

THE QUINONE OUTSIDE INHIBITOR FUNGICIDES, A PERSPECTIVE GROUP OF PLANT PROTECTION PRODUCTS

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Abstract

Strobilurins are a class of fungicides derived primarily from natural substances produced by wood-decaying fungi, particularly those in the genus *Strobilurus*. The discovery of strobilurins dates back to 1970s when researchers identified their unique fungicidal properties. Since then, various synthetic strobilurin analogues called Quinone outside inhibitors have been developed with a wide variety of applications. Due to their broad-spectrum activity and low toxicity to humans and animals, Qols have become some of the most widely used fungicides worldwide. These fungicides are highly effective against a diverse range of fungal pathogens, including those responsible for diseases like powdery mildew, rusts, leaf spots, and blights. They are commonly used in crops such as cereals, field crops, fruits, nuts, vegetables, turfgrass, and ornamentals. Their systemic properties allow them to be absorbed into plant tissues and transported throughout the plant, providing protection to both treated areas and new growth. This enhances their efficacy in managing diseases. Qols are compatible with many agricultural chemicals, such as insecticides and herbicides, making them ideal for integration into pest management programs. Their compatibility also allows for tank mixing, reducing the frequency of applications and saving time and resources for farmers. Additionally, some Qols have been observed to promote plant growth under certain conditions. This review delves into various aspects of Qols, including their mode of action, chemical and fungicidal properties, resistance, limitations and prospectives.

Key words: *strobilurins, Qol fungicides, plant protection, mode of action, fungicidal activity, resistance.*

INTRODUCTION

Strobilurins are versatile fungicides with a wide range of agricultural applications due to their broad-spectrum activity, systemic properties, and ability to enhance plant health. Their primary use is to manage fungal diseases across various crops targeting a broad range of pathogens which has made them indispensable in agriculture production. The discovery of strobilurins dates back to the late 1970s when Anke et al. (1977) isolated strobilurin A and strobilurin B from the basidiomycete fungus *Strobilurus tenacellus* (Pers. ex Fr.) Singer which grows on decaying cones of *Pyrus silverstris*. In fact, strobilurins are common secondary metabolites in Basidiomycetes. *B. lutea* is the only Ascomycete fungus known to produce metabolites from this chemical family (Iqbal et al., 2018). Although strobilurin A showed to be effective in “*in vitro*” it was not effective “*in vivo*” due to its low photochemical stability and high volatility. The discovery of the antimicrobial properties of strobilurins led to the synthesis of

various analogues such as azoxystrobin which was introduced on the market for the first time in 1996 by Zeneca Agrochemicals (now part of Syngenta). This was the first synthetic strobilurin fungicide, making a significant advancement in agricultural disease management due to its low toxicity and broad-spectrum activity, effective across a wide range of crops, such as fruits, vegetables, cereals, nuts, berries, turfgrasses ornamentals etc. Since it was discovered, azoxystrobin has had a profound impact on plant protection. By 2002, it was registered for use in 72 countries and on 84 different crops, achieving sales of \$ 415 million in 1999, making it the top-selling fungicide worldwide (Bartlett et al., 2002). Moreover, its widespread adoption spurred the development of additional fungicides in this chemical group. The same year kresoxim methyl was developed and released on the market by BASF. Afterward, further developments in similar compounds quickly followed. Metominostrobin, was developed by Shionogi and released on the market in 1999. The same year Bayer launched trifloxystrobin. In addition, other fungicidal compounds, chemically distinct from strobilurins but from the same QoI fungicide cross-resistance group were developed such as famoxadone by DuPont launched in 1997 and fenamidone by Aventis in 2001, which broaden the spectrum of available options for disease control. In 2002, BASF launched pyraclostrobin followed by picoxystrobin released by Syngenta the same year. More than a decade later in 2016, Sumitomo Chemical launched on the market mandestrobin. Today, the class of QoI fungicides comprises 21 substances belonging to ten chemically or biologically different group of compounds from which six are approved in EU, six are banned and one (metyltetraprole) has the status of pending for approval in EU (Tab.1). Six new QoI fungicides are in process of development by Chinese manufacturers. SRICI is working on coumoxystrobin, enoxastrobin, flufenoxystrobin, triclopyricarb, and fenaminostrobin, while Shenyang Sciencreat Chemicals is developing pyriminostrobin. However, it remains uncertain whether these companies intend to pursue global registration for these fungicides (Umetsu & Shirai, 2020).

The term 'strobilurins' originally referred to natural fungicidal compounds derived from fungi in the genus *Strobilurus*. Hence, the class also includes synthetic analogues with similar modes of action but different origins, the Fungicide Resistance Action Committee (FRAC) in the early 2000s when dealing with classification of fungicides based on their mode of action renamed the group into 'Quinone Outside Inhibitors' (QoI fungicides or QoIs) and classified them into the FRAC Code 11 to provide clarity and support resistance management strategies.

CHEMICAL PROPERTIES OF QoI FUNGICIDES

Fungi synthesize strobilurins from an essential α -amino acid called phenylalanine when synthesize biomolecules, such as proteins and secondary metabolites, through the shikimic acid pathway (Balba, 2007). The structural molecule of strobilurins contain the specified methyl (E)-3-methoxy-2-(5-phenylpenta-2,4-dienyl) acrylate moiety, attached to the α -position. Compounds with this structure are classified as β -methoxyacrylates (Tab. 1). The (E)- β -methoxyacrylate group is a critical part of their natural fungicidal activity (Bartlett et al., 2002). The α -position of the acrylate is connected to the rest of the strobilurin molecule, which can vary depending on the specific compound (Fig.1). Variations usually arise from substitutions on the aromatic ring at positions 3 and 4 (Fig. 1). However, these natural compounds degrade rapidly when exposed to light, which reduces their practical value and makes them unsuitable for effective plant disease control (Bartlett et al.,2002). This limitation of natural strobilurins has been overcome with development of photostable analogues with numerous practical applications (Iqbal et al., 2018; Kunova et al., 2021). Most modifications focused on altering the α -substitution of the (E)- β -methoxyacrylate group. A significant breakthrough and revolution in this field was achieved by replacing the core toxophoric (E)- β -methoxyacrylate group with a methoxyiminoacetate moiety, a modification which leads to the discovery of azoxystrobin (Fig. 1). Replacing the (E)- β -methoxyacrylate group with a (Z)- α -methoxyiminoacetate group lead to development of trifloxystrobin while a pyridine ring with trifluoromethyl substitution and methyl ester group attached to the methoxyiminoacetate group is a unique feature of fluoxastrobin that distinguishes it from other strobilurin fungicides (Fig 1). In kresoxim methyl a chlorine-substituted pyridine ring (6-chloro-3-pyridinyl) is attached to the methoxyiminoacetate moiety (Fig. 1). A chlorinated pyridine ring (6-chloro-2-

(chloromethyl)-4-pyridyl) and a methyl ester group are attached to the methoxyiminoacetate group in the molecule of pyraclostrobin (Fig. 1). One notable advancement replacing the (E)- β -methoxyacrylate group with 2-methoxyiminoacetamide, resulted in the creation of metominostrobin (Fig.1) (Bartlett et al., 2002). Mandestrobin also a methoxyacetamide based compound has a backbone derived from mandelic acid structure (Fig. 1) (Hiroto mi et al., 2016).

Table 1. Classification and representatives of QoL fungicides (FRAC Code 11) according to the Fungicide Resistant Action Committee (FRAC, 2024c)

MOA	C: respiration									
target site and code	C3 complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site (cyt b gene)									
Group name	QoL-fungicides (Quinone outside Inhibitors)									
FRAC CODE	11									11A
Chemical or biological group	methoxy-acrylates	methoxy-acetamide	methoxy-carbamates	oximino-acetates	oximino-acetamides	oxazolidine-diones	dihydro-dioxazines	imidazolinones	benzyl-carbamates	tetrazolinones
Status in EU	approved non EU non EU non EU banned non EU	approved	approved non EU non EU	approved approved	banned non EU banned banned	banned	approved	banned	nonEU	pending
Common name	azoxystrobin coumoxystrobin enoxastrobin flufenoxystrobin picoxystrobin pyraoxystrobin	mandestrobin	pyraclostrobin pyrametostrobin triclopyr/carb	kresoxim-methyl trifloxystrobin	dimoxystrobin fenaminostrobin metominostrobin orysastrobin	famoxadone	fluoxastrobin	fenamidone	pyribencarb	mety/tetraprole

MODE OF ACTION

A defining characteristic of QoL fungicides is their rapid mode of action. While most of the QoL fungicides are contact, some of them such as azoxystrobin, picoxystrobin and metominostrobin show systemic activity. Metominostrobin shows the highest ability to be absorbed into leaves while picoxystrobin and azoxystrobin showed medium and low uptake by leaf, respectively. All three substances exhibit both translaminar movement and movement through the xylem while picoxystrobin together with kresoxim-methyl and trifloxystrobin can also be molecularly redistributed by air. Kresoxim-methyl, trifloxystrobin and pyraclostrobin showed only low translaminar ability and no systematic activity through the vascular system of the plant (Bartlett et al., 2002).

Many research has shown that spore germination in ascomycetes and basidiomycetes and zoospore motility in Oomycetes are the most critical stages for the thrive of the fungal pathogens. The fact that these stages in fungal development are particularly sensitive to QoL fungicides is pivotal for QoL effectiveness (Fernández-Ortuño et al., 2010). Additionally, this

heightened sensitivity is attributed to the fungicide's biochemical mechanism of action such as the disruption of energy production. As these developmental stages are highly energy-demanding, their inhibition effectively prevents successful plant colonization. Therefore, the majority of QoI fungicides exhibit potent activity against zoospore motility in Oomycetes and spore germination in ascomycetes and basidiomycetes when applied during the early stages of infection which is, after infection has occurred but before visible symptoms develop, hence some QoI fungicides are recognized by their eradicator and antispore activity. Becker et al. (1981), in their study, suggest that the mode of action of QoI fungicides is single-site. Their fungicidal efficacy stems from their ability to inhibit mitochondrial respiration by binding to the Q_o site (outer quinol oxidation site) of the cytochrome bc₁ enzyme complex (complex III). The presence of a carbonyl oxygen moiety which is a shared feature of all QoI compounds, plays a crucial role in binding to the enzyme. This respiratory inhibition disrupts electron transfer between cytochrome b and cytochrome c₁, halting adenosine triphosphate (ATP) production in the mitochondria of the fungal cell, causing an energy deficiency which ultimately leads to the cell death. The membrane protein complex cytochrome bc₁ which is a vital essential for fungal respiration is a main target to QoI fungicide action. In eukaryotes, it comprises 10 to 11 polypeptides with a combined molecular mass of approximately 240 kDa, functioning as a structural and functional dimer. The catalytic core of the enzyme consists of cytochrome b, cytochrome c₁, and the Rieske iron-sulphur protein (ISP). Its catalytic mechanism, known as the Q-cycle, requires two distinct quinone-binding sites: the Q_o site for quinol oxidation and the Q_i site for quinone reduction (Fisher & Meunier, 2008). The precise locations of the quinol/quinone binding sites within the cytochrome b subunit have been identified through X-ray crystallography, using bound inhibitors as models. Detailed insights into the interactions between cytochrome bc₁ and various inhibitors, conducted by Esser et al. (2004) have revealed that, QoI fungicides differ by their mode of binding although, they fit within the enzyme pocket on remarkably similar way.

An interesting characteristic of some QoI is their ability to influence the hormonal system of wheat, leading to delayed leaf senescence, enhanced water retention, and increased grain yield (Vincelli, 2012). These fungicides are also associated with beneficial physiological effects on crop yield, attributed to their biological action in promoting net carbon assimilation, interact with plant mitochondrial respiration and enhance nitrate reductase activity in leaf tissues, and improve plant stress tolerance (Glaab & Kaiser, 1999). Such effects have been referred about azoxystrobin, kresoxim methyl and pyraclostrobin which are found to contribute to greater rooting, branching, and bud development leading to increased plant growth and yield (Wu & Tiedemann, 2001; Vincelli, 2012).

ANTIFUNGAL ACTIVITY OF QoI FUNGICIDES

Since their introduction, quinone outside inhibitors (QoIs) have become indispensable in plant disease management programs due to their broad-spectrum efficacy against numerous agriculturally significant fungal diseases. Registered in numerous countries, QoI fungicides are utilized across a wide range of crops, including cereals, turfgrass, grapevines, vegetables, fruits, berries and ornamental plants. Their success can be attributed to the unique properties of individual active ingredients, which typically exhibit one or more of the following attributes: broad-spectrum activity, effectiveness against fungicide-resistant isolates, low application rates, low toxicity to humans, low environmental toxicity, and significant yield and quality benefits (Bartlett et al., 2002). QoI fungicides have driven transformative changes in disease management protocols for various crops. For instance, they provided grapevine growers with the first single active ingredient capable of controlling both powdery mildew (*Erysiphe necator*) and downy mildew (*Plasmopara viticola*). Similarly, in wheat and barley, QoI fungicides especially azoxystrobin have demonstrated superior yield and quality improvements compared to other fungicide classes. Their utility has extended to resistance management programmes for crops like bananas, where they play a critical role in combating persistent and resistant pathogens. Additionally, QoI fungicides are valuable in the maintenance of protected horticultural crops, particularly in regions like Europe, where the number of available active ingredients has declined due to regulatory compliance. Beyond

their foliar applications, QoI fungicides are increasingly used as seed treatments and in-furrow applications to manage soilborne diseases, further expanding their versatility (Bartlett et al., 2002). Among other, mandestrobin is use to reduce the overwintering source of infection in white mould. It is found to possess an inhibitory effect in almost all stages of the pathogen development and especially is appreciated its' activity against sclerotium formation in *Sclerotinia sclerotiorum* in reducing the overwintering source of infection (Hirotoimi et al., 2016). Some of the trade names and agricultural applications of QoL fungicides are given in Table 2.

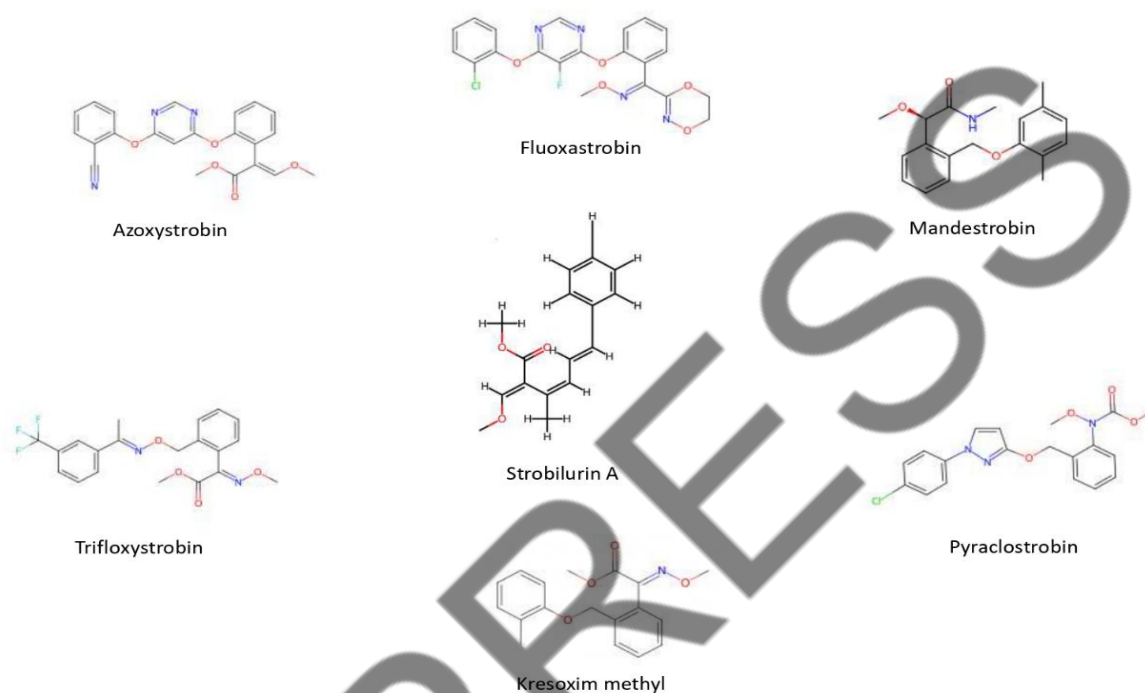


Fig.1 Chemical structural formula of the most important QoI fungicides

Source: Strobilurin A (CSID:4941943, <https://www.chemspider.com/Chemical-Structure.4941943.html>); Azoxystrobin (CSID:2298772, <https://www.chemspider.com/Chemical-Structure.2298772.html>); Trifloxystrobin (CSID:32818261, <https://www.chemspider.com/Chemical-Structure.32818261.html>); Pyraclostrobin (CSID:4928348, <https://www.chemspider.com/Chemical-Structure.4928348.html>); Kresoxim methyl (CSID:4813314, <https://www.chemspider.com/Chemical-Structure.4813314.html>); Fluoxastrobin (CSID:9223963, <https://www.chemspider.com/Chemical-Structure.9223963.html>); Mandestrobin (CSID:34448712, <https://www.chemspider.com/Chemical-Structure.34448712.html>). Accessed 27.11.2024.

RESISTANCE MECHANISM

Because of their one specific site of action against fungal pathogens, QoIs are highly susceptible to resistance. It is considered that this resistance is mediated by two primary mechanisms such as target site mutations and efflux transporters and a secondary mechanism of QoI resistance which involves alternative respiration such as cyanide-resistant respiration mediated by alternative oxidase. In target site mutations the predominant mechanism of QoI resistance involves mutations in the mitochondrial cytochrome b gene (CYTB), leading to changes in the peptide sequence that inhibit fungicide binding. These mutations are localized to regions of CYTB crucial for ligand binding, particularly amino acid positions 120-155 and 255-280. Key substitutions include G143A (glycine to alanine at position 143), F129L (phenylalanine to leucine at position 129), and G137R (glycine to arginine at position 137) which are all based on single nucleotide polymorphisms in the cytochrome b gene (Gisi et al., 2002; Fisher & Meunier, 2008; Fernández-Ortuño et al., 2008). Research investigations showed that pathogens that carried G143A mutations express high (complete) resistance and are hard to manage. Anyway, in some cases despite the significant use of the

Qols, the amino acid substitution of the glycine with alanine at position 143 has not been observed even when the Qols were significantly used in the field. In some species such as *Alternaria solani*, *Pyrenophora teres* and *Puccinia* spp. a non-coding region of DNA (an intron) was observed after the gene that encodes for glycine (FRAC 2011; Grasso et al., 2006). Since this substitution will affect the splicing process and lead to a deficient in cytochrome b, it is considered that the nucleotide substitution with alanine will be lethal and as a consequence resistance based on the G143A mutation is not likely to appear not only in species such as *Alternaria solani*, *Pyrenophora teres* and *Puccinia* spp. but also in other species such as *Uromyces appendiculatus*, *Phakopsora pachyrhizi* and *Hemileia vastatrix* (Fernández-Ortuño et al., 2008). The presence of such an intron was reported in *Monilinia laxa*, *Monilinia fructicola* and *Guignardia bidwellii* (Miessner & Stammler 2010; Miessner et al., 2011). The Qol tolerance of *A. solani* and *P. teres* was indicated by mutations in F129L and/or G137R (Sierotzki et al., 2007) which happen to be of minor importance and according to Semar et al. (2007) have limited impact on the field efficacy of Qols. Pathogens harbouring F129L or G137R mutations are often overcome by standard field application rates of Qol fungicides. In contrast, the G143A substitution confers high resistance, consistently leading to control failures. This mutation has been documented in over 20 species. Soon after the first Qol fungicides were introduced in 1996, resistant isolates of *Blumeria graminis* f. sp. *tritici* and *Plasmopara viticola* showing G143A mutation were identified (Heaney et al., 2000; Sierotzki et al., 2000b). Other pathogens found resistant to Qol fungicides with this mutation include *Blumeria graminis* f. sp. *secalis*, *Blumeria graminis* f. sp. *hordei*, *Zymoseptoria tritici* (sin. *Septoria tritici*) and its teleomorph *Mycosphaerella graminicola*, *Puccinia recondita*, *Puccinia triticina*, *Puccinia striiformis*, *Puccinia hordei*, *Rhizoctonia solani*, *Pyrenophora tritici-repentis*, *Pyrenophora graminea*, *Oculimacula* spp., *Rhynchosporium graminicola* (sin. *Rhynchosporium secalis*), *Ramularia collo-cygni*, *Uncinula necator*, *Venturia inaequalis*, *Podosphaera leucotricha*, *Monilinia* spp., *Stemphylium vesicarium*, *Neofabraea alba*, *N. perennans*, etc. (Tab. 3) (FRAC, 2024b). Despite its clear association with Qol resistance, studying the role of CYTB mutations, particularly G143A, remains challenging due to the mitochondrial origin of the gene and limiting functional genetic studies.

Efflux transporters, specifically members of the ATP-binding cassette (ABC) transporter family and the major facilitator superfamily (MFS), also contribute to Qol resistance by preventing the accumulation of toxic fungicides within fungal cells. These proteins offer broad protection against natural toxins and xenobiotics (Del Sorbo et al., 2000; Stergiopoulos et al., 2003). The first efflux transporter implicated in Qol resistance was MgMfs1, an MFS transporter gene identified in *M. graminicola* (Roohparvar et al., 2007). While overexpression of MgMfs1 is linked to strobilurin resistance, its contribution is typically minor compared to CYTB mutations like G143A.

A secondary mechanism of Qol resistance involves cyanide-resistant respiration mediated by alternative oxidase. This pathway bypasses the cytochrome bc1 complex, sustaining mitochondrial electron transfer and ATP synthesis under fungicide-induced stress (Wood & Hollomon, 2003). However, alternative respiration is energy-inefficient, providing only 40% of the normal ATP yield, which limits its efficacy in planta. Although alternative oxidase may assist fungal survival during late infection stages (e.g., sporulation), it has minimal impact on disease control under the field conditions. Nonetheless, alternative oxidase activity may facilitate the selection of CYTB mutations by reducing reactive oxygen species, potentially promoting the transition from sensitivity to full resistance (Fernández-Ortuño et al., 2008). In addition, pathogens and references linked with the resistance against Qol fungicides according to FRAC are listed in Table 3.

CHALLENGES AND LIMITATIONS

Despite their advantages, Qol fungicides face several challenges that can impact their long-term effectiveness. One of the most significant issues is the development of fungicide resistance in fungal populations. The single-site mode of action of Qols makes them particularly vulnerable to resistance, as a single genetic mutation in the target site can render the fungicide ineffective. According to FRAC, resistance has been documented in almost forty

fungal species from 26 genera (Tab. 3). To mitigate resistance, best management practices are proposed such as alternating QoIs with fungicides that have different modes of action to reduce selection pressure on fungal populations; to combine QoIs with multi-site fungicides or fungicides from other classes to delay resistance development and to restrict the number of QoI applications per season to minimize the chances of resistance emergence (Fernández-Ortuño et al., 2006).

Another limitation of QoI fungicides is their sensitivity to environmental conditions such as rain fastness which can also vary among products. Heavy rainfall shortly after application may wash off the fungicide and reduce its efficacy (Kovacevik et al., 2001). Additionally, the preventative nature of QoIs requires precise timing, as applications made after infection are often less effective.

Table 2. List of some commercial products based on QoI pesticides and their antifungal activity

Active ingredient	Comercial products	Antifungal activity
Azoxystrobin	PROMESA (Galenika-fitofarmacija, SR); CIROSTROBIN (Sharda Cropchem Limited, India); AMISTAR EXTRA (Syngenta Crop Protection AG, Switzerland); AMISTAR (Syngenta Crop Protection AG, Switzerland); UNIVERSALIS (Syngenta Crop Protection AG, Switzerland); ORTIVA TOP (Syngenta Crop Protection AG, Switzerland); QUADRIS (Syngenta Crop Protection AG, Switzerland); SINSTAR (Sinon EU GmbH, Germany); ABAUND (Syngenta Crop Protection, LLC, USA); BANKIT 25 SC (Syngenta East Africa Limited, Kenya); Heritage (Syngenta Crop Protection, LLC, USA); Protégé (Atticus LLC, North Carolina); AZteroid FC (Atticus LLC, North Carolina); Quadris Top SB (Atticus LLC, North Carolina); Quadris Top SBX (Atticus LLC, North Carolina); Quadris Top (Atticus LLC, North Carolina); Quadris Abound (Atticus LLC, North Carolina); Quilt Xcel (Atticus LLC, North Carolina); Protégé-Allegiance WP (Bayer CropScience, US); Protégé FL Seed applied Fungicide (Bayer CropScience, US); SOYGARD Fungicide Containing Protégé and Allegiance (Bayer CropScience, US), Afiance (), AZOXY TEB, CUSTODIA,	- It is use to control rusts, downey mildews, powdery mildews, rice blast, apple scab, crown rot, damping-off, root rot, white mould etc. in vide variety of crops such as grape vines, cereals, potatoes, apples, bananas, citrus fruit, tomatoes, almonds, rice, pistachios, raisins, garlic, turf and ornamental plants. Also, it has a broad spectrum against many important seed and seedling pathogens and it is used in seed treatment, etc.
kresoxim-methyl	Sovran (BASF); Ergon (Various manufacturers); Stroby (BASF); Affinity; Cantos (BASF)	It is used to control apple scab (<i>Venturia inaequalis</i>) and powdery mildew (<i>Podosphaera leucotricha</i>) in apples; powdery mildew (<i>Erysiphe necator</i>) in grapes; leaf spots and molds in citrus fruit; early blight (<i>Alternaria solani</i>) and gray mold (<i>Botrytis cinerea</i>) in tomatoes and potatoes; Powdery mildew (<i>Podosphaera xanthii</i> , <i>Erysiphe cichoracearum</i>) in Cucurbits; powdery mildew (<i>Blumeria graminis</i>), rusts (<i>Puccinia spp.</i>), and leaf spot diseases (<i>Mycosphaerella spp.</i>) in cereals; brown patch (<i>Rhizoctonia solani</i>), dollar spot, and other turfgrass diseases; white mold (<i>Sclerotinia sclerotiorum</i>) in rapeseed, etc.
mandestrobin	SCLEA flowable (Sumitomo Chemical), INTUITY (Sumitomo Chemical)	ASCOMYCOTA: <i>Sclerotinia sclerotiorum</i> , <i>Monilinia fructicola</i> , <i>Monilinia laxa</i> , <i>Monilinia fructigena</i> , <i>Venturia inaequalis</i> , <i>Venturia nashicola</i> , <i>Diplocarpon mali</i> , <i>Diaporthe citri</i> ; BASIDIOMYCOTA: <i>Rhizoctonia solani</i> ; OOMYCOTA: <i>Pythium graminicola</i> ; DEUTEROMYCOTA: <i>Phomopsis sp.</i> , <i>Phomopsis vexanes</i> , <i>Phomopsis fukusii</i> , <i>Alternaria alternata</i> , <i>Botrytis cinerea</i> , <i>Colletotrichum gossypii</i> , <i>Colletotrichum phaseolorum</i> , <i>Colletotrichum simmondsii</i> , <i>Corynespora cassiicola</i> , <i>Cercospora kikuchii</i> , <i>Septoria glycines</i> ; It is used in wide range of crops because of a low risk of phytotoxicity;
pyraclostrobin	SIGNUM 33 WG (BASF SE, Germany), PRIAXOR EC (BASF SE, Germany), REVYCARE (BASF Agro B.V. Arnhem),	ASCOMYCOTA: <i>Botrytis cinerea</i> , <i>Alternaria spp.</i> , <i>Sclerotinia sclerotiorum</i> , <i>Mycosphaerella spp.</i> , BASIDIOMYCOTA: <i>Puccinia spp.</i> , OOMYCOTA:

	BELLIS (BASF SE, Germany), BOS (Sharda, Cropchem Limited, India), Pageant (BASF SE, Germany), Intrinsic (BASF SE, Germany), Empress (BASF SE, Germany), Orkestra (BASF SE, Germany), Cabrio (BASF Corporation, USA), Pristine (BASF), PRIAXOR (BASF), PRIAXOR D (BASF)	<i>Phytophthora</i> spp. <i>Pythium</i> spp. DEUTEROMYCOTA: <i>Colletotrichum</i> spp. <i>Rhizoctonia solani</i> . It is registered for use on a wide variety of crops, including cereals, fruits, berries, vegetables, oilseeds, turf and ornamentals, legumes, etc.
trifloxystrobin	ZATO 50 WG (BAYER CropScience AG, Germany), Flint 500 WG (BAYER CropScience, Australia), Flint Extra (BAYER CropScience US), Stratego (BAYER).	ASCOMYCOTA: <i>Venturia inaequalis</i> , <i>Venturia pirina</i> , <i>Blumeria graminis</i> , <i>Mycosphaerella</i> spp., <i>Sclerotinia sclerotiorum</i> , <i>Podosphaera</i> spp., <i>Erysiphe</i> spp., <i>Monilinia</i> spp., <i>Setoria</i> spp. <i>Spilocaea</i> spp., <i>Cercospora sojina</i> , <i>Stemphylium vesicarium</i> ; BASIDIOMYCOTA: <i>Puccinia</i> spp., <i>Gymnosporangium fuscum</i> ; DEUTEROMYCOTA: <i>Alternaria</i> spp., <i>Botrytis cinerea</i> , <i>Rhizoctonia solani</i> ; OOMYCOTA: <i>Plasmopara viticola</i> ; It is registered in various crops such as brassica vegetables, citrus, cucurbit vegetables, fruiting vegetables, grapes, hops, leafy vegetables, pome fruit, potatoes, rice, root vegetables, stone fruit, strawberries, sugar beets, tree nuts etc.
fluoxastrobin	Teldor (Bayer Cro Science, Australia), EVITO T (Arysta LifeScience, North America)	ASCOMYCOTA: <i>Colletotrichum graminicola</i> , <i>Colletotrichum truncatum</i> , <i>Setosphaeria turcica</i> , <i>Cochliobolus carbonum</i> , <i>Cochliobolus heterostrophus</i> , <i>Aureobasidium zeae</i> , <i>Septoria glycines</i> , <i>Cercospora</i> spp., <i>Diaporthe phaseolorum</i> , <i>Pyrenophora tritici-repentis</i> , <i>Sclerotium rolfsii</i> , <i>Sclerotinia</i> spp., <i>Monilinia</i> spp., <i>Setoria</i> spp., <i>Cercospora sorghi</i> ; BASIDIOMYCOTA: <i>Puccinia</i> spp., <i>Phakopsora</i> spp.; DEUTEROMYCOTA: <i>Alternaria</i> spp., <i>Botrytis cinerea</i> , <i>Rhizoctonia solani</i> ; It is registered in various crops such as corn, soybean, wheat, pinut, grapes, cherry, plum, apricot, peach, nectarine, strawberry, raspberry, tomatoes, eggplant, lettuce, cornsalad, escarole, garden cress, Bermuda cress, arugula, black mustard, French parsley, Chives, leaf celery, parsley, sage, thyme, basil, rosemary, laurel, estragon, zucchini, pepper, bean, cucumber, oriental plants, etc.

FUTURE PERSPECTIVES

The comprehensive understanding of QoI fungicides underpins their pivotal role in modern agricultural disease management. There is no doubt that the future of QoI fungicides lies in addressing their limitations while maximizing their benefits. Since rainfastness is dependent on product formulation, advances in formulation technology can enhance translocation, and extend residual activity overcoming this limitation. For example, encapsulated formulations and nano-carriers are emerging as promising tools to increase the stability and efficacy of fungicides.

Research into the molecular mechanisms of resistance incite the development of the next-generation QoIs with novel modes of action or enhanced binding properties. In addition to this is the fact that there are already several QoI pesticides on the market with such properties like pyribencarb and metyltetraprole registered in Japan with metyltetraprole under review for registration in the European Union. Pyribencarb -is a novel QoI fungicide from the benzyl carbamate group efficient against a wide range of plant pathogenic fungi and active against strobilurin-resistant fungi. Metyltetraprole is another new QoI fungicide possessing a unique tetrazolinone moiety which contributes to its effectiveness against QoI-resistant strains of various pathogen species (Umetsu & Shirai, 2020).

In parallel, integrating QoIs into precision agriculture systems can optimize application timing and dosage, reducing waste and environmental impact.

Biological alternatives, such as biopesticides and microbial antagonists, are increasingly being explored as complementary or substitute options for chemical fungicides (Rocha et al., 2013). While these products currently have limitations in terms of efficacy and consistency, they offer a sustainable approach to disease management and can play a role in reducing reliance on QoIs.

Table 3. List of fungal species with documented resistance to QoI fungicides according to FRAC

Pathogen	Host	Type of resistance	Reference
<i>Alternaria alternata</i> <i>Alternaria tenuissima</i> <i>Alternaria arborescens</i>	Pistachio	G143A	Ma et al., 2003; Ma & Michailides, 2004;
<i>Alternaria alternata</i>	Potato, Tomato	G143A	FRAC 2020
<i>Alternaria mali</i>	Apple	G143A	Lu et al., 2003
<i>Alternaria solani</i>	Potato	F129L	Pasche et al., 2002
<i>Ascochyta rabiei</i>	chickpeas	G143A	Delgado et al., 2012
<i>Blumeria graminis</i> f. sp. <i>tritici</i> and <i>hordei</i>	Wheat & Barley	G143A	Sierotzki et al., 2000b
<i>Botrytis cinerea</i>	Strawberries	G143A	FRAC 2020
<i>Cercospora soja</i>	Soybeans	G143A	Barro et al., 2003
<i>Cercospora beticola</i>	Sugar beet	G143A	Bolton et al., 2012
<i>Cladosporium carpophilum</i>	Almonds	ni	Foerster et al., 2009
<i>Colletotrichum graminicola</i>	Turf grass	G143A	Avila-Adame et al., 2003
<i>Corynespora cassiicola</i>	Cucumber	G143A	Ishii, 2004
<i>Didymella bryoniae</i>	Cucurbit	G143A	Langston, 2002
<i>Erysiphe necator</i>	Grapes	G143A	FRAC 2020
<i>Glomerella cingulata</i> (anamorph <i>Colletotrichum gloeosporioides</i>)	Strawberries	G143A	Ishii, 2004
<i>Microdochium nivale</i> <i>Microdochium majus</i>	Wheat	G143A	Walker et al., 2009;
<i>Mycosphaerella fijiensis</i>	Banana	G143A	Sierotzki et al., 2000a
<i>Mycosphaerella graminicola</i>	Wheat	G143A	Fraaije et al., 2005 Sierotzki et al., 2005
<i>Mycosphaerella musicola</i>	Banana	G143A	FRAC 2020
<i>Mycovellosiella nattrassii</i>	Eggplant	G143A	Ishii, 2004
<i>Phaeosphaeria nodorum</i>	Wheat	G143A	Blixt et al., 2009
<i>Plasmopara viticola</i>	Grape	G143A, F129L	Heaney et al., 2000
<i>Pseudoperonospora cubensis</i>	Cucurbits	G143A	Heaney et al., 2000; Ishii et al., 2001;
<i>Pyrenophora teres</i>	Barley	F129L	Sierotzki et al., 2007; Semar et al., 2007;
<i>Pyrenophora tritici-repentis</i>	Wheat	G143A, F129L, G137R	Sierotzki et al., 2007; Stammler et al., 2006;
<i>Pyricularia grisea</i>	Turf grass	G143A, F129L	Vincelli & Dixon, 2002b; Kim et al., 2003;
<i>Pythium aphanidermatum</i>	Turf grass	F129L	Gisi et al., 2002;
<i>Ramularia areola</i>	Cotton	ni	FRAC 2020
<i>Ramularia collo-cygni</i>	Barley	G143A	FRAC 2020
<i>Rhynchosporium secalis</i>	Barley	G143A	FRAC 2020
<i>Rhizoctonia solani</i> AG1.1A	Rice	F129L	FRAC 2020
<i>Sphaerotheca fuliginea</i>	Cucurbits	G143A	Heaney et al., 2000; Ishii et al., 2001;
<i>Stemphylium vesicarium</i>	Asparagus, Pear	G143A	FRAC 2020
<i>Zymoseptoria tritici</i>	Wheat	ni	Hayes et al. 2013
<i>Venturia inaequalis</i>	Apple	G143A	Steinfeld et al., 2002;

ni – no information

CONCLUSION

The QoIs are well known for their great effectiveness against a wide range of plant pathogens, including the most important genera of Ascomycetes, Basidiomycetes, Deuteromycetes, and Oomycetes. They have proven to be an invaluable tool in modern agriculture, offering broad-spectrum activity, systemic properties, and plant health benefits that enhance crop production. However, their reliance on a single-site mode of action makes them susceptible to resistance development, necessitating careful management and integration with other control strategies. Efflux transporter-mediated resistance and alternative respiration play auxiliary roles compared to CYTB mutations in QoIs resistance. The G143A substitution remains the primary driver of resistance in field isolates, emphasizing the need for integrated resistance management strategies. These may include rotating fungicides with different modes of action, using mixtures to reduce selection pressure, and closely monitoring resistance evolution through robust field studies. While for now, their use has been reduced in certain crops, such as cereals, they continue to play a vital role in many other systems. The

commitment to responsible practices and ongoing research will allow the benefits of this valuable class of fungicides to be leveraged for years to come, safeguarding their role in global crop protection. As agriculture faces emerging challenges such as climate change and increasing pathogen resistance, the judicious and innovative use of QoIs which include precise agriculture and the use of advanced technologies in the formulation such as encapsulation and nano formulation, will be essential in the future.

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ФУНГИЦИДИ ИНХИБИТОРИ НА НАДВОРЕШНИОТ КВИНОН, ПЕРСПЕКТИВНА ГРУПА НА ПРОИЗВОДИ ЗА ЗАШТИТА НА РАСТЕНИЈАТА

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Резиме

Стробилурините се класа на фунгициди добиени првенствено од природни супстанции произведени од габи кои се распаѓаат на дрво, особено оние од родот

Strobilurus. Откривањето на стробилурините датира од 1970-тите кога истражувачите ги идентификуваа нивните уникатни фунгицидни својства. Оттогаш, различни синтетички аналози на стробилурини се развиени со широк спектар на апликации. Поради нивната активност со широк спектар и ниската токсичност за луѓето и животните, стробилурините станаа едни од најкористените фунгициди ширум светот. Овие фунгициди се ефикасни против различни фитопатогени габи, вклучително и оние кои се одговорни за болести како пеплници, 'рѓи, црна дамкавост, антракнози, септориози, гниење на коренот и сл. Тие најчесто се користат во култури како што се полјоделски култури, овошни култури, јаткасти плодови, зеленчук, бобичести видови, треви и украсни растенија. Нивните системични својства им овозможуваат да се апсорбираат во растителните ткива и да се транспортираат низ растението, обезбедувајќи заштита и на третираниите области и на новиот раст што ја зголемува нивната ефикасност и употреба во системите за заштита. Стробилурините се компатибилни со различни производи за заштита на растенијата што ги прави идеални за вклучување во програмите за управување со штетници, плевели и болести. Нивната компатибилност овозможува и мешање во резервоари, намалување на фреквенцијата на апликации и заштеда на време и ресурси за земјоделците. Дополнително, забележано е дека некои стробилурини во одредени услови го поттикнуваат растот на растенијата. Во овој прегледен труд опишани се најзначајните својства на фунгицидите од групата на надворешни инхибитори на квинони. Дополнително во трудот се посветува внимание и на начинот на делување на овие фунгициди, нивните хемиски и фунгицидни својства, резистентноста, недостатоците, можностите и перспективите.

Клучни зборови: *стробилурини, фунгициди, заштита на растенијата, механизам на делување, отпорност.*