score and quartile can be consulted in the Zotero files. The second, complementary approach was by the combined expertise of the researchers working on this project.

Once the publications have been gathered, relevant data can be extracted and summarized into a review.

The table hereunder (Table 4) contains detailed information about the different searches that were done according to the PICO-PECO model.

Table 4: Detailed information on the search performed through scientific literature.

Key elements/concepts	Inclusion Criteria	Comment
a) Does the use of antibiotics in plant agriculture (Intervention) affect the prevalence of antibiotic resistance (Outcome) in Plant Pathogenic Bacteria (Population)? (compared to no treatment (Comparison))		
String search #1: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Plant pathogenic bacteria OR PPB OR plant disease OR phytopathogen (Population) ; AND Antibiotic use OR antibiotic application (Intervention) ; AND Plant agriculture OR crops		
String search #2: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Plant pathogenic bacteria OR PPB OR phytopathogenic bacteria (Population) ; AND Antibiotic use OR antibiotic application (Intervention) ; AND Phytoplasma OR Acidovorax OR Agrobacterium OR Brenneria OR Burkholderia OR Candidatus OR Clavibacter OR Corynebacterium OR Curtobacterium OR Dickeya OR Erwinia OR Enterobacter OR Leifsonia OR Pantoea OR Pectobacterium OR Pseudomonas OR Ralstonia OR Rathayibacter OR Rhizobacter OR Rhizobium OR Rhodococcus OR Samsonia OR Spiroplasma OR Streptomyces OR Xanthomonas OR Xylella (Population)		
String search #3: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Plant pathogenic bacteria OR PPB OR phytopathogenic bacteria (Population) ; AND Antibiotic use OR antibiotic application (Intervention) ; AND Amikacin OR Amoxicillin OR Carbenicillin OR Cefadroxil OR Ceftriaxone OR Cephalexin hydrate OR Cephaloglycin OR Cephaloridine OR Cephalotium sodium salt OR Chloramphenicol OR Cycloserine OR Doxycycline OR Nalidixic acid OR Neomycin OR Gentamicin OR Gentamycin OR Kanamycin OR Kasugamycin OR Ningnamycin OR Nitrapyrin OR Novobiocin OR Oxolinic acid OR Oxytetracycline OR Penicillin OR Phenazine OR Polymyxin OR Rifampicin OR Spiramycin OR Shenqinmycin OR Streptomycin OR Techloftalam OR Tetracycline OR Tobramycin OR Tyrothricin OR Vancomycin OR Zhongshengmycin (Intervention)		
String search #4: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Plant pathogenic bacteria OR PPB OR phytopathogenic bacteria (Population) ; AND Antibiotic use OR antibiotic application (Intervention) ; AND penicillins OR cephalosporins OR Tetracyclines OR macrolides OR phenazines OR fluoroquinolones OR aminoglycosides OR sulfonamides OR carbapenems OR lincosamides OR glycopeptides (Intervention)		
Intervention/Exposure	The publication is related to or mentions antibiotic applications in plant agriculture.	Indirect (e.g. manure) applications will not be considered, but gathered in a separate secondary file if deemed relevant. Antibiotics used in plant agriculture were listed and used as keywords. Important antibiotic classes were also used.

Population	The publication focuses on plant pathogenic bacteria.	An exception will be made for publications that address antibiotic resistance in plant bacteria that are not phytopathogenic but in close contact with phytopathogens.
Outcome	The publication addresses antibiotic resistance.	Publications addressing antibiotic sensitivity will also be considered relevant.
Comparator	Optional – If a comparative study, the comparator must be untreated with antibiotics.	/
b) In plant pathogenic bacteria (P), can ARGs be transferred to other organisms via HGT (O)?		
String search #1: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Plant pathogenic bacteria OR PPB OR plant disease OR phytopathogen OR phytopathogenic bacteria (Population) ; AND Horizontal gene transfer OR HGT OR conjugation OR mobile genetic element OR MGE (Outcome)		
Population	The publication addresses plant pathogenic bacteria.	/
Outcome	The publication addresses horizontal gene transfer of ARGs.	Publications that address the transfer of genes in which a plant pathogenic bacterial cell is the donor, the receiver or both.
c) Does the application of antibiotics on crops (I) impact the pool of ARGs (O) in the surrounding bacterial populations? (P)		
String search #1: Antibiotic resistance OR antimicrobial resistance (Outcome) ; AND Antibiotic use OR antibiotic treatment OR antibiotic application (Intervention) ; AND Plant microbiome OR phyllosphere OR phylloplane OR epiphytic bacteria OR agricultural soil OR rhizosphere OR flower-associated bacteria OR plant-associated bacteria (Population) ; AND plant agriculture OR orchard OR crops OR crop production		
Population	The publication focuses on bacterial populations susceptible to be affected by the direct application of antibiotics on crops.	/
Intervention	The publication mentions application of antibiotics in plant agriculture.	/

Outcome	The publication addresses the presence of antibiotic resistance genes.	/
d) Additional		
Tn*5393*	The publication mentions the Tn*5393* transposon.	This search is meant to establish the host spectrum of this transposon, which is not necessarily restricted to plant pathogens.

Exclusion criteria were defined as follows:

- The publication only focuses on indirect application of antibiotics (e.g. manure, irrigation water, sewage sludge,…).
- The publication focuses on plant pathogenic fungi.
- The publication focuses on antibiotic resistance in livestock, aquaculture,…
- The publication focuses on alternative treatments.
- The publication focuses on the efficacy of an antibiotic against plant diseases (without mention of resistance).

Table 5: Synthesis of the total publications retrieved from the different search strings and the number of selection publications at the end of the selection process. For CAB Abstract, all searches were performed between August 2021 and February 2022.

	Total publications retrieved	Selected publications
CAB Abstract		
A#1	1081	42
A#2	392	42
A#3	274	50
A#4	277	52
B#1	172	19
C#1	354	10
PubMed Central		
A#1	1059	/
A#2	1020	/
A#3	778	/

A#4	788	/
B#1	426	/
C#1	605	/

During the search over Google for grey and technical literature (see section 2.2.2.2. below) with the selected keywords, conferences papers were also retrieved and have also been included in the scientific literature.

2.1.2.2. Review of technical and grey literature (Task 2.2.)

The search for grey and technical literature was briefly explored but did not yield many relevant papers on resistance to antibiotics in PPB for this work package. Keywords such as "streptomycin resistance", "oxytetracycline resistance", "kasugamycin resistance", "oxolinic acid resistance" and "gentamicin resistance" associated with "plant pathogenic bacteria" or "plant protection" were used to search over Google, and the results were retrieved for Task 2.2. Most of the relevant information for this work package was found in the scientific literature search, so the grey and technical literature search was not extensively performed. Additionnally, relevant information were found regarding the authorization of certain antibiotics by specific countries or regarding the use of microorganisms for plant protection but it was not relevant for this work package. Additionnal relevant information was retrieved in the work package 1 (see section 2.1.1.2.). Web pages from different universities, from the Environmental Protection Agency (EPA) from the USA or from governamental organizations were also consulted and reported in this search. The relevant information retrieved with the grey literature was already identified in the scientific literature search.

2.1.2.3. Review of databases for AMR of plant pathogenic bacteria (Task 2.3.)

The approach originally described for Task 2.3. was modified and condensed into Task 2.6., which was the most relevant approach in order to retrieve potential antibiotic resistance genes in PPB genomes. Readers are invited to refer to section 2.2.2.6.

2.1.2.4. Patent search for antibiotic resistance in phytopathogens (Task 2.4.)

A patent search was briefly initiated in order to retrieve patents on Espace Net (https://worldwide.espacenet.com/) on antibiotic resistance in phytopathogens. Two sentences were defined in order to search firstly in the whole text of the patent ("all text") and secondly in the claims of the patent only ("claims") (Table 6).

Table 6: Sentences with keywords and number of results retrieved for the patent search on antibiotic resistance in phytopathogenic bacteria on Espace Net, for searches performed in June 2023.

Sentence with keywords	Number of results retrieved

All text	((nftxt all "plant pathogen" AND nftxt any "resist toleran") OR (nftxt all "plant disease" AND nftxt any "resist toleran") OR (nftxt all "pest" AND nftxt any "resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt any "resistan toleran") AND (nftxt all "Streptomycin" OR nftxt all "Oxytetracycline" OR nftxt all "Gentamicin" OR nftxt all "Oxolinic acid" OR nftxt all "Kasugamycin")	44,495 hits
Claims only	((nftxt all "plant pathogen" AND nftxt any "resist toleran") OR (nftxt all "plant disease" AND nftxt any "resist toleran") OR (nftxt all "pest" AND nftxt any "resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt any "resistan toleran") AND (claims all "Streptomycin" OR claims all "Oxytetracycline" OR claims all "Gentamicin" OR claims all "Oxolinic acid" OR claims all "Kasugamycin")	3,201 hits

An extensive and in-depth patent search was carried out in the framework of Work Package 3, searching for all patents existing regarding potential alternatives to antibiotics in plant protection. Very likely, patents retrieved with the present search were also retrieved in the framework of Work Package 3, as the keywords used are quite similar (see Section 2.2.3.3.). Readers are invited to refer to Section 2.2.3. of the present report. Additionnally, the number of patents retrieved was too important to carry out the search with the patents on antibiotic resistance in PPB, and refining the search did not seem relevant here given the extent of the patent search that was performed in Work Package 3.

2.1.2.5. Collect information available from several surveillance programs of antibiotic use and antibiotic resistance (Task 2.5.)

Most surveillance programs do not have any monitoring implemented for the environment in general, nor for plants. The monitoring is well established for resistance in humans and animals surveillance but the surveillance programs are only starting to think about implementing environmental monitoring of resistance. Most of the relevant information was already retrieved with the grey literature search, readers are invited to refer to the Section 2.2.2.2.

Additionnally, In Belgium, the BELMAP report 2022 has a very small section on “Antibiotic residues and resistance in the environment”, p.68-73. The Food and Agriculture Organization has a web page on antimicrobial resistance associated with plant production (https://www.fao.org/antimicrobial-resistance/key-sectors/plant-production/en/).

2.1.2.6. *In silico* search for AMR in plant pathogenic bacteria (Task 2.6.)

A search methodology over BLAST (Basic Local Alignment Search Tool) NCBI was established. BLAST is an alignment tool, which finds regions of similarity by comparing the sequence entered in the search engine to sequence databases and calculates statistical significance.

Sequences of *strA*, *strB*, *aadA1*, *aac(2’)-IIa*, *aacA3*, *aadA2* and *tetC* were retrieved with their accession numbers (*strA*: AAA98414.2, *strB*: AAA98415.2, *aadA1*: AET43418.1, *aac(2’)-IIa*: BAM16262.1, *aacA3*: AET43407.1, *aadA2*: AAD47997.1, *tetC*: UJO06547.1 and UJO10707.1) and BLASTed against genomes of bacterial genus of interest: *Acidovorax*, *Agrobacterium*, *Burkholderia*, *Clavibacter*, *Dickeya*, *Erwinia*, *Liberibacter*, *Pantoea*, *Pectobacterium*, *Candidatus* Phytoplasma, *Pseudomonas syringae*, *Ralstonia solanacearum*, *Streptomyces*, *Spiroplasma*, *Xanthomonas*, *Xylella*. For Pseudomonas and *Ralstonia*, it was necessary to be more precise than the genus because of the variety of species in these genera that are not linked to PPB. Two types of BLAST analyses were performed: tBLASTn (protein to translated nucleotides) and BLASTp (protein to protein). BLASTp allows us to look for proteins that are similar to our sequences of interest while tBLASTn highlights genomes of species that carry the same sequence of amino acids. The percentage of identity was restrained from 85 to 100%. In fact, in the vast majority of cases, there was a disparity in the results obtained. We could divide the hits in two groups: the first one contained hits with a percentage of identity between 85% and 100% of identity, and the second one contained hits with a percentage of identity closer to 50% or under. The second group had thus a much lower identify with the sequence entered and was considered too distant. So, these hits were discarded. A minimum query cover (number that describes how much of the query sequence is covered by the target sequence) was not set but it was indicated when it is not equal to 100%. Hits with a lower query cover need to be considered carefully. BLAST analyses were carried out from June to September 2022.

This approach can be used with genes that are acquired or present to confer resistance; it is not as well suited to look for mutations, because of the difficulty to identify specific small changes in nucleotide or amino acid sequence or deletions in genes, due to the difficulty to look for a gene that is not present anymore.

2.1.3. Work Package 3 – Collection and review of data and information on alternative and innovative treatments for the control of systemic plant pathogenic bacteria

2.1.3.1. Review of scientific literature for information and data on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (excluding prophylactic use) of systemic bacterial plant diseases (Task 3.1.)

The review of scientific literature was organized according to an extended approach based on the search, study extraction and data extraction as performed for objective 2, using the PICO-PECO conceptual model (EFSA, 2010, Jaspers et al., 2018).

The systematic search used ISI Web of Science - EBSCO CAB Abstract, relying on Boolean string search targeted towards alternatives to antibiotics in controlling systemic plant pathogenic bacteria (PPB). The search was conducted separately for each targeted systemic PPB and results were pooled afterwards.

Following a previous databases' comparison performed in Task 2.1. (ISI Web of Science, EBSCO CAB Abstract, Nature Online, Science Direct, PubMed Central), CAB abstract was selected to perform the search as it was the database that showed the best results with choosen keywords. CAB Abstract proved to be the most suitable database for encompassing the greatest possible amount of scientific evidence regarding efficient and innovative alternatives to the use of antibiotics in managing systemic PPB.

To ensure transparency and minimizing bias in the process, the adopted methodology can be described as a succession of seven steps: (i) gathering of a first set of publications, (ii) selecting relevant publications, (iii) identifying relevant keywords and synonyms out of it, (iv) broadening the search for publications, (v) assessing their reliability, (vi) extracting the data, and (vii) summarizing.

Figure 1 illustrates the used search methodology through a graphical abstract. Briefly, three concepts were connected using AND Boolean operator between each concept and OR Boolean operator within. The first concept includes queries related to the PPB taxon, such as genus, species, subspecies, pathovar, and common synonyms for the disease denomination. The second concept includes terms related to disease control traits. The third concept includes general terms related to plant pathogen management, as well as the specific family to which the targeted PPB belongs. The first two search concepts focused on terms found in the abstract, while the third concept focused on queries found in keywords of the publications.

The initial step of the search was to identify common keywords from a first set of relevant publications extracted from endnote library. These keywords were then used as search queries to conduct a broader search in the scientific literature. Using the appropriate vocabulary is essential to ensure the quality of the search. After several iterations, search strings which yielded an optimal balance between specificity and sensitivity were selected. If too many articles were yielded by the search, it was deemed not specific enough. And inversely, if the number of articles was too low, the search was deemed too restrictive. The "advanced search" option was used directly on the CAB Abstract website using Boolean string search. Inclusion and exclusion criteria were identified to only select relevant publications. For each PICO element, an inclusion criterion was attributed and described in the table below (Table 7).

The collected references were screened for relevance based on Title/abstract answering the questions: is the paper dealing with systemic PPB control measures? – does the paper report results of experiments *in vitro* or *in planta* either in controlled conditions or in field?, and based on full-text screening looking for "active principle" and conclusive proof of its efficacy at controlling the targeted systemic PPB.

The assessment of the reliability of the selected publications ans the quality of the full-text paper was evaluated looking for evidence in figures displayed in tabes and/or charts but also through meaningfull combinations of analytical methodologies.

The quality of a search was evaluated on different levels. Two approaches were used in this regard. First, Scimago was used to retrieve the h-index score associated with the journal, as well as the quartile in which it was found regarding its overall score. The h-index score and quartile can be consulted in the Zotero files. The second, complementary approach was by the combined expertise of the researchers working on this project.

Alternative or combined additional searches, using a snowball search strategy, have also been used to refine the search, for an additional re-check of the literature. All the results have been compiled in ENDnote files.

Once the relevant publications have been gathered, data could be extracted and summarized into a review. Extracted data are provided as an Excel file gathering the following fields: paper category (review or research), genus of the targeted PPB, targeted PPB (genus, species, subsp., pv.), pathogenic strains used in the research (when available), host plant (when *in planta* experiments were done), control strategy, control category, control method's nature, control functionalities, mode of action (MoA), target of the MoA (when known), "active principle", additional information, year of publication, DOI, Title, cited references (when review paper), H-index retrieved from Scimago, is the paper dealing with antibiotic use (following the definition previously suggested: antibiotics are defined as antimicrobial active substances used in human and/or veterinary health).

In order to ease the interpretation of the collected data either from the scientific or patent literature, a classification of the means used to control plant pathogenic bacteria developed in three main levels is suggested. Figure 1 illustrates the succession of these classification levels dispatched from top to bottom through control strategy, control category and nature of the control (detailed in Figure 1). Control strategy level distinguishes strategies focused on: plant resistance, PPB control or vector control. Control category identified five control approaches: breeding approaches, biocontrol agents, chemical substances either from organic and/or synthetic sources, farming practices and physical approaches.

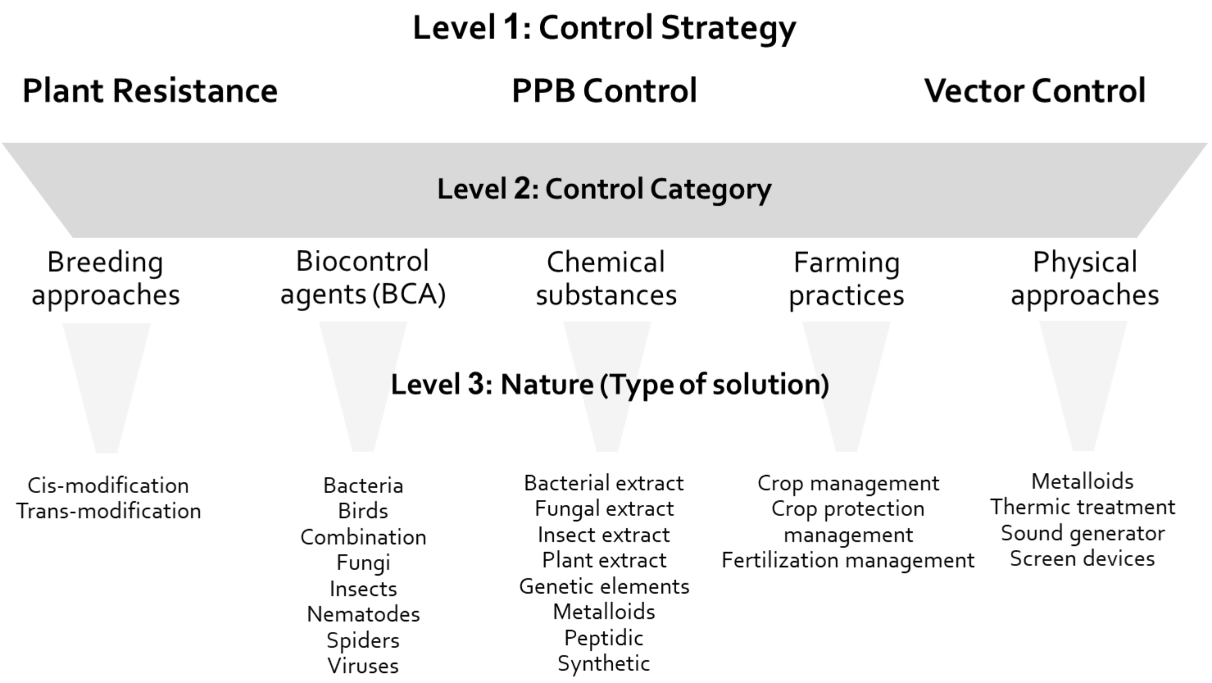

Figure 1: Illustration of the suggested classification of the means used to control plant pathogenic bacteria levels dispatched from top to bottom through control strategy, control category and nature of the control (detailed in Figure 2). Control strategy level distinguishes strategies focused on: plant resistance, ppb control or vector control. Control category identified five control approaches: breeding approaches, biocontrol agents, chemical substances either from organic and/or synthetic sources, farming practices and physical approaches.

The table hereunder (Table 7) contains detailed information about the different searches that were done for scientific publications according to the PICO-PECO model. The ‘C- comparator’ was considered as not relevant. If a comparative study was to be considered, the comparator should include antibiotics or well-known active principle with similar mode(s) of action.

Table 7: Detailed information on the search performed according to the PICO-PECO model through scientific literature.

Key elements/concepts	Inclusion Criteria	Comment
a) Are alternatives to antibiotics available in plant agriculture (Outcome) to control (Intervention) systemic Plant Pathogenic Bacteria (Population)?		
Scientific review **String search concept:** (**within abstract** Genus specie subspecie pathovar synonyms) **(Population) AND (within abstract** control biocontrol biological control protection management antimicrobial antagonis? elicit?) **(Intervention) AND (within keywords** Family (of the target PPB) Phytopathogenic bacteria plant-pathogenic bacteria phytopathogens plant pest pesticides and drugs pest insects biocontrol agents biological control organisms BCA endophyt? plant breeding and genetics host resistance and immunity genetically modified organisms GMO? phage bacteriophage integrated pest management IPM genetically modified plants genetically modified microorganisms control programms **(Outcome)** **String search #1:** (AB Brenneria quercina OR AB Brenneria salicis subsp. OR AB Brenneria salicis OR AB Brenneria) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Pectobacteriaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program) **String search #2:** (AB Candidatus Liberibacter subsp. OR AB Candidatus Liberibacter OR AB Candidatus Liberibacter americanus OR AB Candidatus Liberibacter asiaticus OR AB Candidatus Liberibacter solanacearum OR AB Candidatus)AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Phyllobacteriaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program)		

String search #3:
(AB Curtobacterium flaccumfaciens subsp. OR AB Curtobacterium flaccumfaciens OR AB Curtobacterium) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Microbacteriaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program)

String search #4:
(AB Ralstonia solanacearum subsp. OR AB Ralstonia solanacearum OR AB Pseudomonas solanacearum OR AB Burkholderia solanacearum OR AB Ralstonia pseudosolanacearum OR AB Pseudomonas pseudosolanacearum OR AB Pseudomonas syzygii OR AB Ralstonia) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Burkholderiaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program)

String search #5:
(AB Xanthomonas oryzae subsp. OR AB Xanthomonas oryzae OR AB Xanthomonas oryzae oryzicola OR AB Xanthomonas citri aurantifolii OR AB Xanthomonas citri citri OR AB Xanthomonas) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Xanthomonadaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program)

String search #6:
(AB Xylella fastidiosa subsp. OR AB Xylella fastidiosa OR AB Xylella) AND (AB control OR AB biological control OR AB Protection OR AB Management OR AB biocontrol) AND (SU Xanthomonadaceae OR SU Phytopathogenic bacteria OR SU plant-pathogenic bacteria OR SU phytopathogens OR SU plant pests OR SU pesticides and drugs OR SU pest insects OR SU biocontrol agents OR SU biological control organisms OR SU BCA OR SU plant breeding and genetics OR SU host resistance and immunity OR SU genetically modified organisms OR SU GMOs OR SU phage OR SU bacteriophage OR SU integrated pest management OR SU IPM OR SU genetically modified plants OR SU genetically modified microorganisms OR SU endophyt? OR AB antimicrobial OR AB antagonis? OR AB elicit? OR SU control program)

Intervention/Exposure	The publication is related to or mentions a way to control systemic plant pathogenic bacteria .	Prophylactic measures addressing genetic elements used for detection and/or identification of PPB such as primer pairs or specific amplification methodologies will be discarded.
Population	The publication focuses on systemic plant pathogenic bacteria .	/
Outcome	The publication addresses ways to control systemic plant pathogenic bacteria.	Publications addressing methodologies to control vectors, enhance in any way the resistance or tolerance of host plants, advising specific farming practices will also be considered relevant.
Comparator	Optional – If a comparative study, the comparator should be antibiotics or well-known active principle with similar mode(s) of action.	/

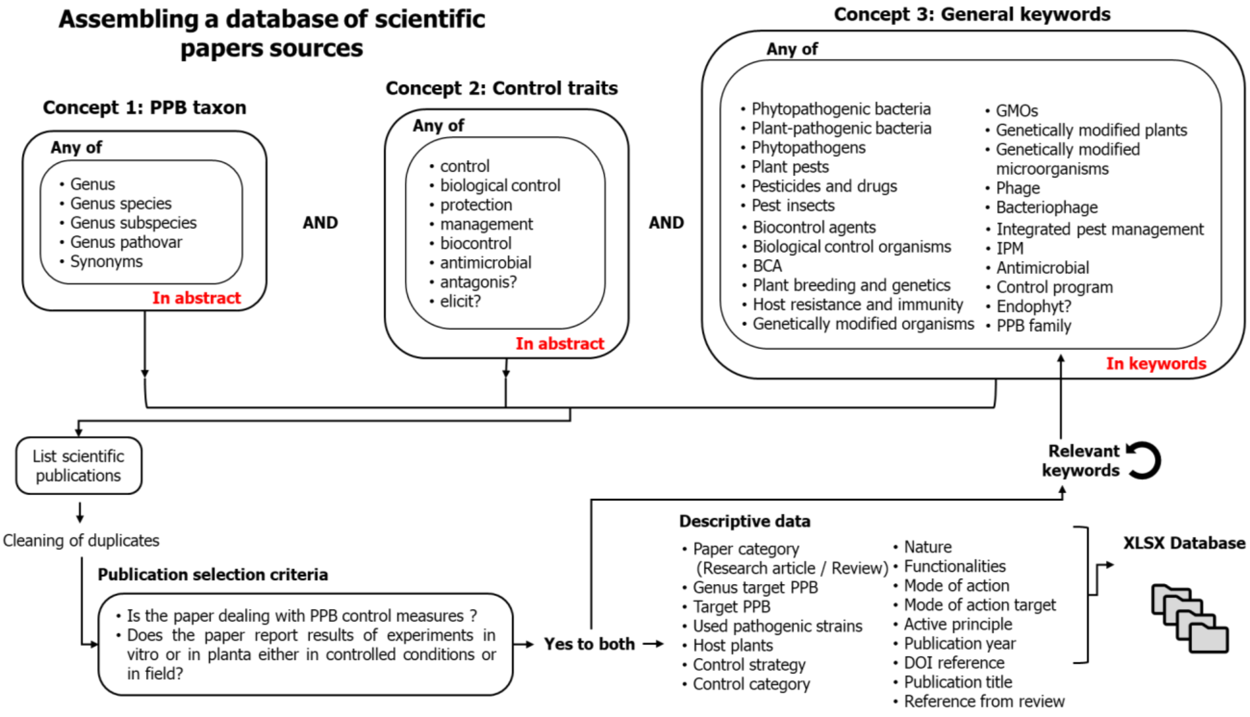

Figure 2: Graphical abstract illustrating the search methodology used to investigate scientific literature. Three concepts are connected using AND Boolean operator between each concept and

OR Boolean operator within. The first concept includes queries related to the PPB taxon, such as genus, species, subspecies, pathovar, and common synonyms for the disease denomination. The second concept includes terms related to disease control traits. The third concept includes general terms related to plant pathogen management, as well as the specific family to which the targeted PPB belongs. The first two search concepts focused on terms found in the abstract, while the third concept focused on queries found in keywords of publications.

2.1.3.2. Review of the technical and grey literature on the effectiveness and, when applicable, side effects of alternative and innovative treatments for the control (including prophylactic use) of systemic bacterial plant diseases

The search over technical and grey literature is organized following approaches used in Task 1.1. and described in 2.2.1.2., as reminder using key elements and search concepts identified to assess where antibiotics are used as control measure against plant pathogenic bacteria and therefore the alternatives also available. The search valorizes the outcome of the Task 1.1.: the list of website encompassing data coming from National Plant Protection Organization (NPPO) dedicated to plant protection products (PPP), established organizations, e.g. US EPA ((https://www.epa.gov/), US FDA (https ://www.fda.gov), EU pesticide database (https://ec.europa.eu/ food/plant/pesticides/eu-pesticides-database) or targeted databases like the FAOSTAT (http://www.fao.org/faostat/en/), the online pesticide or biopesticide manual (British Crop Production Council), will also be systematically consulted, based on the outcome of T1.1. Additionally, a collection of PPP labels dedicated to alternative or innovative treatments of systemic PPB will be made. An XLS data file is provided with the compiled information.

2.1.3.3. Collection of patent information on alternative and innovative treatments for the control (including prophylactic use) of systemic bacterial plant diseases

The review of the patent literature addressing PPB managing methods (excluding the use of antibiotics) followed a similar approach to the one used for scientific literature investigation building up from an adapted methodology using the PICO-PECO conceptual model (EFSA, 2010, Jaspers et al., 2018).

Patents issued for antibiotic's alternatives used as phytosanitary products to control plant pathogenic bacteria have been collected via EspaceNet (see appendix XX). Additional searches for collecting patent information for PPB control have been organized via known sources, like the European patent office (https://www.epo.org), the world intellectual property organization (www.wipo.int/patents/), patent scope or Google patent.

Boolean string search targeting alternatives to antibiotics in controlling systemic plant pathogenic bacteria (PPB) were used in advanced settings of EspaceNet web interface. As for scientific literature, the search was conducted separately for each targeted systemic PPB and relevant results were pooled afterwards.

To ensure transparency and minimize bias in the process, the adopted methodology can be described as a succession of five steps: (i) gathering of patents, (ii) discarding exact duplicates, (iii) assessing and selecting relevant patents, (iv) extracting the data, and (v) summarizing.

Figure 2 illustrates through a graphical abstract the search methodology used here. In short, two main concepts were connected using AND Boolean operator. The first concept includes terms related to disease control traits. This concept is divided into two main search query groups connected by an OR Boolean operator. One of which was subdivided into two subgroups connected by an AND Boolean operator associating terms like plant pathogen or pest with control traits such as suppression, management, control, etc. The second concept includes queries related to the PPB taxon divided into two subgroups connected through AND Boolean operators. The two subgroups gather on one hand the genus of the PPB OR the common single letter abbreviation of the genus AND the species OR subspecies OR pathovar. Using common synonyms for the disease denomination resulted in broader search that returned thousands of patents with a low rate of relevancy. The first concept related to control traits screened for terms found in all text fields, while the second concept linked to PPB taxon focused on queries found in patents' claims.

The relevancy of patents was assessed through analysis of their title, description and claims to answer the questions: is the patents' claims mention the targeted systemic PPB? – do the claims or description of the patent mention any control effect or efficacy of the patent object on the targeted PPB?

For each relevant patent, data were extracted and provided in an Excel file gathering the following fields: title, inventors, applicants, number of publications, country, earliest priority years, earliest priority date, IPC (International Patent Classification), CPC (Cooperative Patent Classification), publication datum, oldest publication datum, family number, control strategy, control category, control method's nature, control functionalities, mode of action (MoA), description, "active principle", additional information.

It's worth mentioning that some patents may have different publication numbers for the same object due to being filed in various geographical locations. These may be considered as duplicates but have been conserved in the final XLSX file.

The table hereunder (Table 8) contains detailed information about the different searches that were done according to the PICO-PECO model on patent literature. Figure 3 illustrates through a graphical abstract the search methodology used here.

Table 8: Detailed information on the searches performed according to the PICO-PECO model through patent literature.

Key elements/concepts	Inclusion Criteria	Comment
a) Are alternatives to antibiotics available in plant agriculture (Outcome) to control (Intervention) Systemic Plant Pathogenic Bacteria (Population)?		

Patent review

Concept #1: within all text field

[Any of (plant pathogen OR pest) AND any of (control OR suppression OR management OR resist? OR toleran?)]

OR any of [plant protection OR crop protection OR biocontrol OR biological control OR Antagonis? OR competit? OR Stimula? OR Defens? OR Defenc? OR Elicit? OR Avirul? OR Endophy? OR Resistan? OR Toleran? OR Breed? OR Cultivar? OR Gmo OR ogm]

Concept #2: only within claims or patent description

AND any of [Genus species OR G?species OR pathovar]

String search #1:

((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "brenneria quercina" OR claims all "brenneria salicis" OR (claims all "brenneria" AND claims any "salicis quercina") OR (claims all "B. quercina" OR claims all "B.quercina" OR claims all "B quercina" OR claims all "Bquercina") OR (claims all "B. salicis" AND claims all "B.salicis" AND claims all "B salicis" AND claims all "Bsalicis"))

String search #2:

((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Candidatus Liberibacter africanus" OR claims all "Candidatus Liberibacter americanus" OR claims all "Candidatus Liberibacter asiaticus" OR (claims all "Candidatus Liberibacter" AND claims any "africanus americanus asiaticus solanacearum") OR (claims all "C. Liberibacter" AND claims any "africanus americanus asiaticus solanacearum") OR claims all "Candidatus Liberibacter solanacearum")

String search #3:

((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Candidatus Phytoplasma"

AND claims any "asteris australiense fragariae mali pruni prunorum pyri rubi americanum phoenicium ulmi")

String search #4:
((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Clavibacter sepedonicus" OR claims all "Clavibacter michiganensis" OR (claims all "C. sepedonicus" OR claims all "C sepedonicus") OR (claims all "C. michiganensis" OR claims all "C.michiganensis") OR (claims all "Clavibacter michiganensis" AND claims any "insidiosus michiganensis") OR (claims all "C. michiganensis" AND claims any "insidiosus michiganensis"))

String search #5:
((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Curtobacterium flaccumfaciens" OR claims all "Curtobacterium flaccumfaciens betae" OR (claims all "C. flaccumfaciens" OR claims all "C flaccumfaciens") OR (claims all "C. flaccumfaciens betae" AND claims all "C.flaccumfaciens betae"))

String search #6:
((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Ralstonia pseudosolanacearum" OR claims all "Ralstonia solanacearum" OR (claims all "Ralstonia syzygii" AND claims any "celebesensis indonesiensis"))

String search #7:
((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul endophy resistan toleran breed cultivar gmo ogm") AND (claims all "Xanthomonas oryzae oryzae" OR claims all "Xanthomonas oryzae oryzicola" OR claims all "Xanthomonas citri aurantifolii" OR claims all "Xanthomonas citri citri")

String search #8:
((nftxt all "plant pathogen" AND nftxt any "control suppression management resist toleran") OR (nftxt all "plant disease" AND nftxt any "control suppression management resist toleran") OR (nftxt all "pest" AND nftxt any "control suppression management resist toleran") OR nftxt all "plant protection" OR nftxt all "crop protection" OR nftxt all "biocontrol" OR nftxt all "biological control" OR nftxt any "antagonis competit stimula defens defenc elicit avirul

endophy resistan toleran breed cultivar gmo ogm") AND (claims all "xylella fastidiosa" OR claims all "xylella fastidiosa multiplex" OR claims all "x fastiodiosa" OR claims all "x. fastidiosa" OR claims all "xylella fastidiosa" OR claims all "xfastidiosa" OR claims all "x.fastidiosa")

Intervention/Exposure	The patent is related to or mentions any way to control systemic plant pathogenic bacteria.	Prophylactic measures addressing genetic elements used for detection and/or identification of PPB such as primer pairs or specific amplification methodologies will be discarded.
Population	The patent's claims mention systemic plant pathogenic bacteria.	/
Outcome	The patent addresses ways to control systemic plant pathogenic bacteria in patents' claims and/or description.	Patent addressing methodologies to control vectors, enhance in any way the resistance or tolerance of host plants, advising specific farming practices will also be considered relevant.

Comparator	Optional – If a comparative study, the comparator should be antibiotics or well-known active principle with similar mode(s) of action.	/

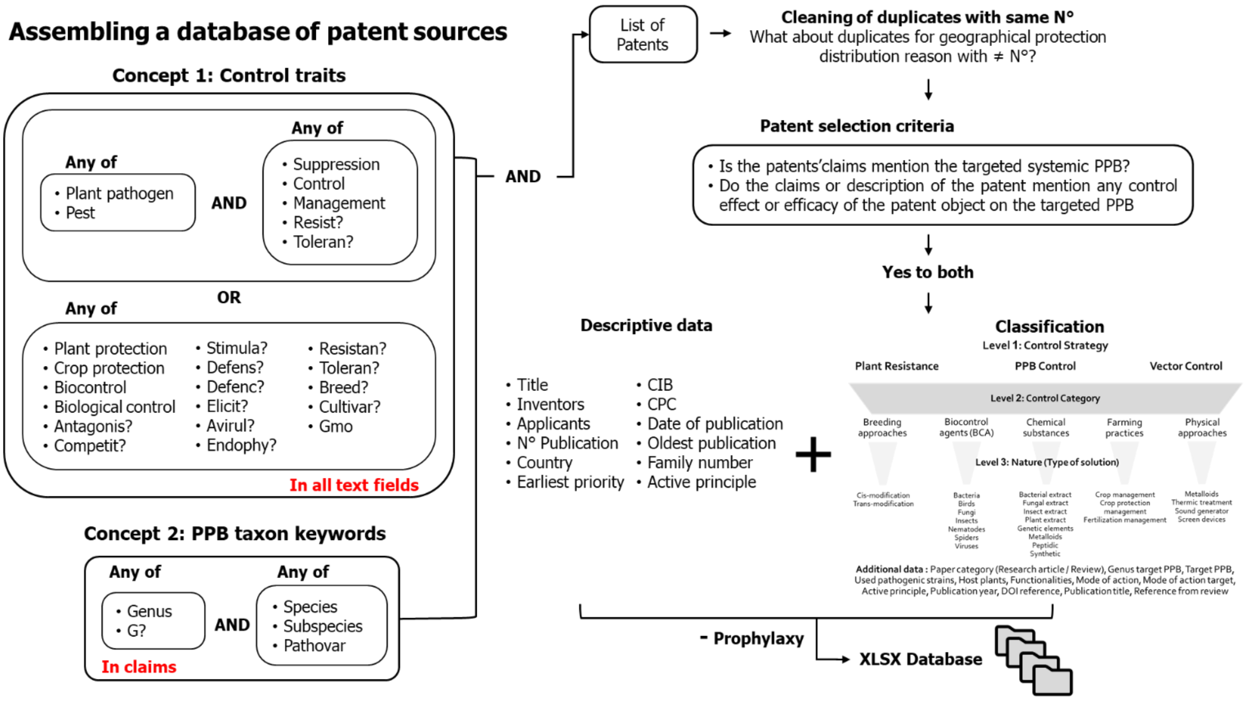

Figure 3: Graphical abstract of the search methodology used in this study to investigate patent literature. Two main concepts were connected using AND Boolean operator. The first concept includes terms related to disease control traits. This concept is divided into two main search query groups connected by an OR Boolean operator. One of which was subdivided into two subgroups connected by an AND Boolean operator associating terms like plant pathogen or pest with control traits such as suppression, management, control, etc. The second concept includes queries related to the PPB taxon divided into two subgroups connected through AND Boolean operator. The two subgroups gather on one hand the genus of the PPB OR the common single letter abbreviation of the genus AND the species OR subspecies OR pathovar. Using common synonyms for the disease denomination resulted in broader search that returned thousands of patents with a low rate of relevancy. The first concept related to control traits screened for terms found in all text fields, while the second concept linked to PPB taxon focused on queries found in patents' claims.

2.1.4. Work Package 4 – Communication and dissemination of project results

The current work collected the first time systematically worldwide data on the use of antibiotics in plant protection and antibiotic resistance of plant pathogenic bacteria. Additionally, information was collected on alternatives to the use of antibiotics. This information is of high relevance and of interest for risk managers, risk assessors and researchers.

The aims of the communication activities were the following:

1. Raising awareness and making the collected information available to relevant stakeholders, risk managers, risk assessors at national, European and international level as well as to researchers in the field of control of plant pathogenic bacteria.
2. Establishing co-operation among institutions in the relevant field of food safety and plant protection such as FAO and to initiate a systematic collection of data on the use of antibiotics in plant protection in the future.
3. Facilitate research activities in the field of alternatives to antibiotic use in plant protection.

To report on the progress of the project and to seek feedback and input from EFSA three different meetings were organised: a kick-off meeting at the beginning, a midterm meeting and a final meeting. Online meetings organized on a bi-montly basis have also been scheduled over the project duration for coordination purposes.

The following communication activities were conducted:

- A meeting in connection with the EFSA ONE conference organized in Brussels in June 2022 and a satellite event dedicated to informing on the project results and establishing co-operation with researchers and representatives of European and Member States organisations was set up and organized in this frame.

- Convention on Phytosanitory Meeting held in March 2022, with the proposal of a concept note.

- Additional meetings have also been organized the Food and Agriculture Organization (FAO), to anticipate possible cooperation between EFSA and FAO on antimicrobial resistance and use, to prepare datasharing with the FAO platform.

- IPPC-CPM parallel session on antibiotic use and resistance in Plant Health, held in Rome in March 2023.
  A concept note was prepared for presenting the project at the International Plant Protection Convention. Presentations on the project have been proposed, one dealing with the use of antibiotic as plant protection products and alternative strategies, another one on resistance to antibiotics in plant pathogenic bacteria and a general overview of antimicrobial resistance activities at the European Food Safety Authority.

- A session on antimicrobial resistance within the International Congress of Plant Pathology, held in Lyon (France) in August 2023.

- The project outcome will also be published in scientific journals. The outcome of work package 1 and 2 has been submitted and accepted for publication in Frontiers for Microbiology in June 2023. Publication of WP3 is also foreseen as a publication series in a scientific journal or as a book on alternative control measures against plant pathogenic bacteria.

- A video highlighting the project outcomes was produced, as well as a graphical abstract, as a support for communication.

- Finally, a dedicated website page compiling key information and outcome of the project, in connection with the EFSA AMR webpage is organized. The project and related activities have been highlighted on social media like Twitter.

3. Assessment/Results

Special attention has been given to the use of different terms linked to the definition of antibiotic, after clarification with EFSA, like antimicrobials, antibacterial, bactericide, biocide, nonantibiotic antiseptic, and additional terms.

Antibiotics are commonly defined as a type of antimicrobial substance produced by a microorganism, and able, in dilute solution, to inhibit or kill another microorganism (Merriam Webster's English dictionary, 2023). EFSA defines antimicrobials as substances used to kill microorganisms or to stop them from growing and multiplying (EFSA, 2023). Thomashow et al. (1997) define antibiotics as a chemically heterogeneous group of organic, low-molecular-weight compounds produced by microorganisms that are deleterious to the growth or metabolic activities of other microorganisms. Miller et al. (2022) define antibiotics in a more restrictive way (i.e. antibiotics are antimicrobials with a spectrum restricted to bacteria), while others restrict antibiotics to those used as medicines.

In the field of plant protection products or pesticides, the term antibiotic is not widely used. Commonly, the generic term pesticide includes, of course, the fungicides with which currently antibiotics used as plant protection products are often grouped. The term bactericide also is not commonly used, even for substances widely commercialized as plant protection products with a well-known effect on PPB like copper-based compounds.

To remain as exhaustive as possible, the report here will stick to the general definition (a substance produced by a microorganism used to inhibit or kill another microorganism). Nevertheless, a distinction will be made between substances used only in agriculture as plant protection products, from those commonly also used as medicine in both animal and human health.

Secondly, an important point when looking for information on the use of antibiotics as plant protection products is the constantly evolving legislation on pesticide, worldwide. A report on the use of e.g. streptomycin in the nineties is maybe not anymore relevant, since several restriction measures have been taken following to address the issue of antimicrobial resistance.

- **Collection and review of data and information on the use of antibiotics for the control of plant pathogenic bacteria**
    - Data from scientific literature

    Table 9 summarizes the use of antibiotics as plant protection products, as reported in the scientific literature. As already mentioned, care should be taken on the fact that a report at a given time does not mean the antibiotic is still authorized for use as plant protection products now. Also, often antibiotics are reported to be used in the frame of a scientific research addressing a wider issue than just reporting antibiotic use. To the best of our knowledge, antibiotic use on a global scale has been reported in different reviews (Vidaver, 2002, McManus et al., 2002, Sundin and Wang, 2018, Taylor and Reeder, 2020, Miller et al., 2022). Additionally, FERA published a detailed report on the topic (Haynes et al., 2020).

The search highlights the use of antibiotics in 20 different countries. Antibiotics also used in human of animal health like gentamicin (5), oxytetracycline or tetracycline (5), oxolinic acid (1) or streptomycin (13) are reported, to target different plant bacterial diseases like fireblight of pear (*E. amylovora*), rice blight (*Xanthomonas oryzae* pv. *oryzae*), *Ralstonia solanacearum*, Huanglongbing or *P. syringae* pv. *actinidia*. Additionally, antibiotics only used as plant protection products, and sometimes also used because of e.g. a fungicidal activity, are also reported. Listed in this category are the kasugamycin (4), the validamycin sometimes also denominated jingganmycin (1), or zhongshengmycin (1). Great care should be taken about these data, since the situation about the type and number of antibiotics authorized is constantly evolving, and data published earlier are maybe not relevant anymore, despite their interest to know where antibiotics have been authorized in the past, which mostly relates to *E. amylovora*, like Austria, Hungary or Switzerland.

The scientific literature also allows finding studies looking at antibiotic molecules effective for use as potential control measures against devastating bacterial diseases, studies usually testing a wider number of antibiotics, like the one of Bleve et al. (2018), Deep et al., (2020), Zhao et al. (2015).

A striking point is the almost absence of surveys or search for use, despite indication of use out of the legal framework, except the study by Chanvatik et al. (2019) which highlights the use of antibiotics like ampicillin, amoxicillin, penicillin (all antibiotics destined for medical use).

Table 9: Some use of antibiotics as reported in the scientific literature (this table was adapted and published in Verhaegen et al., 2023).

Country	Antibiotic	Plant bacteria	Reference
Brazil	Kasugamycin	*Pseudomonas syringae* pv. *garcae*	Barbosa et al., 2017
Canada	Kasugamycin	*Erwinia amylovora*	Sundin and Wang, 2018
	Streptomycin	*E. amylovora*	Stockwell and Duffy, 2012
China	Bismerthiazole	*Xanthomonas oryzae* pv. *oryzae*	Yang et al., 2021
	Zhongshengmycin	*X. oryzae* pv. *oryzae*	Wang et al., 2021b
	Validamycin	*X. oryzae* pv. *oryzae*	Bian et al., 2020
	Streptomycin	*Clavibacter michiganensis*	Lyu et al., 2019
Chile	Streptomycin	*C. michiganensis*	Valenzuela et al., 2019
	Chile	*E. amylovora*	Sundin and Wang, 2018
Chile	Gentamicin	*C. michiganensis*	Vidaver, 2002
Costa Rica	Gentamicin, Oxytetracyline	Iceberg lettuce	Rodriguez et al., 2006
	Gentamicin	*Pectobacterium carotovorum*	Vidaver, 2002
El Salvador	Gentamicin	*P. carotovorum*	Vidaver, 2002
Honduras	Gentamicin	*P. carotovorum*	Vidaver, 2002
Guatemala	Gentamicin	*P. carotovorum*	Vidaver, 2002
Hungary	Streptomycin	*E. amylovora*	Németh, 2004
India	Tetracycline	*Phytoplasma*	Rao et al., 2021
Israel	Oxolinic acid	*E. amylovora*	Dafny-Yelin et al., 2020
	Streptomycin, Oxolinic acid	*E. amylovora*	Stockwell and Duffy, 2012
Japan	Kasugamycin	*X. oryzae* pv. *oryzae*	Sundin and Wang, 2018
		Burkholderia glumae	Yoshii et al., 2012
		Acidovorax avenae	Yoshii et al., 2012
Mexico	Gentamicin	*E. amylovora*	Sundin and Wang, 2018
	Streptomycin	*E. amylovora*	Stockwell and Duffy, 2012
	Gentamicin	*Pectobacterium carotovorum,*	Vidaver, 2002
	Oxytetracycline, Gentamicin	Various bacterial diseases	Stockwell and Duffy, 2012
New Zealand	Streptomycin	*P. syringae* pv. *actinidiae*	Cameron and Sapojni, 2014
		E. amylovora	Stockwell and Duffy, 2012
South Korea	Streptomycin	*P. syringae* pv. *actinidae*	Lee et al., 2020
Switzerland	Streptomycin	*E. amylovora*	Walsh et al., 2014
Thailand	Ampicillin, amoxicillin	Huanglongbing	Chanvatik et al., 2019
USA	Kasugamycin	*E. amylovora*	Sundin and Wang, 2018
	Oxytetracycline Streptomycin	Huanglongbing	Hijaz et al., 2021
			Kiliny et al., 2020
			Vincent et al., 2019
			McVay et al., 2019
USA	Streptomycin	*E. amylovora*	Stockwell and Duffy, 2012
Global	Streptomycin, Tetracycline,	Various	Taylor and Reeder, 2020
Global	Streptomycin, Oxytetracycline	Various	Sundin and Wang, 2018
Global	Streptomycin, Oxytetracycline	Various	McManus et al., 2002
Global	Streptomycin, Oxytetracycline	Various	Miller et al., 2022

Table 10 summarizes the major crops and bacterial diseases for which antibiotics are used as plant protection products. The current reported use of antibiotics to control PPB usually focus on major epidemics or crops, hiding sometimes a multitude of smaller scale usage commonly much less reported, yet possibly not negligible in terms of human exposure, e.g. use in horticulture, on vegetables,…

Diseases listed in table 9 are bacterial diseases of rice (bacterial leaf blight, leaf streak, panicle blight, or sheath rot), pome and stone fruit (Fire blight, bacterial blast and spot), citrus (greening, canker), tomato (wilt, spot, canker), potato (black leg, rot, wilt), kiwi canker and halo blight of beans.

Table 10: Major bacterial diseases targeted by antibiotic use for crop protection.

Host	Disease	Plant pathogenic bacteria
Rice	Bacterial leaf blight	*Xanthomonas oryzae* pv. *oryzae*
	Bacterial leaf streak	*Xanthomonas oryzae* pv. *oryzicola*
	Bacterial panicle blight	*Burkholderia glumae*
	Bacterial sheath rot	*Pseudomonas fuscovaginae*
Pome fruit	Fire blight	*Erwinia amylovora*
Citrus	Citrus greening	*Candidatus Liberibacter* sp.
	Citrus canker	*Xanthomonas axonopodis* pv. *citri*
Tomato	Bacterial wilt	*Ralstonia solanacearum*
	Bacterial canker	*Clavibacter michiganense* subsp. *michiganense*
	Bacterial spot	*Xanthomonas vesicatoria*
	Bacterial speck	*P. syringae* pv. *tomato*
Potato	Black leg, soft rot	*Pectobacterium* sp.
	Bacterial wilt	*R. solanacearum*
	Bacterial rot	*Clavibacter michiganense* subsp. *sepedonicus*
Stone fruit	Bacterial spot	*Xanthomonas arboricola* pv. *pruni*
	Bacterial blast	*P. syringae*
Kiwi fruit	Kiwi canker	*P. syringae* pv. *actinidiae*
Bean	Halo blight	*P. syringae* pv. *phaseolicola*, *X. phaseoli* pv. *phaseoli*

Table 11 shows the type(s) of application possible for different antibiotics used in plant agriculture. Most of the time, antibiotics are used in foliar application but oxytetracycline is also used in injection in tree trunks. Some searches study the efficacy of injection of the other antibiotics and the results are included in the table. If foliar application is efficient, producers prefer to use this method because it is easier for the maintenance of large areas. However, some crops do not allow foliar penetration of the product. Then, often the use of oxytetracycline via injection is favored, especially for systemic bacterial infections.

Table 11: Type(s) of application for different antibiotics used in plant agriculture.

	Foliar application	Injection	References
Streptomycin	Yes	Successfully tested but not usually used	(Ascunce et al., 2019; Hu et al., 2018; Li et al., 2021; Stockwell and Duffy, 2012)
Gentamicin	Yes	No	(Stockwell and Duffy, 2012)
Kasugamycin	Yes	Tested but not approved	(Aćimović et al., 2015)
Oxytetracycline	Yes	Yes	(Miller et al., 2022; Stockwell and Duffy, 2012; Taylor and Reeder, 2020)
Oxolinic acid	Yes	Successfully tested but not usually used	(Kwon et al., 2010; Stockwell and Duffy, 2012; Taylor and Reeder, 2020)
Validamycin	Yes	Tested but not usually used (low to moderate action)	(Ishikawa et al., 2005; Jeon et al., 2022; Zhang et al., 2015)

- Data from grey literature

A grey literature search has been conducted with a focus on National Plant Protection Organization (NPPO) dedicated to plant protection products (PPPs) or via a network of scientists, via a systematic questionnaire (Annex A). Established organizations (e.g. US EPA-Environmental Protection Agency, US FDA (https://www.fda.gov), the EU pesticide database (https://ec.europa.eu/food/ plant/pesticides/eu-pesticides-database) or targeted databases like the FAOSTAT (http://www.fao.org/faostat/en/), the online pesticide or biopesticide manual (British Crop Production Council) have also been systematically consulted, based on the outcome of T1.1. More than 100 countries have thus been examined, for the use of antibiotics as plant protection products. The type and level of information publicly available vary greatly from one country to another. Nevertheless, when an official list of plant protection products exists, it is usually provided and accessible via the web, despite being often accessible via a web page published in the country official language(s).

By organizing the search via such a grey literature search, it is possible to obtain additional and more recent information on the current use of antibiotics as plant protection products.

Table 12 is summarizing the information collected, for countries using antibiotics like gentamicin (15), kasugamycin (29), oxolinic acid (12), oxytetracycline (20), streptomycin (25), tetracycline (7), validamycin (11), with up to 39 countries allowing at least the use of one antibiotic as plant protection products. Additionally, use of ningnangmycin is reported in China, and of zhongshengmycin in China, Nicaragua and Vietnam. In the countries screened for antibiotic use as PPP, 39 are recorded as users, 57 as non-users. For 95 countries, we have not been able to identify an authority or a source to assess the possible use of antibiotics as PPP. These data should be used with caution, knowing the scarcity or imprecision of the information available, the need to cross-check the information collected this way and the possible changes in the legislation on plant protection products, a rapidly evolving domain.

Only a very few countries provide data on the quantity of antibiotics used as plant protection products (India, New Zealand, the USA). It remains an issue to assess quantitatively the use of antibiotics as plant protection products, despite an evident need to assess their potential impact in relation to the use of antibiotics in both animal and human health.

This first search step allows then for a second approach of the commercial products available, to find their commercial names and the companies marketing such products. This approach also allows understanding in more detail the uses of such antibiotic plant protection products, in terms of crops and bacterial disease to control. Such a search is tedious since it has to be conducted often in the country language, yet allows compiling useful information highlighting sometimes a wider use than the one expected when consulting information publicly available in English. Examples of results for this second approach are provided in Table 13.

• Collection and review of data and information on the resistance to antibiotics in plant pathogenic bacteria

Five antibiotics are most often reported to be used in plant agriculture against PPB: streptomycin, oxytetracycline, kasugamycin, oxolinic acid (OA) and gentamicin. Resistant field isolates have been identified for some of these antibiotics. Among them, only kasugamycin is not used in human nor veterinary medicine (Aarestrup et al., 2008; Kumar et al., 2005; McGhee and Sundin, 2011; McManus, 2014; World Health Organization, 2019). Other antibiotics are used on plants (see previous Section) such as ningnanmycin, validamycin, zhongshengmycin, etc. No bacterial field isolate resistant to these antibiotics is known. Relevant information about resistance cases reports and description of the genetic mechanisms involved in resistance is presented in the following Section, when known.

○ Streptomycin resistance

Streptomycin is an aminoglycoside antibiotic used in plant agriculture against various PPB since the 1950s. The most common target of streptomycin is *E. amylovora*, the causal agent of fire blight, which infects apple and pear trees, targeting leaves, flowers and shoots. Streptomycin is usually sprayed during bloom (McManus et al., 2002; Sundin and Wang, 2018).

Several mechanisms can be responsible for streptomycin resistance in PPB. The two main mechanisms are (i) a point mutation of the *rpsL* gene and (ii) the acquisition of the *strA*-*strB* or *aadA* genes (see following Section).

Table 12: Countries where antibiotics are reported as authorized or under use.

Gentamicin	Kasugamycin	Oxolinic acid	Oxytetracycline	Streptomycin	Tetracycline	Validamycin
Argentina	Argentina	Bolivia	Argentina	Argentina	Bangladesh	Cambodia
Belize	Bangladesh	Cambodia	Belize	Bangladesh	Costa Rica	Colombia
Chile	Bolivia	Colombia	Bolivia	Belize	India	Costa Rica
Colombia	Brazil	Ecuador	Chile	Bolivia	Nepal	India
Costa Rica	Cambodia	Egypt	Colombia	Canada	Panama	Japan
Ecuador	Canada	Israel	Costa Rica	Chile	Thailand	Nepal
Guatemala	Chile	Japan	Dominican	Costa Rica	USA	Pakistan
Honduras	China	Nicaragua	Ecuador	Dominican		Panama
Mexico	Colombia	Panama	El Salvador	Ecuador		Peru
NewZealand	Costa Rica	Paraguay	Guatemala	Egypt		South Korea
Nicaragua	Ecuador	Peru	Honduras	El Salvador		Vietnam
Panama	Egypt	South Korea	Japan	Guatemala		
Paraguay	El Salvador	Vietnam	Mexico	Nicaragua		
Peru	Guatemala		New Zealand	Honduras		
Vietnam	India		Nicaragua	India		
	Japan		Panama	Japan		
	Malaysia		Paraguay	Mexico		
	Mexico		Peru	Nepal		
	Mozambique		Philippines	New		
	Nepal		South Korea	Panama		
	New Zealand		USA	Paraguay		
	Nicaragua		Vietnam	South		
	Panama			Thailand		
	Paraguay			USA		
	Peru			Vietnam		
	South Korea					
	USA					
	Vietnam					

In North America, streptomycin resistant *E. amylovora* strains have emerged in various states. In the past, streptomycin usage was not limited to the bloom period, which might have influenced the development of resistant strains. The first report of streptomycin resistant *E. amylovora* was in California, in 1971, followed by reports in Oregon and in Washington in 1972 (Chiou and Jones, 1991; Coyier and Covey, 1975; Loper et al., 1991; Miller and Schroth, 1972). Later, resistance was also reported in the eastern United States, in Michigan in 1990, in New York in 2002, and later again in the western USA in Utah in 2006 (Nischwitz and Dhiman, 2013).

Table 13: Commercial names of antibiotic used as plant protection products, company name (under parentheses) and antibiotic name (mostly sourced out of the Pesticide manual database).

Commercial name	Company	Antibiotic
Agrept	(Meiji Seika)	Streptomycin
Agri-Mycin	(Nufarm America)	Streptomycin
Amunda	(Farm Hannong)	Validamycin
Antisuper	(Agriviet)	Oxytetracycline
AS-50	(Nufarm America)	Streptomycin
Asana	(EcoFarm)	Kasugamycin
Atackin	(Nippon Soda)	Streptomycin
Avalon	(EcoFarm)	Gentamicin
Bac-Master	(Amvac)	Streptomycin
Banking	(EcoFarm)	Oxytetracycline
Biomycin	(Biostadt)	Kasugamycin
Blamycin	(Farm Hannong)	Streptomycin
Biovacare	(Toba)	Validamycin
Captivan	(EcoFarm)	Oxolinic acid
Citimycin	(EcoFarm)	Kasugamycin
Cuprimicin 500	(Adama Mexico)	Mixture copper sulfate Oxytetracycline hydrochloride and Streptomycin
Cuprimycin 17	(Adama Mexico)	Streptomycin
Cuprimycin 100	(Adama Mexico)	Streptomycin sesquisulfate, Oxytetracycline
Cuprimicina agricola	(Adama Mexico)	Oxytetracycline
Damycine	(EcoFarm)	Validamycin
Firewall	(UPL USA)	Streptomycin
Flame out	(UPL USA)	Oxytetracycline
Haifangmeisu	(EcoFarm)	Validamycin
Kasu B	(Dhanuka)	Kasugamycin
Javidacin	(EcoFarm)	Validamycin
Kasugamin	(Dong Bang)	Kasugamycin
Kasumin	(Hokko)(EcoFarm)	Kasugamycin
Kasumin-Bordeaux	(Hokko)	Kasugamycin
Kasurabcide	(Hokko)	Kasugamycin
Kasurabu-Trebon	(Hokko)	Kasugamycin
Kasurabu-validatrebon	(Hokko)	Validamycin+phtalide+etofenprox+ Kasugamycin hydrochloride hydrate
Longantivo	(EcoFarm)	Oxolinic acid
Mycoshield	(Nufarm Americas)	Oxytetracycline
Kasugamin	(Dong Ban)	Kasugamycin
Kasumin	(Hokko)	Kasugamycin
Kasuran	(CPC)	Kasugamycin
Lusatex	(EcoFarm)	Ningnanmycin
Mycojet	(Mauget)	Oxytetracycline
Mepatar	(Mauget)	Oxytetracycline
Ningnanmycin	(Zheijiang Rayfull Chemicals Ltd)	Ningnammycin
Oxycin	(EcoFarm)	Streptomycin
Plantomycin	(Aries)	Streptomycin
Rhizocin	(Sumimoto Chemical)	Validamycin
Riazor	(EcoFarm)	Gentamicin
Rorai	(Ecofarm)	Sreptomycin
Starner	(Sumimoto Chemical)	Oxolinic acid
Sheatmar	(Dhanuka)	Validamycin
Streptrol	(Nufarm America)	Streptomycin
Terramycin 17		Calcium oxytetracycline

Vali TSC 5SL	(Agriviet)	Validamycin
V-3	(Krishi rasayan)	Validamycin
Vacony	(EcoFarm)	Validamycin
Validamycin	(Zheijiang Rayfull Chemicals Ltd)	Validamycin
Vicilin	(Ecofarm)	Sterptomycin
Vivadami	(Vipesco)	Validamycin

The resistant strains initially identified on the West Coast (California, Oregon, Washington) were all *rpsL* mutants. A decline in resistant strains was then observed, and a shift in the dominant resistant mechanism occurred, with most of the resistant strains now containing the *strA-strB* genes. In California, streptomycin resistance declined from a very high incidence in 2006-2007 to very low in 2013-2014. The majority of resistant strains were moderately resistant and carried the Tn*5393*a transposon with the *strAB* genes, while the rest of the resistant strains were highly resistant and carried the *rpsL* mutation (Förster et al., 2015). In Michigan, the resistance was mostly caused by the presence of *strAB* (McManus et al., 2002) but also by an uncharacterized mechanism, suggesting another possible resistance mechanism (McManus and Jones, 1994). In New York, streptomycin resistant strains were identified in 2002 and eradication efforts were undertaken soon after. Streptomycin resistant strains were not detected in 2004-2006 time period, but were isolated again later in 2011-2014 (Tancos et al., 2016).

Outside the United States, other countries have reported streptomycin resistant strains of *E. amylovora* (Table 31). In 1988, streptomycin resistant strains were identified in Egypt (El-Goorani et al., 1989; El-Goorani and El-Kasheir, 1989). They reported high levels of streptomycin resistance and suggested it might be mediated by the *rpsL* mutation, but the resistance mechanism involved was not characterized. In Chihuahua, Mexico, strains carrying the *rpsL* mutation were also reported (de León Door et al., 2013). In this study, streptomycin resistant strains that did not carry the *rpsL* mutation, nor the *strAB* genes, nor the *aadA* gene were identified. This suggests the existence of another unknown streptomycin resistance mechanism, as already previously mentioned. In Syria, a study of 75 strains revealed three strains that were streptomycin-resistant (Al-Daoude et al., 2009). The mechanism involved was not investigated by the authors. Resistant *E. amylovora* were also discovered in New Zealand (Chiou and Jones, 1995a). In Canada, there have been reports of streptomycin resistance in Québec, where *rpsL* mutants were detected (Laforest et al., 2019), and in British Columbia (Sholberg et al., 2001).

Streptomycin resistance genes have also been reported in phytopathogenic species other than *E. amylovora* (Table 31). Several cases of resistant strain of *P. syringae* have been observed across the globe. In 1977, streptomycin resistant strains were retrieved in peach orchards in New Zealand where streptomycin had been applied (Young, 1977). Strains from 1992 to 1993 and 1982 to 1983 were found to be resistant in Oregon (Scheck et al., 1996). Streptomycin resistant strains of *P. syringae* pv. *syringae* were also isolated in Oklahoma and Washington, and streptomycin resistant strains of *P. syringae* pv. *papulans* in Michigan and New York. In Japan and South Korea, streptomycin resistant strains of *P. syringae* pv. *syringae*, *P. syringae* pv. *actinidiae, P. syringae* pv. *tabaci* and *P. marginalis* were identified (Han et al., 2004; Lee et al., 2021, 2020). Additional cases are reported in Table 31.

Several streptomycin resistant *Xanthomonas* species have also been observed (Table 31). In South Korea, *Xanthomonas smithii* subsp. *citri*, which causes citrus canker, resistant strains were identified in citrus orchards in 2003 and 2004 (Hyun et al., 2012). The number of resistant strains correlated positively with the number of sprays in this study. In China, resistant strains of *X. oryzae* pv. *oryzae* were described (Xu et al., 2013, 2010). Cases of streptomycin resistant *Xanthomonas campestris* pv. *vesicatoria* were reported from the USA, Argentina, Taiwan, Brazil and Tonga (Minsavage et al., 1990; Sundin and Bender, 1995). Other cases are reported in Table 31.

Genetics

i) *rpsL*, *aadA* and *strA-strB* genes

The *rpsL* gene encodes the ribosomal protein S12. A high level of resistance is conferred by a point mutation at codon 43 (changing a lysine to an arginine, or rarely a lysine to threonine or lysine to asparagine), which renders the ribosome immune to streptomycin by preventing the binding of streptomycin to ribosome. Another, less common, point mutation in *rpsL* at codon 88 (lysine to arginine) has also been described conferring streptomycin resistance. These point mutations have been observed in PPB such as *E. amylovora* or *C. michiganensis* subsp. *michiganensis* or *in vitro* in *Xanthomonas oryzae* pv. *oryzicola* or *Erwinia carotovora*, now named *Pectobacterium carotovorum* (Barnard et al., 2010; Chiou and Jones, 1995a; Zhang et al., 2011, Valenzuela et al., 2019; Escursell et al., 2021). One single publication reported a point mutation at codon 128 (lysine to arginine) in *C. michiganensis* (Lyu et al., 2019).

Other genetic determinants known to be responsible for streptomycin resistance in PPB are the *aadA1* and *aadA2* genes. They both also confer spectinomycin resistance. *aadA1* was identified in *X. oryzae pv. oryzae* whereas *aadA2* was found in a *Pseudomonas* isolated from an apple orchard in Michigan (Xu et al., 2013) (Schnabel and Jones, 1999).

The *strA-strB* pair of genes confers moderate to high levels of resistance (depending on factors such as the presence of an insertion sequence in the transposon) (Förster et al., 2015). The strA and strB enzymes function as phosphotransferases that modify streptomycin to a non-toxic form. They were identified in *E. amylovora* on pEA8.7 in California, which is very similar or identical to the broad-host-range plasmid RSF1010. The latter is a non-conjugative small plasmid that is involved in streptomycin-resistant infections in humans (Palmer et al., 1997). The main vector of *strA-strB* genes is Tn*5393*. *strAB* genes are frequently associated with streptomycin resistant infections in humans but are also common in human commensal bacteria, probably as a consequence of the use of streptomycin in healthcare contexts (Chiou and Jones, 1993a; Sundin and Bender, 1995; Förster et al., 2015). While they are commonly found on large conjugative plasmids in PPB, they are usually found on small plasmids such as RSF1010 in human pathogens (Förster et al., 2015).

ii) Tn*5393* and its highly similar variants

The Tn*5393* transposon was initially discovered in *E. amylovora*, carried by the 34-kb long pEa34 conjugative plasmid (Chiou and Jones, 1991; Chiou and Jones, 1993a). This 6.7-kb transposon belongs to the Tn*3* family. It encodes a putative transposase (TnpA) and resolvase (TnpR), followed by a putative recombination site (res) and an insertion element (IS*1133* in *E. amylovora*, IS*6100* in *X. campestris*), followed in turn by *strA* and *strB*. In *E. amylovora*, the insertion sequence IS*1133* appeared to be necessary for efficient expression of the *strAB* genes (Chiou and Jones, 1993a; Förster et al., 2015; Sundin and Bender, 1995).

Tn*5393* was also found on the non-conjugative plasmid (29 kb) pEa29 of *E. amylovora* (Table 14). Tn*5393* can insert into pEa29 at several locations. The fact that Tn*5393* can translocate to several plasmids also suggests the risk of insertion into other conjugative plasmids, which could lead to further spread of the resistance genes (Falkenstein et al., 1989; McManus et al., 2002).

Several variants of Tn*5393* have also been identified (nucleotidic sequences are available in Appendix B for Tn*5393* variants found in PPB). An extensive description of these variants is reported in (Verhaegen et al., 2023) but is more briefly summarized here. In *P. syringae* pv. *syringae* and *P. marginalis* on kiwifruits from South Korea, and *P. syringae* pv. *actinidiae* on kiwifruits from Japan, a version of Tn*5393* lacking the IS*1133* insertion sequence, called Tn*5393*a, was identified (Sundin and Bender, 1993, 1995; Han et al., 2004). The plasmidic (or chromosomal) hosts were not identified in the publications. Tn*5393*a was also detected in isolates of *E. amylovora*, and was located on pEU30, a 30-kb conjugative plasmid (Table 14) (Förster et al., 2015; Foster et al., 2004). These strains of *E. amylovora* showed reduced levels of resistance due to the lack of an IS in this version of Tn*5393*.

In *X. campestris*, a version of Tn*5393* containing IS*6100* (but not IS*1133*) was identified and named Tn*5393*b. The presence of IS*6100*, just as the presence of IS*1133* in Tn*5393*, increased the level of resistance compared to the version of Tn*5393* without IS (Sundin and Bender, 1995). IS*6100* is 100% identical to an element also found in *Mycobacterium fortuitum*, *Pseudomonas aeruginosa* and *Flavobacterium* sp., suggesting that its presence might not be restricted to PPB (Sundin and Bender, 1995).

There are also reports of variants of Tn*5393* in bacteria non-pathogenic to plants. A version called Tn*5393*c was found in the fish pathogen *Aeromonas salmonicida*. This version did not carry any insertion sequence, like Tn*5393*a, and they are essentially identical (L'Abée-Lund and Sørum, 2000). Tn*5393*a was also reported on a IncI1 type conjugative plasmid from *Salmonella enterica* (Harmer, 2021). Tn*5393*-like elements were also identified in *Corynebacterium striatum*, *Campylobacter jejuni* and *Pseudomonas aeruginosa*, all human pathogenic species (Sundin, 2000), and in *Snodgrassella alvi* (a honeybee gut symbiont) (Ludvigsen et al., 2018). Tn*5393* has a much higher magnitude of transfer and a broader spectrum of hosts than PPB. It is found in a wide variety of bacteria and ecological niches, from distinct geographical locations (Sundin et al., 1995).

Numerous other variants of Tn*5393* were reported in literature, illustrating again the fact that this transposon is not limited to PPB. These other variants of the transposon have a more complex structure and have gained other mobile genetic elements (MGEs) or antibiotic resistance genes (ARGs). Tn*5393*d was reported in a clinical strain of *Alcaligenes faecalis*, which can be a bacterial pathogen for humans. It also holds genes conferring resistance to kanamycin, streptomycin, amikacin and beta-lactams (Mantengoli and Rossolini, 2005). Tn*5393*e contains another transposon (Tn*6023*) and was found on a plasmid recovered from a multi-resistant *Salmonella enterica* serovar Typhimurium. The Tn*6023* transposon contains the *aphA1b* gene, which confers resistance to aminoglycosides (Cain and Hall, 2011). Tn*5393*f and Tn*5393*g were found in unidentified soil bacteria where manure had been applied (Heuer et al., 2009). These transposons were found on low GC conjugative plasmids carrying other ARGs (such as *sul2*, *aac3*, etc.). Tn*5393*h is derived from Tn*5393*a and includes the tetracycline resistance transposon Tn*10* in the *tnpA* gene (which may render it not mobile). Tn*5393*i includes IS*1133*-like Tn*5393*a, but the IS is not in the same location, namely in the *tnpR* gene (Cain and Hall, 2011). Tn*5393*j was identified in *Klebsiella pneumoniae* and carries an aminoglycoside resistance gene (*aphA6*) (Espedido et al., 2013). Tn*5393*k was described twice (Yao et al., 2021; Adamczuk and Dziewit, 2017). Tn*5393*l was described in *S. enterica* sv. Typhimuirum (Zhang et al., 2019) and Tn*5393*n in *Aeromonas caviae* (Luo et al., 2022).

Tn*5393* was identified in several isolates of clinical importance. In *K. pneumoniae* isolates from humans and chickens, an efflux pump mechanism (*tmexCD1-toprJ1* pump) conferring resistance to tigecycline was identified inside Tn*5393*. The authors suggested that it originated from the chromosome of *Aeromonas* spp. through Tn*5393*-mediated translocation (Sun et al., 2020). In multi-resistant *Acinetobacter baumannii* clinical isolates from China, a tigecycline resistance gene (*tet(Y)*) was located inside Tn*5393*, on plasmid carrying numerous other resistance genes (*aac(6')-Ib3*, *msr(E)*, *mph(E)*, *floR*, *ARR-3*, *sul1*, *dfrA19* and *tet(39)*). Tn*5393* probably played a role in the transmission of *tet(Y)* and might originate from *Aeromonas* spp. (Wang et al., 2021a). In Australia, a fragment of Tn*5393* was found in a multi-resistant *Acinetobacter baumannii* strain (Post and Hall, 2009).

Table 14: Organisms, plasmids and possibility of horizontal gene transfer associated with different variants of Tn*5393*. *E. amylovora*, *P. syringae* and *X. campestris* are PPB; *A. salmonicida*, *A. faecalis* and *S. enterica* are other pathogenic bacteria for humans or animals.

	Tn*5393* variant	**Plasmidic host**	**Horizontal gene transfer**
Organism			
E. amylovora	Tn*5393*	pEa34	Conjugative
	Tn*5393*	pEa29	Non-conjugative
	Tn*5393*a	pEU30	Conjugative
P. syringae	Tn*5393*a	pPSR1	Conjugative
X. campestris	Tn*5393*b	Not determined	Not determined
A. salmonicida	Tn*5393*c	pRAS2	Conjugative
A. faecalis	Tn*5393*d	pFL424	Non-conjugative
S. enterica	Tn*5393*a	I1	Conjugative

BLAST analyses

BLAST analyses were conducted in order to potentially identify similar sequences to ARGs in other genera of PPB. Results of the searches are reported in the Tables 15-22 below. These results were not restrained by the percentage of query cover. If not indicated otherwise, the query cover was 100%. Otherwise, the query cover was lower and thus need to be considered carefully. Two types of BLAST analyses were performed; tBLASTn (Tables 15-18) and BLASTp (Tables 19-22), for four genes; *strA* (Tables 15 and 16), *strB* (Tables 17 and 18), *aadA1* (Tables 19 and 20) and *aadA2* (Tables 21 and 22). The tables are organized to report the bacterial species or protein similar to the resistance gene of interest, the origin of the species, the identity percentage and the GenBank accession number corresponding.

Table 15: Search for identity with *strA* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. In bold: isolates that do not possess a sequence of identity for both *strA* and *strB* but only one of the two genes (and therefore are probably not resistant to streptomycin). NA: information not available. qc: query cover.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Xanthomonas campestris	Argentina	99.63%	**U20588.2**
Pseudomonas syringae	Oklahoma, USA	99.63%	**M77502.2**
Pseudomonas syringae pv. *syringae*	Oklahoma, USA	99.63%	**AF273681.1**
Pseudomonas syringae pv. *actinidae*	Japan	99.25%	**AY533312.1**
Erwinia amylovora	Michigan, USA	99.63%	M95402.1
Xanthomonas arboricola pv. *pruni*	South Carolina,	99.63%	CP091077.1
Xanthomonas arboricola pv. *pruni*	South Carolina,	99.63%	CP091080.1
Agrobacterium larrymoorei	Florida, USA	99.63%	CP072171.1
P. syringae pv. *actinidae*	New Zealand	99.63%	KX009061.1
P. syringae pv. *syringae*	Oklahoma, USA	99.63%	AY342395.1
P. syringae pv. *actinidae*	New Zealand	99.63%	KU950310.1
P. syringae pv. *actinidae*	New Zealand	99.63%	KX009059.1
Agrobacterium sp.	NA	99.63%	KY000037.1
Agrobacterium tumefaciens	NA	99.63%	CP007228.1
Agrobacterium tumefaciens	NA	99.63%	CP007227.1
X. campestris pv. *vesicatoria*	NA	99.63%	CP017190.1
X. campestris pv. *vesicatoria*	NA	99.63%	AM039952.1
Burkholderia cenocepacia	Vancouver,	99.63%	CP019666.1
P. syringae pv. *syringae*	Wisconsin, USA	99.63%	CP000075.1
Acidovorax avenae subsp. *avenae*	Japan	99.25%	AB852526.1
Erwinia amylovora	California, USA	99.63%	CP063698.1
P. syringae pv. *actinidae*	Japan	99.63%	CP024713.1
E. amylovora	California, USA	99.63%	CP063696.1
E. amylovora	California, USA	99.63%	CP063692.1
E. amylovora	California, USA	99.63%	CP063689.1
E. amylovora	California, USA	99.63%	CP063806.1
Xanthomonas vesicatoria	Argentina	99.63%	CP018471.1
Agrobacterium tumefaciens	NA	98.88%	CP039913.1
Burkholderia cenocepacia	Russia	100% (qc=97%)	CP020601.1
Xanthomonas oryzae pv. *oryzae*	India	100% (qc=95%)	CP046148.1
Agrobacterium rubi	Oregon, USA	100%	CP049212.1

Both, *strA* and *strB* are necessary for resistance to streptomycin. Therefore, the tables 15 and 16 were compared and isolates that do not possess a sequence of identity with both genes were highlighted in bold (accession number).

Table 16: Search for identity with *strB* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. In bold: isolates that do not possess a sequence of identity for both *strA* and *strB* but only one of the two genes (and therefore are probably not resistant to streptomycin). NA: information not available. qc: query cover.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Xanthomonas oryzae pv. *oryzae*	India	100%	CP046148.1
Pseudomonas syringae pv. *actinidae*	New Zealand	100%	KX009061.1
P. syringae pv. *actinidae*	New Zealand	100%	KX009059.1
P. syringae pv. *actinidae*	Japan	100%	CP024713.1
P. syringae pv. *actinidae*	New Zealand	100%	KU950310.1
Agrobacterium sp.	NA	100%	KY000037.1
Burkholderia cenocepacia	Russia	100%	CP020601.1
Burkholderia cenocepacia	Vancouver,	100%	CP019666.1
Xanthomonas vesicatoria	Argentina	100%	CP018471.1
X. campestris pv. *vesicatoria*	NA	100%	CP017190.1
Erwinia amylovora	California, USA	100%	CP063806.1
Acidovorax avenae subsp. *avenae*	Japan	100%	AB852526.1
Xanthomonas arboricola pv. *pruni*	South Carolina,	100%	CP091077.1
Xanthomonas arboricola pv. *pruni*	South Carolina,	100%	CP091080.1
E. amylovora	California, USA	100%	CP063696.1
E. amylovora	California, USA	100%	CP063689.1
E. amylovora	California, USA	100%	CP063692.1
E. amylovora	California, USA	100%	CP063698.1
Agrobacterium tumefaciens	NA	100%	CP007228.1
Agrobacterium tumefaciens	NA	100%	CP007227.1
Agrobacterium rubi	NA	100%	CP049212.1
P. syringae pv. *syringae*	Oklahoma, USA	100%	AY342395.1
X. campestris pv. *vesicatoria*	NA	100%	AM039952.1
E. amylovora	Michigan, USA	100%	M95402.1
P. syringae pv. *syringae*	Wisconsin, USA	100%	CP000075.1
P. syringae pv. *syringae*	NA	100%	**AY997127.1**
Agrobacterium larrymoorei	Florida, USA	100%	CP072171.1
Agrobacterium tumefaciens	NA	98.63%	CP039913.1
E. amylovora	New York, USA	100%	**KT899307.1**
Dickeya chrysanthemi	NA	98.21%	**X73255.1**

Table 17: Search for identity with *aadA1* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. qc: query cover.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Xanthomonas oryzae pv. *oryzae*	China	100%	NG_052257.1
Acidovorax defluvii	China	99.24%	EU434617.1
Burkholderia cenocepacia	NA	99.24%	GU186098.1
Pantoea agglomerans	Nigeria	99.61%(qc=96%)	GU990082.1
Burkholderia cepacia	NA	99.24%	HQ880251.1
Pantoea agglomerans	NA	99.24%	EF490315.1
Xanthomonas oryzae pv. *oryzae*	China	100% (qc=93%)	FJ501978.2
Xanthomonas oryzae pv. *oryzae*	China	100%	HQ662555.1
Xanthomonas oryzae pv. *oryzae*	China	100%	HQ662557.1
Xanthomonas oryzae pv. *oryzae*	China	100%	HQ662554.1
Pantoae eucrina	China	99.24%	CP083448.1
Xanthomonas oryzae pv. *oryzae*	India	99.24%	CP046148.1
Xanthomonas oryzae pv. *oryzae*	India	99.24%	CP098032.1
Pectobacterium parmentieri	South Korea	99.24%	CP046376.1
Agrobacterium fabrum	NA	85.55%	CP067036.1

Table 18: Search for identity with *aadA2* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. qc: query cover.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Agrobacterium fabrum	NA	99.26%	CP067036.1
Burkholderia cenocepacia	NA	87.88% (qc=97%)	GU186098.1
Xanthomonas oryzae pv. *oryzae*	NA	85.93%	FJ501978.2
Xanthomonas oryzae pv. *oryzae*	China	85.93%	NG_052257.1
Burkholderia cepacia	NA	87.88% (qc=97%)	HQ880251.1
Xanthomonas oryzae pv. *oryzae*	India	87.88% (qc=97%)	CP046148.1
Xanthomonas oryzae pv. *oryzae*	India	87.88% (qc=97%)	CP098032.1
Pectobacterium parmentieri	South Korea	87.88% (qc=97%)	CP046376.1
Xanthomonas oryzae pv. *oryzae*	China	85.93%	HQ662555.1
Xanthomonas oryzae pv. *oryzae*	China	85.93%	HQ662557.1
Xanthomonas oryzae pv. *oryzae*	China	85.93%	HQ662554.1
Burkholderia cenocepacia	NA	88.89% (qc=66%)	FJ644662.1

Table 19: Search for identity with *strA* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable. qc: query cover.

	Origin of the organism to describe the protein	**Identity percentage**	**Accession number (GenBank)**
Protein			
aminoglycoside O-phosphotransferase APH(3'')-Ib [Bacteria]	/	100%	WP_001082319.1
aminoglycoside O-phosphotransferase APH(3'')-Ib [Burkholderia gladioli]	NA	99.25%	WP_186141663.1
aminoglycoside O-phosphotransferase APH(3'')-Ib [Proteobacteria]	/	99.63%	WP_031943936.1
aminoglycoside O-phosphotransferase APH(3'')-Ib [Agrobacterium tumefaciens]	NA	99.25%	QCM14195.1
aminoglycoside O-phosphotransferase APH(3'')-Ib [Xanthomonas citri pv. citri]	Reunion	100% (qc=98%)	MBD4429513.1
APH(3'') family aminoglycoside O-phosphotransferase [Bacteria]	/	99.60% (qc=94%)	WP_001145207.1
APH(3'') family aminoglycoside O-phosphotransferase [Agrobacterium rubi]	NA	99.60% (qc=94%)	WP_249741178.1
Aminoglycoside 3'-phosphotransferase @ Streptomycin 3'-kinase StrA [Pseudomonas syringae pv. actinidiae]	New Zealand	99.51% (qc=76%)	ARO45008.1
aminoglycoside phosphotransferase [Xanthomonas euvesicatoria]	USA	99.50% (qc=74%)	KLB54723.1
APH(3'') family aminoglycoside O-phosphotransferase [Xanthomonas citri pv. citri]	Reunion	100% (qc=74%)	MBD4638616.1
phosphotransferase [Xanthomonas citri pv. citri]	Reunion	99.42% (qc=64%)	MBD4581011.1
phosphotransferase [Enterobacterales]	/	100% (qc=54%)	WP_072107020.1
phosphotransferase [Xanthomonas citri pv. citri]	Reunion	100% (qc=53%)	MBD4421784.1
aminoglycoside 3'-phosphotransferase [Agrobacterium tumefaciens LBA4213 (Ach5)]	NA	100% (qc=52%)	AHK04642.1
phosphotransferase [Erwinia amylovora]	NA	98.56% (qc=52%)	WP_180269682.1
phosphotransferase [Xanthomonas euvesicatoria]	NA	100% (qc=47%)	WP_046940638.1

Table 20: Search for identity with *strB* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable.

	Origin of the organism to describe the protein	Identity percentage	Accession number (GenBank)
Protein			
aminoglycoside 3'-phosphotransferase 2/Streptomycin 3'-kinase StrB [Burkholderia cenocepacia]	Russia	100%	ARF90387.1
aminoglycoside O-phosphotransferase APH(6)-Id [Bacteria]	/	100%	WP_000480968.1
APH(6)-I family aminoglycoside O-phosphotransferase [Burkholderia cenocepacia]	NA	99.64%	WP_241285245.1
APH(6)-I family aminoglycoside O-phosphotransferase [Burkholderia ambifaria]	NA	99.64%	WP_175715150.1
Aminoglycoside/hydroxyurea antibiotic resistance kinase [Pseudomonas syringae pv. syringae B728a]	Wisconsin, USA	100% (query cover = 99%)	AAY37709.1
APH(6)-I family aminoglycoside O-phosphotransferase [Gammaproteobacteria]	NA	100% (query cover = 96%)	WP_040092069.1
APH(6)-I family aminoglycoside O-phosphotransferase [Xanthomonas citri pv. citri]	Reunion	100% (query cover = 92%)	MBD4579827.1
StrB [Pseudomonas syringae pv. syringae]	NA	99.52% (query cover = 75%)	KPB27291.1
3'-kinase [Gammaproteobacteria]	/	100% (query cover = 38%)	WP_046940641.1

Table 21: Search for identity with *aadA1* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable.

	Origin of the organism to describe the protein	Identity percentage	Accession number (GenBank)
Protein			
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA1 [Xanthomonas oryzae]	NA	100%	WP_071846240.1
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA1 [multiple Bacteria]	/	99.24%	WP_001206316.1
Adenylyltransferase [Pantoea sp. PSNIH2]	USA	98.86%	AIX76346.1
AadA1 [Pantoea agglomerans]	Nigeria	99.61% (query cover = 96%)	ADG01896.1
AadA family aminoglycoside 3’’-O-nucleotidyltransferase [Pantoea sp. PSNIH4]	USA	99.20% (query cover = 95%)	POU53347.1
aminoglycoside adenyltransferase type A1 [Xanthomonas oryzae pv. oryzae]	NA	100% (query cover = 93%)	ACT32447.2
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA2 [Agrobacterium fabrum]	NA	85.55%	QQN14736.1
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA13 [Proteobacteria]	/	85.17%	WP_001424636.1
AadA family amniglycoside 3’’-O-nuleotidyltransferase [Pantoea stewartii]	NA	88.21% (query cover = 87%)	WP_044243720.1
AadA family aminoglycoside 3''-O-nucleotidyltransferase [Xanthomonas citri pv. citri]	Reunion	98.98% (query cover = 74%)	MBD4419152.1
aminoglycoside nucleotidyltransferase [Gammaproteobacteria]	/	98.95% (query cover = 72%)	WP_033581548.1
aminoglycoside nucleotidyltransferase [Pseudomonas syringae]	NA	98.95% (query cover = 72%)	WP_024651181.1
aminoglycoside nucleotidyltransferase [multiple Bacteria]	/	98.87% (query cover = 67%)	WP_039025997.1

aminoglycoside adenylyltransferase family protein [Streptomyces sp. NBS 14/10]	NA	100% (query cover = 58%)	WP_143667959.1
adenyltransferase [Streptomyces sp. NBS 14/10]	Brazil	99.32% (query cover = 55%)	OXL18224.1

Table 22: Search for identity with *aadA2* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable.

Protein	Origin of the organism to describe the protein	Identity percentage	Accession number (GenBank)
AadA family aminoglycoside 3''-O-nucleotidyltransferase [Streptomyces sp. PKU-MA01144]	NA	99.26%	WP_170815175.1
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA2 [Agrobacterium fabrum]	NA	99.26%	QQN14736.1
AadA family aminoglycoside 3''-O-nucleotidyltransferase [Pantoea stewartii]	NA	100.00% (query cover = 91%)	WP_044243720.1
aminoglycoside nucleotidyltransferase [Bacteria]	/	87.88% (query cover = 97%)	WP_039025997.1
aminoglycoside nucleotidyltransferase [Gammaproteobacteria]	/	87.88% (query cover = 97%)	WP_033581548.1
RecName: Full=Aminoglycoside (3'') (9) adenylyltransferase; AltName: Full=Streptomycin 3''-adenylyltransferase; Short=SP-R [Agrobacterium tumefaciens]	NA	90.37%	P14511.1
aminoglycoside nucleotidyltransferase [Pseudomonas syringae]	NA	87.88% (query cover = 97%)	WP_024651181.1
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA13 [Bacteria]	/	86.67%	WP_001424636.1
AadA family aminoglycoside 3''-O-nucleotidyltransferase [Pantoea sp. PSNIH4]	USA	87.88% (query cover = 97%)	POU53347.1

ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA1 [Bacteria]	/	87.88% (query cover = 97%)	WP_001206316.1
adenylyltransferase [Pantoea sp. PSNIH2]	USA	87.88% (query cover = 97%)	AIX76346.1
aminoglycoside adenyltransferase type A1 [Xanthomonas oryzae pv. oryzae]	NA	85.93%	ACT32447.2
ANT(3'')-Ia family aminoglycoside nucleotidyltransferase AadA1 [Xanthomonas oryzae]	NA	85.93%	WP_071846240.1
AadA1 [Pantoea agglomerans]	Nigeria	87.79% (query cover = 97%)	ADG01896.1
aminoglycoside adenylyltransferase family protein [Burkholderia]	NA	85.98% (query cover = 79%)	WP_181002608.1

The origin of the species containing a nucleotide sequence/protein of high similarity with *strA*, *strB* or *aadA1* could not always be determined. However, it can be observed that in many cases the location corresponds with places where antibiotic resistance reports have been made already. Yet, Wisconsin (USA), Russia, Reunion, and Nigeria are places where no antibiotic resistance in PPB has been reported in the scientific literature. There were 27 isolates containing sequences similar to both *strA* and *strB*, among which two originated either from Wisconsin (USA) or Russia, which are places where no antibiotic resistance reports were made.

It is interesting to note that there are not many hits of high correspondence with these ARGs in PPB, either with tBLASTn or BLASTp.

These results must be taken with caution because this work is purely predictive, just like any bioinformatic analysis, and the potential resistance encoded by these genes should be confirmed with laboratory experiments. We can only say here that these isolates possess the genes (or very similar ones) potentially coding for streptomycin resistance.

○ Oxytetracycline resistance

Oxytetracycline belongs to the class of tetracycline antibiotics. It is the second most used antibiotic in plant agriculture and is often used against fire blight when streptomycin resistance is reported. Although, oxytetracycline is considered to be less effective than streptomycin, which is why it is only used as a second line of defense (McManus et al., 2002; Sundin and Wang, 2018).

Several mechanisms can be responsible for tetracycline resistance : efflux pumps that pump the antibiotic out of the cell, ribosomal protection proteins that protects the ribosome from the action of tetracyclines or enzymatic inactivation of the antibiotic (Chopra and Roberts, 2001).

Cases of oxytetracycline resistance in PPB are less common than streptomycin resistance (Table 31). There have been reports of tetracycline resistance in *P. syringae* (Hwang et al., 2005; Silva and Lopes, 1995; Spotts and Cervantes, 1995), *Xanthomonas arboricola* pv. *pruni* (Herbert et al., 2022) and *Agrobacterium tumefaciens* (Luo and Farrand, 1999). In *A. tumefaciens*, the tetracycline resistance reported has not been linked to oxytetracycline application (Luo and Farrand, 1999) and to the best of our knowledge, antibiotics are not used against *A. tumefaciens*. In contrast, antibiotic sprays correlated positively with resistance in *P. syringae* pv. *syringae* (Spotts and Cervantes, 1995). Resistance mechanisms were not investigated, except in *X. arboricola* pv. *pruni*, which carried not only *tetC* and *tetR*, conferring tetracycline resistance by coding for an efflux pump, but also *strAB* on a plasmid with a region similar to Tn*5393* (Herbert et al., 2022). Lacy et al. have shown that oxytetracycline resistant *E. amylovora* strains could be obtained *in vitro* by transfer of the RP1 plasmid carrying an oxytetracycline resistance gene from both *Erwinia herbicola* and *P. syringae* pv. *syringae* to *E. amylovora*. However, the plasmid phenotype could be recovered in only 0.03% of the isolates after pathogenesis (Lacy et al., 1984). Oxytetracycline resistant field isolates of *E. amylovora* have not been isolated yet to the best of our knowledge.

A study on the distribution of tetracycline resistance genes in the phylloplane of Michigan apple orchards was conducted (Schnabel and Jones, 1999). They observed that the use of oxytetracycline generally resulted in lower density of bacterial populations than the use of streptomycin. Streptomycin resistance was much more common than tetracycline resistance. Interestingly, almost all tetracycline resistant strains were also streptomycin resistant and tetracycline resistance genes were found on plasmids that also carried the Tn*5393* transposon. Tetracycline resistant strains were also observed in orchards where tetracycline had not been applied but they obtained higher numbers of tetracycline resistant bacteria where oxytetracycline was applied. Several plasmid-borne tetracycline resistance elements have been found in various epiphytic bacteria and usually the tetracycline resistance was associated with transposons, mainly Tn*5393* (carried by the plasmid).

It is worth mentioning that other studies have reported on oxytetracycline sensitivity. For example, Loper and Henkels tested 138 strains of *E. amylovora* isolated from 44 pear orchards in Washington, USA for streptomycin and oxytetracycline resistance (Loper et al., 1991). While 98 strains from 38 of the 44 orchards were streptomycin resistant, none of the strains appeared to be oxytetracycline resistant. Donat et al. also reported tetracycline sensitivity in 130 strains of *E. amylovora*, isolated in Spain where there is no antibiotic application on plants (Donat et al., 2005).

BLAST analyses were conducted in order to potentially identify similar sequences to ARGs in other genera of PPB. Results of the searches are reported in the Tables 23-26 hereunder. It is necessary to note again that these results were not restrained by the percentage of query cover. If not indicated otherwise, the query cover was 100%. If otherwise indicated, the query cover was lower and thus need to be considered carefully. Two types of BLAST analyses were performed: tBLASTn (Tables 23 and 24) and BLASTp (Tables 25 and 26). The tables are organized to report the bacterial species or protein similar to the resistance gene of interest, the origin of the species, the identity percentage and the GenBank accession number corresponding.

The analysis was performed with two sequences for *tetC* (two different accession numbers), because two tetracycline resistance genes have been reported in literature (Herbert et al., 2022).

Accession number: UJO06547.1 (BioProject PRJNA762221, Assembly GCA_020002335.2, Plasmid pR1 CP091080.1)

Table 23: Search for identity with *tetC* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Xanthomonas arboricola pv. *pruni*	USA, South Carolina	87.12%	CP091077.1
Xanthomonas arboricola pv. *pruni*	USA, South Carolina	87.12%	CP091080.1
Burkholderia cepacia	Thailand	86.87%	CP011301.1
Agrobacterium fabrum	NA	86.87%	CP067031.1
Agrobacterium fabrum strain	NA	88.73% (query cover = 69%)	CP067030.1
Streptomyces albidoflavus	Germany: Saarbruecken	88.73% (query cover = 69%)	CP059254.1
Streptomyces lividans	Germany: Saarbruecken	87.02% (query cover = 66%)	CP071123.1
Streptomyces coelicolor	Canada: Hamilton	98.56% (query cover = 94%)	CP050522.1

Table 24: Search for identity with *tetC* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. /: not applicable.

	Origin of the organism to describe the protein	Identity percentage	Accession number (GenBank)
Protein			

tetracycline efflux MFS transporter Tet(C) [Bacteria]	/	100.00%	WP_000841446.1
tetracycline efflux MFS transporter Tet(C) [Bacteria]	/	99.75%	WP_001297013.1
MFS transporter [Xanthomonas citri pv. citri]	Maldives	100.00% (query cover = 75%)	MBD4865860.1
Tetracycline resistance protein, class C [Streptomyces albidoflavus]	Germany: Saarbruecken	99.64% (query cover = 69%)	QLP92962.1
MFS transporter [Xanthomonas citri pv. citri]	Martinique	99.54% (query cover = 55%)	MBD4786976.1

Accession number: UJO10707.1 (BioProject PRJNA762226, Assembly GCA_020043425.2, Plasmid pT1 CP091076.1)

Table 25: Search for identity with *tetC* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available.

	Origin	**Identity percentage**	**Accession number (GenBank)**
Bacterial species			
Xanthomonas arboricola pv. *pruni*	USA, South Carolina	87.12%	CP091077.1
Xanthomonas arboricola pv. *pruni*	USA, South Carolina	87.12%	CP091080.1
Burkholderia cepacia	Thailand	86.87%	CP011301.1
Agrobacterium fabrum	NA	86.87%	CP067031.1
Agrobacterium fabrum	NA	88.73% (query cover = 69%)	CP067030.1
Streptomyces albidoflavus	Germany: Saarbruecken	88.73% (query cover = 69%)	CP059254.1
Streptomyces lividans	Germany: Saarbruecken	87.02% (query cover = 66%)	CP071123.1

Streptomyces coelicolor	Canada: Hamilton	98.56% (query cover = 94%)	CP050522.1

Table 26: Search for identity with *tetC* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. /: not applicable.

	Origin of the organism to describe the protein	**Identity percentage**	**Accession number (GenBank)**
Protein			
tetracycline efflux MFS transporter Tet(C) [Bacteria]	/	100.00%	WP_000841446.1
tetracycline efflux MFS transporter Tet(C) [Bacteria]	/	99.75%	WP_001297013.1
MFS transporter [Xanthomonas citri pv. citri]	Maldives	100.00% (query cover = 75%)	MBD4865860.1
Tetracycline resistance protein, class C [Streptomyces albidoflavus]	Germany: Saarbruecken	99.64% (query cover = 69%)	QLP92962.1
MFS transporter [Xanthomonas citri pv. citri]	Martinique	99.54% (query cover = 55%)	MBD4786976.1

There are very few hits with the sequence of *tetC.* The origin of the species containing a nucleotide sequence/protein of high similarity with *tetC* could not always be determined. However, it can be observed that in many cases the location does not correspond to places where antibiotic resistance reports have been made already. Thailand, Germany, Canada, Maldives and Martinique are places where no antibiotic resistance in PPB has been reported in the scientific literature.

These results must be taken with caution because this work is purely predictive, just like any bioinformatic analysis, and the potential resistance encoded by these genes should be confirmed with laboratory experiments. We can only say here that these isolates possess the genes (or very similar ones) potentially coding for tetracycline resistance.

- Kasugamycin resistance

Kasugamycin is an aminoglycoside antibiotic. Its antibacterial activity is usually conferred by its ability to interfere with protein synthesis (Fourmy et al., 1996; Magnet and Blanchard, 2005). It is bacteriostatic, unlike other aminoglycosides that are bactericidal (Umezawa et al., 1965). It has been used in plant agriculture since the 1960s in several Asian countries, notably against the fungus *Magnaporthe grisea*, responsible for rice blast, and for the control of bacterial grain and seedling rots of rice. Canada and the USA have authorized its use more recently against *E. amylovora*. It is also used against other bacterial pathogens such as *Erwinia atroseptica*, *Xanthomonas campestris* pv. *vesicatoria*, *Burkholderia glumae* or *Acidovorax avenae* subsp. *avenae* (Ishiyama et al., 1965; McGhee and Sundin, 2011; Sundin and Wang, 2018).

In *E. coli*, a mutation in the *ksgA* gene, encoding a dimethyltransferase, was shown to confer a moderate level of resistance. Mutations in other genes such as *ksgB*, *ksgC* and *ksgD* were also identified to confer kasugamycin resistance (Fouts and Barbour, 1981; Sparling, 1970; Sparling et al., 1973; Yoshii et al., 2012; Yoshikawa et al., 1975).

Different resistance mechanisms have been identified in PPB. In Japan, the presence of the *aac(2')-IIa* gene was responsible for resistance in the bacterial pathogens of rice *B. glumae* and *A. avenae* subsp. *avenae* (Yoshii et al., 2012). It encodes the Aac(2')-IIa acyltransferase, which inactivates kasugamycin through acetylation of the 2'-amino residue of kasugamycin. This novel acetyltransferase is encoded on the IncP genomic island in the chromosome of *B. glumae*, suggesting that this gene was acquired by HGT (Yoshii et al., 2012). Later, the same gene was found on a conjugative IncP-1β plasmid, pAAA83, in an *A. avenae* ssp. *avenae* strain with high levels of kasugamycin resistance, also suggesting that this resistance gene might easily spread (Yoshii et al., 2015).

In *E. amylovora*, another mechanism of kasugamycin resistance has been described. Two major peptide ATP-binding cassette transporter systems, the dipeptide permease (Dpp) and oligopeptide permease (Opp) have been investigated for their potential role in the resistance to kasugamycin and blasticidin S. *In vitro* deletion of both *opp* and *dpp* confer resistance to kasugamycin and blasticidin S, suggesting these permeases act synergistically for the transport of antibiotics to enter the cell.

Additionnally, it has been shown that *in vitro* mutation of the *ksgA* gene in *E. amylovora* confers resistance to kasugamycin. However, the spontaneous resistance requires a two-step mutational process and the mutants were considerably reduced in fitness. Naturally-occurring kasugamycin-resistant *E. amylovora* have not been reported yet (Ge et al., 2018; McGhee and Sundin, 2011).

Kasugamycin resistant isolates could be recovered from apple flowers, leaves and soil samples in experiments conducted in experimental apple orchards that were treated with kasugamycin. No transferrable kasugamycin resistance gene could be identified but the high number of isolates recovered suggests the potential role of nontarget bacteria in the spreading of resistance (McGhee and Sundin, 2011). On the other hand, no kasugamycin resistant bacteria could be isolated in the phyllosphere of New York apple orchards sprayed up to ten times. However the antibiotic application modified the microbial spectrum in the orchard (Tancos and Cox, 2017).

BLAST analyses were conducted in order to potentially identify similar sequences to ARGs in other genera of PPB. Results of the searches are reported in the Tables 27-28 hereunder. It is necessary to note again that these results were not restrained by the percentage of query cover. If not indicated otherwise, the query cover was 100%. If otherwise indicated, the query cover was lower and thus need to be considered carefully. Two types of BLAST analyses were performed: tBLASTn (Table 27) and BLASTp (Table 28). The tables are organized to report the bacterial species or protein similar to the resistance gene of interest, the origin of the species, the identity percentage and the GenBank accession number corresponding.

Table 27: Search for identity with *aac(2')-IIa* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Burkholderia glumae	Japan	100% (query cover = 93%)	NG_047225.1
Burkholderia glumae	Japan	100% (query cover = 93%)	AB669090.1
Acidovorax avenae subsp. *avenae*	Japan	99.59% (query cover = 93%)	AB852526.1

Table 28: Search for identity with *aac(2')-IIa* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable.

	Identity percentage	Accession number (GenBank)
Protein		
Kasugamycin N-acetyltransferase AAC(2')-IIa [Proteobacteria]	100% (query cover = 93%)	WP_063839881.1
Kasugamycin 2'-N-acetyltransferase [Acidovorax avenae subsp. avenae]	99.59% (query cover = 93%)	BAP34640.1

Kasugamycin N-acetyltransferase AAC(2')-IIa [Acidovorax avenae]	99.57% (query cover = 89%)	WP_137496451.1

There are very few hits with the sequence of *aac(2')-IIa* and they originated from Japan.

These results must be taken with caution because this work is purely predictive, just like any bioinformatic analysis, and the potential resistance encoded by these genes should be confirmed with laboratory experiments. We can only say here that these isolates possess the genes (or very similar ones) potentially coding for kasugamycin resistance.

○ Oxolinic acid resistance

Oxolinic acid (OA) is a quinolone antibiotic mainly used in replacement for streptomycin in Israel, where cases of OA resistant *E. amylovora* and *B. glumae* have been reported about two years after the beginning of its use. However, the incidence of OA resistance in *E. amylovora* populations was sporadic and irrespective of the number of sprays applied and the severity of the disease (Kleitman et al., 2005). Quinolones usually act by inhibiting the activity of type II topoisomerases (DNA gyrase or type IV topoisomerase), so resistance to quinolones can be caused by a mutation in these enzymes, or by a reduction in the permeability of the cell membrane (Correia et al., 2017).

Mechanisms of resistance have not been well described yet in PPB. It likely consists of chromosomal mutations rather than acquisition of ARGs through HGT. When the use of streptomycin was abandoned in 1997 in Israel in favour of OA, resistance to streptomycin in orchards decreased from 57% in 1998 to 15% in 2001. They identified OA resistant strains in several orchards but none was resistant to both streptomycin and OA (Manulis et al., 2003).

OA is also used for disease control in Japan (Maeda et al., 2007b). OA resistant *B. glumae* could be obtained *in vitro*. These isolates were able to grow quickly on seedlings and rot the plant only when the seeds were infected with a high number of OA resistant bacteria and are treated with OA. However, these resistant bacteria could not survive in paddy fields. In another study, Maeda and colleagues identified *in vitro* mutant OA resistant *B. glumae* obtained from strains from rice fields in Japan (Maeda et al., 2007b). The GyrA83 mutation (replacement of a serine residue by an arginine or an isoleucine, at position 83) seemed to be responsible for resistance.

○ Gentamicin resistance

Gentamicin is an aminoglycoside antibiotic. Its use in plant agriculture seems to be mostly restricted to central and South American countries (Sundin and Wang, 2018; Vidaver, 2002). There is one report of gentamicin resistance in PPB (*X. oryzae* pv. *oryzae*) in China but it has not been linked with gentamicin use (Xu et al., 2013). The resistance was acquired through the gene *aacA3*, carried by an integron, which is part of a gene cassette containing other ARGs. It seems that *aacA3* conferred resistance to tobramycin, kanamycin and netilmicin in addition to gentamicin in this case.

BLAST analyses were conducted in order to potentially identify similar sequences to ARGs in other genera of PPB. Results of the searches are reported in the Tables 29-30 hereunder. It is necessary to note again that these results were not restrained by the percentage of query cover. If not indicated otherwise, the query cover was 100%. If otherwise indicated, the query cover was lower and thus need to be considered carefully. Two types of BLAST analyses were performed: tBLASTn (Table 28) and BLASTp (Table 29). The tables are organized to report the bacterial species or protein similar to the resistance gene of interest, the origin of the species, the identity percentage and the GenBank accession number corresponding.

Table 29: Search for identity with *aacA3* (tBLASTn). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available.

	Origin	Identity percentage	Accession number (GenBank)
Bacterial species			
Burkholderia cepacia	NA	100%	HQ880250.1
Xanthomonas oryzae pv. *oryzae*	China	100%	HQ662557.1
Xanthomonas oryzae pv. *oryzae*	China	100%	HQ662554.1
Burkholderia cenocepacia	Taiwan	98.92%	CP073674.1
Burkholderia vietnamiensis	USA	82.07%	NG_052221.1
Agrobacterium sp.	Belgium	82.54% (query cover = 34%)	AJ493433.1

Table 30: Search for identity with *aacA3* (BLASTp). Identity percentage with 100% query cover unless otherwise specified. They appear hereunder in the same order as in the BLAST search (most similar at the top of the table, least similar at the bottom). Only sequences with at least 85% identity are shown. NA: information not available. /: not applicable.

	Identity percentage	Accession number (GenBank)
Protein		
aminoglycoside 6'-N-acetyltransferase [Burkholderia cepacia]	100.00%	AEC47400.1
AacA4 family aminoglycoside N(6')-acetyltransferase [Burkholderia cenocepacia]	98.92%	WP_212136801.1
AacA4 family aminoglycoside N(6')-acetyltransferase [Proteobacteria]	88.04%	WP_058131000.1

aminoglycoside 6'-N-acetyltransferase [Burkholderia vietnamiensis]	82.07%	WP_049031504.1
aminoglycoside 6'-N-acetyltransferase AacA38 [Proteobacteria]	80.23% (query cover = 96%)	WP_027814019.1
GNAT family N-acetyltransferase [Xanthomonas citri pv. citri]	80.61% (query cover = 53%)	MBD4360319.1
RecName: Full=Kanamycin resistance protein; Short=KM-R [Agrobacterium tumefaciens]	80.61% (query cover = 53%)	P14510.1

There are very few hits with the sequence of *aacA3* but they originated from various countries: China, Taiwan, USA, Belgium and Reunion. The only resistance report in literature in PPB originated from China (Table 31). It might be more widespread than originally thought.

These results must be taken with caution because this work is purely predictive, just like any bioinformatic analysis, and the potential resistance encoded by these genes should be confirmed with laboratory experiments. We can only say here that these isolates possess the genes (or very similar ones) potentially coding for gentamicin resistance. Moreover, the *aacA3* gene does not only confer gentamicin resistance, as explained above, so it remains to be confirmed that these identified genes confer gentamicin resistance.

○ Other antibiotics

Even though most of the literature focuses on resistance genes associated to antibiotics used in plant agriculture, PPB can also host ARGs to other antibiotics. Co-selection of antibiotic resistance in PPB could potentially occur.

X. oryzae pv. oryzae streptomycin resistant strains were isolated that contained not only the *aadA1* gene (which confers streptomycin and spectinomycin resistance) but also the *aacA3* gene (which confers resistance to tobramycin, gentamicin, netilmicin and kanamycin) and the *arr3* gene (which confers resistance to rifampicin). These ARGs were all carried by a transposon. It is therefore possible that these gene cassettes will be transferred together under the selective pressure of streptomycin. The resistance integron that was characterized *in X. oryzae* might originate from human or animal pathogens treated with antibiotics such as tobramycin, rifampicin, gentamicin, netilmicin or kanamycin (Xu et al., 2013).

Isolates of *P. syringae* sv. *syringae* have been assessed for their resistance to six antibiotics (kanamycin, tetracycline, streptomycin, rifampicin, chloramphenicol and ampicillin). Numerous strains were resistant to several antibiotics at the same time (Hwang et al., 2005).

Other studies described *X. campestris* resistant to amoxicillin, chloramphenicol and penicillin (De Britto, 2012), and a strain of *B. glumae* resistant to polymyxin B was isolated recently (Paz-Carrasco et al., 2018).

Regarding the antibiotics mainly used in China, *in vitro* resistant mutants of *X. oryzae* could be obtained for phenazine-1-carboxylic acid (PCA), also called shenqinmycin in China (Pan et al., 2018), for zhongshengmycin (Wang et al., 2021) and for bismerthiazol (Zhu et al., 2013).

- Global analysis

When looking at the Table 31, which compiles all cases of resistance reported in scientific literature in PPB, some of them being obtained *in vitro*, some general considerations can be drawn. Streptomycin is the antibiotic to which PPB are the most often reported resistant. Streptomycin resistance in PPB has been reported in 18 countries in scientific literature. Globally antibiotic resistance reports arose mainly from the USA and South America, as well as some Asian countries.

There have not been many studies conducted in Europe, probably as a consequence of the fact that the use of antibiotics for plant agriculture is not authorized. However, it is worth mentioning one study of isolates from fields in Spain. 130 strains of *E. amylovora* were recovered and isolated from fire blight in Spanish foci, where there is no antibiotic application on crops (Donat et al., 2005). They were all susceptible to tetracycline, streptomycin, kasugamycin and oxolinic acid.

Among the numerous cases reported all over the world, there is only one study that reported a resistance case in Europe: a *P. syringae* strain isolated in the United Kingdom (Hwang et al., 2005). This highlights the rarity of resistance in Europe, where antibiotics are not allowed in plant agriculture. They studied a collection of 95 *P. syringae* strains. Among other features, they surveyed for resistance to ampicillin, chloramphenicol, rifampin, streptomycin and tetracycline. Out of the 95 strains studied, only one was resistant to kanamycin and tetracycline. This strain was isolated from the UK and is a weak pathogen of lilacs. The authors noted that it is possible that this resistance pattern was due to genetic modifications of the particular isolate. Among their 95 strains, eight were resistant to streptomycin; one from Japan and one from the USA. The other six strains do not have their origin identified. It seems that they did not find strains from Europe resistant to streptomycin. However, the lack of studies in Europe might also introduce a bias as to the actual presence or absence of antibiotic resistant PPB. More studies might be needed to evaluate the current situation in Europe.

Table 31: Reported resistance cases in scientific literature to bismerthiazol, streptomycin, oxytetracycline, kasugamycin, oxolinic acid, shenqinmycin, gentamicin and zhongshenmycin in PPB, with information about the organism, the location, the genetic determinant involved in resistance (ND: not determined), the references and notes if applicable. One lign in the table represents one publication reporting resistance cases, for one type of bacteria, in one location, for one genetic determinant. In some publications, several isolates are described for the same species and in the same location. The table does not represent the number of resistant isolates but rather the number of reports of resistant isolates. The last column describes if the publication referes to a field isolate or an *in vitro* mutant. NA: not available. ND: not determined.

	Organism	**Location**	**Genetic determinant**	**Reference(s)**	**Environmental isolate or *in vitro mutant***
Antibiotic					
Bismerthiazol	*Xanthomonas oryzae* pv. *oryzae*	China	ND	(Zhu et al., 2013; Liang et al., 2018)	Resistance induced *in vitro* and *in vivo*
Gentamicin	*X. oryzae* pv. *oryzae*	China	*aacA3*	(Xu et al., 2013)	Environmental isolate
Kasugamycin	*Acidovorax avenae* ssp. *avenae*	Japan	*aac(2’)-IIa*	(Yoshii et al., 2012)	Environmental isolate
Kasugamycin	*Burkholderia glumae*	Japan	*aac(2‘)-IIa*	(Yoshii et al., 2012)	Environmental isolate
Kasugamycin	*Dickeya dadantii*	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Enterobacter* sp.	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Erwinia amylovora*	Michigan, USA	Spontaneous mutation in *ksgA* gene	(McGhee and Sundin, 2011)	Environmental isolate, resistance induced *in vitro*
Kasugamycin	*Erwinia persicina*	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Pantoea agglomerans*	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Pantoea* sp.	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Pseudomonas* spp.	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Pseudomonas syringae*	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Sphingomonas* sp.	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Xanthomonas campestris*	Michigan, USA	ND	(McGhee and Sundin, 2011)	Environmental isolate
Kasugamycin	*Xanthomonas campestris* pv. *campestris*	Brazil	ND	(Batista et al., 2021)	Environmental isolate
Oxolinic acid	*Acidovorax avenae* ssp. *avenae*	Japan	ND	(Yoshii et al., 2012)	Environmental isolate
Oxolinic acid	*Burkholderia glumae*	Israel	Probable chromosomal mutation	(Kleitman et al., 2005)	Environmental isolate
Oxolinic acid	*B. glumae*	Japan	Probable chromosomal mutation	(Hikichi et al., 2001, 1998)	Environmental isolate (Hikichi et al., 2001).

					In vitro (Hikichi et al., 1998)[1]
Oxolinic acid	*B. glumae*	Japan	GyrA83 mutation (?)	(Maeda et al., 2007a, 2007b)	Environmental isolate (Maeda et al., 2007a). *In vitro* (Maeda et al., 2007b)
Oxolinic acid	*B. glumae*	Japan	ND	(Yoshii et al., 2012)	Environmental isolate
Oxolinic acid	*E. amylovora*	Israel	Probable chromosomal mutation	(Kleitman et al., 2005)	Environmental isolate
Oxolinic acid	*E. amylovora*	Israel	ND	(Manulis et al., 2003)	Environmental isolate
Oxytetracycline	*Agrobacterium tumefaciens*	?	?	(Luo and Farrand, 1999)	Originally environmental isolate but resistance induced *in vitro*
Oxytetracycline	*P. syringae*	United Kingdom	ND	(Hwang et al., 2005)	Originally environmental isolate
Oxytetracycline	*P. syringae* pv. *syringae*	Oregon, USA Washington, USA	ND	(Spotts and Cervantes, 1995)	Environmental isolate
Oxytetracycline	*P. syringae* pv. *tomato*	Brazil	ND	(Silva and Lopes, 1995)	Environmental isolate
Oxytetracycline	*Xanthomonas arboricola* pv. *pruni*	South Carolina, USA	14-20 kb plasmid carrying *tetC*, *tetR* and *strAB*	(Herbert et al., 2022)	Environmental isolate
Shenqinmycin (phenazine-1-carboxylic acid or PCA)	*Xanthomonas oryzae* pv. *oryzae*	China	Reduction of reactive oxygen species (ROS) production and/or increasing ability to metabolize ROS. Exact mechanisms not defined yet	(Pan et al., 2018)	*In vitro*
Streptomycin	*Burkholderia gladiola*	Hawaii, USA	ND	(Keith et al., 2004)	Environmental isolate
Streptomycin	*Clavibacter michiganensis*	China	*rpsL* mutation	(Lyu et al., 2019)	*In vitro*
Streptomycin	*C. michiganensis*	China	Potentially conferred by *03055* and	(Lyu et al., 2019)	Environmental isolate

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[1] Further analyzed in (Maeda et al., 2004a, 2004b)

			03056 genes in strain TX-0702		
Streptomycin	*Clavibacter michiganensis* subsp. *michiganensis*	Chile	*rpsL* mutation	(Valenzuela et al., 2019)	Environmental isolate
Streptomycin	*E. amylovora*	California, USA	ND	(Miller and Schroth, 1972)	Environmental isolate
Streptomycin	*E. amylovora*	California, USA	Chromosomal mutation	(Schroth et al., 1979)	Environmental isolate[2]
Streptomycin	*E. amylovora*	California, USA	*rpsL* mutation	(Chiou and Jones, 1995a; Chiou and Jones, 1995b)	Environmental isolate
Streptomycin	*E. amylovora*	California, USA	*strAB* on plasmid RSF1010	(Palmer et al., 1997)	Environmental isolate[3]
Streptomycin	*E. amylovora*	California, USA	ND	(Adaskaveg et al., 2008)	NA
Streptomycin	*E. amylovora*	California, USA	Tn*5393a* on pEU30	(Förster et al., 2015)	Environmental isolate
Streptomycin	*E. amylovora*	Michigan, USA	Probably conjugative plasmid but ND	(Sobiczewski et al., 1991)	Environmental isolate[4]
Streptomycin	*E. amylovora*	Michigan, USA	ND	(Sobiczewski et al., 1991)	Environmental isolate
Streptomycin	*E. amylovora*	Michigan, USA	Tn*5393* on pEa34	(Chiou and Jones, 1993a, 1993b)	Environmental isolate[5]

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[2] See (Chiou et al., 1995) for strains analysis.
[3] Study of a plasmid from a strain isolated in (McManus and Jones, 1995)
[4] See (Chiou et al., 1995; Chiou and Jones, 1993a) for strains analysis.
[5] Isolation of strains in (Chiou and Jones, 1991)

Streptomycin	*E. amylovora*	Michigan, USA	Tn*5393* (on pEa34 and pEa29). Also uncharacterized mechanism	(McManus and Jones, 1994)	Environmental isolate[6]
Streptomycin	*E. amylovora*	Michigan, USA	Tn*5393* on pEa29	(McGhee et al., 2011)	Environmental isolate
Streptomycin	*E. amylovora*	Michigan, USA	*rpsL* mutation	(Chiou and Jones, 1995a; Chiou et Jones, 1995b)	Environmental isolate
Streptomycin	*E. amylovora*	Michigan, USA	*rspL* mutation	(Jones et al., 1996)	Environmental isolate
Streptomycin	*E. amylovora*	Michigan, USA	Tn*5393* (on pE34, pE29 or chromosome)	(Jones et al., 1996)	Environmental isolate
Streptomycin	*E. amylovora*	New York, USA	Tn*5393* on pEa29	(Tancos et al., 2016)	Environmental isolate
Streptomycin	*E. amylovora*	New York, USA	ND	(Dougherty et al., 2021)	Environmental isolate
Streptomycin	*E. amylovora*	New York, USA	*strA-strB* on Tn*5393*	(Russo et al., 2008)	Environmental isolate
Streptomycin	*E. amylovora*	Oregon, USA	ND	(Coyier and Covey, 1975)	Environmental isolate
Streptomycin	*E. amylovora*	Oregon, USA	*rpsL* mutation	(Chiou and Jones, 1995a; Chiou and Jones, 1995b)	Environmental isolate
Streptomycin	*E. amylovora*	Utah, USA	*rpsL* mutation	(Nischwitz and Dhiman, 2013)	Environmental isolate
Streptomycin	*E. amylovora*	Washington, USA	ND	(Coyier and Covey, 1975)	Environmental isolate
Streptomycin	*E. amylovora*	Washington, USA	*rpsL* mutation	(Chiou and Jones, 1995a; Chiou and Jones, 1995b)	Environmental isolate
Streptomycin	*E. amylovora*	Washington, USA	ND	(Loper et al., 1991)	Environmental isolate
Streptomycin	*E. amylovora*	New Zealand	*rpsL* mutation	(Chiou and Jones, 1995a; Chiou and Jones, 1995b)	Environmental isolate

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[6] See (Chiou et al., 1995) for strains analysis.

Streptomycin	*E. amylovora*	New Zealand	ND (but likely *rpsL* mutation)	(Thomson et al., 1993)	Environmental isolate[7]
Streptomycin	*E. amylovora*	Egypt	ND	(El-Goorani et al., 1989)	Environmental isolate
Streptomycin	*E. amylovora*	Syria	ND	(Al-Daoude et al., 2009)	Environmental isolate
Streptomycin	*E. amylovora*	Chihuahua Mexico	ND	(Chacón et al., 2011)	Environmental isolate
Streptomycin	*E. amylovora*	Chihuahua, Mexico	*rpsL*	(de León Door et al., 2013)	Environmental isolate
Streptomycin	*E. amylovora*	Chihuahua, Mexico	Unknown mechanism	(de León Door et al., 2013)	Environmental isolate
Streptomycin	*E. amylovora*	Mexico	*rpsL*	(Smits et al., 2014)	Environmental isolate
Streptomycin	*E. amylovora*	British Columbia, Canada	ND	(Sholberg et al., 2001)	Environmental isolate
Streptomycin	*E. amylovora*	Québec, Canada	*rpsL* mutation	(Laforest et al., 2019)	Most of them are environmental isolates, but some were provided from other collection and it could not be identified if they were environmental.
Streptomycin	*E. amylovora*	Israel	ND (but suggests not plasmidic)	(Manulis et al., 1999)	Environmental isolate
Streptomycin	*E. amylovora*	Utah, USA	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Ontario, Canada	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Israel	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	New Zealand	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Mexico	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	British Columbia, Canada	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	California, USA	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Washington, USA	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Oregon, USA	*rpsL* mutation	(Parcey et al., 2020)	Environmental isolate

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[7] See (Chiou and Jones, 1995) for strains analysis.

Streptomycin	*E. amylovora*	California, USA	*strA-strB* on pEA8.7	(Parcey et al., 2020)	Environmental isolate
Streptomycin	*E. amylovora*	Japan	Probably conjugative plasmid	(Fukasawa et al., 1980)	Environmental isolate
Streptomycin	*Pectobacterium carotovorum*	New Jersey, USA	*rpsL* mutation	(Barnard et al., 2010)	*In vitro*
Streptomycin	*Erwinia herbicola (Pantoea agglomerans)*	New York, USA	Plasmidic	(Burr et al., 1993)	Environmental isolate
Streptomycin	*Erwinia pyrifoliae*	South Korea	*rpsL* mutation	(Lee et al., 2023)	Environmental isolate
Streptomycin	*Pseudomonas marginalis*	South Korea	Tn*5393*-like (Tn*5393*a?)	(Han et al., 2004)	Environmental isolate
Streptomycin	*P. syringae* pv. *actinidiae*	Japan	Tn*5393*a	(Han et al., 2004)	Environmental isolate
Streptomycin	*P. syringae* pv. *actinidiae*	Japan	*rpsL* mutation	(Han et al., 2004)	Environmental isolate
Streptomycin	*P. syringae* pv. *actinidiae*	South Korea	ND	(Lee et al., 2020)	Environmental isolate
Streptomycin	*P. syringae* pv. *actinidiae*	South Korea	*strAB*	(Lee et al., 2021)	Environmental isolate
Streptomycin	*P. syringae* pv. *lachrymans*	Japan	ND	(Hwang et al., 2005)	Environmental isolate
Streptomycin	*P. syringae* pv. *papulans*	New York, USA	*strAB* on pCPP501	(Burr et al., 1988; Norelli et al., 1991)	Environmental isolate[8]
Streptomycin	*P. syringae* pv. *papulans*	Michigan, USA	ND	(Jones et al., 1991)	Environmental isolate

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[8] The probe SMP3 was utilized to detect streptomycin resistance; this probe contains portions of the *strA* and *tnpR* genes from Tn*5393*a.

Streptomycin	*P. syringae* pv. *papulans*	New York, USA	Conjugative plasmid (named pCPP501)	(Burr et al., 1988)	Environmental isolate[9]
Streptomycin	*P. syringae* pv. *papulans*	New York, USA	Plasmidic	(Huang and Burr, 1999)	Environmental isolate
Streptomycin	*P. syringae* pv. *papulans*	New York, USA	Plasmidic	(Burr et al., 1993)	Environmental isolate
Streptomycin	*P. syringae* pv. *syringae*	Oklahoma, USA	Tn*5393*a (on pPSR1)	(Sundin and Bender, 1993)	Environmental isolate[10]
Streptomycin	*P. syringae* pv. *syringae*	South Korea	Tn*5393*a	(Han et al., 2004)	Environmental isolate
Streptomycin	*P. syringae* pv. *syringae*	Oregon, USA Washington, USA	ND	(Spotts and Cervantes, 1995)	Environmental isolate
Streptomycin	*P. syringae* pv. *syringae*	USA	ND	(Hwang et al., 2005)	Environmental isolate
Streptomycin	*P. syringae* pv. *tabaci*	China	ND	(Li, 2007)	Environmental isolate
Streptomycin	*P. syringae* pv. *tomato*	Brazil	ND	(Silva and Lopes, 1995)	Environmental isolate
Streptomycin	*Pantoea agglomerans*	New York, USA	Plasmidic	(Huang and Burr, 1999)	Environmental isolate
Streptomycin	*Pseudomonas cichorii*	Florida, USA	ND	(Pohronezny et al., 1994)	Environmental isolate[11]
Streptomycin	*Pseudomonas lacrymans*	Japan	ND	(Yano et al., 1978a; Yano et al., 1978b)	Environmental isolate[12]

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[9] Significant association between the number of streptomycin sprays applied and the detection of streptomycin-resistant *P. s.* pv. *papulans*

[10] See also (Sundin and al., 2004; Sundin and Bender, 1994)

[11] In celery seedbeds

[12] On cucumber

Streptomycin	*Pseudomonas savastanoi* sv. *savastanoi*	Morocco	ND	(Abdelaaziz et al., 2019)	Environmental isolate
Streptomycin	*Pseudomonas* sp.	New York, USA	Plasmidic	(Huang and Burr, 1999)	Environmental isolate
Streptomycin	*Pseudomonas* sp.	New York, USA	Plasmidic	(Burr et al., 1993)	Environmental islate
Streptomycin	*Pseudomonas syringae*	Oregon, USA	*strAB*	(Scheck et al., 1996)	Environmental isolate[13]
Streptomycin	*P. syringae*	British Columbia, Canada	ND	(De Boer, 1980)	Environmental isolate[14]
Streptomycin	*P. syringae*	New Zealand	ND	(Young, 1977)	Environmental isolate
Streptomycin	*P. syringae*	?	ND	(Hwang et al., 2005)	Environmental isolate
Streptomycin	*P. syringae*	Michigan, USA	ND	(Sobiczewski et al., 1991)	Environmental isolate[15]

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[13] Presence of the *strAB* genes was determined by hybridization, but structural genes of Tn*5393* were not screened for.

[14] Isolation of streptomycin-resistant bacteria from a nursery where streptomycin had been used for control.

[15] In this paper, there are other resistant epiphytic bacteria that were found (not PPB) but they are not reported in this table.

Streptomycin	*P. syringae*	Oklahoma, USA	*strA-strB* on Tn*5393*	(Sundin et al., 1995)	Environmental isolate[16]
Streptomycin	*P. syringae*	Oklahoma, USA	Plasmidic	(Sundin et al., 1994)	Environmental isolate
Streptomycin	*X. axonopodis* pv. *diefenbachiae*	Los Banos, Philippines	ND	(Valencia et al., 2005)	Environmental isolate
Streptomycin	*Xanthomonas axonopodis* pv. *punicae*	India	*rpsL* mutation or *strA-strB*	(Krishna et al., 2020)	Environmental isolate
Streptomycin	*X. campestris* pv. *malvacearum*	India	ND	(Nafade and Verma, 1985)	NA
Streptomycin	*Xanthomonas arboricola* pv. *pruni*	South Carolina, USA	14-20 kb plasmid carrying *tetC*, *tetR* and *strAB*	(Herbert et al., 2022)	Environmental isolate
Streptomycin	*Xanthomonas axonopodis* pv. *vesicatoria*	Brazil	ND	(Quezado-Duval et al., 2003)	Environmental isolate
Streptomycin	*Xanthomonas campestris* pv. *vesicatoria*	Argentina	Tn*5393*b	(Sundin and Bender, 1995)	Environmental isolate[17]
Streptomycin	*X. campestris* pv. *vesicatoria*	Florida, USA	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Ohio, USA	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Georgia, USA	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	California, USA	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Pennsylvania, USA	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Argentina	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Taiwan	ND	(Minsavage et al., 1990)	Environmental isolate

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[16] Also some phylloplane isolates that were streptomycin resistant

[17] Strains from (Garde and Bender, 1991) and (Minsavage et al., 1990)

Streptomycin	*X. campestris* pv. *vesicatoria*	Brazil	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*X. campestris* pv. *vesicatoria*	Tonga	ND	(Minsavage et al., 1990)	Environmental isolate
Streptomycin	*Xanthomonas gardneri*	Brazil	ND	(Quezado-Duval et al., 2003)	Environmental isolate
Streptomycin	*Xanthomonas oryzae* pv. *oryzae*	China	*aadA1*	(Xu et al., 2013). (see also (Xu et al., 2010))	Environmental isolate
Streptomycin	*X. oryzae* pv. *oryzicola*	China	*rpsL* mutation	(Zhang et al., 2011)	*In vitro* induced resistance. Unclear if the original strain is environmental or not
Streptomycin	*Xanthomonas perforans*	North Carolina, USA	ND	(Adhikari et al., 2019)	Environmental isolate
Streptomycin	*Xanthomonas smithii* subsp. *citri*	South Korea	*strB*	(Hyun et al., 2012)	Environmental isolate[18]
Streptomycin	*Xanthomonas* spp.	Brazil	ND	(Araújo et al., 2012)	Environmental isolate
Streptomycin	*Xanthomonas vesicatoria*	Brazil	ND	(Quezado-Duval et al., 2003)	Environmental isolate
Zhongshengmycin	*X. oryzae*	China	Increased fatty acid biosynthesis. Exact mechanisms are not known yet	(Wang et al., 2021a)	*In vitro*

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[18] Presence of the *strB* gene was determined by PCR but *strA* or structural genes of Tn*5393* were not screened for.

The resistances acquired by HGT can be easily transferred between bacteria since they are often found on MGEs. There are multiple genes encoding resistance for one antibiotic, which means that bacteria have several ways to resist to a single antibiotic. This illustrates very well the complexity of antibiotic resistance. In particular, the gene pair *strA-strB* is often found on a remarkable transposon, Tn*5393*. It can be found in a variety of bacterial species and on a variety of plasmids too, some of which have the potential to be transferred, allowing bacteria to exchange genetic material between them at the time being. In that way, ARGs can possibly spread between bacteria.

Globally, there are very few resistance reports except for streptomycin, which is the most used antibiotic in plant agriculture. Streptomycin resistance found in 18 countries. For gentamicin, there is only one report of resistance from 2013, in China, where gentamicin is not officially used. For oxolinic acid, there are only two countries where resistance was reported and they both used oxolinic acid in crop protection. For oxytetracycline, resistance is reported in countries where it is used (USA) and also in countries where it is not used (Brazil and UK). The report of resistance originating from the UK is from 1997. At that time, streptomycin, oxytetracycline and kasugamycin were used on ornamentals in the UK (Young et al., 1999). Carrying out a study today in the UK to see if resistant strains can still be isolated could be of interest. The other report of resistance from Brazil is from 1995, which could provide a hint that Brazil used this antibiotic in the past. This would need to be investigated further and highlights another challenge of this project: to retrieve information on the currently approved uses and on uses that were approved in the past. For kasugamycin, resistances were only reported in countries where it is used. A summary of Table 31 compiling all resistance cases known is presented at Table 32.

Regarding streptomycin, the situation is more complex as it is the most used antibiotic. Seventy-eight percent of resistance cases were reported in countries where streptomycin is used on crops (Annex B). In China, Brazil and Israel, there are both old and recent resistance reports. For the other countries (Morocco, Philippines, Syria, Taiwan, Tonga), resistance reports are older so we cannot exclude a previous use of antibiotics on crops. For five antibiotics, world maps were established illustrating where resistance cases are reported and where the corresponding antibiotic is used (Annex B).

Table 32: Summary of resistance reports by locations. Number of cases = number of publications reporting resistance cases. In some publications, several isolates are described.

	Number of cases	Locations
Antibiotic		
Streptomycin	104	Argentina (1.9%), Brazil (5.7%), Canada (4.8%), Chile (1%), China (4.8%), Egypt (1%), India (1.9%), Israel (1.9%), Japan (4.8%), Mexico (4.8%), Morocco (1%), New Zealand (3.7%), The Philippines (1%), South Korea (5.7%), Syria (1%), Taiwan (1%), Tonga (1%), USA (53%)
Oxytetracycline	5	Brazil, UK, USA
Oxolinic acid	7	Israel, Japan
Kasugamycin	13	Brazil, Japan, USA

Gentamicin	1	China
Bismerthiazol	1	China
Shenqinmycin	1	China
Zhongshengmycin	1	China

- **Collection and review of data and information on alternative and innovative treatments for the control of systemic plant pathogenic bacteria**
    - Data from scientific literature

Integrated management of plant pathogenic bacteria encompasses many concepts that can be considered as alternatives to the use of antibiotics. The management and control of these bacterial pathogens require a comprehensive approach that goes beyond the traditional reliance on synthetic chemical substances. To implement efficient integrated management of PPB various concepts and practices need to be addressed to minimize disease incidence and severity. This multifaceted approach incorporates a range of alternative measures, including cultural practices, biological control agents, host resistance, and advanced diagnostic techniques. By adopting an integrated approach, farmers and plant health professionals could mitigate the impact of bacterial diseases while minimizing the risks associated with antibiotic use. The investigation of the scientific literature performed in this work delves into the principles and components of integrated management, exploring the diverse strategies that could offer promising alternatives to antibiotics fighting against plant pathogenic bacteria.

In this work, the analysis of the scientific literature gathered mainly publications dealing with the management of *R. solanacearum* (35%), *Xanthomonas citri and Xanthomonas oryzae* and *Xanthomonas oryzicola* (22%), *Candidatus Liberibacter* (21%), *Erwinia* and *Pectobacterium* (10%) and *Xylella fastidiosa* (9%). Most alternatives focused on the direct control of plant pathogenic bacteria (50% of publications). Solutions increasing host resistance, either through plant defense stimulation or breeding resistant cultivars were also well represented (29%) and distributed among all investigated PPB. Strategies addressing vector controls were specific to insect-transmitted PPB *Candidatus Liberibacter* and *Xylella fastidiosa*.

The use of biocontrol agents (BCA) is a very popular alternative studied by the scientific community. About half of active principles identified in this work are BCA categorized according their use as: antimicrobial producer, competitor, parasite, parasitoid, phage, plant defense inducer, plant growth promoter or predator (cfr. Supplementary Table Plantibio-EFSA-WP3-Scientific-literature-database). Most of retrieved BCA are bacteria (47%) that belongs for a large part to genera of *Bacillus* sp., *Pseudomonas* sp., *Streptomyces* sp. and *Pantoea* sp.. *Bacillus* bacteria account for 41% of all retrieved bacterial BCA and are mainly strains of: *Bacillus amyloliquefaciens*, *Bacillus subtilis*, *Bacillus thuringiensis* and *Bacillus cereus*. *Bacillus thuringiensis* are well-known bioinsecticide and have been proposed as a way to control vectors of PPB such as *Candidatus Liberibacter* or *Xylella fastidiosa* (de Oliveira Dorta *et al*., 2018). *Bacillus cereus* are more surprisingly referenced as plant growth promoters along with some *Bacillus amyloliquefaciens* and *Bacillus subtilis* (Caulier *et al*., 2018). These last two are also well-known antimicrobial producers. The table hereunder summarizes and categorizes microbial biocontrol agents retrieved in this study (Table 33).

Table 33: Microbial biocontrol agents retrieved in this work.

Species	Strain	Targeted PPB	Reference
Antimicrobial producer			
Achromobacter xylosoxidans	AF302097	*Pectobacterium carotovora subsp. atroseptica*	Reiter *et al.* (2002)
	unspecified	*Xylella fastidiosa*	Rolshausen *et al.* (2017)
Acinetobacter baumanni	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Acinetobacter sp.	C1010	*Pectobacterium carotovorum*	Kang *et al.* (2004)
	Xa6	*Ralstonia solanacearum*	Xue *et al.* (2009), Xue *et al.* (2013)
Agrobacterium tumefaciens	IISRGAB24	*Ralstonia pseudosolanacearum*	Prameela *et al.* (2019)
Arthrobacter sp.	IBN110	*Pectobacterium carotovorum*	Park *et al.* (2003)
	SJN5	*R. solanacearum*	Zhang *et al.* (2018)
Aureobasidium pullulans	CF10, CF40	*Erwinia amylovora*	Kunz (2004)
Bacillus amyloliquefaciens	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	Hg77	*E. amylovora*	Kunz (2004)
	Ba_Abi	*R. solanacearum*	Sakthivel *et al.* (2019)
	BgC31		Hu *et al.* (2010)
	IMA1, IMA10, IMA2, IMA6,		Alamer *et al.* (2020)
	5YN8		Yang *et al.* (2012)
	PMB05		Ho *et al.* (2020)
	S13-3		Yamamoto *et al.* (2015)
	S20		Chen *et al.* (2014)
	SQR-101,		Yuan *et al.* (2014)
	SQY 162		Wu *et al.* (2014), Wu *et al.* (2015a)
	T-5		Tan *et al.* (2016)
	VLY24		Athira *et al.* (2020)
	QL-18		Wei *et al.* (2015c)
	VLY24		Athira *et al.* (2020)
	ZM9		Wu *et al.* (2016)
	IUMC7		Sotoyama *et al.* (2017)
	WG6-14	*Xanthomonas axonopodis pv. citri*	Huang *et al.* (2012)
	D29	*X. oryzae pv. oryzae*	El-Shakh *et al.* (2015), Abdallah *et al.* (2016)
	A1, A13, 13		El-Shakh *et al.* (2015)
	D747, N3.2, S106.1b, S109.3, S77.1	*Xylella fastidiosa*	Zicca *et al.* (2020)
Bacillus atrophaeus	Sb3-13	*R. solanacearum*	Koberl *et al.* (2013)
Bacillus cereus	unspecified		Xia *et al.* (2016)
	IMA11, IMA4, IMA7		Alamer *et al.* (2020)
	UFV-6		Santiago *et al.* (2015)
	AR156		Wang *et al.* (2019)

Bacillus licheniformis	GAP 107	*Ralstonia pseudosolanacearum*	Bhai *et al.* (2019)
	IISRGAB 107		Prameela *et al.* (2019)
Bacillus macroides	MB16RNAA	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
Bacillus marisflavi	IISRGAB 43	*Ralstonia pseudosolanacearum*	Prameela *et al.* (2019)
Bacillus megaterium	AF142677	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
	Bx160Bx62, Bx95	*E. amylovora*	Jock *et al.* (2002)
	TR6	*R. solanacearum*	Nguyen *et al.* (2010)
B. methylotrophicus	DR-08	*C. michiganensis*	Im *et al.* (2020)
		R. solanacearum	
		Xanthomonas axonopodis pv. citri	
		Xanthomonas oryzae pv. oryzae	
	SQR-29	*R. solanacearum*	Yuan *et al.* (2014)
	H8	*Xanthomonas oryzae pv. oryzae*	El-Shakh *et al.* (2015), Abdallah *et al.* (2016)
	A2		El-Shakh *et al.* (2015)
Bacillus mojavensis	Mc3-4	*R. solanacearum*	Koberl *et al.* (2013)
	N67.B2	*Xylella fastidiosa*	Zicca *et al.* (2020)
Bacillus pumilus	WP8	*R. solanacearum*	Shen *et al.* (2018)
	S110.1	*Xylella fastidiosa*	Zicca *et al.* (2020)
	L36		Mourou *et al.* (2022)
Bacillus safensis	S109.4		Zicca *et al.* (2020)
Bacillus simplex	N58.2		Zicca *et al.* (2020)
Bacillus sp.	unspecified	*Pseudomonas syringae pv. syringae*	Poveda *et al.* (2021)
	CB00687, CB00729, CB00893,	*Candidatus Liberibacter asiaticus*	Blacutt *et al.* (2020)
	YD1	*Pectobacterium carotovorum*	Liao (2009)
	DR238, DR242, DR243,	*R. solanacearum*	Ho *et al.* (2020)
	EB69, RP7		Raman *et al.* (2012)
	EC13, EC4, RCh6		Ramesh *et al.* (2009)
	CB64		Kariuki *et al.* (2020)
	SS12.9	*Xanthomonas oryzae pv. oryzae*	Berić *et al.* (2012)
Bacillus spizizenii	Mc2Re-2, Sd8Re-6	*R. solanacearum*	Koberl *et al.* (2013)
Bacillus subtilis	unspecified	*Candidatus Liberibacter asiaticus*	Poveda *et al.* (2021)
	unspecified	*R. solanacearum*	Santiago *et al.* (2015)
	unspecified		Abd-El-Khair *et al.* (2012)
	unspecified		Elazouni *et al.* (2019)
	unspecified		Xia *et al.* (2016)
	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	unspecified	*Xanthomonas oryzae pv. oryzae*	Rashidah Abd *et al.* (2020)
Bacillus subtilis	L1-21	*Candidatus Liberibacter asiaticus*	Li *et al.* (2022)

	ALB629	*Curtobacterium flaccumfaciens pv. flaccumfaciens*	Martins *et al.* (2014)
	BD170	*E. amylovora*	Kunz (2004), Broggini *et al.* (2005)
	QRD-137		Stockwell *et al.* (1996)
	IISRGAB 5	*Ralstonia pseudosolanacearum*	Prameela *et al.* (2019)
	CYBS-1, CYBS-12, CYBS-13,	*R. solanacearum*	Chen *et al.* (2013)
	Lu144		Ji *et al.* (2008b)
	SSL2		Jinal *et al.* (2020)
	Mc3Re-13, Mc5-19, Mc5Re-15, Sb1-6, Sb3-5, Sb4-23, Co1-6		Koberl *et al.* (2013)
	B2G		Lemessa *et al.* (2007)
	AR12		Li *et al.* (2008)
	AR12, SM21		Liu *et al.* (2014)
	B-001		Peng *et al.* (2017)
	B315		Prihatiningsih *et al.* (2020)
	Bs_Adg, Bs_Ahv, Bs_Ane, Sm4		Sakthivel *et al.* (2019)
	1JN2		Yang *et al.* (2012), Yang *et al.* (2018b)
	TKS1-1	*Xanthomonas axonopodis pv. citri*	Huang *et al.* (2012)
	NIBSM_OsR10, NIBSM_OsS1,	*Xanthomonas oryzae pv. oryzae*	Vinay *et al.* (2020)
	A15		El-Shakh *et al.* (2015), Abdallah *et al.* (2016)
	L39	*Xylella fastidiosa*	Mourou *et al.* (2022)
	N67.A		Zicca *et al.* (2020)
Bacillus tequilensis	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Bacillus thermophilus	NIBSM_OsR15	*Xanthomonas oryzae pv. oryzae*	Vinay *et al.* (2020)
Bacillus thuringiensis	B18, COT1	*Pectobacterium carotovorum*	Dong *et al.* (2004)
	CR-371	*R. solanacearum*	Elsharkawy *et al.* (2015)
	UFV-56		Santiago *et al.* (2015)
	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Bacillus thuringiensis subsp. leesis	BMB821A	*Pectobacterium carotovorum*	Zhu *et al.* (2006)
Bacillus thuringiensis subsp. israelensis	B23		Dong *et al.* (2004)
Bacillus thuringiensis subsp. kurstaki	B2, B22		
Bacillus thuringiensis subsp. thuringiensis	B1		
Bacillus thuringiensis subsp. wuhanensis	B17		
Bacillus vallismortis	Wb2n-1	*R. solanacearum*	Koberl *et al.* (2013)
Bacillus velezensis	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	9D-6	*R. solanacearum*	Grady *et al.* (2019)
	B63		Elsayed *et al.* (2020)
	FJAT-46737		Chen *et al.* (2020a)

	GL3, GL5, GMC2		Heena *et al.* (2020)
	PCSE10		Athira *et al.* (2020)
	NIBSM_OsS6	*Xanthomonas oryzae pv. oryzae*	Vinay *et al.* (2020)
	QST713	*Xylella fastidiosa*	Zicca *et al.* (2020)
Bipolaris panici-miliacei	DX-FOL2	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
Brevibacillus brevis	X23	*R. solanacearum*	Chen *et al.* (2012)
Burkholderia cepacia	EB9		Ramesh *et al.* (2009)
Burkholderia sp.	SJN3		Zhang *et al.* (2018)
Candida ethanolica	unspecified		Nguyen *et al.* (2010)
Chryseobacterium sp.	R89		Liu *et al.* (2014)
Cladosporium cladosporiodes	unspecified	*Candidatus Liberibacter asiaticus*	Poveda *et al.* (2021)
	CF0052, CF0053		Blacutt *et al.* (2020)
Clavibacter michiganensis	CLBSSRI	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
Cochliobolus sp.	unspecified	*Xylella fastidiosa*	Rolshausen *et al.* (2017)
Cryptococcus magnus	unspecified	*E. amylovora*	Pusey *et al.* (2009)
Curtobacterium sp.	CB00892, CB00945	*Candidatus Liberibacter asiaticus*	Blacutt *et al.* (2020)
Curtobacterium flaccumfaciens	unspecified	*Xylella fastidiosa*	Poveda *et al.* (2021)
Cyathus berkeleyanus	KKUNN1	*R. solanacearum*	Sutthisa *et al.* (2018)
Cyathus earlei	KKULP1		
Cyathus pallidus	KKITN3/KKULN 3, KKUITN2/KKUL		
Cyathus stercoreus	KKITP3/KKULP 3		
Cyathus striatus	KKU1, KKU2, KKU3, KKU4,		
Dendryphiella sp.	DX-FOF2	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
Drechslera gigantea	unspecified	*Xylella fastidiosa*	Poveda *et al.* (2021)
Enterobacter asburiae	NIBSM_OsR14, NIBSM_OsL2, NIBSM_OsR16	*Xanthomonas oryzae pv. oryzae*	Vinay *et al.* (2020)
Enterobacter cloacae	TR12	*R. solanacearum*	Nguyen *et al.* (2010)
Enterobacter sp.	EB44		Ramesh *et al.* (2009)
	En38		Kheirandish *et al.* (2015)
	Xy3		Xue *et al.* (2009)
Enterococcus mudtii	MC6	*Pectobacterium carotovorum* *Xanthomonas campestris pv.*	Trias *et al.* (2008)
Erwinia amylovora	Ea153 hrpL	*E. amylovora*	Johnson *et al.* (2009)
Epicoccum nigrum	CF0051	*Candidatus Liberibacter asiaticus*	Blacutt *et al.* (2020)
Flavobacterium sp.	B17 AB027704	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
Frateuria aurantia	FAU10481		
Geobacillus sp.	RC-14	*R. solanacearum*	Wei *et al.* (2015)
Geobacillus thermoparaffinivorans	unspecified	*Xanthomonas oryzae pv. oryzae*	Rashidah Abd *et al.* (2020)

Lactobacillus plantarum	TC110	*Xanthomonas campestris pv.*	Trias *et al.* (2008)
Lysinibacillus sphaericus	Ls_Agu	*R. solanacearum*	Sakthivel *et al.* (2019)
Lysobacter antibioticus	13-1	*Xanthomonas oryzae pv. oryzae*	Ji *et al.* (2008a)
Metarhizium anisopliae	unspecified		Kakumoni *et al.* (2020)
Methylobacterium mesophilicum	unspecified	*Xylella fastidiosa*	Poveda *et al.* (2021)
Methylobacterium sp.	unspecified	*Candidatus Liberibacter asiaticus* *Xylella fastidiosa*	Poveda *et al.* (2021)
Meyerozyma guilliermondii	TA-2	*R. solanacearum*	Elsharkawy *et al.* (2015)
Microbacterium oxydans	BA104	*Xylella fastidiosa*	Mourou *et al.* (2022)
Microbacterium sp.	AB004713	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
Microbispora sp.	SBP1L6	*Xanthomonas oryzae pv. oryzae*	Kampapongsa *et al.* (2016)
Micrococcus luteus	IISRGAB 48	*Ralstonia pseudosolanacearum*	Prameela *et al.* (2019)
Mitsuaria sp.	TWR114		Marian *et al.* (2019)
Myroides odoratimimus	3YW8	*R. solanacearum*	Yang *et al.* (2012)
Nocardioides sp.	A-1	*Xanthomonas oryzae pv. oryzae*	Gesheva *et al.* (2012)
Paenibacillus polymyxa	HY96-2	*R. solanacearum*	Yi *et al.* (2019)
	IMA5		Alamer *et al.* (2020)
	MB02-1007		Algam *et al.* (2010)
Paenibacillus rigui	S55	*Xylella fastidiosa*	Mourou *et al.* (2022)
Paenibacillus sp.	AF245034	*Pectobacterium carotovorum*	Reiter *et al.* (2002)
	Pb28	*R. solanacearum*	Kheirandish *et al.* (2015)
Pantoea agglomerans	unspecified	*Curtobacterium flaccumfaciens pv. flaccumfaciens*	Huang *et al.* (2007)
	Eh1087	*E. amylovora*	Giddens *et al.* (2003)
	unspecified	*Xylella fastidiosa*	Arora *et al.* (2020)
Pantoea agglomerans	unspecified	*E. amylovora*	Pusey *et al.* (2009)
	LRC 8311	*Curtobacterium flaccumfaciens pv. flaccumfaciens*	Hsieh *et al.* (2005)
	C9-1	*E. amylovora*	Anderson *et al.* (2004), Pusey *et al.* (2009)
	E325		Pusey *et al.* (2008)
	C-91		Stockwell *et al.* (1996)
	Eh252		Anderson *et al.* (2004)
	H.M. 32/99		Bubán *et al.* (2004)
	C9-1S		Johnson *et al.* (2009)
	ABc5	*R. solanacearum*	Xue *et al.* (2013)
	CFSAN047153, MSMHa, S33	*Xanthomonas oryzae pv. oryzae*	Yang *et al.* (2020b)
Pantoea ananatis	EM2-53, GDYCa, Os_Ep_VSA_42, OsEnb_PLM_L19.1, PA, PP1, ZFZa		Yang *et al.* (2020b)
Pantoea dispersa	N10	*R. solanacearum*	Zhang *et al.* (2018)
Pantoea sp.	CB0072	*Candidatus Liberibacter asiaticus*	Blacutt *et al.* (2020)
Paraburkholderia phytofirmans	PsJN	*Xylella fastidiosa*	Baccari *et al.* (2019)

Penicillium funiculosum	DX-FOS2	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
Penicillium roqueforti	CGF-1	*R. solanacearum*	Muhammad *et al.* (2019b)
Phoma sp.	DX-FOF4, DX-FOF6, DX-	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
Pichia guillermondii	LR10	*R. solanacearum*	Nguyen *et al.* (2010)
Piriformospora indica	unspecified	*R. solanacearum*	Athira *et al.* (2020)
Pseudomonas aeruginosa	unspecified	*Candidatus Liberibacter asiaticus*	Poveda *et al.* (2021)
	unspecified	*R. solanacearum*	Mohammed *et al.* (2020)
	unspecified		Elazouni *et al.* (2019)
	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	BRp3	*Xanthomonas oryzae pv. oryzae*	Sumera *et al.* (2017)
	VIH2	*R. solanacearum*	Ge *et al.* (2017)
Pseudomonas alcaligenes	unspecified	*R. solanacearum*	Mohammed *et al.* (2020)
Pseudomonas brassicacearum	93D8, Wood 1R	*Ralstonia pseudosolanacearum*	Subedi *et al.* (2020)
Pseudomonas denitrificans	unspecified	*R. solanacearum*	Mohammed *et al.* (2020)
Pseudomonas entomophila	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Pseudomonas fluorescens	unspecified	*R. solanacearum*	Mohammed *et al.* (2020)
	unspecified		Xia *et al.* (2016)
	unspecified		Elazouni *et al.* (2019)
	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	unspecified	*Xylella fastidiosa*	Rolshausen *et al.* (2017)
	PfG32R	*Clavibacter michiganensis ssp. michiganensis*	Alit-Susanta *et al.* (2006a)
	A506	*E. amylovora*	Stockwell *et al.* (1996), Stockwell and Stack
	EPS62e		Bonaterra *et al.* (2007)
			Cabrefiga *et al.* (2007)
	AG3A, 2-79	*Pectobacterium carotovorum*	Liao (2009)
	P3/pME6863		Molina *et al.* (2003)
	PfG32R		Alit-Susanta *et al.* (2006)
		R. solanacearum	Alit-Susanta *et al.* (2006a)
	P142		Elsayed *et al.* (2020)
	Pf11, Pf16, Pp23		Kheirandish *et al.* (2015)
	APF1		Lemessa *et al.* (2007)
	SN15-2		Lou *et al.* (2018)
	EB89		Ramesh *et al.* (2009)
	WCS417r		Ran *et al.* (2005)
	P60		Soesanto *et al.* (2019)
	DABBV4		Vanitha *et al.* (2009)
	T5		Wang *et al.* (2005)

	J2		Zhou *et al.* (2014)
	PDY7	*Xanthomonas oryzae pv. oryzae*	Palaniyandi *et al.* (2013)
	Pf-4-R		Hunjan *et al.* (2017)
	PTB9		Palaniyandi *et al.* (2006)
Pseudomonas mallei	ET17, RBG4	*R. solanacearum*	Raman *et al.* (2012)
Pseudomonas protegens	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
	Clinto 1	*Ralstonia pseudosolanacearum*	Subedi *et al.* (2020)
Pseudomonas putida	A1	*R. solanacearum* *Xanthomonas axonopodis pv. citri* *Xanthomonas oryzae pv. oryzae*	Sun *et al.* (2017)
	EB8		Kakumoni *et al.* (2020)
	IMA3	*R. solanacearum*	Alamer *et al.* (2020)
	Pp17		Kheirandish *et al.* (2015)
	PP3WT		Kurabachew *et al.* (2013)
	BP25		Agisha *et al.* (2019)
Pseudomonas sp.	R4D2		Le *et al.* (2018)
	EB67		Ramesh *et al.* (2009)
	unspecified	*X. axonopodis pv. citri*	Poveda *et al.* (2021)
Pseudomonas stutzeri	unspecified	*R. solanacearum*	Mohammed *et al.* (2020)
Pseudomonas syringae	unspecified		Mohammed *et al.* (2020)
	ESC-10, ESC-11	*E. amylovora*	Stockwell and Stack (2007)
Pseudomonas taiwanensis	CMS	*Xanthomonas oryzae pv. oryzae*	Chen *et al.* (2020)
Rahnella aquatilis	39	*E. amylovora*	Kunz (2004)
Rhizobium leguminosarum	BR, R12, R21	*Curtobacterium flaccumfaciens*	Huang *et al.* (2007)
Rhizobium phaseoli	unspecified	*R. solanacearum*	Xia *et al.* (2016)
Rhizobium radiobacter	PCRE10		Athira *et al.* (2020)
Sarocladium sp.	DX-FOS3	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
Serratia nematodiphila	CT-78		Nguyen Dac *et al.* (2016)
Serratia sp.	Se40	*R. solanacearum*	Kheirandish *et al.* (2015)
Sphingobacterium sp.	unspecified	*Candidatus Liberibacter asiaticus*	Poveda *et al.* (2021)
Sporobolomyces roseus	CF35	*E. amylovora*	Kunz (2004)
Staphylococcus haemolyticus	IISRGAB146	*Ralstonia pseudosolanacearum*	Prameela *et al.* (2019)
Staphylococcus warneri	GL1	*R. solanacearum*	Heena *et al.* (2020)
Stenotrophomonas maltophilia	2JW6		Yang *et al.* (2012)
Stenotrophomonas maltophilia	PD4560		Elhalag *et al.* (2015)
Stenotrophomonas maltophilia	SMA293463, SMA293464	*Pectobacterium carotovorum*	Reiter *et al.* (2002)

Stenotrophomonas rhizophila	BA102	*Xylella fastidiosa*	Mourou *et al.* (2022)
Streptomyces avermectinius	NBRC14893	*R. solanacearum*	Elsharkawy *et al.* (2015)
Streptomyces diastaticus subsp. ardesiacus	FJAT-31547		Zheng *et al.* (2019a)
Streptomyces fimicarius	S2	*Xanthomonas oryzae pv. oryzae*	Kakumoni *et al.* (2020)
Streptomyces indianesis	TY68-3	*Xanthomonas oryzae pv. oryzicola*	Muangham *et al.* (2015)
		Xanthomonas oryzae pv. oryzae	
Streptomyces laurentii	S15		Kakumoni *et al.* (2020)
Streptomyces leeuwenhoekii	KBT004	*R. solanacearum*	Athira *et al.* (2020)
Streptomyces mycarofaciens	SS-2-243		Boukaew *et al.* (2011)
Streptomyces panaciradicis	NEAU-HV9		Ling *et al.* (2020)
Streptomyces peucetius	Wb2n-2		Koberl *et al.* (2013)
Streptomyces philanthi	RL-1-178		Boukaew *et al.* (2011)
Streptomyces physcomitrii	LD120		Zhuang *et al.* (2020)
Streptomyces scabiei	Wb1n-4		Koberl *et al.* (2013)
Streptomyces sp.	SBP4L3, SBP4LS20, SBP4LS21, SBP6LS4, SBP6LS8,	*Xanthomonas oryzae pv. oryzae*	Kampapongsa *et al.* (2016)
Streptomyces sp.	AB131-1, AB131-2,		Hastuti *et al.* (2012)
Streptomyces subrutilus	Wb2n-11	*R. solanacearum*	Koberl *et al.* (2013)
Streptomyces virginiae	E36, Y30		Tan *et al.* (2011)
Trichoderma album	unspecified		Abd-El-Khair *et al.* (2012)
Trichoderma asperelloides	T136		Khan *et al.* (2020b)
Trichoderma hamatum	unspecified		Abd-El-Khair *et al.* (2012)
Trichoderma harzianum	unspecified	*Xylella fastidiosa*	Poveda *et al.* (2021)
Trichoderma pseudoharzianum	T113, T129, T160	*R. solanacearum*	Khan *et al.* (2020b)
Trichoderma reesei	CGF-11		Muhammad *et al.* (2019b)
Trichoderma sp.	DX-FOR3	*Xanthomonas oryzae pv. oryzae*	Wang *et al.* (2015)
	unspecified	*R. solanacearum*	Elazouni *et al.* (2019)
	T1		Kariuki *et al.* (2020)
Competitor			
Alcaligenes xylosoxidansdenitrificans	unspecified	*Xylella fastidiosa*	Ramirez *et al.* (2008)
Arthrobacter gandensis	unspecified	*Xanthomonas axonopodis pv. passiflorae*	Halfeld-Vieira *et al.* (2015)
Arthrobacter koreensis			
Arthrobacter luteolus			
Bacillus amyloliquefaciens	SQY 162	*R. solanacearum*	Wu *et al.* (2017b)
Bacillus sp.	RCh6		Ramesh *et al.* (2012)
Bacillus subtilis	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)

Candidatus Phytoplasma	mali 1/93Tab, mali 1/93Vin	*Candidatus Phytoplasma mali*	Schneider *et al.* (2014)
Candidatus sulcia muelleri	unspecified	*Candidatus Phytoplasma sacchari*	Wangkeeree et al (2012)
Chryseobacterium nankingense	WR21	*R. solanacearum*	Huang *et al.* (2017)
Curtobacterium citreum	unspecified	*Xanthomonas axonopodis pv. passiflorae*	Halfeld-Vieira *et al.* (2015)
Enterobacter nimipressuralis			Halfeld-Vieira *et al.* (2015)
Enterobacter sp.	Xy3	*R. solanacearum*	Xue *et al.* (2013)
E. amylovora	Ea153 hrpL	*E. amylovora*	Johnson *et al.* (2009)
E. amylovora	PMV6023, PMV6046, hrpL		Faize *et al.* (2002)
Methylobacterium mesophilicum	SR1.6/6	*Xylella fastidiosa*	Gai *et al.* (2009)
Methylobacterium sp.	Sphingomonas sp. Methylocystaceae sp.	*Candidatus Liberibacter asiaticus*	Poveda *et al.* (2021)
Microbacterium oxydans	unspecified	*Xanthomonas axonopodis pv. passiflorae*	Halfeld-Vieira *et al.* (2015)
Mild strains	unspecified	*Candidatus Phytoplasma mali*	Schneider et al (2014)
Pseudomonas fluorescens	A506	*E. amylovora*	Anderson *et al.* (2004)
Pseudomonas fluorescens	EPS62e		Pujol *et al.* (2005)
Pseudomonas plecoglossicida	unspecified	*Xanthomonas axonopodis pv. passiflorae*	Halfeld-Vieira *et al.* (2015)
Ralstonia pickettii	QL-A6	*R. solanacearum*	Wei *et al.* (2013), Wei *et al.* (2017)
Ralstonia solanacearum	8103PC, 8224PC		Nakahara *et al.* (2016)
	FJAT-1458		Zheng *et al.* (2019b)
	PRS-84-4-49		Zhang *et al.* (2020b)
	ΔhrpB		Feng *et al.* (2012)
Stenotrophomonas sp.	unspecified	*Xanthomonas axonopodis pv. passiflorae*	Halfeld-Vieira *et al.* (2015)
Xanthomonas axonopodis	copA::Tn5	*Xanthomonas axonopodis pv. citri*	Teixeira *et al.* (2008)
Xylella fastidiosa	cutC	*Xylella fastidiosa*	Ge *et al.* (2022)
	EB92-1, Syc86-1		Hopkins *et al.* (2005)
Entomopathogen			
Bacillus thuringiensis	Cry10, Cry11, Cry2Aa, Cyt1A, S1989,	*Candidatus Liberibacter asiaticus*	Oliveira Dorta *et al.* (2018)
Acrostalagmus	unspecified		Hall *et al.* (2013)
Beauveria bassiana	unspecified		Hall *et al.* (2013)
	unspecified		Grafton-Cardwell *et al.* (2013)
	unspecified	*Candidatus Liberibacter solanacearum*	Vereijssen *et al.* (2018)

	unspecified		Villegas-Rodríguez *et al.* (2017)
	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
	from *C. pomonella*	*Candidatus Liberibacter solanacearum*	Lacey *et al.* (2009)
	BB42		Villegas-Rodríguez *et al.* (2017)
	HIB-24	*Candidatus Liberibacter asiaticus*	Gandarilla-Pacheco *et al.* (2013)
Caenorhabditis elegans	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Capnodium citri	unspecified	*Candidatus Liberibacter asiaticus*	Hall *et al.* (2013)
Cladosporium spec.	unspecified		
Conidiobolus sp.	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Cordyceps bassiana	unspecified	*Candidatus Liberibacter solanacearum*	Lezama-Gutiérrez *et al.* (2012)
Cordyceps fumosorosea	IF010	*Candidatus Liberibacter asiaticus*	Ou *et al.* (2019)
Cordyceps heteropoda	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Cordyceps javanica	GZQ-1	*Candidatus Liberibacter asiaticus*	Ou *et al.* (2019)
Cordyceps owariensis	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Corynebacterium			
Entomophtora			
Erynia gigantea			
Heterorhabditis amazonensis			
Heterorhabditis bacteriophora			
Heterorhabditis heliothidis			
Heterorhabditis sonorensis			
Heterorhabditis sp.			
Hexamermis dactylocercus			
Hirsutella			
Hirsutella citriformis	2H	*Candidatus Liberibacter asiaticus*	Hussain *et al.* (2018)
Hirsutella citriformis	HC3D		Hussain *et al.* (2018)
Hirsutella citriformis	IB-Hir-1, IB-Hir-2, INIFAP-Hir-1, INIFAP-Hir-2, INIFAP-Hir-2		Pérez-González *et al.* (2016)
Hirsutella citriformis	INIFAP-Hir-2, CHE-CNRCB339		Pérez-González *et al.* (2020)
Hirsutella citriformis	Speare		Hall *et al.* (2013)
Hirsutella citriformis	Speare		Grafton-Cardwell *et al.* (2013)
Hirsutella citriformis	unspecified		Cruz-Juárez *et al.* (2018)
Hirsutella homalodiscae	unspecified	*Xylella fastidiosa*	Boucias *et al.* (2007)
Hirsutella homalodiscae	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Isaria cicadae	unspecified		
Isaria fumosorosea	3A Ifr, 5F Ifr	*Candidatus Liberibacter asiaticus*	Hussain *et al.* (2018)
	HIB-19, HIB-32		Gandarilla-Pacheco *et al.* (2013)
	Wize (Paecilomyces fumosoroseus)		Grafton-Cardwell *et al.* (2013)
	Wize (Paecilomyces fumosoroseus)		Hall *et al.* (2013)

	PS Ifr		Hussain *et al.* (2018)
	unspecified	*Candidatus Liberibacter solanacearum*	Lacey *et al.* (2009)
	unspecified		Lacey *et al.* (2011)
	unspecified		Lezama-Gutiérrez *et al.* (2012)
	unspecified		Vereijssen *et al.* (2018)
	from Diaphorina citri Kuwayama 36		Lacey *et al.* (2009)
	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Isaria javanica	CHE-CNRCB 307	*Candidatus Liberibacter asiaticus*	Mellín-Rosas *et al.* (2016)
Isaria poprawskii	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Lecanicillium lecanii	unspecified	*Candidatus Liberibacter asiaticus*	Hall *et al.* (2013)
	unspecified		Grafton-Cardwell *et al.* (2013)
Lecanicillium attenuatum	ZJLA08	*Candidatus Liberibacter asiaticus*	Lu *et al.* (2015)
Lecanicillium muscarium	unspecified	*Candidatus Liberibacter solanacearum*	Vereijssen *et al.* (2018)
Lecanicillium psalliotae	ZJLP09	*Candidatus Liberibacter asiaticus*	Lu *et al.* (2015)
Lecanicillium sp.	ZJLSP07		
Isaria sinclairii	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Massopora cicadina	unspecified		
Massospora levispora	unspecified		
Massospora sp.	unspecified		
Metarhizium anisopliae	CNGD7	*Candidatus Liberibacter asiaticus*	Freed *et al.* (2011)
	unspecified	*Candidatus Liberibacter solanacearum*	Vereijssen *et al.* (2018)
	unspecified		Lacey *et al.* (2011)
	unspecified		Lezama-Gutiérrez *et al.* (2012)
	unspecified		Lacey *et al.* (2009)
	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
	DWR 346	*Candidatus Liberibacter solanacearum*	Lacey *et al.* (2009)
	F52		Lacey *et al.* (2011)
Metarhizium cylindrosporae	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Metarhizium cylindrosporum			
Metarizhium anisopliae	MA28	*Candidatus Liberibacter solanacearum*	Villegas-Rodríguez *et al.* (2017)
Nomuraea cylindrospora	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Nomuraea viridulus	unspecified		
Paecilomyces javanicus	unspecified	*Candidatus Liberibacter asiaticus*	Hall *et al.* (2013)
Penicillium sp	unspecified	*Xylella fastidiosa*	Serio *et al.* (2019)
Photorabhdus laumondii	MW574908		Vicente-Díez *et al.* (2021)
Xenorhabdus bovienii	MW467374		
Xenorhabdus nematophilus	MW574906		
Xenorhabdus kozodoii	MW467375		
Pseudogibellula sp.	unspecified		Boucias *et al.* (2007)
Pseudogibellula sp.	unspecified		Serio *et al.* (2019)
Purpureocillium lilacinum	ZJPL08	*Candidatus Liberibacter asiaticus*	Du *et al.* (2020)

Serratia marcescens	unspecified		Arp *et al.* (2017)
Sporothrix sp.	unspecified	*Xylella fastidiosa*	Boucias *et al.* (2007)
Sporothrix sp.	unspecified		Serio *et al.* (2019)
Steinernema sp.	unspecified		
Plant defense inducer			
Azospirillum brasilense	unspecified	*Candidatus Liberibacter asiaticus*	Trinidad-Cruz *et al.* (2019)
Bacillus amyloliquefaciens	unspecified		Poveda *et al.* (2021)
	IN937a	*R. solanacearum*	Jetiyanon *et al.* (2002)
	CM-2, T-5		Tan *et al.* (2013a)
	WBB70	*Xanthomonas oryzae pv. oryzae*	Akansha *et al.* (2020)
	Lx-11	*Xanthomonas oryzae pv. oryzicola*	Zhang *et al.* (2012)
Bacillus cereus	AR156	*R. solanacearum*	Niu *et al.* (2012)
Bacillus luciferensis	HRS4		Lee *et al.* (2020b)
Bacillus niacini	HRS2		
Bacillus pumilus	INR-7	*Erwinia tracheiphila*	Zehnder *et al.* (2001)
	IN937b, INR7, SE34, SE49,	*R. solanacearum*	Jetiyanon *et al.* (2002)
	SE34, T4	*Xanthomonas oryzae pv. oryzae*	Chithrashree *et al.* (2011)
Bacillus sphaericus	SE56	*R. solanacearum*	Jetiyanon *et al.* (2002)
Bacillus subtilis	ALB629, UFLA285	*Curtobacterium flaccumfaciens pv. flaccumfaciens*	Martins *et al.* (2013)
	L1-21	*Candidatus Liberibacter asiaticus*	Munir *et al.* (2020)
	168, OKB105, OKBHF	*R. solanacearum*	Gao *et al.* (2013)
	SSR2I		Jinal *et al.* (2020)
	GBO3	*Xanthomonas oryzae pv. oryzae*	Chithrashree *et al.* (2011)
	OKB105 harboring	*Xanthomonas oryzae pv. oryzicola*	Wu *et al.* (2009)
Bacillus thuringiensis subsp. fukuokaensis	B88-82	*R. solanacearum*	Takahashi *et al.* (2014)
Brevibacterium frigoritolerans	HRS1	*R. solanacearum*	Lee *et al.* (2020b)
Enterobacter cloacae	PS14		Mohamed *et al.* (2020)
Lactobacillus paracasei	unspecified		Konappa *et al.* (2016)
Lysinibacillus sphaericus	unspecified	*Xanthomonas oryzae pv. oryzae*	Leiwakabessy *et al.* (2018)
Methylobacterium sp.	CBMB12, CBMB15, CBMB27	*R. solanacearum*	Yim *et al.* (2013)
Pseudomonas aeruginosa	unspecified	*X. axonopodis pv. citri*	Poveda *et al.* (2021)
Pseudomonas chlororaphis	O6	*Pectobacterium carotovorum*	Spencer *et al.* (2003)
Pseudomonas fluorescens	Pf2	*R. solanacearum*	Abo-Elyousr *et al.* (2012)
Pseudomonas geniculata	unspecified	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Ralstonia solanacearum	ZJ3721:phcA	*R. solanacearum*	Chen *et al.* (2015a)

Serratia marcescens	Bizio 90-166,	*Erwinia tracheiphila*	Zehnder *et al.* (2000)
Solibacillus silvestris	HRS3	*R. solanacearum*	Lee *et al.* (2020b)
Stenotrophomonas maltophilia	PD4560	*R. solanacearum*	Elhalag *et al.* (2016)
Xanthomonas axonopodis pv. citri	AT, Xfa	*Xanthomonas axonopodis pv. citri*	Poveda *et al.* (2021)
Aspergillus spinulosporus	WBF4	*Xanthomonas oryzae pv. oryzae*	Akansha *et al.* (2020)
Epicoccum nigrum	unspecified	*Candidatus Phytoplasma mali*	Musetti *et al.* (2011)
Glomus mosseae	171	*R. solanacearum*	Yuan *et al.* (2016)
Penicillium chrysogenum	PenC_JSB41	*R. solanacearum*	Jogaiah *et al.* (2013)
Pythium oligandrum	unspecified	*R. solanacearum*	Takenaka *et al.* (2008)
	MMR2	*R. solanacearum*	Hase *et al.* (2006), Masunaka *et al.* (2009)
Rhizophagus irregularis	unspecified	*Candidatus Phytoplasma rubi* *Candidatus Liberibacter solanacearum*	Rufo *et al.* (2017)
Trichoderma asperellum	T34	*R. solanacearum*	Mohamed *et al.* (2020)
Trichoderma harzianum	SQR-T037	*R. solanacearum*	Yuan *et al.* (2016)
	TriH_JSB27		Jogaiah *et al.* (2013)
Plant growth promoter			
Achromobacter insolitus	RZ2.1AP4	*R. solanacearum*	Trimurti *et al.* (2018)
Agrobacterium tumefaciens	XB86		Achari *et al.* (2014)
Alcaligenes faecalis	AJ14	*Xanthomonas oryzae pv. oryzae*	Rahma *et al.* (2019)
Bacillus amyloliquefaciens	LH23	*R. solanacearum*	Ding *et al.* (2013)
	SQR7		Yuan *et al.* (2014)
Bacillus cereus	AJ34	*Xanthomonas oryzae pv. oryzae*	Rahma *et al.* (2019)
	BC1AW, BC2BA, BC3AW,	*R. solanacearum*	Kurabachew *et al.* (2013)
	XB177		Achari *et al.* (2014)
	JN233	*Ralstonia syzygii subsp. indonesiensis*	Yanti *et al.* (2017)
Bacillus pumilus	unspecified	*R. solanacearum*	Kurabachew *et al.* (2014)
Bacillus sp.	BB11		Guo *et al.* (2004)
	Rh219	*Xanthomonas oryzae pv. oryzae*	Sumera *et al.* (2016)
Bacillus subtilis	LH36	*R. solanacearum*	Ding *et al.* (2013)
	PFMRI		Naser *et al.* (2008)
Burkholderia sp.	PsJN		Wang *et al.* (2006)
Flavomonas oryzihabitans	INR-5	*Erwinia tracheiphila*	Zehnder *et al.* (2001)
Paenibacillus macerans	BS-DFS, PF9	*Ralstonia solanacearum*	Naser *et al.* (2008)
Pseudomonas putida	89B61		Anith *et al.* (2004)
Pseudomonas fluorescens	ATCC 13525		Singh *et al.* (2012a)
Pseudomonas hibiscicola	RZ1.1AG4		Trimurti *et al.* (2018)
Pseudomonas oleovorans	Tm-Ab01		Thomas *et al.* (2016)
Pseudomonas putida	89B61	*Erwinia tracheiphila*	Zehnder *et al.* (2001)
Pseudomonas sp.	J3	*R. solanacearum*	Guo *et al.* (2004)

	s188, s215, s288		Srinivasamurthy *et al.* (2012)
	E227, E233, Rh323	*Xanthomonas oryzae pv. oryzae*	Sumera *et al.* (2016)
Serratia sp.	J2	*R. solanacearum*	Guo *et al.* (2004)
	Rh269	*Xanthomonas oryzae pv. oryzae*	Sumera *et al.* (2016)
Staphylococcus gallinarum	XB169	*R. solanacearum*	Achari *et al.* (2014)
Stenotrophomonas malthopilia	LMTSA5.4	*Xanthomonas oryzae pv. oryzae*	Rahma *et al.* (2019)
Stenotrophomonas pavanii	KJKB5.4		
Streptomyces sp.	XB200	*R. solanacearum*	Achari *et al.* (2014)

Combination of biological control agents, bacteria-bacteria or bacteria-fungi, seems to offer in specific case better efficacy than solo-use of BCA therefore rising the interest of scientific community in microbial consortium approaches (Table 34). *Trichoderma sp.,* another well-known fungal BCA, is often combined with other biocontrol agents and is well represented in collected data along with other genera: *Cladosporium* sp., *Cyathus* sp., *Glomus* sp., *Penicillium* sp. and *Phoma* sp.

Table 34: Bacterial biocontrol agent combination retrieved in this work.

Biocontrol agents	Targeted PPB	Host plant	Reference
Bacteria-bacteria			
Bacillus amyloliquefaciens + Bacillus tequilensis + Bacillus subtilis	*Xanthomonas axonopodis pv. citri*	Citrus	Poveda *et al.* (2021)
Bacillus amyloliquefaciens IN937a + Bacillus sphaericus SE56 + Bacillus pumilus IN937b, SE34, SE49, T4, and INR7	*Ralstonia solanacearum*	Tomato	Jetiyanon *et al.* (2002)
Bacillus amyloliquefaciens IN937a + Bacillus pumilus IN937b			
Bacillus subtilis GB03 + Bacillus amyloliquefaciens IN937	*R. solanacearum*		Anith *et al.* (2004)
Methylobacterium mesophilicum + Curtobacterium flaccumfaciens	*Xylella fastidiosa*	Citrus	Poveda *et al.* (2021)
Methylobacterium sp. + Sphingobacterium sp.	*Candidatus Liberibacter asiaticus*	Citrus	Poveda *et al.* (2021)
Methylobacterium sp. + Sphingomonas sp. + Methylocystaceae sp.			
P. fluorescens + P. viridiflava + P. syringae + Bacillus spp.	*Xanthomonas axonopodis pv. citri*	Citrus	Poveda *et al.* (2021)
PaeniBacillus rigui S55 + Bacillus subtilis L39 + Bacillus pumilus L36 + Microbacterium oxydans BA104 + Stenotrophomonas rhizophila BA102	*Xylella fastidiosa*	Olive	Mourou *et al.* (2022)
Pseudomonas fluorescens A506 + Pantoea agglomerans C9-1S	*Erwinia amylovora*		Johnson *et al.* (2009)
Pseudomonas fluorescens A506 + Pantoea agglomerans C9-1S + Erwinia amylovora Ea153 hrpL			
Pseudomonas fluorescens AG3A + Bacillus sp. YD	*Pectobacterium carotovorum*	Pepper	Liao (2009)
Pseudomonas putida EB8 + Streptomyces fimicarius S2 + Streptomyces laurentii S15	*Xanthomonas oryzae pv. oryzae*	-	Kakumoni *et al.* (2020)
Pseudomonas spp. + Bacillus sp.	*Xanthomonas axonopodis pv. citri*	Citrus	Poveda *et al.* (2021)
Streptomyces spp. + Pseudomonas spp. + Burkholderia spp.			
Bacteria-fungi			
Bacillus amyloliquefaciens IN937a + Trichoderma asperellum T8	*R. solanacearum*	Tomato	Narasimhamurthy *et al.* (2020)
Bacillus amyloliquefaciens IN937a + Trichoderma harzianum UNS35		-	
Bacillus amyloliquefaciens IN937a + Trichoderma longibrachiatum UNS11		-	
Bacillus amyloliquefaciens IN937a + Trichoderma viride UNS42		-	
Bacillus amyloliquefaciens WBB70 + Aspergillus spinulosporus WBF4	*Xanthomonas oryzae pv. oryzae*	-	Akansha *et al.* (2020)
Bacillus sp. CB64 + Trichoderma sp. T1	*R. solanacearum*	Tomato	Kariuki *et al.* (2020)

Bacillus subtilis SE34 + Trichoderma asperellum T8	*R. solanacearum*	Tomato	Narasimhamurthy *et al.* (2020)
Bacillus subtilis SE34 + Trichoderma harzianum UNS35			
Bacillus subtilis SE34 + Trichoderma longibrachiatum UNS11			
Bacillus subtilis SE34 + Trichoderma viride UNS42			
Burkholderia metallica + Bacillus territorii + P. granadensis + P. geniculata + Rhodococcus jialingiae + Bacillus pumilus	*Candidatus Liberibacter asiaticus*	Citrus	Poveda *et al.* (2021)
Piriformospora indica + Bacillus amyloliquefaciens VLY24	*R. solanacearum*	Tomato	Athira *et al.* (2020)
Piriformospora indica + Bacillus velezensis PCSE10			
Piriformospora indica + Streptomyces leeuwenhoekii KBT004			
Pseudomonas fluorescens Pf3 + Trichoderma asperellum T8	*R. solanacearum*	Tomato	Narasimhamurthy *et al.* (2020)
Pseudomonas fluorescens Pf3 + Trichoderma harzianum UNS35			
Pseudomonas fluorescens Pf3 + Trichoderma longibrachiatum UNS11			
Pseudomonas fluorescens Pf3 + Trichoderma viride UNS42			

Among fungal biocontrol agents identified in this work, a large set categorizes as entomopathogens. Fungal entomopathogens gathered here belongs in most parts to: *Isaria* sp., *Hirsutella* sp. (*Cordyceps* sp. anamorph), *Metarhizium* sp., *Beauveria* sp. and *Cordyceps* sp. species.

Parasitism of vectors of systemic PPB like *Candidatus Liberibacter* or *Xylella fastidiosa* through use of fungal entomopathogen is a well-investigated topic in biocontrol approaches. More peculiar is the use of insect's viruses as entomopathogen. Marutani-Hert *et al.* (2019) investigated two reoviruses-like coming from the cicadella *Nilaparvata lugens* as a potential biocontrol mean of *Diaphorina citri* transmitting the PPB *Candidatus Liberibacter asiaticus*.

Parasitoids, on the other hand, are well-known insect biological control agents. A vast array of those retrieved here and by EFSA (Serio *et al.,*2019) belongs to: *Anagrus* sp., *Gonatocerus* sp. and *Tamarixia* sp. species. In particular, three species of *Tamarixia* sp. (*Tamarixia dryi, Tamarixia radiata* and *Tamarixia triozae*) seem to be efficient at controlling the two main vectors of *Candidatus Liberibacter*: *Bactericera cockerelli* and *Diaphorina citri* (Qureshi *et al.*, 2009; Li *et al.,* 2018; Rasowo *et al.*, 2021*)*. Lourdes Ramírez-Ahuja *et al*. (2017) highlights the interest to combine the use of parasitoids and insect predators targeting different developmental stages of *Bactericera cockerelli* and yielding notable additive mortality. This study performed *in vitro* still needs in field confirmation but might be another valuable approach in preventing PPB vector dissemination. However, despite the identification of many PPB vector's predators, their use and effectiveness in the field remains poorly investigated and probably rely more on farming practices promoting their presence and early proliferation than their exogenous introduction.

Interestingly, it was suggested that insect BCA can be used as plant defense inducers. Yang et al. (2011), Liu et al. (2020) and Lee et al. (2012) report aphid's infestation on tobacco and pepper to prime plant defenses via salicylic acid pathway conferring protection against *R. solanacearum* and *Xanthomonas axonopodis* pv. *vesicatoria*. Besides plant defense induction, authors argue an impact of foliar aphid feeding on rhizospheric microbiota richness and structure increasing abundance of benefical microorganisms and decreasing population of the pathogen, *R. solanacearum*. Numerous studies are now focusing on biotic and abiotic factors impacting plant physiology and the associated microbiota trying to increase beneficial services.

Investigating the multipartite interactions among a pathogen, a nonvector, and a plant host, Prager et al. (2015) show Tobacco mosaic virus (TMV) to impact tomato physiology and notably affect the behavior of *Bactericera cockerelli*, vector of *Candidatus* Liberibacter solanacearum. Authors observe sugar ratio modifications in TMV-infected tomatoes leading to a reduction of psyllid attractiveness resulting in decreased infection by the PPB. This study highlights the potential interest in using attenuated plant viruses in vaccinelike strategies bringing other ways to prime plant defenses than known elicitors, later discussed.

Another well-known application of viruses as biocontrol agent is the used of bacteriophages targeting specifically plant pathogenic bacteria. An extensive set of PPB-phages are collected in this study and listed in the Table 35 hereunder. Identified PPB bacteriophages belong to four main families: Inoviridae, Myoviridae, Podoviridae and Siphoviridae. Bacteriophages from the Myoviridae, Podoviridae, Siphoviridae, and Inoviridae families exhibit distinct morphological characteristics. These differences arise from variations in the structure of their heads and tails. Myoviridae, Podoviridae and Siphoviridae are characterized by icosahedral head while the genetic material of Inoviridae is contained within a helical protein coat. Myoviridae phages have elongated contractile tails, Podoviridae phages possess short, non-contractile tails and Siphoviridae phages have long, non-contractile tails. Inoviridae phages have filamentous shapes. Understanding these morphological variations is essential for classifying and studying these phages, as well as exploring their potential applications in areas such as phage therapy either for human, veterinary or plant health.

Table 35: Bacteriophages targeting plant pathogenic bacteria.

	Family	Phage	Reference
Targeted PPB			
Agrobacterium tumefaciens	Myoviridae	Atu_ph02	Attai *et al.* (2018)
		Atu_ph03	
	Podoviridae	Atu_ph07	Attai *et al.* (2017)
Candidatus xenohaliotis californiensis	Siphoviridae	pCXc	Cruz-Flores *et al.* (2018)
Erwinia amylovora	Myoviridae	φEa116C	Schnabel and Jones (2001)
		M7	Born *et al.* (2011)
		Y2	
		PEaI(H)	Ritchie (1979)
		PEa7	
		phiEa2809	Lagonenko *et al.* (2015)
		φEa104	Müller *et al.* (2011)
		φEa116	
		ΦEa2345-6	Boulé *et al.* (2011)
		ΦEa21-4	Parcey *et al.* (2020)
		ΦEaH2A	Schwarczinger *et al.* (2017)
		ΦEaH5K	
		ΦEaH7B	
	Podoviridae	L1	Born *et al.* (2011)
		S6	
		phiEaP-8	Park *et al.* (2018)
		ΦEa1337-26	Boulé *et al.* (2011)
		ΦEa46-1-A1	Parcey *et al.* (2020)
	Siphoviridae	phiEaH1	Meczker *et al.* (2013)

		phiEaH2	Dömötör *et al.* (2012)
Pseudomonas syringae pv. *actinidiae*	Myoviridae	φPsa21	Wojtus *et al.* (2019)
		PN05	Ni *et al.* (2020)
		PN09	
		φXWY0014	Yin *et al.* (2019)
	Podoviridae	PPPL-1	Song *et al.* (2021)
		φPsa17	Frampton *et al.* (2015)
		φPSA2	Di Lallo *et al.* (2014)
		φXWY0026	Yin *et al.* (2019)
	Siphoviridae	φXWY0013	
Pseudomonas syringae pv. *aesculi*	Myoviridae	RC5CS	James *et al.* (2020)
	Podoviridae	2KS	
Pseudomonas syringae pv. *morsprunorum*	Podoviridae	MR8	Rabiey *et al.* (2020)
Pseudomonas syringae pv. *syringae*	Cystoviridae	Φ6	Pinheiro *et al.* (2019)
	Podoviridae	MR8	Rabiey *et al.* (2020)
Ralstonia solanacearum	Inoviridae	φRSM	Yamada *et al.* (2013)
		φRSM	Yamada *et al.* (2007)
		φRSS	
		φRSM3	Addy *et al.* (2012)
	Myoviridae	φRSL	Yamada *et al.* (2007)
		φRSA	
		φRSA1	Fujiwara *et al.* (2011)
		φRSL1	
		J6	Bhunchoth *et al.* (2015)
	Podoviridae	M5	Ramírez *et al.* (2020)
		M8	
		NJ-P3	Wang *et al.* (2019)
		NB-P21	
		NC-P34	
		NN-P42	
		φRSB1	Fujiwara *et al.* (2011)
		φRSB2	Bhunchoth *et al.* (2015)
		RsPod1EGY phage	Elhalag *et al.* (2018)
		vRsoP-WF2	Álvarez *et al.* (2019)
		vRsoP-WM2	
		vRsoP-WR2	
		NJ-P3	Wang *et al.* (2019)
		NB-P21	
		NC-P34	
		NN-P42	
		NJ-P3 + NB-P21 + NC-P34 + NN-P42	
		M5 + M8 phages	Ramírez *et al.* (2020)

	Siphoviridae	Reminis	Amarillas et. (2020)
	Unspecified	ΦRS5	Iriarte *et al.* (2012)
Xanthomonas albilineans	Podoviridae	FC24-Teja	Clavijo-Coppens *et al.* (2021)
		FC08-Olaya	
		FC15-Bolivar	
		FC17-Usaquen	
		FC25-Alcala	
		FC47-Fontebon	
		FC57-Sumapaz	
	Siphoviridae	FC41-Suba	
		FC44-Bosa	
	Unspecified	FC32-Tabio	
Xanthomonas arboricola pv. *juglandis*	Podoviridae	f20-Xaj	Retamales *et al.* (2016)
		f29-Xaj	
		f30-Xaj	
		P1–P12, P14, P17-18, P20	Romero-Suarez *et al.* (2012)
		Xaj2	Dömötör *et al.* (2016)
	Siphoviridae	P13, P15-16, P19, P21-26	Romero-Suarez *et al.* (2012)
		Xaj24	Dömötör *et al.* (2016)
		FC12-Bacata	
Xanthomonas axonopodis pv. *citri*	Inoviridae	XacF1	Ahmad *et al.* (2014)
	Podoviridae	FC28-Sopo	Clavijo-Coppens *et al.* (2021)
		FC30-Tabio	
		FC39-Tenjo	
		CP2	Balogh *et al.* (2008)
		Cp2	Ahmad *et al.* (2014)
	Siphoviridae	Cp1	Ahern *et al.* (2014)
		Cp1	Ahmad *et al.* (2014)
	Unspecified	XacN1	Yoshikawa *et al.* (2018)
		ΦXac2005-1	Balogh *et al.* (2008)
		ccΦ7	
		ccΦ13	
		ΦXacm2004-4	
		ΦXacm2004-16	
		ΦX44	
		ΦXaacA1	
Xanthomonas axonopodis pv. *citrumelo*	Unspecified	ΦXacm2004-4 + ΦXacm2004-16 + ΦX44	Balogh *et al.* (2008)
		ccΦ13 + α-MME + Φ5536	
Xanthomonas oryzae pv. *oryzae*	Inoviridae	Xf	Kuo *et al.* (1969)
	Myoviridae	OP2	Inoue *et al.* (2006)
		X1	Ogunyemi *et al.* (2019)

		X2	
		X3	
		X4	
		X5	
		OP2	Yoshimura *et al.* (1960)
		OP1	Wakimoto S (1954)
		OP1h	
		OP1h2	
	Siphoviridae	Xp10	Yuzenkova *et al.* (2003)
		φXo411	Lee *et al.* (2006)
	Unspecified	Xp12	Kuo *et al.* (1968)
		Xp10	
Xylella fastidiosa	Podoviridae	Paz	Ahern *et al.* (2014)
		FC24-Teja	Clavijo-Coppens *et al.* (2021)
		FC03-Usme	
	Siphoviridae	Salvo	Ahern *et al.* (2014)
		Sano	
		FC41-Suba	Clavijo-Coppens *et al.* (2021)
		FC44-Bosa	
		FC12-Bacata	
	Unspecified	FC32-Tabio	
		FC34-Tenjo	
		FC23-Cota	

Chemicals either synthetic or organic-based are the second most popular alternative investigated in the scientific community. Half of active substances identified in this work are of synthetic origin followed by plant extracted substances that account for a quarter of collected data. Other active substances are from microbial, insect or animal origin, also metalloids, antibodies and nucleotidic elements are retrieved. Chemical substances categorize according to their use: antimicrobial delivery system, antimicrobial substance, behaviour impairement substance (PPB and/or vector), insecticide, photosensitizer, plant defense inducer, plant growth promoter, physical barrier, substance interfering at RNA level (RNAi), biocide use for sanitization and trap system for vectors and PPB. As foreseeable, two third of identified active substances are described as antimicrobial substances and are listed in Supplementary Table Plantibio-EFSA-WP3-Scientific-literature-database.

In addition to antimicrobial substances, numerous synthetics found in PPB-related scientific literature serve as insecticides, a widely discussed topic when addressing vector transmitted PPB. Most studies focus on determining the efficacy of insecticides, either individually or in combination, in an attempt to decipher the insect's control specificity and its impact on different developmental stages. Interestingly coming after antimicrobial substances and insecticides, plant defense inducing synthetic substances are well listed in scientific papers (Table 36). Three substances seem to focus the interest and/or be used as references in host defense induction studies: acibenzolar-S-methyl, salicylic acid and potassium silicate.

Table 36: Chemical plant defense inducer retrieved in this study.

	Substance	Host plant	Reference
Targeted PPB			
Candidatus Liberibacter asiaticus	2,1,3-benzothiadiazole	Citrus	Li *et al.* (2016)
	2,6-dichloroisonicotinic acid		
	acibenzolar-S-methyl	Citrus	Hu *et al.* (2018)
	ascorbic acid	Citrus	Li *et al.* (2016)
	b-aminobutyric acid		
	epibrassinolide	Citrus	Canales *et al.* (2016)
	epibrassinolide		
	hexaacetyl-chitohexaose	Citrus	Shi *et al.* (2019)
	hexaacetyl-chitohexaose	Citrus	QuingChun et al (2019)
	imidacloprid	Citrus	Gatineau et al (2010)
	manganese	Citrus	Kadyampakeni et al (2019)
	methyl jasmonate	Sweet orange	Patt *et al.* (2018)
	nonmetabolizable glucose analog 2-deoxy-D-glucose (2-DDG)	Citrus	Li *et al.* (2016)
	oak extracts	Citrus	Pitino et al (2020)
	oxalic acid	Citrus	Hu *et al.* (2018)
	potassium phosphate		
	salicylic acid	Sweet orange	Patt *et al.* (2018)
	salicylic acid	Citrus	Hu *et al.* (2018)
	salicylic acid, Azospirillum brasilense Cd and chitosan	Citrus	Trinidad-Cruz et al (2019)
Candidatus Phytoplasma aur antifolia	Camellia sinensis	Citrus	Mollaei et Ghanavi (2020)
Erwinia amylovora	acibenzolar-S-methyl	Apple tree	Brisset *et al.* (2000)
		Apple tree	Baysal and Zeller (2004)

		Apple tree	Bubán *et al.* (2004)
		pear	Mazzucchi and Brunelli (2008)
		Loquat	Bastas and Maden (2007)
		Apple tree	Brisset *et al.* (2000)
	benzothiadiazole	Pear	Tsiantos *et al.* (2003)
		Pear	Sparla *et al.* (2004)
	fosetyl-Al	Pear	Tsiantos *et al.* (2003)
	hedera helix	Apple tree	Baysal and Zeller (2004)
Pseudomonas syringae pv. *tomato*	rutin		Yang *et al.* (2016b)
Ralstonia solanacearum	acibenzolar-S-methyl		Mamphogoro *et al.* (2020)
			Anith *et al.* (2004)
			Pradhanang *et al.* (2005)
		Tomato	Hacisalihoglu *et al.* (2007)
		Tomato	Ji *et al.* (2007)
		Tomato	Abo-Elyousr *et al.* (2012)
		Tomato	Ganiyu *et al.* (2018)
		Tomato	Ganiyu *et al.* (2020)
	calcium silicate	Pepper	Alves *et al.* (2015)
	cinnamaldehyde	Potato	Abdelrasoul *et al.* (2020)
	cis-abienol	Tomato	Seo *et al.* (2012)
	DL-3-aminobutyric acid	Tomato	Hassan *et al.* (2013)
	potassium silicate	Tomato	Wang *et al.* (2013a)
		Tomato	Kurabachew *et al.* (2014)
		Tomato	Chen *et al.* (2015b)
	riboflavin	Tobacco	Liu *et al.* (2010)
	rutin		Yang *et al.* (2016b)
	saccharum officinarum	Tomato	Yang *et al.* (2010)
	sclareol	Tomato	Seo *et al.* (2012)

	thymol	Tomato	Ganiyu *et al.* (2018)
	validamycin A		Rosskopf *et al.* (2005)
	validoxylamine		Rosskopf *et al.* (2005)
Xanthomonas axonopodis pv. *citri*	acibenzolar-s-methyl	Swingle citrumelo	Francis *et al.* (2008)
		Grapes	Graham *et al.* (2009)
	imidacloprid	Grapes	Graham *et al.* (2009)
		Swingle citrumelo	Francis *et al.* (2008)
	isonicotinic acid	Swingle citrumelo	Francis *et al.* (2008)
	thiamethoxam	Grapes	Graham *et al.* (2009)
Xanthomonas campestris	harpin		Obradovic *et al.* (2004)
Xanthomonas oryzae pv. *oryzicola*	fragment HpaG10-42	Rice	Chen *et al.* (2008)
	rutin		Yang *et al.* (2016b)
Xanthomonas oryzae pv. *oryzae*	acibenzolar-S-methyl	Rice	Babu *et al.* (2003)
	bismerthiazol		Liang *et al.* (2015)
	chromolaena odorata Extract	Rice	Khoa *et al.* (2011)
	daturilin	Rice	Sateesh *et al.* (2004)
	HrpZPsg protein	Rice	Wu *et al.* (2017a)
	niclosamide		Kim *et al.* (2016)
	Phosphite (PHI)		Huang *et al.* (2020)
	Rutin		Yang *et al.* (2016b)
	salicylic acid		Shasmita *et al.* (2019)
		Rice	Toan Le *et al.* (2017)
		Rice	Leiwakabessy *et al.* (2018)
	sulfated RaxX peptide		Wei *et al.* (2016)

Xylella fastidiosa	tolprocarb		Hagiwara *et al.* (2020)
	vitex nedungo		Selvamathiazhagan *et al.* (2012)
	zinc thiazole		Liang *et al.* (2015)
	abscisic acid		Meyer *et al.* (2011)
	NuovOlivo	Olive	Bruno *et al.* (2021) Morelli *et al.* (2021)
	harpin	Grapes	Tubajika *et al.* (2007)
			Serio *et al.* (2019)

Besides synthethics, plant extracts are also known to prime host defenses. Ganiyu *et al*. (2018) report significant results in the field of the combined application of thymol, extracted from *Thymus vulgaris*, and acibenzolar-S-methyl which reduced bacterial wilt disease and increased tomato yield. Abdelrasoul *et al.* (2020) show cinnamaldehyde to increase activity of peroxidase (POD), polyphenol oxidase (PPO) and the total phenolic content of potato tubers preventing infection of *R. solanacearum*. Several genes related to defense molecule biosynthesis and MAPK cascade components have been shown responsive to a diterpene extracted from *Salvia sclarea,* sclareol. Seo *et al.,* (2012) confirmed significant attenuation of wilt disease by sclareol and sclareol-related compound, cis-abienol, on tomatoes arguing the involvement of multiple host factors in the observed disease reduction. Other compounds such as rutin flavonoids, broadly distributed in fruits and vegetables, or daturilin, extracted from *Datura metel,* are reported to increase accumulation of pathogenesis related (PR) proteins enhancing defenses of rice, tobacco and tomato against *Xanthomonas oryzae* pv. *oryzae*, *R. solanacearum*, and *P. syringae* (Yang *et al*., 2016; Sateesh *et al*., 2004). Cannales *et al.* (2016) suggest epibrassinolide applied as a foliar spray to effectively reduced bacterial titers of *Candidatus* Liberibacter asiaticus, causal agent of Huanglongbing, in citrus both in greenhouse and field trials. Authors observed impact of the brassinosteroid application on the expression of known defense-related genes: superoxide dismutase, glutathione peroxidase, chitinase (CHI1), beta-1,3-glucanase, penylalanine ammonia-lyase, allene oxide synthase and fatty acid hydroperoxide lyase. Their results suggest epibrassinolide to be a potential valuable tool for managing HLB.

Plant extracts can be used to impair behavior of vectors transmitting PPB. Data collected here highlight the possibility to use them as repellent or attractant, usually displayed on sticky trap, but also to attract natural enemies in crop plots or to use them to interfere with vector mating behavior or disrupt host preference as showed by Martini *et al.* (2016). The main targets of such approaches are *Philaenus spumarius* transmitting *Xylella fastidiosa* and vectors of *Candidatus Liberibacter* bacteria: *Diaphorina citri*, *Bactericera cockerelli* and *Trioza erytreae*. When dealing with behavior disruption of insects transmitting PPB, the use of sound generator displaying white noise or playbacks obtained i.e. from prerecorded *P. spumarius* or *D. citri* might in the future help at preventing PPB dissemination (Lujo *et al.*, 2016; Gordon *et al.*, 2017; Avosani *et al.*, 2021).

Impairing behavior of organisms is a common approach developed in pest management but is more peculiar when targeting directly phytopathogens. In that particular perspective, Tran *et al.* (2016) are remarkably outlining in their review, how DNA-containing extracellular traps produced by plant root border cells in response to pathogenic infection, might be used as a potential defense mechanism against PPB. Indeed, emerging research indicates that border cells function in a comparable way to mammalian neutrophils, as both cell types release a combination of extracellular DNA (exDNA) and antimicrobial proteins. This intricate blend serves as a defense mechanism by ensnaring pathogens and thwarting their invasion into host tissues. However, despite the potential of this strategy in controlling bacterial phytopathogen, Tran *et al.* (2016) show *R. solanacearum* able to escape and degrade these traps by the production of specific DNases emphasizing the importance of also targeting these virulence factors for effective control of bacterial wilt disease. Exploring the potential for breeding selection methods that promote increased production of neutrophil extracellular traps and recruitment of rhizospheric beneficial microorganisms could offer a valuable approach to managing soil-borne plant pathogenic bacteria.

Numerous plant beneficial microorganisms produce secondary metabolites that act as antimicrobials or plant defense inducers. The bioactive substances synthesized by *Bacillus* sp., *Pseudomonas* sp., and *Streptomyces* genera listed in the Table 37 are recognized as such. Lipopeptides of *Bacillus* and *Pseudomonas* bacteria are notably known from scientific literature to be versatile weapons against phytopathogens (Ongena & Jacques, 2008; Raaijmakers *et al*., 2010; Caulier *et al*., 2018). In addition to bacterial antimicrobials, oxalic acids and cladosporols produced by fungi seem to exert significant activites helping at controlling *Xanthomonas axonopodis* pv. *citri*, *Pectobacterium carotovorum*, *R. solanacearum* and *Candidatus Liberibacter asiaticus* (Kwak *et al*., 2016; Blacutt *et al*., 2020).

Table 37: Antimicrobial bacterial substance targeting plant pathogenic bacteria.

Features	Targeted PPB	Producing bacteria	Antimicrobial substance
Antimicrobial substance			
	Candidatus Liberibacter asiaticus	*Bacillus* sp.	surfactin
	Clavibacter michiganensis subsp. michiganensis	*Bacillus subtilis*	difficidin
	Pseudomonas syringae	*Bacillus* sp.	decyl alcohol
			3,5,5-trimethylhexanol
		Pseudomonas sp.	bacteriocin LlpABW11M1
			bacteriocin LlpA1Pf-5
			bacteriocin LlpAPss642
	Ralstonia solanacearum	*Bacillus amyloliquefaciens*	fengycin
			2-nonanone
			2-undecanone
			7-O-malonyl macrolactin A
			bacillomycin D
			benzothiazole
			butylated hydroxytoluene
			macrolactin A
			nonanal
			surfactin B
			volatile organic compounds
			xylene
		Bacillus megaterium	pyrazine, 2-ethyl-3-methyl
		Bacillus methylotrophicus	difficidin
			oxydifficidin
		Bacillus subtilis	3,5,5-trimethylhexanol
			decyl alcohol
		Bacillus velezensis	fengycin
		Escherichia coli	cyclo(L-Pro-D-Ile)
		Ideonella sp.	β-hydroxypalmitate methyl ester hydrolase
		Pseudomonas fluorescens	volatile organic compounds
		Pseudomonas putida	bacterial Laccase
		Streptomyces panaciradicis	actinomycin D
	Xanthomonas axonopodis pv punicae	*Bacillus megaterium*	pyrazine, 2-ethyl-3-methyl
	Xanthomonas axonopodis pv. citri	*Bacillus subtilis*	oxydifficidin
			difficidin
		Pseudomonas sp.	bacteriocin LlpAXcm761

	Xanthomonas axonopodis pv.manihotis	*Pseudomonas* sp.	bacteriocin LlpAXcm761
	Xanthomonas oryzae pv. oryzicola	*Bacillus subtilis*	bacilysin
			difficidin
			decyl alcohol
			3,5,5-trimethylhexanol
		Pseudomonas aeruginosa	chumacin-1
			chumacin-2
		Pseudomonas sp.	phenazine-1-Carboxylic Acid
		Virgibacillus dokdonensis	1-deoxy-N-acetylglucosamine
	Xanthomonas oryzae pv. oryzae	*Bacillus subtilis*	difficidin
			oxydifficidin
			bacilysin
			decyl alcohol
			3,5,5-trimethylhexanol
			unkown peptide
		Bacillus velezensis	C15 surfactin A
		Pseudomonas aeruginosa	phenazine-1-carboxamide
			chumacin-1
			chumacin-2
		Pseudomonas sp.	phenazine-1-Carboxylic Acid
		Streptomyces palmae	(Z)-12-(2-methylphenyl)-11-dodecenoic acid
		Streptomyces sp.	staurosporine
		Virgibacillus dokdonensis	1-deoxy-N-acetylglucosamine
	Xanthomonas translucens pv. graminis	*Pseudomonas* sp.	bacteriocin LlpAXcm761
	Xanthomonas vasicola pv. holcicola	*Pseudomonas* sp.	bacteriocin LlpAXcm761
Plant defense inducer			
	Ralstonia solanacearum		riboflavin
	Xanthomonas oryzae pv. oryzicola	*Xanthomonas oryzae* pv. *oryzicola*	fragment HpaG10-42
	Xanthomonas oryzae pv. Oryzae	*Pseudomonas savastanoi* pv. *glycinea*	HrpZPsg protein
		Xanthomonas sp.	sulfated RaxX peptide
Vector behaviour impairement			
	Xylella fastidiosa	*Bacillus* sp.	volatile organic compounds

Breeding plant cultivars with resistance to plant pathogenic bacteria has been a longstanding approach in plant breeding programs. Rice lines resistant to *Xanthomonas oryzae* pv. *oryzae* and *Xanthomonas oryzae* pv. *oryzicola* are widely represented in the collected data. The review of scientific literature highlights traditional methods involved the identification and selection of naturally occurring resistant individuals or crossing them with susceptible varieties to transfer resistance genes but also the application of more recent methodologies. Indeed, numerous retrieved publications rely on marker-assisted selection (MAS) providing efficient selection methods. Additionally, genetic engineering approaches introducing resistance genes and genome editing technologies offer powerful tools for enhancing resistance traits. Through a combination of traditional breeding methods and cutting-edge technologies, the improved development of plant cultivars resistant to plant pathogenic bacteria, help at delivering new solutions for PPB management.

Finaly as aforementioned, PPB management needs multifaceted approach that must incorporate sounded and integrated farming practices. Implementation of quarantine regulations, along with early and efficient diagnosis, plays a crucial role in ensuring the use of healthy plant material. Effectiveness of thermal treatment for sanitizing plant material is also investigated, as it has been reported to be efficient against *Candidatus* Liberibacter asiaticus, *R. solanacearum*, *Xanthomonas oryzae* pv. *oryzae* and *Xylella fastidiosa* (Munir *et al.,* 2018; EFSA Journal 13.9, 2015; Jiang *et al.,* 2014). Altering planting timing to avoid periods of high disease incidence (Wei *et al.*, 2015; Lin *et al.,* 2013), promoting intercropping to enhance biodiversity and disrupt pathogen cycles (Lai *et al.,* 2011; Hall *et al.*, 2013, adapting crop rotation to break disease cycles and reduce pathogen buildup (Chellemi *et al*., 2013; Messiha *et al.,* 2019), implementing cover crops to suppress pathogens and improve microbial soil health (Morente *et al.*, 2022), grafting plants onto resistant rootstock to confer disease resistance traits (Proietti *et al.,* 2008; Uehara and Nakaho, 2017; Ganiyu *et al.*, 2020), and selecting specific organic soil amendments such as sugarcane bagasse (Ayana et al., 2011; Mamphogoro *et al.*, 2020) or vermicompost (Singh *et al.*, 2012) supplemented with plant growth-promoting microorganisms to create an unfavorable environment for pathogenic bacteria (Liu *et al.,* 2015; Dong *et al.,* 2020) and improve plant nutrition status are all addressed by the scientific literature. They are a key element of strategies that can help minimize the impact of PPB. By integrating these practices into agricultural systems, farmers can improve disease management, reduce reliance on chemical intervention, and grow healthier and more resilient crops.

- Data from grey literature

A direct search on the www, and specifically on the EU pesticide database on the one hand, and on the other hand, on the EPA website, targeted commercially available biocontrol measures and officially authorized both in the EU (Table 38) and in the US (Table 39), with products based on the yeast *Aureobasidium pullullans*, the bacteria *Bacillus amyloliquefaciens, B. mycoides, B. pumilus, B. subtilis, B. velezensis, Pseudomonas chlororaphis* or *Streptomyces* like *S. lydicus*. It shows that there are already commercially distributed biocontrol tools, for a wide range of plant pathogenic bacteria (from *Candidatus Liberibacter, Clavibacter michiganensis, Erwinia, Pectobacterium* sp., *Pseudomonas* sp., *Xanthomonas oryzae*). Nevertheless, with the exception of products targeting Huanglongbing, there is almost no alternative control measures for bacteria like Xylella or Phytoplasmas located into the xylem or the phloem if infected plants, respectively. This might be due to the difficulty of targeting such bacteria in such a specific niche.

This search also shows the number of emerging strategies for control with biocontrol agents like bacteria, also raising the question of the fact that such bacteria might also carry also resistance to antibiotics, possibly in association with mobile genetic elements, a possible risk to be assessed certainly prior approval of such biocontrol measures.

Table 38: Plant pathogenic bacteria biocontrol measures authorized in the EU.

PPB	Biocontrol bacteria	Status	Commercial designation
Candidatus Liberibacter sp.	*Bacillus amyloliquefaciens*	Approved	TAEGRO/SERIFEL/SERENADE ASO
	Bacillus subtilis strain IAB/BS03	Approved	FUNGISEI/PORTENTO/ SUBELUS/MILDORE/SEITYLIS
	Bacillus velezensis strain RTI301	Pending	/
Clavibacter michiganensis subsp. michiganensis	*Bacillus amyloliquefaciens*	Approved	TAEGRO/SERIFEL/SERENADE ASO
	Bacillus subtilis strain IAB/BS03	Approved	FUNGISEI/PORTENTO/SUBELUS/ MILDORE/SEITYLIS
	Trichoderma harzianum	Approved/pending	TRIANUM-GR/TRIANUM-P
Erwinia amylovora	*Aureobasidium pullulans*	Approved	BLOSSOM PROTECT/BOTECTOR
	Bacillus amyloliquefaciens	Approved	TAEGRO/SERIFEL/SERENADE ASO
	Pseudomonas chlororaphis	Approved	CERALL
Pectobacterium sp	*Bacillus amyloliquefaciens*	Approved	TAEGRO/SERIFEL/SERENADE ASO
	Bacillus pumilus QST 2808	Approved	BALLAD/PILOSEIN IT/SONATA
	Bacillus subtilis strain IAB/BS03	Approved	FUNGISEI/PORTENTO/SUBELUS/ MILDORE/SEITYLIS
	Bacteriophage	Approved	/
	Streptomyces K61	Approved	MYCOSTOP
	Streptomyces lydicus WYEC 108	Approved	/
	Trichoderma harzianum	Approved/pending	TRIANUM-GR/TRIANUM-P
Pseudomonas syringae pv. phaseolicola	*Bacillus subtilis strain IAB/BS03*	Approved	FUNGISEI/PORTENTO/SUBELUS/ MILDORE/SEITYLIS
Pseudomonas syringae pv. tomato	*Bacillus amyloliquefaciens*	Approved	TAEGRO/SERIFEL/SERENADE ASO
	Bacillus pumilus QST 2809	Approved	BALLAD/PILOSEIN IT/SONATA
Xanthomonas oryzae pv. oryzicola	*Bacillus velezensis strain RTI301*	Pending	/
Xanthomonas vesicatoria	*Bacillus pumilus QST 2808*	Approved	BALLAD/PILOSEIN IT/SONATA

Table 39: Plant pathogenic bacteria biocontrol measures authorized in the US.

Target PPB	Biocontrol bacteria	Status	Commercial designation

Candidatus Liberibacter sp.	*Bacillus amyloliquefaciens*	Registered	GH DNMT/CX-9025-TGAI/DOUBLE NICKEL LC RTU/CX-9030/CX-9032/F4120-2/F4120-1/WG Biological Fungicide/Varnimo WSP/COMPANION MAXX LIQUID BIOLOGICAL FUNGICIDE/ENV503 Biofungicide Wettable Powder
Candidatus Liberibacter sp.	*Bacillus subtilis*	Registered	BACILLUS SUBTILIS CX-9090/Mildore/Fungisei/Milagrum Plus/Shielder/BACIX/F4018-4/CX-9032/CX-9030/DOUBLE NICKEL LC RTU/CX-9025-TGAI/GH DNMT
Candidatus Liberibacter sp.	*Bacillus velezensis strain RTI301*	Registered	
Clavibacter michiganensis	*Bacillus amyloliquefaciens*	Registered	GH DNMT/CX-9025-TGAI/DOUBLE NICKEL LC RTU/CX-9030/CX-9032/F4120-2/F4120-1/WG Biological Fungicide/Varnimo WSP/COMPANION MAXX LIQUID BIOLOGICAL FUNGICIDE/ENV503 Biofungicide Wettable Powder
Clavibacter michiganensis	*Bacillus subtilis*	Registered	BACILLUS SUBTILIS CX-9090/Mildore/Fungisei/Milagrum Plus/Shielder/BACIX/F4018-4/CX-9032/CX-9030/DOUBLE NICKEL LC RTU/CX-9025-TGAI/GH DNMT
Erwinia amylovora	*Aureobasidium pullulans*	Registered	BOTECTOR/BLOSSOM PROTECT
E. amylovora	*Bacillus amyloliquefaciens*	Registered	GH DNMT/CX-9025-TGAI/DOUBLE NICKEL LC RTU/CX-9030/CX-9032/F4120-2/F4120-1/WG Biological Fungicide/Varnimo WSP/COMPANION MAXX LIQUID BIOLOGICAL FUNGICIDE/ENV503 Biofungicide Wettable Powder
E. amylovora	*Pseudomonas chlororaphis*	Registered	
Pectobacterium sp	*Bacillus amyloliquefaciens*	Registered	GH DNMT/CX-9025-TGAI/DOUBLE NICKEL LC RTU/CX-9030/CX-9032/F4120-2/F4120-1/WG Biological Fungicide/Varnimo WSP/COMPANION MAXX LIQUID BIOLOGICAL FUNGICIDE/ENV503 Biofungicide Wettable Powder
Pectobacterium sp	*Bacillus pumilus*	Registered	CARTISSA G/CARTISSA S

Pectobacterium sp	*Bacillus subtilis*	Registered	BACILLUS SUBTILIS CX-9090/Mildore/Fungisei/Milagrum Plus/Shielder/BACIX/F4018-4/CX-9032/CX-9030/DOUBLE NICKEL LC RTU/CX-9025-TGAI/GH DNMT Pectobacterium sp
P. syringae pv. phaseolicola	*Bacillus subtilis*	Registered	BACILLUS SUBTILIS CX-9090/Mildore/Fungisei/Milagrum Plus/Shielder/BACIX/F4018-4/CX-9032/CX-9030/DOUBLE NICKEL LC RTU/CX-9025-TGAI/GH DNMT
P. syringae pv. tomato	*Bacillus amyloliquefaciens*	Registered	GH DNMT/CX-9025-TGAI/DOUBLE NICKEL LC RTU/CX-9030/CX-9032/F4120-2/F4120-1/WG Biological Fungicide/Varnimo WSP/COMPANION MAXX LIQUID BIOLOGICAL FUNGICIDE/ENV503 Biofungicide Wettable Powder
P. syringae pv. tomato	*Bacillus pumilus*	Registered	CARTISSA G/CARTISSA S
Xanthomonas oryzae	*Bacillus velezensis* strain RTI301	Registered	
Xanthomonas vesicatoria	*Bacillus pumilus*	Registered	CARTISSA G/CARTISSA S

- Data from patent literature

Analysis of the patent literature related to PPB control shows a massive proportion of patents filed in China (52.5%) followed by patent seeking protection on other markets such as the USA (13%), worldwide level (12%), South Korea (11%), Europe (4%) and Japan (2%) (Figure 4.A). The large representation of patent coming from China is not surprising and might be due to non-market factors as suggested by the U.S. Patent and Trademark Office (2021).

From a temporal standpoint, patent literature dedicated to the management of PPB has been increasing since 2007 highlighting a growing interest in PPB on the crop protection market. The increase coincides with a rising concern about antimicrobial resistances (AMR) (Figure 4.B) and with the first limitation of antibiotic use in agriculture by European Union (Sundin, 2016). The use of antibiotics such as streptomycin and oxytetracycline was progressively limited in the EU. Their use in protecting crops appears to have been subject to a derogation and limited to certain crops, e.g. fruit production, in response to occasional outbreaks of fire blight.

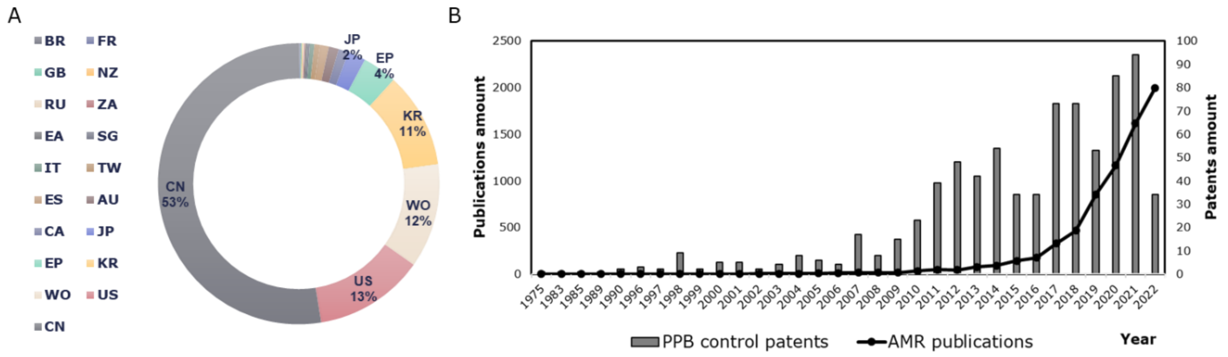

Figure 4: A) Distribution proportions of patents according to their geographical origin and B) temporal evolution of patented PPB control means (histogram) and number of scientific publications including the term antimicrobial resistance (AMR) in keywords retrieved from https://www.scinapse.io/ for the time period 1975-2022 (curve).

Most retrieved patents favour antibiotic-like approaches relying on direct PPB control strategy (70%), very few claims an enhancing of plant resistance either through breedings (14%) or defense stimulation (1.4%) (Figure 5). As a consequence, a large proportion of patents are dedicated to chemical substances (45%), either synthetic or organic-based, but also biocontrol agents (40%) exerting antagonistic activities towards PPB (Figure 5.A). Still, biocontrol agents (BCA) are frequently marketed as plant growth promoters in patents, which might be a more strategic approach for gaining market access. Bacteria such as *Bacillus* sp., *Pseudomonas* sp., *Paenibacillus* sp. and *Streptomyces* sp. account for a large part of patented BCA (71%) claiming bactericide activities often with vague description of their mode of actions (Figure 5.B). The second-largest group of BCA consists of viruses, specifically lytic bacteriophages primarily targeting *R. solanacearum* and *Xanthomonas* sp. Using bacteriophages to control PPB is a promising alternative to antibiotics but are rarely patented. Those retrieved in this study belong to two major companies (BASF and PhageLux) and universities in China, the USA, Japan and Spain. Despite their potential as BCA, the patenting of avirulent strains remains underrepresented and is often not the primary option considered by the market. Retrieved patents of avirulent PPB strains were of *R. solanacearum* and one of *Xylella fastidiosa*, EB92-1.

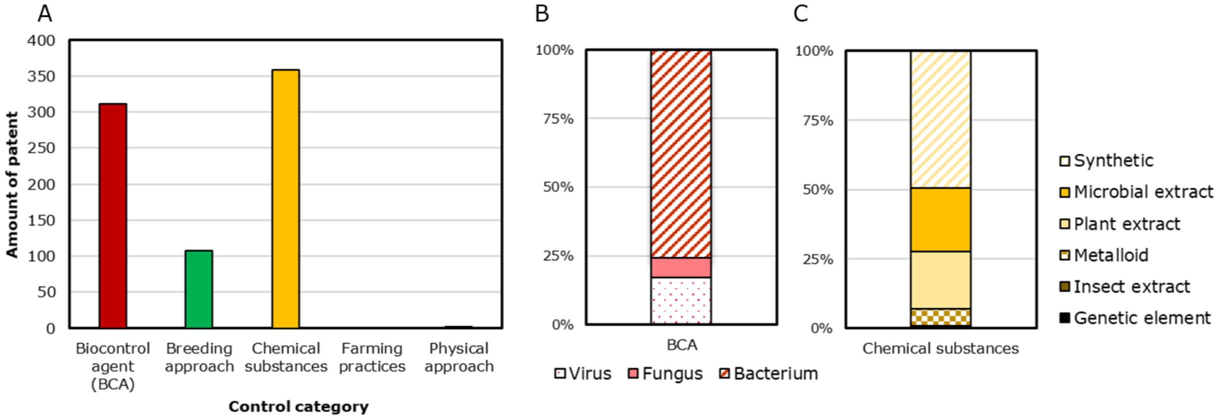

Figure 5: A) Distribution of patent amount retrieved in this study among control category, B) distribution proportions of biocontrol agent-related patents according to their nature and C) distribution proportions of chemicals' substances-related patents according to their nature.

A vast proportion of patent addresses combination of chemical substances with others but also with biocontrol agents. Half of patented chemical substances (49%) claiming PPB control effect are synthetic compounds often presented as derivatives of existing fungicides (Figure 5.C). Azole-containing and carboxamides derivatives are especially well represented among the investigated patent literature. Azole-containing derivatives can be associated with metalloids such as copper or zinc claiming bacteriostatic and bactericide effects. Chemical substances coming from plant extracts are well represented as well and are essentially developed in China and South Korea encompassing more than 65% of patented plant extracts retrieved in this study. Microbial extracts either from bacteria or fungi represent another interesting alternative to antibiotics arguing no use in human health care and promising efficacy of compounds produced by *Streptomyces* sp. (kobutimycin B, signamycin, ningnanmycin, wuyiencin, zhongshengmycin), *Bacillus* sp. (fengycins, iturins, surfactins) or *Pseudomonas* sp. (Shenzimycin = Phenazine-1-carboxylic acid).

The retrieval rates of patents addressing other PPB management strategies such as plant resistance enhancement or vector control are quite low compared to direct PPB control measures. This is easily explained by the fact that insect control solutions rarely claim an effect on the transmission of systemic plant-pathogenic bacteria and regarding resistant cultivars, it might rely on the difficulty to patent an existing plant leading commercial companies to favour protection by secrecy. This last point could evolve in regards to the emergence of gene-editing technologies.

- **Communication and dissemination of project results**

Three different meetings were anticipated at the project start. First, a kick-off meeting, organized on April 16, 2021, to set up the working network as well as for connecting people both at EFSA and UCLouvain on the project. The midterm meeting was organized back-to-back with the EFSA ONE conference, as a satellite workshop, with more than 50 registered participants from 14 different countries - Belgium, Germany, Italy, India, Colombia, Sweden, Bangladesh, Serbia, the USA, the UK, Norway, Ukraine, Ireland, Malta,... (Table 40).

Table 40: Presentations and discussions proposed at the One Conference satellite event on Plantibio.

- Workshop introduction – The Plantibio initiative by the European Food Safety Authority – G. Stancanelli (EFSA)
- Antimicrobial Use and Resistance in Plant Agriculture: A One Health Perspective – Jorge Pinto Fereira (FAO)
- Improving data collection on antibiotic use in plant health – challenges and perspectives – C. Bragard (SAVE,
- How classical plant risk analysis may be applied to AMR risk in trade – J. Smith (Protecting Crops and Environment
- Antibiotic resistance in Plant pathogenic bacteria - Marie Verhaegen, Jacques Mahillon (UCLouvain)
- Monitoring and Managing Streptomycin Resistant *Erwinia amylovora* and epiphytic bacterial populations in Ohio
- AMR-array for the detection of antibiotic resistance in bacteria - an example - Cécile Boland (Sciensano)
- Bacteria in avocado: sensitivity to antibiotics for agricultural use - Liliana Hoyos (University of Colombia)
Round table – how to improve data collection on antibiotic use as plant protection products and AMR in plant health, in a ONE Health Perspective? Panel members - G. Stancanelli, J. Pinto Fereira, J. Smith, M. Ivey

https://www.youtube.com/watch?v=49qyGeRbprM&list=PLGDvgn1aAEEaKVbCmWDf2T6X2hoiqlp3n&index=2

A poster presenting the Plantibio project was also proposed at the One health Conference (Annex C).

Also, a concurrent session organized in the frame of the International Congress of Plant Pathology held in Lyon (France) has been organized on the Impact of Resistance to Antibiotics and Fungicides in Plant Pathogens (session C7.4) (Table 41).

Table 41: ICPP23 Session on Impact of Resistance to Antibiotics and Fungicides in Plant Pathogens (session C7.4).

Title of the proposed communications
- Medical implications of azole fungicide use on Aspergillus fumigatus: a one health challenge requiring a multidisciplinary approach, by Paul VERWEIJ (Nijmegen, NETHERLANDS)
- Sensitivity to azole fungicides in nordic populations of parastagonospora nodorum causing stagonospora nodorum blotch of wheat and Aspergillus fumigatus causing invasive aspergillosis in humans, by Andrea FICKE (Aas, NORWAY)
- The hunt for killer Aspergillus fumigatus in the environment - surveillance of tomato and corn fields in Ohio, by Melanie IVEY (Wooster, UNITED STATES)

- Elucidating the impacts of anthropogenic activities on beneficial and pathogenic plant microbe interactions, by Wisnu Adi WICAKSONO (Graz, AUSTRIA)

- Use of antibiotics to control plant pathogenic bacteria: genetic and genomic considerations, by Marie VERHAEGEN (Louvain-La-Neuve, BELGIUM)

- EFSA activities addressing antimicrobial resistance through one health including the global use of antibiotics in plant health, by Franz Streissl (Parma, ITALY)

A poster session dedicated on the topic has also been organized.

A concept note was prepared to present the ongoing project at the International Plant Protection Convention (IPPC) - Convention on Phytosanitory Meeting (CPM) held in March 2022. This triggered the proposition of a IPPC-CPM parallel session on antibiotic use and resistance in Plant Health, held in Rome in March 2023 (Table 42).

Table 42: IPPC-CPM parallel session on antibiotic use and resistance in Plant Health.

Title of the proposed communications
- An introduction to AntiMicrobial Resistance in One Health and the scope of the EFSA Plantibio project (Ernesto Llebana, European Food Safety Authority)
- Antibiotic use as plant protection products – a global search for information via scientific literature and grey literature searches (Claude Bragard, UCLouvain)
- Overview on resistance to antibiotics in plant pathogenic bacteria – a global search for data (Marie Verhaegen, UCLouvain)
- Work ongoing (search on alternatives to antibiotics as plant protection products) and next steps of the project (Claude Bragard, UCLouvain)

The outcome of the project have also been communicated at the 26th Belgian Society for Food Microbiology (BSFM) Conference in Brussels, October 2022 (Poster presentation, see Annex D).

A video presentation was also prepared and proposed at the High-Level meeting on Antimicrobial resistance, held in Stockholm on March 6 and 7, 2023, under the Sweddish Presidency of the European Union (https://swedish-presidency.consilium.europa.eu/en/events/high-level-meeting-on-antimicrobial-resistance-amr-6-73/). The video is accessible at https://www.dropbox.com/sh/pjfo9ezp2uolaz5/AAAw9rU3N_LPh2DJkC0XwBDla?dl=0&preview=capsule+version+longue+ST+GB.mp4

Based on the project outcome, synergies quickly appeared between several EFSA and FAO initiatives on AMR, including the use of antibiotics as plant protection products and on resistance to antibiotics. Following several online meetings, a FAO-EFSA/UCL meeting on antimicrobial use and resistance in plant agriculture was held on March 28, 2023 at FAO.

The participants identified possible convergence and cooperation between EFSA and FAO in plant health, along different topics, like the need to consider not only AMR but also AMU, the interest of understanding AMU and AMR at regional and country level, the need to find solutions for sustainable plant protection, as alternative to antimicrobial uses in agro-ecosystems, additional questions like emerging ONE HEALTH questions, such as azole resistance and the need for raising communication and awareness and building capacity in sustainable plant protection. Several areas of possible future co-operation among EFSA, FAO UCLouvain have been identified as

1. Datasharing – EFSA and UCLouvain to make the PLANTIBIO global data on AMU and AMR available for the FAO platform.

2. Datasharing on alternative methods to the use of pesticides. PLANTIBIO data to be made available to FAO, FAO to inform EFSA on available information and FAO projects on alternative methods to pesticides.

3. Joint workshop on specific crop systems where alternative methods to AMU can be applied. Alternatives to chemical pesticides are very important for food safety and this an issue of common interest between EFSA and FAO.

Finally, the project outcome has been published (Verhaegen M, Bergot T, Liebana E, Stancanelli G, Streissl F, Mingeot-Leclercq M-P, Mahillon J and Bragard C, 2023. On the use of antibiotics to control plant pathogenic bacteria: a genetic and genomic perspective. Frontiers in Microbiology, 14:1221478. doi: 10.3389/fmicb.2023.1221478. Published on 27/06/2023).

4. Conclusion

Data on the use of antibiotics as plant protection products against phytobacteria can be collected via systematic scientific literature or grey literature searches, taking into consideration the limitation of such exercise. The major limitations (data gaps) for scientific literature analysis are i) the relative lack of scientific analysis or reviews on the topic in comparison with the abundance of literature on antibiotic use and resistance in both animal and human health, ii) the frequent changes in legislation on pesticide use at country level, with the need to focus on a time window relatively limited to avoid bias, and the difficulty to trace back what has been authorized in the past. Grey literature search provides a very useful tool to search for information. Here, among the three different approaches that have been tested (search in generic databases on pesticides, search companies producing antibiotics and search via national plant protection organizations), the last one was identified as the most suitable to provide an accurate view on the antibiotic currently authorized as plant protection products. Yet here also some limitations have to be underlined: the need to use the country language for such a search, the time constraint linked to the evolution of the country legislation and in several countries, the absence of a dedicated webpage displaying openly the searched information. Nevertheless, we have been, following this search line, able to assess the use of antibiotics in up to 39 different countries. Similarly, such use is not officially authorized in 57 countries. It is useful also to stress the difficulty to collect the information which is available in different formats, languages, not to mention, if not a hidden, at least not easily accessible information. Nevertheless, there are indications that even if antibiotics are not officially authorized, there is also sometimes a use of antibiotics which is therefore under-reported.

Among the antibiotics used in agriculture to protect crops against PPB, two categories can be delineated. First, antibiotics also used in animal and human health, like gentamicin, streptomycin, tetracycline and oxytetracycline, oxolinic acid, and second, antibiotics for which the use is restricted only to plant protection, like kasugamycin, ningnanmycin, validamycin, zkhongshengmycin.

Not surprisingly, the use of antibiotics is focused on major plant bacterial diseases, historically, on *E. amylovora*, agent of the Rosaceae fireblight, but also on Citrus greening, *Xanthomonas oryzae*, or *P. syringae* pv. *actinidiae*. Nevertheless, an analysis of the commercialized product descriptions or of the official authorisations displays often a much wider use, on ornamental plants, sometimes to protect vegetables or cash crops.

Finally, with the view of assessing the risk of antibiotic use as plant protection products, or for a better understanding of antibiotic resistance in PPB and the risk it poses to animal or human health, collecting quantitative data on the use of antibiotics is of the uttermost importance. Here again, except a few exceptions, there is a major lack of data to precisely appraise the quantities of antibiotics used in plant health. India, New Zealand and the USA are providing figures, but this remains very limited.

Resistance reports often coincide with antibiotic use, especially for streptomycin, as it is the documented. In fact, 82% of resistance cases were reported in countries where it is used on plants. However, there is a possible bias since studies are most probably mainly carried out where antibiotics are used but not really elsewhere, which calls for a more systematic research. There are very few studies performed in Europe even if it is necessary to monitor the appearance of resistance, even in countries where antibiotics are not used in crop protection. As a matter of fact, ARGs have emerged in PPB and therefore the contribution of MGEs to the spread of antibiotic resistance in PPB, as well as their ability to transfer to other bacteria, need to be carefully investigated. Whether they have an impact on the global problematic of antibiotic resistance also remains unanswered.

If data on relative frequency of resistance genes and genetic environments in the different sources and compartments was available, a model could be established to estimate the probability of a transfer from each of the sources. However, all this surveillance data is lacking and it is a challenge to convince the different countries that it is necessary to do surveillance in crops because it is not easy to show evidence of public health risk and therefore it does not seem worth the investment.

Another worrying aspect is the potential presence of antibiotics or antibiotic residues on crops and their effect on the consumers' food, in particular when antibiotics are applied on fruits such as apples or pears that are eaten raw by the consumers. The human exposure through diet is not well studied.

It also remains useful to stress the fact that PPB are not the only bacteria and microorganisms associated with plants. Phytobiome studies have underlined the importance of plant-associated bacteria and their sometimes very positive effects on plant health. An underreported question is certainly the effect of antibiotic use on non-pathogenic plant-associated bacteria. If bacteria present on plants have the potential to transfer their genetic material with bacteria from the microbiota, they could have an impact on the consumer. The uptake of resistance genes by crops is not well known.

Also, plant-associated bacteria might be exposed to antibiotics not only via direct sprays of plant protection products, but also via contaminated irrigation water, wastewater and soil (including manure and animal dejection). What is the level of such possible contamination route versus the one of pesticide use is another key question. Attention must also be paid to the use of copper or other fungicides on plants since cross-resistance have been reported between antibiotics and minerals use.

There is also a need for studies related to the link between antibiotic use on crops and antibiotic resistance appearance in PPB or phytobiome-associated bacteria.

From another point of view, many resistance genes and antibiotic resistant bacteria are already present in the soil before antibiotics were even applied to plants. For example, the gene pair *strA-strB* is present anyway in the environment (soil, water, etc.). Similarly, tetracycline resistant bacteria and tetracycline resistance genes are often found in human waste, soil, manure and in the phylloplane. Therefore, what is the impact of antibiotic applications in small amounts in comparison to the genes and resistant bacteria that are already present in soil (Sundin and Wang, 2018; Heuer et al., 2009; Petrova et al., 2008; Skandalis et al., 2021; Hu et al., 2010)?

In order to assess the potential transfers between the human, animal and plant microbiomes, it is crucial to use modern tools to carry out genetic analyses. Whole Genome Sequencing (WGS) and metagenomics could highlight where are the genes located and how they can be transferred (presence on MGEs). Prediction of resistance genes can be done with the help of many databases, but DeepARG seems of particular interest in our case (Arango-Argoty et al., 2018). It consists of deep learning models predicting antibiotic resistance determinants with high precision. These bioinformatics tools could help to trace back the genes by sequence alignment and similarity: is the resistance coming from the use of antibiotics in the past or from the soil, which represents a huge reservoir of genes? Is the resistance stable?

New, rapid and inexpensive tests and/or tools are needed to facilitate the identification of PPB but also characterize their resistomes. A modern tool of potential interest was developed by Cécile Boland and her team at Sciensano and presented during the ONE Conference, held in Brussels on 21st June 2022. They created the AMR-ARRAY, a modular bead-array able to screen numerous antibiotic resistance determinants (genes and/or mutations) at low cost and quickly (Timmermans et al., 2022). Development of probes to target antibiotic resistance determinants known in PPB could maybe serve as a monitoring tool for antibiotic resistance in PPB. This could be an answer to the necessity to have tools to characterize the resistomes of PPB.

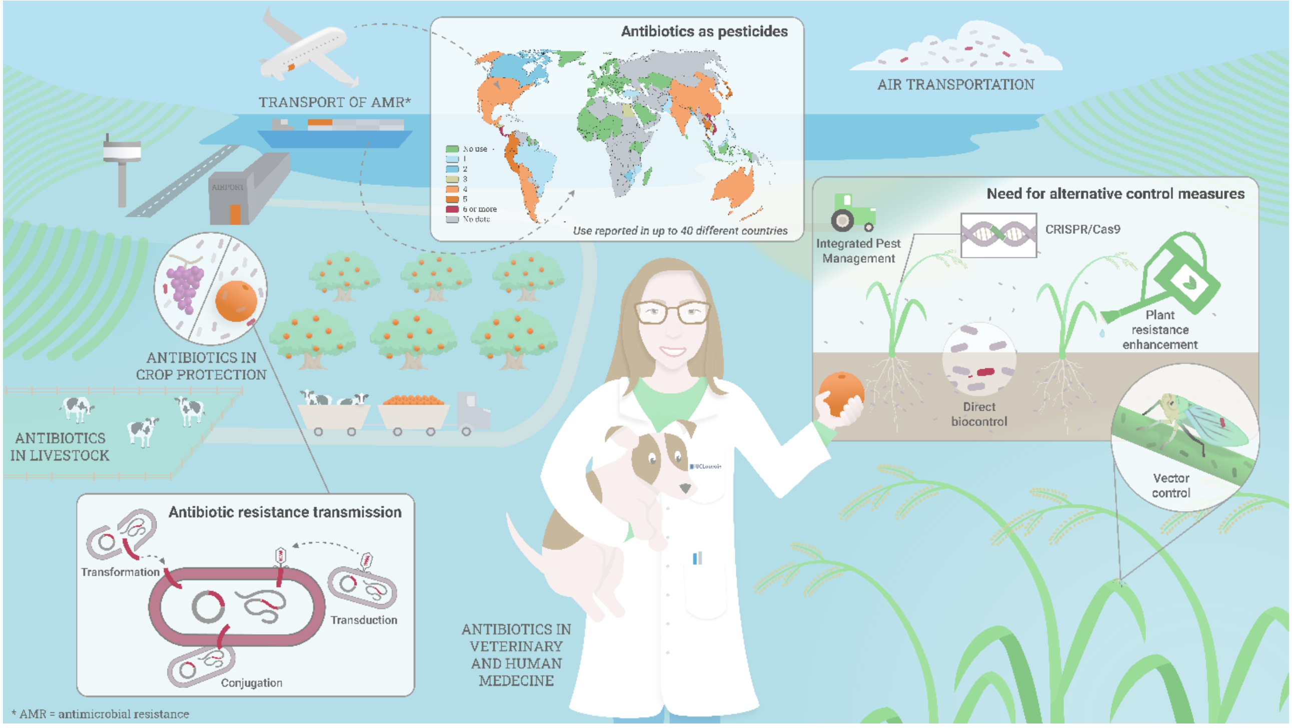

Figure 6: Graphical abstract for the Plantibio project (illustration by Morgane Goyens).

5. Recommendations

It is sometimes difficult to connect the field of plant health to AMR or animal health. However, this project has highlighted the potential links between antibiotic use as plant protection products and resistance to antibiotics in plant pathogenic bacteria with other AMR risk assessment areas.

We list here several initiatives or ways that could be developed and followed up.

- Set up a database of web or scientific literature sources for the use of antibiotics as plant protection products and for identified resistance to antibiotics in plant pathogenic bacteria.
- Search and evidence unauthorized use of antibiotics as plant protection products or an unauthorized sale of antibiotics.
- Conduct a robust data collection, in a quantitative way (possibly associated with the need to set up in a legal framework or set up quantitative crop-based estimations? Or interactions with other agencies like FAO, EPPO, etc.).
- Ideally, develop surveillance programs, accessible even for low- and middle-income countries, that are consistent and collect quantitative data about the use and the sales of antibiotics, the area where they are applied and on which crops.
- Develop surveillance for antibiotic residues and antibiotic resistance on plant protection products.

- Extend surveillance for AMR to the phytobiome and plant resistome (Chen et al., 2019), and thus monitor potential contamination from environmental sources (surface or irrigation waters, manure); A key point is the emergence of biocontrol strategies including large-scale use of plant protection products based on bacteria, which, to the best of our knowledge, are not yet assessed for antimicrobial resistance.
- Development in the management of resistance is probably the communication and spread of information to the farmers. It is primordial to engage, dialogue and train the farmers.
- Strong antimicrobial stewardship practices, paradigm shift in behavior and management.
- Advising and raising awareness about plant health, not only by the farmers, but also by the consumers, the veterinarians, by highlighting the links between human, plant and animal microbiomes.
- Raise awareness on the possible risks linked with the use of antibiotics as plant health products, not only for antimicrobial resistance, but also with regards to mobile genetic elements that might carry multiple resistance (e.g. heavy metals, other pesticides, multiple antibiotic resistance, etc.).
- Enhance communication and raise awareness on alternative control measures for plant pathogenic bacteria, test and evaluate alternative control measures in terms of efficacy in comparison with antibiotics.

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Glossary [and/or] Abbreviations

AMR	Antimicrobial resistance
AMU	Antimicrobial use
ARG	Antibiotic resistance gene
ATP	Adenosine triphosphate
BLAST	Basic Local Alignment Search Tool
CARD	The Comprehensive Antibiotic Resistance Database
DNA	Deoxyribonucleic acid
Dpp	Dipeptide permease
EFSA	European Food Safety Authority
EPPO	European Public Prosecutor's Office
EU	European Union
FAO	Food and Agriculture Organization
GC	Guanine-Cytosine
HLB	Huanglongbing
HGT	Horizontal gene transfer
IPM	Integrated Pest Management
IUPAC	International Union of Pure and Applied Chemistry
MGE	Mobile genetic element
ND	Not determined
NPPO	National Plant Protection Organisation
OA	Oxolinic acid
Opp	Oligopeptide permease
PCA	Phenazine-1-carboxylic acid (Shenqinmycin)
PICO-	Population-Intervention/Exposure-Comparison-Outcome
PO	Population and outcome of interest
PPB	Plant pathogenic bacteria
PPP	Plant protection product
pv.	pathovar
RND	Nodulation-division family
SmR	Streptomycin resistant
spp.	Several species
subsp.	Subspecies
sv.	serovar
TetR	Tetracycline resistance
USA	United States of America
WGS	Whole Genome Sequencing

Appendix A – List of websites used to compile the list of countries in which antibiotics are used as plant protection products

Websites consulted for table 2. All websites have been consulted between January and June 2022.

In the 195 countries screened for antibiotic use as PPPs, ca. 35 are recorded as users, 87 as non-user. For 77 countries, we have not been able to identify an authority or a source to assess the possible use of antibiotic as PPP.

Algeria - https://www.inpv.edu.dz/
Antigua and Barbuda- https://cahfsa.org/registered-pesticides/antigua-barbuda
Argentina - https://www.argentina.gob.ar/senasa/programas-sanitarios/productosveterinarios-fitosanitarios-y-fertilizantes/registro-nacional-de-terapeutica-vegetal
Australia - https://portal.apvma.gov.au/pubcris
Bengladesh - https://portal.apvma.gov.au/pubcris
Barbados - https://cahfsa.org/registered-pesticides/barbados
Belize - https://cahfsa.org/registered-pesticides/belize
Benin - http://csp.dev4u.it/index.cfm
Bhutan - http://csp.dev4u.it/index.cfm
Bolivia - https://paititi.senasag.gob.bo/egp/productosAgroquimicos.html
Burkina faso - http://csp.dev4u.it/index.cfm
Côte d'Ivoire - http://csp.dev4u.it/index.cfm
Cabo Verde - http://csp.dev4u.it/index.cfm
Cameroon - https://drcq-minader.org/docs/Liste_Pesticides_Homologues_042019.pdf
Canada - https://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php, https://pesticide-registry.canada.ca/en/active-ingredient-search.html
Chad - http://csp.dev4u.it/index.cfm
Chile –
China –
Colombia - https://www.ica.gov.co/getdoc/d3612ebf-a5a6-4702-8d4b-8427c1cdaeb1/registros-nacionales-pqua-15-04-09.aspx
Costa Rica –
Dominica - https://cahfsa.org/registered-pesticides/dominica
Ecuador - https://www.agrocalidad.gob.ec/366-2/
Egypt - http://www.apc.gov.eg/en/
Estonia - https://portaal.agri.ee/avalik/#/taimekaitse/taimekaitsevahendid-otsing/en
Finland - https://www.kemidigi.fi/kasvinsuojeluainerekisteri/haku
France - https://ephy.anses.fr/
Gambia - http://csp.dev4u.it/index.cfm
Georgia - https://nfa.gov.ge/Ge/Page/Informationonagrochemicalsandpesticides/
Germany - https://apps2.bvl.bund.de/psm/jsp/index.jsp?modul=form
Ghana - http://csp.dev4u.it/index.cfm
Greece - http://csp.dev4u.it/index.cfm
Guatemala –
Guinea - http://csp.dev4u.it/index.cfm
Guinea-Bissau - http://csp.dev4u.it/index.cfm
Guyana - https://cahfsa.org/registered-pesticides/guyana-pesticides
India - http://ppqs.gov.in/divisions/cib-rc/registrered-products
Indonesia - 20720-ID-kajian-pestisida-berbahan-aktif-antibiotika(1).pdf
Ireland - 20720-ID-kajian-pestisida-berbahan-aktif-antibiotika(1).pdf
Israel - 20720-ID-kajian-pestisida-berbahan-aktif-antibiotika(1).pdf
Italy - https://www.sian.it/fitovis/
Jamaica - https://www.caribpesticides.net
Japan - http://www.acis.famic.go.jp/eng/indexeng.htm
Kazakhstan - https://ipen.org/sites/default/files/documents/final_en_kazakhstan_hhp_report_summary_18_may_2020_0.pdf
Kenya - https://pcpb.go.ke/listofregproducts/List%20of%20Registered%20Products%20%20Version%201_2018.pdf
Latvia - https://pcpb.go.ke/listofregproducts/List%20of%20Registered%20Products%20%20Version%201_2018.pdf
Lithuania - http://www.vatzum.lt/lt/#raap
Luxemburg - https://saturn.etat.lu/tapes/
Madagascar - https://apimadagascar.files.wordpress.com/2013/03/liste-pesticide-autorisc3a9-c3a0-madagascar.pdf
Malaysia - https://apimadagascar.files.wordpress.com/2013/03/liste-pesticide-autorisc3a9-c3a0-madagascar.pdf
Mali - http://csp.dev4u.it/index.cfm
Mauritania - http://csp.dev4u.it/index.cfm
Mexico - http://siipris03.cofepris.gob.mx/Resoluciones/Consultas/ConWebRegPlaguicida.asp
Morocco - http://eservice.onssa.gov.ma/IndPesticide.aspx
Mozambique - https://fdocuments.net/document/annex-1-list-of-pesticides-registered-in-mozambique-public-disclosure-authorized.html

Nepal - http://www.npponepal.gov.np/downloadsdetail/2/2018/39799637/
Niger - http://csp.dev4u.it/index.cfm
Nigeria - http://csp.dev4u.it/index.cfm
Norway - https://www.mattilsynet.no/
Panama - https://mida.gob.pa/wp-content/uploads/2020/05/Listado-de-Insumos-Fitosanitarios-Registrados.pdf?csrt=3439629386443367864
Paraguay –
Peru - https://cdn.www.gob.pe/uploads/document/file/1676334/ANEX2.pdf.pdf
Philippines - https://fpa.da.gov.ph/NW/index.php/information-resources/data/registered-products
Saint Lucia - https://cahfsa.org/registered-pesticides/st-lucia
Saint Vincent and the Grenadines - https://cahfsa.org/registered-pesticides/st-vincent-and-the-grenadines
Saudi Arabia - https://www.sfda.gov.sa/en/informationlist/65748
Senegal - http://csp.dev4u.it/index.cfm
Seychelles - https://seylii.org/sc/legislation/consolidated-act/164a
Sierra Leone - http://csp.dev4u.it/index.cfm
Sri Lanka - https://doa.gov.lk/rop-downloads/#1588566175088-0ea325ae-0f35
Suriname - https://cahfsa.org/registered-pesticides/suriname
Sweden - https://www.kemi.se/
Switzerland - https://www.psm.admin.ch/fr/produkte
Tanzania - https://www.tpri.go.tz/registered-pesticides-intanzania
Togo - http://csp.dev4u.it/index.cfm
Trinidad and Tobago - https://cahfsa.org/registered-pesticides/trinidad
Tunisia - http://www.agridata.tn/dataset/liste-des-pesticides-homologues-en-tunisie
Uganda - https://www.agriculture.go.ug/agrochemicals-list/
United Kingdom - https://www.hse.gov.uk/pesticides/
U.S.A. - https://ordspub.epa.gov/ords/pesticides/f?p=chemicalsearch:
Vietnam - http://ppd.gov.vn/
Yemen - http://www.plant-protection-yem.org/content.php?lng=english&id=30
Zambia - https://www.zema.org.zm/
Zimbabwe - http://www.drss.gov.zw/index.php/examinations/category/6-registered-pestcides-active-ingrediets-in-zimbabwe

Appendix B – Nucleotide sequence of Tn*5393* and its variants used for BLAST analyses

Tn*5393* (*E. amylovora*)

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GGGGTCGTTTGCGGGAGGGGGCGGAATCCTACGCTAAGGCTTTGGCCAGCGATATTCTCCGGTGAGATTG
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CGCTTCAGCGCATGATGACGTTCGCCTTTGTTGAGCCCGATCTGGGCACGCCGTTGGAGTTCGGCATCCA
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GCAGGTGCGCCGGGGCGGCCGACGGATTGAACGCGTAGAGCCGTTTGGATGGCAGGTCGCGGATGCGCGG
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GGTATTGCCATATTTCGCGTTGACCAGGTTCATGGCCTCACCTTGCTCTGTAGCGACGAAGAACTGTCCG
TCGCTCGAAGCCGACGTGCCCATGCCCCAGAACCGGGCCATGGGTAACGCTGCCTGTGCCTCGACCACCA
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CATCCACCTCCAGCAGGAGATCGGTGATGCGCGTGGGCGGGATCTGCTTGTAGAGATCGAGCACCAGATC
TTCGGCGCCTGTCGGCGCGGCGGCTTCGAGTTTCTCGATATGCAGAACGCCGTTTTCAATCGACCCGCCC
GGGATCGTGCCTGCGCGAGCGGCACGGCCAACGTCGCGCAACCGCATGTCGAGGCGAGCTTGCCGGTCTG
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CCAGCCATTCCTCCGGCCGCAATGGCACAGCGAGACGACCGCCTTCCGCGATGGATTGTGCCGGAACGAG
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ATTTCGAGCTGGGCCGCAAGAAGCTGGTCATCGCGGCATCGTTCAAACCGGTACGAAGGGCCGTCACCGC
TTCCAGAAGCGGCAGTGCAACGGGCGCAGCTCGCAGATCGAGCAGGCGCAACATGCGTGGAGCGTATCGG
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GCTTCGTCTGCGACCTTTGCATGGCAAATACGCTCCGAAGCACGGTAGAGACGGCCGACGATCCGGTCGT
GGGTTTCGACCACTGCGTCGGCCAACATCGCCTGCCATTCCGAGACGCAAACAGCCAAGATCGCAAGCCG
CCTGTCCTCCGGGAGATCGCGCATGCCGTCGGCATAATACCGTTCACCCTGCCTGCGCAGACGAGTCACC
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GCAACAGCGCGTCTTTCTGCCGATCGGTTAGAGTGACGCGACGCGGCATACATGTTCCTTTTTCAAAATC
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CGTCCGGTCGCATGGTGTTCGGAATCTTCGCCACCTTGGCCGAGTTCGAGCGGGATCTGATCCGAGAGCG
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GCTCAGGTGCGTCTCGCGCAAGCCGCCATGGCCCAGCGCGATACTTCAGTTTCCGATCTCTGCAAGGAAC
TCGGCATCGAGCGCGTCACTCTCTACCGATATGTCGGTCCCAAAGGCGAGCTCAGAGACCATGGAAAGCA
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Tn*5393*a (*P. syringae* pv. *syringae*)

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Tn*5393*b (*X. campestris*)

Sequence not found.

Tn*5393*c (*Aeromonas salmonicida*)

Same as Tn*5393*a, as BLAST suggests.

Tn*5393*d (*Alcaligenes faecalis*)

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Tn*5393*e (*S. enterica*)

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Appendix C – Gentamicin datasheet (ex PUBMED)

Gentamicin

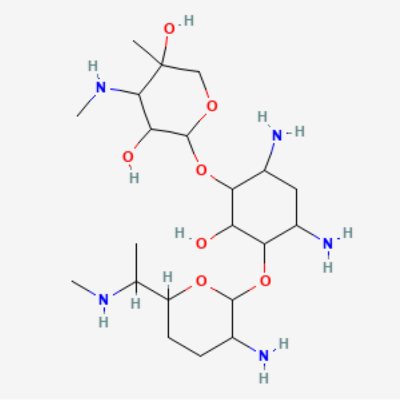
Gentamicin is a bactericidal aminoglycoside that was discovered and isolated from Micromonospora purpurea in 1963. It is one of the most frequently prescribed aminoglycosides due to its spectrum of activity, low cost, and availability. Gentamicin is effective against both gram-positive and gram-negative organisms but is particularly useful for the treatment of severe gram-negative infections including those caused by Pseudomonas aeruginosa. There is the added benefit of synergy when Gentamicin is co-administered with other antibacterials such as beta-lactams. This synergistic activity is not only important for the treatment of complex infections, but can also contribute to dose optimization and reduced adverse effects.

IUPAC name

2-[4,6-diamino-3-[3-amino-6-[1-(methylamino)ethyl]oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol

Molecular formula

$C_{21}H_{43}N_5O_7$



Synonyms

G Myticin

G-Myticin

Garamycin

Gentacycol

Gentamicin

Gentamicin Sulfate

Gentamicin Sulfate (USP)

Gentamicins

Gentamycin

Gentamycins

Gentavet

Genticin

GMyticin

Sulfate, Gentamicin

Depositor supplied names

gentamicin

Gentavet

Gentamicins

GENTAMYCIN

Gentamicin sulphate sterile

Gentacycol

1403-66-3

Gentamycin C1

Cidomycin

Gentamicinum

Gentamycinum

Refobacin

Garasol

Refobacin TM

2-[4,6-diamino-3-[3-amino-6-[1-(methylamino)ethyl]oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-(methylamino)oxane-3,5-diol

Gentamicina

Gentamicine

Gentocin

Gentamycin-creme

Gentamycins

Gentamicine [INN-French]

Gentamicinum [INN-Latin]

Gentamycin-creme [German]

Gentamicina [INN-Spanish]

Oksitselanim

Centicin

Lyramycin

Septigen

Gentamicin (TN)

Gentamicin (BAN)

Gentamicin [INN]

HSDB 3087

Gentamicin [INN:BAN]

EINECS 215-765-8

4,6-diamino-3-{[3-deoxy-4-c-methyl-3-(methylamino)pentopyranosyl]oxy}-2-hydroxycyclohexyl 2-amino-2,3,4,6,7-pentadeoxy-6-(methylamino)heptopyranoside

SCHEMBL537630

CHEMBL329592

GTPL2427

SCHEMBL19996168

STL454325

AKOS015961211

DB00798

J4.074F

2-[4,6-diamino-3-[3-amino-6-(1-methylaminoethyl)oxan-2-yl]oxy-2-hydroxycyclohexyl]oxy-5-methyl-4-methylaminooxane-3,5-diol

AC-13386

FT-0626646

FT-0668965

D08013

123871-EP2292088A1

123871-EP2295422A2

123871-EP2295439A1

Q422482

Chemical vendors

THE BioTek (China)
Purchasable Chemical: CSSB00102519291
Hangzhou APIChem Technology (China)
Yuhao Chemical (China)
Smolecule (USA)
Vitas-M Laboratory (Hong Kong)
BenchChem (USA)
MuseChem (USA)
AKos Consulting & Solutions (Germany)
Finetech Industry Limited (China)
MicroCombiChem GmbH (Germany)
Achemtek (USA)
3WAY PHARM INC (China)

Appendix D – Kasugamycin datasheet (ex PUBMED)

Kasugamycin

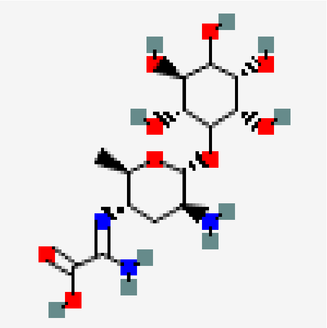
Kasugamycin is an amino cyclitol glycoside that is isolated from Streptomyces kasugaensis and exhibits antibiotic and fungicidal properties. It has a role as a bacterial metabolite, a protein synthesis inhibitor and an antifungal agrochemical. It is an amino cyclitol glycoside, an aminoglycoside antibiotic, a monosaccharide derivative, a carboxamidine and an antibiotic fungicide.

IUPAC name

2-amino-2-[(2R,3S,5S,6R)-5-amino-2-methyl-6-[(2R,3S,5S,6S)-2,3,4,5,6-pentahydroxycyclohexyl]oxyoxan-3-yl]iminoacetic acid

Molecular formula

$C_{14}H_{25}N_3O_9$



Synonyms

3-O-(2-amino-4((carboxyiminomethyl)amino)-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranosyl)-D-chiroinositol
kasugamycin
kasugamycin hydrochloride
kasugamycin hydrochloride monohydrate
kasugamycin monohydrochloride
kasugamycin, phosphate salt
kasugamycin, sulfate salt

Depositor supplied synonyms

KASUGAMYCIN
6980-18-3
Kasumin L
Kasumin 2L
Kasuminl
UNII-O957UYB9DY
alpha-D-lyxo-
O957UYB9DY
CHEBI:81419
2-amino-2-[(2R,3S,5S,6R)-5-amino-2-methyl-6-[(2R,3S,5S,6S)-2,3,4,5,6-pentahydroxycyclohexyl]oxyoxan-3-yl]iminoacetic acid
19408-46-9
Kasu B
(1s,2r,3s,4r,5s,6s)-2,3,4,5,6-Pentahydroxycyclohexyl 2-Amino-4-{[carboxy(Imino)methyl]amino}-2,3,4,6-Tetradeoxy-Alpha-D-Arabino-Hexopyranoside
HSDB 6695
KSM
BRN 1403823
SR-05000001429
C14H25N3O9
EINECS 234-260-3
NSC 100858
SCHEMBL70535
CHEMBL1631109
DTXSID1040374
SCHEMBL12858482
SCHEMBL16011710
HMS2089A11
ZINC4216682
AKOS025310863
ZINC100042889
ZINC100045947
11030-24-3
3-O-(2-Amino-4-((carboxyiminomethyl)amino)-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranosyl)-D-chiro-inositol sulphate
D-chiro-Inositol, 3-O-(2-amino-4-((carboxyiminomethyl)amino)-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranosyl)-
X6751
C17968
Q3193879
SR-05000001429-1
(1S,2R,3S,4R,5S,6S)-2,3,4,5,6-PENTAHYDROXYCYCLOHEXYL

(1S,2R,3S,4R,5S,6S)-2,3,4,5,6-pentahydroxycyclohexyl 2-amino-4-{[(Z)-carboxy(imino)methyl]amino}-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranoside
2-((2R,3S,5S,6R)-5-amino-2-methyl-6-((1S,2R,3S,4R,5S,6S)-2,3,4,5,6-pentahydroxycyclohexyloxy)tetrahydro-2H-pyran-3-ylamino)-2-iminoacetic acid
2-[[(2R,3S,5S,6R)-5-amino-2-methyl-6-[(2R,3S,5S,6S)-2,3,4,5,6-pentahydroxycyclohexoxy]tetrahydropyran-3-yl]amino]-2-imino-acetic acid
2-AMINO-4-{[CARBOXY(IMINO)METHYL]AMINO}-2,3,4,6-TETRADEOXY-ALPHA-D-ARABINO-HEXOPYRANOSIDE
3-O-[2-amino-4-[(carboxyiminomethyl)amino]-2,3,4,6-tetradeoxy-alpha-D-arabino-hexopyranosyl]-D-chiro-inositol

Chemical vendors

AA BLOCKS
PubChem SID: 381990262
Purchasable Chemical: AA00FH4P
AK Scientific, Inc. (AKSCI)
PubChem SID: 252553368
Purchasable Chemical: X6751
3B Scientific (Wuhan) Corp
PubChem SID: 375089301
Purchasable Chemical: 3B2-3064
Chem-Space.com Database
PubChem SID: 434738900
Purchasable Chemical: CSSB00020648120
AKos Consulting & Solutions
PubChem SID: 252817816
Purchasable Chemical: AKOS025310863
TargetMol
PubChem SID: 443837638
Purchasable Chemical: T2762L
Changzhou Highassay Chemical Co., Ltd
PubChem SID: 313081209
Purchasable Chemical: my_sub2241 *(URL not provided...)*
ZINC
PubChem SID: 268752094
Purchasable Chemical: ZINC100042889
Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd.
PubChem SID: 441075044
Purchasable Chemical: PH-1911A *(URL not provided...)*
THE BioTek
PubChem SID: 434136236
Purchasable Chemical: bt-253749

MuseChem
PubChem SID: 355175311
Purchasable Chemical: I011940
MolPort
PubChem SID: 354417826
Purchasable Chemical: MolPort-044-559-917
BenchChem
PubChem SID: 446424287
Purchasable Chemical: B1663007
labseeker
PubChem SID: 318166293
Purchasable Chemical: SC-14174
A2B Chem
PubChem SID: 444178130
Purchasable Chemical: AH21941
AHH Chemical co.,ltd
PubChem SID: 252351089
Purchasable Chemical: MT-53026
Smolecule
PubChem SID: 438443730
Purchasable Chemical: S005675

Appendix E – Streptomycin datasheet (ex PUBMED)

Streptomycin

Streptomycin is an aminoglycoside antibiotic derived from Streptomyces griseus with antibacterial activity. Streptomycin irreversibly binds to the 16S rRNA and S12 protein within the bacterial 30S ribosomal subunit. As a result, this agent interferes with the assembly of initiation complex between mRNA and the bacterial ribosome, thereby inhibiting the initiation of protein synthesis. In addition, streptomycin induces misreading of the mRNA template and causes translational frameshift, thereby results in premature termination. This eventually leads to bacterial cell death.

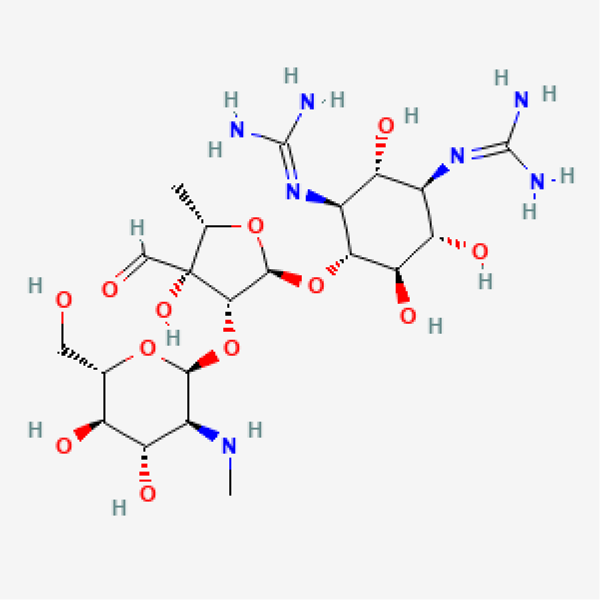
It has a role as an antimicrobial agent, an antimicrobial drug, an antibacterial drug, a protein synthesis inhibitor, a bacterial metabolite and an antifungal agrochemical. It is an antibiotic antifungal drug, an antibiotic fungicide and a member of streptomycins.

IUPAC name

2-[(1R,2R,3S,4R,5R,6S)-3-(diaminomethylideneamino)-4-[(2R,3R,4R,5S)-3-[(2S,3S,4S,5R,6S)-4,5-dihydroxy-6-(hydroxymethyl)-3-(methylamino)oxan-2-yl]oxy-4-formyl-4-hydroxy-5-methyloxolan-2-yl]oxy-2,5,6-trihydroxycyclohexyl]guanidine

Molecular formula

$C_{21}H_{39}N_7O_{12}$



Synonyms

Estreptomicina CEPA
Estreptomicina Clariana
Estreptomicina Normon
Strepto Fatol
Strepto Hefa
Strepto-Fatol
Strepto-Hefa
Streptomycin
Streptomycin Grünenthal
Streptomycin Sulfate
Streptomycin Sulfate (2:3) Salt
Streptomycin Sulphate
Streptomycine Panpharma

Depositor supplied synonyms

streptomycin
57-92-1
Streptomycin A
Strepcen
Gerox
Streptomycine
Streptomycin sulphate
Chemform
Streptomycin sulfate
Agrimycin
Agrept
Neodiestreptopab
2,4-Diguanidino-3,5,6-trihydroxycyclohexyl 5-deoxy-2-O-(2-deoxy-2-methylamino-alpha-glucopyranosyl)-3-formylpentofuranoside
Streptomicina
Streptomycinum
Streptomyzin
Hokko-mycin
SRY

Streptomycin Sesquisulfate Hydrate

Caswell No. 804

Streptomyzin [German]

Streptomicina [Italian]

NCGC00159339-02

Streptomycin [INN:BAN]

Streptomycin, Sulfate Salt

streomycin

Geroxeg

Estreptomicina [INN-Spanish]

Streptomycin,(S)

1-[(1S,2R,3R,4S,5R,6R)-2-[(2R,3R,4R,5S)-3-[(2S,3S,4S,5R,6S)-4,5-dihydroxy-6-(hydroxymethyl)-3-(methylamino)tetrahydropyran-2-yl]oxy-4-formyl-4-hydroxy-5-methyl-tetrahydrofuran-2-yl]oxy-5-guanidino-3,4,6-trihydroxy-cyclohexyl]guanidine

Streptomycin (TN)

EINECS 200-355-3

Streptomycin (INN)

EPA Pesticide Chemical Code 006306

Liposomal Streptomycin

Chemical vendors

labseeker (China)

Chem-Space.com Database (Lettonie)

THE BioTek (China)

BenchChem (USA)

DAOGE BIOPHARMA (China)

LabNetwork, a WuXi AppTec Company (USA)

BOC Sciences (USA)

ZINC (USA)

Hairui Chemical (China)

MuseChem (USA)

Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd. (Hong Kong)

Sinfoo Biotech (China)

AKos Consulting & Solutions (Germany)

Smolecule (USA)
DC Chemicals (China)
MolPort (Lettonie)
AA BLOCKS (USA)
3WAY PHARM INC (China)
Key Organics/BIONET (UK)
abcr GmbH (Germany)
Acorn PharmaTech Product List (USA)
A2B Chem (USA)
AstaTech, Inc. (USA)
3B Scientific (Wuhan) Corp (China)
Parchem (USA)
Aaron Chemicals LLC
Apexmol (China)
OChem (USA)

Appendix F – Oxytetracycline datasheet (ex PUBMED)

Oxytetracycline is a tetracycline used for treatment of infections caused by a variety of Gram positive and Gram negative microorganisms including Mycoplasma pneumoniae, Pasteurella pestis, Escherichia coli, Haemophilus influenzae (respiratory infections), and Diplococcus pneumoniae. It has a role as an antibacterial drug, a protein synthesis inhibitor, an antimicrobial agent, an anti-inflammatory drug and a bacterial metabolite. It is a tautomer of an oxytetracycline zwitterion.

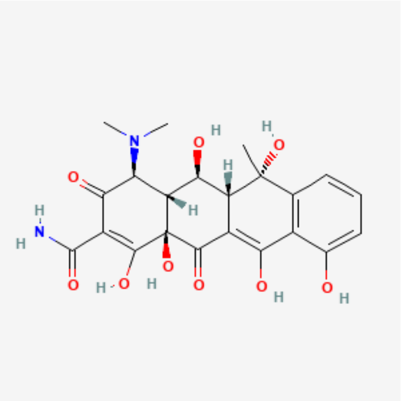
A tetracycline analog isolated from the actinomycete streptomyces rimosus and used in a wide variety of clinical conditions.

IUPAC name

(4S,4aR,5S,5aR,6S,12aR)-4-(dimethylamino)-1,5,6,10,11,12a-hexahydroxy-6-methyl-3,12-dioxo-4,4a,5,5a-tetrahydrotetracene-2-carboxamide

Molecular formula

$C_{22}H_{24}N_2O_9$



Synonyms

Bisolvomycin

Geomycin

Hydroxytetracycline

Oxyterracin

Oxyterracine

Oxytetracid

Oxytetracycline

Oxytetracycline Anhydrous

Oxytetracycline Calcium

Oxytetracycline Dihydrate

Oxytetracycline Hydrochloride

Oxytetracycline Monohydrochloride

Oxytetracycline Sulfate (2:1)

Oxytetracycline, (4a beta,5 beta,5a beta,12a beta)-Isomer

Oxytetracycline, (5 beta)-Isomer

Oxytetracycline, Anhydrous

Oxytetracycline, Calcium (1:1) Salt

Oxytetracycline, Disodium Salt, Dihydrate

Oxytetracycline, Sodium Salt

Terramycin

Depositor supplied names

Stecsolin

Oxydon

TM 5

2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-

2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6S,12aS)-

Oxytetracid

E703

NCI-C56473

SMR000059000

Terramycin im

NSC 9169

Terramycin Q50

Q63393012

Ossitetraciclina [DCIT]

Oxytetracyclinum [INN-Latin]

Oxitetraciclina [INN-Spanish]

Terramicina Oftalmica

79-57-2 (ANHYDROUS)

Geomycin (Streptomyces vimosus)

HSDB 3145

EINECS 201-212-8

LA 200

BRN 2714587

Embryostat

Galsenomycin

Oxitetracycline

SR-01000003006

Hydroxytetracyclinum

Oxytetracycline,(S)

2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-, (4S-(4alpha,4aalpha,5alpha,5aalpha,6beta,12aalpha))-

5-Hydroxy-Tetracycline

Spectrum_001055

Opera_ID_661

Prestwick0_000307

Prestwick1_000307

Prestwick2_000307

Prestwick3_000307

Spectrum2_000988

Spectrum3_000536

Spectrum4_000466

Spectrum5_001148

Oxytetracycline(Terramycin)

SCHEMBL2899

CHEMBL1517

DSSTox_CID_14260

DSSTox_RID_79133

DSSTox_GSID_34260

BSPBio_000274

BSPBio_002151

KBioGR_000912

KBioSS_001535

4-14-00-02633 (Beilstein Handbook Reference)

DivK1c_000225

SCHEMBL560497

SPBio_001055

SPBio_002493

BPBio1_000302

CHEMBL461529

CHEMBL1401333

CHEMBL4280957

DTXSID1034260

NSC9169 (HCL)

SCHEMBL13169109

SCHEMBL13782651

GTPL10919

KBio1_000225

KBio2_001535

KBio2_004103

KBio2_006671

KBio3_001651

6153-64-6 (di-hydrate)

NINDS_000225

BDBM241973

(4S,4aR,5S,5aR,6S,12aR)-4-(dimethylamino)-1,5,6,10,11,12a-hexahydroxy-6-methyl-3,12-dioxo-4,4a,5,5a-tetrahydrotetracene-2-carboxamide

HY-B0275

2058-46-0 (mono-hydrochloride)

Tox21_302380

LMPK07000005

MFCD00003700

s1773

ZINC95626782

AKOS015951277

AKOS015961254

ZINC100026355

ZINC100303028

CCG-269334

DB00595

MCULE-5398230579

CAS-79-57-2

IDI1_000225

NCGC00091268-04

NCGC00091268-05

NCGC00091268-06

NCGC00091268-07

NCGC00091268-08

NCGC00091268-09

NCGC00091268-11

NCGC00091268-12

NCGC00188956-01

NCGC00255168-01

AC-12777

AC-13466

S470

7179-50-2 (calcium (1:1) salt)

SBI-0051473.P003

SW196796-3

3,5,6,10,12,12a-hexahydroxy-6-methyl-

C06624

E75911

Oxytetra Selective Supplement, for microbiology

AB00053514_04

AB00053514_05

AB01274728-01

AB01274728_02

135740-EP2275422A1

135740-EP2292608A1

6153-65-7 (di-hydrochloride salt, di-hydrate)

A839720

Q411646

(4S,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-

SR-01000003006-5

1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene

Oxytetracycline, British Pharmacopoeia (BP) Reference Standard

Oxytetracycline, European Pharmacopoeia (EP) Reference Standard

(4S,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-4,4a,5,5a-tetrahydrotetracene-2-carboxamide

Chemical vendors

BioCrick (China)

Hangzhou APIChem Technology (China)

VladaChem (Germany)

AA BLOCKS (USA)

Sigma-Aldrich (USA)

AK Scientific, Inc. (AKSCI) (USA)

Hairui Chemical (China)

AKos Consulting & Solutions (Germany)

MuseChem (USA)

Amadis Chemical (China)

Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd. (Hong Kong)

AbaChemScene (USA)

AHH Chemical co.,ltd (China)

MolPort (Lettonie)

MedChemexpress MCE (USA)

Pi Chemicals (China)

AbMole Bioscience (USA)

Aaron Chemicals LLC (China)

BLD Pharm (China)

ZINC (USA)

AstaTech, Inc. (USA)

3B Scientific (Wuhan) Corp (China)

LabNetwork, a WuXi AppTec Company (USA)

Yuhao Chemical (China)

A2B Chem (USA)

AbovChem LLC (USA)

Activate Scientific (Germany)

eNovation Chemicals (USA)

ChemShuttle (China)

Mcule (Hungary)

Parchem (USA)

Selleck Chemicals (USA)

TargetMol (Target Molecule Corp.) (USA)

Chem-Space.com Database (Lettonie)

ApexBio Technology (USA)

abcr GmbH (Germany)

CSNpharm (USA)

Appendix G – Oxolinic acid datasheet (ex PUBMED)

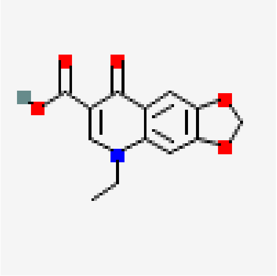
Oxolinic acid is a quinolinemonocarboxylic acid having the carboxy group at position 7 as well as oxo and ethyl groups at positions 4 and 1 respectively and a dioxolo ring fused at the 5- and 6-positions. A synthetic antibiotic, it is used in veterinary medicine for the treatment of bacterial infections in cattle, pigs and poultry. It has a role as an antiinfective agent, an antibacterial drug, an enzyme inhibitor, an antimicrobial agent and an antifungal agent. It is a quinolinemonocarboxylic acid, an organic heterotricyclic compound, an aromatic carboxylic acid, an oxacycle and a quinolone antibiotic. It is a conjugate acid of an oxolinate.

IUPAC name

5-ethyl-8-oxo-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid

Molecular formula

$C_{13}H_{11}NO_5$



Synonyms

Acid, Oxolinic
Gramurin
Oxolinate, Sodium
Oxolinic Acid
Sodium Oxolinate

Depositor supplied synonyms

oxolinic acid
14698-29-4
Nidantin

Dioxacin
Emyrenil
Prodoxal
Prodoxol
Utibid
Gramurin
Oksaren
Oxolinic
Ossian
Uroxol
Acide oxolinique
Uritrate
Urotrate
Oxoboi
Pietil
Starner
Ultibid
Acido oxolinico
Uro-alvar
Acidum oxolinicum
Urinox
NSC-110364
5-Ethyl-8-oxo-5,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid
5-Ethyl-8-oxo-5,8-dihydro[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid
5-ethyl-8-oxo-[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid
NSC 110364
W 4565
1-Ethyl-6,7-methylenedioxy-4-quinolone-3-carboxylic acid
UNII-L0A22B22FT
MFCD00056775
1-Ethyl-1,4-dihydro-6,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid
5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo(4,5-g)quinoline-7-carboxylic acid
L0A22B22FT
CHEBI:138856
1,3-Dioxolo(4,5-g)quinoline-7-carboxylic acid, 5-ethyl-5,8-dihydro-8-oxo-
1,3-Dioxolo[4,5-g]quinoline-7-carboxylic acid, 5-ethyl-5,8-dihydro-8-oxo-
NSC110364
NCGC00015762-06
Cistopax
Orthurine
Tiurasin
Acido ossolico
CAS-14698-29-4
DSSTox_CID_1089
DSSTox_RID_75935

DSSTox GSID 21089
Acido ossolico [DCIT]
5-Ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid
Acide oxolinique [INN-French]
Acido oxolinico [INN-Spanish]
Acidum oxolinicum [INN-Latin]
CCRIS 6301
HSDB 3243
SR-01000076042
EINECS 238-750-8
BRN 0620635
Aqualinic
Inoxyl
oxolinic-acid
Oxolinic acid [USAN:INN:BAN]
S-0208
Aqualinic (TN)
quinolone antibiotic
Prestwick 629
Spectrum 001397
Oxolinic acid impurity B
Prestwick0 000193
Prestwick1_000193
Prestwick2 000193
Prestwick3 000193
Spectrum2 000933
Spectrum3 001490
Spectrum4 000073
Spectrum5_001176
Lopac-O-0877
Oxolinic acid (USAN/INN)
Lopac0 000952
Oprea1 169598
SCHEMBL24445
BSPBio 000145
BSPBio 003079
KBioGR 000625
KBioSS 001877
MLS000028501
DivK1c 000659
SPECTRUM1502030
SPBio 000866
SPBio 002066
BPBio1 000161
CHEMBL416755

ZINC1875
DTXSID1021089
HMS502A21
KBio1_000659
KBio2_001877
KBio2_004445
KBio2_007013
KBio3_002579
AOB5349
NINDS_000659
HMS1568H07
HMS1921F12
HMS2092P09
HMS2095H07
HMS3262P06
HMS3712H07
Oxolinic acid, analytical standard
Pharmakon1600-01502030
Oxolinic acid, quinolone antibiotic
ACT03284
HY-B1002
Tox21_110216
Tox21_202787
Tox21_500952
AC8065
BBL009934
CCG-39666
NSC758177
s4537
STK801351
5,8-Dihydro-5-ethyl-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid
5-ethyl-8-oxo-5-hydro-2H-1,3-dioxoleno[4,5-g]quinoline-7-carboxylic acid
AKOS000282622
Tox21_110216_1
CS-4499
DB13627
LP00952
MCULE-2131347036
NSC-758177
SDCCGSBI-0050926.P004
IDI1_000659
NCGC00015762-01
NCGC00015762-02
NCGC00015762-03
NCGC00015762-04

NCGC00015762-05
NCGC00015762-07
NCGC00015762-08
NCGC00015762-09
NCGC00015762-10
NCGC00015762-11
NCGC00015762-13
NCGC00015762-17
NCGC00093361-02
NCGC00093361-03
NCGC00093361-04
NCGC00093361-05
NCGC00260333-01
NCGC00261637-01
AS-12087
SMR000058314
SY066716
SBI-0050926.P003
DB-042865
EU-0100952
FT-0637128
VU0243182-3
D02301
O 0877
W-4565
WLN: T C566 DO FO JN MV EHJ J2 LVQ
698O294
A808577
Q287840
SR-01000076042-1
SR-01000076042-4
SR-01000076042-6
W-108119
BRD-K73394555-001-08-6
5-Ethyl-5,3-dioxolo[4,5-g]quinoline-7-carboxylic acid
F3351-0487
1-Ethyl-1,7-methylenedioxy-4-oxo-3-quinolinecarboxylic acid
Oxolinic acid, European Pharmacopoeia (EP) Reference Standard
1,5-g]quinoline-7-carboxylic acid, 5-ethyl-5,8-dihydro-8-oxo-
1.4-Dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-3-carboxylic acid
5-Ethy1-5,8-dihydro-8-oxo-1,3-dioxolo[4,5]quinoline-7-carboxylic acid
5-ETHYL-8-OXO-2H,5H,8H-[1,3]DIOXOLO[4,5-G]QUINOLINE-7-CARBOXYLIC ACID
5-Ethyl-8-oxo-5,8-dihydro[1,3]dioxolo[4,5-g]quinoline-7-carboxylic acid #
W-4565; 5,8-Dihydro-5-ethyl-8-oxo-1,3-dioxolo[4,5-g]quinoline-7-carboxylic acid

Chemical vendors

Thermo Fisher Scientific
PubChem SID: 459216800
Purchasable Chemical: GID 900000004586605
Aaron Chemicals LLC
PubChem SID: 406513785
Purchasable Chemical: AR0032W5
AEchem Scientific Corp., USA
PubChem SID: 252307207
Purchasable Chemical: AE1-007595
AbaChemScene
PubChem SID: 312323770
Purchasable Chemical: CS-4499
LGC Standards
PubChem SID: 340510114
Purchasable Chemical: DRE-C15788000
Hairui Chemical
PubChem SID: 375668141
Purchasable Chemical: HR129219
Alfa Chemistry
PubChem SID: 438656944
Purchasable Chemical: ACM14698294
Accela ChemBio Inc.
PubChem SID: 381142468
Purchasable Chemical: SY066716
BLD Pharm
PubChem SID: 434214948
Purchasable Chemical: BD01195127
Amadis Chemical
PubChem SID: 131299404
Purchasable Chemical: A808577
Biosynth Carbosynth
PubChem SID: 255381570
Purchasable Chemical: W-108119
ACT Chemical
PubChem SID: 165235874
Purchasable Chemical: ACT03284
Sigma-Aldrich
PubChem SID: 329760414
Purchasable Chemical: 67126 SIAL
AHH Chemical co.,ltd
PubChem SID: 252376911
Purchasable Chemical: MT-20552
Glentham Life Sciences Ltd.

PubChem SID: 310278429
Purchasable Chemical: GA2313
ChemShuttle
PubChem SID: 329590399
Purchasable Chemical: 151936
ZINC
PubChem SID: 255513199
Purchasable Chemical: ZINC1875
MolCore BioPharmatech
PubChem SID: 446228778
Purchasable Chemical: DY524987
AbMole Bioscience
PubChem SID: 348397403
Purchasable Chemical: M5842
Chemenu Inc.
PubChem SID: 443502085
Purchasable Chemical: CM249569
A2B Chem
PubChem SID: 443812476
Purchasable Chemical: AB42617
Smolecule
PubChem SID: 438484906
Purchasable Chemical: S538400
3WAY PHARM INC
PubChem SID: 438617486
Purchasable Chemical: SWA-02530
001Chemical
PubChem SID: 440002810
Purchasable Chemical: DY524987
TargetMol
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Purchasable Chemical: T1233
Eximed Laboratory
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Purchasable Chemical: EiM17-02737 *(URL not provided...)*
Achemo Scientific Limited
PubChem SID: 316959872
Purchasable Chemical: AC-20150
AstaTech, Inc.
PubChem SID: 458726423
Purchasable Chemical: AC8065
3B Scientific (Wuhan) Corp
PubChem SID: 375146570
Purchasable Chemical: 3B3-011305
eNovation Chemicals

PubChem SID: 441393795
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Angene Chemical
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Purchasable Chemical: AGN-PC-07Y4TM
Innovapharm
PubChem SID: 385394088
Purchasable Chemical: BBS-00030530 *(URL not provided...)*
Norris Pharm
PubChem SID: 383394174
Purchasable Chemical: NSZB-A196001 *(URL not provided...)*
AK Scientific, Inc. (AKSCI)
PubChem SID: 162174269
Purchasable Chemical: 69069
Ambinter
PubChem SID: 370609448
Purchasable Chemical: Amb19133547
MolPort
PubChem SID: 88533494
Purchasable Chemical: MolPort-000-885-505
AOBIOUS INC
PubChem SID: 252450985
Purchasable Chemical: AOB5349 *(URL not provided...)*
MuseChem
PubChem SID: 355037777
Purchasable Chemical: I001785
Vitas-M Laboratory
PubChem SID: 125324612
Purchasable Chemical: BBL009934
Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd.
PubChem SID: 441076471
Purchasable Chemical: PH-2989A *(URL not provided...)*
Mcule
PubChem SID: 169651915
Purchasable Chemical: MCULE-2131347036
Life Chemicals
PubChem SID: 165111866
Purchasable Chemical: F3351-0487
AA BLOCKS
PubChem SID: 375229519
Purchasable Chemical: AA00324D
VladaChem
PubChem SID: 381011720
Purchasable Chemical: VL266819-5G
OtavaChemicals

PubChem SID: 441624298
Purchasable Chemical: 1284475
THE BioTek
PubChem SID: 434302727
Purchasable Chemical: bt-278055
Achemtek
PubChem SID: 381394098
Purchasable Chemical: 0104-010303
DC Chemicals
PubChem SID: 439507864
Purchasable Chemical: DC34252
Key Organics/BIONET
PubChem SID: 354266443
Purchasable Chemical: AS-12087
Debye Scientific Co., Ltd
PubChem SID: 202557939
Purchasable Chemical: DB-042865
BenchChem
PubChem SID: 445800689
Purchasable Chemical: B1678063
Finetech Industry Limited
PubChem SID: 164820921
Purchasable Chemical: FT-0637128
Chem-Space.com Database
PubChem SID: 434381098
Purchasable Chemical: CSSB00000021082
Oakwood Products
PubChem SID: 312605301
Purchasable Chemical: 242886
Elsa Biotechnology
PubChem SID: 441563681
Purchasable Chemical: ELSA20-11091 *(URL not provided...)*
Selleck Chemicals
PubChem SID: 347914866
Purchasable Chemical: S4537
Changzhou Highassay Chemical Co., Ltd
PubChem SID: 313081786
Purchasable Chemical: my_sub2897 *(URL not provided...)*
AbovChem LLC
PubChem SID: 319556767
Purchasable Chemical: HY-B1002 *(URL not provided...)*
Combi-Blocks
PubChem SID: 374036260
Purchasable Chemical: QA-7859
OChem

PubChem SID: 341834686
Purchasable Chemical: 4525
Pi Chemicals
PubChem SID: 322081908
Purchasable Chemical: PI-24117
abcr GmbH
PubChem SID: 316562994
Purchasable Chemical: AB376298
Clinivex
PubChem SID: 463925588
Purchasable Chemical: RCLTRO857500
MedChemexpress MCE
PubChem SID: 254804095
Purchasable Chemical: HY-B1002
Yuhao Chemical
PubChem SID: 355044232
Purchasable Chemical: LT3778
AKos Consulting & Solutions
PubChem SID: 104831045
Purchasable Chemical: AKOS000282622
Clearsynth
PubChem SID: 313076737
Purchasable Chemical: CS-O-02036

Appendix H – Validamycin datasheet (ex PUBMED)

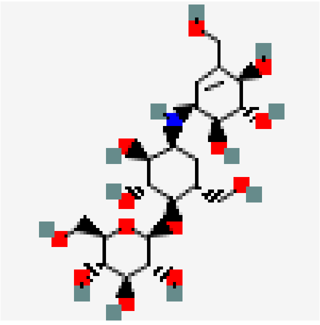
Validamycin A is a member of the class of Validamycins that is (1R,2S,3S,4S,6R)-4-amino-6-(hydroxymethyl)cyclohexane-1,2,3-triol in which the hydroxy group at position 1 has been converted to its beta-D-glucoside and in which one of the hydrogens attached to the nitrogen is replaced by a (1R,4R,5R,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl group. It is the major Validamycin produced by Streptomyces hygroscopicus. It has a role as an EC 2.4.1.231 [alpha,alpha-trehalose phosphorylase (configuration-retaining)] inhibitor, an EC 2.4.1.64 (alpha,alpha-trehalose phosphorylase) inhibitor, an EC 3.2.1.28 (alpha,alpha-trehalase) inhibitor and an antifungal agrochemical. It is a member of Validamycins, a secondary amino compound, a polyol and an antibiotic fungicide. It is a conjugate base of a Validamycin A(1+).

IUPAC name

(2R,3R,4S,5S,6R)-2-[(1R,2R,3S,4S,6R)-2,3-dihydroxy-6-(hydroxymethyl)-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl]amino]cyclohexyl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol

Molecular formula

$C_{20}H_{35}NO_{13}$



Synonyms

Validamycin
VALIDAMYCIN A
37248-47-8
Validacin
Valimon

Depositor supplied synonyms

Validamycin
VALIDAMYCIN A
37248-47-8
Validacin
Valimon
UNII-313E9620QS
T-7545-A
(2R,3R,4S,5S,6R)-2-[(1R,2R,3S,4S,6R)-2,3-dihydroxy-6-(hydroxymethyl)-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl]amino]cyclohexyl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol
CHEBI:29703
313E9620QS
(1S-(1alpha,4alpha,5beta,6alpha))-1,5,6-trideoxy-4-O-beta-D-glucopyranosyl-5-(hydroxymethyl)-1-((4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-D-chiro-inositol
1L-(1,3,4/2,6)-2,3-Dihydroxy-6-hydroxymethyl-4-((1S,4R,5S,6S)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enylamino)cyclohexyl beta-D-glucopyranoside
D-1,5,6-Trideoxy-3-O-beta-D-glucopyranosyl-5-(hydroxymethyl)-1-((4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-D-chiroinositol
jinganmycin A
HSDB 6745
(+)-validamycin A
Validamycin (technical)
(1R,2R,3S,4S,6R)-2,3-dihydroxy-6-(hydroxymethyl)-4-{[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl]amino}cyclohexyl beta-D-glucopyranoside
SCHEMBL3121491
CHEMBL1923413
DTXSID4058073
C20H35NO13
HY-B0856
ZINC8437016
MFCD09028089
AKOS016012982
AG-F-30599
(1S-(1a,4a,5B,6a))-1,5,6-Trideoxy-3-O-B-D-glucopyranosyl-5-(hydroxymethyl)-1-((4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-d-chiro-inositol
1L-(1,3,4/2,6)-2,3-Dihydroxy-6-hydromethyl-4-((1S,4R,5S,6S)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enylamino)cyclohexyl beta-D-glucopyranoside
AC-32607
AS-15281
O743
CS-0012869
248V478

Validamycin A, PESTANAL(R), analytical standard
W-204201
D-chiro-Inositol, 1,5,6-trideoxy-3-O-|A-D-glucopyranosyl-
D-Chiro-inositol,1,5,6-trideoxy-3-O-beta-D-glucopyranosyl-
(2R,3R,4S,5S,6R)-2-((1R,2R,3S,4S,6R)-2,3-dihydroxy-6-(hydroxymethyl)-4-((1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-enylamino)cyclohexyloxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol
(2R,3R,4S,5S,6R)-2-[(1R,2R,3S,4S,6R)-2,3-dihydroxy-6-(hydroxymethyl)-4-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)cyclohex-2-en-1-yl]amino]cyclohexoxy]-6-(hydroxymethyl)tetrahydropyran-3,4,5-triol
1,5,6-trideoxy-4-O-beta-D-glucopyranosyl-5-(hydroxymethyl)-1-[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-D-chiro-inositol
D-chiro-Inositol, 1,5,6-trideoxy-3-O-beta-D-glucopyranosyl-5-(hydroxymethyl)-1-((4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl)amino)-, (1S-(1-alpha,4-alpha,5-beta,6-alpha))-

Chemical vendors

ZINC
PubChem SID: 258539447
Purchasable Chemical: ZINC8437016
BenchChem
PubChem SID: 446132187
Purchasable Chemical: B014589
OChem
PubChem SID: 341835756
Purchasable Chemical: 5606
Hangzhou APIChem Technology
PubChem SID: 440703256
Purchasable Chemical: AC-32607 *(URL not provided...)*
BioAustralis Fine Chemicals
PubChem SID: 463935383
Purchasable Chemical: BIA-V1561
Clearsynth
PubChem SID: 341136562
Purchasable Chemical: CS-CM-00183
Achemtek
PubChem SID: 381375222
Purchasable Chemical: 0104-058173
Alfa Chemistry
PubChem SID: 277330041
Purchasable Chemical: 37248-47-8
BOC Sciences
PubChem SID: 254791518
Purchasable Chemical: 37248-47-8
AA BLOCKS

PubChem SID: 381939536
Purchasable Chemical: AA007A34
AKos Consulting & Solutions
PubChem SID: 163851894
Purchasable Chemical: AKOS016012982
Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd.
PubChem SID: 441076670
Purchasable Chemical: PH-3176EA *(URL not provided...)*
BLD Pharm
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Purchasable Chemical: BD69083
Key Organics/BIONET
PubChem SID: 354268805
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Aaron Chemicals LLC
PubChem SID: 406549705
Purchasable Chemical: AR007AUW
MedChemexpress MCE
PubChem SID: 433790017
Purchasable Chemical: HY-B0856
AbaChemScene
PubChem SID: 433790916
Purchasable Chemical: CS-0012869
THE BioTek
PubChem SID: 439459649
Purchasable Chemical: bt-315954
MuseChem
PubChem SID: 355433098
Purchasable Chemical: R001150
Starshine Chemical
PubChem SID: 464774906
Purchasable Chemical: starbld0609653 *(URL not provided...)*
Sigma-Aldrich
PubChem SID: 329754148
Purchasable Chemical: 32347_SIAL
AHH Chemical co.,ltd
PubChem SID: 252358359
Purchasable Chemical: MT-60328
labseeker
PubChem SID: 335959486
Purchasable Chemical: SC-81107
Combi-Blocks
PubChem SID: 374034908
Purchasable Chemical: QA-6237
Smolecule

PubChem SID: 439369631
Purchasable Chemical: S601169
Hairui Chemical
PubChem SID: 375682005
Purchasable Chemical: HR122337
3B Scientific (Wuhan) Corp
PubChem SID: 375204769
Purchasable Chemical: 3B2-1963
LGC Standards
PubChem SID: 340511074
Purchasable Chemical: DRE-C17899900
AstaTech, Inc.
PubChem SID: 458752484
Purchasable Chemical: C15695
eNovation Chemicals
PubChem SID: 441401506
Purchasable Chemical: Y1055346
abcr GmbH
PubChem SID: 374383433
Purchasable Chemical: AB508865
AK Scientific, Inc. (AKSCI)
PubChem SID: 162182851
Purchasable Chemical: O743
Norris Pharm
PubChem SID: 383470194
Purchasable Chemical: NSZB-A280898 *(URL not provided...)*
Glentham Life Sciences Ltd.
PubChem SID: 310281623
Purchasable Chemical: GA4672
LabNetwork, a WuXi AppTec Company
PubChem SID: 347247255
Purchasable Chemical: LN01326614
Biosynth Carbosynth
PubChem SID: 255375092
Purchasable Chemical: W-204201
Chem-Space.com Database
PubChem SID: 434696542
Purchasable Chemical: CSSB00016991225
A2B Chem
PubChem SID: 444109803
Purchasable Chemical: AD39564
MolPort
PubChem SID: 189562535
Purchasable Chemical: MolPort-023-220-452

Appendix I – Patent search and link to selected websites

Patent search for antibiotic currently used as plant protection products
Searched via Patentscope - https://patentscope.wipo.int/search/en/search.jsf

Search on antibiotic – 45110 results
Search on antibiotic and plant protection – 2303 results

Streptomycin (2355 results, sort by ascending date)

GB – 1947 – process for purifying streptomycin - Merck & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=AU193890220&_cid=P20-L5HY2I-45628-1
GB – 1949 – process of preparing salts of streptomycin – Merck & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134516818&_cid=P20-L5HW7S-09188-3
GB – 1953 – method for isolation and purification of streptomycin – Merck & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134594855&_cid=P20-L5HW7S-09188-1
GB – 1953 – process for the production of streptomycin – Merck & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134602809&_cid=P20-L5HW7S-09188-3
GB – 1957 – streptomycin and isonicotinyl hydrazine preparations – Pfizer & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134692172&_cid=P20-L5HW7S-09188-1

Oxytetracycline (1229 results, sort by ascending date)

Au – 1919 – rhodium containing catalyst and use of thereof in preparation of 6-deoxy-5-oxytetracycline – Pfizer inc
https://patentscope.wipo.int/search/en/detail.jsf?docId=AU194058432&_cid=P20-L5HY4V-46579-1
GB - 1959 – Antibiotic composition – Merck & Co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134716238&_cid=P20-L5HWTL-20208-1
CN – 2015 – oxytetracycline preparation and preparation method
https://patentscope.wipo.int/search/en/detail.jsf?docId=CN142939681&_cid=P20-L5HWHC-14110-1

CN – 2021 – preparation method of high-quality oxytetracycline - YANGZHOU LIANBO PHARMACEUTICAL CO., LTD.
https://patentscope.wipo.int/search/en/detail.jsf?docId=CN326422179&_cid=P20-L5HWHC-14110-2

Kasugamycin (527 results, sort by ascending date)

AU – 1960 – Kasugamycin and processes for the preparation thereof - Zaidan Dojin Biseibutsu Kagaku Kenkyukai
https://patentscope.wipo.int/search/en/detail.jsf?docId=AU193968270&_cid=P20-L5HZ80-65946-1
US – 1967 – Antibiotic Kasugamycin – Hamao Umezawa
https://patentscope.wipo.int/search/en/detail.jsf?docId=US36270359&_cid=P20-L5HZ80-65946-1
CN – 2008 – Agricultural chemical composition containing carbendazim and kasugamycin – Jiangmen plant protection Co, Ltd
https://patentscope.wipo.int/search/en/detail.jsf?docId=CN83443447&_cid=P20-L5HYZN-62199-1

Gentamicin (1257 results, sort by ascending date)

GB – 1976 – Gentamicin derivatives – Bristol myers
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB135618172&_cid=P20-L5HWZ4-23291-1
NZ – 1977 - 1-N-SUBSTITUTED DERIVATIVES OF 4,6-DI-(AMINO GLYCOSYL)-1,3-DIAMINOCYCLITOLS AND PHARMACEUTICAL COMPOSITIONS – Scherico Ltd
https://patentscope.wipo.int/search/en/detail.jsf?docId=NZ178935248&_cid=P20-L5HWZ4-23291-1

Oxolinic acid (86 results, sort by ascending date)

US – 1973 – process for the production of ethyl hydroxy 3 dioxolo (4,5G) quinoline carboxylate – Warner Lambert company
https://patentscope.wipo.int/search/en/detail.jsf?docId=US36645344&_cid=P20-L5HY8Y-48939-1
GB – 1989 – pesticidal compositions comprising oxolinic acid or salts thereof – Sumitomo chemical co
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB136850470&_cid=P20-L5HY8Y-48939-2

Validamycin (495 results, sort by ascending date)

GB – 1972 – New antibiotic – Takeda Chemical Industries Ltd -
https://patentscope.wipo.int/search/en/detail.jsf?docId=GB135461918&_cid=P20-L5HXGI-34464-1

CN – 2017 – Validamycin composition for preventing and controlling rice sheath blight and preparation method thereof – Wuhu Foman

Zhongshengmycin (177 results, sort by ascending date)

CN – 2004 – antibiotic agricultural chemicals wettable powder and its preparation method – institute of biological control, Chinese academy of agricultural science
https://patentscope.wipo.int/search/en/detail.jsf?docId=CN82735126&_cid=P20-L5HYMN-54968-1
CN – 2006 – agricultural sterilizing composition aimed at plant disease
https://patentscope.wipo.int/search/en/detail.jsf?docId=CN82924421&_cid=P20-L5HYMN-54968-1

Annex A – Questionaire for scientific survey on antibiotic use as plant protection product

In the frame of a scientific survey by our Plantibio team at UCLouvain, you are invited to complete this short survey on the use of antibiotic (bactericide) as plant protection product in your country at origin

E-mail :

Country where do you come from :

If you wish, please provide your Name (this will help us to provide you with feedback or to contact you for further inquiries, if you accept). Data you provide here will only be used in the frame of our study, and under the GDPR regulation. By providing us with your Name, do you agree that such data is stored in our database during the length of the project (only for the purpose of the study on use of antibiotics as plant protection products) and that we might contact you.

Q1- In your country, do you know if the following antibiotics are authorized for plant protection ?

No antibiotic is authorized
Gentamicin
Kanmycin
Kasugamycin
Streptomycin
Tetracycline or Oxytetracycline
Other

Q2- Are antibiotics (bactericides) officially authorized as plant protection products in your country ?

Yes
No
Maybe

Q3- If antibiotics (bactericides) are officially authorized, please provide any relevant information (current official regulation, website, any publication or authorized information source)

Q4- Do you know companies commercializing antibiotics as plant protection products ? If yes, please provide your answer

Q5- Do you know an expert in this field in your country at origin ? Please provide his name and email

Annex B – World maps for resistance and use of antibiotics in plant protection

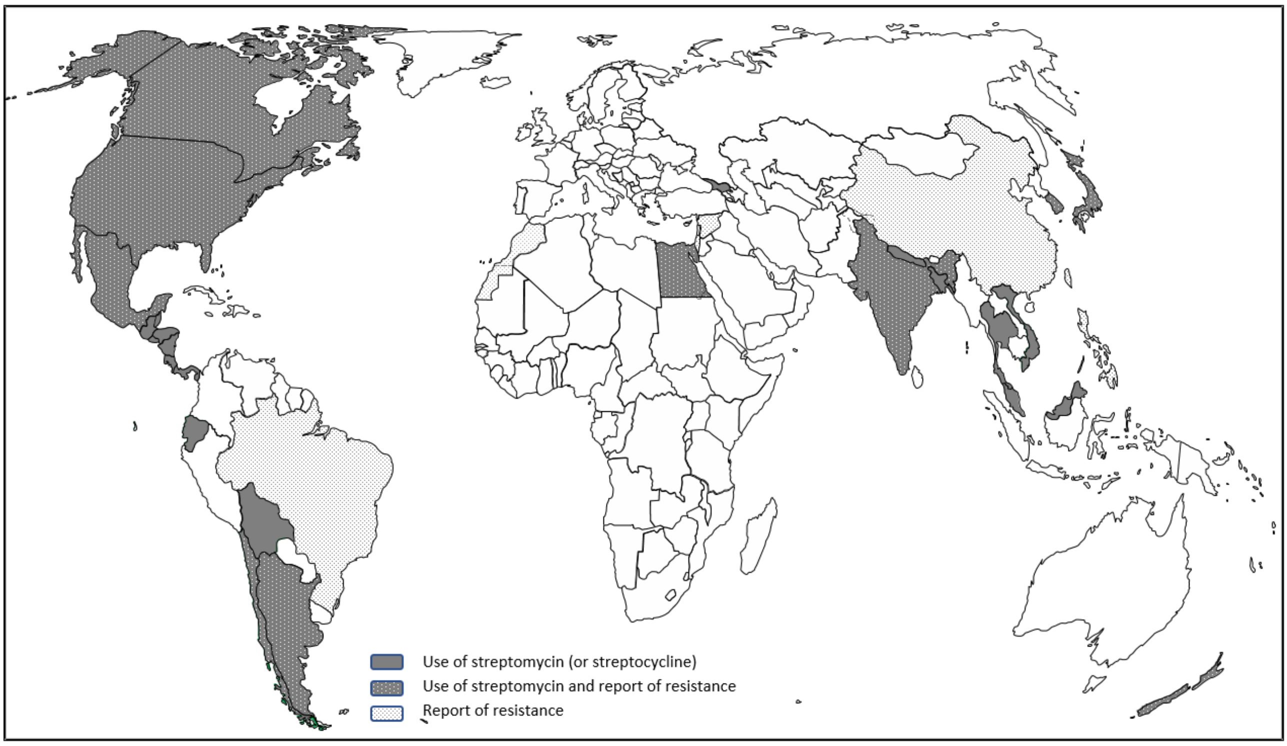


Figure S1: World map of countries where streptomycin is used and/or where resistance cases were reported, compiled from scientific literature and grey literature, as of August 2023.

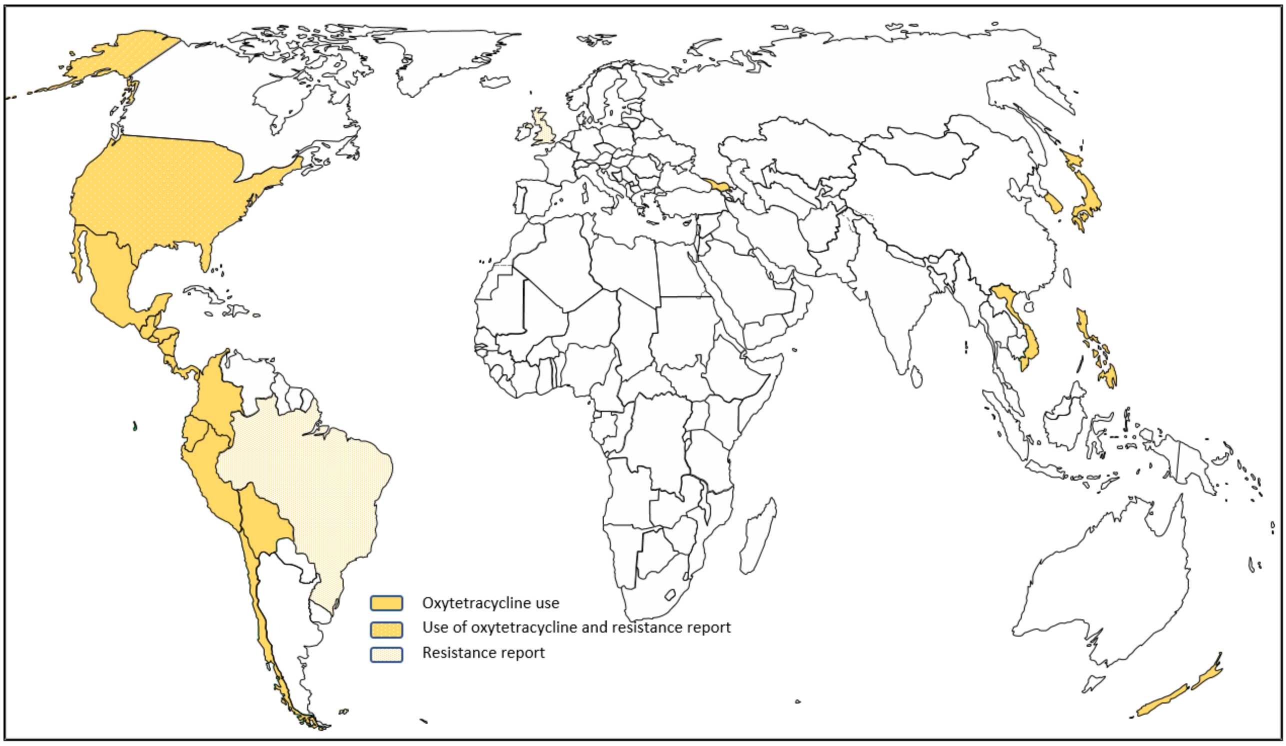


Figure S2: World map of countries where oxytetracycline is used and/or where resistance cases were reported, compiled from scientific literature and grey literature, as of August 2023.

Figure S3: World map of countries where gentamicin is used and/or where resistance cases were reported, compiled from scientific literature and grey literature, as of August 2023.

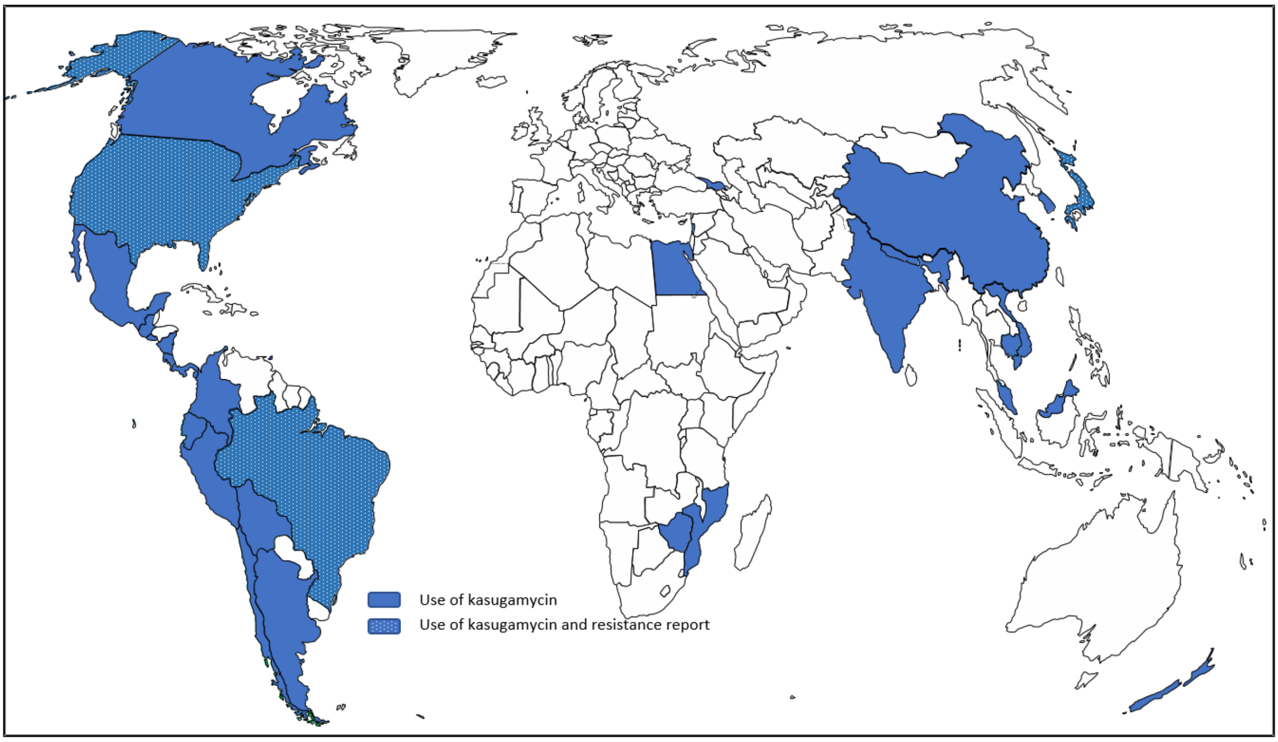


Figure S4: World map of countries where kasugamycin is used and/or where resistance cases were reported, compiled from scientific literature and grey literature, as of August 2023.

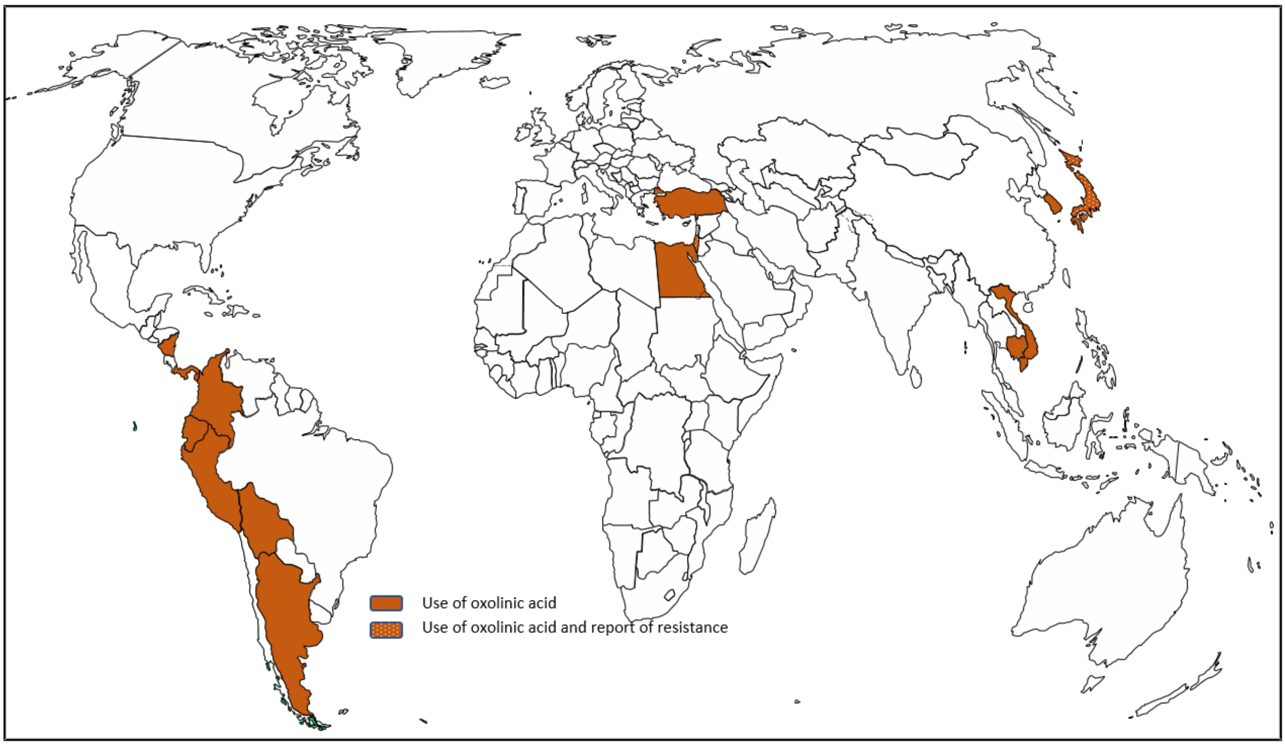
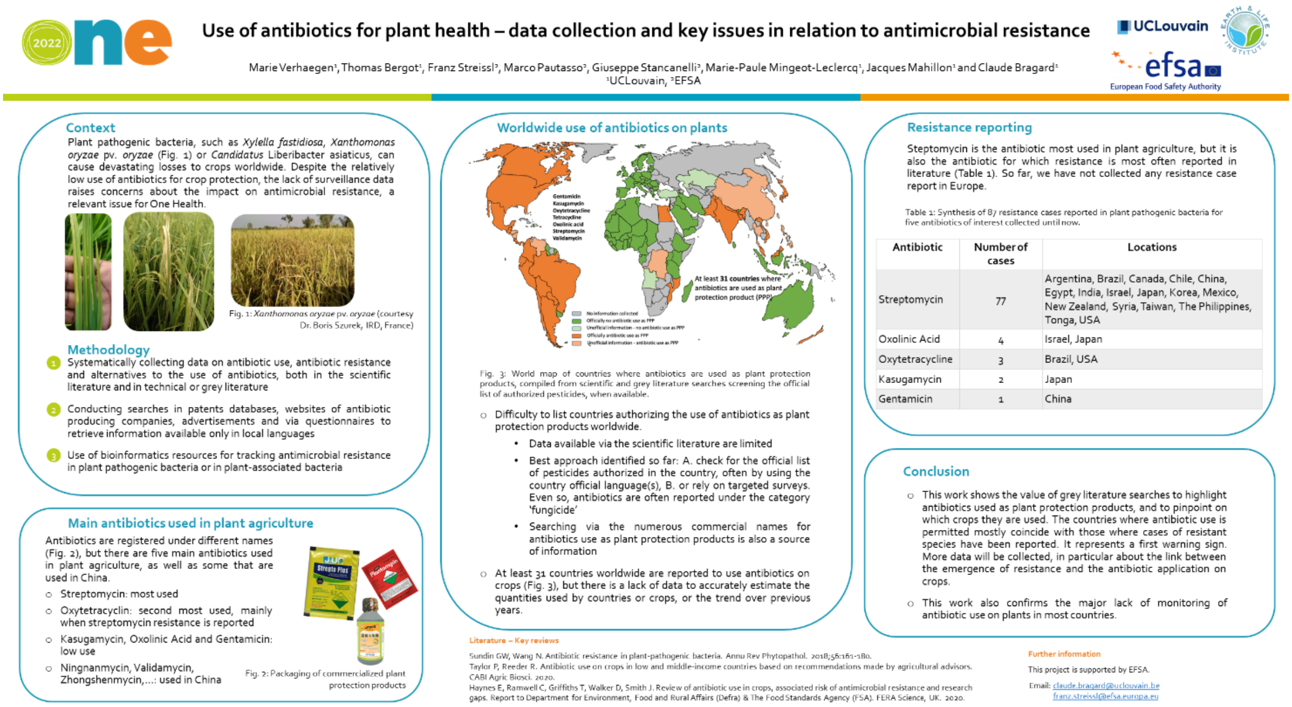


Figure S5: World map of countries where oxolinic acid is used and/or where resistance cases were reported, compiled from scientific literature and grey literature, as of August 2023.

Annex C – Poster presentation for One Health Conference – June 2022



Use of antibiotics for plant health – data collection and key issues in relation to antimicrobial resistance

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Context

Plant pathogenic bacteria, such as *Xylella fastidiosa*, *Xanthomonas oryzae* pv. *oryzae* (Fig. 1) or *Candidatus* Liberibacter asiaticus, can cause devastating losses to crops worldwide. Despite the relatively low use of antibiotics for crop protection, the lack of surveillance data raises concerns about the impact on antimicrobial resistance, a relevant issue for One Health.

Fig. 1: *Xanthomonas oryzae* pv. *oryzae* (courtesy Dr. Boris Szurek, IRD, France)

Methodology

1. Systematically collecting data on antibiotic use, antibiotic resistance and alternatives to the use of antibiotics, both in the scientific literature and in technical or grey literature
2. Conducting searches in patents databases, websites of antibiotic producing companies, advertisements and via questionnaires to retrieve information available only in local languages
3. Use of bioinformatics resources for tracking antimicrobial resistance in plant pathogenic bacteria or in plant-associated bacteria

Main antibiotics used in plant agriculture

Antibiotics are registered under different names (Fig. 2), but there are five main antibiotics used in plant agriculture, as well as some that are used in China.

- Streptomycin: most used
- Oxytetracyclin: second most used, mainly when streptomycin resistance is reported
- Kasugamycin, Oxolinic Acid and Gentamicin: low use
- Ningnanmycin, Validamycin, Zhongshenmycin,...: used in China

Fig. 2: Packaging of commercialized plant protection products

Worldwide use of antibiotics on plants

Fig. 3: World map of countries where antibiotics are used as plant protection products, compiled from scientific and grey literature searches screening the official list of authorized pesticides, when available.

- Difficulty to list countries authorizing the use of antibiotics as plant protection products worldwide.
  - Data available via the scientific literature are limited
  - Best approach identified so far: A. check for the official list of pesticides authorized in the country, often by using the country official language(s), B. or rely on targeted surveys. Even so, antibiotics are often reported under the category 'fungicide'
  - Searching via the numerous commercial names for antibiotics use as plant protection products is also a source of information
- At least 31 countries worldwide are reported to use antibiotics on crops (Fig. 3), but there is a lack of data to accurately estimate the quantities used by countries or crops, or the trend over previous years.

Resistance reporting

Steptomycin is the antibiotic most used in plant agriculture, but it is also the antibiotic for which resistance is most often reported in literature (Table 1). So far, we have not collected any resistance case report in Europe.

Table 1: Synthesis of 87 resistance cases reported in plant pathogenic bacteria for five antibiotics of interest collected until now.

Antibiotic	Number of cases	Locations
Streptomycin	77	Argentina, Brazil, Canada, Chile, China, Egypt, India, Israel, Japan, Korea, Mexico, New Zealand, Syria, Taiwan, The Philippines, Tonga, USA
Oxolinic Acid	4	Israel, Japan
Oxytetracycline	3	Brazil, USA
Kasugamycin	2	Japan
Gentamicin	1	China

Conclusion

- This work shows the value of grey literature searches to highlight antibiotics used as plant protection products, and to pinpoint on which crops they are used. The countries where antibiotic use is permitted mostly coincide with those where cases of resistant species have been reported. It represents a first warning sign. More data will be collected, in particular about the link between the emergence of resistance and the antibiotic application on crops.
- This work also confirms the major lack of monitoring of antibiotic use on plants in most countries.

Literature – Key reviews

Sundin GW, Wang N. Antibiotic resistance in plant-pathogenic bacteria. Annu Rev Phytopathol. 2018;56:161-180.
Taylor P, Reeder R. Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. CABI Agric Biosci. 2020.
Haynes E, Ramwell C, Griffiths T, Walker D, Smith J. Review of antibiotic use in crops, associated risk of antimicrobial resistance and research gaps. Report to Department for Environment, Food and Rural Affairs (Defra) & The Food Standards Agency (FSA). FERA Science, UK. 2020.

Further information

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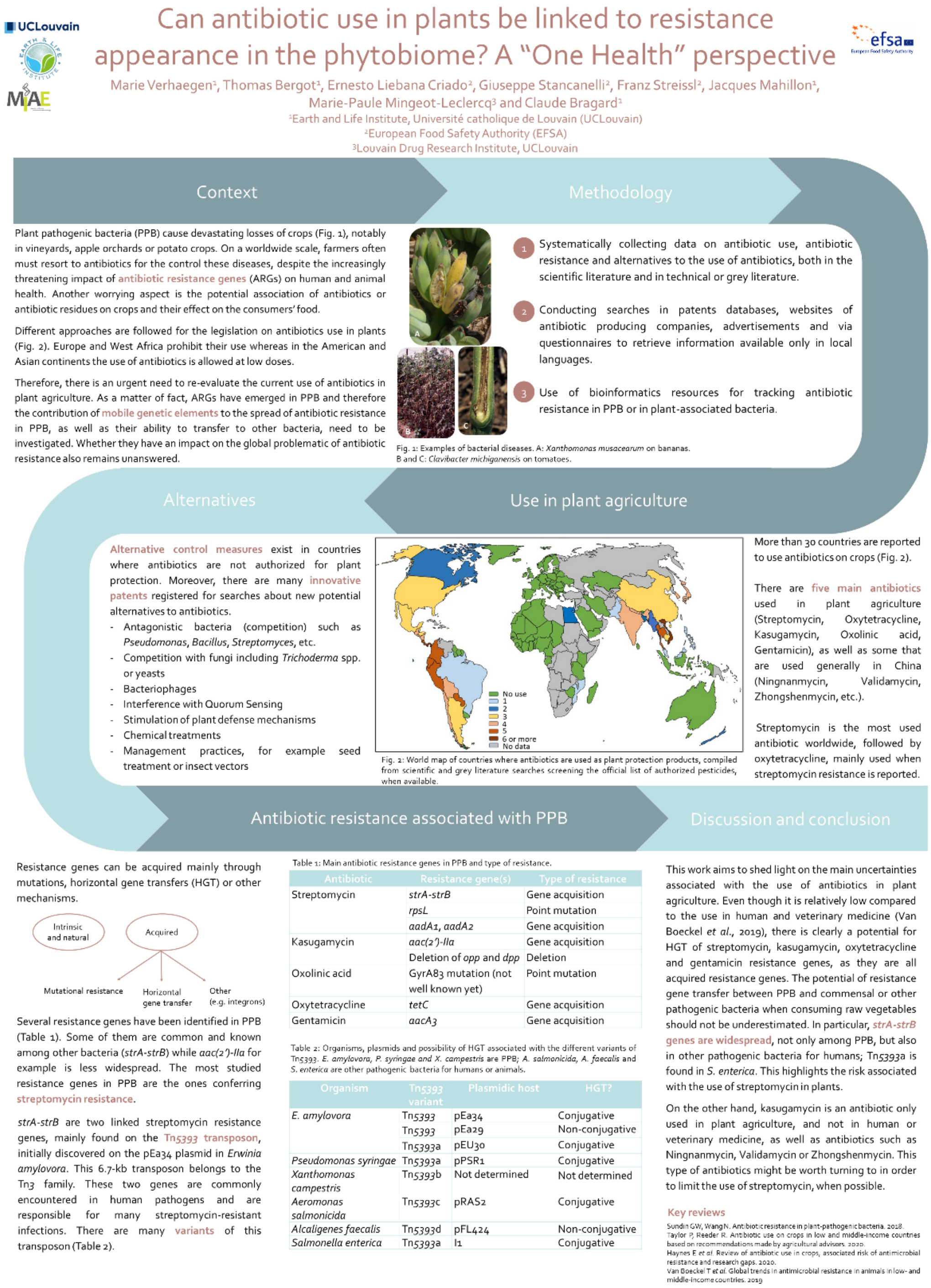
Annex D – Poster presentation for Belgian Society for Food Microbiology conference – October 2022



Can antibiotic use in plants be linked to resistance appearance in the phytobiome? A "One Health" perspective

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Context

Plant pathogenic bacteria (PPB) cause devastating losses of crops (Fig. 1), notably in vineyards, apple orchards or potato crops. On a worldwide scale, farmers often must resort to antibiotics for the control these diseases, despite the increasingly threatening impact of **antibiotic resistance genes** (ARGs) on human and animal health. Another worrying aspect is the potential association of antibiotics or antibiotic residues on crops and their effect on the consumers' food.

Different approaches are followed for the legislation on antibiotics use in plants (Fig. 2). Europe and West Africa prohibit their use whereas in the American and Asian continents the use of antibiotics is allowed at low doses.

Therefore, there is an urgent need to re-evaluate the current use of antibiotics in plant agriculture. As a matter of fact, ARGs have emerged in PPB and therefore the contribution of **mobile genetic elements** to the spread of antibiotic resistance in PPB, as well as their ability to transfer to other bacteria, need to be investigated. Whether they have an impact on the global problematic of antibiotic resistance also remains unanswered.

Fig. 1: Examples of bacterial diseases. A: *Xanthomonas musacearum* on bananas. B and C: *Clavibacter michiganensis* on tomatoes.

Methodology

1. Systematically collecting data on antibiotic use, antibiotic resistance and alternatives to the use of antibiotics, both in the scientific literature and in technical or grey literature.
2. Conducting searches in patents databases, websites of antibiotic producing companies, advertisements and via questionnaires to retrieve information available only in local languages.
3. Use of bioinformatics resources for tracking antibiotic resistance in PPB or in plant-associated bacteria.

Use in plant agriculture

Fig. 2: World map of countries where antibiotics are used as plant protection products, compiled from scientific and grey literature searches screening the official list of authorized pesticides, when available.

More than 30 countries are reported to use antibiotics on crops (Fig. 2).

There are **five main antibiotics** used in plant agriculture (Streptomycin, Oxytetracycline, Kasugamycin, Oxolinic acid, Gentamicin), as well as some that are used generally in China (Ningnanmycin, Validamycin, Zhongshenmycin, etc.).

Streptomycin is the most used antibiotic worldwide, followed by oxytetracycline, mainly used when streptomycin resistance is reported.

Alternatives

Alternative control measures exist in countries where antibiotics are not authorized for plant protection. Moreover, there are many **innovative patents** registered for searches about new potential alternatives to antibiotics.

- Antagonistic bacteria (competition) such as *Pseudomonas*, *Bacillus*, *Streptomyces*, etc.
- Competition with fungi including *Trichoderma* spp. or yeasts
- Bacteriophages
- Interference with Quorum Sensing
- Stimulation of plant defense mechanisms
- Chemical treatments
- Management practices, for example seed treatment or insect vectors

Antibiotic resistance associated with PPB

Resistance genes can be acquired mainly through mutations, horizontal gene transfers (HGT) or other mechanisms.

Several resistance genes have been identified in PPB (Table 1). Some of them are common and known among other bacteria (*strA-strB*) while *aac(2')-IIa* for example is less widespread. The most studied resistance genes in PPB are the ones conferring **streptomycin resistance**.

strA-strB are two linked streptomycin resistance genes, mainly found on the **Tn*5393* transposon**, initially discovered on the pEa34 plasmid in *Erwinia amylovora*. This 6.7-kb transposon belongs to the Tn*3* family. These two genes are commonly encountered in human pathogens and are responsible for many streptomycin-resistant infections. There are many **variants** of this transposon (Table 2).

Table 1: Main antibiotic resistance genes in PPB and type of resistance.

Antibiotic	Resistance gene(s)	Type of resistance
Streptomycin	*strA-strB*	Gene acquisition
	rpsL	Point mutation
	aadA1, aadA2	Gene acquisition
Kasugamycin	*aac(2')-IIa*	Gene acquisition
	Deletion of *opp* and *dpp*	Deletion
Oxolinic acid	GyrA83 mutation (not well known yet)	Point mutation
Oxytetracycline	*tetC*	Gene acquisition
Gentamicin	*aacA3*	Gene acquisition

Table 2: Organisms, plasmids and possibility of HGT associated with the different variants of Tn*5393*. *E. amylovora, P. syringae and X. campestris* are PPB; *A. salmonicida, A. faecalis* and *S. enterica* are other pathogenic bacteria for humans or animals.

Organism	Tn*5393* variant	Plasmidic host	HGT?
E. amylovora	Tn*5393*	pEa34	Conjugative
	Tn*5393*	pEa29	Non-conjugative
	Tn*5393*a	pEU30	Conjugative
Pseudomonas syringae	Tn*5393*a	pPSR1	Conjugative
Xanthomonas campestris	Tn*5393*b	Not determined	Not determined
Aeromonas salmonicida	Tn*5393*c	pRAS2	Conjugative
Alcaligenes faecalis	Tn*5393*d	pFL424	Non-conjugative
Salmonella enterica	Tn*5393*a	I1	Conjugative

Discussion and conclusion

This work aims to shed light on the main uncertainties associated with the use of antibiotics in plant agriculture. Even though it is relatively low compared to the use in human and veterinary medicine (Van Boeckel *et al.*, 2019), there is clearly a potential for HGT of streptomycin, kasugamycin, oxytetracycline and gentamicin resistance genes, as they are all acquired resistance genes. The potential of resistance gene transfer between PPB and commensal or other pathogenic bacteria when consuming raw vegetables should not be underestimated. In particular, ***strA-strB* genes are widespread**, not only among PPB, but also in other pathogenic bacteria for humans; Tn*5393*a is found in *S. enterica*. This highlights the risk associated with the use of streptomycin in plants.

On the other hand, kasugamycin is an antibiotic only used in plant agriculture, and not in human or veterinary medicine, as well as antibiotics such as Ningnanmycin, Validamycin or Zhongshenmycin. This type of antibiotics might be worth turning to in order to limit the use of streptomycin, when possible.

Key reviews

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Van Boeckel T *et al.* Global trends in antimicrobial resistance in animals in low- and middle-income countries. 2019