

1 Review

2 Biocontrol of cereal crop diseases using 3 streptomycetes

4 Jake T. Newitt^{1#}, Samuel M. M. Prudence^{1#}, Matthew I. Hutchings^{1,*} and Sarah F. Worsley^{1,*}

5 ¹ School of Biological Sciences, University of East Anglia, Norwich Research Park, Norwich, Norfolk, United
6 Kingdom. NR4 7TJ.

7 # These authors contributed equally

8 * Correspondence: m.hutchings@uea.ac.uk (MIH); s.worsley@uea.ac.uk (SFW)

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11 **Abstract:** A growing world population and an increasing demand for greater food production
12 requires that crop losses caused by pests and diseases are dramatically reduced. Concurrently,
13 sustainability targets mean that alternatives to chemical pesticides are becoming increasingly
14 desirable. Bacteria in the plant root microbiome can protect their plant host against pests and
15 pathogenic infection. In particular, *Streptomyces* species are well-known to produce a range of
16 secondary metabolites that can inhibit the growth of phytopathogens. *Streptomyces* are abundant in
17 soils and are also enriched in the root microbiomes of many different plant species, including those
18 grown as economically and nutritionally valuable cereal crops. In this review we discuss the
19 potential of *Streptomyces* to protect against some of the most damaging cereal crop diseases,
20 particularly those caused by fungal pathogens. We also explore factors that may improve the
21 efficacy of these strains as biocontrol agents *in situ*, as well as the possibility of exploiting plant
22 mechanisms that enable the recruitment of microbial species from the soil to the root microbiome.
23 We argue that a greater understanding of these mechanisms may enable the development of
24 protective plant root microbiomes with a greater abundance of beneficial bacteria such as
25 *Streptomyces* species.

26 **Keywords:** *Streptomyces*; biocontrol; cereals; root microbiome; rhizosphere

27

28 1. Introduction

29 Cereal crops or 'cereals' are plants belonging to the grass family *Poaceae* that are grown and
30 harvested primarily for their edible grain [1]. The economic and social importance of cereal crops
31 cannot be understated, as they provide fundamental nutrition for the vast majority of the world's
32 population. Most cereal crops are grown primarily for their grain, which contains a nutritional
33 starchy endosperm, and forms a staple part of the human diet [1]. However, many cereals can also
34 be used for the upkeep of animal livestock and their utility is further enhanced by their capacity for
35 long term storage [1]. The focus of this review is directed at key global cereal crops, for example
36 maize, wheat, rice, barley, sorghum, millet, oats, and rye [1]. The FAO predicts that 2,609 million
37 tonnes of such cereal crops were produced in 2018 [2].

38

39 One of the greatest challenges facing the world today is to match the demand of a rapidly
40 expanding global population with an increase in food production, whilst simultaneously ensuring
41 that this is done sustainably and within the limitations of land availability for agriculture [3]. In order
42 to meet this target, it will be necessary to pursue two intimately linked goals. The first is to increase
43 crop yield, particularly that of cereal crops, which can be attained through various methods such as
44 selective breeding, genetic modification as well as carefully controlled irrigation and fertilisation

45 regimes [3,4]. The second is to minimise crop losses caused by pests and diseases, which are
46 conservatively estimated to cause between 20-40% of losses to yield, with further consequences for
47 livelihoods, public health and the environment [3-7]. The implementation of strategies to achieve the
48 latter are challenging, particularly as the factors that underpin plant disease are highly complex and
49 multivariate [6].

50

51 Many different types of organism can infect cereal crops including a range of bacteria,
52 oomycetes, fungi, viruses and nematodes [8]. Fungal diseases, in particular, are considered to be one
53 of the most dominant groups of cereal crop pathogens, with agents causing disease at every level of
54 plant physiology [8,9]. Different fungal infections can thus cause a wide range of symptoms which
55 can all contribute to yield losses. For example, infection by several fungal pathogens results in the
56 formation of necrotic lesions on leaves and stems which can eventually lead to leaf senescence and a
57 reduction in grain quantity; this is the case for rust infections caused by *Puccinia* species and also for
58 rice blast fungus, caused by the species *Magnaporthe oryzae* [8-11]. Rice blast can be incredibly
59 destructive, and is estimated to be responsible for 30% of losses to rice crops globally [12]. Other
60 pathogenic soil-borne fungal species invade primarily at the plant roots, causing root rot from the
61 base of the plant upwards, whilst simultaneously sapping the host plant of its nutrients; this is the
62 case for the causative agent of wheat Take-all disease, *Gaeumannomyces graminis*, which in some cases
63 can eliminate an entire wheat crop [13]. Thus, *G. graminis* is often cited as the most important root
64 disease of wheat worldwide [13-16]. Additionally, many fungal species (such as *Fusarium* spp.) don't
65 cause plant senescence, but instead can negatively impact yield by causing a dramatic reduction in
66 grain quality via the production of high concentrations of mycotoxins [8,17].

67

68 The most widely used method to combat the losses caused by crop disease, is the routine
69 application of chemical pesticides to crops, with the aim of eliminating or limiting the severity of
70 disease phenotypes. However, it is increasingly becoming clear that the long-term use of chemical
71 pesticides can have several negative side-effects. For example, many pesticides can lead to both acute
72 and chronic toxicity in humans and they are increasingly being shown to cause wide-spread damage
73 to the wider ecosystem, by impacting non-target organisms such as pollinator species and also through
74 the pollution of soil and water systems [18-20]. The use of chemical pesticides is additionally
75 hampered by the evolution of microbial resistance. In much the same way that we face a crisis in
76 modern medicine due to antimicrobial resistance, so too do we face a decline in the effectiveness of
77 pesticides due to phytopathogen resistance [21,22].

78

79 As a result of the issues and side-effects of using chemical pesticides to control crop diseases,
80 research is beginning to re-focus on finding alternative solutions to combat pathogenic infection.
81 Crop rotation has played a vital role in phytosanitation throughout history, and aims to prevent the
82 accumulation of soil-borne pathogens specific to certain families of plant, by alternating with an
83 incompatible host [13,23]. However, crop rotation is not always an economically viable strategy for
84 farmers to adopt. In addition to rotation, selective breeding programs aim to introduce plant disease
85 resistance genes (for example R genes) into modern cultivars [24-26]. However, in some cases this can
86 be challenging and there are several crop species for which there are no resistant cultivars
87 available [24]. In addition, pathogens can quickly overcome plant host resistance mechanisms,
88 particularly when resistance is encoded for by a single gene [24]. As an example, rice cultivars that
89 are resistant to *M. oryzae* typically become ineffective every 2-3 years [18]. These problems combined,
90 have led to the search for further alternatives. Increasingly, it is being realised that the
91 microorganisms living within soil and in close association with plant roots can make large
92 contributions to plant health and could be engineered as biocontrol agents.

93

2. Plant-microbe interactions and their effect on plant health

94

95 The vast majority of eukaryotes, including plants, interact extensively with a diverse community
of microorganisms. In plants, interactions particularly emerge at the interface between the plant roots

96 and the soil environment, whereby bacteria from the soil abundantly colonise the soil layer, known
97 as the “rhizosphere”, that is immediately surrounding and influenced by the plant root system [27-
98 30]. Several microbial species are also capable of attaching to the root surface (a region called “the
99 rhizoplane”) and a small subset of the soil community additionally enter the plant root tissue
100 [28,29,31]. The latter group of microorganisms are adapted to survive within the inter or intracellular
101 spaces within the plant roots, which are collectively known as the “endophytic compartment”
102 [28,29,31]. Advances in next generation sequencing (NGS) techniques have facilitated deeper probing
103 into the microbial ecology of the plant root microbiome. Although abiotic factors such as soil
104 characteristics appear to influence the composition of the microbiome, it is also clear that host genetics
105 play a key role in root microbiome assembly and plants are likely to select beneficial species from
106 their environment [32-35]. Factors such as differences in root architecture can influence this assembly
107 process [31,36]. Additionally, around 20-40 % of photosynthetically fixed carbon is exuded from
108 plants into the rhizosphere; these exudates include a broad range of organic compounds that can be
109 utilized by microorganisms and may help to select certain species from the soil community
110 [27,31,37,38].
111

112 It has been known for some time that both soil and plant-associated microbes can contribute to
113 plant health, since the presence of certain microbial species can result in a reduction in plant disease
114 incidence and severity [39-42]. Additionally, specific isolates from the plant root microbiome produce
115 a range of secondary metabolites that can inhibit plant pathogens both *in vitro* and *in vivo*
116 [15,18,20,40]. In particular, the potential of a Gram positive genus of Actinobacteria, called
117 *Streptomyces*, has drawn the attention of many in the scientific and industrial communities.
118 Streptomycetes are saprotrophic organisms, best known for their role as producers of clinically useful
119 antibiotics, of which they are responsible for approximately 55% [43-45]. This genus is characterised
120 by their polar filamentous growth, their spore-forming capabilities and, particularly, their extensive
121 secondary metabolism [43,45,46]. These secondary metabolites are known to have a diverse range of
122 activities and have been used for a wide range of applications including as antibacterials, antifungals,
123 anti-cancer and anti-helminthic drugs [43,45]. Since *Streptomyces* are abundant in soil and have been
124 shown to suppress a range of phytopathogenic organisms both *in vitro* and *in vivo*, these organisms
125 are gaining interest as potential biocontrol agents, that could be used in place of conventional
126 chemical treatments [20,47]. In this review, we specifically focus on reviewing research that
127 investigates the role that *Streptomyces* can play in inhibiting pathogens of cereal crops, particularly
128 fungal pathogenic species. We focus on this in particular, due to the global importance of cereal crops,
129 the large socioeconomic impacts of yield losses caused by fungal disease and the lack of other
130 alternatives for controlling many of these pathogens. Several excellent reviews [e.g. 18,20,47,48] have
131 discussed the general potential of *Streptomyces* as biocontrol agents or their application to one specific
132 crop species and we extend this literature by specifically focusing on cereal crops.

133 3. *Streptomyces* - plant interactions

134 The evolution of the first true streptomycetes approximately 450 million years ago is thought to
135 have been largely stimulated by the transition of plants onto land, approximately 550 million years
136 ago [44]. Millions of years of plant-streptomycete interactions may explain why *Streptomyces* are often
137 found to be abundant in the rhizosphere and roots of a variety of different plant species. For example,
138 *Streptomyces* have been shown to be enriched in the roots and rhizosphere of *Arabidopsis thaliana*
139 [33,34,49], as well as in important crop species such as potatoes [50], rice [51], wheat [52,53] and
140 oilseed rape [35]. A long period of coevolution with plants might also have resulted in several aspects
141 of the growth and metabolism of this genus. For example, selective pressures to break down plant
142 material are thought to have driven the evolution of a saprotrophic and filamentous lifestyle, which
143 would have enabled early streptomycetes to penetrate living and dead plant material in order to
144 access otherwise unavailable nutrients stored in complex molecules such as cellulose [44,54]. This
145 may have eventually led to an endophytic lifestyle and, indeed, fluorescent microscopy has shown
146 that streptomycetes can exist endophytically within the roots of several different plant species,

147 including lettuce, wheat and pea, and that they may be able to penetrate plant roots by entering
 148 openings that occur at the bases of root hairs and lateral roots [53,55-57]. *Streptomyces* are also capable
 149 of producing an array of cellulolytic and hydrolytic enzymes which might allow forced entry into
 150 plant material, by breaking down the epidermal cell walls and middle lamellae between plant cells
 151 [20]. Their ability to produce a diverse array of antimicrobial secondary metabolites, may additionally
 152 allow them to compete for niche space and the carbon-rich resources that are exuded by plants.

153

154 Given their ability to colonise plant roots and produce potent antimicrobial secondary
 155 metabolites, the genus *Streptomyces* are becoming an increasingly obvious choice when looking for
 156 novel biocontrol agents (Table 1). This is particularly the case as, in addition to contributing to plant
 157 protection, members of this genus are frequently found to contribute to plant growth promotion
 158 (PGP), under both ambient and stressful environmental conditions such as high salinity [20,44,58-60];
 159 these additional benefits could form the basis for highly desirable biocontrol agents that can both
 160 enhance plant growth and protect against disease.

161

162 **Table 1.** Economically important cereal crop pathogens and associated biocontrol studies involving
 163 *Streptomyces* species.

Pathogen	Cereal crop host	Symptoms	Impact	<i>Streptomyces</i> as biocontrol
<i>Magnaporthe oryzae</i> (Rice blast)	Rice, Wheat	Panicle, leaf and head blast.	Yield losses and mycotoxin contamination	Greenhouse and <i>in vitro</i> studies. [18,61,62]
<i>Fusarium spp.</i>	All cereals	Head, root, crown and stem blight in addition to wilt and grain contamination.	Yield losses and mycotoxin contamination	Greenhouse, <i>in vitro</i> and field studies. [63-70]
<i>Rhizoctonia solani</i>	All cereals	Seed damping off, and infection of stems, roots and foliage.	Yield losses and reduction in grain quality.	<i>In vitro</i> and growth chamber studies [60,62,67,71-74]
<i>Gaumannomyces graminis</i> (Wheat Take-all)	Wheat, Barley, Rye, Rice, Oat, Maize	Root lesions and rot that spreads upwards to aerial parts of the plant.	Yield losses	<i>In vitro</i> and greenhouse studies. [15,53]
<i>Pythium spp.</i>	Wheat, Barley, Rice, Maize	Seed damping off, as well as root and stem rot.	Yield losses	<i>In vitro</i> and growth chamber studies. [72,75]

164

165 It is important for us to note that, although many *Streptomyces* are either beneficial or passive
 166 colonisers of the plant microbiome, certain species have evolved a phytopathogenic lifestyle.
 167 Perhaps the most well-studied example is *Streptomyces scabei*, the causative agent of common potato
 168 scab [76-78]. Several virulence factors have been found to be associated with this disease-causing

169 lifestyle, including small molecules such as coronafacic acid and thaxtomin, the latter of which is
170 located on a pathogenicity island within the genome of plant-pathogenic strains [79]. Only a handful
171 of *Streptomyces* species have these genes, and it is suggested that their acquisition was a singular event
172 and does not represent the interactions that are characteristic of plant-*Streptomyces* relationships.
173 Indeed, out of over 500 isolated *Streptomyces* species, only 10 are deemed to be pathogenic [20,80].
174 Thus, there is a huge diversity of strains that could be screened for their potential to act as beneficial
175 biocontrol agents. In the following sections we review the multitude of ways in which *Streptomyces*
176 species can contribute to the suppression of cereal crop diseases, both directly and indirectly. We also
177 extend this to a discussion of how such strains might be applied to cereal crops in practice, and the
178 factors that can influence the competitiveness and efficacy of biocontrol agents and thus need to be
179 considered during the development of such strains as biocontrol agents.

180 3.1 *Streptomyces* in disease suppressive soils

181 *Streptomyces* can confer plant host protection against pathogens in the soil, rhizosphere and
182 endosphere directly, through the production of antimicrobial compounds or via specific enzymes
183 [46]. Disease suppressive soils are perhaps some of the best known examples of microbial-based
184 defense against soil-borne pathogens, and several studies have used these soils as a source of novel
185 bioactive microbial strains [39,42]. Suppressiveness soils are those in which plants are protected from
186 infection, due to the antagonistic activities of a community of microorganisms, or a specific microbial
187 species, found in the soil and rhizosphere community [39]. They often occur in areas in which there
188 has been continuous monoculture, and can be disrupted by particular farming practices such as crop
189 rotation [39,42,64]. The mechanisms underpinning suppressiveness are only just beginning to be
190 understood, but antibiotic-producing *Streptomyces* species have often been found to be enriched in
191 these soils; a combination of metagenomics, strain isolation, genome sequencing and genome mining,
192 has enabled the isolation of contributing species and their associated bioactive compounds [64,81-84].
193 For example, the strain *Streptomyces* S4-7 was originally isolated from a Korean soil that showed
194 suppressiveness against *Fusarium* wilt disease [64]. Following genome sequencing, this strain was
195 found to encode 35 biosynthetic gene clusters encoding putative antimicrobial agents. A novel
196 thiopeptide was purified and shown to have potent inhibitory activity against fungal cell wall
197 biogenesis in *Fusarium*, suggesting natural products such as this may be contributing to the disease
198 suppressive nature of the original soil [64]. *Streptomyces* species were also found to make a major
199 contribution to the suppressiveness of light coloured *Sphagnum* peat in Finland, which inhibits the
200 development of a range of soil-borne pathogens, including *Rhizoctania solani* and *Fusarium spp.*, and
201 is therefore commonly adopted for glasshouse cultivation [39,85]. An analysis of the microbial
202 composition of this soil led to the isolation of the bioactive strain *Streptomyces griseoviridis*; this was
203 then used to formulate the broad-spectrum biofungicide Mycostop® which is active against a number
204 of crop diseases, including wheat head blight caused by *Fusarium* species [66].

205 3.2 Antimicrobials against phytopathogens of cereal crops

206 In addition to disease suppressive soils, there have been many efforts to isolate strains of
207 *Streptomyces* from other environments that are capable of inhibiting some of the most detrimental
208 cereal crop pathogens. Many studies have found *Streptomyces* species that can inhibit a range of
209 phytopathogens *in vitro*, including *Magnaporthe oryzae* (responsible for rice blast), *Gaeumannomyces*
210 *graminis* var. *tritici* (the cause of wheat take-all fungus), *Fusarium* species (responsible for head blight,
211 root rot, wilt and grain contamination in a variety of species), as well as *Rhizoctania solani* (a soil-borne
212 pathogen with a wide host range) [8,15,18,62,67] (Table 1). However, such inquiries only form the
213 beginning of a chain of experiments required to identify novel biocontrol agents. In soil, *Streptomyces*
214 bacteria interact with a diverse community of both prokaryotic and eukaryotic organisms which may
215 alter their competitive ability and potential to produce antimicrobial compounds. Thus, there is a real
216 need to demonstrate that isolates can also confer plant protection *in vivo*, both in green house
217 experiments and in field trials.

218

219 Several greenhouse and growth chamber experiments have been carried out with bioactive
220 compounds purified from cultures of *Streptomyces* species (Table 1). For example, a soil isolate, named
221 N2, was shown to inhibit a broad spectrum of phytopathogenic fungi *in vitro*, including the mycelial
222 growth of *R. solani* as well as the germination of its sclerotia [71,74]. Sclerotia mediate the dispersal,
223 propagation and long-term survival of the fungus in soil and are persistent under unfavourable
224 environmental conditions [71,74]. A novel antifungalmycin was found to be responsible for the
225 inhibitory effects of N2 [74] and, when directly applied, was also able to reduce the symptoms of
226 sheath blight on rice leaves and in pot experiments [71]. Another study has shown that culture
227 filtrates of the strain *Streptomyces globisporus* JK-1 can control *M. oryzae* more effectively than
228 tricyclazole, a commonly used chemical fungicide for the control of rice blast fungus [61]. Indeed,
229 several antifungal compounds purified from *Streptomyces* species have been commercialized as
230 fungicides against *M. oryzae* infections, for example, Kasugamycin (isolated from *S. kasugaensis*), is
231 commercially produced under the trade name Kasumin, and is used in Japan to protect against rice
232 blast disease [18].
233

234 Other studies have used live strains of *Streptomyces* during *in vivo* trials rather than purified
235 bioactive compounds [15,18,63,65] (Table 1). For example, the strain *Streptomyces* BN1, isolated from
236 rice grains contaminated with *Fusarium*, was able to mitigate the reduction in seedling length caused
237 by *Fusarium* when applied as a spore preparation to seeds. BN1 also significantly reduced *Fusarium*
238 head blight symptoms when sprayed onto wheat heads [63], suggesting that the application of viable
239 spores can be an effective way to reduce the competitive ability of pathogenic strains. Spore-coatings
240 were also used in a study investigating the ability of *Streptomyces* species (isolated from healthy cereal
241 crops) to inhibit wheat take-all infection by *G. graminis* var. *tritici* [15]. Spore-coated seeds
242 significantly reduced wheat infection in field soils that were infested with the take-all fungus [15];
243 this may have been aided by the ability of these strains to colonise the endophytic compartment of
244 wheat roots [53]. There is currently a lack of wheat cultivars with resistance to *G. graminis* and
245 chemical agents are variable in their ability to control the disease [13,15,42]. *Pseudomonas* species have
246 been investigated as potential biocontrol agents against take-all, but often these strains only colonise
247 wheat plants during the early stages of growth before being out-competed, and they are also sensitive
248 to desiccation [15,42]. *Streptomyces* may make a viable alternative, since their saprotrophic and spore-
249 forming lifestyle means that they survive well under unfavourable conditions [46]. They can also
250 colonise the mature roots of cereal crops [15].

251 3.3 Enzymatic control of phytopathogens: chitinases

252 The majority of *Streptomyces* species encode an enormous variety of secreted proteins that have
253 a diverse range of extracellular activities [86]. This includes the production of enzymes called
254 chitinases, which degrade the biomolecule chitin. Chitin is an insoluble, nitrogen-containing,
255 polysaccharide that is abundant in fungal cell walls [86,87]. *Streptomyces* are unusual amongst
256 bacterial taxa in that they can use it as both a carbon and a nitrogen source [86]. Chitinases isolated
257 from *Streptomyces* species have been shown to inhibit a broad spectrum of phytopathogenic fungi
258 and oomycetes *in vitro*, including economically important genera such as *Fusarium*, *Rhizoctania* and
259 *Pythium*, and are therefore receiving increasing interest from a biocontrol perspective [88-91].
260 Chitinases are thought to contribute to the *in vivo* antifungal activity demonstrated by the broad-
261 spectrum biocontrol strain *Streptomyces lydicus* WYEC108 which is the active ingredient in the
262 commercially-available biocontrol agent Actinovate®. Purified chitinase from this species was able
263 to lyse the cell walls of various phytopathogenic fungi, including several species of *Pythium* which
264 can cause root rot in a variety of cereal crops [75]. Finally, transgenic expression of the *S. griseus*
265 chitinase-encoding gene *chiC* conferred an increased level of resistance to the blast fungus
266 *Magnaporthe grisea* on rice plants, suggesting that *Streptomyces* species may also represent an
267 important genetic resource [92].
268
269

270 3.4 Direct inhibition by Volatile Organic Compounds

271 In addition to soluble compounds and enzymes, many *Streptomyces* are prolific producers of
272 Volatile Organic Compounds (VOCs) [93]. These are characteristically small compounds with low
273 molecular weights and high vapour pressures, meaning that they can easily diffuse through water
274 and gas-filled pores in soil [41,94]. Strains can produce complex and diverse mixtures of VOCs that
275 have a diverse range of functions, many of which are only just beginning to be understood [95].
276 Several VOCs have been identified that have antimicrobial activities against phytopathogenic
277 species, for example, profiling of *Streptomyces* strains isolated from a soil suppressive to *R. solani*,
278 revealed that a range of VOCs had potent antifungal activity against the pathogen *in vitro* and
279 additionally resulted in an increased plant root and shoot growth [81,82,93]. Other studies have also
280 isolated streptomycete VOCs active against *R. solani in vitro*, in addition to species of *Fusarium* and
281 *Aspergillus* [68,73]. Such studies introduce the possibility that VOCs could be applied as biofumigants
282 to suppress the growth of pathogenic species and may also have significant impacts on soil-borne
283 pathogens when produced by *Streptomyces* species growing in the rhizosphere. However, more
284 studies are needed to verify that these compounds are both produced *in vivo* in the plant root system
285 and effective under natural conditions.

286 3.5 Antihelmintic compounds

287 In addition to antimicrobials, *Streptomyces* are also known to produce potent anthelmintic
288 compounds. This includes the compound avermectin, produced by *Streptomyces avermitilis*, which
289 can cause extensive mortality to nematode populations *in vivo* [96,97]. Cereal cyst nematodes
290 parasitise host plants by forming root cysts in which they tap into the nutrients present in the plant
291 vascular system; as a result they can cause extensive damage to wheat and maize crops and are
292 prevalent in the majority of the cereal growing regions of the world [98,99]. A small number of studies
293 have documented *Streptomyces* species that can control populations of cereal cyst nematodes [100-
294 102]. Given the enormous variety of natural products produced by *Streptomyces* strains and the fact
295 that, in soil, they are likely to encounter and compete with a diverse population of nematode species,
296 a greater number of such compounds may be discovered.

297 3.6 Indirect inhibition of phytopathogens of cereal crops

298 In addition to direct inhibition via the production of antagonistic compounds, *Streptomyces* can
299 also inhibit plant pathogens indirectly. The simplest way in which this can occur is via competitive
300 exclusion, whereby strains take up niche space and resources, therefore preventing pathogens from
301 colonizing [20,103]. This is not mutually exclusive from direct antagonism since antimicrobials may
302 be produced as a byproduct of interference competition over the resources provided via plant root
303 exudates or organic matter in the soil. However, a further mechanism by which *Streptomyces* can
304 indirectly provide protection to their plant host is through the activation of host resistance pathways
305 [20,104,105]. In this case, *Streptomyces* strains are recognized as mildly intrusive by the host plant,
306 which leads to the activation of phytohormone defense signaling pathways, including those
307 producing jasmonic acid (JA) and ethylene (ET), as well as the salicylic acid (SA) dependent signaling
308 pathway which can lead to systemic acquired resistance (SAR) to plant pathogens in distal parts of
309 the plant [106,107]. The activation of these pathways by plant-associated microbes is known as
310 induced systemic resistance (ISR) and acts to prime the plant immune system to deal with future
311 pathogenic attack more efficiently [107].

312
313 Endophytic *Streptomyces* strains isolated from healthy wheat tissue have been shown to trigger
314 ISR against the phytopathogenic bacterium *Erwinia carotovora* as well as the fungus *Fusarium*
315 *oxysporum* in *A. thaliana* plants; root infection by streptomycetes in the absence of the pathogen led to
316 low levels of gene expression in defence signaling pathways [108]. Expression significantly increased
317 upon pathogenic attack and was more rapid and greater in plants that had been pre-treated with
318 *Streptomyces* versus untreated controls, suggesting an absence of priming in the latter treatment [108].

319 Different streptomycetes activated ISR via either the JA/ET pathway or the SAR pathway, likely
320 through a combination of excreted secondary metabolites and physical interactions with the plant
321 roots [108]. *Streptomyces* strains isolated from sorghum stems were also suggested to inhibit the
322 infection of rice by both *M. oryzae* and *R. solani* *in vitro* via ISR pathways, since several genes involved
323 in plant defense signaling were upregulated upon colonisation by *Streptomyces* species [60].

324 4. The potential of *Streptomyces* bacteria as efficient biocontrol agents

325 The ability of *Streptomyces* species to produce plant-protective compounds such as enzymes,
326 secondary metabolites and volatile organic compounds as well as their ability to induce the plant
327 immune system to rapidly respond to pathogens suggests that they would be good candidates for
328 biocontrol agents. Biocontrol strategies can overcome some of the issues of chemical pesticides by
329 offering a low cost alternative with greater potential for long-term sustainability [109]. Since many of
330 the strains being developed as biocontrol agents, such as *Pseudomonas* and *Streptomyces* species, are
331 often naturally abundant in soils it is likely that they will cause less damage to the surrounding
332 ecosystem [20,80]. Additionally, microbes that have evolved in close symbiosis with eukaryotic
333 organisms, such as plants, may cause fewer unwanted side-effects in other eukaryotic organisms,
334 including humans [80,110]. One of the key issues of chemical pesticides is that disease-causing agents
335 can rapidly evolve resistance. Streptomycetes have the advantage that apart from being a potentially
336 co-evolving force that could engage in an arms race with pathogenic species, many also encode
337 numerous putative antimicrobial biosynthetic gene clusters (BGCs), resulting in the simultaneous
338 production of a multitude of different antibiotics with different modes of action; this could help to
339 reduce the rate at which resistance evolves [46].

340
341 Currently, there are two commercially available biocontrol products whose active ingredients
342 are live *Streptomyces* strains. They are Mycostop® (*Streptomyces griseoviridis* K61 [66]) and
343 Actinovate® (*Streptomyces lydicus* WYEC 108 [111]). The strains are purchased as dried spore
344 preparations and applied as a seed treatment, or as an irrigative growth medium additive. Both
345 *Streptomyces* species have demonstrated PGP and disease suppressive characteristics in a laboratory
346 setting [57,112]. However, their efficacy as disease suppressing agents in an agricultural scenario can
347 be inconsistent. For example, Actinovate® was found to be poor at suppressing Fusarium Wilt disease
348 (*Fusarium oxysporum* f. sp. *niveum*) of Watermelon in field trials [111] and whilst it promoted the
349 growth of Summer Squash, it was inconsistent in its ability to provide protection against powdery
350 mildew (*Podosphaera xanthii*) [113]. Another study that assessed the effectiveness of treating Barley
351 (*Hordeum vulgare*) and spring wheat (*Triticum aestivum*) with Mycostop® at the same field site over
352 five years, showed that, although there was an initial increase in yield in both crop species, the results
353 were inconsistent across the years, with a similar inconsistency in disease suppression [114]. Despite
354 Mycostop® reducing the incidence of root rot overall, it performed poorly when compared to
355 treatment with a conventionally used (although widely banned) organomercurial pesticide [114].
356 This study demonstrates that yearly abiotic variation as well as biotic variation between crop species
357 can significantly impact the potential of biocontrol treatments, but also that existing biocontrol
358 strategies do not always match, or outperform, the performance of conventional pesticide treatments.
359 The inconsistency of biocontrol strains such as Mycostop® and Actinovate® also demonstrates the
360 need for a greater understanding of the factors that influence strain competitiveness and their long-
361 term establishment within the root microbiome of different crop species.

362
363 There are numerous factors influencing the composition of soil and root-associated microbial
364 communities and that, in turn, could influence the success of biocontrol strategies. Broadly, these
365 factors can be divided into two categories. Firstly, abiotic factors such as soil type (which is defined
366 by characteristics such as nutrient levels, water content, pH and trace metals) [115,116], climate (and
367 climate change) [117] and farming practice (e.g. irrigation, fertilisation, tillage and pre-cropping
368 [118,119]) can all impact on microbial assemblages. Secondly, biotic factors include host crop species
369 [35,51,120], host genetics [51,121], root exude profiles [121,122], plant age at the time of application

370 [123,124], and competing microorganisms already present in the plant microbiome [125].
371 Additionally, many of these factors may vary significantly each growing season, adding an additional
372 layer of complexity to the factors that influence root microbiome assembly. A detailed understanding
373 of how these factors influence biocontrol success, and how to mitigate them, is a priority for the
374 development of consistently effective biocontrol strategies. Progress is beginning to be made on this
375 front, for example the Microbiome Stress project is an ambitious open access database collating and
376 analysing 16S rRNA gene amplicon sequencing data [126]. The goal is to identify how bacterial
377 communities respond to various environmental stressors, information which could be used to predict
378 the efficacy of biocontrol strategies in different environmental conditions. This will be particularly
379 important for developing robust biocontrol strategies in the face of climate change.

380 4.1 Abiotic factors influencing biocontrol efficacy

381 Numerous studies have experimented with strategies to improve the consistency and
382 effectiveness of *Streptomyces* biocontrol agents by changing abiotic factors, such as the soil
383 environment [127]. For example, an early study found that the application of wood chip-
384 polyacrylamide medium (PAM) around the plant root significantly increased the ability of
385 *Streptomyces lydicus* WYEC108 to protect potato crops from *Verticillium* wilt (caused by *Verticillium*
386 *dahlia*) [128]. By pre-inoculating the PAM medium with *S. lydicus* WYEC108 spores, the strain was
387 able to germinate and establish mycelia with reduced competition from the surrounding soil
388 microbiota. Application of the pre-inoculated medium led to a reduced level of pathogen infection,
389 as *V. dahlia* had to traverse the wood chip-PAM mixture colonised by antibiotic-producing *S. lydicus*
390 before invading the plant [128]. Similarly, another study showed that pre-inoculating soil with *S.*
391 *analatus* S07, a strain originally isolated from an *Heterodera filipjevi* nematode cyst, significantly
392 reduced the infection of wheat roots with this nematode in a field trial [102]. In order to give the
393 *Streptomyces* strain an advantage within the soil environment, an established pure culture was added
394 to ground wheat grain; this was then incubated at the strains optimal temperature, before being
395 applied to the soil in field plots [102]. The efficacy of disease control by *S. analatus* S07 was shown to
396 match that of an established nematicide, avermectin, which is significant given the damage
397 avermectin can cause to the wider ecosystem [102,129]. Such studies suggest that reducing abiotic
398 stress on the biocontrol strain, by helping it become pre-established in the soil, can improve the
399 efficacy of biocontrol strategies.

400

401 Apart from strain inoculation, a wide range of agricultural practices are thought to influence the
402 composition and establishment of species within the plant root microbiome, including irrigation
403 [118], tillage [119] and different cropping practices [130]. Agro-chemicals such as pesticides and
404 fertilisers are also known to influence the composition and functioning of the plant root and soil
405 microbiome, in ways that can help to protect against crop disease [131,132]. For example, ammonia
406 fumigation has been shown to suppress *Fusarium* wilt disease in Banana (*Musa acuminata Cavendish*)
407 and also leads to a shift in the composition of the microbial community in the surrounding soil, with
408 a significant reduction in the abundance of *Fusarium* species [132]. Other studies have suggested that,
409 when organic fertiliser is applied in combination with biocontrol strains, the extent of disease
410 suppression can be further enhanced. For example, suppression of the disease-causing bacterium
411 *Ralstonia solanacearum* by *Streptomyces rochei* is significantly increased when applied in combination
412 with organic fertiliser [133]. It is thought that adding a biocontrol strain to organic fertiliser prior to
413 treatment generates a more favourable soil environment for the strain, with more nutrients available
414 to support growth, increasing root colonisation and biocontrol efficacy [134]. This strategy is known
415 as bio-organic fertiliser application and is widely reported as an effective method of enhancing
416 disease suppression [131,135,136].

417

418 There are numerous other examples of chemical additives that are being trialed to augment
419 disease suppression in agricultural systems. For example the addition of chemical factors known to
420 promote antibiotic production in *Pseudomonas* (e.g. glucose and zinc) have been shown to increase

421 biocontrol efficacy [137]. This implies that factors known to increase antibiotic biosynthesis in
422 *Streptomyces* (for example N-acetylglucosamine, rare earth metals like scandium or siderophores
423 [138] and some plant phytohormones [46]) could, where practical, be used as an additive in
424 streptomycete biocontrol formulations to maximise disease suppression. Conversely, some chemical
425 additives have been demonstrated to be detrimental to the biocontrol efficacy of *Bacillus* species *in*
426 *vitro*, for example pesticides that contain heavy metals such as copper and zinc, and a number of
427 fungicides and herbicidal compounds [139]. Despite this observation, biocontrol strain *Streptomyces*
428 sp. A6 was found to be highly tolerant to a number of commonly used fungicidal compounds, and
429 simultaneous application of the strain with these fungicides resulted in more effective *Fusarium* wilt
430 control in pigeon pea (*Cajanus cajan*) and a 50% lower dose of fungicide was needed for effective crop
431 protection [140]. This demonstrates that combining chemical and biological pest control methods can
432 increase biocontrol efficacy, while simultaneously decreasing the required dose of chemical
433 pesticides. Whilst together these studies imply that farming practices could be optimised to maximise
434 disease suppression, comprehensive research into this is still lacking. Such research is complex, as it
435 is likely that the best approach will depend upon the pathogen of concern, as well as the relevant
436 climatic and edaphic conditions.

437 4.2 Optimising biocontrol delivery systems involving *Streptomyces*

438 Various methods are available for delivering biocontrol strains to crops and could further
439 influence the consistency of biocontrol strategies. Products like Actinovate® and Mycostop® come
440 as dried formulations containing spores and mycelia; these can either be suspended in liquid and
441 sprayed onto crops (foliar spraying), folded into the soil prior to sowing (soil inoculation) or be used
442 as a seed coating [141,142]. Foliar spraying approaches often seem attractive, particularly in
443 developed countries where equipment for spraying is already available. However, microbial
444 suspensions can damage or clog machinery by settling out of solution, and stresses caused by passage
445 through spraying apparatus (such as heat stress or shearing forces) can decrease biocontrol strain
446 viability [143]. Foliar spray is also typically used for microbial inoculants designed to counter foliar
447 diseases [144], and so may be less apt for controlling root-diseases like wheat take-all fungus. Soil
448 inoculation is another recommended mode of application, typically used if biocontrol strains are
449 particularly vulnerable to desiccation [144]. As discussed previously, methods like bio-organic
450 fertiliser application [131,133,135,136] and strain pre-establishment [102] can increase biocontrol
451 success when using this method. Often however, these strategies will add to the expense and
452 complexity of applying disease suppressive measures, and the strategies used to augment biocontrol
453 success can have unknown or even conflicting effects by altering the soil chemistry and microbiome
454 composition [119,132].

455

456 Techniques that directly inoculate the plant microbiome with biocontrol strains, circumvent
457 issues of soil-survivability measures, as the strain does not pass through an environmental medium
458 prior to root colonisation. Examples of this include methods that apply biocontrol agents directly
459 onto the plants root, such as fluid drill inoculation and root transplant dip. Both methods allow
460 biocontrol strains to colonise roots in a controlled scenario; for root dip, roots of plant seedlings are
461 incubated in a liquid cell suspension before transfer to the field [144] and in fluid drill methods seeds
462 are allowed to pre-germinate within a gel containing the biocontrol strain [144,145]. In some cases,
463 root dip has been shown to increase root colonisation by streptomycetes compared to soil inoculation
464 [55], and this method has successfully been used to apply strains that can protect crops from diseases
465 like *Fusarium* wilt [146]. However, pre-germinating plants and manually inoculating the roots is
466 labour-intensive compared to purchasing pre-coated seeds and also requires large quantities of
467 bacterial inoculum to be grown for this purpose [142]. Fluid drill methods have also been shown to
468 increase colonisation of plant roots by inoculated bacterial strains and a limited number of studies
469 show that this can result in efficient disease suppression [147,148]. However, there is little work
470 investigating the ecological impact of fluid drill gel application.

471

472 As mentioned, plants can also be colonised by coating the seed in a formulation of biocontrol
473 strain spores or cells. Seed coatings use a variety of methods to adhere biocontrol strains to the seed
474 surface. For example, seeds can be immersed in a microbial suspension and dried before germination
475 (bio-priming) [149], or a liquid cell suspension or an adhesive is used to coat the seed in bacterial cells
476 (called film coating) [142]. Seed coating technologies can effectively deliver biocontrol strains directly
477 to the soil immediately surrounding a germinating seed and the rhizosphere [142,144] and there are
478 numerous examples where seed coating approaches have proven effective at suppressing disease in
479 both field and laboratory experiments [149-153]. This includes numerous studies showing that seed
480 coatings are an effective delivery method for *Streptomyces* biocontrol strains [55,154-156], to cereal
481 crops like maize [69] and wheat [70]. While seed treatment is an effective inoculation method,
482 practical issues like shelf-life and storage conditions remain an issue in many cases [142,157].
483 However, certain spore preparations of streptomycetes have been suggested to have a greater
484 potential for long-term viability [158].

485 4.3 Exploiting plant recruitment mechanisms to improve biocontrol agents

486 In addition to enhancing the competitiveness of strains when applied to seeds and soil, it is
487 possible that the mechanisms that enable plants to selectively recruit certain microbial species from
488 the soil could be exploited to improve the efficacy of biocontrol strains [127,159,160]. As mentioned,
489 plants exude approximately 20-40% of photosynthetically fixed carbon out of their roots into the
490 surrounding soil [27,161]. This exudate contains a whole range of compounds including those with
491 low molecular weights such as ions, amino acids, sugars and phenolics, as well as high molecular
492 weight compounds such as mucilage, other polysaccharides and proteins [37,161-164]. The release of
493 exudates into soil results in a large increase in microbial abundance and activity in the region of soil
494 directly surrounding the roots; this is known as the "rhizosphere effect" and occurs because many
495 microbes are attracted to the carbon-rich nutrients exuded from the roots [27,37]. However, exudates
496 could also act as a filtering mechanism, enabling plants to selectively enrich for specific microbial
497 species with particular metabolic capabilities [37]. This hypothesis is supported by experiments that
498 have profiled the root exudates of *Arabidopsis thaliana* and found that certain groups of exudate
499 compound correlate with the abundances of particular bacterial taxa [38,123,163]. For example,
500 various phenolic compounds have been suggested to act as specific substrates or signaling molecules
501 for particular microbial species, since they positively correlate with the abundances of specific genera,
502 including *Streptomyces* bacteria [38,123,163,165]. Stable isotope probing experiments, that track ¹³C
503 isotopes from plant metabolites to bacterial RNA, DNA or proteins, have also revealed that different
504 microbial taxa are actively metabolising the root exudates of different plant host species, presumably
505 due to differences in exudate composition [35,161,166]. In addition to host plant species, root
506 exudation can also be altered by abiotic and biotic factors. For example, several studies on barley and
507 *Arabidopsis* plants, have indicated that root exudate profiles change in response to foliar and soil-
508 borne pathogens which, in turn, leads to changes in the rhizosphere and endosphere bacterial
509 community composition [167-169].

510
511 In addition to changes in abundance, root exudates may also alter the functionality of the root
512 microbiome to the benefit of the host plant, by altering microbial gene expression [123]. Increasing
513 amounts of phenolic-related compounds are exuded by *A. thaliana* roots at later developmental stages
514 and these have been shown to correlate with an increased number of microbial transcripts related to
515 antimicrobial production, including streptomycin produced by *Streptomyces* species, independent of
516 changes to bacterial abundance [123]. These antagonistic molecules may be beneficial to the plant at
517 later developmental stages as it could encourage the suppression of pathogenic species or priming of
518 the plant immune system, providing the host with protection against infection at the flowering stage
519 [123]. Several plant root exudate compounds have also been shown to modulate the production of
520 antimicrobials by *Streptomyces* species *in vitro*, including the plant phytohormones, salicylic acid,
521 jasmonic acid and indole-3 acetic acid (IAA) [170,171].

522

523 Correlations between root exudate composition, microbial community structure and
524 microbiome functionality open the exciting opportunity to tap into these chemical interactions in a
525 way that enables improvements to crop productivity and health. For example, it may be possible to
526 engineer plants that produce certain types of root exudate, that in turn improve the colonisation
527 potential and efficacy of beneficial species and biocontrol agents such as *Streptomyces* species. Indeed
528 mutant lines of *Arabidopsis* that have been engineered to have altered root exudation profiles have
529 been shown to recruit different types of bacterial species, including greater numbers of beneficial
530 plant-growth-promoting rhizobacteria [121,172,173]. Thus, it may be possible to introduce similar
531 changes into cereal crops through breeding or genetic modification. However, there is still a huge
532 knowledge gap regarding which compounds act as signals and nutrients for bacteria of interest. Such
533 cues are only known in detail for a small number of plant-microbe symbioses, such as the role of
534 flavonoids in legume- rhizobia interactions [164]. The vast majority of other systems are not so well-
535 defined. Tools such as stable isotope probing [161,174], metabolomics [162], dual RNA sequencing
536 [175,176] and imaging mass spectrometry [177-179] are beginning to shed light on these interactions
537 and may enable a more detailed understanding of plant-microbe interactions in the future.

538 5. Conclusions and perspectives

539 In summary, the use of microorganisms to suppress plant disease and increase crop productivity
540 is gaining increasing interest as a sustainable alternative to chemical approaches to suppress crop
541 disease. *Streptomyces* species have a long history of coevolution with plants and other organisms and,
542 as a result, have evolved a plethora of secondary metabolites and enzymes that function to interact
543 with host organisms and inhibit competitors. Many of these molecules can provide significant
544 benefits to plants, by promoting plant growth and reducing the incidence of plant disease. These
545 characteristics, along with the resilience of this genus to environmental stressors, suggests that they
546 could be extremely useful as biocontrol agents. However, as highlighted in this review, a highly
547 complex, interconnected network of factors can influence the efficacy of biocontrol in the field.
548 Research into these factors is lacking but should be made a priority in order to enable the wide-spread
549 application of highly effective biocontrol agents to cereal crops globally. Optimising the mode of
550 delivery of biocontrol strains, for example by decreasing abiotic and biotic stressors, has shown some
551 success in assisting soil and root establishment by these strains and for increasing the potency of
552 biocontrol. However, other factors that affect plant microbiome establishment, such as agricultural
553 practices, remain less well-studied, despite the fact that biocontrol optimisation is likely to be farm-
554 specific. It is possible that we may be able to exploit pre-existing signals between plants and microbes
555 to increase the colonisation potential of desirable strains but in most cases these specific signals
556 remain to be identified. For the future development of more consistent biocontrol strategies the most
557 successful approach is likely to be combinatorial, considering delivery mechanisms, formulation
558 additives, agricultural practices and the specific details of plant-microbe interactions.

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