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Understanding Efflux-Mediated Multidrug Resistance in *Botrytis cinerea* for Improved Management of Fungicide Resistance

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ABSTRACT

Botrytis cinerea is a major fungal pathogen infecting over 1400 plant species. It poses a significant threat to agriculture due to multiple fungicide resistance and multidrug resistance, involves resistance to fungicides with different modes of action. Multiple fungicide resistance is mostly due to an accumulation of point mutations in target genes over time, and MDR is result from efflux (e-MDR) and metabolism (m-MDR). This review introduces the occurrence of e-MDR of *B. cinerea*, the key mechanisms, origins and management strategies of e-MDR in fields. New materials such as nanomaterials become a strategy to overcoming MDR via inhibition of ABC transporter. A deeper understanding of efflux-mediated MDR will provide a support for the MDR management of *B. cinerea* and the efficient utilization of fungicides.

1 | Problem Statement

Botrytis cinerea is a fungal pathogen that can infect more than 1400 plant species (Figure 1). It ranks as the second most important plant pathogen (Dean et al. 2012). Chemical control remains the most effective and efficient method in managing grey mould (Alzohairy et al. 2023). However, the development of resistance to different classes of fungicides by *B. cinerea* presents a significant threat to modern agriculture. Among them, one type of resistance has been described as multidrug resistance (MDR) (Sun et al. 2010), which is indicated by resistance to two or more fungicides with different modes of action (MOAs). From the perspective of mechanisms, MDR can be further categorised as that caused by efflux (e-MDR) and metabolism (m-DMR) (Kretschmer et al. 2009; Zhang and Yang 2021; Cheng et al. 2022, 2023; Wang et al. 2024), while MFR is related to Several studies have shown that *B. cinerea* strains, isolated from vineyards, tomato farms and strawberry farms, exhibit resistance to three or more fungicides, with a resistance frequency as high as 70% and an MDR rate reaching up to 30% (Nielsen et al. 2022; Sofianos, Samaras, and Karaoglanidis 2023). The high risk of resistance development has resulted in a growing number of previously efficacious fungicides becoming ineffective against grey mould, necessitating higher application rates and dosages, which in turn raises concerns regarding human health, environmental safety and food security.

2 | The Development of MDR due to Fungicide Use

Alarmingly, the occurrence of MDR in the field is often observed shortly after the introduction of some new fungicides for the control of diseases in various crops (Ishii et al. 2009; Rupp et al. 2016), such as dollar spot of lawn grasses, wheat leaf blight and apple blue mould (Song et al. 2021; Sofianos, Samaras, and Karaoglanidis 2023). *Botrytis cinerea* has developed MDR against several commonly used fungicides belonging

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FIGURE 1 | Infection of *Botrytis cinerea* in (a) strawberry, (b) grape, and (c) tomato fruit or plant. (a) Symptoms of *Botrytis cinerea* infection in strawberry fruit grown in plantation; (b) Symptoms of disease caused by artificial inoculation of *B. cinerea* spores on the leaves of grapes grown in greenhouse; (c) Symptoms of tomato calyx infection with *B. cinerea* grown in plantation.

TABLE 1 | Fungicides contributing to multidrug resistance in *Botrytis cinerea* in the field.

Years of release	Representative fungicides	Groups	Target protein	Years resistance reported	References
1960s	Benomyl, carbendazim	Methyl benzimidazole carbamates (MBCs)	β-tubulin	1970s	Bollen and Scholten (1971); Wang et al. (2022)
1970s	Imazalil, prochloraz	Demethylation inhibitors (DMIs)	CYP51	1970s	Stehmann and De Waard (1995); Zhang et al. (2020)
1970s	Procymidone, iprodione	Dicarboximides (DCFs)	BcOs1	1980s	Katan (1982); Adnan et al. (2018)
1980s	Diethofencarb	N-phenylcarbamate (NPC)	—	1980s	Katan, Elad, and Yunis (1989); Fan et al. (2017)
1990s	Pyrimethanil	Anilinopyrimidine (APs)	Protein kinase	1990s	Chapeland et al. (1999); Nielsen et al. (2022)
1960s	Fludioxonil	Phenylpyrroles (PPs)	Protein kinase	1990s	Faretra and Pollastro (1993); Liu et al. (2023)
1990s	Azoxystrobin	Quinone outside inhibitors (QoIs)	Cytochrome b	2000s	Markoglou et al. (2006); Harper et al. (2022)
2000s	Boscalid, fluxapyroxa	Succinate dehydrogenase inhibitors (SDHIs)	Succinate dehydrogenase	2000s	De Miccolis Angelini et al. (2010); Malandrakis et al. (2022)

to benzimidazoles, dicarboximides, demethylation inhibitors (DMIs), quinone outside inhibitors (QoIs) and succinate dehydrogenase inhibitors (SDHIs) across cultivation areas of grape, tomato and strawberry as shown in Table 1 (Kretschmer et al. 2009; Adnan et al. 2019).

3 | Overexpression of ABC and MFS Transporters Mediates e-MDR

The overexpression of key efflux proteins in fungi, specifically those in the ATP-binding cassette (ABC) and the major facilitator superfamily (MFS), is considered the primary cause for the emergence of low-level resistance populations in the field (Kretschmer et al. 2009; Walker et al. 2013; Hahn 2014; Sun et al. 2022). Field populations of *B. cinerea* predominantly consist of strains overexpressing these two types of protein families Hayashi, Schoonbeek, and De Waard (2002); Kretschmer et al. (2009); Nielsen et al. (2022).

ABC efflux transporters can expel various toxic substances from the cell, playing an important role in the e-MDR of *B. cinerea* (Schoonbeek, van Nistelrooy, and de Waard 2003; Sun et al. 2022). *B. cinerea* contains 14 ABC efflux proteins (BcatrA-BcatrN), four of which are related to the MDR phenotype, namely BcatrB, BcatrD, BcatrK and BcatrO. The BcatrB protein primarily interacts with aromatic compounds (Vermeulen, Schoonbeek, and De Waard 2001; Schoonbeek, van Nistelrooy, and de Waard 2003) and has been confirmed to be involved in the resistance of *B. cinerea* to fludioxonil, dicarboximide fungicides and the phytoalexin resveratrol secreted by the host plant. Complementation of the *BcatrB* gene in *B. cinerea* mutants leads to a reduction in the accumulation of fungicides, concomitantly diminishing fenpiclonil

and fludioxonil sensitivity compared to the knockout mutant Schoonbeek, Del Sorbo, and De Waard (2001; Kretschmer et al. (2009). The sensitivity of *B. cinerea* to oximidazole, pyrrole and DMI fungicides increases when the *BcatrD* gene is knocked out (Hayashi et al. 2001). Additionally, the *BcatrK* (*BMR1*) knockout strain exhibits increased sensitivity to polyoxin and iprobenfos, and the *BcatrO* knockout strain has an enhanced sensitivity to H_2O_2 and fenpiclonil (Pane et al. 2008). Furthermore, the MDR mutants of *B. cinerea*, obtained by procymidone adaptation, exhibit a significant upregulation of *BcatrG* (Wu et al. 2024c). The ABC transporter genes, including *BcATRO*, *BMR1*, *BMR3* and *BcNMT1*, are upregulated in fludioxonil-resistant strains, indicating that the overexpression of these efflux transporters may be responsible for the fludioxonil resistance in *B. cinerea* (Liu et al. 2023).

Meanwhile, MFS transporters can also expel chemical compounds from the cell. These fungal transporters are involved in the efflux of natural toxic compounds such as camptothecin, cercosporin and DMIs fungicides (Hayashi, Schoonbeek, and De Waard 2002). MFS transporter genes, including *BcAMF1*, *BcTOP1*, *BcVBA2* and *BcYHK8*, are also upregulated in fludioxonil-resistant *B. cinerea* (Liu et al. 2023). *MfsG* transporter is a virulence factor that increases tolerance to glucosinolates (Vela-Corcia et al. 2019). A comprehensive and systematic investigation of these transporter genes and their interactions is needed in future studies.

4 | Regulation of ABC Expression

The expression of ABC transporter genes is modulated by factors such as promoter regions of ABC transporters and their transcription factors (Kretschmer et al. 2009). In *B. cinerea*, the transcription factor *Mrr1* has been reported to positively regulate *BcatrB* expression (Kretschmer et al. 2009). The point mutations V575M in *Mrr1* resulted in upregulation of *BcatrB* in the MDR1 strain. Additionally, the transcription factor *XDR* found from *Sclerotinia homoeocarpa* has been proved to engage the ability to regulate the expression of *BcatrD* and *BcCYP65* in *B. cinerea* (Sang et al. 2018). Meanwhile, a rearrangement in the upstream region of *mfsM2*, caused by the insertion of a foreign gene fragment and concurrent deletion of a portion of the putative *mfsM2* promoter, leads to the overexpression of *mfsM2* (Kretschmer et al. 2009). Resent research has found procymidone-induced mutations on target gene *BcBos1* linked to the overexpression of *BcatrG* in *B. cinerea*. Although no direct association has been identified between *BcBos1* belonged to the MAPK pathway and expression of ABC transporters, the overexpressed of *BcatrG* expression was speculatively regulated by this regulatory pathway through *BcBos1* mutation (Wu et al. 2024a, 2024c). The identification of more novel regulators or mechanisms of MDR through the xenobiotic efflux pathway in filamentous fungi may facilitate the discovery of new antifungal fungicides to control pathogenic fungi.

5 | Tracking the Origin of Multidrug Resistance in the Fields

To the best of our knowledge, the current understanding does not fully explain the field origin of MDR in plant pathogens. One of the laboratory techniques for inducing resistant strains involves selection of pathogens on agar media amended with fungicides, utilising a stepwise cultivation process with increasing fungicide concentrations. Our recent studies have demonstrated that the uncoupler fungicide SYP-14288 can induce MDR of *Rhizoctonia solani*, resulting in resistance to fluazinam, chlorothalonil, fludioxonil, difenoconazole, azoxystrobin, fentin chloride, cyazofamid and 2,4-dinitrophenol. Similarly, MDR strains of *Phytophthora capsici* were obtained through selection with SYP-14288, showing resistance to fluazinam, chlorothalonil and oxathiapiprolin (Cheng et al. 2020; Dai et al. 2022). Furthermore, UV irradiation-produced *Phytophthora infestans* mutants showed a reduced sensitivity to metalaxyl, enoylpyrazole, carbendazim, ether fungicide and antimycin A (Ziogas et al. 2006). In vitro induction of DMI fungicides led to the development of MDRs in *Penicillium digitatum* to DMIs, cycloheximide, 4-nitroquinoline-N-oxide and acriflavin (Nakaune et al. 1998). These studies suggest that the occurrence of MDR in plant pathogens is associated with the use of DMIs, uncouplers and UV irradiation.

Research has demonstrated that MDR in *B. cinerea* is not solely induced by fungicides like procymidone (Wu et al. 2024b, 2024c), but also induced by plant secondary metabolites, such as rishitin, capsidiol, camptothecin, flavanone and resveratrol (Kuroyanagi et al. 2022; Bulasag et al. 2023; Wu et al. 2024b, 2024c). Our recent work provides insight into the mechanisms underlying the role of ABC transporters in facilitating MDR induced by plant secondary metabolites (Wu et al. 2024b, 2024c). Overexpression of the ABC transporter genes, namely *BcatrB*, *BcatrD* and *BcatrK*, enables *B. cinerea* to pre-adapt to the pressure of antifungal plant secondary metabolites (Wu et al. 2024b, 2024c). This pre-adaptation leads to enhanced efflux activities for fungicides, including sterol synthesis inhibitors, osmotic signal inhibitors and methionine inhibitors. These findings suggest that ABC transporters can be stimulated by exogenous chemicals, resulting in an adjusted ability to efflux fungicides with different MOAs, playing a crucial role in the development of MDR.

6 | New Strategy for Management of Multidrug Resistance

Addressing the emergence of resistance in the field presents a significant challenge for future research. Various strategies based on nanomaterials, as well as physical approaches, highlight their pivotal roles in overcoming MDR (Duan et al. 2023). Specifically designed nanoparticles can bypass P-glycoprotein (P-gp)-mediated cancer MDRs by increasing surface area, encapsulating a variety of guests, and attaching targeting ligands to enhance therapeutic delivery (Xia et al. 2022; Duan et al. 2023). Previous studies have proposed innovative strategies for fungicide formulation, emphasising the rapid and targeted release of nano-carriers at the site of infestation. These approaches aim to minimise adverse effects on non-target organisms (Gao et al. 2023).

Concurrently, plant-derived phytochemicals capable of modulating various signal transduction pathways and inhibiting transcription factor translocation have been used to reverse P-gp-mediated MDRs in the medical field (Ganesan et al. 2021). These studies have explored various available opportunities for

therapeutic design in human pathogens, including altered therapeutic regimens through drug combinations and P-gp inhibitors such as verapamil, dexverapamil, dexniguldipine and tariquidar (Palmeira et al. 2012; Abdallah et al. 2015; Dong et al. 2020). This concept can also be applied to the control of plant pathogens in previous research (Liu et al. 2020; Liu, Sun, Cheng, et al. 2021; Liu, Sun, Liang, et al. 2021; Prigigallo et al. 2023; Wu et al. 2024a, 2024b, 2024c). A new perspective on synergistic effects via efflux inhibition with fungicides may open opportunities to overcome MDR in plant pathogens.

7 | Conclusion

In conclusion, efflux pumps in *B. cinerea* play a crucial role in the development of e-MDR. Certain exogenous substances, such as plant secondary metabolites and fungicides, can upregulate the expression of these pumps through pre-adaptation or a specific pathway, subsequently triggering e-MDR to fungicides with different modes of action. Consequently, the effective regulation of these pumps represents a promising strategy to manage e-MDR in *B. cinerea*.

Author Contributions

Zhaochen Wu: conceptualization, writing – original draft. **Junting Zhang:** writing – original draft. **Jianjun Hao:** writing – review and editing. **Pengfei Liu:** writing – review and editing, supervision, funding acquisition. **Xili Liu:** writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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