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PATHOGEN PROFILE

Genetic and molecular landscapes of the generalist phytopathogen *Botrytis cinerea*

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Abstract

Botrytis cinerea Pers. Fr. (teleomorph: *Botryotinia fuckeliana*) is a necrotrophic fungal pathogen that attacks a wide range of plants. This updated pathogen profile explores the extensive genetic diversity of *B. cinerea*, highlights the progress in genome sequencing, and provides current knowledge of genetic and molecular mechanisms employed by the fungus to attack its hosts. In addition, we also discuss recent innovative strategies to combat *B. cinerea*.

Taxonomy: Kingdom: Fungi, phylum: Ascomycota, subphylum: Pezizomycotina, class: Leotiomycetes, order: Helotiales, family: Sclerotiniaceae, genus: *Botrytis*, species: *cinerea*.

Host range: *B. cinerea* infects almost all of the plant groups (angiosperms, gymnosperms, pteridophytes, and bryophytes). To date, 1606 plant species have been identified as hosts of *B. cinerea*.

Genetic diversity: This polyphagous necrotroph has extensive genetic diversity at all population levels shaped by climate, geography, and plant host variation.

Pathogenicity: Genetic architecture of virulence and host specificity is polygenic using multiple weapons to target hosts, including secretory proteins, complex signal transduction pathways, metabolites, and mobile small RNA.

Disease control strategies: Efforts to control *B. cinerea*, being a high-diversity generalist pathogen, are complicated. However, integrated disease management strategies that combine cultural practices, chemical and biological controls, and the use of appropriate crop varieties will lessen yield losses. Recently, studies conducted worldwide have explored the potential of small RNA as an efficient and environmentally friendly approach for combating grey mould. However, additional research is necessary, especially on risk assessment and regulatory frameworks, to fully harness the potential of this technology.

KEYWORDS
cross-kingdom sRNA, genetic diversity, grey mould, necrotrophy

1 | INTRODUCTION

Botrytis cinerea, commonly known as grey mould, is a necrotrophic polyphagous pathogen belonging to the phylum Ascomycota. *B. cinerea* has a remarkable ability to infect a wide range of plant species, similar to *Sclerotinia sclerotiorum*, which causes white mould disease in diverse plant species (Derbyshire et al., 2022). The pathogen is highly successful due to its prolific reproductive capacity, remarkable survival mechanisms, and multifaceted infection strategies. This combination of characteristics contributes to its global distribution and has listed it amongst the top 10 most economically devastating phytopathogens (Dean et al., 2012).

The life cycle of *B. cinerea* involves both asexual (*B. cinerea*) and sexual (*Botryotinia fuckeliana*) stages. Initially, taxonomic ambiguity existed between the *Botryotinia* spp. and *Botrytis* spp.; however, they were demonstrated to represent the different stages of a single fungal species (Gregory, 1949). During the asexual cycle, a mature conidiophore releases conidial spores, which are a major means of disease transmission and primary inoculum. Additionally, *B. cinerea* forms melanized resting structures known as sclerotia during winter or under unfavourable conditions. Sclerotia, diseased stubbles, and infected seeds can serve as secondary sources of inoculum (Fillinger & Elad, 2016). Under favourable environmental conditions, the microconidia fertilize sclerotia and form apothecia that undergo meiosis and produce sexual ascospores (Amselem et al., 2011). However, the sexual cycle is rarely identified in natural environments. Furthermore, the development of sclerotia, conidia, and other developmental stages, as well as the ability to infect hosts, is heavily influenced by factors such as light intensity, light quality, pH, and biological clock. For instance, during continuous darkness and at lower temperatures, the fungus redirects its resources toward sclerotia production, while in light most genotypes tend to produce conidia (reviewed in Hua et al., 2018; Schumacher, 2017).

To invade and suppress host defences, the fungus uses sophisticated penetration, infection, and colonization strategies. Infection is primarily initiated by conidia that attach to and germinate on the plant surface. *B. cinerea* can penetrate host tissues through natural openings such as stomata or wounds. Moreover, to penetrate the host tissue directly, germinating conidia form germ tubes that differentiate into appressoria and infection cushions, specialized structures for host penetration (Dinh et al., 2011; Veloso & van Kan, 2018). During the early stage of infection, *B. cinerea* secretes an arsenal of toxins, cell wall-degrading enzymes, and cell death-inducing proteins along with modulating host apoptotic machinery to facilitate local host cell death (Bi et al., 2023; Govrin & Levine, 2000; Shlezinger et al., 2011). This is the crucial stage in *B. cinerea*–host interaction, as the balance between *B. cinerea* and the plant's cell death pathway determines whether the infection will be halted or progress to the next phase. After successfully establishing inside the host, the fungus expands to surrounding cells. This vigorous growth of *B. cinerea* is followed by fungal sporulation, production of new conidia, and further disease development. These processes enable *B. cinerea* to cause pre- and postharvest losses by infecting all parts of its hosts, with organ choice dependent on environmental conditions (Hua et al., 2018; Lecompte et al., 2017; Williamson et al., 2007).

B. cinerea has become a model for studying necrotrophic and host generalist mechanisms due its significant impact on global agriculture, broad host range, ease of handling, and ability to infect model plants. Earlier a *B. cinerea* pathogen profile was published by Williamson et al. (2007) who focused on the epidemiology and genes/pathways identified in this pathogen. In this updated profile, we extend this to highlight recent advancements in genetics and molecular biology. We discuss the extensive genetic diversity observed in *B. cinerea* populations, the progress in genome sequencing efforts, and newly identified molecular arsenals of *B. cinerea* (especially after 2007) and propose potential avenues for further research.

2 | VAST HOST RANGE OF *B. CINEREA* ACROSS THE PLANT KINGDOM

In 2016, researchers compiled an extensive list of 1565 plant species known to be infected by *B. cinerea*, demonstrating its remarkable adaptability to infect a diverse range of plant species, including both phanerogams and cryptogams (Elad et al., 2016). To extend this analysis to 2023, we used a combination of the search terms "*Botrytis cinerea*" and "first report" in Google Scholar and PubMed to identify reports of *B. cinerea* on new hosts. From this survey, we identified 41 new plant species (including 21 new genera) as hosts of this pathogen (Aktaruzzaman et al., 2017, 2022; Azevedo et al., 2020; Cao et al., 2020; Chen et al., 2017, 2019, 2020, 2021; Dumin et al., 2020; Fekrikohan et al., 2022; Feres et al., 2018; Freitas & Pereira, 2022; Fu et al., 2018; Garibaldi et al., 2016, 2017, 2022; Guo et al., 2021; Isidoro-Gonzales et al., 2023; Jeon et al., 2020; Jin et al., 2022; Li et al., 2016, 2022, 2023; Liu et al., 2017; Paula et al., 2018; Plaza et al., 2018; Reboledo et al., 2021; Silva, Corrêa, et al., 2016; Silva, Lisboa, et al., 2016; Song et al., 2017; Wang, Jin, et al., 2017; Wang, Jing, et al., 2017; Wang, Yang, & Bai, 2017; Xue et al., 2016, 2017; Yang, Chen, et al., 2020; Yang et al., 2020a, 2020b; You et al., 2020).

In total, *B. cinerea* infects 616 genera (Figure 1). Eudicots were the majority with 447 genera, while 128 genera were monocots. Furthermore, *B. cinerea* infects 6 genera of basal angiosperms, 20 genera of gymnosperms, 15 genera of pteridophytes, and 1 genus of bryophytes. Using the Angiosperm Phylogeny Group classification system, we showed that *B. cinerea* has evidence for viable hosts in 46 out of 66 orders (not including pteridophytes and bryophytes) (Figure 1; Table S1). It is unclear if the remaining 20 orders have not been reported as hosts because they have not been tested or because they are not infected by *B. cinerea*. Given this host range, it is likely that the actual host range of *B. cinerea* is much larger and this estimate is constrained by the ability or economical need to conduct new studies on new hosts. Identifying the mechanisms enabling infection of this host range is a key objective for studies into *B. cinerea* and plant pathology more broadly.

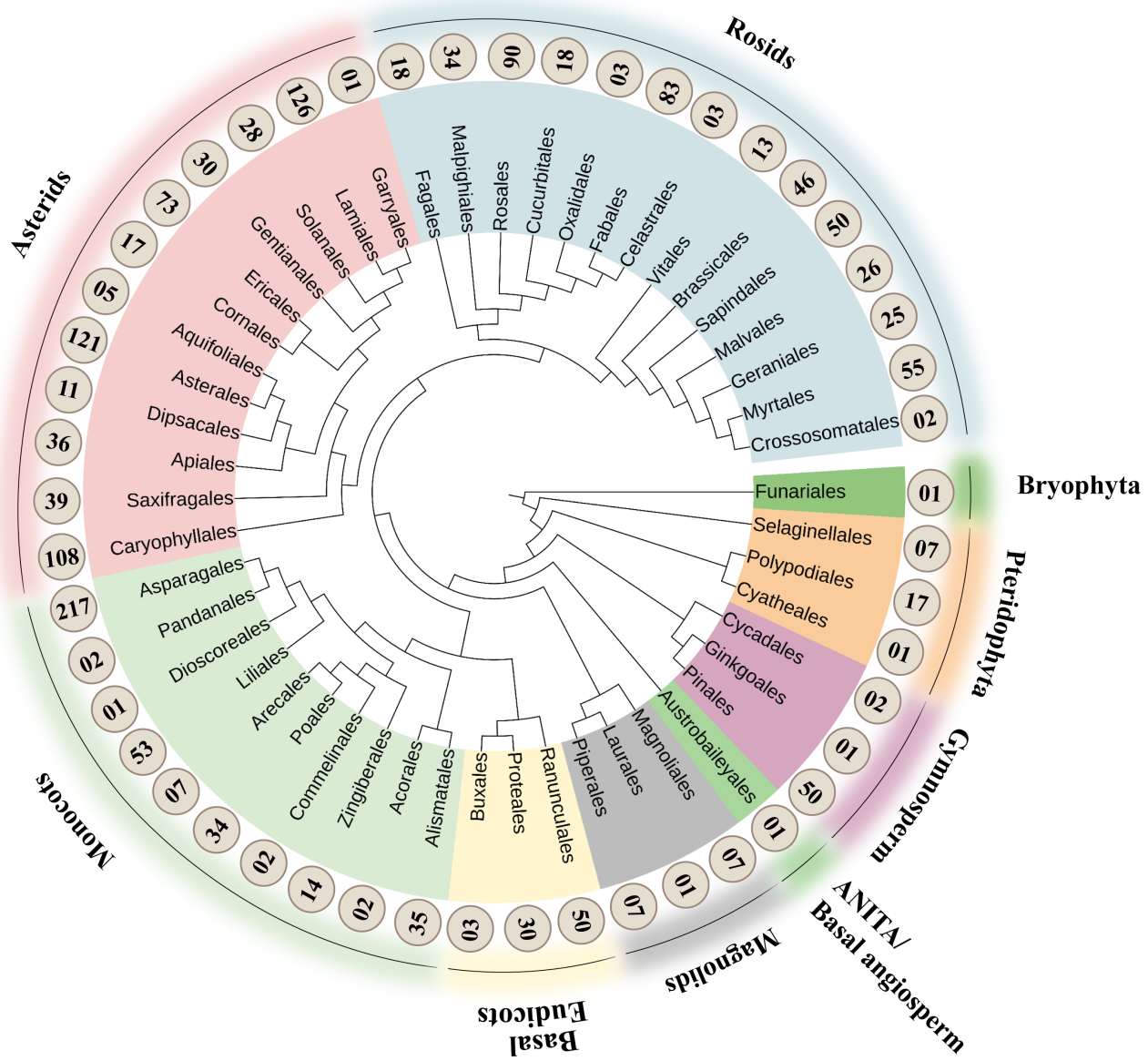

FIGURE 1 Phylogenetic tree representing the host plants of *Botrytis cinerea* across the plant kingdom. The tree shows orders from the eudicots (asterids and rosids), basal eudicots, monocots, magnolids, basal angiosperms, gymnosperms, pteridophytes, and bryophytes. The numbers at the end of the branches indicate the number of genera infected by *B. cinerea* within each respective order. The tree was derived from the Missouri Botanical Garden Angiosperm Phylogeny (http://www.mobot.org/MOBOT/research/APweb/) and visualized using iTOL (https://itol.embl.de/).

3 | GENOME SEQUENCING OF *B. CINEREA* REVEALS ITS HIGH GENETIC DIVERSITY

One potential basis for this wide host range is the extensive standing genetic variation present amongst *B. cinerea* strains. Efforts to characterize this diversity first began with a myriad of genetic markers and have started moving to whole genome analysis. Sanger sequencing provided the first genome sequences of *B. cinerea* strains B05.10 and T4, which were then updated with short-read sequencing data, yielding a prediction of approximately 14,000 protein-coding genes (Table 1) (Amselem et al., 2011; Staats & van Kan, 2012). Subsequent updates to the B05.10 genome include a nearly complete assembly obtained by combining Illumina and PacBio sequencing data with linkage and optical map data (Van Kan et al., 2017). This sequencing effort identified 18 chromosomes (named as BCIN1–BCIN18), of which 16 are core and 2 are accessory (Van Kan et al., 2017). These 18 chromosomes encompass 42.9 Mb with 11,701 complete gene models with 10 chromosomes completely sequenced from telomere to telomere (Van Kan et al., 2017). Notably, the genome size of *B. cinerea* is relatively small compared to those of other plant-pathogenic fungi, with a high gene density and many duplicated genes.

To gain a further comprehensive understanding of recombination and diversity in *B. cinerea*, genome sequencing efforts have expanded to studying additional strains (Blanco-Ulate et al., 2013;

TABLE 1 Assembly and statistics of different *Botrytis cinerea* genomes.

	Isolate					
	T4	**B05.10**	**B05.10**	**BcDW1**	**SI3**	**Vv3**
Sequencing platform	Sanger sequencing (Illumina HiSeq2000)	Sanger sequencing (Illumina HiSeq2000)	Illumina and PacBio sequencing platform supported by an optical map and linkage map	Illumina HiSeq2000	PacBio sequencing	PacBio sequencing
Host plants from where isolated	*Solanum lycopersicum*	*Vitis vinifera*	*V. vinifera*	*V. vinifera* 'Sémillon'	*S. lycopersicum* 'Moneymaker'	*V. vinifera* 'Pinot Noir'
Location	Eyragues, France	NA	NA	Napa, USA	Champagne, France	Champagne, France
Coverage	10× (>100×)	4.5× (>100×)	90×	>100×	>100×	>100×
Assembly size (Mb)	39.5 (41.6)	42.3 (41.2)	42.9	42.1	43.2	44.9
N50	562 (1710)	257 (970)	2.44 Mb	194 kb		
Gaps in the assembly	Yes	Yes	Nine chromosome ends lack telomeres	58 kb	12 chromosome ends lack telomeres (eight chromosomes lack one end and two chromosomes lack both ends)	15 chromosome ends are not sequenced
GC content (%)	43.2 (42.4)	43.1 (42.8)	42	42	42	42.2
Scaffold	118 (56)	588 (82)	128	453	NA	NA
Complete gene models	13,664	14,270	11,701	11,073	11,661	11,609
Mitochondrial genome (kb)	NA	82	NA	84	NA	NA
Accessory chromosomes	NA	NA	BCIN17 and BCIN18	BCIN17 and BCIN18	BCIN17 and BCIN18	BCIN17 and BCIN19
Reference	Amselem et al. (2011); Staats and van Kan (2012)	Amselem et al. (2011); Staats and van Kan (2012)	Van Kan et al. (2017)	Blanco-Ulate et al. (2013)	Simon et al. (2022)	Simon et al. (2022)

Simon et al., 2022) (Table 1). Comparison of the B05.05 genome with the genomes of strains Sl3 and Vv3 revealed variations in the gene content, with 36 and 197 unique genes in Sl3 and Vv3, respectively (Simon et al., 2022). These genomes also showed presence/absence variation in the accessory chromosomes. For instance, B05.10, BcDW1, and Sl3 have BCIN17 and BCIN18 accessory chromosomes, while Vv3 has BCIN19 instead of BCIN18. No accessory chromosomes were reported for the T4 strain but it remains unclear whether this is a biological result or due to technical difficulties. Beyond chromosomal presence/absence variation, a comparison of BcDW1, B05.10, and T4 genomes identified 162,000 single-nucleotide polymorphisms (SNPs) (approximately 4 SNPs/kb). Additionally, whole genome resequencing of 84 *B. cinerea* strains, including a majority from California (Atwell et al., 2015, 2018) and 32 strains from France (Mercier et al., 2021), gave a deeper view of the high level of genetic variation in this species. SNPs called using the 84 strains revealed genetic variants at every 27 bp, a high rate for phytopathogens (Atwell et al., 2018). Annotation of those SNPs and insertions/deletions suggests naturally occurring gene knockouts in more than 10% of the genes across the strain collection. Those estimates need to be refined by long-read sequencing of large and diverse strain populations as SNP and insertion/deletion calls using short-read sequencing are known to struggle with repetitive sequences and structural variants (De Coster et al., 2021).

Whole genome sequencing also showed a decay of linkage disequilibrium, suggesting extensive recombination amongst natural strains despite the paucity of reports of the sexual cycle in the wild (Atwell et al., 2018; Mercier et al., 2021). This high rate of recombination would allow rapid shuffling of alleles, further contributing to the extensive genomic diversity and the wide host range of the pathogen. However, to clearly understand this, a global sampling of *B. cinerea* strains collected from diverse hosts and organs on different continents and in different bioclimates is required. Further, high-quality genome sequencing of diverse *B. cinerea* strains will contribute to the understanding of the phenotypic and genotypic variability of the species and the occurrence of strain-dependent virulence factors.

4 | EXTENSIVE GENETIC DIVERSITY OF *B. CINEREA*

Most published efforts to characterize the genetic diversity of *B. cinerea* involved classical molecular genetic markers (transposons, microsatellites, and mating-type [MAT] locus and/or gene sequencing data used for identification or fungicide resistance diagnostics) rather than whole genome analyses. These large collections of studies provide the ability to conduct a meta-analysis of the factors influencing *B. cinerea's* extensive genetic diversity. To summarize findings of these studies, we performed a meta-analysis by compiling the publicly available data for >10,000 strains across 58 publications (Abdel Wahab, 2015; Acosta Morel et al., 2018; Albertini & Leroux, 2004; Albertini et al., 2002; Aliaga, 2013; Amiri et al., 2018; Asadollahi et al., 2013; Beever & Parkes, 1993; Ben Ahmed & Hamada, 2005; Campia, 2014; Cettul et al., 2008; Ciliberti et al., 2016; DeLong et al., 2020; Diao et al., 2019; Emilda, 2015; Esterio et al., 2011; Fan et al., 2015; Fekete et al., 2012; Fournier et al., 2005, 2013; Giraud et al., 1997; Giraud et al., 1999; Hu et al., 2018; Isenegger et al., 2008; Johnston et al., 2013; Kecskeméti et al., 2014; Kumari et al., 2014; Kuzmanovska et al., 2012; Leyronas et al., 2014; Lorenzini & Zapparoli, 2014; Ma & Michailides, 2005; Makris et al., 2022; Martinez et al., 2003; Mercier et al., 2019; Moparthi et al., 2023; Muñoz & Campos, 2013; Muñoz et al., 2002, 2016; Naegele et al., 2021; Pei et al., 2019; Polat et al., 2018; Rajaguru & Shaw, 2010; Román Ramos, 2013; Tanović et al., 2009, 2014; Testempasis et al., 2020; Toffolatti et al., 2020; Topolovec-Pintarić et al., 2004; Törün & Biyik, 2022; Vaczy et al., 2008; Vatsa-Portugal et al., 2014; Vercesi et al., 2014; Walker, 2013; Wessels et al., 2013, 2016; Zhang et al., 2018). The metadata is accessible on Dryad https://doi.org/10.5061/dryad.tmpg4f556. These strains were collected from 1990 to 2018 across 30 countries (Figure 2a). Latitude and longitude were estimated from location/province names and associated bioclimatic variables (https://worldclim.org/). Most strains were sampled between the 25th and 55th parallel North with a second smaller distribution between the 20th and 45th parallel South (Figure 2b). The host plants represent over 30 plant families, with most strains sampled on grape and strawberry, shaping the distribution toward rosids (Figure 2b). Temporally, *Botrytis* was sampled across all seasons, with autumn the most frequent season, followed by spring.

The majority of studies documented the presence or absence of boty (a gipsy retrotransposon) and flipper (a Tc1/mariner DNA transposon), allowing a global meta-analysis with 8130 strains. The transposa genotype, that is, the presence of both boty and flipper, is the most frequent, followed by the genotype with only boty. The genotypes with only the flipper transposon or the absence of both boty and flipper, vacuma, are the least prominent (Figure 2b,c). Correlations to virulence suggested that the vacuma genotype was more associated with a saprophytic lifestyle (Giraud et al., 1999; Martinez et al., 2005). Supporting this was the recent observation that gipsy retrotransposons are associated with the production of small RNAs (sRNAs) that may contribute to pathogenicity (Porquier et al., 2021). This association with sRNAs might explain the prevalence of boty and the variation in association of transposons with pathogenicity across populations (Wagih et al., 2020, Yang, Li, et al., 2020, Simon et al., 2022). While the transposa genotype is predominant across the global *B. cinerea* population, the ratios of these variants are dynamic across the past three decades, showing the potential for dynamism and fluctuation in this widespread pathogen (Figure 2c). Given the diversity in sampling regimes and known impacts of fungicide treatments on local genetic diversity, it is not clear if these changes are caused by changes in genotype frequency over time or shifts in sampling biases. This will require the development of a consistent sampling regime with local resampling over time to capture. Moreover, genomic sequencing is also showing the potential for revealing dynamic qualitative and quantitative variation in transposons across all transposon families (Simon et al., 2022).

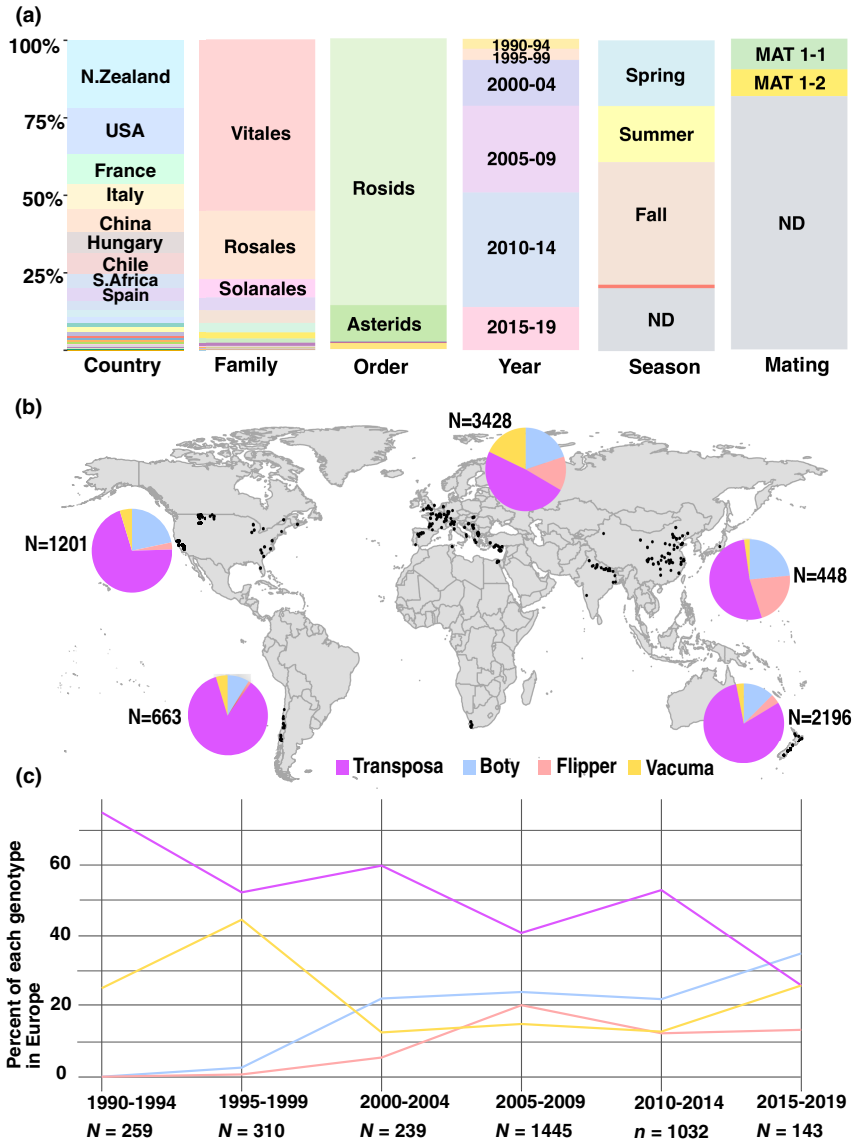

FIGURE 2 Meta-analysis of *Botrytis cinerea* strains genetics. (a) Overview of the origin of the strains by country, host families and orders, range of years they were isolated, information on season if available, and mating locus. ND stands for "not determined." (b) World map of strains for which a location was provided with pie charts representing the percentage of transposons on each continent. (c) Percentage of each transposon genotype over time in Europe.

Microsatellites are the next most common measure of genotypic diversity in *B. cinerea* populations. Microsatellites are spread across the genome with high variability at each locus, allowing population-level analyses. To assess biotic and geographic components possibly shaping the *B. cinerea* species, we created a metadataset of five microsatellites (BC1, BC3, BC6, BC7, BC10) across 845 strains. Principal component analysis revealed partitioning that might be partially shaped by geographic distance, but given the unequal sampling of host plants between regions, the relative contribution of host and geography is not fully resolvable (Figure 3a) (Diao et al., 2019; Kozhar et al., 2020; Leyronas et al., 2014; Mercier et al., 2019; Plesken et al., 2021; Walker et al., 2014). Further complicating this analysis is the identification of *B. cinerea* strains sampled from nonplant environmental sources, showing the possibility of an extensive and potentially undersampled genotypic reservoir (Bardin et al., 2018). To attempt and parse these factors, we used a linear modelling method to estimate the geographical, bioclimatic, and host patterns influencing these microsatellites in *B. cinerea* (Figure 3b). This suggested that the bioclimatic and geographic variables had a major influence, with a secondary influence of the host plants. This meta-analysis suggests that it is necessary to consider both the biotic and abiotic factors in the environment that may be driving genome variation. Given the rapidly shrinking cost of genome sequencing, global surveys of population diversity in *B. cinerea* using whole genome sequencing will be required to measure how genetic diversity is affecting the virulence and host specificity of this necrotrophic pathogen.

5 | MOLECULAR BASIS OF *B. CINEREA*'S HOST TARGETING MECHANISMS

5.1 | Insight into genetic strategies of *B. cinerea*

While variation in specialist pathogens' virulence is mainly controlled by a few large-effect molecular weapons (qualitative virulence), the genetic architecture of virulence and host specificity of generalist and necrotrophic pathogens such as *B. cinerea* is quantitative and polygenic. Current studies have suggested that the loci controlling

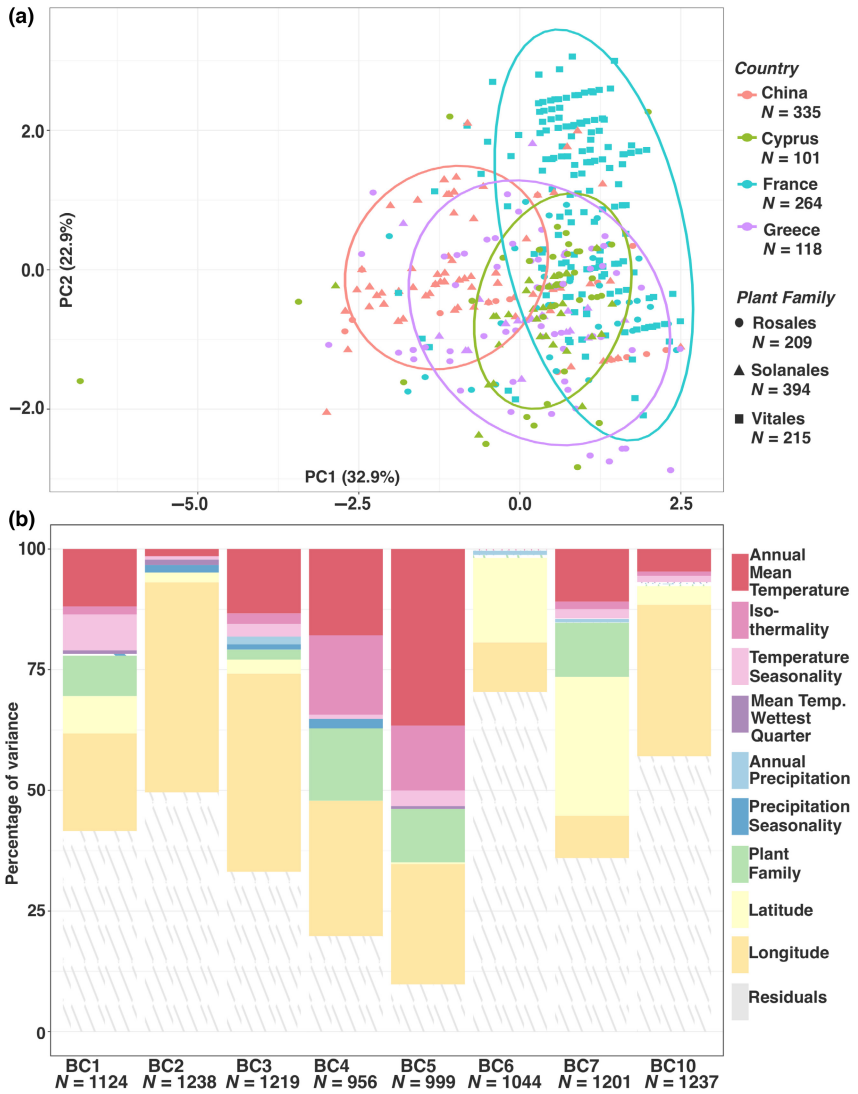

FIGURE 3 Meta-analysis of publicly available data of eight microsatellites in *Botrytis cinerea* from six countries (China, Cyprus, France, Greece, Hungary, United States) compiled from seven publications (Diao et al., 2019; Fournier et al., 2013; Hu et al., 2018; Makris et al., 2022; Naegele et al., 2021; Vaczy et al., 2008; Walker, 2013). (a) Principal component analysis of a subset of five microsatellites (BC1, BC3, BC6, BC7, BC10) for 845 strains. PC1 and PC2 together account for 54.8% of the variance in the data. (b) Linear modelling of microsatellite length is explained by latitude + longitude + host + bio1 + bio3+ bio4 + bio8 + bio12 + bio15. Bar plots represent the additive percentage of variance for each parameter. Plain colours signify the significance, while stripe patterns signify the nonsignificance of the parameter in the model.

variation in virulence may represent a significant percentage of its entire genome. One common model of variation in virulence is the two-speed genome hypothesis, where a rapidly evolving section of the genome creates the virulence variation, while a relatively slowly evolving section is responsible for other processes (Möller & Stukenbrock, 2017). Currently, there is no evidence of a two-speed genome structure in *B. cinerea* as genome scans for signatures of selection revealed a genome-wide distribution (Atwell et al., 2018; Mercier et al., 2021). Further, correlating lesion area (necrosis) with SNPs along the genomes in various genome-wide association studies showed a distributed pattern with hundreds of genes scattered along the genome (Atwell et al., 2018; Caseys et al., 2021; Soltis et al., 2019). The likely causal genes found by these approaches are equally distributed in mechanism as they are in genomic position. The candidate genes identified by genome-wide association studies showed minimal enrichment for specific pathways or gene ontologies, partly due to the low level of functional gene annotation in *B. cinerea* and other filamentous fungal pathogens. A specific mechanistic test of extensive polygenicity of *B. cinerea* came from a study that generated mutants in up to 12 known virulence factor genes. This showed predominantly quantitative effects in delayed infection and reduced lesion area on different plants (Leisen et al., 2022). Even with all 12 genes inactivated, *B. cinerea* was still able to infect hosts, demonstrating the redundancy in small-effect virulence factors that are mixed into complex cocktails to successfully infect diverse hosts.

5.2 | Insight into molecular arsenals of *B. cinerea* for virulence

The polygenic nature of *B. cinerea* virulence emphasizes the significance of understanding its full repertoire of virulence factors and signal transduction pathways. This will be crucial for developing effective strategies to combat *B. cinerea* infections and mitigate its impact on agricultural and horticultural crops. In recent years, researchers have extensively investigated *B. cinerea* genes through gene deletion or knockout studies, revealing significant impacts on pathogenicity (Bi et al., 2023; Cheung et al., 2020; Veloso & van Kan, 2018). There are diverse transformation protocols to generate defined *B. cinerea* mutants, ranging from homologous recombination

to CRISPR/Cas editing (Frandsen et al., 2008; Hahn & Scalliet, 2021; Schumacher, 2012). These methods make use of diverse vectors and delivery techniques, including *Agrobacterium tumefaciens*-mediated transformation in conidia (Rolland et al., 2003), protoplast-based transformation (Van Kan et al., 1997), and even incorporation of linear DNA into wounded sclerotia (Ish-Shalom et al., 2011).

In this section, we primarily focus on genes and pathways studied after Williamson et al. (2007) using gene deletion or knockout approaches, highlighting their functions and impact on pathogenesis. A nonexhaustive list of 116 genes having a role in pathogenicity is provided in Table S2. This list complements the online host–pathogen interaction database (http://www.phi-base.org/) and *B. cinerea* mutant database (https://bioinfo.bioger.inrae.fr/botpubmut/). We also do not focus on the arsenal of secreted proteins that control virulence as these are covered in detail by Bi et al. (2023). In brief, cell wall-degrading enzymes and nonselective toxins are major virulence factors as they are exported to degrade the host's cell wall, not only contributing to *B. cinerea*'s penetration ability but also activating the host immune response and spreading cell death (Bi et al., 2023). For instance, the secretory proteins snod-prot-like protein 1 (BcSPL1), xylanase 1 (BcXyl1), and cell death inducing 1 (BcCDI1) of *B. cinerea* have the ability to directly induce the plant hypersensitive response and cell death response by interacting with the leucine-rich repeat receptor-like kinases BAK1 and SOBIR1 (Frías et al., 2011; Yang et al., 2018; Zhu et al., 2023). In addition to these secreted proteins, *B. cinerea* uses diverse infection structures such as infection cushions to penetrate the host (Backhouse & Willetts, 1987; Dugan, 1988). Hyphal branching-related factor1 (BcHBF1) was reported for its important role in hyphal branching, infection structure formation, and sclerotia formation (Liu et al., 2019). Recently, a transcriptome analysis revealed that over 1000 genes are up-regulated in infection cushions (Choquer et al., 2021). However, the regulatory and developmental genes controlling those diverse infection structures remain largely unknown.

In the following subsections we explore the pathways that exhibit a strong influence on pathogenicity, with particular emphasis on the cyclic adenosine monophosphate (cAMP)-dependent and -independent, mitogen-activated protein kinase (MAPK), reactive oxygen species (ROS), cross-kingdom metabolic interaction, and cross-kingdom sRNA (ck-sRNA) pathways, which have been a major focus of research during this time period.

5.3 | cAMP-dependent and -independent signalling pathways

The cAMP-dependent and -independent signalling pathways are essential for growth and pathogenesis in various organisms. They are initiated by G protein-coupled receptors (GPCRs), which recognize external signals and activate heterotrimeric GTP-binding proteins (G proteins) composed of Gα, Gβ, and Gγ subunits (Brown et al., 2018; Li et al., 2007). These G proteins trigger multiple signalling cascades, including the cAMP-dependent pathway, small GTPases, and the Ca^{2+}/calcineurin-dependent pathway (El-Defrawy & Hesham, 2020; Li et al., 2007).

In *B. cinerea*, three GPCRs (BcGPR1, BcGPR3, and BcGPR5) were identified by sequence homology to *Neurospora crassa*, *Saccharomyces cerevisiae*, and *Magnaporthe grisea*, with the involvement of BcGPR3 in the cAMP signalling pathway confirmed through RNA interference (RNAi) studies (Lin et al., 2019). Further, the role of the Gα subunit of the G protein in pathogenicity was confirmed with a *BcBCG1* deletion mutant showing reduced virulence (Schumacher, Viaud, et al., 2008). BcBCG1 activates adenylate cyclase (BcBAC) and promotes cAMP production, thus activating the cAMP-dependent signalling cascades (Gronover et al., 2001). The increased cAMP levels activate protein kinases that phosphorylate downstream proteins. In *B. cinerea* this protein kinase A phosphorylation is controlled by two catalytic subunits (BcPKA1 and BcPKA2) and one regulatory subunit (BcPKAR). Deletion of *BcPKA1* and *BcPKAR* resulted in reduced virulence (Schumacher, Kokkelink, et al., 2008) (Figure 4a). Moreover, the Gα subunit is not the only trigger of BcBAC, as BcRAS2, a Ras GTPase protein, can also activate the cAMP pathway through BcBAC (Figure 4a). This was confirmed through *BcRAS2* deletion mutants, which exhibited delayed germination and reduced growth rates, which could be partially restored by exogenous cAMP (Schumacher, Kokkelink, et al., 2008). Additional investigation is required to identify the whole downstream signalling cascades involved in this interplay.

In addition to the cAMP pathway, the G proteins also interact with phospholipase C (BcPLC1) to activate the Ca^{2+}/calcineurin-dependent signalling pathway (Figure 4a). This connection was confirmed as knockdown of *BcPLC1* resulted in decreased expression of genes dependent on both BcBCG1 and calcineurin (Schumacher, Kokkelink, et al., 2008). Activated BcPLC1 induces an increase in calcium levels, leading to activation of calcineurin, which dephosphorylates and activates the transcription factor (TF) BcCRZ1. This was supported by the observation that Δ*BcCRZ1* mutants showed a similar phenotype to Δ*BcPLC1*, confirming that this TF acts downstream of calcineurin (Schumacher, de Larrinoa, & Tudzynski, 2008). Additionally, Δ*BcPLC1* and Δ*BcCRZ1* mutants showed reduced growth, conidiation, and germination, thus hampering the virulence of *B. cinerea*. Further regulation of the Ca^{2+}/calcineurin-dependent pathway was identified through the cyclophilin mutants (Sun et al., 2021). BcCYP2 inhibits calcineurin through its association with the immunosuppressive drug cyclosporine A (Figure 4a). Disruption of *BcCYP2* causes delayed conidial germination and germling development, altered conidial and sclerotial morphology, and reduced infection cushion formation, sclerotia production, and virulence (Sun et al., 2021). This *BcCYP2* mutant phenotype indicates a role of cyclophilins in pathogenicity. Together, these findings shed light on the intricate roles of the cAMP-dependent and -independent pathways and their interactions with phosphorylation- and calcium-dependent signalling pathways in fungal growth, development, and pathogenesis. Nevertheless, further research is imperative to gain a comprehensive understanding of the cross-talk between these pathways, their evolutionary origins, and their regulatory mechanisms.

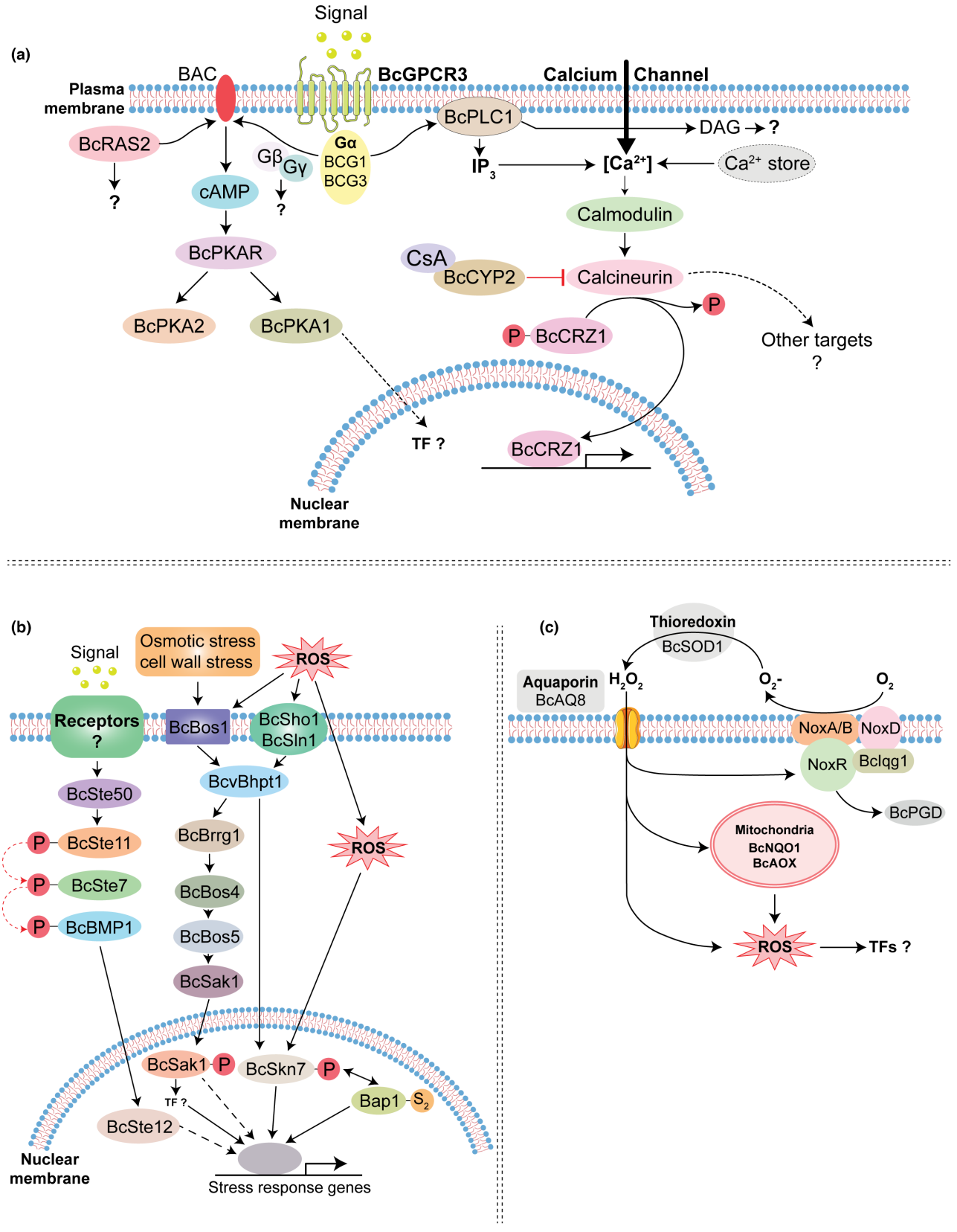

FIGURE 4 Signalling pathways of *Botrytis cinerea*. (a) Cyclic adenosine monophosphate (cAMP)-dependent and -independent pathways. (b) Conserved mitogen-activated protein kinase (MAPK) and high-osmolarity glycerol (HOG) pathways. (c) Reactive oxygen species (ROS) generation and scavenging.

Identifying yet undiscovered components in these signalling transduction processes will further enhance our understanding.

5.4 | MAPK signal transduction in *B. cinerea*

All eukaryotes including phytopathogens rely on highly conserved MAPK signalling cascades to govern diverse processes including pathogenicity, growth, and development. Each classical MAPK cascade comprises three interconnected protein kinases that undergo sequential phosphorylation to create an active signal: MAPK kinase kinases (MAPKKKs), MAPK kinases (MAPKKs), and finally MAPKs (Alonso-Monge et al., 2009; Martínez-Soto & Ruiz-Herrera, 2017). Comparative genomics, with yeast as a reference, identified most MAPK components in filamentous fungi. In *B. cinerea*, pathogenicity-associated MAPK signalling components were identified as BcSte11 (MAPKKK), BcSte7 (MAPKK), BcBmp1 (MAPK), and BcSte50 (an adaptor MAPK) (Schamber et al., 2010) Figure 4b). Deletion mutants of each of these proteins individually exhibit similar phenotypes such as germination defects, delayed vegetative growth, absence of sclerotia formation, reduced conidia, and loss of pathogenicity. This phenotypic resemblance suggests the absence of branching events in the cascade upstream of BcBmp1 (MAPK). BcBmp1 phosphorylates and activates BcSte12, a TF that controls the penetration efficiency of *B. cinerea* (Schamber et al., 2010).

One of the most studied MAPK cascades is the high-osmolarity glycerol signalling pathway, which regulates diverse responses, including those associated with pathogenicity, osmotic stress, and fungicides (Liu et al., 2008; Ma & Li, 2013; Yaakoub et al., 2022). This pathway involves the sensor histidine kinase (HK), histidine phosphotransferase protein (Hpt), a response regulator (RR), and three-tiered MAPK modules (Figure 4b). In *B. cinerea*, BcBos1, a HK, is involved in osmosensing. In addition to being sensitive to osmotic stress, *BcBos1* mutants also lack macroconidia and have reduced virulence on bean and tomato leaves, indicating a role in pathogenicity (Viaud et al., 2006). Additional membrane-spanning HKs include BcSho1 and BcSln1, whose mutants exhibit altered mycelial growth, conidiation, and sclerotia formation (Ren et al., 2019). All three HKs relay signals to BcBhpt1, a Hpt, and BcBrrg1, an RR. Deletion of *BcBrrg1* resulted in enhanced H_2O_2-generated oxidative stress, osmotic stress, and loss of conidiation (Banno et al., 2007; Yan et al., 2011; Yang et al., 2015). This signal then relies on a MAPK cascade involving BcBos4, BcBos5, and BcSak1. Deletion mutants of these MAPKs showed phenotypes similar to those of mutants in the upstream pathway, including impairments in vegetative and pathogenic development (Segmüller et al., 2007; Yan et al., 2010). Furthermore, in addition to the BcBos1–BcSak1 pathway, downstream of BcBos1 another RR called BcSkn7 was identified (Yang et al., 2015). Disruption of *BcSkn7* enhances sensitivity to osmotic and oxidative stress, along with impaired conidiation and sclerotia formation. BcSkn7 phosphorylates the TF BcBap1, which regulates the oxidative stress response (Viefhues et al., 2015). Also, this pathway operates independently of the BcBos1 phosphorelay. Moreover, the integrity and development of the cell wall, as well as mycelium-derived penetration, are associated with the BcBos1–BcSak1 pathway (Figure 4b). These reports indicate that the high-osmolarity glycerol pathway not only contributes to the osmotic stress response but also plays a significant role in *B. cinerea's* pathogenicity, affecting various aspects of development, stress responses, and the integrity of the cell wall.

Many aspects of MAPK signalling remain unexplored, including unidentified MAPK components, potential interactions with other signalling pathways, evolutionary conservation, and downstream targets. Further research efforts addressing these areas will enhance our understanding of this signalling process. In the near future, research will be focused on the components linking the receptor complexes and MAPK cascades, as well as the substrates of MAPKs. Additionally, exploring MAPK signalling as a potential target for protecting crops against *B. cinerea* infections holds promise for future agricultural applications.

5.5 | ROS generation, signalling, and scavenging in *B. cinerea*

In phytopathogenic fungi, as well as their host plants, the generation and manipulation of ROS such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) initiates different signalling cascades, governing diverse processes (Takemoto et al., 2007). NADPH oxidases (Nox), including catalytic (NoxA, NoxB, and NoxD) and regulatory (NoxR) subunits, are central components in ROS signalling by generating superoxide. In *B. cinerea*, single mutants of Δ*BcNoxA*, Δ*BcNoxB*, and Δ*BcNoxD* show reduced virulence, impaired conidiation, and decreased sclerotia production, while ROS production remains unaffected (Segmüller et al., 2008; Siegmund et al., 2015). This suggests that *B. cinerea* Nox catalytic subunits do not significantly contribute to the H_2O_2 oxidative burst mechanism but are primarily involved in differentiation processes. Intriguingly, mutants of the regulatory gene *BcNoxR* had a higher oxidation level of 6-phosphogluconate dehydrogenase (BcPGD), an enzyme involved in the pentose phosphate pathway and NADPH production (Li et al., 2019). Further, both Δ*BcPGD* and Δ*BcNoxR* are sensitive to oxidative stress and show reduced virulence. This indicates that *BcNoxR* might regulate the oxidative stress response and pathogenesis at least partially by affecting the oxidation state of BcPGD (Figure 4c; Li et al., 2019).

Being signalling molecules, ROS need to move from their site of origin to the site of action; however, H_2O_2 cannot cross the lipid bilayer membrane through simple diffusion (Seaver & Imlay, 2001). In *B. cinerea*, BcAQP8, an aquaporin, was identified as an integral plasma membrane protein that functions as a water channel and is involved in mediating the uptake of H_2O_2. Additionally, BcAQP8 also regulates the expression of *BcNoxR*, as evidenced by the *BcAQP8* deletion mutant, which exhibits decreased expression of *BcNoxR* along with a complete lack of conidia and infection structure (An et al., 2016). Further observations revealed that both *BcAQP8* and *BcNoxR* influence the distribution of ROS in the hyphal tips of *B.*

cinerea (Figure 4c). Furthermore, Δ*ΔBcAQP8* showed loss of oxidative burst, indicating that BcAQP8 might be required to induce ROS-mediated pathways by interacting with ROS-generating members such as BcSOD1, a copper-zinc superoxide dismutase. Copper-zinc superoxide dismutases convert O_2^- into H_2O_2, as evidenced by plants infected with Δ*BcSOD1* mutants accumulating less H_2O_2 and more O_2^- (Figure 4c; Rolke et al., 2004). In addition, compared to wild-type *B. cinerea*, Δ*BcSOD1* exhibits reduced radial growth and lesions on plant species, suggesting its role in pathogenicity (López-Cruz et al., 2017; Patel et al., 2008; Rolke et al., 2004).

While attacking the host, *B. cinerea* experiences an internal redox imbalance due to various stresses, such as host ROS production, nutrient fluctuations, compromised antioxidant defences, redox-active host metabolites, cell wall remodelling, and altered redox signalling (Heller & Tudzynski, 2011; Klotz, 2002). To maintain redox homeostasis, fungal oxidative stress defence systems employ a complex network of signalling pathways, antioxidant enzymes, and redox-active compounds (Hall et al., 2009; Nelson et al., 2011; Nelson & Parsonage, 2011; Stincone et al., 2015). In *B. cinerea*, thioredoxins (BcTRX1 and BcTRX2) and thioredoxin reductase (BcTRR1) are crucial for maintaining redox homeostasis, as evidenced by impaired virulence and enhanced oxidative stress sensitivity in their knockout mutants (Viefhues et al., 2014). In contrast, the glutathione redox system has minor impacts on development and virulence, as exhibited by mutants in the glutathione reductases BcGlr1 and BcGlr2. This indicates the significant role of thioredoxins in *B. cinerea*, in contrast to other fungi where both thioredoxin and glutathione systems play major roles. Another important component is alternative oxidase (AOX), which modulates the ROS levels within cells by alleviating electron leakage from the respiratory chain, thereby reducing the generation of superoxide radicals (O_2^-). In *B. cinerea*, deletion of *BcAOX* resulted in defects in mycelial growth, sporulation, spore germination, and virulence (Lin et al., 2019). This together suggests that besides modulating ROS levels, BcAOX is also involved in vegetative development and virulence.

Notably, plants and pathogens both generate the same types of ROS during their interaction. However, the mechanism underlying the goals and uses of host and pathogen ROS in mediating the interactions remains elusive. This knowledge gap is largely due to most studies typically focusing on either the host or the pathogen without simultaneous manipulation of both organisms' ROS mechanisms. To get a comprehensive picture of host–pathogen interactions, an integrated study is required, where both sides of the coin should be considered to draw biologically relevant conclusions.

5.6 | Cross-kingdom metabolic interactions

In addition to cell wall-degrading enzymes, secretory proteins, and ROS, *B. cinerea* also secretes toxic metabolites to attack hosts. These phytotoxins are of two main categories: botryane-type sesquiterpenes and polyketides (da Silva Ripardo-Filho et al., 2023). Botrydianes induce a hypersensitive response through the salicylic acid and jasmonic acid pathways (Rossi et al., 2011). They are synthesized through a five-gene cluster (*BcBot1–5*) on chromosome BCIN12 that is regulated by the BcBot6 TF (Porquier et al., 2016; Siewers et al., 2005). The polyketides, including botcinic acid and botcinins, are synthesized through a 17-gene cluster (*BcBoa1–17*) at the beginning of chromosome BCIN01 and are regulated by BcBoa13 (Porquier, 2019). These two families of phytotoxins were shown to be redundant in function (Dalmais et al., 2011). In the Δ*BcBot2* Δ*BcBoa6* double mutant, the synthesis of both types of phytotoxins is stopped, while growth is slower and virulence is reduced. Both gene clusters were shown to be under the control of G proteins and MAPK signalling cascades, but other regulatory mechanisms might also be involved (Dalmais et al., 2011; Heller et al., 2012; Porquier et al., 2016).

B. cinerea virulence results not only from its ability to induce a hypersensitive response and feed from the dead host cells, but also from its ability to survive host defence, including plant specialized metabolite defence compounds. These toxic plant metabolites are very diverse in structure across the known host plants, ranging from isoflavones to indoles and a multitude of terpenoids (Westrick et al., 2021). Necrotrophs have various strategies to cope with this diversity of toxins: They can detoxify them through catalysis or modification (Pedras et al., 2011), sequester them, or actively export them. The roles of ABC and MSF transporters in the efflux of plant defence compounds have been demonstrated in multiple cases (Perlin et al., 2014; Stefanato et al., 2009; Vela-Corcía et al., 2019); in addition, they contribute to *B. cinerea* fungicide resistance (Hayashi et al., 2002). Furthermore, it was recently shown that *B. cinerea* is equipped to detect host phytoalexins such as capsidiol and activate specific detoxification genes (Kuroyanagi et al., 2022).

The regulation of chemical weaponry is developing as a key factor of plant–*B. cinerea* interactions. This is exemplified by *Arabidopsis* and *B. cinerea* metabolisms that are interconnected within cotranscriptome networks with the expression of phytotoxin genes correlated with that of plant defence metabolite genes (Zhang et al., 2019). In addition to accumulation of secondary metabolites, such cross-kingdom gene regulation networks highlight the essential role of vesicular transport and RNA and protein synthesis.

5.7 | ck-sRNAs as virulent effectors in *B. cinerea*–host interactions

In addition to all the virulence factors described above, *B. cinerea* secretes immune-suppressing sRNAs that induce host gene silencing via hijacking the host's RNAi mechanisms. *B. cinerea* synthesis of these mobile sRNAs is mediated by the Dicer proteins BcDCL1 and BcDCL2 (Weiberg et al., 2013). The sRNAs are then loaded into extracellular vesicles (EVs) for protection and transport into the host. The tetraspanin protein punchless 1 (BcPLS1) is a biomarker for these EVs. The EVs are then internalized by plants through clathrin-mediated endocytosis, enabling the delivery of sRNAs into host

cells (He et al., 2023). Ultimately, the sRNAs bind the plant host's argonaute protein (AtAGO1), hijacking the host's RNAi machinery to silence host genes.

In *B. cinerea*, 73 virulence sRNAs were identified that target different host immune genes of *Arabidopsis thaliana* and *Solanum lycopersicum* (Weiberg et al., 2013). For instance, *Bc-siR3.2* targets the host MAPK pathway by silencing *MPK1* and *MPK2* in *Arabidopsis*, while targeting the evolutionarily unrelated *MAPKKK4* in *S. lycopersicum*. Similarly, *Bc-siR3.1* and *Bc-siR5* target *Arabidopsis* oxidative stress-related genes, i.e., peroxiredoxin (*PRXIIF*) and genes encoding cell wall-associated kinases, respectively. A majority of the identified sRNAs are produced from the long terminal repeat of the Copia_4 and Gypsy_7 retrotransposons (Porquier et al., 2021; Simon et al., 2022). Additionally, sRNAs are synthesized from other intergenic and protein-coding regions (Weiberg et al., 2013). One such example is *Bc-siR37*, derived from *BcATPase* (*Bcin12G_06020*) and potentially targeting 15 immune-associated genes in *Arabidopsis*, including genes encoding a leucine-rich repeat receptor-like kinase (*AtFEI2*), a cell wall-modifying enzyme (*AtPMR6*; pectin lyase), and a WRKY TF (*AtWRKY7*) (Wang, Weiberg, et al., 2017). Interestingly, similar to the *Arabidopsis* and tomato MPK/MPKKK, these host genes have little to no evolutionary relationships and the sRNA target site is not the result of evolutionary conservation. This raises the idea that sRNAs may contribute to the extensive host range by allowing the genome to contain a collection of sRNAs specifically evolved to target diverse defence genes in various plant species. An alternative idea arises from the observation that of the sRNA source transposable elements can be highly variable across populations. Specifically, this variation in sRNAs could suggest that they function as a stochastic mix of sequences that are exported into the host to confuse the host regulatory machinery by randomly hitting genes. This possibility is supported by the observation that the targets for these sRNAs change between host species and are largely not conserved across diverse hosts (Weiberg et al., 2013). This is also supported by the fact that the retrotransposons providing the sRNAs are highly variable in *B. cinerea*, creating a system that can stochastically attack plant genomes while simultaneously limiting the ability of hosts to counteradapt (Mercier et al., 2021).

6 | EMERGING STRATEGIES FOR DISEASE CONTROL OF *B. CINEREA*

The global distribution, genetic diversity, and ability to be stratospherically spread complicate the creation of a single treatment to block *B. cinerea*. As a result, growers adopt integrated management strategies to minimize crop losses. These strategies combine multiple approaches such as cultural practices, chemical and biological controls, and use of tolerant/resistant varieties (Chen et al., 2023; Hua et al., 2018; Orozco-Mosqueda et al., 2023). Because the quantitative nature of host resistance confounds breeding efforts, chemical fungicides are the primary means of control. Quinone outside inhibitors, methyl-benzimidazole carbamates, succinate dehydrogenase inhibitors, dicarboximides, phenylpyrroles, and anilinopyrimidines are some of the major groups of fungicides used against *B. cinerea* (Fillinger & Walker, 2016; Richards et al., 2021). However, their effectiveness varies depending on the timing of application and environmental factors (Kim et al., 2016). Further, the overuse of fungicides raises concerns about environmental protection and food security. To address these challenges, researchers are exploring alternative strategies that are efficient and environmentally friendly for controlling *B. cinerea* infections. The use of plant-derived bioactive substances and antagonistic microorganisms has shown some promise in limiting grey mould infection, although only few of these biological agents have demonstrated persistent efficacy in field trials (Almasaudi et al., 2022; El-Baky & Amara, 2021). Antagonistic microorganisms (yeasts, fungi, and bacteria) can effectively inhibit *B. cinerea* through various mechanisms such as competition for resources, induction of host resistance, and production of cell wall lytic enzymes (Chan & Tian, 2005; Hermosa et al., 2012; Navazio et al., 2007; Tian et al., 2007; Yang et al., 2009). However, their effectiveness is generally not as pronounced as that of fungicides, necessitating the combination of both approaches (Droby et al., 2009). Furthermore, a wide range of antifungal compounds derived from plants and animals have been reported (Hua et al., 2018; Romanazzi et al., 2016, 2018). Plant volatiles such as acetaldehyde, allicin, benzyl alcohol, benzaldehyde, ethanol, ethyl benzoate, ethyl formate, methyl salicylate, hexanal, (*E*)-2-hexenal, lipoxygenases, jasmonates, glucosinolates, and isothiocyanates have been shown to inhibit *B. cinerea* infection on various commodities when tested under laboratory and small-scale conditions (Romanazzi et al., 2016; Tripathi & Dubey, 2004). However, their practical efficacy in large-scale and commercial settings requires further verification, along with addressing safety concerns. The use of essential oils for postharvest decay control is also gaining interest (Abdollahi et al., 2012; Sivakumar & Bautista-Baños, 2014). However, it is crucial to consider factors such as formulation, application methods, phytotoxicity, and the preservation of organoleptic quality. Furthermore, due to the polygenicity of resistance mechanisms, breeding for resistance against *B. cinerea* with genetic engineering methods rather than classical breeding could be a cost-effective option depending on consumer acceptance.

Recent efforts to protect plants from fungal pathogens rely on a newly developed exogenous RNAi application method based on spray-induced gene silencing (SIGS). SIGS offers an alternative to conventional fungicides as *B. cinerea* can take up both single-stranded and double-stranded RNA molecules from the environment (Qiao et al., 2021; Wang, Weiberg, et al., 2017). Wang, Weiberg, et al. (2017) conducted a pioneering study where single-stranded and double-stranded RNAs that target dicer-like proteins, BcDCL1 and BcDCL2 of *B. cinerea* were applied to the surfaces of fruits, vegetables, and flowers, resulting in reduced *B. cinerea* infection. Similar positive results were obtained when a synthetic double-stranded RNA targeting ergosterol biosynthesis was used, leading to

decreased conidial germination, mycelial growth, and pathogenicity of *B. cinerea* on various fruits (Duanis-Assaf et al., 2022). For the successful field implementation of this approach, it is important to design double-stranded RNA molecules that efficiently target key genes for silencing and are sufficiently stable for field application. Genome sequencing of diverse *B. cinerea* strains can aid in the identification of invariant genes, limiting the potential for pathogen escape.

While SIGS-based disease control shows promise, there are challenges to overcome. The effect of SIGS on plants may last only a few days due to RNA degradation, and the level of protective RNA in the plant could be limited by uptake efficiency, requiring regular reapplication of sRNA or double-stranded RNA. Double-stranded RNA uptake can be enhanced through using formulations or carriers that protect it from degradation by environmental factors and facilitate its movement within the plant. Delivery methods such as high-pressure spraying may not always achieve the desired gene silencing (Uslu et al., 2020). Manufacturing costs could be high, but new approaches, such as using bacteria to produce sRNAs, are being developed (Goodfellow et al., 2019). To date, no SIGS methods have been tested in large-scale field trials, and testing of different delivery methods is required for wider acceptance. Additionally, consumer acceptance of this RNAi-based innovation is yet to be assessed.

7 | CONCLUSION

In this pathogen profile, we summarized recent advancements in our understanding of the genomics and molecular biology of *B. cinerea*. We showed that the genetic diversity of *B. cinerea* is explained by geography, climate conditions, and plant hosts, with probably a major role played by transposable elements and their association with sRNAs. Furthermore, it is also important to consider that different *B. cinerea* isolates display diverse levels and mechanisms of virulence. Thus, it is most likely that some of the virulence genes mentioned in this review contribute differently depending on the pathogens' genetic background. To fully understand the extent of genetic and molecular diversity within *B. cinerea*, future research efforts should aim for comprehensive studies that encompass a wide range of isolates. Also, with over 5000 genes that do not have any annotations and fewer than 500 genes that have been fully investigated for their role, over 95% of *B. cinerea* genes remain to be explored for their molecular function. Further, we highlighted the complexity of the virulence mechanisms, a network of small-effect and redundant genes that render breeding for plant resistance challenging. We also mentioned the emerging theme of plant–*B. cinerea* interactions being cross-kingdom genetic exchanges with chemical and nucleic battles. With the expanding scope of genomic and RNA sequencing studies and the increasing prevalence of Big Data biology, we anticipate numerous fascinating discoveries concerning *B. cinerea* in the coming decades. Future research should aim to elucidate the intricacies of the pathogen's genetic and molecular diversity, its virulence mechanisms, and its interactions with host plants, ultimately contributing to more effective strategies for disease management and crop protection.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed.

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SUPPORTING INFORMATION

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