Critical Assessment of *Streptomyces* spp. Able to Control Toxigenic *Fusarium* in Cereals: A Literature and Patent Review

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Received: 23 September 2019; Accepted: 1 December 2019; Published: 4 December 2019

Abstract: Mycotoxins produced by *Fusarium* species on cereals represent a major concern for food safety worldwide. Fusarium toxins that are currently under regulation for their content in food include trichothecenes, fumonisins, and zearalenone. Biological control of *Fusarium* spp. has been widely explored with the aim of limiting disease occurrence, but few efforts have focused so far on limiting toxin accumulation in grains. The bacterial genus *Streptomyces* is responsible for the production of numerous drug molecules and represents a huge resource for the discovery of new molecules. *Streptomyces* spp. are also efficient plant colonizers and able to employ different mechanisms of control against toxigenic fungi on cereals. This review describes the outcomes of research using *Streptomyces* strains and/or their derived molecules to limit toxin production and/or contamination of *Fusarium* species in cereals. Both the scientific and patent literature were analyzed, starting from the year 2000, and we highlight promising results as well as the current pitfalls and limitations of this approach.

Keywords: mycotoxin; deoxynivalenol; fumonisin; biocontrol; antagonism; bioactive compounds; wheat

1. Introduction

Mycotoxins are extracellular metabolites produced by filamentous fungi that contaminate cereals, grains, fruits, and vegetables. The most important *Fusarium* toxins are trichothecenes, zearalenone (ZEN), and fumonisins (FBs), that are dangerous for human and animal health, and their presence in food is regulated worldwide [1]. Mycotoxin co-occurrence in food is a real and relatively underestimated issue [2], as is the modification of toxins by plant metabolism (creating masked mycotoxins) [3]. Both factors mean that the levels of toxins measured in food, and therefore being ingested, are significantly underestimated. Due to this, it is likely that normative limits will be lowered by the regulatory agencies in the future.

Cereals, the staple foods of diets all over the world, are perfect hosts for pathogenic and toxigenic fungi and represent one of the main sources of mycotoxin contamination for humans and animals [4]. Among toxigenic species, *Fusarium* spp. (Division Ascomycota) are major producers of mycotoxins in cereals [5].

Trichothecenes A and B are mainly associated with *Fusarium* head blight (FHB) and crown rot (FCR) in wheat and barley. The major group of *Fusarium* spp. responsible for these diseases includes *Fusarium graminearum* species complex (FGSC; [6]) that exhibits a diverse distribution of species across the different continents [7]. The most important species are *F. graminearum*, *F. culmorum*, and *F. pseudograminearum* [8,9]. Grain quality decrease and yield are of concern [10]. The trichothecenes type B are the most prevalent and comprise deoxynivalenol (DON) and nivalenol (NIV) and their
acetylated forms 3-ADON, 15-ADON, and 4-ANIV [11]. They are immunosuppressant and neurotoxic and cause intestinal irritation, leading to feed refusal in livestock [12,13]. In maize, _F. graminearum_ and other related species were found to be associated with Fusarium ear rot (FER), contaminating grains with ZEN. ZEN displays estrogenic activity, causing reproductive problems in animals, in addition to cytotoxic and immunosuppressive effects [14,15].

Fusarium ear rot in maize is also caused by _F. verticillioides_ (syn. _F. moniliforme_ [16]) and _F. proliferatum_, which produce fumonisins [17]. Fumonisins have been classified as Group 2B carcinogens (i.e., as possibly carcinogenic to humans [18]), and fumonisin B1 (FB1) is the most abundant analogue found in contaminated samples [19]. Moreover, _Fusarium_ spp. infecting cereals can also produce other minor mycotoxins with cytotoxic effects such as enniatins, beauvericin, and moniliformin. Knowledge gaps regarding the occurrence, toxicity, and toxicokinetic data for these compounds in cereal crops represent a major and immediate problem [20].

_Fusarium_ spp. infections of cereals are therefore a major concern for both the growers and the food chains associated with the processing of grains. Several control strategies against this complex group of pathogens have been developed and include host resistance, the application of fungicides, and the implementation of specific agricultural practices [21]. However, effective management of _Fusarium_ pathogens and the related toxins cannot be achieved through the use of a single control strategy because each has its own limitations [22]. Therefore, at least in Europe, integrated disease management is urgently needed, favored by European Regulation 1107/2009/EC and European Directive 128/2009/EC [23,24]. Moreover, biocontrol approaches are becoming increasingly important due to the limitation on the use of certain fungicides. Among the biocontrol agents (BCAs) used to control toxigenic _Fusarium_ spp. in cereals, bacteria have shown a number of successful outcomes. For instance, strains of _Bacillus_ spp. [25–28], _Brevibacillus_ sp. [29], _Pseudomonas_ spp. [27,30], and _Lysobacter enzymogenes_ [31] were applied to limit pathogen development, reducing disease severity and mycotoxin production. Microbial communities or single strains were also tested to detoxify contaminated substrates as reviewed by McCormick in 2013 [32].

_Bacteria of the genus Streptomyces_ display promising plant growth-promoting features and biocontrol efficacy against plant pathogens. They belong to the phylum of Gram-positive Actinobacteria, which is one of the largest taxonomic units within the bacterial domain, and include microorganisms relevant to human and veterinary medicine, biotechnology as well as ecology [33]. Streptomycetes are the most abundant actinobacteria in soil [34]. They display a unique life cycle, and after germination grow through a combination of tip extension and the branching of mycelia. They first form a vegetative mycelium firmly attached to the growth substrate and, subsequently, due to nutrient depletion and under environmental stress signals, develop an aerial mycelium. Each aerial mycelium then differentiates into a long chain of pre-spore compartments which subsequently mature into individual spores [35]. The ability to produce a variety of secondary metabolites, including anti-infective agents, has an important ecological role including the inhibition of competitors during the transition from mycelial to aerial growth [36]. These various characteristics enable them to colonize different substrates and establish symbiotic interactions with plant tissues and other eukaryotes [37]. The ability to produce numerous secondary metabolites means they are the most exploited bacterial genus in natural product research. Notably, more than half of all antibiotics in current clinical use are derived from actinobacterial secondary metabolites [38]. Furthermore, _Streptomyces_ spp. were evaluated as plant growth-promoting bacteria (PGPB), as they can inhibit pathogen development, enhance nutrient uptake by mineral solubilization, and increase plant growth by nitrogen fixation and phytohormone synthesis [39]. Streptomycetes have therefore been investigated for their possible use in agriculture, including cereal crops [40].

The diversity of secondary metabolite production plus their reported endophytic features make the genus _Streptomyces_ a perfect candidate to control toxigenic _Fusarium_ spp. development and related toxin production [41,42]. Endophytic microorganisms have been reported as useful antagonists against Fusarium head blight, and are able to reduce disease severity on spikelets [43]. Nevertheless,
the incredible diversity and potentiality of these microorganisms against mycotoxigenic fungi and their possible influence on toxin accumulation have been rarely explored and deserve further investigation [44]. This review describes reports in which streptomycetes, or molecules derived from them, were exploited against Fusarium spp., and will pay special attention to the possible influence on toxin production. The scientific and patent literature were analyzed from the period 2000–2018.

2. Critical Assessment of Literature

Despite the huge amount of literature regarding the biological control of Fusarium mycotoxigenic isolates in cereals, only two products have found a consistent market niche [45]. These are based on Pseudomonas chlororaphis and Pythium oligandrum and are marketed in Europe as Cerall® (Belchim Crop Protection) and Polyversum® (Biopreparáty/De Sangosse), respectively [46]. Furthermore, no Streptomyces product is officially registered to be used for this purpose [47]. The main obstacles for biocontrol agents are due to the lack of consistency when microbial inoculants are applied under complex environmental conditions, and to the complexity of finding appropriate formulation and timing for application [48]. Biological, ecological, toxicological, and regulatory cost factors also influence the effectiveness and marketability of biological control products [49].

In order to verify the status of research using Streptomyces strains, and their derived molecules, to limit toxigenic Fusarium spp. infections and/or toxin contamination, we screened the published literature. To critically assess the status of each research paper, a set of definitions describing the type of study and their accuracy was established as follows.

1. Streptomyces species definition. Species identification is essential as approximately 10 Streptomyces species have been described as plant pathogens, causing economically important diseases on underground plant structures such as tuber/root crops. The best studied and characterized of these is Streptomyces scabies which causes potato scab [50,51]. Moreover, from a food safety perspective, Streptomyces isolates are able to produce dangerous metabolites for human and animal health, such as antimycin A found on wheat and barley grains [52]. Therefore, it is essential that species and strain characterization is performed accurately.

2. In vitro testing for antifungal activity. This is generally the first step for identifying antifungal microorganisms or molecules produced by them. Such studies help define the mechanism(s) of action of the Streptomyces species(s) and lead to the identification of potential interactions with the target organism. Assessment of bioactivity should consider the diversity of targets (verifying if pathogen diversity influences the consistency of the BCA or derived product). Indeed, specific interactions occur among bacterial and fungal strains [53] and this may impact the biocontrol capability of a strain [54,55].

3. The effect of culture media in the bioassays in vitro. Media composition modulates secondary metabolite production in actinomycetes [55–57], and optimizing laboratory selection procedures should broaden the number of interesting BCAs that can be identified.

4. The use of fermentation extracts to perform bioassays. During screening procedures, it would be ideal to identify the metabolite(s) responsible for the observed antifungal effect. The screening of crude extracts is generally followed by further steps of purification and chemical analysis, and retesting of purified compound(s) [58].

5. Evaluation of the antifungal mode of action. Risks concerning the use of these antibiotic-producing bacteria associated with events of horizontal gene transfer and the development of antibiotic resistance are still under debate within the scientific community [44]. However, given the current legislative requests [59], understanding the mode of action is essential in order to proceed with the registration of a BCA, in order to avoid risks of spreading dangerous metabolites for human and animal health in the environment [60].

6. Assessment of the ability to colonize treated plant organs. Many BCAs are rhizosphere-colonizing microorganisms and can be applied as seed coatings [61]. However, some Streptomyces spp. can
exhibit endophytic behavior, colonizing different parts of the plant (e.g., roots, stem, leaves) [41]. Some BCAs exhibit activity both in the rhizosphere and after infection of the plant and function inside the root at the same time. Therefore, the colonization niche of the strain should be investigated in order to warrant a consistent protection [62]. These studies are fundamental to providing an assessment of the durability of the protection warranted by the BCA.

7. Testing the influence of complex environmental conditions. As for pathogens during disease development, antagonist strains are influenced by environmental factors that strongly impact the ability of the BCAs to exert their biocontrol activity [40]. Assessing the impact of environmental parameters on BCAs using both greenhouse and field trials is essential to selecting strains with consistent biocontrol activity.

8. Assessment of antifungal and plant growth-promoting effect in planta. This step is essential, given that the BCA will ultimately be employed in the field. Very often, there is poor correlation between in vitro and in planta trials [55,63,64]. Moreover, the wide range of metabolites produced may have direct influences on plant development, altering growth and plant fitness both positively and negatively [39]. Indeed, negative effects cannot be underestimated—some *Streptomyces* can be pathogens (see before) or produce phytotoxic and herbicidal substances [65].

9. Assessment of the method used for application. Selecting an appropriate delivery system for the BCA as well as an optimized formulation can determine its efficacy in the field [66].

10. The effects of the BCA on the pathogen inoculum in planta. Due to the complex epidemiology of *Fusarium* diseases in cereals, quantification of the pathogen in planta is important to verify if the treatment can, for example, effectively reduce the source of overwintering inoculum, limiting the infection pressure at the subsequent infection season [67].

11. Quantification of the mycotoxin. It is essential to verify if the BCA limits toxin production, specifically given that there is a lack of full correlation between the presence of the fungus and the amount of toxin that is found in the grains [68,69]. Moreover, some secondary metabolites can limit toxin production without impairing growth of the pathogen [70]. Biological interactions can also lead to unexpected crosstalk between the BCA and pathogen that can lead to an overproduction of toxins and secondary metabolites [71–75].

3. Literature Analysis

To guide future implementation of biocontrol research using *Streptomyces* spp., it is essential to identify the strengths and weaknesses of past and present research in this domain. Therefore, we reviewed the published literature, focusing on the methods used for the selection of promising biocontrol streptomycetes and on the results achieved.

We searched the Scopus and Google Scholar databases for articles including the words “*Fusarium*” and “*Streptomyces*” that were published during the timeframe 2000–2018. The resulting articles were read and individually screened leading to the identification of 63 articles that dealt with the ability of *Streptomyces* or their derived metabolites to limit the growth or toxin production of toxigenic *Fusarium* spp. in cereals (Table 1).

*Streptomyces* spp. or their derived molecules have been tested mostly against *Fusarium* spp. producing trichothecenes, including DON. The species investigated are all usually found to infect cereals and include *F. graminearum*, *F. culmorum*, *F. poae*, *F. cerealis*, *F. sporotrichioides*, and *F. equiseti*. The most studied interactions address the wheat–*F. graminearum* pathosystem, which is the most important cause of DON (and derivatives) accumulation in grains [76]. Less frequently, streptomycetes have been tested against fumonisin producers in maize, all belonging to the *F. fujikuroi* species complex [77].

3.1. Streptomyces Identification

Regarding the identification of *Streptomyces* species, most studies focused on the integration of morphological and molecular characteristics. Given the complexity of streptomycete biology [33],
the use of 16S rRNA alone as molecular marker is not sufficient to achieve species discrimination. Multi-locus sequence typing [78] integrated with biochemical and morphological identification would be a preferred option, but none of the studies used this approach. On this basis, all the species identifications reported in the selected papers should be treated with caution. Looking forward, the increasing number of Streptomyces strain genomes now available may help in correct species identification [79].

3.2. Screening for Antifungal Activity: In Vitro Tests

Among the selected articles, in vitro testing is the most commonly used first-line screening method. Indeed, dual-culture assays on solid media are exploited in all the studies as a preliminary screen, evaluating the inhibition halo between the growth of the streptomycete and the fungal target or measuring the radial growth of the Fusarium colony in comparison with an untreated control to obtain a percentage of growth inhibition. Rather than use these standard in vitro inhibition assays, some research groups [80–82] characterize the type of interactions occurring in dual culture by using the index of dominance (ID) [83]. The ID consists of visually observing antagonist and pathogen growth in dual culture, testing different media or water activity ($a_w$) of the culture medium, and classifying the type of interactions occurring based on predefined scores, namely, mutual intermingling (1/1), mutual inhibition on contact (2/2), mutual inhibition at a distance (3/3), dominance of one species on contact (4/0), and dominance at a distance (5/0). This method evaluates whether the inhibition is due to the production of antifungal metabolites diffusible in the media or whether the mycelium is parasitized by the antagonists. Moreover, the negative effect of the target pathogen on the potential antagonists can be noted. Therefore, the selection of biocontrol agents is carried out by evaluating the biocontrol interactions (e.g., mycoparasitism, competition, or antibiosis) established under different growth conditions.

For most reports, growth of the Streptomyces inoculum to some predefined point usually takes place on agar media before addition of the pathogen in order to allow a complete establishment of these growing bacteria [80,84].

The use of a diverse range of growth media and fungal strains was evaluated in our analysis, given the importance that these criteria have in the estimation of the biocontrol activity in vitro [55]. Interestingly, the influence of growth media was seldomly evaluated in these types of experiments [84,85] as well as the assessment of antifungal activity on different Fusarium strains belonging to a single species [80,86–88].

Given the lack of a standardized protocol when performing dual-culture assays (e.g., Fusarium strains on which the biocontrol activity should be tested, position and distance between streptomycetes and Fusarium strain inoculum, timing of observation after pathogen inoculum, culture medium), it is difficult to compare the results between studies. However, here we report some examples of the wide range of activities recorded against mycelial proliferation. For instance, growth inhibition percentages against F. graminearum and F. verticillioides ranged from the weakest (<20%) [84,89] up to 60–90% of inhibition [87,90]. Yekkour et al. [91] obtained different levels of inhibition in dual culture for isolated streptomycetes—indeed, only 6 out of 133 isolates displayed an anti-Fusarium activity and in particular only F. culmorum was significantly inhibited (inhibition halo >20 mm). Less sensitive fungal species were F. moniliforme, F. sporotrichoides, F. graminearum, and F. proliferatum [91].

3.3. Evaluation of Antifungal Mechanism of Action

The importance of the identification of any antifungal molecules involved in the bioactivity led some researchers to achieve a complete characterization of the compounds involved. The fermentation process and the optimization of all the parameters (e.g., medium, agitation rate, pH, temperature) were strain- and laboratory-dependent [92–95]. For instance, it has been reported that some of the Streptomyces strains which are active against F. moniliforme on solid media lack antibiotic production in submerged liquid culture, highlighting the importance of an appropriate optimization of laboratory procedures and
media in the stimulation of secondary metabolites [96]. The first attempt of compound purification is commonly carried out by crude extract fractionation [97,98]. Often the bioactivity of the selected strain is not related to a single mechanism, and different metabolites, enzymes, or volatile organic compounds likely contribute to the overall antifungal activity. Many studies exploited the fermentation broth as a source of bioactive compounds [99–101]. Therefore, several compounds were purified and tested against toxigenic Fusarium spp. For example, strain PAL114 produced saquayamycins A and C which inhibited the growth of F. culmorum at the minimum inhibitory concentrations of 75 ug/mL [102]. Three allelochemicals (5,7-dihydroxyflavone, 5-hydroxy-7-methoxyflavone, and di-(2-ethylhexyl) phthalate) able to inhibit mycelial growth of F. graminearum were isolated and purified from the fermentation broth of Streptomyces sp. 6803 [103]. In vitro cultures of Streptomyces sp. 201 produced 2-methylheptyl isonicotinate able to inhibit the growth of F. moniliforme more efficiently than a natural analogue (isoniazid) [98]. On the other hand, modest activity was observed by the metabolites extracted from Streptomyces LZ35 against F. verticillioides [104]. For several studies, chitinase activity, rather than antibiotic production, was shown to play a role in the antifungal mechanism [105–108]. In addition, new antifungal proteins have been characterized, such as the one isolated from Streptomyces sp. C/33-6 culture supernatants which displayed a fungicidal activity, determining complete inhibition of conidia germination of F. graminearum [109].

Secondary metabolites exhibiting anti-Fusarium activity can also include volatile organic compounds (VOCs). For example, Streptomyces alboflavus TD-1 was able to reduce the mycelial growth of F. moniliforme when volatile metabolites were applied as fumigants [110]. Inhibition of growth, sporulation, and conidial germination has been recorded when culturing this strain on wheat seeds. In addition, the VOC activity increased the fungal membrane permeability as observed by significant leakage of mycelial materials. Chemical analysis of these VOCs identified a high quantity of 2-methylisoborneol and 2-methyl disulphide, which were further tested for their antifungal activity [110,111]. VOC production was also linked to the antagonist activity of Streptomyces philanthi RM-1-138 cultured on wheat seeds, which inhibited mycelium growth of F. fujikuroi by 50% [112]. Chemical analysis showed that a complex mixture of volatile metabolites was involved [112].

It is evident from our analysis that the biocontrol activity of Streptomyces strains involves a large range of bioactive molecules. The exploitation of Streptomyces spp. has been, and will in future also be, hindered by the variability of the production of these metabolites. Therefore, to exploit the huge diversity of streptomycetes for successful disease management, different factors, such as the age of the fungal colony, culture conditions, temperature, and other environmental parameters, will have to be carefully studied, even at the very early stages of investigation. Transferring the outputs of these laboratory studies to the field remains one of the major challenges in exploiting Streptomyces spp. as BCAs for tackling toxigenic Fusarium spp.

3.4. Assessment of Streptomyces Effects in Planta

The literature reports a lack of durable and consistent effects when streptomycetes or commercially available formulations have been applied in greenhouse experiments and field trials [40]. It is likely that the ability to cope in a complex environment, which comprises the plant, the presence of the pathogens as well as several abiotic factors, varies depending on the fitness of the strain and its formulation in the field. For this reason, verifying the level of colonization achieved by the strain when used as BCA is essential to confirming its ecological fitness. Only a few papers have addressed this question in detail. It is notable that most of these were published recently, which indicates an increasing level of attention regarding Fusarium–plant–Streptomyces interactions [113,114].

Moreover, in planta experiments are essential during the process of BCA selection to confirm their ability to significantly decrease Fusarium spp. infections. Indeed, BCAs can influence crop growth and disease severity, and can reduce Fusarium inoculum levels on stubble after harvest as well as ideally the presence of mycotoxins [115]. However, only a limited number of studies (N = 16) performed complete in planta studies. The application of streptomycetes was tested on seeds [84,116–118], on the
main emerged spike [80,84,86,87] as well as wheat stubble [86]. Indeed, these bacteria can contribute to the reduction of FHB on wheat at different times in the *Fusarium* spp. life cycle. In a research study conducted by Palazzini et al. [80] in 2007, isolates from wheat anthers were applied to wheat heads grown in greenhouse and, after 16 days, their influence on FHB severity was estimated. Despite the slight reduction of disease symptoms in comparison to the control, streptomycete BRC 87B decreased the DON content in spikes to below a detectable level. For this reason, in a subsequent study it was tested in the field, showing the ability to decrease FHB severity and DON amounts, as well as the *F. graminearum* inoculum on wheat stubble [86].

Testing the efficacy in the field also requires specific assessments of the way the strains are inoculated. For example, the use of a Korean strain isolated from rice kernels led to a significant reduction of the disease severity after its inoculation using a spore spraying method that was not achieved using the point inoculation method on wheat heads [84]. This is actually the only study where the influence of the BCA application method was taken into account, and shows that, depending on the application of the BCA, different results can be obtained [47].

Differences in the level crop protection have also been reported against other *Fusarium* spp. For instance, two *Streptomyces* strains designated as DAUFPE 11470 and DAUFPE 14632 were isolated from maize rhizosphere in Brazil and tested against maize seed pathogenic fungi. Treatments on seeds with biomass derived from streptomycete fermentation or with cell-free filtrate reduced significantly *Fusarium subglutinans* incidence on stored maize seeds [119]. The same strains were also tested as spore suspension to assess their effects on seedling blight caused by *F. moniliforme* in greenhouse [120]. Bacterial treatments significantly reduced disease incidence compared with the controls, with protection level variable according to the tested pathogen inoculum concentrations. Indeed, the disease incidence was significantly reduced at low and high antagonist and pathogen concentrations, respectively. Moreover, their ability to reduce chlamydospore germination was assessed—the percentage of germinated propagules was evaluated after antagonist treatments in sterilized soil added with glucose, to recreate the natural environment and enhance spore germination. The addition of glucose increased propagule germination in all the treatments, but the presence of the antagonists decreased this parameter up to 65%. This study stressed therefore the important influence of both antagonist and pathogen concentrations and the presence of nutrients in the final biocontrol efficacy obtained in planta [120].

*Streptomyces* strains, as reported above, can be helpful in reducing disease symptoms, acting also as plant growth-promoting bacteria. Despite the wide range of metabolites produced by them, their ability to influence plant development has been seldomly studied by the current literature addressing the biological control properties of the strain. A few positive examples include the report of a negative influence on seed germination and seedling development [91] as well as an improvement in plant growth parameters [87].
Table 1. Published studies regarding the efficacy of *Streptomyces* spp. (and derived molecules) against *Fusarium* toxigenic species in vitro, in planta, and under different environmental conditions. The methods used for the identification of the *Streptomyces* strain are also reported. Data were obtained combining the results of Scopus and Google Scholar searches with the following search words, “*Fusarium*” and “*Streptomyces*”, limiting the period of publication from 2000 to 2018. Legend: M (Morphological identification), B (Biochemical identification), BCA/s (Biocontrol agent/s), GC (Growth chamber), G (Greenhouse), F (Field), * possibly misleading identification.

| Fusarium spp Studied | Streptomycete Identification | In Vitro Tests for Antifungal Activity | Influence of Pathogen Diversity | Influence of Culture Media on BCAs | In Vitro Tests Using BCA Extracts | Evaluation of Antifungal Mode of Action | BCAs' Survival on Plants | Environment of Trials in Planta | Evaluation of BCA Application | BCAs' Effects on Plants | BCAs' Effects on Disease | BCAs' Effects on Fusaria Inoculum | Toxin Measurement | References |
|----------------------|------------------------------|--------------------------------------|-------------------------------|----------------------------------|----------------------------------|-------------------------------------|------------------------|-----------------------------|---------------------------|---------------------|----------------------|-----------------------------|------------------|-----------|
| F. avenaceum         |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [95]      |
| F. avenaceum         |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [124]     |
| F. avenaceum, F. oxysporum, F. solani |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [125]     |
| F. coeruleum, Gibberella saubinetii | 16S rRNA                    |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [101]     |
| F. crocodilense, F. oxysporum          |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [107]     |
| F. culmorum         |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [126]     |
| F. culmorum         | M/B/16S rRNA                 |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [114]     |
| F. culmorum         | M                               |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [116]     |
| F. culmorum         | M                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [114]     |
| F. culmorum         | 16S rRNA                      |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [91]      |
| F. culmorum, F. moniliforme, F. sporotrichoides, F. graminearum, F. proliferatum |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [127]     |
| F. culmorum, F. equiseti, F. proliferatum, F. graminearum, F. sporotrichoides, F. moniliforme |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [128]     |
| F. oxysporum         | M/B/16S rRNA                 |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [118]     |
| F. culmorum, F. graminearum, F. proliferatum, F. oxysporum          | 16S rRNA                      |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [130]     |
| F. cultorum, F. oxysporum          | M/B/16S rRNA                 |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [103]     |
| F. culmorum, F. oxysporum          | M/B/16S rRNA                 |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [103]     |
| F. fujikosii         |                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [112]     |
| F. graminearum       | M/B/16S rRNA                 |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [112]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [106]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [103]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [113]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [64]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [131]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [80]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [90]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [96]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [96]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [80]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [86]      |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [132]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [132]     |
| F. graminearum       | x                              |                                      |                               |                                  |                                  |                                     |                        |                             |                           |                     |                     |                             |                  | [132]     |

References:
[95] [124] [125] [101] [107] [102] [126] [99] [116] [114] [91] [127] [128] [108] [118] [112] [130] [106] [103] [113] [64] [131] [80] [90] [96] [86] [80] [132] [67]
Table 1. Cont.

| Fusarium spp. Studied | Streptomycete Identification | In Vitro Tests for Antifungal Activity | Influence of Pathogen Diversity | Influence of Culture Media on BCAs | In Vitro Tests Using BCA Extracts | Evaluation of Antifungal Mode of Action | BCAs' Survival on Plants | Environment of Trials in Planta | Evaluation of BCA Application | BCAs' Effects on Plants | BCAs' Effects on Disease | BCAs' Effects on Fusaria Inoculum | Toxin Measurement | References |
|-----------------------|-----------------------------|-------------------------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------|-----------------|---------------------------|----------------|-----------|
| F. graminearum, F. culmorum | 16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [43] |
| F. graminearum, F. culmorum, F. oxysporum | M/B | x | x | x | x | x | x | x | x | x | x | x | [133] |
| F. graminearum, F. oxysporum | x | x | x | x | x | x | x | x | x | x | x | x | [134] |
| F. graminearum, F. oxysporum | x | x | x | x | x | x | x | x | x | x | x | x | [135] |
| F. graminearum, F. oxysporum, F. solani | x | x | x | x | x | x | x | x | x | x | x | x | [105] |
| F. graminearum, F. oxysporum, F. sporotrichioides, F. oxysporum | x | x | x | x | x | x | x | x | x | x | x | x | [109] |
| F. graminearum, F. verticillioides, F. culmorum | M/16S rRNA | x | x | G | x | x | x | x | x | x | x | x | [137] |
| F. graminearum, F. moniliforme, F. oxysporum, F. solani | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [100] |
| F. graminearum, F. moniliforme | M/B | x | x | x | x | x | x | x | x | x | x | x | [136] |
| F. moniliforme | x | x | x | x | x | x | x | x | x | x | x | x | [120] |
| F. moniliforme | x | x | x | x | x | x | x | x | x | x | x | x | [119] |
| F. moniliforme | M/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [138] |
| F. moniliforme | M/B | x | x | x | x | x | x | x | x | x | x | x | [96] |
| F. moniliforme | M/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [93] |
| F. moniliforme | x | x | x | x | x | x | x | x | x | x | x | x | [94] |
| F. moniliforme | M/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [111] |
| F. moniliforme | x | x | x | x | x | x | x | x | x | x | x | x | [110] |
| F. moniliforme | M/B/16S rRNA | x | x | G | x | x | x | x | x | x | x | x | [139] |
| F. moniliforme, F. oxysporum | M/B | x | x | x | x | x | x | x | x | x | x | x | [98] |
| F. moniliforme, F. oxysporum, F. semitectum | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [97] |
| F. moniliforme, F. oxysporum; F. semitectum, F. solani | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [97] |
| F. moniliforme | x | x | x | x | x | x | x | x | x | x | x | x | [122] |
| F. oxysporum | M/B | x | x | x | x | x | x | x | x | x | x | x | [140] |
| F. oxysporum | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [141] |
| F. poae | x | x | x | x | x | x | x | x | x | x | x | x | [142] |
| F. poae | M/B | x | x | x | x | x | x | x | x | x | x | x | [143] |
| F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
| F. poae, F. poae, F. poae, F. poae | M/B/16S rRNA | x | x | x | x | x | x | x | x | x | x | x | [144] |
3.5. Evaluation of Streptomycete Activity against Mycotoxin Production

As noted above, it is essential to accurately determine the concentration of mycotoxins present in grains destined for human or animal consumption. Similarly, verification of the toxin content under experimental conditions is vital for the future of potential streptomycete biocontrol agents. Indeed, it should be possible that the reduction of disease severity does not positively correlate with a reduction of the mycotoxin content in grain samples. So far, only one research group has evaluated the reduction of DON mycotoxins by Streptomyces strains isolated from wheat anthers, in comparison to the level of infection, in vitro, in greenhouse, and in the field [80,86]. Indeed, they showed that their streptomycete strains (BRC 87B and BRC 273) were able to significantly reduce DON levels on wheat grains, without influencing disease severity caused by Fusarium infections [80]. This suggests the existence of a specific mechanism of inhibition uncoupling fungal fitness and toxin production. Follow-up research by the same group evaluated in the field the use of BRC 87B, which showed strong inhibition of DON production in wheat spikes [86].

Preliminary in vitro studies have also been conducted to verify the ability of streptomycetes to limit fumonisin accumulation. Strains isolated from soil samples amended with different organic manures by Nguyen et al. were tested against fumonisins FB$_1$ and FB$_2$ production by F. verticillioides [121]. They significantly decreased (by up to 98.2%) the level of FB$_1$ and FB$_2$ in agar plate cultures [121]. Inhibition of FB$_1$ accumulation on milled maize agar was also demonstrated in another in vitro study using Streptomyces sp. AS1 [122], a strain isolated from peanuts in Egypt. Further, El-Naggar et al. [123] showed the ability of Streptomyces isolates to reduce accumulation of a wide range of mycotoxins including total aflatoxins, fumonisin, zearalenone, T-2 toxin, AOH, and AME. However, the identity of the Fusarium spp. producers was based only on morphological characteristics and should be considered with caution.

4. Patent Search

To have a complete overview of the work using Streptomyces against toxigenic fusaria, a research of the major patent databases was carried out. Using both Espacenet and Orbit intelligence, a total of 233 results were obtained using the keywords “Fusarium” and “Streptomyces”. By manually screening the titles and abstracts, a total of 25 patents were retained and added to Table 2. Given the use of different languages (most not English), only certain abstracts could be accessed, and it was therefore not possible to apply the same critical criteria used in our literature search. Most of the patents claimed general activity of strains and derived molecules against a large set of microorganisms including toxigenic fusaria. Only a single patent in its claim directly addressed the ability to limit F. graminearum growth on cereals [147]. Two documents patented the antifungal metabolites isolated from streptomycete strains and tested them against toxigenic Fusarium spp. [148,149]. The other patents are related to specific formulation methods, using live streptomycetes, proposed as biocontrol products against plant pathogens, among them Fusarium spp. of cereal crops.

Interestingly, most of the patents are concentrated in the last five years (Table 2), therefore further developments could also be expected towards novel industrial applications in the near future.
Table 2. Patent lists of Streptomyces spp. (and derived molecules) against Fusarium toxigenic species.

Data were obtained combining the results of Espacenet and Orbit Intelligence with the following search words, “Fusarium” and “Streptomyces”, limiting the period of publication from 2000 to 2018.

| Publication Number | Publication Date | Target Fusarium spp. | Source | Reference |
|--------------------|------------------|-----------------------|--------|-----------|
| RU2003100579 A     | 27/07/2004       | F. moniliforme, F. sambucinum, F. avenaceum | Espacenet [150] |
| KR100914225 B1     | 26/08/2009       | F. graminearum        | Espacenet [151] |
| CN101698827 B, CN101698827 A | 28/04/2010 | F. moniliforme | Espacenet [152] |
| CN101122272 A      | 09/09/2010       | F. avenaceum, F. semitectum | Orbit Intelligence [153] |
| KR101198620        | 22/12/2011       | F. proliferatum       | Orbit Intelligence [154] |
| CN102433281 A, CN102433281 B | 20/05/2012 | F. graminearum | Espacenet [155] |
| KR101211681        | 12/12/2012       | F. fujikuroi         | Orbit Intelligence [156] |
| CN102835423 B, CN102835423 A | 26/12/2012 | F. nivale, F. graminearum | Espacenet [157] |
| CN1031114064 B, CN103114064 A | 22/05/2013 | F. moniliforme, F. graminearum | Espacenet [158] |
| CN10380351 A, CN10380351 B | 28/05/2014 | F. moniliforme, F. graminearum | Espacenet [148] |
| CN101430965 A      | 5/11/2014        | F. moniliforme       | Espacenet [159] |
| CN101419982 A      | 12/11/2014       | F. moniliforme       | Espacenet [160] |
| CN105060951 A      | 18/11/2015       | F. moniliforme       | Espacenet [161] |
| EPI9348980 A1      | 3/08/2016        | F. calmarum          | Orbit Intelligence [162] |
| CN105866428 A      | 24/08/2016       | F. verticillioides   | Espacenet [163] |
| CN106676640        | 17/05/2017       | F. graminearum      | Orbit Intelligence [164] |
| CN107059131        | 18/08/2017       | F. graminearum      | Orbit Intelligence [167] |
| CN10714259 A       | 13/07/2017       | F. calmarum          | Espacenet [165] |
| CN107287130 A      | 24/10/2017       | F. verticillioides   | Espacenet [166] |
| WO201535482 A1     | 16/04/2018       | F. proliferatum      | Orbit Intelligence [167] |
| CN108042805 A1     | 18/05/2018       | F. graminearum      | Espacenet [168] |
| CN108102961 A      | 1/06/2018        | F. graminearum      | Espacenet [169] |
| CN108165506        | 15/06/2018       | F. graminearum      | Orbit Intelligence [170] |
| CN108208016        | 29/06/2018       | F. graminearum      | Orbit Intelligence [149] |
| CN108587981        | 28/09/2018       | F. graminearum      | Orbit Intelligence [171] |

5. Conclusions and Perspectives

Our review of the literature and patents clearly identifies a growing interest in the use of Streptomyces spp. as biological control agents against toxigenic Fusarium spp., both to inhibit growth and to limit toxin accumulation (contamination). However, it is clear that for the majority of the available studies, the findings are preliminary. In most cases, a clear understanding of the role of the BCA, the identification of the molecules or mechanisms of inhibition, as well as the fungal targets are lacking [172]. Moreover, most of the data are limited to laboratory in vitro experiments and lack validation in planta or in the field.

The future of research on streptomyocetes as biocontrol agents for Fusarium will need to integrate diverse expertise and may profit from new methods able to better mimic in the laboratory interactions occurring in the field [55]. Novel formulation and application techniques will be needed to enable individual beneficial microbes and microbial consortia to exert their activity in a consistent manner for different crops and soils [173]. For instance, one biocontrol approach to further investigate could be combining multiple strains to build consortia able to exert complementary activities [174]. Indeed, understanding the ecological role, including specific interactions with other microorganisms and the host, is essential for developing effective and long-lasting approaches of biocontrol. Reaching a better understanding of microbes–Fusarium interactions could help to provide effective biocontrol strains among natural endophytes present in the wheat microbiome [175] and within graminaceous plant rhizosphere [176]. The effect of specific interactions as well as the ability to shift metabolic profiles within the same Streptomyces species, niche and also among individuals [177], suggest that studies on the efficacy of strains should encompass a broad range of conditions mimicking the agricultural milieu [55]. Appropriate fitness tests able to predict the behavior in the field are needed at the selection level. Novel BCAs or their metabolites could also be identified and produced integrating appropriate novel genome editing [178] as well as adaptive evolution techniques [179]. A better understanding of secondary metabolite regulation during the interaction with fungi will help to increase their discovery for agricultural purposes [53].

Our analysis of the literature leads to the observation that each single paper only addresses a few aspects of the proposed criteria that would have to be evaluated in identifying effective
**Streptomyces**-based BCAs. This review may serve as a proposal for future research efforts which will likely profit from an integrated analysis of the different parameters that we have identified.

The increasing interest within industry, proven by the increasing number of patents that address and refer to the use of Streptomyces spp. to limit Fusarium spp. in grains, is a further indication of the potential role that this powerful group of microorganisms can play in the future of agricultural research. In conclusion, by performing a complete analysis of the literature regarding the use of Streptomyces spp. for the biological control of mycotoxigenic fusaria, we identified a set of parameters that we consider essential for enabling their implementation for biological and toxin contamination control. Our review suggests that streptomycetes have the potential to play a crucial role both as BCAs, and as producers of novel inhibitory molecules, for the combined control of Fusarium infection and to limit the accumulation of mycotoxins in crops [180,181].

**Author Contributions:** Conceptualization, M.P. and E.M.C.; Methodology, M.P. and E.M.C.X.; Validation, A.K., M.S., and P.C.; Formal Analysis, E.M.C.; Investigation, M.P. and E.M.C.; Resources, M.S. and P.C.; Data Curation, E.M.C. and A.K.; Writing—Original Draft Preparation, E.M.C. and M.P.; Writing—Review & Editing, M.P., A.K., P.C. and M.S.; Supervision, M.P. and M.S.; Funding Acquisition, M.S., P.C. and M.P.

**Funding:** The Department of Food, Environmental and Nutritional Sciences, University of Milan partially covered the open access article processing costs.

**Acknowledgments:** We thank Barrie Wilkinson for the helpful suggestions and the English revision of the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Wu, F.; Groopman, J.D.; Pestka, J.J. Public health impacts of foodborne mycotoxins. *Annu. Rev. Food Sci. Technol.* 2014, 5, 351–372. [CrossRef]

2. Smith, M.C.; Madec, S.; Coton, E.; Hymery, N. Natural co-occurrence of mycotoxins in foods and feeds and their in vitro combined toxicological effects. *Toxins* 2016, 8, 94. [CrossRef]

3. Stoev, S.D. Foodborne mycotoxicoses, risk assessment and underestimated hazard of masked mycotoxins and joint mycotoxin effects or interaction. *Environ. Toxicol. Pharmacol.* 2015, 39, 794–809. [CrossRef]

4. Pinotti, L.; Ottoboni, M.; Giromini, C.; Dell’Orto, V.; Cheli, F. Mycotoxin contamination in the EU feed supply chain: A focus on cereal by products. *Toxins* 2016, 8, 45. [CrossRef]

5. Lee, H.J.; Ryu, D. Worldwide occurrence of mycotoxins in cereals and cereal-derived food products: Public health perspectives of their co-occurrence. *J. Agric. Food Chem.* 2017, 65, 7034–7051. [CrossRef] [PubMed]

6. O’Donnell, K.; Ward, T.J.; Geiser, D.M.; Corby Kistler, H.; Aoki, T. Genealogical concordance between the mating type locus and seven other nuclear genes supports formal recognition of nine phylogenetically distinct species within the *Fusarium graminearum* clade. *Fungal Genet. Biol.* 2004, 41, 600–623. [CrossRef] [PubMed]

7. Aoki, T.; Ward, T.J.; Kistler, H.C.; O’Donnell, K. Systematics, phylogeny and trichothecene mycotoxin potential of Fusarium head blight cereal pathogens. *Mycotoxins* 2012, 62, 91–102. [CrossRef]

8. Pasquali, M.; Beyer, M.; Logrieco, A.; Aduenaert, K.; Balmas, V.; Basler, R.; Boutigny, A.L.; Chrpová, J.; Czembor, E.; Gagkaeva, T.; et al. A European database of *Fusarium graminearum* and *F. culmorum* trichothecene genotypes. *Front. Microbiol.* 2016, 7, 406. [CrossRef] [PubMed]

9. Summerell, B.A.; Laurence, M.H.; Liew, E.C.Y.; Leslie, J.F. Biogeography and phylogeography of *Fusarium*: A review. *Fungal Divers.* 2010, 44, 3–13. [CrossRef]

10. Salgado, J.D.; Madden, L.V.; Paul, P.A. Quantifying the effects of Fusarium head blight on grain yield and test weight in soft red winter wheat. *Phytopathology* 2015, 105, 295–306. [CrossRef]

11. Bakker, M.G.; Brown, D.W.; Kelly, A.C.; Kim, H.S.; Kurtzman, C.P.; McCormick, S.P.; O’Donnell, K.L.; Proctor, R.H.; Vaughan, M.M.; Ward, T.J. Fusarium mycotoxins: A trans-disciplinary overview. *Can. J. Plant Pathol.* 2018, 40, 161–171. [CrossRef]

12. Eriksen, G.S.; Pettersson, H. Toxicological evaluation of trichothecenes in animal feed. *Anim. Feed Sci. Technol.* 2004, 114, 205–239. [CrossRef]
13. Maresca, M. From the gut to the brain: Journey and pathophysiological effects of the food-associated trichothecene mycotoxin deoxynivalenol. *Toxins* **2013**, *5*, 784–820. [CrossRef] [PubMed]

14. Kostro, K.R.; Gajecka, M.; Lisiecka, U.R.; Majer-Dziedzic, B.A.; Obremski, K.; Zielonka, L.; Gajecki, M. Subpopulation of lymphocytes CD4+ and CD8+ in peripheral blood of sheep with zearalenone mycotoxicosis. *Bull. Vet. Inst. Pulawy* **2011**, *55*, 241–246.

15. El-Makawy, A.; Hassanane, M.S.; Alla, E.-S.A.A. Genotoxic evaluation for the estrogenic mycotoxin zearalenone. *Reprod. Nutr. Dev.* **2001**, *41*, 79–89. [CrossRef] [PubMed]

16. Seifert, K.A.; Aoki, T.; Baayen, R.P.; Brayford, D.; Burgess, L.W.; Chulze, S.; Gams, W.; Geiser, D.; De Gruyter, J.; Leslie, J.F.; et al. The name *Fusarium moniliforme* should no longer be used. *Mycol. Res.* **2003**, *107*, 643–644. [CrossRef]

17. Rheeder, J.P.; Marasas, W.F.O.; Vismer, H.F. Production of fumonisin analogs by *Fusarium* species. *Appl. Environ. Microbiol.* **2002**, *68*, 2101–2105. [CrossRef]

18. International Agency for Research on Cancer. *Toxins Derived from Fusarium moniliforme: Fumonisins B1 and B2 and Fusarin C*; IARC: Lyon, France, 1993; pp. 445–466.

19. Marasas, W.F.O. Fumonisins: History, World-Wide Occurrence and Impact. In *Fumonisins in Food. Advances in Experimental Medicine and Biology*; Jackson, L.S., DeVries, J.W., Bullerman, L.B., Eds.; Springer: Boston, MA, USA, 1996; pp. 1–17. ISBN 978-1-4899-1381-4.

20. Fraeyman, S.; Croubels, S.; Devreeese, M.; Antonissen, G. Emerging *Fusarium* and *Alternaria* mycotoxins: Occurrence, toxicity and toxicokinetics. *Toxins* **2017**, *9*, 228. [CrossRef]

21. Dweba, C.C.; Figlan, S.; Shimelis, H.A.; Motaung, T.E.; Sydenham, S.; Tsilo, T.J. Fusarium head blight of wheat: Pathogenesis and control strategies. *Crop Prot.* **2017**, *91*, 114–122. [CrossRef]

22. Edwards, S.G. Influence of agricultural practices on *Fusarium* infection of cereals and subsequent contamination of grain by trichothecene mycotoxins. *Toxicol. Lett.* **2004**, *153*, 29–35. [CrossRef]

23. European Commission. Commission Regulation (EC) 1107/2009. *Off. J. Eur. Union* **2009**, L 309, 1–50.

24. European Commission. Commission Directive (EC) 128/2007. *Off. J. Eur. Union* **2007**, L 309, 71–86.

25. Pan, D.; Mionetto, A.; Tiscornia, S.; Bettucci, L. Endophytic bacteria from wheat grain as biocontrol agents of Fusarium graminearum and deoxynivalenol production in wheat. *Mycotoxin Res.* **2015**, *31*, 137–143. [CrossRef] [PubMed]

26. Palazzini, J.M.; Dunlap, C.A.; Bowman, M.J.; Chulze, S.N. *Bacillus velezensis* RC 218 as a biocontrol agent to reduce Fusarium head blight and deoxynivalenol accumulation: Genome sequencing and secondary metabolite cluster profiles. *Microbiol. Res.* **2016**, *192*, 30–36. [CrossRef] [PubMed]

27. Schisler, D.A.; Khan, N.I.; Boehm, M.J.; Lippes, P.E.; Slininger, P.J.; Zhang, S. Selection and evaluation of the potential of choline-metabolizing microbial strains to reduce Fusarium head blight. *Biol. Control* **2006**, *39*, 497–506. [CrossRef]

28. Zhao, Y.; Selvaraj, J.N.; Xing, F.; Zhou, L.; Wang, Y.; Song, H.; Tan, X.; Sun, L.; Sangare, L.; Minnie, Y.; et al. Antagonistic action of *Bacillus subtilis* strain SG6 on *Fusarium graminearum*. *PLoS ONE* **2014**, *9*, e92486. [CrossRef] [PubMed]

29. Palazzini, J.M.; Ramirez, M.L.; Albereone, E.J.; Torres, A.M.; Chulze, S.N. Osmotic stress adaptation, compatible solutes accumulation and biocontrol efficacy of two potential biocontrol agents on Fusarium head blight in wheat. *Biol. Control* **2009**, *51*, 370–376. [CrossRef]

30. Khan, M.R.; Doohan, F.M. Bacterium-mediated control of Fusarium head blight disease of wheat and barley and associated mycotoxic contamination of grain. *Biol. Control* **2009**, *48*, 42–47. [CrossRef]

31. Jochum, C.C.; Osborne, L.E.; Yuen, G.Y. Fusarium head blight biological control with *Lysobacter enzymogenes* strain C3. *Biol. Control* **2006**, *39*, 336–344. [CrossRef]

32. McCormick, S.P. Microbial detoxification of mycotoxins. *J. Chem. Ecol.* **2013**, *39*, 907–918. [CrossRef]

33. Barka, E.A.; Vatsa, P.; Sanchez, L.; Gaveau-Vaillant, N.; Jacquard, C.; Klenk, H.-P.; Clément, C.; Ouhdouch, Y.; van Wezel, G.P. Taxonomy, physiology, and natural products of Actinobacteria. *Microbiol. Mol. Biol. Rev.* **2016**, *80*, 1–43. [CrossRef] [PubMed]

34. Williams, S.T.; Vickers, J.C. Detection of Actinomycetes in the Natural Environment: Problems and Perspectives. In *Biology of Actinomycetes*; Okami, Y., Beppu, T., Ogawara, H., Eds.; Japan Scientific Societies Press: Tokyo, Japan, 1988; pp. 165–270.

35. Bush, M.J.; Tschowri, N.; Schlimpert, S.; Flärdh, K.; Buttner, M.J. C-di-GMP signalling and the regulation of developmental transitions in streptomycetes. *Nat. Rev. Microbiol.* **2015**, *13*, 749–760. [CrossRef] [PubMed]
36. Challis, G.L.; Hopwood, D.A. Synergy and contingency as driving forces for the evolution of multiple secondary metabolite production by Streptomyces species. *Proc. Natl. Acad. Sci. USA* 2003, 100, 14555–14561. [CrossRef] [PubMed]

37. Seipke, R.F.; Kaltenpoth, M.; Hutchings, M.I. *Streptomyces* as symbionts: An emerging and widespread theme? *FEMS Microbiol. Rev.* 2012, 36, 862–876. [CrossRef] [PubMed]

38. Bérdy, J. Bioactive microbial metabolites: A personal view. *J. Antibi.* 2005, 58, 1–26. [CrossRef] [PubMed]

39. Viaene, T.; Langendries, S.; Beirinckx, S.; Maes, M.; Goormachtig, S. *Streptomyces* as a plant’s best friend? *FEMS Microbiol. Ecol.* 2016, 92, 119. [CrossRef]

40. Newitt, J.T.; Prudence, S.M.M.; Hutchings, M.I.; Worsley, S.F.; Newitt, J.T.; Prudence, S.M.M.; Hutchings, M.I.; Worsley, S.F. Biocontrol of cereal crop diseases using streptomycetes. *Pathogens* 2019, 8, 78. [CrossRef]

41. Qin, S.; Xing, K.; Jiang, J.-H.; Xu, L.-H.; Li, W.-J. Biodiversity, bioactive natural products and biotechnological potential of plant-associated endophytic actinobacteria. *Appl. Microbiol. Biotechnol.* 2011, 89, 457–473. [CrossRef]

42. Zamoum, M.; Goudjal, Y.; Sabaou, N.; Barakate, M.; Mathieu, F.; Zitouni, A. Biocontrol capacities and plant growth-promoting traits of endophytic actinobacteria isolated from native plants of Algerian sahara. *J. Plant Dis. Prot.* 2015, 122, 215–233. [CrossRef]

43. Comby, M.; Gacoin, M.; Robineau, M.; Rabenoelina, F.; Ptas, S. Screening of wheat endophytes as biological control agents against Fusarium head blight using two different in vitro tests. *Microbiol. Res.* 2017, 202, 11–20. [CrossRef]

44. Rey, T.; Dumas, B. Plenty is no plague: *Streptomyces* symbiosis with crops. *Trends Plant Sci.* 2017, 22, 30–37. [CrossRef] [PubMed]

45. Nguyen, P.A.; Strub, C.; Fontana, A.; Schorr-Galindo, S. Crop molds and mycotoxins: Alternative management using biocontrol. *Biol. Control* 2017, 104, 10–27. [CrossRef]

46. Todd, J.; Antonet, K.; Svircev, M.; Goettel, M.S.; Woo, S.G. The Use and Regulation of Microbial Pesticides in Representative Jurisdictions Worldwide; Todt, J., Antonet, K., Svircev, M., Goettel, M.S., Woo, S.G., Eds.; IOBC Global: Hong Kong, China, 2010; p. 99.

47. Vurukonda, S.S.K.P.; Giovanardi, D.; Stefani, E. Plant growth promoting and biocontrol activity of *Streptomyces* spp. as endophytes. *Int. J. Mol. Sci.* 2018, 19, 952. [CrossRef] [PubMed]

48. Alabouvette, C.; Olivain, C.; Steinberg, C. Biological control of plant diseases: The European situation. *Eur. J. Plant Pathol.* 2006, 114, 329–341. [CrossRef]

49. Kagot, V.; Okoth, S.; De Boevre, M.; De Saeger, S. Biocontrol of *Aspergillus* and *Fusarium* mycotoxins in Africa: Benefits and limitations. *Toxins* 2019, 11, 109. [CrossRef]

50. Loria, R.; Kers, J.; Joshi, M. Evolution of plant pathogenicity in *Streptomyces*. *Annu. Rev. Phytopathol.* 2006, 44, 469–487. [CrossRef]

51. Zhang, Y.; Bignell, D.R.D.; Zuo, R.; Fan, Q.; Huguet-Tapia, J.C.; Ding, Y.; Loria, R. Promiscuous pathogenicity islands and phylogeny of pathogenic *Streptomyces* spp. *Mol. Plant Microbe Interact.* 2016, 29, 640–650. [CrossRef]

52. Rasimus-Sahari, S.; Mikkola, R.; Andersson, M.A.; Jestoi, M.; Salkinoja-Salonen, M. *Streptomyces* strains producing mitochondriotoxic antimycin A found in cereal grains. *Int. J. Food Microbiol.* 2016, 218, 78–85. [CrossRef]

53. van der Meij, A.; Worsley, S.F.; Hutchings, M.I.; van Wezel, G.P. Chemical ecology of antibiotic production by actinomycetes. *FEMS Microbiol. Rev.* 2017, 41, 392–416. [CrossRef]

54. Schisler, D.A.; Slininger, P.J.; Hanson, L.E.; Loria, R. Potato cultivar, pathogen isolate and antagonist cultivation medium influence the efficacy and ranking of bacterial antagonists of *Fusarium* dry rot. *Biocontrol. Sci. Technol.* 2000, 10, 267–279. [CrossRef]

55. Colombo, E.M.; Pizzatti, C.; Kunova, A.; Gardana, C.; Saracchi, M.; Cortesi, P.; Pasquali, M. Evaluation of in-vitro methods to select effective streptomycetes against toxigenic fusaria. *PeerJ* 2019, 7, e6905. [CrossRef] [PubMed]

56. Sánchez, S.; Chávez, A.; Forero, A.; García-Huante, Y.; Romero, A.; Sánchez, M.; Rocha, D.; Sánchez, B.; Valos, M.; Guzmán-Trampe, S.; et al. Carbon source regulation of antibiotic production. *J. Antibiot.* 2010, 63, 442–459. [CrossRef] [PubMed]

57. Abdelmohsen, U.R.; Grkovic, T.; Balasubramanian, S.; Kamel, M.S.; Quinn, R.J.; Hentschel, U. Elicitation of secondary metabolism in actinomycetes. *Biotechnol. Adv.* 2015, 33, 798–811. [CrossRef] [PubMed]
58. Bucar, F.; Wube, A.; Schmid, M. Natural product isolation—How to get from biological material to pure compounds. Nat. Prod. Rep. 2013, 30, 525–545. [CrossRef] [PubMed]
59. European Commission. Commission regulation (EU) 546/2011. Off. J. Eur. Union 2011, L155, 127–167.
60. Cook, R.J.; Bruckart, W.L.; Coulson, J.R.; Goettel, M.S.; Humber, R.A.; Lumsden, R.D.; Maddox, J.V.; Mcmanus, M.L.; Moore, L.; Meyer, S.F.; et al. Safety of microorganisms intended for pest and plant disease control: A framework for scientific evaluation. Biol. Control 1996, 7, 333–351. [CrossRef]
61. O’Callaghan, M. Microbial inoculation of seed for improved crop performance: Issues and opportunities. Appl. Microbiol. Biotechnol. 2016, 100, 5729–5746. [CrossRef]
62. Pliego, C.; Ramos, C.; de Vicente, A.; Cazorla, F.M. Screening for candidate bacterial biocontrol agents against soilborne fungal plant pathogens. Plant Soil 2011, 340, 505–520. [CrossRef]
63. Colombo, E.M.; Pizzatti, C.; Kunova, A.; Saracchi, M.; Cortesi, P.; Pasquali, M. Selection of an endophytic Streptomyces sp. strain DEF09 from wheat roots as a biocontrol agent against Fusarium graminearum. Front. Microbiol. 2019, 10, 2356. [CrossRef]
64. Whitaker, B.K.; Bakker, M.G. Bacterial endophyte antagonism toward a fungal pathogen in vitro does not predict protection in live plant tissue. FEMS Microbiol. Ecol. 2018, 95, 237.
65. Omura, S.; Iwai, Y.; Sakagawa, A.; Oiwa, H.; Hasegawa, Y. Herbimycin, a new antibiotic produced by a strain of Streptomyces. J. Antibiot. 1979, 32, 255–261. [CrossRef] [PubMed]
66. Jambhulkar, P.P.; Sharma, P.; Yadav, R. Delivery Systems for Introduction of Microbial Inoculants in the Field. In Microbial Inoculants in Sustainable Agricultural Productivity. Vol. 2: Functional Applications; Singh, D., Singh, H., Prabha, R., Eds.; Springer: New Delhi, India, 2016; pp. 199–218. ISBN 9788132226444.
67. Legrand, F.; Picot, A.; Cobo-Díaz, J.F.; Chen, W.; Le Floch, G. Challenges facing the biological control strategies for the management of Fusarium head blight of cereals caused by F. graminearum. Biol. Control 2017, 113, 26–38. [CrossRef]
68. He, J.; Boland, G.J.; Zhou, T. Concurrent selection for microbial suppression of Fusarium graminearum, Fusarium head blight and deoxynivalenol in wheat. J. Appl. Microbiol. 2009, 106, 1805–1817. [CrossRef] [PubMed]
69. Dalíć, D.; Pinson-Gadais, L.; Atanasova-Penichon, V.; Marchegay, G.; Barreau, C.; Deschamps, A.; Richard-Forget, F. Impact of Pediococcus pentosaceus strain L006 and its metabolites on fumonisin biosynthesis by Fusarium verticillioides. Food Control 2012, 23, 405–411. [CrossRef]
70. Sakuda, S. Mycotoxin production inhibitors from natural products. Mycotoxins 2010, 60, 79–86. [CrossRef]
71. Schroechk, V.; Scherlach, K.; Nützmann, H.W.; Shelest, E.; Schmidt-Heck, W.; Schuemann, J.; Martin, K.; Hertweck, C.; Brakhage, A.A. Intimate bacterial-fungal interaction triggers biosynthesis of archetypal polyketides in Aspergillus nidulans. Proc. Natl. Acad. Sci. USA 2009, 106, 14558–14563. [CrossRef]
72. Zuck, K.M.; Shipley, S.; Newman, D.J. Induced production of N-formyl alkaloids from Aspergillus fumigatus by co-culture with Streptomyces peucetius. J. Nat. Prod. 2011, 74, 1653–1657. [CrossRef]
73. Ola, A.R.B.; Thomy, D.; Lai, D.; Brötz-Oesterhelt, H.; Proksch, P. Inducing secondary metabolite production by the endophytic fungus Fusarium tricinctum through coculture with Bacillus subtilis. J. Nat. Prod. 2013, 76, 2094–2099. [CrossRef]
74. Rateb, M.E.; Hallyburton, I.; Houssen, W.E.; Bull, A.T.; Goodfellow, M.; Santhanam, R.; Jaspars, M.; Ebel, R. Induction of diverse secondary metabolites in Aspergillus fumigatus by microbial co-culture. RSC Adv. 2013, 3, 14444–14450. [CrossRef]
75. Marmann, A.; Aly, A.H.; Lin, W.; Wang, B.; Proksch, P. Co-cultivation—A powerful emerging tool for enhancing the chemical diversity of microorganisms. Mar. Drugs 2014, 12, 1043–1065. [CrossRef]
76. Pasquali, M.; Migliori, Q. Genetic approaches to chemotype determination in type B-trichothecene producing Fusaria. Int. J. Food Microbiol. 2014, 189, 164–182. [CrossRef] [PubMed]
77. O’Donnell, K.; Nirenberg, H.I.; Aoki, T.; Cigelnik, E. A multigene phylogeny of the Gibberella fujikuroi species complex: Detection of additional phylogenetically distinct species. Mycoscience 2000, 41, 61–78. [CrossRef]
78. Guo, Y.P.; Zheng, W.; Rong, X.Y.; Huang, Y. A multilocus phylogeny of the Streptomyces griseus 16S rRNA gene clade: Use of multilocus sequence analysis for streptomyces systematics. Int. J. Syst. Evol. Microbiol. 2008, 58, 149–159. [CrossRef] [PubMed]
79. Yoon, S.H.; Ha, S.M.; Kwon, S.; Lim, J.; Kim, Y.; Seo, H.; Chun, J. Introducing EzBioCloud: A taxonomically united database of 16S rRNA gene sequences and whole-genome assemblies. Int. J. Syst. Evol. Microbiol. 2017, 67, 1613–1617.
80. Palazzini, J.M.; Ramirez, M.L.; Torres, A.M.; Chulze, S.N. Potential biocontrol agents for Fusarium head blight and deoxynivalenol production in wheat. *Crop Prot.* 2007, 26, 1702–1710. [CrossRef]

81. Sultan, Y.; Magan, N. Impact of a *Streptomyces* (AS1) strain and its metabolites on control of *Aspergillus flavus* and aflatoxin B1 contamination in vitro and in stored peanuts. *Biocontrol Sci. Technol.* 2011, 21, 1437–1455. [CrossRef]

82. Verheecke, C.; Liboz, T.; Darriet, M.; Sabaou, N.; Mathieu, F. In vitro interaction of actinomycetes isolates with *Aspergillus flavus*: Impact on aflatoxins B1 and B2 production. *Lett. Appl. Microbiol.* 2014, 58, 597–603. [CrossRef]

83. Magan, N.; Lacey, J. Effect of water activity, temperature and substrate on interactions between field and storage fungi. *Trans. Br. Mycol. Soc.* 1984, 82, 83–93. [CrossRef]

84. Jung, B.; Park, S.Y.; Lee, Y.W.; Lee, J. Biological efficacy of *Streptomyces* sp. strain BN1 against the cereal head blight pathogen *Fusarium graminearum*. *Plant Pathol.* J. 2013, 29, 52–58. [CrossRef]

85. Pei-Sheng, Y.; Cui-Juan, S.; Chun-Chun, H.; Guang-Feng, K. Inhibition of vomitoxin-producing *Fusarium graminearum* by marine actinomycetes and the extracellular metabolites. In Proceedings of the International Conference on Human Health and Biomedical Engineering, Jilin, China, 19–22 August 2011; pp. 454–456.

86. Palazzini, J.M.; Yerkovich, N.; Alberione, E.; Chiotta, M.; Chulze, S.N. An integrated dual strategy to control *Fusarium graminearum sensu stricto* by the biocontrol agent *Streptomyces* sp. RC 87B under field conditions. *Plant Gene* 2017, 9, 13–18. [CrossRef]

87. Nourozian, J.; Etebarian, H.R.; Khodakaramian, G. Biological control of *Fusarium graminearum* on wheat by antagonistic bacteria. *Songklanakarin J. Sci. Technol.* 2006, 28, 29–38.

88. Palazzini, J.; Roncallo, P.; Cantoro, R.; Chiotta, M.; Yerkovich, N.; Palacios, S.; Echenique, V.; Torres, A.; Ramirez, M.; Karlovsky, P.; et al. Biocontrol of *Fusarium graminearum sensu stricto*, reduction of deoxynivalenol accumulation and phytohormone induction by two selected antagonistic strains. *Toxins* 2018, 10, 88. [CrossRef] [PubMed]

89. Ranjbariyan, A.R.; Shams-Ghahfarokhi, M.; Kalantari, S.; Razzaghi-Abyaneh, M. Molecular identification of antagonistic bacteria from Tehran soils and evaluation of their inhibitory activities toward pathogenic fungi. *Iran. J. Microbiol.* 2011, 3, 140–146. [PubMed]

90. Solans, M.; Scervino, J.M.; Messuti, M.I.; Vobis, G.; Wall, L.G. Potential biocontrol actinobacteria: Rhizospheric isolates from the Argentine pampas lowlands legumes. *J. Basic Microbiol.* 2016, 56, 1289–1298. [CrossRef] [PubMed]

91. Yekkour, A.; Sabaou, N.; Zitouni, A.; Erraki, R.; Mathieu, F.; Lebrìhi, A. Characterization and antagonistic properties of *Streptomyces* strains isolated from Saharan soils, and evaluation of their ability to control seedling blight of barley caused by *Fusarium culmorum*. *Lett. Appl. Microbiol.* 2012, 55, 427–435. [CrossRef]

92. Al-Askar, A.A.; Khair, A.; Rashad, W.M. In vitro antifungal activity of *Streptomyces sporarvaeus* RDS28 against some phytopathogenic fungi. *Afr. J. Agric. Res.* 2011, 6, 2835–2842.

93. Singh, L.S.; Mazumder, S.; Bora, T.C. Optimisation of process parameters for growth and bioactive metabolite produced by a salt-tolerant and alkaliphilic actinomycete, *Streptomyces tanashiensis* strain A2D. *J. Mycol. Med.* 2009, 19, 225–233. [CrossRef]

94. Tripathi, C.K.M.; Praaven, V.; Singh, V.; Bihari, V. Production of antibacterial and antifungal metabolites by *Streptomyces violaceusniger* and media optimization studies for the maximum metabolite production. *Med. Chem. Res.* 2004, 13, 790–799. [CrossRef]

95. Mitrovi, I.Z.; Grubovac, J.A.; Dodi, J.M.; Grubovac, M.S. Effect of agitation rate on the production of antifungal. *Acta Period. Technol.* 2017, 48, 231–244. [CrossRef]

96. Singh, L.S.; Baruaah, I.; Bora, T.C. Actinomycetes of Loktak habitats: Isolation and screening for antimicrobial activities. *Biotechnology* 2006, 5, 217–221.

97. Alam, M.; Dharni, S.; Abdul-Khaliq Srivastava, S.K.; Samad, A.; Gupta, M.K. A promising strain of *Streptomyces* sp. with agricultural traits for growth promotion and disease management. *Indian J. Exp. Biol.* 2012, 50, 559–568. [PubMed]

98. Bordoloi, G.N.; Kumari, B.; Guha, A.; Bordoloi, M.; Yadav, R.N.S.; Roy, M.K.; Bora, T.C. Isolation and structure elucidation of a new antifungal and antibacterial antibiotic produced by *Streptomyces* sp. 201. *Biosci. Biotechnol. Biochem.* 2001, 65, 1856–1858. [CrossRef] [PubMed]

99. Koch, E.; Löffler, I. Partial characterization of the antimicrobial activity of *Streptomyces antimycoticus* FZB53. *J. Phytopathol.* 2009, 157, 235–242. [CrossRef]
100. Pan, H.Q.; Yu, S.Y.; Song, C.F.; Wang, N.; Hua, H.M.; Hu, J.C.; Wang, S.J. Identification and characterization of the antifungal substances of a novel Streptomyces cavourensis NAAS. J. Microbiol. Biotechnol. 2015, 25, 353–357. [CrossRef] [PubMed]

101. Wang, T.; Jiang, Y.; Ma, K.X.; Li, Y.Q.; Huang, R.; Xie, X.S.; Wu, S.H. Two new butenolides produced by an actinomycete Streptomyces sp. Chem. Biodivers. 2014, 11, 929–933. [CrossRef] [PubMed]

102. Chen, M.; Xie, L.J.; Zhou, J.R.; Song, Y.Y.; Wang, R.L.; Chen, S.; Su, Y.J.; Zheng, R.S. Collection, purification and structure elucidation of allelochemicals in Streptomyces sp. 6803. Allelopath. J. 2010, 25, 93–106.

103. Chen, M.; Xie, L.J.; Zhou, J.R.; Song, Y.Y.; Wang, R.L.; Chen, S.; Su, Y.J.; Zheng, R.S. Collection, purification and structure elucidation of allelochemicals in Streptomyces sp. 6803. Allelopath. J. 2010, 25, 93–106.

104. Deng, J.; Lu, C.; Li, Y.; Li, S. Cuevaenes C–E: Three new triene carboxylic derivatives from Streptomyces sp. 2014, 11, 929–933. [CrossRef] [PubMed]

105. Gomes, R.C.; Semedo, L.T.A.S.; Soares, R.M.A.; Linhares, L.F.; Ulhoa, C.J.; Alviano, C.S.; Coelho, R.R.R. Purification of a thermostable endochitinase from Streptomyces RC1071 isolated from a cerrado soil and its antagonism against phytopathogenic fungi. J. Appl. Microbiol. 2001, 90, 653–661. [CrossRef]

106. Baharlouei, A.; Sharifi-Sirchi, G.R.; Shahidi Bonjar, G.H. Identification of an antifungal chitinase from a potential biocontrol agent, Streptomyces plicatus strain 101, and its new antagonistic spectrum of activity. Philipp. Agric. Sci. 2010, 93, 439–445.

107. Shi, P.; Yao, G.; Yang, P.; Li, N.; Luo, H.; Bai, Y.; Wang, Y.; Yao, B. Cloning, characterization, and antifungal activity of an endo-1,3-beta-D-glucanase from Streptomyces sp. S27. Appl. Microbiol. Biotechnol. 2010, 85, 1483–1490. [CrossRef] [PubMed]

108. Swiontek Brzezinska, M.; Jankiewicz, U.; Burkowska, A. Purification and characterization of Streptomyces albidoflavus antifungal components. Appl. Biochem. Microbiol. 2013, 49, 451–457. [CrossRef]

109. Fulgueira, C.L.; Amigot, S.L.; Magni, C. Growth inhibition of toxigenic fungi by a proteinaceous compound from Streptomyces sp. C/33-6. Curr. Microbiol. 2004, 48, 135–139. [CrossRef] [PubMed]

110. Wang, C.; Wang, Z.; Qiao, X.; Li, Z.; Li, F.; Chen, M.; Wang, Y.; Huang, Y.; Cui, H. Antifungal activity of volatile organic compounds from Streptomyces albiflavus TD-1. FEMS Microbiol. Lett. 2013, 341, 45–51. [CrossRef] [PubMed]

111. Wang, Z.; Wang, C.; Li, F.; Li, Z.; Chen, M.; Wang, Y.; Qiao, X.; Zhang, H. Funigant activity of volatiles from Streptomyces albiflavus TD-1 against Fusarium moniliforme Sheldon. J. Microbiol. 2013, 51, 477–483. [CrossRef] [PubMed]

112. Boukaew, S.; Plubrukam, A.; Prasertsan, P. Effect of volatile substances from Streptomyces philianthi RM-1-138 on growth of Rhizoctonia solani on rice leaf. BioControl 2013, 58, 471–482. [CrossRef]

113. Han, D.; Wang, L.; Luo, Y. Isolation, identification, and the growth promoting effects of two antagonistic actinomycete strains from the rhizosphere of Mikania micrantha Kunth. Microbiol. Res. 2018, 208, 1–11. [CrossRef]

114. Toumatia, O.; Companat, S.; Yekkour, A.; Goudjal, Y.; Sabaou, N.; Mathieu, F.; Sessitsch, A.; Zitouni, A. Biocontrol and plant growth promoting properties of Streptomyces mutabilis strain IAI isolated from a Saharan soil on wheat seedlings and visualization of its niches of colonization. S. Afr. J. Bot. 2016, 105, 234–239. [CrossRef]

115. Wachowska, U.; Kucharska, K.; Jedryczka, M.; Łobik, N. Microorganisms as biological control agents against Fusarium pathogens in winter wheat. Pol. J. Environ. Stud. 2013, 22, 591–597.

116. Mouloud, G.; Samir, M.; Hani, B.; Daoud, H. Biocontrol of wheat Fusarium Head Blight (FHB) by Streptomyces spp. isolated from the rhizosphere of Astragalus gombo Coss. & Dur. and Ononis angustissima Lam. Am. Euras. J. Agric. Environ. Sci. 2016, 15, 2499–2511.

117. Orakçi, G.E.; Yamaç, M.; Amoroso, M.J.; Cuozzo, S.A. Selection of antagonistic actinomycete isolates as biocontrol agents against root-rot fungi. Fresenius Environ. Bull. 2010, 19, 417–424.

118. Koch, E.; Weil, B.; Wächter, R.; Wohlleben, S.; Spiess, H.; Krauthausen, H.J. Evaluation of selected microbial strains and commercial alternative products as seed treatments for the control of Tilletia tritici, Fusarium culmorum, Drechslera graminea and D. teres. J. Plant Dis. Prot. 2006, 113, 150–158. [CrossRef]

119. Bressan, W. Biological control of maize seed pathogenic fungi by use of actinomycetes. BioControl 2003, 48, 233–240. [CrossRef]

120. Bressan, W.; Figureiredo, J.E.F. Efficacy and dose-response relationship in biocontrol of Fusarium disease in maize by Streptomyces spp. Eur. J. Plant Pathol. 2008, 120, 311–316. [CrossRef]
121. Nguyen, P.-A.; Strub, C.; Durand, N.; Alter, P.; Fontana, A.; Schorr-Galindo, S. Biocontrol of *Fusarium verticillioides* using organic amendments and their actinomycete isolates. *Biol. Control* **2017**, *118*, 55–66. [CrossRef]

122. Samsudin, N.I.P.; Mañan, N. Efficacy of potential biocontrol agents for control of *Fusarium verticillioides* and fumonisin B₁ under different environmental conditions. *World Mycotoxin J.* **2016**, *9*, 205–213. [CrossRef]

123. El-Naggar, M.A.; Alkahtani, M.D.F.; Thabit, T.M.; Sarhan, E.A.; Morsy, K.M. In vitro study on influence of some *Streptomyces* strains isolated from date palm rhizosphere soil on some toxigenic fungi. *Foodborne Pathog. Dis.* **2012**, *9*, 646–654. [CrossRef]

124. Shirokikh, I.G.; Merzaeva, O.V. Biological activity of *Streptomyces hygroscopicus* against phytopathogenic fungus *Fusarium avenaceum* in rhizosphere. *Mikol. Fitopatol.* **2008**, *42*, 586–591.

125. Mizuhara, N.; Kuroda, M.; Ogita, A.; Tanaka, T.; Usuki, Y.; Fujita, K.I. Antifungal thiopeptide cyclothiazomycin B₁ exhibits growth inhibition accompanying morphological changes via binding to fungal cell wall chitin. *Bioorg. Med. Chem.* **2011**, *19*, 5300–5310. [CrossRef]

126. Aouar, L.; Lerat, S.; Ouffroukh, A.; Boulahrouf, A.; Beaulieu, C. Taxonomic identification of rhizospheric actinobacteria isolated from Algerian semi-arid soil exhibiting antagonistic activities against plant fungal pathogens. *Can. J. Plant Pathol.* **2012**, *34*, 165–176. [CrossRef]

127. Khebizi, N.; Boudjella, H.; Bijani, C.; Bouras, N.; Klenk, H.P.; Pont, F.; Mathieu, F.; Sabau, N. Oligomycins A and E, major bioactive secondary metabolites produced by *Streptomyces* sp. strain HG29 isolated from a Saharan soil. *J. Mycol. Med.* **2018**, *28*, 150–160. [CrossRef] [PubMed]

128. Passari, A.K.; Mishra, V.K.; Gupta, V.K.; Saikia, R.; Singh, B.P. Distribution and identification of endophytic *Streptomyces* species from *Schima wallichii* as potential biocontrol agents against fungal plant pathogens. *Pol. J. Microbiol.* **2016**, *65*, 319–329. [CrossRef] [PubMed]

129. Golińska, P.; Dahm, H. Antagonistic properties of *Streptomyces* isolated from forest soils against fungal pathogens of pine seedlings. *Dendrobiology* **2013**, *69*, 87–97. [CrossRef]

130. Al-Askar, A.A. Endophytic *Streptomyces olivaceisceroticus* Endo-1: Biocontrol agent and growth promoter of wheat. *J. Pure Appl. Microbiol.* **2014**, *8*, 307–317.

131. Khieu, T.N.; Liu, M.J.; Nimaichand, S.; Quach, N.T.; Chu-Ky, S.; Phi, Q.T.; Vu, T.T.; Nguyen, T.D.; Xiong, Z.; El-Naggar, M.A.; Alkahtani, M.D.F.; Thabit, T.M.; Sarhan, E.A.; Morsy, K.M. In vitro study on influence of some *Streptomyces* isolates as biocontrol agents against *Fusarium graminearum* in rhizosphere. *Mikol. Fitopatol.* **2016**, *65*, 319–329. [CrossRef] [PubMed]

132. Perez, C.; Dill-Macky, R.; Kinkel, L.L. Management of soil microbial communities to enhance populations of *Fusarium graminearum*-antagonists in soil. *Plant Soil* **2008**, *302*, 53–69. [CrossRef]

133. Ursan, M.; Boui-Sicuia, O.A.; Voaides, C.; Stan, V.; Bubueanu, C.; Cornea, C.P. The potential of new *Streptomyces* isolates as biocontrol agents against *Fusarium* spp. In *Agriculture for Life, Life for Agriculture*; Sciendo: Warsaw, Poland, 2018; pp. 594–600.

134. Chen, M.; Zhou, J.R.; Li, C.Y.; Song, Y.Y.; Xie, L.J.; Chen, S.; Zeng, R.S. Isolation, identification and bioactivity of allelochemicals of *Streptomyces* sp. strain 6803. *Allelopath. J.* **2009**, *23*, 411–424.

135. Ye, L.; Zhu, H.; Tian, M.; Huang, X. Structure elucidation and activity of compound H6794-A, a fungal cell wall inhibitor. *Chin. J. Antibiot.* **2010**, *35*, 77–80.

136. Wei, Z.; Xu, C.; Wang, J.; Lu, F.; Bie, X.; Lu, Z. Identification and characterization of *Streptomyces flavogriseus* NJ-4 as a novel producer of actinomycin D and holomycin. *PeerJ* **2017**, *5*, e3601. [CrossRef]

137. Apichaisatienchote, B.; Altenbuchner, J.; Buchenauer, H. Isolation and identification of *Streptomyces fradiae* SU-1 from Thailand and protoplast transformation with the chitinase B gene from *Nocardiosis prasina* OPC-131. *Curr. Microbiol.* **2005**, *51*, 116–121. [CrossRef]

138. Silva-Lacerda, G.R.; Santana, R.C.F.; Vicalvi-Costa, M.C.V.; Solidônio, E.G.; Sena, K.X.F.R.; Lima, G.M.S.; Araújo, J.M. Antimicrobial potential of actinobacteria isolated from the rhizosphere of the Caatinga biome plant *Caesalpinia pyramidalis* Tul. *Genet. Mol. Res.* **2016**, *15*, 1–12. [CrossRef] [PubMed]

139. Kaur, T.; Manhas, R.K. Antifungal, insecticidal, and plant growth promoting potential of *Streptomyces hygroscopicus* DH16. *J. Basic Microbiol.* **2014**, *54*, 1175–1185. [CrossRef] [PubMed]

140. Charousová, I.; Medo, J.; Halenárová, E.; Maková, J.; Javoreková, S. Effect of fertilization on biological activity of community of soil streptomycetes. *J. Cent. Eur. Agric.* **2016**, *17*, 1134–1149. [CrossRef]
141. Kovácsővá, S.; Javoreková, S.; Medo, J.; Charousová, I.; Elbl, J.; Plošek, L. Characteristic of Streptomyces species with antimicrobial activity against selected phytopathogenic bacteria and fungi. J. Microbiol. Biotechnol. Food Sci. 2015, 5, 55–59. [CrossRef]

142. Paškevičius, A.; Ėvedienė, J.; Levinskaite, L.; Repečkiene, J.; Raudoniene, V.; Melvydas, V. The effect of bacteria and essential oils on mycotoxin producers isolated from feed of plant origin. Vet. Zootech. 2014, 65, 52–60.

143. Guoying, Z.; Guangtao, S.; Lei, Y. Fungistatic activity and identification of antagonistic actinomycetes to camellia diseases from soil. In Proceedings of the International Conference on Challenges in Environmental Science and Computer Engineering, Wuhan, China, 6–7 March 2010; pp. 475–478.

144. Sadeghy, B.; Hatami, N. Screening biological activities of soil-borne Streptomyces sp. against several phytopathogenic fungi. Arch. Phytopathol. Plant Prot. 2014, 47, 954–958. [CrossRef]

145. Wardecki, T.; Brötz, E.; De Ford, C.; Von Loewenich, F.D.; Rebets, Y.; Tokovenko, B.; Luzhetskyy, A.; Merfort, I. Endophytic Streptomyces in the traditional medicinal plant Arnica montana L.: Secondary metabolites and biological activity. Int. J. Gen. Mol. Microbiol. 2015, 108, 391–402. [CrossRef]

146. Novikova, I.I.; Litvinenko, A.I.; Boikova, I.V.; Yaroshenko, V.A.; Kalko, G.V. Biological activity of new microbiological preparations alirins B and S designed for plant protection against diseases. I. Biological activity of alirins against diseases of vegetable crops and potato. Mikol. Fitopot. 2003, 37, 92–98.

147. Xu, J.; Shi, J.; Kou, C.; Wang, G.; Xu, L.; Pan, L. Strain of Streptomyces metropsis and Application Thereof. C.N. Patent No 107,058,131, 18 August 2017.

148. Pan, H.; Yu, S.; Hu, J.; Wang, S. Streptomyces cavourensisi and Application Thereof 2014. C.N. Patent No. 103,820,351 A, 28 May 2014.

149. Gromovykh, T.I.; Litovka, J.A.; Sadykova, V.S. Actinomyces Strain and Treating Alamo Grey Speck Disease Germs. C.N. Patent No 104,130,965 A, 5 November 2014.

150. Gromovykh, T.I.; Litovka, J.A.; Sadykova, V.S. Actinomyces Strain and Application Thereof. C.N. Patent No 103,820,351 A, 28 May 2014.

151. Wu, W.; Guo, Y.; Meng, F.; Qi, L.; Xia, N.; Jiao, Z. Erythrochromogenes and Use Thereof in Biological Control of Plant Diseases Using the Same. K.R. Patent No 100,914,225 B1, 26 August 2009.

152. Wu, W.; Guo, Y.; Meng, F.; Qi, L.; Xia, N.; Jiao, Z. Erythrochromogenes and Use Thereof in Biological Control of Plant Diseases 2010. C.N. Patent No. 101,698,827 A, 28 April 2010.

153. Caixia, D.; Gao, S.; Jing, R.; Peng, L.; Wei, L.; Aiping, L.; Xing, L.; Yaxue, L.; Yaqin, S.; Na, T.; et al. Streptomyces griseoflavus and Application Thereof in Biological Prevention and Control of Plant Diseases. C.N. Patent No 101,822,272 A, 8 September 2010.

154. Suh, J.W.; Yoon, T.M.; Yang, S.H.; Kim, J.Y.; Lee, S.K.; Cheng, J.H. Streptomyces cinnamoneus Mjm8987 Producing Antifungal Substances Ys-822a and Its Use. K.R. Patent No 101,098,280, 23 December 2010.

155. Yang, M.; Shu, C.; Zhou, E.; Gao, Y.; Zhang, D.; Fan, J. Streptomyces katrac NB20, as well as Culture Method and Application Thereof. C.N. Patent No 102,433,281 A, 2 May 2012.

156. Shin, J.G.; Shin, M.U.; Im, Y.M.; Park, S.W.; Son, H.N.; Shim, N.G.; Cho, J.H. Biological Agent for Plant Diseases Using Streptomyces nigrogriseolus Cmc0647. K.R. Patent No 101,211,681, 12 December 2012.

157. Ma, G.; Pu, Z.; Wang, S.; Wu, S.; Fu, H.; Ge, P. Streptomyces mediolani ZW-1 Bacterial Strain, and Bacteriostatic Application of Fermentation Broth Thereof. C.N. Patent No 102,835,423 A, 26 December 2012.

158. Lu, L.; Du, D.; Pu, Z.; Hu, X.; Chen, G.; Huang, Z.; Zhang, X.; Zhang, L. Marine Actinomycete with Antibacterial Activity to Multiple Plant Pathogens. C.N. Patent No 103,114,064 A, 22 May 2013.

159. Liu, X.; Ma, L.; Liu, X. Streptomyces with Inhibiting Effect on Poplar Gray Leaf Spot Pathogen. C.N. Patent No 104,130,965 A, 5 November 2014.

160. Liu, X.; Liu, X.; Ma, L.; Zhang, J.; Shi, F. Method for Preparing Streptomyces Fermentation Liquor for Preventing and Treating Alamo Grey Speck Disease Germs. C.N. Patent No 104,140,982 A, 12 November 2014.

161. Huang, H.; Tao, T. Active Enzyme Biological Leaf Fertilizer and Preparation Method Thereof. C.N. Patent No 105,886,428 A, 18 November 2015.

162. Errakhi, R.; Attia, F.; Cabanes, C. Isolated Bacterium of the Genus Streptomyces. E.P. Patent No 3,048,890 A1, 3 August 2016.

163. Shaojie, L.; Zhenying, Z.; Xianyun, S. Streptomyces albidoaflatus and Applications Thereof in Microbial Fertilizers. C.N. Patent No 105,886,428 A, 24 August 2016.
164. Wang, C.; Zhao, C.; Cui, J.; Liu, S.; Lu, Z.; Dou, S.; Xie, X.; Wang, Y.; Li, L.; Ma, X. *Streptomyces griseoplanus*, Application Thereof and Microbial Agent. C.N. Patent No 106,676,040, 17 May 2017.

165. Yu, J.; Wang, X.; Guo, C.; Liu, C.; Liu, A.; Li, X.; Al, E. *Streptomyces samsunensis* and Application Thereof. C.N. Patent No 107,164,259 A, 15 September 2017.

166. Li, S.; Zhang, Z.; Sun, X. *Streptomyces albidosflavus* Strain as Well as Application Thereof in Pesticide. C.N. Patent No 107,287,130 A, 24 October 2017.

167. Kim, S.H.; Yun, Y.H. Novel Strain of *Streptomyces* sp., ducc501, Having Antifungal Activity and Plant Disease Controlling Composition Comprising Said Novel Strain. W.O. Patent No 201,553,482 A1, 16 April 2018.

168. Li, X.; Liu, Z.; Gu, L.; Zhang, C.; Zhang, N.; Zhang, Y.; Wu, M.; Al, E. *Streptomyces deccanensis* QY-3 and Application Thereof. C.N. Patent No 108,048,380 A, 18 May 2018.

169. Jing, T.; Zang, X.; Xie, J.; Wang, L.; HE, Y.; Ding, Z.; Zhou, D.; Chen, Y. *Streptomyces samsunensis* and Application Thereof. C.N. Patent No 108,102,961 A, 1 June 2018.

170. Zhou, D.; Chen, Y.; Xie, J.; Wang, F.; Zhang, M.; Qi, D.; Feng, R.; Wang, W.; Jing, T.; Zang, X. *Streptomyces sangleri* and Application Thereof. C.N. Patent No 108,165,506, 15 June 2018.

171. Shunpeng, H.L.; Yu, Y.; Ceng, Y.; Luo, F.; Yang, C.; Zhang, X.H. Multifunctional Algae Strains of Mold *Streptomyces* and Application Thereof. C.N. Patent No 108,587,981, 28 September 2018.

172. Chen, Y.; Wang, J.; Yang, N.; Wen, Z.; Sun, X.; Chai, Y.; Ma, Z. Wheat Microbiome Bacteria Can Reduce Virulence of a Plant Pathogenic Fungus by Altering Histone Acetylation. *Nat. Commun.* 2018, 9, 3429. [CrossRef]

173. Syed Ab Rahman, S.F.; Singh, E.; Pieterse, C.M.J.; Schenk, P.M. Emerging microbial biocontrol strategies for plant pathogens. *Plant Sci.* 2018, 267, 102–111. [CrossRef]

174. Jain, A.; Singh, A.; Singh, B.N.; Singh, S.; Upadhay, R.S.; Sarma, B.K.; Singh, H.B. Biotic Stress Management in Agricultural Crops Using Microbial Consortium. In *Bacteria in Agrobiology: Disease Management*; Maheshwari, D., Ed.; Springer: Berlin/Heidelberg, Germany, 2013; pp. 427–448. ISBN 9783642336393.

175. Rojas, E.C.; Sapkota, R.; Jensen, B.; Jørgensen, H.I.L.; Henriksson, T.; Jørgensen, L.N.; Nicolaisen, M.; Collinge, D.B. Fusarium Head Blight modifies fungal endophytic communities during infection of wheat spikes. *Microb. Ecol.* 2019. [CrossRef] [PubMed]

176. Essarioui, A.; LeBlanc, N.; Kistler, H.C.; Kinkel, L.L. Plant community richness mediates inhibitory interactions and resource competition between *Streptomyces* and *Fusarium* populations in the rhizosphere. *Microb. Ecol.* 2017, 74, 157–167. [CrossRef] [PubMed]

177. Seipke, R.F. Strain-level diversity of secondary metabolism in *Streptomyces albus*. *PLoS ONE* 2015, 10, e0116457. [CrossRef] [PubMed]

178. Alberti, F.; Corre, C. *Editing Streptomycte Genomes in the CRISPR/Cas9 Age*; Royal Society of Chemistry (RSC): London, UK, 2019; pp. 1237–1248.

179. Harir, M.; Bendif, H.; Bellahcene, M.; Fortas and Rebecca Pogni, Z. *Streptomyces Secondary Metabolites*. In *Basic Biology and Applications of Actinobacteria*; Enany, S., Ed.; IntechOpen: London, UK, 2018.

180. Manteca, A.; Yagüe, P. *Streptomyces as a Source of Antimicrobials: Novel Approaches to Activate Cryptic Secondary Metabolite Pathways*. In *Antimicrobials, Antibiotic Resistance, Antibiofilm Strategies and Activity Methods*; Kursmsauoagli, S., Ed.; IntechOpen: London, UK, 2019.