



Strategies for managing fungicide resistance in the Brazilian tropical agroecosystem: Safeguarding food safety, health, and the environmental quality

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Abstract

Fungicide resistance is an alarming challenge for the Brazilian tropical agricultural systems, with major implications for food safety, human and animal health, as well as for the environment. This review explores strategies to address fungicide resistance within the Brazilian agroecosystem context. We examined historical and current scenarios of fungicide resistance in the Brazilian agroecosystems and the approaches to delay the emergence and mitigate the selection of resistant variants. Our review indicates that the prevalence of resistance in field populations of key plant pathogens in Brazil was due to failures in the implementation of preventive measures. To address this issue, alternative evolutionary-smart strategies against fungicide resistance are proposed, emphasizing institutional actions and public policies. Crucial steps involve strengthening national networks for large-scale foliar and seed fungicide efficacy testing and resistance monitoring, as well as imposing tighter restrictions on the labeling of high-risk single-active formulations. Additionally, the integration of non-chemical disease management strategies and the establishment of a centralized database and information system on fungicide resistance in Brazil are identified as essential for effective resistance monitoring and informed decision-making. To enhance fungicide resistance management, the adoption of a warning system (e.g., based on aerobiology- or on weather-monitoring) for predicting disease epidemics and minimizing fungicide applications is recommended. Increased funding, collaboration, mandatory reporting, and capacity building are required to overcome these challenges. In addition, promoting integrated disease management approaches is vital. By implementing these tailored strategies, Brazil can actively contribute to safeguarding its food safety, protecting human and animal health, and preserving the delicate balance of its unique agroecosystem. The adoption of evolutionary-smart strategies against fungicide resistance will prolong fungicide efficacy, reduce economic costs, and minimize environmental impacts, ensuring sustainable and resilient agriculture in Brazil.

Keywords Aerobiology-based inoculum monitoring tools · Evolutionary-smart anti-resistance strategies · Centralized database on fungicide resistance · Information system · Sustainable and resilient agriculture · *Mycosphaerella* spp. · *Phakopsora pachyrhizi* · *Pyricularia oryzae*

Fungicide resistance in the Brazilian tropical agroecosystem

Fungicide resistance in the agroecosystem is considered one of the most serious threats to food security (Fisher et al. 2012, 2018). Since the 1970s, resistance to the major classes

of modern site-specific selective fungicides in several plant pathogenic fungi species has compromised the management of plant diseases worldwide, limiting fungicide options or even making them unavailable for agriculture (Brent and Hollomon 2007; Thind 2012; Lucas et al. 2015). As fungicide resistance becomes more prevalent, the effectiveness of fungicides decreases, leading to increased crop losses (Thind 2012; Valarmathi 2018; Steinberg and Gurr 2020). Therefore, fungicide resistance can have substantial economic

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impacts on farmers profits and the country's trading revenues from agricultural gross domestic product (Corkley et al. 2022). An increase in the number of sprays due to resistance can lead to excessive fungicides use resulting in adverse effects on the environment. Fungicides can contaminate soil, water, and affect non-target organisms, disrupting ecosystems and causing ecological imbalances (Zubrod et al. 2019). Furthermore, continued reliance on ineffective fungicides, by increasing doses and spraying frequency to compensate for resistance, can contribute to pesticide resistance in other non-target organisms, including human and animal fungi pathogens (Fraaije et al. 2021). For instance, public health concerns have been raised on an environmental route of azole resistance selection through an unintended exposure of the human pathogen *Aspergillus fumigatus*, one of the most ubiquitous species in the environment (Stensvold et al. 2012; Arastehfar et al. 2021; Burks et al. 2021). Agricultural azole fungicides are chemically close to antifungal medicines (Fisher et al. 2018; Burks et al. 2021; Fraaije et al. 2021). In summary, fungicide resistance undermines the long-term sustainability of agricultural systems, food safety and security, human and animal health.

Although fungicide resistance in plant pathogenic fungi is a global threat to food production and security, surprisingly little is known on the prevalence and the evolutionary processes underlying the emergence and spread of fungicide resistance in most of the tropical agroecosystems worldwide (Fisher et al. 2018). Particularly in Brazil, research contributions on the scope and importance of fungicide resistance for most of the locally important pathosystems were scarce and limited to literature reviews until recently (Forcelini et al. 2001; Ghini and Kimati 2002). This scenario has changed in early 2000, as information on fungicide resistance for several plant pathogenic fungi species has started to increase with many cases reported (Table 1, Figs. 1 and 2).

A summary covering approximately 10 years of reports, from 2013 up to 2023, on fungicide resistance in populations of distinct plant pathogenic fungi species in major field crops of the Brazilian agroecosystems is presented in Table 1 and Figs. 1 and 2. These fungi species include *Botrytis cinerea* (gray mold on strawberries), *Colletotrichum acutatum* (bitter rot on apple and post bloom fruit drop on citrus), *C. musae* (anthracnose on bananas), *Corynespora cassiicola* (target leaf spot on soybean), *Lasiodiplodia theobromae* and other Botryosphaeriaceae species (dieback and stem-end rot of papaya and mango), *Monilinia fruticola* (brown rot on stone fruits), *Mycosphaerella fijiensis* (black Sigatoka on bananas), *M. musicola* (yellow Sigatoka on bananas), *M. thailandica* (leaf spot on bananas), *Neophytopella meliosmaerianthae* and *N. tropicalis* (rust on grapes), *Phakopsora pachyrhizi* (Asian soybean rust), *Pyricularia oryzae* *Oryzae* and *Triticum* lineages (rice and wheat blast), *Ramulariopsis glycines* (Ramulariopsis leaf spot on cotton), and *Sclerotinia*

sclerotiorum (white mold on common beans). Though this is not an exhaustive list, as there might be many other plant fungi pathogens for which fungicide resistance has been reported in Brazil, it does provide a snapshot of the findings on the prevalence, the levels, and the mechanisms of resistance to a diversity of site-specific fungicide classes. This information will contribute to understanding the extent and impact of fungicide resistance in Brazilian agriculture and point to the needs for developing effective disease management strategies. It should be pointed out that no resistance was detected between 1999 and 2016 in populations of *C. acutatum* from citrus, probably due to the adoption of appropriate fungicide mixtures, acting as an anti-emergence strategy against the development of fungicide resistance (Gama et al. 2020).

The data compiled in Table 1 and Figs. 1 and 2 suggest that fungicide resistance is indeed a significant issue as resistance has become pervasive in populations of the major plant pathogenic fungi for the Brazilian agroecosystems. Here, there are some key points that support this assertion: **a) High prevalence of fungicide resistance** detected in several populations of plant pathogenic fungi, including *B. cinerea*, *C. acutatum*, *C. musae*, *C. cassiicola*, *L. theobromae*, *M. fruticola*, *M. fijiensis*, *M. musicola* and *M. thailandica*, *N. meliosmaerianthae*, *P. pachyrhizi*, *P. oryzae* *Oryzae* and *Triticum* lineages, and *R. glycines*; **b) Distinct classes of the major systemic site-specific fungicides affected by resistance**, including dicarboximides, methyl benzimidazoles (MBC), quinone outside inhibitors (QoI), demethylation inhibitors (DMI), and succinate dehydrogenase inhibitors (SDHI). This indicates that resistance was not limited to a specific fungicide group but is found in fungicides with different modes of action; **c) The occurrence of multiple (i.e. simultaneous) fungicide resistance**, including dual and triple resistance, suggesting the coexistence of resistance mechanisms in the same pathogen population and even in a single individual genotype. Examples of multiple resistance to distinct fungicide classes were observed in *C. acutatum*, *C. cassiicola*, *L. theobromae*, *M. fruticola*, *Mycosphaerella* spp., *P. pachyrhizi*, and *P. oryzae* *Oryzae* and *Triticum* lineages; **d) Increasing prevalence of resistance over time**: The data cover a timeline of approximately 10 years, a period that we detected an increase in the prevalence of fungicide resistance over time leading to the fixation of resistance, both within populations and across geographical regions; **e) Positive selection favoring the spread of target-site mutations associated with fungicide resistance**: For instance, the emergence and subsequent countrywide spread of the specific mutation F129L mutation in the *cytB* gene associated with QoI resistance, and more recently the SdhC I86F substitution linked to SDHI resistance, both in *P. pachyrhizi*; **f) High stability of resistance under continuous fungicide selection pressure, despite**

Table 1 Large scale surveys on fungicide resistance monitoring and detection in populations of plant pathogenic fungi from major crops in Brazil from 2013 up to 2023

Pathogen	Disease	Crop	Fungicide classes*, active ingredients and remarks	N	Resistance** (% of the population sampled)	Geographical origin*** (states and/or region), major observations and reference
<i>Botrytis cinerea</i>	Gray mold	strawberry	MBC (thiophanate-methyl) QoI (azoxystrobin) Dicarboximide (procyimdone) Antinopyrimidine (pyrimethanil) MBC (thiophanate-methyl) QoI (azoxystrobin) Dicarboximide (procyimdone) DMI (difenoconazole) SDHI (boscalid)	99 150	78.0 68.0 58.0 20.0 94.6 90.0 40.0 36.0 43.0 100 16.7	Samples from BA, ES, MG, and SP, 2013 to 2015 (Baggio et al. 2018) PR (Maia et al. 2021) Samples from PR, 2010 to 2011 (Moreira et al. 2019)
<i>Colletotrichum acutatum</i> species complex	Bitter rot and Glomerella leaf spot	apple (C. <i>nympheae</i> and C. <i>paranaense</i>)	MBC (thiophanate-methyl) QoI (azoxystrobin)	114 ...	100 ...	Samples from SP. No resistance was detected between 1999 and 2016, probably due to appropriate fungicide mixtures, acting as anti-emergence strategy against fungicide resistance (Gamma et al. 2020)
<i>Colletotrichum musae</i>	Postbloom fruit drop	citrus	MBC (carbendazim) DMI (difenoconazole) DMI (tebuconazole) QoI (trifloxystrobin) MBC (thiophanate-methyl)	254 ... 164 ... 139	0 0 0 0 6.5	Population samples from several Brazilian states (AL, BA, DF, ES, GO, MG, PA, PE, PR, SC, and SP), from 2012 to 2013. Resistant and sensitive isolates were equally fit (Vieira et al. 2017) Population samples from several Brazilian states (BA, DF, ES, GO, MG, PE, PR, SC, and SP) from 2012 to 2013. No fitness cost associated with resistance to thiabendazole or imazalil (Leite et al. 2020)
<i>Corynespora cassicola</i>	Target leaf spot	soybean	MBC (carbendazim, thiophanate-methyl) QoI (azoxystrobin, picoxystrobin, pyraeostrobin)	59 ...	44.0 47.0	Samples from MS, MT and PR (Brazil, N=57) and from Paraguay (N=2), from 2014 to 2016 (Mello et al. 2022)
<i>Lasiodiplodia theobromae</i>	Stem-end rot	papaya	MBC (thiophanate-methyl) QoI (azoxystrobin) DMI (difenoconazole)	64 ... 9	28.0 46.9 66.7	Population samples from BA, PB, PE, and RN, from 2011 (Chen et al. 2020). Most with reduced sensitivity (Chen et al. 2020). Samples from BA, PB, PE, and RN, from 2007. <i>LCYP51</i> gene overexpression and difenoconazole-resistant isolates have fitness penalty (Li et al. 2020)
<i>Lasiodiplodia</i> spp. and other Boryosphaeria-ceae species	Dieback and stem-end rot	mango	MBC (thiophanate-methyl) MBC (thiabendazole)	154 ...	33.8 66.3	Population samples from BA, PE and RN states, from 2010 to 2013. Resistant and sensitive isolates were equally fit (Santos et al. 2019)
<i>Monilia fructicola</i>	Brown rot	stone fruits (peach, plum)	QoI (azoxystrobin) Dicarboximide (iprodione)	143 174	9.8 0	Population samples from PR, RS, SC and SP, from 2002 to 2011. Most of the isolates were sensitive; nine had reduced sensitivity (Pereira et al. 2017) Population samples from PR, RS and SP. A total of 71.8% of the isolates were extremely sensitive (Dutra et al. 2019)
...

Table 1 (continued)

Pathogen	Disease	Crop	Fungicide classes*, active ingredients, and remarks	N	Resistance** (% of the population sampled)	Geographical origin** (states and/or region), major observations and reference
<i>Monilinia fructicola</i>	Brown rot	stone fruits (peach, plum)	DMI (tebuconazole)	58	15.5	Population samples from PR, RS, SC, and SP, from 2002 to 2015 (Lichtenberg et al. 2017)
			DMI (tebuconazole)	52	42.0	Population samples from PR, RS and SP (Dutra et al. 2020)
			DMI (propiconazole)	...	7.7	
			DMI (prothioconazole)	...	5.8	
...	DMI (tebuconazole) Population from PR: 2012/2013 2015/2016 Population from SP: 2012/2013 2015/2016	28 40 40 40	35.6 25.0 100.0 0.0	Population samples from PR and SP. Discontinuance of tebuconazole in the field restored sensitivity in the pathogen population after 3 years (Pereira et al. 2020b)
...	MBC (thiophanate-methyl) Historical population (2003 to 2010) Current population (2017)	58 77	48.2 4.0	Population samples from SP, PR and RS. Low (LR) and highly resistant (HR) isolates (Fischer et al. 2023) Sensitive isolates increased 3-fold, from 29 to 96% (Fischer et al. 2023)
<i>Mycosphaerella fijiensis</i>	Black Sigatoka	banana	QoI (azoxystrobin)	2	0	Samples from Ribeira Valley, SP, 2018 (Malimpensa 2018)
			QoI (azoxystrobin or pyraclostrobin)	10	10.0	Population samples from Ribeira Valley, SP, 2021 (Oliveira et al. 2022)
			DMI (propiconazole or tebuconazole)	9	100	... (A. G. da Silva, personal information)
		
...	SDHI (boscalid) SDHI (fluxapyroxad) QoI (azoxystrobin) QoI (azoxystrobin or pyraclostrobin) DMI (propiconazole or tebuconazole) SDHI (boscalid) SDHI (fluxapyroxad) DMI (several fungicides) QoI (azoxystrobin)	10 ... 1 96 42 57 ... 48 12 13 55	100 70 100 9.4 14.3 93.0 57.9 10.4 91.2 84.6 9.1	... Silva (2023) Samples from Ribeira Valley, SP, 2018 (Malimpensa 2018) Population samples from MG and SP, from 2021 (Oliveira et al. 2022) ... (A. G. da Silva, personal information) ... Silva (2023) Population samples from DF, 2015 (Brito et al. 2020) Samples from Ribeira Valley, SP, 2018 (Malimpensa 2018) Population samples from MG and SP, 2021 (Oliveira et al. 2022) No CYP51 mutation associated with resistance (Santos et al. 2021)
<i>M. thailandica</i>	Leaf spot	...	DMI (tebuconazole)	13	84.6	
			QoI (pyraclostrobin)	...	0	No inron immediately after codon 143 at <i>cytB</i> , potential for QoI resistance (Santos et al. 2021)
			MBL-R (tricyclazole)	10	10.0	Samples from TO (Bezerra et al. 2021)
			DMI (tebuconazole)	60	16.7	Samples from GO, over a 26-year sampling period, an exponential increase in the EC ₅₀ estimates for sensitivity for all fungicides, particularly for azoxystrobin (D'Ávila et al. 2021)
<i>Neophytopella melios-mae-myrianthae</i>	Rust	grape	QoI (azoxystrobin)	...	21.7	
			MBL-R (tricyclazole)	...	ND	
			QoI (azoxystrobin)	179	89.4	Population samples from RS, PR, MG, SP, MS, GO, and DF, from 2005 and 2012 (Castrogudín et al. 2015)
			
<i>N. tropicalis</i>	Blast	rice	QoI (azoxystrobin)	13	100	Population samples from MG, from 2018 to 2019 (Cazón et al. 2023)
			MBL-R (tricyclazole)	13	69	...
			QoI (pyraclostrobin)	179	100	Population samples from RS, PR, MG, SP, MS, GO, and DF, from 2005 and 2012 (Dorigan et al. 2019; Poloni et al. 2021)
			DMI (tebuconazole, epoxiconazole)	157	4.5	From the same populations from 2012 as above. A total of 4.5% (N=7) with moderate resistance (EC ₅₀ > 20 µg.mL ⁻¹) and 94.3% (N = 148) with reduced sensitivity (EC ₅₀ > 3 and < 20 µg.mL ⁻¹) (Vicentini et al. 2022a).
<i>Pycularia oryzae</i> Oryza lineage	...	wheat	SDHI (fluxapyroxad)	

Table 1 (continued)

Pathogen	Disease	Crop	Fungicide classes*, active ingredients, and remarks	N	Resistance** (% of the population sampled)	Geographical origin*** (states and/or region), major observations and reference
<i>Pyricularia oryzae</i> Trileucum lineage	Blast	Wheat	SDHI (fluxapyroxad)	103	47.6	Population samples from MG, PR and SP from 2018. As a remark, 97.3% were resistant to QoIs, 91.8% were resistant to DMI fungicides, while 89.1% were resistant to both (Vicentini et al. 2022a)
...	QoI (azoxystrobin), DMI (tebuconazole, epoxiconazole) and/or SDHI (fluxapyroxad)	16	81.3 to 100%	Efflux pump mechanism associated with DMI but not with SDHI resistance (Vicentini et al. 2022c)
...	QoI (azoxystrobin)	8	50.0	Increased fitness associated with QoI resistance (Dorigan et al. 2022)
<i>Phakopsora pachyrhizi</i>	Asian rust	soybean	QoI (azoxystrobin and pyraclolostrobin)	38	0	Samples from GO, MG, MS, MT, PR, RS, and SP, from 2009 to 2010. No F129L or any other mutation in the <i>cytB</i> gene was found (Schmitz et al. 2014)
...	DMI (cyproconazole, metconazole, epoxiconazole and tebuconazole)	...	84.2–89.5%	...
...	QoI	41	51.2	Samples from GO, MG, MS, MT, PR, SP, and RS, from 2012 to 2014. Detection of F129L in half of the samples from Brazil (Klosowski et al. 2016b)
...	DMI and QoI	-	-	Samples from GO, PR and SP, from 2009 to 2010.
...	Resistance and fitness components	QoI-resistant isolate with F129L mutation in the <i>cytB</i> gene competed equally with a QoI-sensitive, wild-type <i>cytB</i> ; isolates with lower DMI sensitivity and different <i>CYP51</i> alleles had competitive disadvantages compared with a DMI-sensitive, wild-type (Klosowski et al. 2016a)
...	Multiple resistance to DMI and QoI fungicides	32	56.3	Samples from southern PR, from 2012 to 2014. Contrast between an organic and a conventional soybean production systems (Klosowski et al. 2018)
...	QoI fungicides	...	28.1	Twelve populations from PR, Brazil, and five from Canindeyú, Paraguay, from 2017/2018. Average decreased sensitivity of 8.7% (from 1.5 to 26%) in 12 from the 17 populations analyzed (Braga et al. 2020)
...	DMI (prothioconazole)	17	70.6	Samples from MT, PR, SP and RO, from 2013 to 2017. Report of the SdhC I86F substitution in three isolates (Müller et al. 2021)
...	Multiple resistance to DMI, QoI and SDHI fungicides	21	80.1, 90.0 and 14.3%, respectively	Samples from Passo Fundo, RS, 2016. First report of reduced sensitivity to SDHI. Report of the SdhC I86F substitution in nine <i>Pp</i> isolates, at distinct frequencies (Simões et al. 2018)
...	SDHI (benzovindiflupyr, fluxapyroxad, fluopyram)	21	42.9	Population samples from PR, RS, SC, MG, SP, GO, MS, MT, BA, MA, PA, PI and TO, from 2015 to 2019. The high frequency of SDHC I86F mutation and low sensitivity to SDHIs are widely distributed in the main soybean growing regions in Brazil. A total of 162 wild type populations were detected (Mello et al. 2021)
...	SDHI (benzovindiflupyr and fluxapyroxad)	770	79.0	SdhC-I86F mutation was stable and could be related to some fitness penalties (Chaus et al. 2022)
...	SDHI resistance and fitness component	-	-	Population samples from several Brazilian states (BA, GO, MG, MS, MT, PR, SC, SP, RS) and from Paraguay, from 2018 and 2021. The newly identified mutation combinations F120L + Y130A + Y131F, F120L + Y131H + I145Y and F120L + Y131H + F154Y were associated with different sensitivities to DMIs (Stilgenbauer et al. 2023)
...	DMIs	139	100	Population samples from BA, GO, MS, and MT, from 2017 – 2020 (Mathioni et al. 2022)
...	Samples from Brazil	6	100	Population samples from BA, GO, MG, and SP, from 2010 – 2012 (Lehner et al. 2015)
...	Samples from Paraguay	6	100	Population samples from BA, GO, MS, and MT, from 2017 – 2020 (Mathioni et al. 2022)
<i>Ramulariopsis glycines</i>	Ramulariopsis leaf spot	cotton	QoI (azoxystrobin)	165	100	Population samples from BA, GO, MG, and SP, from 2010 – 2012 (Lehner et al. 2015)
<i>Sclerotinia sclerotium</i>	White mold	common beans	MBC (thiophanate-methyl)	282	0.35	Population samples from BA, GO, MG, and SP, from 2010 – 2012 (Lehner et al. 2015)
...	Dicarboximide (procyimidone)	...	0	Population samples from BA, GO, MG, and SP, from 2010 – 2012 (Lehner et al. 2015)
...	2,6 dinitroanilines (fluzamam)	...	0	Population samples from BA, GO, MG, and SP, from 2010 – 2012 (Lehner et al. 2015)

N = sample size of the fungal population screened for fungicide resistance in the respective study

*FRAC codes for specific fungicide classes: 1, MBC (methyl benzimidazole carbamates); 2, Dicarboximide; 3, DMI (demethylation inhibitors, sterol biosynthesis inhibitors class I, SBI); 7, SDHI (succinate dehydrogenase inhibitors); 9, Anilinopyrimidines; 11, QoI (quinone outside inhibitors); 16.1, MBI-R (melanin biosynthesis inhibitors reductase, thiazolo-benzothiazole); 29, 2,6 dinitroanilines

** Resistance detected by fungicide sensitivity phenotyping, by detection of resistance mechanisms and associated target gene mutations and corresponding amino acid substitutions, or by both methods

***Brazilian states acronyms: AC = Acre, AL = Alagoas, BA = Bahia, ES = Espírito Santo, GO = Goiás, MA = Maranhão, MG = Minas Gerais, MS = Mato Grosso do Sul, MT = Mato Grosso, PA = Pará, PE = Pernambuco, PI = Piauí, PR = Paraná, RN = Rio Grande do Norte, RO = Rondônia, RR = Roraima, RS = Rio Grande do Sul, SC = Santa Catarina, SP = São Paulo, TO = Tocantins

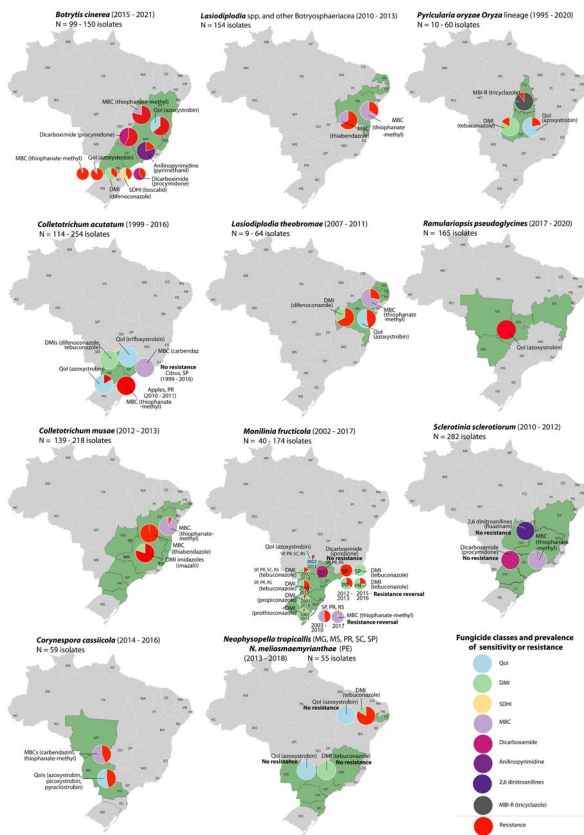


Fig. 1 Prevalence of fungicide resistance in populations of 11 plant pathogenic fungi from major crops in distinct Brazilian agroecosystems from 2013 up to 2023. *-*-*-*-* * Comprehensive data on fungicide resistance prevalence in Brazil were compiled for the following plant pathogenic fungi: *B. cinerea* (Baggio et al. 2018; Maia et al. 2021), *C. acutatum* (Gama et al. 2020; Moreira et al. 2019), *C. musae* (Leite et al. 2020; Vieira et al. 2017), *C. cassiicola* (Mello et al. 2022), *Lasiodiplodia* spp. (Santos et al. 2019), *L. theobromae* (Chen et al. 2020; Li et al. 2020), *M. fructicola* (Dutra et al. 2019, 2020; Fischer et al. 2023; Lichtemberg et al. 2017; Pereira et al. 2017, 2020b;), *N. tropicalis* and *N. meliosmaemyrianthae* (Santos et al. 2021), *P. oryzae Oryza* lineage (Bezerra et al. 2021; D'Ávila et al. 2021), *R. pseudoglycinis* (Mathioni et al. 2022), and *S. sclerotiorum* (Lehner et al. 2015)** Brazilian States colored in green indicate the origin and geographical distribution of the fungal plant pathogen sampling. *N* indicates the sample size range from each fungal species examined. *** Mean prevalence of fungicide sensitivity and/or resistance, for the combined geographical samples, is represented by a pie chart with distinct colors according to the fungicide classes. Resistance is depicted in red. Sequential pie charts of the same color indicate a time series evolution in the frequency of fungicide sensitivity and/or resistance in populations of the pathogens

associated fitness penalties: Some studies indicated that resistant isolates may exhibit fitness penalties compared to sensitive ones, suggesting that resistance mechanisms come at a cost to the pathogen, but despite this, resistance still persisted and evolved in agroecosystems (Claus et al. 2022; Klosowski et al. 2016a); **g) Stability of resistance in the absence of continued fungicide selection, when there is**

no fitness penalties (Dorigan et al. 2022; Klosowski et al. 2016a; Leite et al. 2020; Vieira et al. 2017). Overall, these lines of evidence indicate the importance of fungicide resistance in the Brazilian agroecosystems, and its accelerated evolution.

An example of accelerated evolution for fungicide resistance in agriculture can be depicted from the timeline of events spanning the historical evolution for resistance to the three major classes of medium to high risk fungicides in populations of the wheat blast pathogen, *Pyricularia oryzae Triticum* lineage (*PoTl*) (Castroagudín et al. 2015; Poloni et al. 2021; Vicentini et al. 2022a) based on several studies (Figs. 2 and 3, Table 1). This timeline virtually began in 1978 with the labeling of the first DMI fungicide for the management of wheat diseases. The first epidemics of wheat head blast disease was reported a few years later with the historic outbreak in Londrina, Paraná State, in 1985 (Ceresini et al. 2018). DMI fungicides were the choice for management of wheat blast due to their systemic prophylactic properties. In subsequent years, a few other DMI fungicides were labeled for controlling wheat diseases, which included propiconazole in 1985, tebuconazole and cyproconazole in the early 1990s, and epoxiconazole in the early 2000s. Despite the reports that fungicides for wheat blast, including the DMIs, were not fully effective on controlling the disease, resistance to DMI fungicides was not explored as a plausible explanation, until 2020 (Poloni et al. 2021). Even so, DMIs were recognized as a medium-risk fungicide for the emergence of resistance (Kuck and Russell 2006; Fungicide Resistance Action Committee (FRAC) 2022b). They were sprayed intensively as single active formulations, probably with no precautions of adopting anti-resistance strategies, at least not on-label until 2012 (Ministry of Agriculture, Livestock and Supply (MAPA) / Coordination of Pesticides and Related Products 2012). Only in 2012 pesticide labeling policies requiring risk assessment of resistance for pesticides and commercial labels containing resistance management recommendations were introduced in Brazil. Furthermore, DMIs were intensively used in calendar-based sprays programs, up to five sprays, on-label, per cropping season, targeting several wheat diseases, including rusts, necrotic leaf spots, Fusarium head blight, and wheat blast (Ministry of Agriculture, Livestock and Supply (MAPA) 2023). With basically non-stop selection pressure for up to 30 years of DMI fungicides sprays (totalling approximately 150 sprays), the evolutionary outcome was the emergence, selection and widespread distribution of a highly resistant *PoTl* population across all wheat producing areas in Central-southern Brazil (Poloni et al. 2021; Figs. 2 and 3, Table 1).

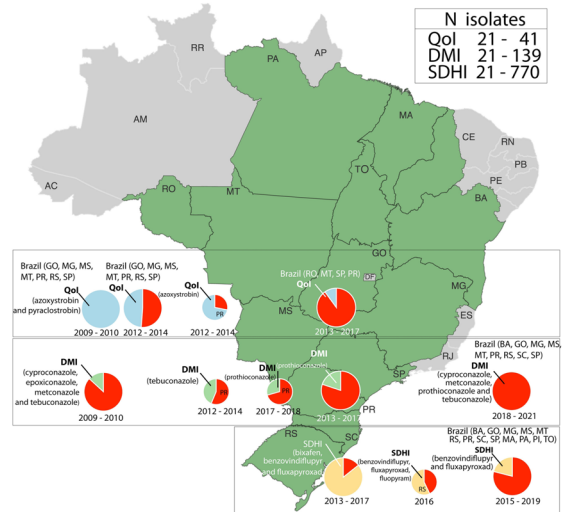
The evolutionary outcome of resistance to the high risk QoI fungicides in *PoTl* populations was somewhat distinct, as it happened quicker. Azoxystrobin was the first QoI fungicide labeled in Brazil in early 2000s (Fig. 3). Although the

Fig. 2 Prevalence of resistance to fungicides QoI, DMI and SDHI in ► populations of the Asian soybean rust (A), banana Sigatoka disease complex (B) and wheat blast (C) pathogens from Brazil indicating an accelerated evolution for resistance over the past 10 years, from 2013 up to 2023.*****. * Comprehensive data on fungicide resistance prevalence in Brazil were compiled for the following plant pathogenic fungi: A. *Phakopsora pachyrhizi* (Klosowski et al. 2016b; Mello et al. 2021; Müller et al. 2021; Schmitz et al. 2014; Simões et al. 2018; Stilgenbauer et al. 2023), B. *Mycosphaerella fijiensis*, *M. musicola* and *M. thailandica* (A. G. da Silva (personal communication); Brito 2015; Brito et al. 2020; Gomes et al. 2014; Hanada et al. 2015; Malimpensa 2018; Oliveira et al. 2022; Silva 2023), and C. *Pyricularia oryzae* *Triticum* lineage (Castroagudín et al. 2015; Cazón et al. 2023; Dorigan et al. 2019; Poloni et al. 2021; Vicentini et al. 2022a, c).** Brazilian States colored in dark gray or in green indicate the origin and geographical distribution of the fungal plant pathogen sampling. *N* indicates the sample size range from each fungal species examined.*** Mean prevalence of fungicide sensitivity and/or resistance, for the combined geographical samples, is represented by a pie chart with distinct colors according to the fungicide classes. Resistance is depicted in red. Sequential pie charts of the same color indicate a time series evolution in the frequency of fungicide sensitivity and/or resistance in populations of the pathogens

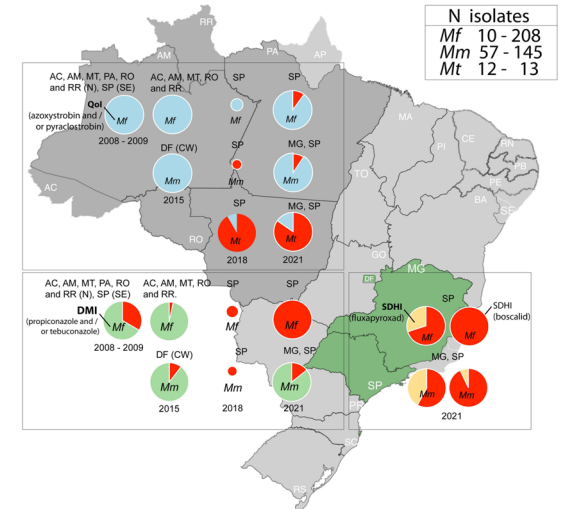
first report of QoI resistance was in 2015, the study included resistant *PoTl* isolates sampled in 2005, only five years after the labeling for management of wheat diseases (Castroagudín et al. 2015). QoI resistance is now widespread in all wheat cropping regions from Brazil (Castroagudín et al. 2015; Vicentini et al. 2022a) (Figs. 2 and 3, Table 1). Similarly to the scenario that resulted in resistance to DMIs, the high risk QoI fungicides were sprayed intensively on calendar-based schedules as a single active formulation, exerting a high selection pressure on populations of *PoTl* (Castroagudín et al. 2015; Vicentini et al. 2022a).

The adoption of the official on-label recommendations of anti-resistance strategies described in Figs. 4 and 5 (such as rotating fungicides with distinct modes of action, carry out frequent disease monitoring on the cropping area, adopt integrated disease management strategies) has failed to delay the emergence and spread of fungicide resistance in *PoTl* populations since they lacked three key strategies: a) Fungicides that had lost efficacy due to resistance should be withdrawn from the spraying portfolio, specially when supported by large scale monitoring of fungal population across the country; b) The lack of an official channel to report the initial emergence of fungicide resistance at local (field) scale, before it becomes widespread; c) The lack of an alternative system to prevent unnecessary calendar-based fungicide spraying hindered the on-label anti-resistance strategy primary goal of reducing the selection pressure on the pathogen's populations. (Vicentini et al. 2022a). Additionally, they did not emphasize the recommendation of spraying multisite fungicides as an important anti-resistance IPM component (Fig. 5) and often one of the few fungicides that will work when resistance to the single-sites becomes widespread (Brent and Hollomon 2007; Brent 2012; Thind 2012).

A. Asian soybean rust: *Phakopsora pachyrhizi* (Pp), 2009 - 2021
N = 21 - 770 Pp isolates (Brazil)



B. Banana Sigatoka disease complex: *Mycosphaerella fijiensis* (Mf), *M. musicola* (Mm) or *M. thailandica* (Mt), 2008 - 2021



C. Wheat blast: *Pyricularia oryzae* *Triticum* lineage (*PoTl*), 2005 - 2019
N = 103 - 183 *PoTl* isolates (Brazil); N = 13 - 40 isolates (MG)

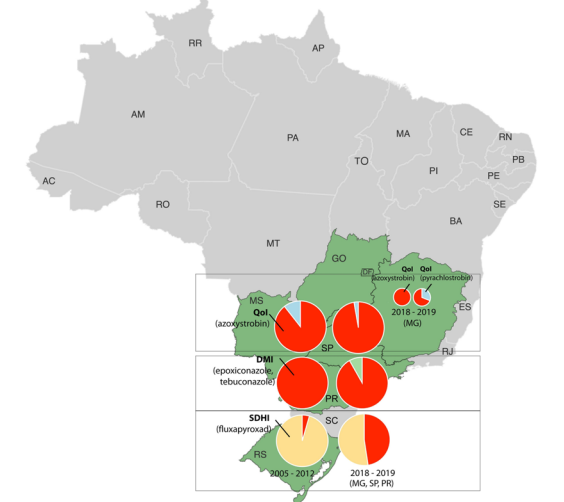
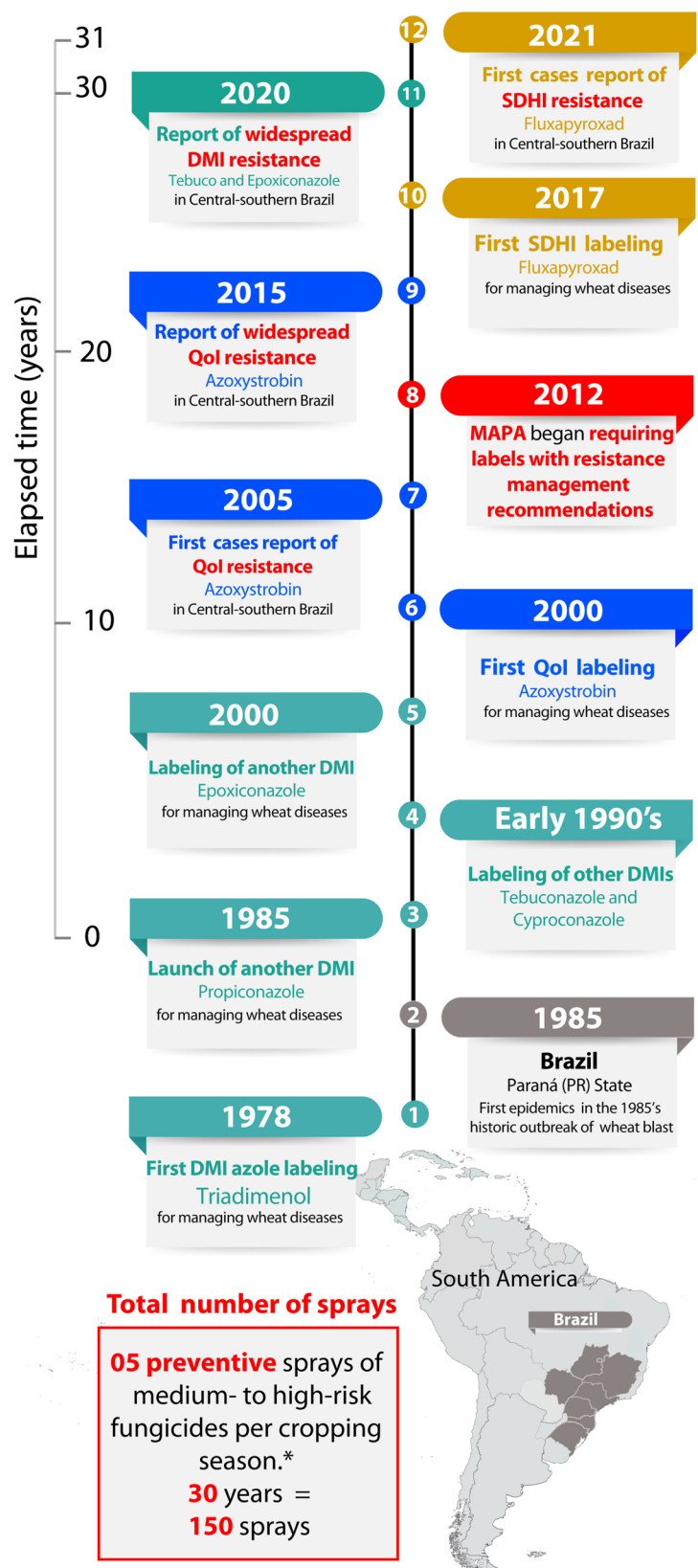


Fig. 3 Timeline depicting the emergence of the wheat blast pathogen *Pyricularia oryzae Triticum* lineage in South America in the mid 1980's and the events leading to the accelerated evolution and the widespread distribution of fungicide resistance in Brazil.***. *Colored shappes indicate the dates of the events (ribbons) and the order in the timeline (numbered circles). Green colored ribbons indicate events associated with the labeling, deployment of DMI fungicides and reports of resistance. Blue colored ribbons indicate events associated with the labeling, deployment and reports of resistance to QoI fungicides. The red colored ribbon indicates the date MAPA began requiring labels with anti-resistance strategies on agricultural fungicides. Bege colored ribbons indicate events associated with the labeling, deployment and reports of resistance to the recent labeled SDHI fungicides. ** Source: Castroagudín et al. 2015; Cazón et al. 2023; Ceresini et al. 2018, 2019; Dorigan et al. 2019; Poloni et al. 2021; Vicentini et al. 2022a, c



Source: * MAPA - Brazilian Ministry of Agriculture, Livestock and Food Supply

A. Anti-emergence strategy: resistant lineages have not yet emerged	
• Expected effect	Stopping fungicide resistant lineages of a plant pathogen from emerging
• Major strategy	No release of single-site medium to high-risk fungicide molecule in the market as sole active, but only in co-formulation in mixture with a low risk fungicide (i.e., a multi-site fungicide) *
• Major key player for implementing	Fungicide agrochemical companies can take full responsibility, under the scrutiny of public policies
• Feasibility and limitations	Considered completely feasible
• Pros for the local growers, for the environment, for the country's economy and for the society	In principle, very simple to implement as the choice of fungicide mixture is already an embedded anti-emergence strategy that requires no other complex strategy, such as the decision on rotating fungicides with distinct modes of action. No environmental spread of fungicide resistant lineages of plant pathogenic fungi. No significant yield losses, and therefore no impact on gross domestic product from agricultural commodities trading.
• Pros for the fungicide companies	Prolonged lifespan of the agricultural fungicides as their efficacy and profitability are kept along the years.
• Scientific support for the present assertions	(Hobbelen et al. 2014; Corkley et al. 2022)

Fig. 4 Description of the effects and major characteristics of **(A)** anti-emergence and **(B)** anti-resistance strategies against fungicide resistance in populations of plant pathogens in the agroecosystem.**

*MAPA, together with the Ministry of Environment and the Brazilian Health Regulatory Agency (Anvisa), as regulatory bodies, oversight the labeling of fungicides formulations for controlling crop diseases, including fungicides co-formulations. For this reason, co-formulations attend the standards of agronomical efficacy, public health safety and reduced environmental impact. MAPA's pesticide databank on currently labeled fungicides registered for agricultural use in Brazil (https://agrofit.agricultura.gov.br/agrofit_cons/principal_agrofit_cons) contains a total of 410 fungicide formulations, from which 172 are co-formulations. The co-formulations of single-site at-risk fungicides with multisite low risk fungicides totalled 26 prod-

In recent years, new fungicide formulations have been labeled and introduced for the management of wheat diseases in Brazil. These fungicides include the second-generation carboxamide fluxapyroxad, a SDHI that is considered at medium risk for fungicide resistance emergence (FRAC 2022a). Unexpectedly from the point of view of anti-resistance strategies, since 2017 these fungicides have been co-formulated with high risk QoI or moderate risk DMI molecules (pyraclostrobin or epoxiconazole), for which resistance has been reported for *PoTl* populations (Vicentini et al. 2022a; MAPA – Ministério da Agricultura Pecuária e Abastecimento - Brazil 2023). This labeling strategy represented a continuing selection pressure favoring the survival of DMI and QoI resistant strains of *PoTl*, that could have contributed to the onset of resistance to SDHIs (Figs. 2 and 3, Table 1) because of the co-formulation with fungicides molecules that had lost the efficacy (Vicentini et al. 2022a). In fact, SDHI-resistant isolates were detected in both older pre-SDHI (2012) and newer post-SDHI (2018) populations of the wheat blast pathogen (Vicentini et al. 2022a).

ucts, including double or triple co-formulations with chlorothalonil, copper oxychloride, or mancozeb and: azoxystrobin; azoxystrobin + cyproconazole; azoxystrobin + difenoconazole; azoxystrobin + prothioconazole; azoxystrobin + tebuconazole; benalaxil; cymoxanil; cyproconazole + picoxystrobin; difenoconazole; difenoconazole + trifloxystrobin; fluxapyroxad; fluxapyroxad + prothioconazole; imipifloxam + metominostrobin; tebuconazole; tebuconazole + trifloxystrobin; and thiophanate-methyl. The other 146 co-formulations are mixtures of multisite fungicides only, or mixtures of single site at-risk fungicides.

**These anti-resistance strategies indicated in bold are similar to ones proposed in the Brazilian official fungicide labels described in Fig. 5, except for the contents in brackets

Evolutionary drivers and trajectory of fungicide resistance in the agroecosystem

Fungicides resistance can emerge in populations of target plant pathogenic fungi soon after exposure to a fungicide (Deising et al. 2008; Lucas et al. 2015; Yin et al. 2023). Fungicide resistance can be defined as “the stable new and heritable trait associated with reduction in the sensitivity of an individual fungus to a specific fungicide” (Delp and Dekker 1985; McGrath 2004).

The emergence of fungicide resistance in populations of plant pathogens in the agroecosystem is a dynamic evolutionary process by which the frequency of resistance alleles changes over time, which is likely to affect the field efficacy of fungicides (Yin et al. 2023). These evolutionary changes usually result either in advantages or disadvantages for the pathogen's survival, growth, and reproduction under fungicide selection stress or not (Hawkins and Fraaije 2018).

Fungicide resistance appears to evolve from new point mutations (*de novo* mutations) in genes encoding the target site. In the simplest cases, such as the QoI resistance,

B. Anti-resistance strategies: resistant lineages have already emerged	
<ul style="list-style-type: none"> Expected effect Strategies 	<p>Lower the prevalence of recently emerged / or established fungicide resistant lineages by reducing / removing the selection pressure from the extensive deployment of high-risk fungicides in the country</p> <p>Alternate sprays of fungicides formulated in mixtures [specially co-formulations of single-site at risk with multisite fungicides], rotating fungicides with distinct modes of action.</p> <p>Never spray single site at-risk fungicides preventively, but rather follow disease epidemics forecast systems that advise on weather favorability and risks for disease incidence to guide spray decisions.</p> <p>Alternatively, in the absence of weather-based disease forecast systems carry out frequent disease monitoring on the cropping area to detect any temporal shift towards an increase in incidence.</p> <p>Consider spraying multisite fungicides alone, as an IPM component.</p> <p>Adopt integrated disease management strategies to minimize fungicide sprays, such as available resistant cultivars, crop rotation, health seeds, biological control with biofungicides, and other cultural practices that interfere with the off-season survival, reduce the levels of pathogen's inoculum, and long range dispersal.</p>
<ul style="list-style-type: none"> Major key player for implementing Feasibility and limitations 	<p>Growers, agriculture technical assistance and extension plant pathologists.</p> <p>In principle, some decision-based strategies on fungicide choice seem easily applicable and effective. However, they are mostly not effective because they are heavily dependent on fitness costs associated with resistance, in the absence of the fungicide spray. Besides, as they include no recommendation to prevent sprays of a particular high-risk fungicide that lost efficacy due to resistance (besides the plausible cross-resistance among fungicides with the same mode of action), the resistant lineages tend to persist in the environment and increase in frequency. In addition, some pathogens are easily spread at long distances, invalidating non-concerted regional efforts to block the dispersal and re-introduction of resistance lineages.</p>
<ul style="list-style-type: none"> Feasibility and limitations 	<p>These strategies that are aimed to prevent prophylactic fungicide sprays are hard to implement by growers, agriculture technical assistance and extension plant pathologists in the developing world, as plant disease epidemics are hard to predict due to lack of national and regional forecasting systems, resulting in calendar-based excessive fungicide sprays.</p> <p>A massive effort for detection and monitoring shifts in fungicide resistance prevalence, <i>in loco</i>, is required to validate the effects of the strategy and support further decisions based on fungicides at risk. It also requires highly skilled scientific and lab support for resistance molecular detection and automated monitoring of inoculum levels, at regional or countrywide scale, which demand proper and steady funding.</p>
<ul style="list-style-type: none"> Cons for the local growers, for the environment, for the country's economy and for the society. 	<p>Disease control failure and high yield losses as fungicide resistance persists. Unnecessary fungicides sprays escalate. Environmental spread of fungicide resistant lineages of plant pathogenic fungi (and other non-target fungal species, including human and animal pathogens). Gross domestic product from agricultural commodities trading drops.</p>
<ul style="list-style-type: none"> Cons for the fungicide companies 	<p>Fungicide actives lose efficacy and the agrochemical companies lose credibility and finances. Liability for transferring to third parties their responsibility of monitoring and limiting the spread of fungicide resistance and its environmental and financial impacts.</p>
<ul style="list-style-type: none"> Scientific support for the assertions 	<p>(Mikaberidze et al. 2014; van den Bosch et al. 2014a; Hawkins and Fraaije 2018)</p>

Fig. 4 (continued)

fungicide resistance evolves when a single mutation conferring a high level of resistance with negligible adaptive costs emerges and is selected for in a population of a plant pathogen (Lucas et al. 2015). However, the resistance to some fungicides, such as the DMIs, is generally more complex, as

this simpler scenario of single point mutation determining resistance usually does not occur. For instance, a total of nine mutations detected in the *CYP51* (F120L, V130A, Y131F/H, K142R, I145V/F, F154Y, I475T) in the ASR pathogen *P. pachyrhizi*, and present in different combinations, determines

A. [General] recommendations on [fungicide] resistance management [for most of the plant pathogenic fungi]
<p>The successive use of fungicides with the same mode of action to control the same target can contribute to an increase in the population of plant pathogenic fungi resistant to this mode of action, leading to loss of efficacy of the [commercial] fungicide and consequent yield losses. As a practice for management of resistance to fungicides and to avoid problems thereafter, here are some recommendations:</p> <ul style="list-style-type: none"> • Alternate sprays of fungicides formulated in mixtures, rotating the different mode of action of Groups C2 [SDHI: succinate-dehydrogenase inhibitors], C3 [Quinone outside Inhibitors] and G1 [DeMethylation Inhibitors] whenever possible; • Adopt other best agricultural practices to reduce the population of [fungal] plant pathogens, such as crop rotation, other cultural control practices, cultivars with resistance genes, when available, and so on. • Spray the [respective] commercial fungicide only at the recommended dose and spray technology, as described in its leaflet; • Always consult an agronomist for guidance on the main regional strategies and technical instruction on spray technology to prolong the fungicide effectiveness; <p>Information on possible cases of resistance to fungicides in the control of [plant] pathogenic fungi should be consulted and/or reported to: the Brazilian Society of Plant Pathology (SBF: www.sbfito.com.br), the Brazilian Fungicide Resistance Action Committee (FRAC - BR: www.frac-br.org), and the Ministry of Agriculture, Livestock and Supply (MAPA: www.agricultura.gov.br).</p>

Fig. 5 (A) General and (B) specific recommendations of fungicide resistance management strategies included in the Brazilian official label leaflets of commercial fungicide formulations (Ministry of Agriculture, Livestock and Supply (MAPA) 2023). *Contents in brackets were included by the authors for better explaining the information quoted from the original label leaflet. Text in bold emphasizes

the level of DMI sensitivity (Stilgenbauer et al. 2023). Furthermore, the limited knowledge on mutations for fungicide resistance outside the range of known target genes is still challenging for understanding the pathways to resistance to particular fungicides, such as the DMIs. As whole-genome sequencing data in combination with association mapping become more accessible, these more comprehensive analytic tools will help to reveal the multilocus genetic architecture of fungicide resistance in populations of important fungal pathogens (Pereira et al. 2020a). The unique application of these combined analytic tools revealed significant differences in azole resistance among global field populations of the important wheat pathogen *Parastagonospora nodorum*. These populations evolved distinctive combinations of azole resistance alleles, including polymorphisms in major facilitator superfamily transporters, which could interact when co-occurring in the same fungal genetic background (Pereira et al. 2020a).

The evolution towards fungicide resistance in populations of plant pathogens can be split into an emergence phase and a selection phase (Hobbelen et al. 2014). In the **emergence phase**, the resistant strain arises by mutation and subsequently invades the pathogen population. At this stage, the

strategy. According to the definitions proposed in Fig. 4, these are mainly anti-resistance strategies, except for the strategies indicated in **red**, which contradicts the principle of minimizing unnecessary fungicide sprays to reduce selection pressure against the pathogen populations

number of lesions derived from fungicide-resistant strains is very small and resistant strains may become extinct as a result of a simple stochastic variation, although fungicide sprays can provide higher adaptability to resistant strains than to sensitive ones. In the **selection phase**, a resistant strain is already present in a pathogen's population and is positively selected by the spray of specific fungicides (Hobbelen et al. 2014).

Under the effect of single-site fungicides, where a single mutation in the target protein can confer a high level of resistance, a qualitative phenotypic change in the pathogen population usually results in two populations with a bimodal distribution for sensitivity. With multi-site fungicides, or with some single-site fungicides where more than one allele contributes to resistance, a unimodal distribution with quantitative changes is observed (Georgopoulos and Skylakakis 1986; Deising et al. 2008; Lucas et al. 2015). In both cases, directional selection is observed towards lower sensitivity acting on discrete variation, in the case of qualitative resistance. In contrast, a continuous distribution for quantitative resistance is observed by gradual changes towards resistance over time (Georgopoulos and Skylakakis 1986; Deising et al. 2008; Lucas et al. 2015).

B. Specific recommendations on [fungicide] resistance management for the [Asian] soybean rust
<p>The successive use of fungicides with the same mode of action to control the same target can contribute to an increase in the population of plant pathogenic fungi resistant to this mode of action, leading to loss of efficacy of the [commercial] fungicide and consequent yield losses. As a practice to delay the decrease in efficacy of fungicides [against] the fungus that causes the Asian soybean rust, here are some recommendations:</p> <ul style="list-style-type: none"> • Alternate sprays of fungicides formulated in mixtures, rotating the different mode of action of Groups C2 [SDHI: succinate-dehydrogenase inhibitors], C3 [Quinone outside Inhibitors] and G1 [DeMethylation Inhibitors] whenever possible; if the [commercial] fungicide has only one mechanism of action, never deploy it alone; • Respect the sanitary void [legislation] and eliminate voluntary soybean plants; • Sow early soybean cultivars, concentrating sowing at the beginning of the recommended cropping season for each region (adoption of an escape tactics); • Never cultivate soybeans off-season (second cropping); • Use cultivars with incorporated resistance gene[s], when available; • [Adopt] sowing density that allows higher leaf aeration, higher [canopy] penetration and better coverage by the fungicide spray; • Adopt other best agricultural practices to reduce the population of [fungal] plant pathogens, such as crop rotation, healthy seeds, balanced fertilization, [proper] water management system, other cultural control practices, and so on. • Whenever possible, carry out sprays aiming at the most susceptible phases of the plant pathogen to be controlled; • Spray the [respective] commercial fungicide only at the recommended timing, dose and spray intervals; • Always consult an agronomist for guidance on the main regional strategies for resistance management and technical instructions for fungicide spray; • Carry out disease monitoring on the crop; • Adopt a preventive spray tactics; • Follow a maximum interval of 14 days between sprays; • Carry out, at most, the number of sprays of the commercial fungicide as described in its label leaflet; • Always consult an agronomist for guidance on the main regional strategies and technical instruction on spray technology to prolong the fungicide effectiveness; <p>Information on possible cases of resistance to fungicides in the control of [plant] pathogenic fungi should be consulted and/or reported to: the Brazilian Society of Plant Pathology (SBF: www.sbfito.com.br), the Brazilian Fungicide Resistance Action Committee (FRAC - BR: www.frac-br.org), the Ministry of Agriculture, Livestock and Supply (MAPA: www.agricultura.gov.br).</p>

Fig. 5 (continued)

The agroecosystem under conventional disease management is considered a hotspot for the emergence of fungicide resistance. Five main factors associated with conventional disease management contribute to the emergence and spread of fungicide resistance in the agroecosystem: **a) Monoculture farming.** While this approach simplifies management and harvesting, the highly homogenous and non-fragmented tropical agricultural landscape favors the emergence and spread of fungicide resistance (Papaix

et al. 2015). In fact, the extensive use of fungicides with a similar mode of action on a homogeneous and highly connected cropping area over multiple seasons provides strong selection pressure that favors the survival and proliferation of resistant strains (Pretty and Bharucha 2014; Valarmathi 2018). **b) Dependence on a limited number of fungicides mode of action:** Conventional disease management in agriculture often relies heavily on a small number of at risk fungicides. When these fungicides are

used repeatedly and exclusively, populations of plant pathogenic fungi with emerging *de novo* mutations or natural standing genetic variation for fungicide resistance can rise by selection followed by adaptation. Limited fungicide options also limit the possibility to rotate or mix different fungicides, which can help mitigate resistance development (van den Bosch et al. 2014b). **c) Improper fungicide application:** Incorrect application techniques, such as inadequate dosages or improper timing, can contribute to the emergence of resistance. Stress from exposure to sub-lethal doses of fungicides can cause genomic instability in fungi, accelerating the emergence of fungicide resistance or other adaptive traits in populations of fungal plant pathogens (Gambhir et al. 2021). Sublethal doses of fungicides can also increase selection in pathogen populations, allowing resistant strains to survive and proliferate. In addition, inadequate coverage of crops during application can leave certain areas untreated, favoring resistant lineages (Brent and Hollomon 2007; Hollomon 2015a, b). **d) Lack of diversity in disease management strategies:** Over reliance on fungicides as the primary means of disease control, without integrating other management practices, can contribute to the emergence of resistance. Integrated Pest Management (IPM) approaches, which combine several strategies such as crop rotation, resistant varieties, cultural practices, and biological control, can help reduce the dependence on chemical fungicides and minimize the risk of resistance development (McDonald and Linde 2002; Stukenbrock and McDonald 2008; Lucas et al. 2015). **e) Limited research and development of new fungicides:** The slow pace to develop new fungicides, coupled with the rapid evolution of resistance in populations of plant pathogenic fungi, further exacerbates the problem. The limited availability of novel fungicides hampers the ability to effectively control resistant strains and restricts the options for disease management (Corkley et al. 2022; FRAC 2022b).

Three major drivers can determine the rate of evolution and the fate of fungicide resistance in populations of plant pathogens (Fisher et al. 2018). The first major driver is the **heritable genetic variation** for fungicide resistance, either as naturally occurring genetic variation or *de novo* fungicide-driven mutations that subsequently sweeps through the fungal population. The accelerated emergence of *de novo* alleles conferring fungicide resistance in fungi has been associated with the use of sublethal doses of fungicides, which can act as a genomic stressor and promote mutagenesis (Boyce et al. 2017; dos Reis et al. 2019; Gambhir et al. 2021; Healey et al. 2016). The levels of heritable genetic variation for fungicide resistance are dependent on the pathogen effective population size, derived primarily from both historical and current genetic variation processes, including sexual recombination and mutation rates. This also depends

on the potential for gene flow, ranging from a regional to a global dispersal of fungicide resistant strains by trade in infected seeds, by which new genes and genotypic diversity are introduced (Fisher et al. 2018).

The second major evolutionary driver for fungicide resistance is **the high reproductive rate of fungal pathogens in the agroecosystem** (Fisher et al. 2018), which is usually rapid in the agriculture environments as a result of the high genetic homogeneity of host plants in extensive monocultures of susceptible varieties and intensive fungicide use (McDonald and Linde 2002; Croll and McDonald 2017).

The third major evolutionary driver is the **differential survival of resistant lineages** under strong selection pressure by fungicide sprays lacking chemical diversity, over a long course of prophylactic and/or empirical, and repeated, treatments with fungicides with the same mode of action. Predictions regarding the fate of evolution towards fungicide resistance in field populations of plant pathogens depend on the adaptive cost of mutations associated with resistance (Fisher et al. 2018). To persist in the field, resistant mutants must be pathogenic *in planta* and competitive against other strains of the pathogen and other microorganisms (Brasseur et al. 1996). As a consequence, mutations that confer high levels of resistance, with lower adaptive cost, are positively selected and tend to persist and become prevalent in the field over time (Hobbelen et al. 2014; Lucas et al. 2015; Hawkins and Fraaije 2018). If there is an adaptive cost, discontinuance of fungicide spray in the field could restore the sensitivity of populations of plant pathogenic fungi. This was detected for *M. fructicola* in stone fruit orchards from Brazil after discontinuing the use of the MBC thiophanate-methyl for seven years (Fischer et al. 2023) or the DMI tebuconazole for at least three years (Pereira et al. 2020b).

Therefore, fungicide resistance often provides an adaptive advantage to plant pathogen populations under fungicide selection pressure, but mutations that confer resistance can also result in adaptive penalties, such as an evolutionary trade-off (Hobbelen et al. 2014; Lucas et al. 2015; Hawkins and Fraaije 2018). These penalties come from functional restrictions arising from the evolution of a target site or from the costs of reallocating cellular resources through gene overexpression or active transport of the fungicide (Hawkins and Fraaije 2018). The distinct complement of resistance mutations present in populations of plant pathogenic fungi can be complex and challenging in predicting the evolutionary trajectory of fungicide adaptation (Pereira et al. 2020a). The analysis of adaptive landscapes from an evolutionary point of view, combined with genomic-functional tools to investigate the effects of mutations individually and in different combinations, allows a better understanding of the evolutionary trajectories of plant pathogen populations under fungicide selection pressure (Hawkins and Fraaije 2018; Pereira et al. 2020a).

Risks of resistance based on the fungicide chemical mode of action

It has been widely accepted that the chemical mode of action of fungicides is a key factor determining the risks for the development of resistance in populations of plant pathogens (Brent and Hollomon 2007; Brent 2012; Thind 2012). Based on this criterion, there are systemic site-specific fungicides, which interrupt particular cellular processes and bind to specific target proteins such as the MBCs, e.g. thiophanate-methyl and carbendazim; the DMIs, e.g. the azoles epoxiconazole, propiconazole, tebuconazole and others; the QoIs, e.g. azoxystrobin, pyraclostrobin and trifloxystrobin; the SDHIs, e.g. bixafen, boscalid, fluxapyroxad (Brent 2012; Thind 2012). These fungicides are considered to possess medium to high risk for resistance because selection within a population of a plant pathogenic fungus favoring mutants with a single mutation in the target gene could result in loss of fungicide efficacy (Brent and Hollomon 2007; Grimmer et al. 2014, 2015). Therefore, high risk is associated with the high selection pressure exerted by the single-site fungicides as a consequence of their specific mode of action, their high efficacy (i.e., high activity at low doses) and their intensive (and extensive) usage, thus accelerating the evolution for resistance in populations of plant pathogens (Grimmer et al. 2014, 2015). These fungicides contrast with the class of multisite fungicides [the copper-based fungicides, e.g. copper oxychloride; the dithiocarbamates, e.g. mancozeb; and the tetra phthalonitriles, e.g. chlorothalonil] targeting and interfering with a range of cellular and metabolic processes, and that are considered to have lower risk for resistance. Unlike single-gene mutations that confer resistance to single-site fungicides, the occurrence of mutants with simultaneous mutations in multiple target genes would be needed to confer resistance to multisite fungicides (Brent and Hollomon 2007; Brent 2012; Thind 2012). Hence, resistance to multisite fungicides is rare and its mechanisms are not known.

However, the chemical mode of action of a fungicide cannot be considered as the single parameter defining the risk of resistance. For instance, a risk assessment model proposed by the FRAC considers a matrix to calculate the risk of resistance to fungicides, initially based on three criteria derived from practical experience: a) the risk associated with the chemical mode of action of the fungicide; b) the risk attributed to the plant pathogen; and c) the agronomic risk, an indication of the favorability of the agroecosystem (Kuck and Russell 2006; Brent and Hollomon 2007). However, this risk matrix model for fungicides proposed by FRAC showed no correlation with the observed number of years prior to the emergence of resistance ($r_s = -0.06$, $p = 0.6474$) (McDonald and Linde 2002), and has limited predictive value within the dominant category of high risk fungicides (Grimmer et al. 2014).

In contrast, a more thorough risk assessment model proposed by Grimmer et al. (2015) included the identification of key characteristics as important determinants of resistance risk. This model includes the pathogen's latent periods in the year [a measure of the duration of the disease epidemic divided by the time between infection and pathogen reproduction], the number of plant species and cultivars infected by the pathogen [narrow versus wide host range, with more intensive fungicide selection active for the latter], production under protected versus open field cropping systems [with higher selection of resistant strains indoors] and the complexity of the fungicide molecule [where high-complexity molecules exhibiting higher target-site binding specificity are more likely to be compromised by small changes in efficacy]. The model combining these key features explained 61% of the temporal variation for the emergence of resistance to high-risk site-specific fungicides. Risk assessment based on these key characteristics could then be used to determine resistance risk for fungicides with novel modes of action, for which there is no prior information on resistance behavior (Grimmer et al. 2015).

Risk for fungicide resistance based on the evolutionary adaptive potential of plant pathogens

An evolutionary risk model based on population biology parameters, such as population size, reproductive rate, reproductive mode, gene flow and long-distance dispersal capacity was a better predictor of evolution of plant pathogenic fungi towards fungicide resistance (r_s for pathogen migration parameters = -0.72 ; $p = 0.0001$) than the former one based on a risk matrix (McDonald and Linde 2002). In conclusion, though risk matrix-based models can offer a general guide to risk, they cannot predict when or where fungicide resistance will occur, or how quickly it may spread and compromise plant disease management decisions. Such predictions require precise measurements of the adaptive potential for fungicide resistance, which can be derived from estimates of genetic variance for a fitness-related trait (van den Bosch and Gilligan 2008; Willi et al. 2011; Ferro et al. 2020), the population size and mutation rates, the predominant reproductive mode [from sexual to clonal, outcrossing to selfing, or mixed), the extent of gene flow (McDonald and Linde 2002), and the selection coefficient [determined by the difference in adaptability of sensitive strains in relation to resistant to a given fungicide (van den Bosch et al. 2014a)], as well as on other factors influencing the survival and invasion of resistant strains (Gubbins and Gilligan 1999).

Therefore, fungicide resistance cases provide fascinating evidence of accelerated evolution under strong selection pressure derived from intensive fungicide sprays. This can be used to address fundamental questions regarding the

evolutionary origins of resistance and the adaptive potential of populations of plant pathogens to new molecules (Lucas et al. 2015). For instance, (a) whether this adaptive potential stems primarily from new mutations or pre-existing variation; (b) which pre-existing traits in plant pathogen populations could form the basis of resistance adaptations; and (c) whether the recurrence of common resistance mechanisms among plant pathogen species results from outcrossing and horizontal gene transfer or from independent parallel evolution (Hawkins and Fraaije 2018).

Major fungicide resistance mechanisms

To understand the emergence of fungicide resistance in field populations of plant pathogens, the mechanisms that result in reduced sensitivity and the genetic basis of resistance should be determined. Eight mechanisms associated with the development of resistance to fungicides in populations of plant pathogenic fungi have been described so far (Hu and Chen 2021). These mechanisms can be: a) Conformational changes in the protein target site due to mutations in the gene's coding region, a major mechanism particularly for specific single-site fungicides such as MBC, DMI, QoI and SDHI (Lucas et al. 2015); b) Overexpression of the target site protein, which results in an increase in the fungicide inhibitory concentration (Cools et al. 2012); c) Non-target site mechanism, such as alternative respiration pathways triggering the synthesis of alternative oxidase (AOX) thus providing a QoI-insensitive pathway for oxidation of NADH (Wood and Hollomon 2003); d) Efflux of fungicides, usually involved in multidrug resistance and often associated with overexpression of efflux transporters with broad substrate specificity; these efflux transporters are members of the ATP-binding cassette (ABC) or major facilitator superfamily (MFS) transporter proteins (Rajendran et al. 2011; Perlin et al. 2014); e) Paralog re-emergence as an adaptive pathway, by which a historically contingent dispensable paralogous gene that determine fungicide resistance present at low levels in natural populations of plant pathogens at the point when selection pressures changed its frequency due to anthropogenic fungicide sprays (Hawkins et al. 2014; Mair et al. 2016b; Steinhauer et al. 2019); f) Regulation of environmental stress response in fungi, such as the osmosensors in the high osmolarity glycerol (HOG) pathway, interfered by phenylpyrroles, including fludioxonil and fenpiclonil (Kilani and Fillingner 2016), and mutations in the same osmotic sensitivity loci oftentimes lead to resistance to phenylpyrroles (Zhang et al. 2002); and g) Fungicide degradation by detoxification via metabolic enzymes, which is less common in fungi (Sang et al. 2018), although reported for herbicide resistance in grasses (Cummins et al. 2013) and is also common for insecticide resistance (Nardini et al. 2012). We will discuss in more details the mechanisms associated

with fungicide resistance in three major pathosystems for the Brazilian tropical agroecosystem.

Fungicide resistance scenario in three major Brazilian pathosystems

Asian soybean rust

Since its first introduction in Brazil in 2001 and emergence as a major crop disease, the **Asian soybean rust** (ASR) caused by the obligate parasite *Phakopsora pachyrhizi* (*Pp*) has spread widely and became the most important soybean disease in the country (Yorinori 2021a). Further, the disease has caused yield losses of up to 90% on susceptible varieties under favorable weather conditions when fungicides were not applied (Juliatti and Zambolim 2021). Yield losses have been recurrent along the years, ranging from a minimum of 363.5 thousand tons in 2011/2012 (\cong 0,6%) up to a historical 4.6 million tons in 2003/2004 (\cong 9,6%), heavily impacting the Brazilian economy which is based mainly on the export of commodities (CONAB 2004, 2013; Godoy et al. 2016; Juliatti and Zambolim 2021). With the crop distributed throughout the country, epidemics of the disease are very common in different agroecosystems where the fungus can survive all year round on soybean volunteer plants (Fanaro et al. 2011; Garcés Fiallos 2011a, b; Yorinori 2021b). Mandatory regulation enforcing fallow cropping (a soybean-free period of 60 to 90 days in the off-season) was adopted to restrict the occurrence of late-season soybean volunteer plants and consequently reducing the survival of inoculum between growing seasons (MAPA / Secretariat of Agricultural Defense (SDA) 2021a, 2021b, 2022). Despite these measures, 573 ASR infected field sites were reported in the 2021/22 cropping season (\cong 23% of the country's soybean fields), which was 41.5% higher than 2020/21 and the highest in the past decade (Consórcio Antiferrugem 2023).

Major host resistance genes have been mapped and incorporated in the soybean cultivars (Li et al. 2012; Childs et al. 2018; Lin et al. 2022). However, this resistance has not been durable and stable due to the rapid breakdown of resistance genes by the emergence and selection of new compatible virulent fungus genotypes (Hartman et al. 2005; Yorinori et al. 2005; Akamatsu et al. 2013, 2017; Yorinori 2021c). Therefore, disease management has relied mainly on chemical control with systemic fungicides, but the fungicide efficacy has decreased steadily over the past two decades in Brazil from complete control to only around 20% efficacy (Godoy et al. 2016; Dalla Lana et al. 2018; Barro et al. 2021). This is probably due to the emergence of resistance to the two major classes of fungicides, i.e. QoIs and DMIs (Schmitz et al. 2014; Müller et al. 2021). The emergence

of fungicide resistance can be attributed to high selection pressure on the ASR pathogen populations, as a response to large-scale use of calendar-based prophylactic fungicide spray programs (Godoy et al. 2016; Yorinori 2021d). Due to problems faced by the current fungicide-dependency and the lack of ASR control, the Brazilian MAPA, followed by the Paraná Agricultural Defense Agency (ADAPAR), suspended the recommendation of 63 mixtures of commercial fungicides to control the disease (ADAPAR 2015; MAPA / Secretariat of Agricultural Defense (SDA) 2016). Despite this, the chemical control of ASR with fungicides still represents a cost of up to US\$ 2,2 billion per year for the Brazilian soybean industry (Godoy et al. 2016; Yorinori 2021a, e; Ishikawa-Ishiwata and Furuya 2021).

As odd as it seems, it was only after resistance to the systemic single-site DMI and QoI fungicides became widespread in Brazil (Schmitz et al. 2014; Müller et al. 2021) that the chemical management of ASR has begun to rely on old broad-spectrum protectant multisite fungicides, such as copper and dithiocarbamates, with some acceptable efficacy (Godoy et al. 2016; Juliatti et al. 2017; Netto et al. 2020). On the other hand, the SDHI fungicides, the latest group of systemic fungicides introduced in the Brazilian market in 2013 are available for management of soybean diseases. However, considered as medium to high-risk fungicide group for selecting resistance in exposed populations (Simões et al. 2018; Borba 2020), they were introduced in mixtures with QoI and DMI fungicides, for which shifts in sensitivity had already been detected in *Pp* populations (Klosowski et al. 2016a, b, 2018; Müller et al. 2021). Perhaps not surprisingly, insensitivity to SDHI had already been reported in *Pp* isolates from Brazil shortly after the labeling of these fungicides (Simões et al. 2018; Müller et al. 2021).

Fungicide resistance mechanisms in the ASR pathogen

Resistance to QoI and DMI fungicides is widespread in Brazil, and has been reported in the states of Goiás (GO), Mato Grosso (MT), Mato Grosso do Sul (MS), Minas Gerais (MG), São Paulo (SP), Paraná (PR) and Rio Grande do Sul (RS) (Klosowski et al. 2016b, 2018; Müller et al. 2021) (Fig. 2A, Table 1). This distribution and prevalence of resistance is probably associated with a countrywide concerted pattern of fungicide recommendation from similar mode of action over two decades (MAPA 2023), or perhaps due to the pathogen efficient long distance dispersal (Twizeyimana et al. 2011). For the QoI-resistant strains, a *cytB* mutation resulting in the *cytB* b F129L substitution was detected as prevalent in Brazil (Klosowski et al. 2016b) (Table 2). Multiple target site mutations detected in the *CYP51* gene of the DMI-resistant strains (F120L, V130A, Y131F/H, K142R, I145V/F, F154Y, I475T, totalling nine mutations), as single

or in combinations of double or triple mutations, determine the specificity and the levels of sensitivity to DMIs (Klosowski et al. 2016a, 2018; Müller et al. 2021; Stilgenbauer et al. 2023) (Table 2). *CYP51* overexpression can also reduce the sensitivity to DMIs, as reported for other rust fungi (Stammler et al. 2009). For the first time since the recent deployment of SDHIs, reduced sensitivity to SDHIs was detected in *Pp* isolates sampled during the 2015/2016 cropping season (Müller et al. 2021). The insensitive isolates carried a mutation in the *SdhC* gene, resulting in the SdhC-I86F target alteration (Müller et al. 2021) (Table 2). A selective advantage of this mutation is probably responsible for the accumulation of this allele and its fast spread in soybean fields across Brazil from 2015 through 2019, under fungicide pressure (Mello et al. 2021). The mutation in the *SdhC* gene reached similar relevance as the mutations for QoI and DMI resistance.

Banana Sigatoka disease complex

The Banana Sigatoka disease complex (BSDC) includes the Black and Yellow Sigatokas. In Brazil, Black Sigatoka [caused by *Mycosphaerella fijiensis* (*Mf*) (syn. *Pseudocercospora fijiensis*)] was first reported in 1998 in the Amazon region (Gasparotto et al. 2000; Brito et al. 2015). Since then, the disease has been detected in 19 states (Uchôa et al. 2021), including the two most important banana producing states: São Paulo (Ferrari et al. 2005) and Bahia (Ramos et al. 2018). Black Sigatoka is regarded as the major constraint to banana production, reducing yield up to 100% (Brilo et al. 2015; Nomura et al. 2020). However, some reports indicate that the Black Sigatoka may have been misdiagnosed as the less devastating Yellow Sigatoka [caused by *M. musicola* (*Mm*) (syn: *P. musae*)] (Gomes et al. 2013). Yellow Sigatoka, first reported in the Amazon region in 1944, is more widespread and known to be present in all banana-growing regions from Brazil (Gomes et al. 2018). Yield losses of up to 50% have been reported for yellow Sigatoka (Brilo et al. 2015; Nomura et al. 2020). In addition, *M. thailandica* (*Mt*) (syn. *Parapallidocercospora thailandica*) (Crous et al. 2004; Arzanlou et al. 2008), highly prevalent in Ribeira Valley, SP (Malimpensa 2018), and the less frequent eumusae leaf spot pathogen *M. eumusae* (syn. *P. eumusae*) (Carlier et al. 2000; Brito et al. 2015, 2020) can also cause leaf spots on bananas and are present in Brazilian banana producing regions. Black and Yellow Sigatoka are still considered the two most relevant diseases of the BSDC in Brazil, though (Santos 2005; Rocha et al. 2012; Nomura et al. 2020; Oliveira et al. 2022).

BSDC are polycyclic diseases and the pathogens *Mf* and *Mm* have a mixed reproductive system, with a predominant clonal epidemic dispersal via conidia and a cyclic sexual

Table 2 Timeline of the emergence of resistance to the high risk fungicides QoI, DMI and SDHI in populations of the Asian soybean rust pathogen *Phakopsora pachyrhizi* from Brazil indicating an accelerated evolution for resistance over the past 10 years

Group of fungicides and year of detection	Geographical origin (States and/or Region)	Isolates (N)	Prevalence of resistance (NR)	Resistance mechanism and point mutations detected	Reference and/or remarks
QoI					
2009 - 2010	GO, MG, MS, MT, PR, RS, and SP	38	0	None found at <i>cytB</i> gene	(Schmitz et al. 2014)
2012 - 2014	...	41	20	CytB F129L; CytB G143A and G137R not found.	(Klosowski et al. 2016b)
2013 - 2017	MT, PR, RO, and SP	21	19	CytB F129L detected in 90% of the isolates	(Müller et al. 2021)
DMI					
2009 - 2010	GO, MG, MS, MT, PR, RS, and SP	38	32	CYP51 F120L, Y131F, Y131H, K142R, I145F and I475T; overexpression of <i>CYP51</i>	(Schmitz et al. 2014)
2013 - 2017	MT, PR, RO, and SP	21	18	CYP51 F120L + Y131H most frequent	(Müller et al. 2021)
2021	Brazil (several states) Paraguay	139 6	139 6	CYP51 V130A, I145V, F154Y	Three new mutations identified (Stilgenbauer et al. 2023)
SDHI					
2016	RS	21	9	F120L+Y131H+I145V (low frequency, in BA), and	Triple combinations of mutations associated with different sensitivities to DMI's (Stilgenbauer et al. 2023)
2013 - 2017	MT, PR, RO, and SP	21	3	F120L+Y131H+F154Y (in 2018 but not in 2021)	Frequency increased by the intensive use of pro-thioconazole (Stilgenbauer et al. 2023)
2015 - 2019	RS, SC, MG, SP, GO, MS, MT, BA, MA, PA, PI, and TO	770	608	F120L+V130A+Y131F (in GO, MS, MT, PR, SC and RS states)	
				SdhC I86F	(Simões et al. 2018)
				SdhC I86F, in samples from PR and RO in 2016/2017	(Müller et al. 2021)
				SdhC I86F widely distributed in Brazil. The frequency of the wild type populations decreased from 93.1% (2015/2016), 11.5% (2016/2017), 32.1% (2017/2018) to 9.6% (2018/2019).	(Mello et al. 2021)

reproduction followed by the release of ascospores (Burt 1994; Beltrán-García et al. 2014). Populations of *Mf* and *Mm* from Brazil, Mexico, and the Philippines have high genotypic variation arising both from sexual reproduction and gene flow originating from distant migration of the pathogens (Brito et al. 2015; Gomes et al. 2018; Manzo-Sánchez et al. 2019; Mendoza and Ardales 2019). Genetic resistance to BSDC is absent or partial in most of the commercial banana cultivars (Churchill 2011). Therefore, disease control strategies are mainly based on programmed calendar-based systemic or protectant fungicides sprays (Brito et al. 2015). Up to 52 sprays of protectant or 26 sprays of systemic fungicides can be applied per year under high disease pressure, particularly in Costa Rica and Ecuador (Malimpensa 2018; Uchôa et al. 2021; Brito et al. 2015). Contrastingly, in commercial banana plantations from the Ribeira Valley, Brazil, the control of Black Sigatoka is made by weekly monitoring of the disease, which results in as much as 15–20 fungicide sprays per year (Uchôa et al. 2021). Sigatoka control is highly dependent on frequent use of the systemic site-specific QoI and DMI fungicide applications (Churchill 2011). The consequences of the excessive use of fungicides are increased production costs, a negative impact on the environment, and a high selective pressure on pathogen populations, which can lead to emergence, selection and spread of fungicide resistant strains (Cañas-Gutiérrez et al. 2009; Grice et al. 2013; Diaz-Trujillo et al. 2018; Brito et al. 2020; Oliveira et al. 2022).

Fungicide resistance in BSDC pathogens

In the last decade, only a limited number of studies have been published on fungicide resistance in *Mf*, *Mm*, and *Mt*, mostly for QoI and DMI fungicides, besides a single contemporary study with reduced sensitivity to SDHIs (Fig. 2B, Tables 1 and 2). QoI resistance based on *cytB* G143A has developed rapidly in *Mf* populations in several countries since 2000 (Sierotzki et al. 2000; Amil et al. 2007), while the first report for *Mm* populations is from 2012 in Australia (Grice et al. 2013). In Brazil, no QoI resistance was detected in populations of *Mf* from the Amazon (Northern Brazil) and from Ribeira Valley in São Paulo (Southeastern Brazil, SP), as well as in populations of *Mm* from the Federal District (Central Western) and São Paulo states sampled as early as 2008 and as recently as 2018 (Gomes et al. 2014; Brito 2015; Hanada et al. 2015). In a more recent survey, a total of 10.0%, 9.4% and 85% of all isolates of *Mf*, *Mm* and *Mt*, respectively, sampled from banana fields under different fungicide spray regimes at four distinct locations in São Paulo and Minas Gerais states (Southeastern Brazil) were QoI resistant carrying the G143A substitution in *cytB* (Oliveira et al. 2022). Pathogens populations from the field

where conventional or intensive use of fungicides was done had a higher frequency of resistant isolates than populations from no fungicide input. The species *M. thailandica*, in particular, was highly prevalent in the populations from Ribeira Valley, representing more than 45% of the isolates sampled independently in 2018 and in 2021 from leaves with Black Sigatoka like symptoms, and most of these isolates were QoI-R (Malimpensa 2018; Oliveira et al. 2022).

Although studies on DMI fungicides resistance phenotypes linked to mutations in the corresponding target genes were largely scarce in Brazil until 2015, there are evidences of reduced sensitivity in the same *Mf* populations from the Amazon back to 2008 - 2009 (Gomes et al. 2014) and 2015 (Hanada et al. 2015) (Table 3). Concerning the mechanisms of resistance to DMI fungicides in *Mf* and *Mm*, *CYP51* changes have been reported elsewhere for both species (Cañas-Gutiérrez et al. 2009; Brito et al. 2020), while *CYP51* overexpression associated with different tandem repeats in *CYP51* promoter sequences has also been reported for *Mf* (Diaz-Trujillo et al. 2018). In Brazil, the target site alterations CYP51 G462D and Y463H (Malimpensa 2018), and CYP51 T18I, V106D, Y461D and Y463D (A. G. da Silva, personal communication) in *Mf*, CYP51 A381G, Y461N and Y463H (Brito 2015; Malimpensa 2018; Brito et al. 2020), and CYP51 V106D, Y136F, A446S, Y461H, Y461N, and Y463D (A. G. da Silva, personal communication) in *Mm* have been associated with resistance to DMIs in insensitive strains of the pathogens (N=2—10 *Mf* and 1—44 *Mm*) from the Federal District (Central Western), Northern Minas Gerais, Western and Ribeira Valley regions in São Paulo (Southeastern Brazil). As DMI fungicide sprays are very frequent in banana plantations (Gasparotto et al. 2000; Martínez-Bolaños et al. 2012; Chong-Aguirre 2016; Moraes and Nomura 2020), constant monitoring of *Mf* and *Mm* populations and detailed investigation regarding the evolution, emergence, spread and persistence of resistance to DMIs in distinctively favorable agroecosystems for each of the pathogens is urgently needed. Without up-to-date information on optimal fungicide risk and disease management strategies, a more sustainable control cannot be devised (Cools et al. 2013; Corkley et al. 2022).

Concerning the site-specific SDHI fungicides, they were labeled for BSDC management in 2014, and present a medium to high risk for the emergence of resistance if deployed intensively and singly (Sierotzki and Scalliet 2013). Currently, the SDHI fungicides labeled for the management of the BSDC pathogens in banana plantations elsewhere include boscalid, fluopyram, fluxapyroxad, and isopyrazam (FRAC 2022c). Particularly in Brazil, only a single co-formulation fungicide (Collis™, from BASF) containing the SDHI boscalid and the QoI kresoxim-methyl has been labeled (MAPA 2023). *In vitro* SDHI sensitivity testing of *Mf* and *Mm* populations sampled from banana

Table 3 Timeline of the emergence of resistance to the high risk fungicides QoI, DMI and SDHI in populations of the Black and Yellow Sigatoka pathogens *Mycosphaerella fijiensis*, *M. musicola* and *M. thalassica* from Brazil indicating an accelerated evolution for resistance in the past 10 years.*

Group of fungicides and year of detection	Species	Location (State and Region)	Isolates (N)	Prevalence of resistance (NR)	Resistance mechanism and point mutations detected	Reference
QoI						
2008 - 2009	<i>Mf</i>	AC, AM, MT, PA, RO, and RR (N) and SP (SE)	36	0	CytB G143A not detected (ND)	(Gomes et al. 2014)
2015	<i>Mf</i>	AC, AM, MT, RO, and RR (N)	150	0	ND	(Hanada et al. 2015)
2015	<i>Mm</i>	DF (CW)	48	0	ND	(Brito 2015)
2018	<i>Mf</i>	SP (SE)	2	0	0	(Malimpensa 2018)
...	<i>Mm</i>	...	1	1	CytB G143A	...
...	<i>Mt</i>	...	12	11
2021	<i>Mf</i>	...	10	1	...	(Oliveira et al. 2022)
...	<i>Mm</i>	MG and SP (SE)	96	9
...	<i>Mt</i>	...	13	11
DMI						
2008 - 2009	<i>Mf</i>	AC, AM, MT, PA, RO, and RR (N) and SP (SE)	45	15	ND	(Gomes et al. 2014)
2015	<i>Mf</i>	AC, AM, MT, RO, and RR (N), from plantains in areas with no fungicide sprays	150 ascospore isolates	5	ND	(Hanada et al. 2015)
2015	<i>Mm</i>	DF (CW)	48	5	CYP51 Y461N	(Brito 2015; Brito et al. 2020)
2018	<i>Mf</i>	SP (SE)	2	2	CYP51 G462D and Y463H	(Malimpensa 2018)
...	<i>Mm</i>	...	1	1	CYP51 A381G and Y463H	...
2021	<i>Mf</i>	SP (SE)	9	9	CYP51 T181, V106D, Y46 ID and Y463D	A. G. da Silva (personal communication)
...	<i>Mm</i>	MG and SP (SE)	42	6	CYP51 V106D, Y136F, A446S, Y461H-N, and Y463D	...
SDHI						
2021	<i>Mf</i>	SP (SE)	10	7	SDHC N55D; efflux pump	(Silva 2023)
...	<i>Mm</i>	MG and SP (SE)	57	33	SDHB E196Q; SDHD K57N; efflux pump	...
...			...	53	(boscalid)	...

*Brazilian regions: CW, Central western; N, Northern; SE, Southeastern

plantations in different geographical regions of Southeastern Brazil in 2021 revealed that resistance was already present (Silva 2023) (Fig. 2B, Table 1). Further research is needed to translate the results from the *in vitro* tests into efficacy loss of practical disease control under field conditions. Among the 10 *Mf* and 57 *Mm* isolates for which the *sdhB*, *sdhC* and *sdhD* genes were examined, only one (*Mf* SdhC N55D) and two (*Mm* SdhB E196Q and SdhD K66N) Sdh target site alterations, respectively, were detected (Silva 2023) (Table 3). We highlight that, to our knowledge, none of these substitutions has been associated with resistance to SDHI fungicides in the BSDC pathogens according to the most recent survey conducted by the SDHI Working Group in 2022 (FRAC 2022a). Further monitoring for Sdh target mutations is important, but other resistance mechanisms such as the presence of multiple Sdh paralogs (Yamashita and Fraaije 2018; Steinhauer et al. 2019), and multidrug resistance (MDR) associated with efflux pump mechanism cannot be ruled out (Silva 2023).

Wheat blast disease

Wheat blast (WB), caused by the hemibiotroph ascomycete *Pyricularia oryzae Triticum* lineage (*PoTl*) (Castroagudín et al. 2016; Gladioux et al. 2018), has been a major disease across Central and Southern Brazil since it was first reported in Paraná state in 1985 (Igarashi et al. 1986). Following the emergence of wheat blast in Bangladesh in 2016 (Islam et al. 2016) and its further spread into Zambia, East Africa, in 2017 (Tembo et al. 2020), *PoTl* came to the attention of Asian and African governments and the international research community, bringing to light an urgent need to develop plans to contain the spread of this destructive pathogen in Asia and Africa (Islam et al. 2016; Ceresini et al. 2018, 2019; Tembo et al. 2020). Strategies for WB management must be based on information on *PoTl* biology and epidemiology, including the pathogen's life cycle, survival, spread, host range and reproductive mode(s) and environmental conditions triggering disease (Ceresini et al. 2018, 2019). The two most common disease management strategies, use of resistant varieties and fungicide sprays, are likely to fail if applied individually. Fungicides are considered only partially effective, for reasons detailed in the next topic (Pagani et al. 2014; Rocha et al. 2014; Sharma 2017; Cruz and Valent 2017; Cruz et al. 2019; Ascari et al. 2021). Although sources of durable resistance to *PoTl* have been identified (Cruz et al. 2010; Wang et al. 2018; Cruppe et al. 2020; Dianese et al. 2021), major host resistance genes are likely to be overcome by the emergence of virulent races from the highly diverse pathogen population (Maciel et al. 2014; Ceresini et al. 2018). Integrated disease management (IDM) strategies are needed to reduce crop losses without impacting

the environment (Maciel 2011; Mehta 2014; Cruz and Valent 2017; Ceresini et al. 2019). The implementation of IDM strategies should be coordinated locally, taking into account the particular circumstances of each country or region (Ceresini et al. 2018).

Low efficacy of fungicides to control wheat blast in Brazil

Fungicides are regularly used to manage WB and ear-associated diseases. However, the field efficacy of fungicides is considered low, resulting in only small decreases in blast severity on symptomatic spikes. A meta-analysis from 42 field trials over a nine year period, from 2012 through 2020, pointed to an average control efficacy of QoIs and azoles (DMIs) fungicides ranging from 43% up to 58% (Ascari et al. 2021). Disease control of no more than 50%, in comparison to untreated plots (Maciel 2011), and reduced crop losses were only achieved when mixtures of DMIs and QoIs were applied early on moderately resistant wheat varieties under low or moderate disease pressure (Rios et al. 2016). The effectiveness of applications at early heading and early grain-filling stages seemed to be associated with a reduction in *PoTl* inoculum produced on the lower leaves, leading to a reduction in ear infections (Cruz et al. 2015). The limited efficacy of fungicide treatments is likely to be due to several factors, including the difficulty of reaching the infection sites on spikelets, the high diversity of *PoTl* strains, the highly favorable weather conditions coupled with high levels of varietal susceptibility, and the low intrinsic efficacy of some fungicides, such as the methyl benzimidazole carbamates (Maciel 2011; Ceresini et al. 2018; Torres et al. 2022). In addition, *PoTl* has a broad host range, including several invasive grass species present in or near wheat fields, which do not receive fungicides sprays, thus providing a continuous external source of new inoculum (Ceresini et al. 2018).

A total of 49 fungicides have been labeled for management of WB disease in Brazil, comprising 17 azoles and seven co-formulations of azoles and QoIs (MAPA 2023). These two fungicide groups have been used extensively for management of rusts and other wheat leaf and head diseases for one to three decades (Poloni et al. 2021; Torres et al. 2022; Vicentini et al. 2022a). Their poor performance against wheat blast and lower profitability may have resulted from the emergence of fungicide resistance (Castroagudín et al. 2015; Poloni et al. 2021; Vicentini et al. 2022a; Cazón et al. 2023). New fungicide formulations labeled locally since 2017 for wheat diseases are mixtures of the second-generation carboxamide fluxapyroxad, a SDHI, combined with the QoI pyraclostrobin or the azole epoxiconazole, two active ingredients to which populations of *PoTl* were already found to be resistant (Dorigan et al. 2019; Poloni et al. 2021; Vicentini et al. 2022a; Cazón et al. 2023). The efficacy of

melanin biosynthesis inhibitors targeting polyhydroxynaphthalene reductase (MBI-R fungicides, such as tricyclazole) and plant defense activators (PDA, such as acibenzolar-S-methyl) controlling wheat blast is yet unknown, though they are labeled either for rice blast control or for controlling other foliar diseases on wheat, respectively (MAPA 2023).

Fungicide resistance mechanisms in *PoTl* field populations

In recent years, Brazilian *PoTl* populations sampled in 2012 and 2018, across the major wheat growing areas of Central and Southern Brazil, showed moderate to high levels of resistance to all the three major groups of medium to high-risk systemic site-specific fungicides labeled for management of WB in Brazil (Castroagudín et al. 2015; Poloni et al. 2021; Vicentini et al. 2022a; Cazón et al. 2023) (Fig. 2C, Tables 1 and 4). These fungicides included the DMIs (Dorigan et al. 2019; Poloni et al. 2021; Vicentini et al. 2022a; Cazón et al. 2023), QoIs (Castroagudín et al. 2015; Vicentini et al. 2022a; Cazón et al. 2023), and the SDHI fluxapyroxad (Vicentini et al. 2022a) (Table 4). The *in vitro* sensitivity tests indicated that resistance to azoles and QoI fungicides was widespread in the country, with prevalence higher than 89% (Castroagudín et al. 2015; Dorigan et al. 2019; Poloni et al. 2021). For SDHI sensitivity, moderate resistance to fluxapyroxad ($EC_{50} > 20 \mu\text{g}\cdot\text{mL}^{-1}$) were detected in isolates from five out of the six field populations sampled in 2012 (4.5% of the total sample) and in 47.6% of the *PoTl* strains isolated in 2018 (Vicentini et al. 2022a) (Fig. 2C, Table 4). In addition, *in vivo* fungicide sensitivity tests for *PoTl* under controlled environment conditions has also indicated moderate to high levels of resistance to multiple fungicides of these three groups, with blast control efficacy as low as 3.3% for the QoI azoxystrobin, 31.3% for the QoI pyrachlostrobin, 31.0% for fluxapyroxad, and 51.0% for the epoxiconazole (Cazón et al. 2023).

QoI resistance is linked to cytb G143A (Castroagudín et al. 2015; Vicentini et al. 2022a; Cazón et al. 2023), a well-known target site alteration conferring high levels of resistance in other pathogens, including *Mf* and *Mm* (Oliveira et al. 2022). For the azole resistance mechanism, the *CYP51A* and *B* haplotypes are not predictive of phenotype. For instance, isolates carrying a prevalent *CYP51A* R158K substitution were not more resistant than those expressing R158 (Dorigan et al. 2019; Poloni et al. 2021). Similarly, no association was found between target site mutations in the *sdhB*, *sdhC*, and *sdhD* genes and the levels of SDHI resistance, indicating that a pre-existing resistance mechanism not associated with target site mutations is probably present in the Brazilian wheat blast populations. However, under additional selection of SDHI fungicides, it is plausible that populations of *PoTl* will evolve target-site mutations as

resistance mechanisms similar to the ones already reported for other cereal fungal pathogens such as *Zymoseptoria tritici*, *Pyrenophora teres*, or *Ramularia collo-cygni* (Mair et al. 2016a). In addition, the multiple fungicide resistance, or multidrug resistance (MDR), detected both *in vitro* and *in vivo* (Cazón et al. 2023) was probably due to enhanced efflux pump activity in *PoTl* populations (Vicentini et al. 2022c).

Strategies for fighting against fungicide resistance in the agroecosystem

We will discuss the practical management of resistance to fungicides, looking to answer the following questions: (i) Is it possible to prevent resistance to a fungicide from occurring?, and (ii) Is it possible to manage resistance to fungicides once its emergence has been identified?

In our Review the term 'emergence' is employed to encompass a range of scenarios where resistant individuals, within a pathogen population, become established. This includes the natural occurrence of rare mutations that confer resistance as well as mutations that may arise due to the direct effect of fungicides. Given the widespread and extensive use of fungicides in agriculture, it is conceivable that *de novo* mutations for fungicide resistance induced directly by the fungicide's effects on the fungal genome may be more prevalent in certain cases. This phenomenon occurs when sublethal doses of fungicides exert selection pressure on the pathogen population, leading to the survival and reproduction of individuals with resistance-conferring mutations (Boyce et al. 2017; dos Reis et al. 2019; Gambhir et al. 2021; Healey et al. 2016). In practical terms, distinguishing between these sources of resistance mutations can be challenging. Therefore, we have chosen to use the term 'emergence' broadly to acknowledge that resistance can arise through various mechanisms, whether driven by natural genetic variability or induced by fungicide exposure.

Therefore, we postulate that, in general, the overall objective of resistance management strategies is twofold: first, to delay the emergence of variants of plant pathogens that can resist a fungicidal treatment (in the emergence phase of resistance development), and second, to reduce the selection of such variants (in the selection phase) (van den Bosch et al. 2014a).

For pathogens whom resistance to a specific fungicide mode of action has never been detected, the basic anti-emergence strategies should be to prevent resistant lineages from emerging in the agroecosystem (Hobbelen et al. 2014; Corkley et al. 2022). As simple as it seems, a systemic single-site high-risk agricultural fungicide molecule should not be released in the market as a solo active, but only in co-formulations with low risk fungicide (i.e., a protectant multisite fungicide) (Fig. 4A). It may be very simple to implement,

Table 4 Timeline of the emergence of resistance to the high risk fungicides QoI, DMI and SDHI in populations of the wheat blast pathogen *Pyricularia oryzae* *Triticum* lineage from Brazil indicating an accelerated evolution for resistance over the past 10 years

Group of fungicides and year of detection	Location (State and/or Region)	Isolates (N)	Prevalence of resistance (NR)	Resistance mechanism and point mutations detected	Reference
QoI					
2005, 2012	RS, PR, MG, SP, MS, GO, and DF	179	160	CytB G143A	(Castroagudín et al. 2015)
2018	MG, SP and PR	183	178	...	(Vicentini et al. 2022a)
2018 - 2019	MG	13	13 (azoxystrobin) 9 (pyraclostrobin)	CytB G143A (in a subsample of 4 resistant isolates)	(Cazón et al. 2023)
DMI					
2005 - 2012	RS, PR, MG, SP, MS, GO, and DF	179	179	Isolates carrying the CYP51A R158K substitution were not more resistant than those expressing R158. DMI resistance associated with a non-target-site efflux pump mechanism.	(Dorigan et al. 2019; Poloni et al. 2021)
2018	MG, SP and PR	183	168	...	(Vicentini et al. 2022a)
2018 - 2019	MG	40	40 (MR to HR, mean EC ₅₀ tebuconazole = 1.08 µg.mL ⁻¹ ; mean EC ₅₀ epoxiconazole = 0.64 µg.mL ⁻¹)	Genotype not predictive of phenotype	(Cazón et al. 2023)
SDHI					
2012	RS, PR, MG, SP, MS, GO, and DF	157	155	No point mutations detected in <i>sdhB</i> , <i>C</i> or <i>D</i> , nor insertions in the promoter regions. A pre-existing resistance mechanism not associated with target site mutations. MDR was not associated with SDHI resistance.	(Vicentini et al. 2022a, c)
2018	MG, PR and SP	103	N = 7 (4.5%) with moderate resistance (EC ₅₀ = 20 — 50 µg.mL ⁻¹); N = 148 (94.3%) with reduced sensitivity (EC ₅₀ = 3 — 20 µg.mL ⁻¹). N = 49	Genotype not predictive of phenotype	(Vicentini et al. 2022a)
2018 - 2019	MG	13	Mycelial growth > 50% at DD of 3 µg.mL ⁻¹ N = 6 (fluxapyroxad) Moderate (EC ₅₀ = 20 — 50 µg.mL ⁻¹) to highly resistant (EC ₅₀ > 50 µg.mL ⁻¹)	Genotype not predictive of phenotype	(Cazón et al. 2023)

DD = Discriminatory dose

indeed, as the choice of a fungicide mixture is already an embedded anti-emergence strategy against the development of resistance that requires no other complex strategy, such as the decision on rotating fungicide with distinct modes of action. The lifespan of the high-risk agricultural fungicides is prolonged as their efficacy and profitability are kept along the years. Consequently, no environmental spread of fungicide resistant lineages of plant pathogenic fungi occurs (Fig. 4A). The relative effect of the doses of the multisite in mixture with the single-site fungicide on reducing the rate of selection for resistance should be determined (van den Bosch et al. 2014b). Unfortunately, anti-emergence strategies against fungicide resistance are not a choice any longer for the relevant plant pathogens of Brazilian agriculture (Figs. 1 and 2, Table 1).

The recurrent scenario of fungicide resistance becoming prevalent in field populations of several important plant pathogens for Brazilian tropical agriculture (Table 1) is rather serious and should be addressed as a general strategic failure in developing and deploying high-risk single-site agricultural fungicides properly. This also indicates that the application of the anti-resistance strategies (Fig. 5, A and B), legally included in fungicide labels since 2012 (MAPA / Coordination of Pesticides and Related Products 2012), have failed to delay the emergence and spread of resistance. It is particularly true for new fungicide molecules released thereafter (Mello et al. 2021; Müller et al. 2021; Vicentini et al. 2022a; Silva 2023). This has occurred despite the large amount of information derived from historical cases reported on fungicide resistance in populations of local key pathogens such as the ones of ASR, BSDC and WB (Schmitz et al. 2014; Klosowski et al. 2016b, 2018; Brito et al. 2020; Oliveira et al. 2022).

The anti-resistance strategies described in Fig. 5 (MAPA / Coordination of Pesticides and Related Products 2012) include general recommendations based on individual actions (Fig. 5A), for most of the plant pathogenic fungi, and specific recommendations for the ASR pathogen (Fig. 5B). Among them is the general recommendation to rotate sprays of fungicides formulated in mixtures, alternating distinct modes of action and never spray a commercial fungicide from a single mode of action alone. The objective is to avoid successive sprays of fungicides with the same mode of action as that could lead to an increased selection pressure for resistance in the pathogen populations. As an anti-resistance strategy, we would expect to lower the prevalence of recently emerged or established fungicide resistant lineages by reducing or removing the selection pressure from the extensive spraying of high-risk fungicides in the country [Fig. 4B; (Mikaberidze et al. 2014; van den Bosch et al. 2014a)].

Individual decision-based strategies on fungicide choice may be easily applicable. However, the effectiveness is

heavily dependent on fitness cost associated with resistance, under the absence of the fungicide sprays (Hawkins and Fraaije 2018). These strategies usually do not include a key recommendation to prevent the spray of a particular high-risk fungicide that lost efficacy due to resistance, or for which there is cross-resistance among actives from the same mode of action. Consequently, the resistant lineages tend to persist in the environment and to increase in frequency as the fungicide selection pressure persists (Hawkins and Fraaije 2018). In addition, some plant pathogenic fungi, such as the ASR, the BSDC and the WB pathogens, as well several others, are easily spread at long distance, overcoming non-concerted regional efforts to block the dispersal and re-introduction of resistance lineages (Twizeyimana et al. 2011; Maciel et al. 2014; Gomes et al. 2018; Brito et al. 2020).

Particularly for ASR, four of the anti-resistance strategies recommended contradict the principle of minimizing unnecessary fungicide sprays to reduce selection pressure for resistance, i.e., adoption of preventive spray tactics; including spray of the [respective] commercial fungicide only at the recommended timing and spray intervals; to follow a maximum interval of 14 days between spraying; carry out, at most, the number of sprays of the commercial fungicide as described in the label. Rather, growers and extension plant pathologists should be advised to avoid unnecessary preventive fungicide sprays, but to follow disease epidemics forecast systems based on weather favorability and risks for disease development to guide spray decisions (Fig. 4 B). Paradoxically, the disease epidemics forecast systems are virtually non-existent for most of the Brazilian states, with the exception of the Epagri/Ciram Agroconnect from Santa Catarina (available at the URL: <https://ciram.epagri.sc.gov.br/agroconnect/>). Alternatively, growers, technical assistants and agricultural extensionists are recommended to carry out frequent disease monitoring on the cropping area to detect any shift towards an increase in disease incidence. As plant disease epidemics are hard to predict, either institutionally or individually, calendar-based excessive fungicide sprays persist.

Validation of the effects of each of these anti-resistance strategies, and support for further decisions based on fungicides mode of action at risk, requires a massive effort for detection and monitoring shifts in fungicide resistance prevalence, *in loco*. This also requires highly skilled scientific and lab support for resistance detection and monitoring, at regional or countrywide scale, which demand appropriate and steady funding (Fig. 4B).

Alternatively, we have proposed evolutionary-smart anti-resistance strategies based on the reduction of the fungicide selection pressure on the pathogen populations, which are warranted to prolong the efficacy lifespan of agricultural fungicides (Mikaberidze et al. 2014; Corkley et al. 2022).

Although they are not really new strategies, they differ from the former anti-resistance strategies as they are not focused on individual actions, but rather are focused on institutional actions, either from the public or private sectors involved, and also include public policies.

The evolutionary-smart anti-resistance strategies aimed to prolong the efficacy of fungicides in agriculture by reducing the rate of evolution of plant pathogenic fungi towards fungicide resistance are:

- a) Strengthening of the existing Tropical Plant Health Network (URL <https://www.fitossanidadetropical.org.br/informacoes-tecnicas/areas-de-atuacao>). This is an official national network on foliar and seed fungicide testing to provide consistent, large-scale, and meta-analytic evaluation of fungicide efficacy, as well as crop yield response under disease-conducive environments over time and space. The network also aimed to monitor early negative trends in crop yield, pointing to the emergence of fungicide resistance in the field, and granting rapid and open access to the relevant information (Dalla Lana et al. 2018; Custódio et al. 2020, 2022; Ascari et al. 2021).
- b) Capacity building and establishment of a network for early detection of fungicide resistance emergence and increased dispersal by continual large scale monitoring of pathogen populations for fungicide sensitivity, analyses and compilation of phenotypic metadata, interpretation and consistent public release of the relevant information;
- c) Limiting the labeling of solo-active formulations of the high-risk single-site fungicides such as the SDHIs, or premixtures with other high risk fungicides for which resistance has been prevalent, such as QoIs or DMIs (Mikaberidze et al. 2014);
- d) Preferential labeling of premixtures of single-site at-risk fungicides with multi-site fungicides such as mancozeb (FRAC group M03), chlorothalonil (FRAC group M05) (Godoy et al. 2016; Netto et al. 2020) or copper-based actives (FRAC group M01) (Juliatti et al. 2017), as they have low-risk for fungicide resistance emergence; though all three fungicides are facing scrutiny due to environmental and health concerns in Canada, European Union, and United States (Jones et al. 2020), they remain labeled in Brazil (MAPA 2023);
- e) Constant reassessment of fungicides labeled for controlling ASR, BSDC, WB, and several other plant pathogens, for which a decrease in field efficacy as well as resistance has been detected, using the facilities of the network described previously in (a), and allowing prompt actions from the pesticide regulating agencies at federal and state levels (MAPA / Secretariat of Agricultural Defense (SDA) 2017);
- f) Technical recommendation, included in the fungicide labels, and information-transfer by the agricultural extension services, discouraging prophylactic, calendar-based, sequential sprays of active ingredients from medium to high-risk, single-site fungicide groups (SDHI, as case example), particularly in disease-conducive environments; recommending the choice of pre-mixtures of new SDHIs with multi-site fungicides, instead (Brent and Hollomon 2007; Fraaije et al. 2012);
- g) Advising, in the fungicide label and reinforced by the agricultural extension services, the need for integration of diverse disease management strategies other than fungicide sprays only, which include, as specific example, the full adherence to any mandatory off-season crop-free policy (MAPA / Secretariat of Agricultural Defense (SDA) 2022, p. 607), early sowing to escape favorable conditions for disease incidence (Koga et al. 2014; Dias et al. 2014), choice and deployment of resistant cultivars, particularly those with complete resistance, so fungicides sprays are not required (Hartman et al. 2005; Childs et al. 2018; Yorinori 2021c), and others, such as biological control with biofungicides.

Prospects and challenges

Establishment of a smart disease surveillance and fungicide resistance monitoring network to rationalize fungicide application

Lessons learned from the accelerated evolution and prevalence of fungicide resistance in populations of plant pathogenic fungi from Brazilian tropical agriculture should be applied to implement new disease management strategies to minimize fungicide sprays.

Smart surveillance and monitoring tools are needed in order to rationalize fungicide applications, e.g. choice of products, dose rate, frequency and timing of sprays and mixing or alternating fungicides. These tools will enable the quantification of inoculum levels of plant pathogens and the detection of alleles that confer resistance to fungicides. All these in combination with systems to predict the occurrence of diseases, in real time, by using automated spore capture and molecular detection of specific DNA markers of plant pathogens. These tools will be also important to test the efficacy of anti-resistance strategies aimed at reducing disease inocula, such as the implementation of cropping-free periods, to delay the evolution and the spread of resistance to current and new fungicides

As a result, the molecular mechanisms underlying resistance, i.e. functional characterization of the alleles that confer resistance, to the main fungicidal chemical groups, must be described and characterized for a

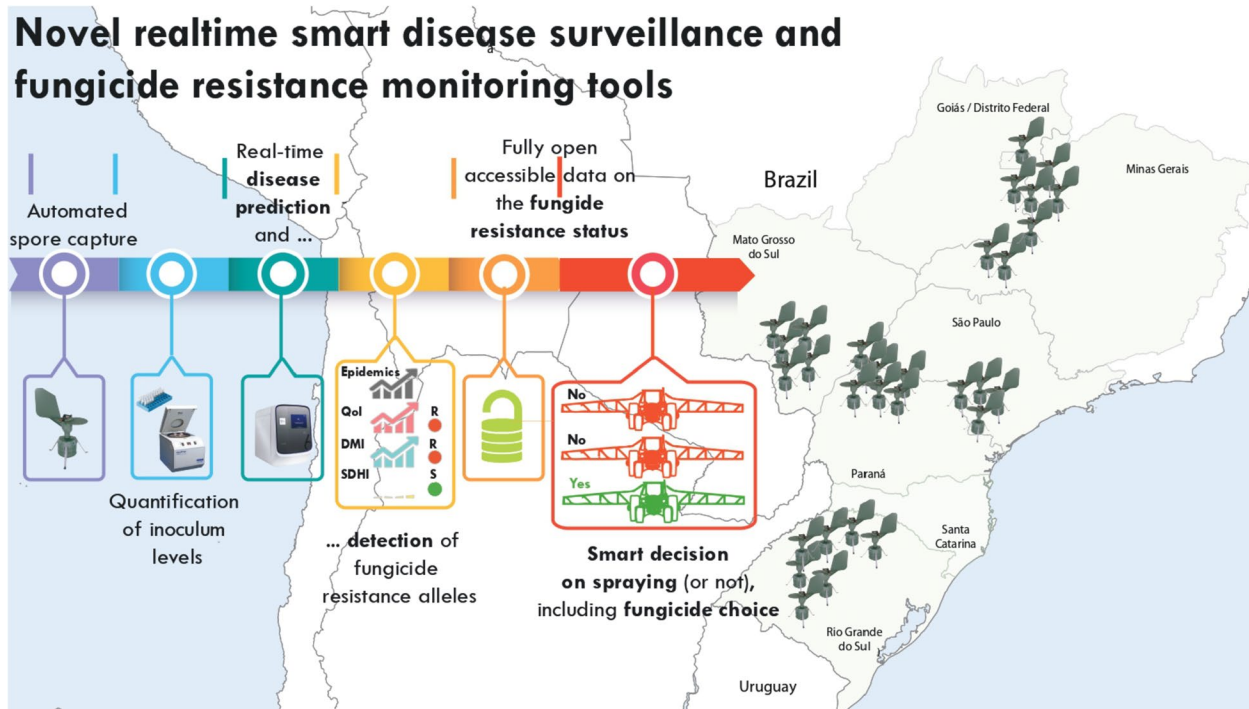


Fig. 6 Novel real-time disease surveillance and fungicide resistance monitoring network to foster a smart and sustainable crop protection platform in Brazil*. * Model description, rationale, fundamentals,

and the association of state of the art technology and open information sharing are discussed in detail in this item of the review

considerably larger range of plant pathogens important to Brazilian agriculture. High-throughput molecular diagnostics for real-time monitoring of resistance to fungicides in the agroecosystem must also be developed.

Therefore, we propose, as a smart anti-resistance strategy, the test and implementation of an aerobiology-based warning system to predict fungal diseases epidemics and to help minimize fungicide sprays (Fig. 6). Fundamentally, this smart and improved system implies the direct and early automated capture of airborne inoculum levels, in combination with molecular detection of the pathogen and fungicide resistance alleles. Further, the system can be useful in providing more accurate predictions of the risks of severe plant disease epidemics (Del Ponte et al. 2006; do Nascimento et al. 2012; Danelli and Reis 2016; Minchio et al. 2018; Beruski et al. 2019). It can also provide predictions of the spread of fungicide resistance alleles, preferentially before it occurs, as already reported for few important pathosystems (Luo et al. 2007; Deising et al. 2008; van der Heyden et al. 2021; Vicentini et al. 2022b, 2023).

Such a smart and improved disease forecasting system optimized for monitoring the fungicide resistance, and individualized for each crop, would benefit the growers by reducing the cost of production and prolonging the

effectiveness of the fungicides, and the consumers by increasing food safety and security and reducing fungicide residues in foods. The environment will also benefit due to reduction in the applications of pesticides, by avoiding unnecessary fungicide sprays or the use of inefficient ones due to the occurrence of high levels of resistance.

Establishment of a centralized database and information system on fungicide resistance in Brazil

Several stakeholders and segments of the Brazilian tropical agroecosystem may have interest in cataloging, reporting and sharing data on fungicide resistance in Brazil. These segments typically include:

- Agricultural research institutions:** Government and private Institutions involved in research, development, and innovation activities related to agriculture are often interested in sharing data on fungicide resistance to contribute to the scientific information and to give support to evidence-based decisions in disease management.
- Governmental agricultural agencies:** Agencies responsible for agricultural policies and regulations, such as the

Brazilian Ministry of Agriculture, Livestock and Supply (MAPA), have an interest in disseminating data on fungicide resistance to establish policies, to develop guidelines, and to promote sustainable agricultural practices.

- c. **Industry associations and agricultural manufacturers:** Associations representing agricultural industries, including fungicide manufacturers and distributors, may have an interest in publicizing the data to raise awareness on resistance issues and to promote responsible fungicide use.

Notwithstanding, the permanent cataloging and reporting of data on fungicide resistance in Brazil faces limitations and challenges that include inadequate funding and the absence of specific public policies mandatory for the comprehensive monitoring of fungicide efficacy and resistance. Efforts to monitor fungicide resistance in Brazil in the last decade have been made independently by several research groups from quite a few institutions and agricultural organizations. However, the coverage and extent of these efforts were limited and varied across regions and crops. Some of the factors contributing to these limitations include:

- a. **Funding constraints:** Adequate funding is crucial to carry out comprehensive monitoring programs, research projects, and data collection related to fungicide resistance. Limited financial resources can hamper the scale and scope of the monitoring efforts, making it difficult to gather large amounts of data on fungicide resistance for different crops and regions.
 - b. **Lack of specific public policies:** The absence of explicit public policies mandating comprehensive monitoring of fungicide efficacy and resistance can impact the priority given to these activities. In the absence of clear directives, there may be variations on the commitment and resources allocated to monitor fungicide resistance at a national or regional level.
 - c. **Emphasis on immediate yield quality protection:** In agricultural systems focused primarily on maximizing immediate yields, fungicide efficacy is often prioritized over long-term resistance management. This emphasis on short-term gains can result in a reduced emphasis on monitoring and documenting fungicide resistance.
 - d. **Limited coordination and infrastructure:** Coordinated efforts and infrastructure for collecting, analyzing, and disseminating data on fungicide resistance may be lacking or underdeveloped. The absence of centralized data repositories or standardized protocols for monitoring fungicide resistance can make it challenging to gather and share comprehensive information.
- To overcome the lack of an official public open access data repository to accommodate permanent fungicide
- resistance information in Brazil, several key strategies can be implemented:
- a. **Strengthening efforts on research and monitoring fungicide resistance:** Increase in investments on research and monitoring programs on fungicide resistance is essential. This involves allocating adequate funding and resources to support comprehensive studies on different crops, regions, and pathogens. Research institutions, agricultural organizations, and governmental agencies should collaborate to establish robust monitoring systems and standardized protocols for data collection.
 - b. **Enhancing collaboration and information sharing:** Encouraging collaboration among researchers, institutions, and stakeholders is crucial for sharing expertise, data, and best practices. This can be facilitated through partnerships, research networks, and platforms for information exchange. Encouraging open communication and collaboration can help overcome barriers and ensure a more comprehensive understanding of fungicide resistance in Brazil.
 - c. **Implementation of mandatory reporting and surveillance:** Introduction of regulations or policies that enforce reports on fungicide resistance cases can improve the availability of data. This can be achieved through partnerships between governmental agencies, research institutions, and agricultural industry stakeholders. Mandatory reports would ensure a more accurate and comprehensive assessment of the prevalence and distribution of fungicide resistance on different regions and crops.
 - d. **Building capacity and awareness:** Investments in training programs and capacity-building initiatives for researchers, extension agents, and farmers is essential. These initiatives should focus on enhancing information on fungicide resistance, promoting best management practices, and raising awareness on the importance of monitoring and management of resistance. Building capacity at all levels of the agricultural system will contribute to a more informed and proactive approach in regard to fungicide resistance.
 - e. **Implementations of integrated disease management strategies:** Shifting from overconfidence on fungicides to a more integrated disease management approach is crucial. This includes implementation of cultural, biological, and chemical control methods to reduce the selection pressure for fungicide resistance. Crop rotation, diversification of planting materials, use of resistant cultivars, and adoption of best agricultural practices can help minimize the dependence on fungicides and mitigate the development of resistance.

- f. **Establishment of centralized databases and information systems:** Development of centralized databases or information systems dedicated to cataloging and sharing data on fungicide resistance in Brazil would streamline and facilitate access to information. Such systems should be user-friendly, accessible to researchers, extension professionals, and farmers, and regularly updated with new findings. Centralized databases would help to consolidate information, facilitate data analysis, and provide a comprehensive overview on fungicide resistance trends in the country.

A vital alliance: The strategic inclusion of extension service and growers in the fight against fungicide resistance in the Brazilian agriculture

By the end of this review we addressed the importance of relationship between extension personnel and farmers in strategies to fight fungicide resistance in the tropical Brazilian agroecosystem while considering the challenges that can be faced.

In regard to the ongoing efforts to fight against fungicide resistance, it is imperative to recognize the major role of the farmers and the extension service personnel to implement effective strategies. The success of any strategy designed to deal with fungicide resistance relies on the active engagement and collaboration of these two key players. However, we recognize the unique structural challenges presented by the literacy rates of the Brazilian growers, as reported by the 2017 Brazilian Agricultural Census (available at <https://censoagro2017.ibge.gov.br/resultados-censo-agro-2017.html>), where 17.2% are illiterate, and a significant portion has limited formal education.

The inclusion of farmers and extension service personnel in a policy to fight against fungicide resistance is not just a desirable aspect for the solution; it is an integral part of it. Without an active participation and full commitment, any proposed strategy for fungicide resistance management would be at risk of faltering and could result in eventual failure. Therefore, we must work collectively by integrating farmers and extension service personnel into the process of fungicide resistance management, to ensure that they not only understand but also accept the strategies proposed here for an effective fungicide resistance management.

Therefore, only individuals with certified technical expertise should play a central role in disease management practices based on fungicide applications. This includes both farmers and extension personnel with the necessary professional expertise. We recognize, though, that until a lasting solution is found for improvements to occur on the basic educational level of the Brazilian growers, their direct involvement in fungicide-related disease management decisions could pose risks to the environment, agricultural productivity, and public health.

Thus, we support a certified technical assistance as a prerequisite for all stages of the responsible choosing,

recommending, handling and applying of fungicides. In regard the certified technical assistance, we should ensure that fungicide-related practices are carried out with precision, and responsibility, and in a way that preserve the interests of agriculture, the environment, and public health. This approach protects against unintended consequences arising from insufficient knowledge and expertise. Fortunately, the current legislation approved in 2022 (at both Federal and State levels) regulates the registration of companies that provide pesticides application services for agricultural needs and the appointment of extension agents, i.e. certified agronomists, for prescription of pesticides, and technical responsibility concerning their correct and safe use (Secretariat of Agriculture and Supply (SAA) from São Paulo State (2022)).

In conclusion, we are firm in our commitment to a sustainable fungicide resistance management in the Brazilian agriculture.

By implementing these strategies, Brazil can improve the understanding of fungicide resistance, enhancing data collection and sharing, and promoting more effective management policies. The collaboration among growers and extension service personnel, investment in research and monitoring, and the adoption of proactive strategies are key to address the lack of consistent information on fungicide resistance and will encourage sustainable disease management practices in the Brazilian tropical agriculture.

Finally, the fight against fungicide resistance today and its increasing threats requires the adoption of the “One Health” as a transdisciplinary and collaborative approach proposed by WHO (World Health Organization) when releasing new treatments or therapies for control of fungal diseases, recognizing the interconnection among plants, people, animals, and their shared environment (Fraaije et al. 2021; Woods et al. 2023)

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Data availability All data generated or analysed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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