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Review

Biological Guardians: Unveiling Microbial Solutions to Combat *Cannabis sativa* Fungal Pathogens

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Abstract: *Cannabis* (*Cannabis sativa* L.) is one of the earliest cultivated crops and is valued for its medicinal compounds, food, fibre, and bioactive secondary metabolites. The rapid expansion of the cannabis industry has surpassed the development of production system knowledge. The scientific community currently focuses on optimising agronomic and environmental factors to enhance cannabis yield and quality. However, cultivators face significant challenges from severe pathogens, with limited effective control options. The principal diseases include root rot, wilt, bud rot, powdery mildew, cannabis stunt disease, and microorganisms that reduce post-harvest quality. Sustainable management strategies involve utilising clean planting stocks, modifying environmental conditions, implementing sanitation, applying fungal and bacterial biological control agents, and drawing on decades of research on other crops. Plant–microbe interactions can promote growth and regulate secondary metabolite production. This review examines the recent literature on pathogen management in indoor cannabis production using biocontrol agents. Specific morphological, biochemical, and agronomic characteristics hinder the implementation of biological control strategies for cannabis. Subsequent investigations should focus on elucidating the plant–microbe interactions essential for optimising the effectiveness of biological control methodologies in cannabis cultivation systems.

Keywords: endophytes; *Cannabis sativa*; phytocannabinoids; fungal pathogen biocontrol; induced systemic resistance

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1. Introduction

Cannabis sativa L. (Hemp), an annual and dioecious plant belonging to the Cannabaceae family, encompasses the following two significant crop species cultivated globally: cannabis (marijuana), valued for its medicinal and psychotropic properties, and hemp, utilised for fibre and oil seed production [1–4]. Globally, hemp cultivation serves both agricultural and industrial purposes [5]. This versatile crop finds applications in numerous sectors, including the production of medicinal substances, fabric goods, renewable fuels, building supplies, paper products, and materials for thermal insulation [5,6]. Hemp and cannabis contain a broad range of other cannabinoids, terpenes, and phenolic compounds [7]. The

plant is rich in substances of pharmaceutical interest, notably phytocannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD), which exhibit various psychotropic effects [2,5,7–10].

In comparison to other domesticated plant species, scientific knowledge regarding cannabis production remains limited, primarily due to the illicit status of marijuana, which has directed researchers' focus towards distinguishing marijuana from hemp for law enforcement purposes. Over the past two decades, there has been a significant increase in scientific publications on cannabis, coinciding with legislative relaxation in several countries, attributable to its substantial economic value [8,11,12]. Medicinal and recreational marijuana are cultivated both outdoors and indoors, whereas hemp is predominantly grown outdoors [11,13]. The cultivation of cannabis and its cannabinoid yield are subject to various environmental and biological influences. Abiotic factors, including photoperiod, ambient temperature, soil pH levels, and nutrient availability, significantly impact plant development [14]. Additionally, biotic elements such as pathogenic microorganisms, insect infestations, and predator interactions play crucial roles in shaping cannabis growth and cannabinoid synthesis [15]. The expansion of hemp cultivation faces challenges including seed quality and pressure from weeds, insects, and diseases [7]. Both cropping systems require improvements in cultivation practices and fungal disease management [11].

The expansion of *C. sativa* cultivation has been linked to a rise in the occurrence and intensity of fungal infections, including new pathologies such as vascular wilt, root and crown rot, damping-off, powdery mildew, head blight, and bud rot [1–4,10]. These are caused by various fungi, including *Fusarium*, *Botrytis*, *Diaporthe*, *Pythium*, *Sclerotinia*, and *Sclerotium* [1–4,10]. These fungal diseases present considerable challenges to worldwide agriculture and food security [1–3,5,15]. Synthetic fungicides are the primary control method in most crops, targeting various cellular processes such as respiration, cytoskeleton assembly, osmoregulation, sterols, and amino acid biosynthesis [12]. Nevertheless, the application of fungicides has led to the development of resistant fungal strains due to metabolic detoxification, increased activity of efflux membrane transporters, and alterations in target sites [12]. Furthermore, fungicide application to cannabis is heavily regulated in numerous countries owing to health and environmental concerns [12]. Although chemical fungicides can effectively control these diseases, they also present risks including environmental pollution, fungal resistance, and reduced populations of beneficial soil microbes [2,11,16].

The endophytic/epiphytic microbiome influences the plant phenotype, determines its phytochemical profile, and mediates functional trait expression, irrespective of the colonisation mode [5,9,15,17,18]. These microbes are vital in the production of plant growth promoters (PGPs), which facilitate plant and root expansion whilst bolstering plant resistance mechanisms [2,9,11,15]. The defensive strategy known as antagonism manifests in two forms—direct and indirect. Direct antagonism employs protective substances such as antibiotics, antibacterial toxins (including peptides and proteinaceous compounds), bacteriocins, hydrolytic enzymes, volatile organic compounds (VOCs), siderophores, and cyclic lipopeptides. Indirect antagonism, on the other hand, activates the plant host's defensive mechanisms, specifically induced systemic resistance (ISR) and systemic acquired resistance (SAR), to combat rival organisms [9,15]. Considering these attributes, biological control agents are regarded as a sustainable substitute for chemical interventions in cannabis production. Nevertheless, it is crucial to recognise that the capacity of these agents to suppress diseases through direct or indirect antagonistic interactions within the cannabis plant has not been specifically investigated [2,11,15].

Researchers have employed diverse experimental techniques to investigate and elucidate beneficial relationships between plants and soil bacteria [19]. These methodologies

encompass various approaches, with some examining plant alterations, whereas others focus on analysing beneficial plant growth-promoting microbes' physiological and biochemical aspects (PGPM). In this context, we have presented a synthesis of several contemporary studies that have explored the interactions between cannabis pathogens and PGPM to identify efficacious biocontrol agents.

2. Biocontrol by PGPM: A Mechanistic Point of View

Various biological (bacterial and fungal) strategies have been implemented to mitigate plant fungal diseases, thereby reducing dependence on synthetic agrochemicals for vegetable production [20,21]. PGPMs are advocated as an ecological and economical disease management approach and a sustainable biological alternative to agrochemicals thus conserving natural resources [22]. PGPMs are extensively utilised in sustainable agriculture to enhance biodiversity, improve crop yields, and restrict pathogen infection [20,21]. These free-living soil microorganisms effectively colonise plant roots and form endophytic bacterial populations, demonstrating their adaptability to specific ecological niches [20,21]. They are recognized for optimising plant development and performance through both direct and indirect processes [20–22].

Microorganisms produce a diverse array of low-molecular-weight compounds known as secondary metabolites, which are not crucial for survival under typical conditions. These substances encompass a wide range of compounds, including "antibiotics, toxins, and various peptides such as ribosomal peptides (RPs) and non-ribosomal peptides (NRPs). Additionally, they comprise chitinase, hydrogen cyanide (HCN), polyketides (PKs), enzymes that detoxify reactive oxygen species (ROS), antioxidant enzymes, and volatile organic compounds (VOCs)". The list includes alkaloids, polyenes, phenazines, lipopeptides, amino sugars, macrolactone, aminoglycosides, indole-3-acetic acid (IAA), and iron-chelating siderophores [18,23–25]. These secondary metabolites exhibit remarkable structural diversity and serve various functions beyond the essential survival needs. These compounds compete for ecological niches or nutrients (carbon/energy sources) and secrete organic acids, phosphatases, and other enzymes to break down complex phosphorus compounds [20,21,26–29]. These mechanisms are widely recognized as direct biocontrol strategies (Figure 1).

Immunity is triggered when PRRs or R-proteins detect microbe-, pathogen-, or damage-associated molecular patterns (MAMPs, PAMPs, DAMPs) or intracellular effectors, respectively, leading to PTI/ETI [30–35]. PRRs, which include receptor-like kinases (RLKs) and receptor-like proteins (RLPs), initiate the production of signalling molecules such as ROS, Ca^{2+}, RNS (NO), G-protein, and SA. These molecules contribute to SAR in biotrophic pathogen–plant interactions. Alternatively, JA or ET are involved in ISR during beneficial plant–microbe interactions [30,31]. This process activates NPR1, modifies transcription factors (TFs) and MAPK cascades and regulates defence gene expression. The latter includes the production of antimicrobial compounds, PR, and secondary metabolites [26,31,32,36]. Additionally, it promotes callose deposition, suberin and lignin formation [20,21,31], programmed cell death (PCD), and hypersensitive response (HR), ultimately enhancing the plant's resistance to pathogens [20,21,31].

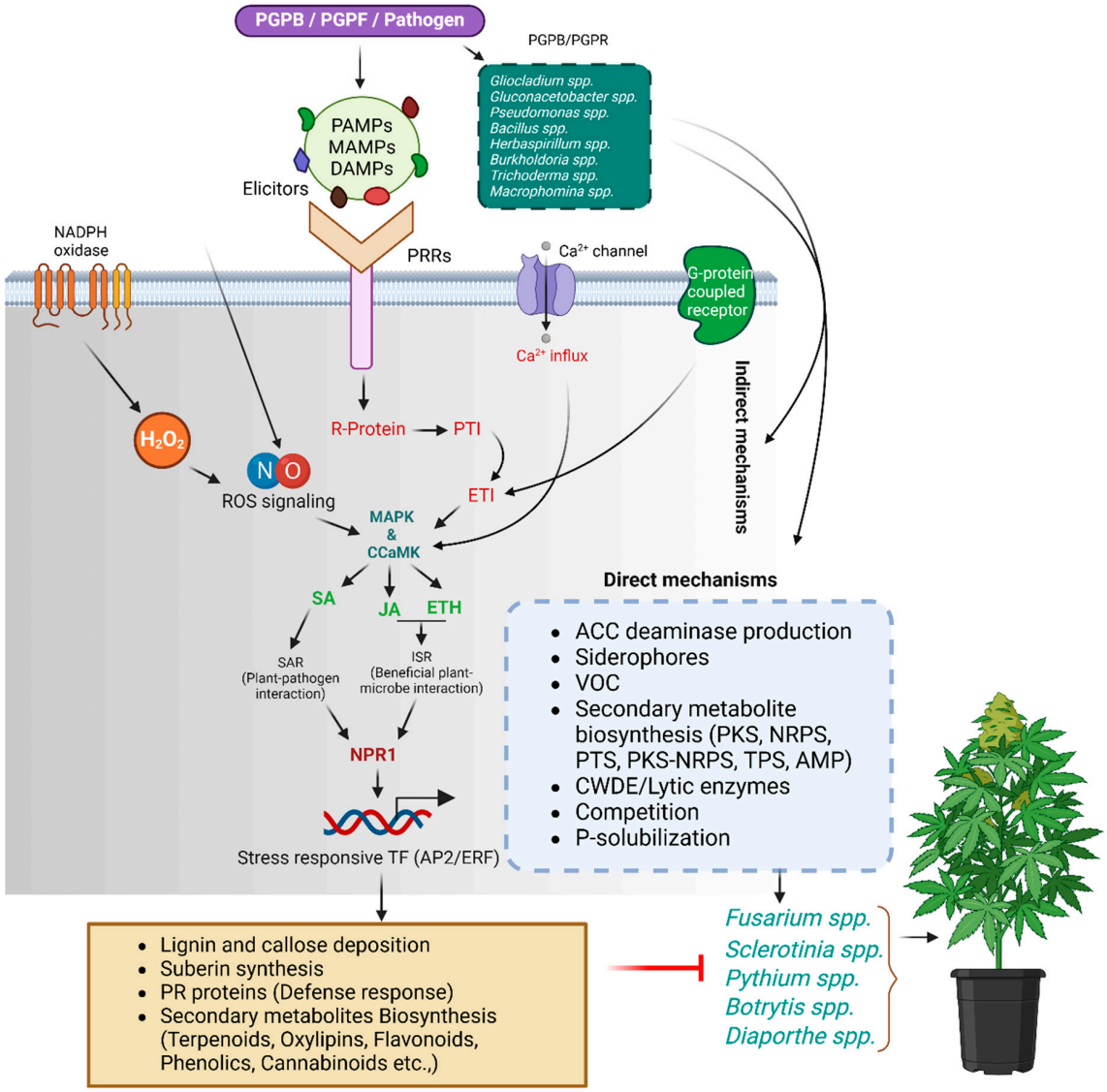

Figure 1. The diagram illustrates both direct and indirect pathways of microbe-associated biocontrol for *Cannabis sativa* pathogens. In the indirect route, pattern recognition receptors (PRRs) detect microbe-, pathogen-, or damage-associated molecular patterns (MAMPs, PAMPs, DAMPs) from PGPR/PGPF/Pathogens, whilst R-proteins recognise intracellular effectors. This recognition triggers PAMP-triggered immunity (PTI) or effector-triggered immunity (ETI). These immune responses initiate calcium influx (Ca^{2+}) via G-protein-coupled membrane receptors and Ca^{2+} channels, generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), and produce salicylic acid (SA) to activate SAR, as well as jasmonic acid (JA) or ethylene (ETH) to activate ISR. Additionally, they stimulate mitogen-activated protein kinase (MAPK) cascades, calcium- and calmodulin-dependent protein kinase (CCaMK), and NPR1. These processes lead to the transcriptional regulation of defence genes, including pathogenesis-related (PR) proteins, lignin and callose deposition, suberin synthesis, and the production of secondary metabolites (terpenoids, oxylipins, flavonoids, phenolics, cannabinoids). In the direct mechanism, PGPR/PGPF function as bioinoculants, enhancing plant growth and modulating gene expression in secondary metabolite biosynthesis pathways. This includes the production of hormones, siderophores, AMP, VOC, PKS, NRPS, PTS, hybrid PKS–NRPS, PTS, enzymes for nutrient solubilisation, and ethylene dissociation enzymes (ACC deaminase). MAMP, microbe-associated molecular pattern; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PGPR, plant growth-promoting rhizobacteria; PGPF, plant growth-promoting fungi; PKS, polyketide synthases; AMP, antimicrobial peptides; NRPS, non-ribosomal peptide synthetases; TPS, terpene synthases; PTS, prenyltransferases; NPR1, nonexpressor of pathogenesis-related genes 1; SAR, systematic acquired resistance; ISR, induced systemic resistance.

3. Microbial Biocontrol of Major Cannabis Pathogens: Recent Updates

3.1. Biocontrol of Fusarium Species in Cannabis sativa

The genus *Fusarium* encompasses numerous species capable of inflicting considerable financial harm on *Cannabis sativa* crops through plant illnesses and mycotoxin deposits. Researchers have identified sixteen *Fusarium* species linked to cannabis cultivation, which are grouped into the following six complexes: *Fusarium oxysporum*, *F. solani*, *F. incarnatum-equiseti*, *F. sambucinum*, *F. tricinctum*, and *F. fujikuroi*. Many of these species are known to act as opportunistic pathogens in humans and animals. The mycotoxins generated by the *Fusarium* species exhibit a broad spectrum of chemical compositions, ranging from basic to intricately complex molecules [37].

The *Fusarium* spp. are known to induce vascular wilts and can also cause various plant diseases, including seedling damping-off, rotting of different plant parts, and blights affecting heads and grains. These fungi typically produce asexual spores, with some strains capable of forming sexual ascospores. The nature and quantity of asexual spores differ among species. Additionally, certain *Fusarium* spp. generate durable chlamydospores. *Fusarium* wilts are globally significant, with disease severity enhanced in warm climates and soil conditions. These fungi reside in the soil and survive between crop cycles as mycelia in plant remnants or as micro- or macroconidia or chlamydospores. The high spore production of *Fusarium* can result in indefinite soil contamination. *Fusarium* wilt infection occurs when germinating spores or mycelia infiltrate healthy plant root tips, either through wounds or at the origins of lateral roots. The mycelium grows between cells in the root cortex and enters the xylem vessels via pits, generating upward microconidia. These microconidia become lodged in the xylem vessels, germinate, and produce mycelia that penetrate vessel walls, leading to further microconidia formation and upward spread. The mycelium also expands laterally to adjacent vessels through pits. The obstruction of vessels by fungi, tylosis, gels, and gums impedes water uptake, resulting in stomatal closure, leaf wilting, and, ultimately, plant death. Subsequently, the fungus invades the plant extensively and produces spores prolifically [1,11,37] (Table 1).

Fusarium oxysporum, a common fungal pathogen, induces wilt disease in both nursery and field settings, leading to significant financial losses [38]. The dual culture technique was employed to assess in vitro antagonistic activity. A consortium was formed by combining strains of *Gluconacetobacter diazotrophicus*, *Herbaspirillum seropedicae*, and *Burkholderia ambifaria*, which demonstrated over 50% inhibition. This consortium was tested for its planta antagonistic properties during the pre-and post-emergence phases. The results showed that the consortium effectively countered *Fusarium* infection at both stages [38].

The process of endophytic colonisation by *Herbaspirillum* spp. commences with the attachment of bacteria to root surfaces, subsequently progressing to colonisation at sites where the lateral roots emerge and the epidermal discontinuities occur. This colonisation involves various bacterial components, including lipopolysaccharide (LPS), exopolysaccharide (EPS), adhesins, and the type three secretion system (T3SS), but does not necessitate cell wall-degrading enzymes. Following this initial stage, the bacteria inhabit intercellular spaces and proliferate to the xylem and aerial portions of the host plant. The plant recognises these bacteria as non-pathogenic, eliciting induced systemic resistance (ISR) against pathogens. This response activates phytohormone signalling cascades that influence plant physiology. The interaction between *Herbaspirillum* spp. and their plant hosts can result in enhanced plant growth and biocontrol effects [39]. *Burkholderia* spp. promote plant growth by secreting allelochemicals, producing antibiotics and siderophores, and demonstrating biocontrol against phytopathogens through nutrient and space competition, antifungal metabolite production, and ISR induction via the JA/ET pathway [40].

Gluconacetobacter demonstrates a well-established symbiotic relationship with plants, facilitating atmospheric nitrogen fixation and promoting growth through various mechanisms, including N2 fixation, phytohormone synthesis, phosphorus and zinc solubilisation, biocontrol, and induced systemic resistance (ISR) [41,42]. Its inoculation enhances plant defences by restricting pathogens via structural barriers such as lignin, suberin, and callose deposition [42].

A recent investigation revealed that applying "Stargus® (*Bacillus amyloliquefaciens*), Lalstop® (*Gliocladium catenulatum*, Prestop®), RootShield® Plus WP (*Trichoderma harzianum* and *Trichoderma virens*), and Asperello® (*Trichoderma asperellum*)" to cannabis cuttings before inoculation with *F. oxysporum* substantially decreased the average disease severity by 30 to 56.3% ($p < 0.05$). Endophytic colonisation was observed within 2 and 7 days after applying Rootshield, Asperello, and Lalstop. The effectiveness of *G. catenulatum* in combating *Fusarium* is believed to stem from various mechanisms, including the production of enzymes that degrade cell walls, mycoparasitism, and improved colonisation. Similarly, *Trichoderma* spp. exert biocontrol through direct pathogen interactions, enzyme secretion, antibiosis, mycoparasitism, resource competition, and plant interactions [1,43].

Several studies have elucidated the diverse biological protective mechanisms of *Bacillus*, *Trichoderma*, and *Gliocladium* spp. These species directly suppress plant pathogens by releasing antagonistic metabolites, including antimicrobial peptides, competition for nutrients and space, mycoparasitism, resistance induction, secretion of secondary metabolites, lytic and hydrolysing enzymes, antibiotics, and colonisation. Indirectly, they induce plant defence responses via nitrogen-containing compounds, polyketides (PKs), terpenoids, NRPS, volatile organic compounds (VOCs), and induced systemic resistance (ISR). Furthermore, the exogenous *Bacillus* strains can enhance specific indigenous soil microbes with direct biocontrol activity or synergistic effects with other beneficial agents to suppress plant diseases [44–46]. In vitro antagonism assays have demonstrated that these three species inhibit *Fusarium* growth [1,11].

3.2. Biocontrol of Botrytis Species in Cannabis sativa

The fungal pathogen *Botrytis cinerea* is known to infect more than 1000 plant species, including ornamental greenhouse crops and vegetables. In *Cannabis sativa* L., it causes various diseases such as "bud rot, leaf blight, and seedling damping-off". Cannabis inflorescences are particularly susceptible to rapid deterioration when exposed to optimal humidity levels and moderate temperatures during greenhouse cultivation [47]. Initial symptoms manifest as water-soaked spots that progress to brown and necrotic lesions, potentially resulting in leaf blight, blossom blight, and postharvest fruit rot. The disease can occur both preharvest and postharvest, occasionally causing losses of up to 30%. The epidemiology of *Botrytis cinerea* is significantly influenced by plant debris, including dead and dying tissues [47] (Table 1).

B. cinerea, a necrotrophic pathogen, predominantly colonises and flourishes in ageing or compromised plant tissues, leading to cellular death. The widespread conidia of *B. cinerea*, stemming from infected plant material, penetrates the host via natural apertures and lesions [48]. The infection process of *B. cinerea* commences with a short, symptomless biotrophic phase during the initial stages of disease progression, subsequently transitioning to an intense necrotrophic phase as the plant organs age or deteriorate [48]. *B. cinerea*, a necrotrophic pathogen, cannot obtain nutrients from living plant tissues. Instead, it must first breach the host's outer layer before triggering cell death and breaking down plant cells to support its growth [11]—this necrotrophic phase results in the disintegration of infected tissues [48]. When airborne conidia land on an appropriate host, they need external sources of nutrients and moisture on the plant's surface to germinate, develop appressoria, and

begin infection [11]. This requirement makes germinating conidia vulnerable to various factors in the phyllosphere, including competition from other microorganisms, inhibitory compounds, and interference from other microbial entities [11]. Conidia produced abundantly in these tissues are disseminated by wind, water, rain, and infected pollen. Botrytis may also arise from seed-borne infections [47]. Sclerotia production during unfavourable conditions facilitates pathogen survival and provides inoculum during the growing season [47]. Cannabis workers, especially those on outdoor farms, face occupational health risks from aerial conidia, including allergic sensitisation and hypersensitivity pneumonitis. B. cinerea is the most common fungus in these environments, comprising 34% of airborne fungal samples [1,12]. The current studies have illuminated the multifaceted nature of *B. cinerea* infection, highlighting various elements that influence the severity and advancement of the disease [48].

The gammaproteobacteria *Pseudomonas protegens* (Pf-5) functions as an efficacious biocontrol agent, inhibiting various crop pathogens, including *Botrytis cinerea*, the aetiological agent of grey mould in *Cannabis sativa* [3,11]. Research has demonstrated that the antibiotics pyoluteorin (PLT) and 2,4-diacetylphloroglucinol (DAPG), synthesised through a PKS–NRPS hybrid pathway, are essential for Pf-5's biocontrol efficacy. To investigate the influence of PLT and DAPG on *B. cinerea* control in the *C. sativa* phyllosphere, researchers generated two Pf-5 mutants by eliminating the *pltD* or *phlA* genes, which are critical for PLT and DAPG production, utilising a two-step allelic exchange methodology. Experiments conducted in growth chambers revealed that the ΔpltD and ΔphlA mutants reduced grey mould disease by only 10% and 19%, respectively, whereas the wild type achieved a 40% reduction. These findings underscore the significance of PLT and DAPG biosynthesis for optimal Pf-5 antagonism against *B. cinerea* [3].

A subsequent experiment examined the effect of four bacterial strains on cannabis seedlings subsequently challenged with *B. cinerea* [12]. The research employed two *Pseudomonas* (LBUM223, WCS417r) and two *Bacillus* (LBUM279, LBUM979) isolates. Scientists analysed the expression patterns of eight defence-related genes linked to either the SA-mediated SAR pathway (PR1, PR2, PR5, NPR1) or the JA/ET-mediated ISR pathway (LOX5, ERF1, HEL, PAL). The investigation included four SA-mediated markers encoding cannabis homologues of PR proteins (PR1, PR2, and PR5), as well as the transcriptional co-activator NPR1 [12].

Without stress, NPR1, a crucial regulator of plant defence signalling and transcription co-activator, forms oligomers in the cytoplasm. When pathogens attack, changes induced by salicylic acid and shifts in redox state cause NPR1 to disassemble. The resulting NPR1 monomers move to the nucleus, where they engage TGA transcription factors to activate salicylic acid-inducible *PR* genes [12].

ERF1, an AP2/ERF transcription factor, is one of three potential JA/ET-mediated markers that show increased expression in cannabis leaves infected with *B. cinerea*. Another gene that exhibits significant upregulation in infected leaves encodes a hevein-like HEL protein (AMP). The third markedly upregulated marker, PAL, likely codes for phenylalanine ammonia-lyase. This enzyme initiates the biosynthesis of phenylpropanoids, producing flavonoid pigments, antimicrobial phytoalexins, and lignin. Interestingly, the *LOX5* gene, which encodes a 9S lipoxygenase, was the sole JA/ET pathway marker to show decreased expression following infection. LOX enzymes are responsible for catalysing the dioxygenation of polyunsaturated fatty acids, resulting in the production of oxylipins [12].

Biocontrol strains of *Bacillus* and *Pseudomonas* and their secondary metabolites contribute to plant health through antibiosis, plant growth promotion, and the induction of systemic resistance. These taxonomic groups often demonstrate direct antimicrobial effects, elicit induced systemic resistance within their host plants, and vie for nutritional resources

and physical space. They also induce systemic resistance through volatile substances. Lipopeptides, polyketides, and terpenoid volatiles from these genera can activate the JA, SA, and ET pathways, stimulating the expression of pathogenesis-related proteins. *Bacillus* and *Pseudomonas* produce chitinases, glucanases, and proteases that suppress fungal diseases [1,31–33]. Recent studies indicate that *Trichoderma* and *Gliocladium* spp. inhibit *B. cinerea* growth through similar mechanisms [1] (Table 1).

3.3. Biocontrol of Diaporthe Species in Cannabis sativa

Diaporthe spp., isolated from various hosts, are globally distributed and recognised as plant pathogens, endophytes, or saprobes. Their phomopsis-like asexual state is among numerous plant species' most prevalent endophytic fungi. Natural product chemists have extensively investigated these organisms, elucidating the production of unique low-molecular-weight metabolites with diverse bioactivities, including antibacterial, anticancer, antifungal, antimalarial, antiviral, cytotoxic, and herbicidal properties. *Diaporthe* spp. are plant pathogens that induce economically significant diseases in numerous plants, including "root and fruit rot, dieback, cankers, leaf spots, blights, decay, and wilt" in *Cannabis sativa* [49]. Research has shown that specific biological control agents, including species of *Bacillus*, *Trichoderma*, and *Gliocladium*, can effectively inhibit *Diaporthe* spp. in *Cannabis sativa* [1,11] (Table 1).

Table 1. Different bacterial and Fungal Biocontrol agents with their mode of action against prominent fungal pathogens in *Cannabis sativa*.

SL No.	Variety	Disease Agent	Biocontrol Agent	Mode of Action	References
1.	Seeds (Colombia Landrace, Mango Elite plus)	*Fusarium oxysporum*	*Bacillus* strain	• *Bacilli* maintain high seed germination, inhibit *Fusarium* mycelial growth and solubilize phosphorus, improving its bioavailability for plants.	[15]
2.	Cutting of strain (Moby Dick' or 'White Rhino)	*Fusarium oxysporum Pythium* spp.	*Bacillus subtilis B. amyloliquefaciens*, *Gliocladium catenulatum*, *Trichoderma harzianum*, *T. virens*, *T. asperellum*	• Enzyme production inhibits pathogen growth. • Mycoparasitic activity suppresses pathogens, and improved root colonisation combats *Fusarium* and *Pythium*.	[43]
3.	Not mentioned	*Botrytis cinerea*	*Pseudomonas protegens* Pf-5	• *P. protegens* Pf-5 produces antimicrobial metabolites with antifungal activities. • The PLT and DAPG biosynthesis pathways are essential for antagonistic activity. • Deletion of *pltD* or *phlA* genes results in reduced antibiotic production.	[3]
4.	Seeds (*C. sativa* L. cultivar Anka)	*Botrytis cinerea*	*B. velezensis* LBUM279, *B. subtilis* LBUM979 and *P. synxantha* LBUM223, *P. simiae* WCS417r	• SA-mediated markers activate *cannabis* defence genes against pathogens, including *ERF1*, *HEL*, *PAL*, *PR1*, and *PR2* are upregulated.	[12]

Table 1. *Cont.*

SL No.	Variety	Disease Agent	Biocontrol Agent	Mode of Action	References
5.	Leaves (*Cannabis sativa*)	*Agroathelia rolfsii*	*Bacillus velezensis*	• *Bacillus* can produce volatile organic including isobutyric acid, trans-2-octenal and tiglic acid and exhibited inhibitory effects on *Agroathelia rolfsii*.	[5]
6.	Seeds (*C. sativa* L. cultivar Anka)	*Botrytis cinerea*	*Bacillus velezensis* LBUM279, FZB42, LBUM1082, *Bacillus subtilis* LBUM979, *P. synxantha* LBUM223, and *P. protegens*Pf-5	• *Bacillus* spp. and *Pseudomonas* spp. inhibit fungal pathogens via antibiosis. • Preventive treatments allow time for biocontrol agents to establish populations. • Direct antagonism with beneficial bacteria controls cannabis fungal diseases in plants.	[11]
7.	Finola	*Fusarium oxysporum*	*Azospirillum brasilense*, *Gluconacetobacter diazotrophicus*, *Herbaspirillum seropedicae* and *Burkholderia ambifaria*	• Both direct antagonism of the pathogen and enhancement of plant growth and development contribute to effective disease control.	[38]
8.	D. Bubba Hash Plant, White Rhino, Island Honey, Pink Kush	*Botrytis cinerea* *Sclerotinia sclerotiorum* *Diaporthe eres* *Fusarium graminearum*	*Bacillus* spp., *Trichoderma asperellum* and *Gliocladium catenulatum*	• *Trichoderma*, *Gliocladium*, and *Bacillus* suppress pathogen growth through competition. • Biocontrol agents are established before harvest to reduce disease symptoms. • *Bacillus* inhibits *Botrytis* growth, forming a zone of inhibition.	[1]

Note: PLT, Pyoluteorin; DAPG, 2,4-diacetylphloroglucinol; ERF, Ethylene Responsive Factor; PAL, Phenylalanine ammonia-lyase; PR1 and PR2, pathogenesis-related gene 1 and pathogenesis-related gene 2; phlA, 2,4-DAPG hydrolase A; pltD, pyoluteorin biosynthetic gene D.

3.4. Biocontrol of Pythium Species in Cannabis sativa

Pythium spp. induce pre- and post-emergence damping-off in the seed or seedling stages, causing decay in seeds before and in seedlings after soil emergence. Mature plants may also exhibit root rot symptoms. *Pythium* predominantly affects younger tissues that lack secondary thickening thus targeting seeds, seedlings, and young roots. Post-emergence damping-off in seedlings manifests as reduced growth, water-soaking, wilting, discolouration, and root rot. In mature plants, the symptoms include water-soaked roots, stem lesions at the soil line, stunted growth, and root discolouration. *Pythium* spp. is responsible for damping-off, root rot, collar rot, soft rot, and stem rot in nurseries, greenhouses, and agricultural fields. Although they are no longer classified as true fungi, *Pythium* spp. possess mycelium, sporangia, zoospores, and oospore stages [50] (Table 1).

Pythium propagules persist in soil through (1) constitutive dormancy of oospores, necessitating internal stimulation for germination, and (2) the formation of secondary resting propagules when nutrients are scarce. Propagules rapidly germinate and penetrate host plants in response to root exudates and other stimuli, complicating their control efforts. Sporangia infect plants directly via hyphal tubes or by producing zoospores under high moisture conditions. *Pythium* also survives saprophytically, as the mycelium in the soil competes with other soil colonisers. *Pythium* survives necrotrophically in seeds,

seedlings, and young roots, resulting in plant mortality. Disease development involves carbohydrate-active enzymes (CAZymes) such as glycoside hydrolases, cellulases, pectinases, polysaccharide lyases, carbohydrate esterases, and proteases, which facilitate plant cell wall penetration and colonisation [50,51].

Root rot, crown rot, and damping-off caused by *Pythium* species affect crops globally. Cannabis exhibits susceptibility to *P. myriotylum*, *P. dissotocum*, and *P. aphanidermatum*, particularly under conditions of extreme heat, resulting in rapid wilting and substantial losses [43]. A recent study demonstrated that *Bacillus amyloliquefaciens*, *Gliocladium catenulatum*, *Trichoderma harzianum*, *Trichoderma virens*, and *Trichoderma asperellum* could confer protection against *Pythium* spp. through pre-emptive colonisation [43].

3.5. Biocontrol of Sclerotinia Species in Cannabis sativa

Diseases caused by *Sclerotinia sclerotiorum* are challenging to control and result in significant losses in horticultural crops globally due to several factors including the following: (i) crop specialisation leading to pathogen accumulation in the soil, (ii) absence of a safe, efficient soil fumigation method, and (iii) the pathogen's life cycle, involving resilient sclerotia. Environmental factors affecting sclerotia survival and ascospore dissemination are crucial because plants are primarily infected by airborne ascospores from sclerotia germination. The inefficacy of synthetic agents against *S. sclerotiorum* has led to an interest in biological control, focusing on microorganisms with mycoparasitic activity to reduce sclerotia in the soil. This review examines the utilisation of antagonistic fungi and bacteria to control *S. sclerotiorum* and discusses the suppressive effects of organic amendments. Control is difficult because of the persistence of sclerotia and airborne ascospore production [52].

Upon plant surface colonisation, the fungus secretes pathogenic factors, including pectinases, cellulases, beta-1,3-glucanases, xylanases, and glycosidases, which facilitate plant penetration and tissue maceration. Pectinases, which are crucial because pectins are primary cell wall components, are produced optimally at pH 4–5. Infection also leads to oxalic acid secretion and pH reduction, causing bud rot in *Cannabis sativa* [1,11,15,53] (Table 1).

In vitro antagonism tests have revealed that *Bacillus* spp., *Trichoderma asperellum*, and *Gliocladium catenulatum* effectively inhibit *S. sclerotiorum* colony growth, inducing diverse defence mechanisms [1,44–46].

3.6. Biocontrol of Sclerotium Species in Cannabis sativa

Sclerotial rot, collar rot, stem rot, and southern blight, caused by the fungal pathogen *Sclerotium* (Athelia) *rolfsii*, are significant diseases. The sexual state of *Athelia rolfsii* is rare in comparison to the asexual state of *Sclerotium rolfsii* [54]. This necrotrophic, soilborne fungus, prevalent in warm temperate, tropical, and subtropical regions, primarily causes stem rot in plants [54]. *Athelia rolfsii* targets plant stems but can affect leaves, flowers, fruits, petioles, and roots under favourable conditions, producing cell-degrading enzymes [54]. It is the causative agent of southern blight in industrial hemps, resulting in substantial economic losses [5]. The disease affects hemp roots and stems at all growth stages, from seedling to harvest [5]. The pathogen forms mycelia on the plant surface within 2 to 10 days [54], producing toxic organic acids and penetrating the stem, causing tissue necrosis [54]. Symptoms include abundant white mycelia and small brown sclerotia [54]. The mycelium produces enzymes that degrade the outer cell layer of the host, leading to tissue decay and further mycelium and sclerotia formation [54]. Pathogen sclerotia can undergo hyphal or eruptive germination under various environmental conditions [54], rendering it highly resilient and difficult to control because of its long-term soil survival [5].

Industrial hemp leaf tissue yielded an endophytic bacterium, SEC-024A (*Bacillus velezensis*), which demonstrated potent antagonism towards *A. rolfsii*. This strain achieved an impressive 80.5% plate inhibition rate and 74.1% pot control effect. The bacterium's genome encompasses clusters for secondary metabolite production and genes that enhance plant growth, colonisation, and pathogen resistance. SEC-024A's primary fungistatic agents include volatile organic compounds (VOCs) such as "linoleic, stearic, α-linoleic, palmitic, myristic, and arachidic acids, as well as rhamnose". Furthermore, it produces antimicrobial substances, precisely polyketide compounds (Macrolactin A), non-ribosomal peptides (Rhizoxin), isobutyric acid, tiglic acid, trans-2-octenal, and 2-decanone. These compounds demonstrate significant inhibitory effects against *A. rolfsii* [5] (Table 1).

Studies have revealed that three species of endophytic fungi exhibit inhibitory capabilities against *A. rolfsii* mycelial growth. Specifically, Trichoderma lixii CSS1, Lasiodiplodia brasiliensis WS-TS-A1, and Macrophomina phaseolina SS1R1 demonstrated growth reduction rates of 65%, 67%, and 20%, respectively. These fungal species synthesise extracellular enzymes, including β-1,3 glucanase and chitinase. Notably, *L. brasiliensis* WS-TS-A1 exhibited the highest enzymatic activity amongst the fungal endophytes, resulting in the most efficacious sclerotium suppression. This suggests that these fungi hold potential for development as biocontrol agents to combat *S. rolfsii* [2]. It is important to note that both *Lasiodiplodia* spp. and *Macrophomina* spp. possess the capacity to colonise diverse plant species, functioning in dual roles as endophytes and pathogens [54].

Certain endophytic fungi generate various antifungal substances, including 6PAP (2-hydroxypropyl-5,6-n-pentyl-2H-pyran-2-one) and DHMB (2,3-dihydro-5-hydroxy-2-methyl-4H-1-benzopyran-4-one), which show efficacy against *S. rolfsii*. The mycoparasitic and endophytic species *L. brasiliensis* WS-TS-A1 has shown the capacity to shield hosts from plant pathogens. Interestingly, *M. phaseolina*, a well-known plant pathogen belonging to the Hypocreales family, has been found to offer advantages to plants, indicating the possibility of additional plant-beneficial activities. Moreover, endophytic fungi release indole-like compounds such as diacetamide and sesquiterpene, which have lethal effects on other microorganisms that are harmful to their host plants [2,54] (Table 1).

4. Conclusions and Future Prospects

The research findings corroborate the efficacy of currently approved biocontrol products for managing diverse fungal ailments in cannabis. Nonetheless, additional studies are imperative to assess these products' performance on a more extensive scale, across prolonged periods, and in varied cultivation environments. Moreover, it is crucial to investigate the effects of repeated applications during later growth stages and the viability of microbial agents within the substrate. Notably, several biocontrol agents have exhibited the capacity to endophytically inhabit cannabis stem tissues. Further exploration is warranted to determine their persistence within cannabis structures, as well as their ability to enhance growth and inhibit pathogens. The implications of these findings could inform the formulation of microbial consortia by combining these strains with additional beneficial microorganisms to assess their mutual compatibility and complementary effects. Further research is required to investigate the molecular mechanisms of pathogen sensitivity to diverse metabolites, the implications for pathogen dissemination and virulence, and the alterations in cannabis immune responses and microbiota following bacterial colonisation. Elucidating the biochemical basis of inflorescence susceptibility to pathogens, host gene expression changes, and microbiome composition will facilitate the management of destructive bud pathogens. Evaluating its efficacy in natural environments through field studies is imperative. These trials should also focus on enhancing VOC synthesis and improving fungicidal activity.

The transition of biological control agents (BCAs) from controlled experiments to open crop fields presents significant challenges due to environmental influences. The efficacy of these agents is dependent upon several factors, including the plant species and genotype, as well as the ecological fitness and genetic variability of pathogens. Notably, the performance of BCAs exhibits variation across different species. Environmental factors significantly influence the capacity of BCAs to target pathogens. Formulation development necessitates considering several aspects, including active constituents, carrier materials, auxiliary substances, production expenditure, and compatibility with agricultural implements. Pest management solutions based on nanotechnology offer an efficient and environmentally sound approach to biopesticide application. Nano-biopesticides have the potential to revolutionise global agriculture by improving formulation, delivery strategies, manufacturing scale-up, regulatory adherence, and cost-effectiveness, thereby protecting crops for sustainable agriculture. Understanding the biosynthetic mechanisms of antimicrobial compounds in BCAs is crucial for improving their effectiveness. To enhance the production of secondary metabolites in BCAs and potentially create new antimicrobial substances, metabolic engineering is necessary. This method offers innovative approaches to enhance BCA effectiveness, selectivity, and environmental compatibility [26]. Various techniques, including plasmid engineering, RNA interference, and CRISPR-based genome editing, have demonstrated potential in enhancing strains [26]. Further research is required in areas such as the development of advanced BCAs and the utilisation of biotechnology in conjunction with "omics" approaches and next-generation sequencing (NGS) to improve biocontrol efficacy in *Cannabis sativa*.

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