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REVIEW

Fungicides: The uncharted domain

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Fungicides have revolutionized agriculture by reducing crop losses due to diseases. In the early 1800s, plant scientists and chemists began the quest for fungicides, leading to the discovery of lime sulfur and Bordeaux mixture for the control of powdery mildew of fruit trees and downy mildew on grapes respectively and they were grouped as the first-generation fungicides. These inventions raised farmers' expectations for the next breakthrough in performance.As the damaging effects of crop diseases became evident, research to discover novel active materials accelerated. Prophylactic second generation of fungicides, including dithiocarbamates quinones, captan and chlorothalonil came to the vogue. Subsequently, third generation of systemic fungicides such as 2-aminopyrimidines, benzimidazoles, carboxamides, phenylamides, fosetyl-Al, azoles and related compounds, offered new opportunities in disease control.As new areas of chemistry were introduced, research-based organizations have adopted patent-busting tactics to capitalize on the growing fungicide market. New-generation, highly specific fungicides that target the disease triangle in several ways were anticipated by the researchers and the academia.Besides their therapeutic impact, fungicides can also alter the host's carbohydrate levels or mimic the host defense mechanism. Boscalid, Metconazole, Fluxapyroxad, Mefenoxam, and Penflufen are examples of fungicides available in the global market that possess these properties.Triflumizole, Amisulbrom, Cyflufenamid-Valifenalate are anticipated to take centre stage in the fight against oomycetes due to their low doses and capacity to reduce the danger of resistance.Another class of fungicides, are non-fungitoxic *in vitro* but possess a potential to combat plant diseases by impeding the mechanisms which enable fungi to colonise the plant or by enhancing the host plant's resistance. For instance, probenazole stimulates plant defence systems whereas tricyclazole induces malfunctioning fungal appressoria.Plant pathologists endure significant concerns in fungicide resistance and future potency of chemical disease control relies on continuing to invest heavily in research. Although many disease control issues remain unresolved, toxicological reviews, resistance-marketing requirements place a high priority on the discovery and development of replacement fungicides. The development of fungicides will depend extensively on developments in comparative biochemistry, plant pathogen genetics and epidemiology, as well as computational chemistry.

Keywords: Fungicides, fungicide evolution, chemical disease control

INTRODUCTION

The conflict between plant pathogens and fungicides is there since time immemorial. The relentless efforts of the pathogens to cause a dent in the pride of human intellect has goaded the human mind to scour the nook and corner of the brain in search of new avenues. The nascent steps of fungicides which commenced with copper salts gradually treaded into the roads of new chemistries with unique modes of action. The dreaded famines which shook the foundation of civilization perhaps could have been mitigated with the fungicides, if the human minds would have delved intensely into their research faculties. However, the unveiling of the fungicidal domains by Millardet, Delp, Von Schmeling and Kulka, Staub and other doyens of the fungicidal world opened the floodgates of synthesis and registration of new molecules. These new molecules were the arsenals of plant pathologists to halt the onward march of the obnoxious plant pathogens.The question which has plagued the crop protection vertical is that are the

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molecules which are in vogue, efficient enough to counter the emerging pathogens? Are the moieties novel enough to annihilatethe new pathogens? The microbial world, though puny, perhaps can render the most effective fungicide null and void, simply by a point mutation or just through by-passing a particular metabolic pathway. Some pathogens can flex their power by the expulsion of the active ingredient of the fungicide from them and in such cases, the research world is intrigued to find a way out.

To pave out a probable path which will benefit the farmers, development of new fungicides at regular interval through intensive research appears to be the cornerstone of the foundation of Plant Pathology. Hence, the voyage towards the uncharted seas should begin.

Overview of fungicide evolution

The history of using chemical fungicides in agriculture dated since 19th century Lime Sulphur was introduced by William Forsyth and recommended for the control of powdery mildew diseases of fruit trees. The next significant development was introduction of Bordeaux mixture, a copper-based remedy, to fight the newly discovered downy mildew pathogen *Plasmopara viticola* in grapes by Millardet in 1885.The first organic (carbon-based) fungicide, chloro (2-hydroxyphenyl) mercury was synthesized in a laboratory was used for seed treatments in Germany in 1913.Organic substances like phthalimides and dithiocarbamates have been crucial disease-controlling agents since the 1930s as they were having “multisite” action. Their mode of action involved simultaneous inhibition of a range of enzymes and cellular structures. It provides preventive protection of plants against various diseases in a non-systemic way at the surface of the plant. From 1940 to 1970, a number of new chemistry classes were introduced as fungicides. It is worth noting that during this time period: (i) several of these classes of chemistry also gave rise to herbicides e.g., triazines and nitroanalines, (ii) an antibiotic was introduced to control rice blast in Japan, (iii) the swing had taken place towards the reliance on commercially produced products helping to give rise to the crop protection industry. With this swing came the interest in the biochemical mode of action of fungicides.The decade from 1960 to 1970 saw a rapid expansion of research and development along with the catapulting of the fungicide market. The first fungicides with a specific mode of action viz. the benzimidazoles, carboxamides, and early sterol biosynthesis inhibitors (SBI) such as triforine were discovered in the 1960s and early 1970s.In this time span, the most widely used protectant fungicides, mancozeb and chlorothalonil, were introduced. The decade also witnessed the emergence of first broad-spectrum foliar systemic fungicide thiabendazole, and the systemic seed treatment fungicide carboxin.Since, 1970, a cascade of new fungicide groups were introduced like benzimidazoles, morpholins, piperazines, imidazoles, pyrimidines, triazoles and anilides. During the late 1970s and the early 1980s, dicarboximides, phenylamides and the first triazole, were introduced in the arena. Specific fungicide works at much lower rate and control plant pathogens more efficiently as compared to multisite contact fungicides. Most of the specific fungicides are systemic in nature with apoplast movement through xylem vessel of plants and helps to control the disease infection away from the point of contact of fungicide spray.As a result, they permitted a significant reduction in dose rate and number of applications of the fungicide. Specific mode of action of the fungicide was the origin of a new phenomenon i.e.the selection of resistant individuals in fungal populations, and the development of practical field resistance, which perhaps instigated the intense research of new fungicide discovery and development.

General trends in fungicide development

Fushikida (2018) and Umetsu *et al.* (2020) reported the first general trend in fungicide development being the development of three major fungicides viz. SDHI (succinate dehydrogenase inhibitors), DMI(demethylation inhibitors) and QoI (quinone outside inhibitors / QiI (quinone inside inhibitors).SDHIs have become one of the largest groups of agricultural fungicides, along with DMI (demethylation inhibitors) and inhibitors of the mitochondrial electron transport chain complex III, i.e., QoI (quinone outside inhibitors) and QiI (quinone inside inhibitors). The SDHIs act on complex II of the mitochondrial electron transport chains. The number of developed SDHIs has become comparable to those of DMI and QoI, and in recent times post-SDHI fungicides are now desired due to successive reports on fungal

pathogen resistance to existing SDHIs. DMIs, specifically sterol biosynthesis inhibitors, continue to play an important role in controlling plant diseases due to their broad spectrum, high therapeutic effect, and relatively slow development of resistance. Therefore, the development of a few, if not all, new DMI fungicides is in progress in response to the appearance of resistance to existing DMIs and the fact that many important DMIs are listed in the compounds suspected to have endocrine disrupting effects in Europe have also showed down the process of development. As a QoI fungicide that acts at the quinone outside (Qo) site of the inner membrane of complex III, 10 compounds have been developed since 2010. As a QiI fungicide that acts at the quinone inside (Qi) site of the inner membrane of complex III, two compounds have been developed since 2010. The second general trend is the development of fungicides with a novel mode of action and a unique chemical structure. Other trends are the development of novel plant defense activators and natural product origin fungicides, which could be a game changer in the times to come.

New generation fungicides in plant disease management

The process of fungicides discovery has undergone a noteworthy change over the period of time. After the era of broad spectrum multisite and site specific systemic fungicides, several novel action fungicides of different chemical classes had been developed in the past two decades. These are more ecofriendly as they are used at more economical doses as compared to the earlier compounds. In India a few of the recently developed new generation fungicides have been registered for use and many are currently under evaluation for different diseases like, scab of apple, late blight of potato, anthracnose of chilli, powdery and downy mildew of grapes etc. Some of the new generation fungicides registered in India for use against important diseases includes strobilurins (azoxystrobin, kresoxim methyl, trifloxystrobin, pyraclostrobin) against powdery mildew and downy mildew in grapevine and cucurbits,valinamides (iprovalicarb, benthiovalicarb) against Oomycetous diseases in grapevine, potato, tomato and cucurbits, oxazolidinediones (famoxadone) against potato late blight, phenyl-ureas (pencycuron) against black scurf of potato and mandelamides (Mandipropamid) against late blight of potato and downy mildew of grapevine (Kumar 2003).Other important fungicides introduced for the control of diverse diseases in the last decade are phenoxyquinolines, (quinoxyfen), anilinopyrimidines (cyprodinil, pyrimethanil), phenylpyrroles (fenpicloil, fludioxonil), melanin biosynthesis inhibitors (MBIs) (carpropamid) spiroketalamines (spiroxamine), mandelamides (mandipropamid), cyanoimidazoles (cyazofamid), thiocarbamates (ethaboxam), amdoximes (cyflufenamid), phe-noxyquinolines (quinoxyfen), imidazoles (fenamidone), benzamides (fluopicolide, zoxamide) representing different chemistries and mode of action (Thind 2012). These recently introduced new generation fungicides in the global market represent major advances in technology, potency against target diseases, selectivity, safety and rate reduction.

Recently launched or under development

Fungicides which are recently launched or under development are as follows**.**

SDHI fungicides

About seventeen SDHI fungicides were developed after 2010 and commercialized. Isofetamid was registered in December 2014 in Canada, inJuly 2015 in the USA, and in November 2017 in Japan. It has broad-spectrum antifungal activity against Ascomycota (such as *Botrytis* spp., *Sclerotinia* spp., *Monilinia* spp., and *Venturia* spp.)and Deuteromycota (such as *Alternaria* spp. and *Mycovellosiella*spp.) and is effective against existing SDHI-resistant pathogens (Araki, 2018;Yoneda *et al.* 2019). In 2018, Pyraziflumid acquired registration in Japan. It is a versatile fungicide having pyrazine carboxami deske leton and is applicable to a wide range of crops such as rice, horticulture products and turf (Oda *et al*. 2017;Hakuno, 2018). Inpyrfluxam exhibits high efficacy against major plant diseases in the European region, such as brown rust on wheat, net blotch on barley and is black scurf on potatoes (Anonymous, 2019). Flubeneteram, is an anilide fungicide and on considered to be an SDHI based on its chemical structure. It has just obtained an ISO common name in early 2020 (Anonymous, 2020a).

Isopyrazam is for foliar application to control rust and net blotch of wheat while Sedaxane is a seed-

treatment fungicide for wheat, beans and potatoes. Benzovindiflupyr is a rust-control fungicide for soybeans. Pydiflumetofen is for thecontrol of powdery mildew and *Alternaria* disease of vegetables,fruit trees, etc., as well as wheat leaf blight and wheat scab (Stierli *et al.* 2019).

Bayer launched bixafen, penflufen and fluopyram. Isoflucypram,under development by Bayer, exhibits efficacy for the control of leaf spot diseases on a large range of crops (Becker *et al.* 2019). Similarly, Pyrapropoyne is under development by Nissan Chemical.

Inhibitors of the mitochondrial electron transport chain complex III

A total of 12 compounds have been launched or are under development as inhibitors of the mitochondrial electron transport chain complex III since 2010. It comprises of 10 QoI and QiI fungicides.

Pyribencarb (K-I Chemical Research Institute and KumiaiChemical) was registered in 2012 in Japan. It is a novel benzyl carbamate-type fungicide against a wide range of plant pathogenic fungi, especially gray mold and stem rot (Takagaki *et al.* 2014). Though pyribencarb belongs to QoI group, it is active against strobilurin-resistant fungi, which is its major advantage.

Picoxystrobin was discovered by Syngenta and transferred to DuPont in 2006. DuPont registered it in theUSA in 2012. Nihon Nohyaku marketed it in 2016 in Japan.

Mandestrobin (Sumitomo Chemical), a strobilurin fungicide, was discovered by Shionogi & Co., Ltd., and commercially developed by Sumitomo Chemical. It is effective against *Sclerotinia* rot, fruit tree scab, etc., with a low risk of phytotoxicity (Hirotomi *et.al*., 2016, Imanishi, 2016). It was launched in 2016 in Japan and is under commercial development in many countries.

Metyltetraprole (Sumitomo Chemical) is a new broad spectrum fungicide with a unique tetrazolinone moiety that is effective against pathogens resistant to existing fungicides. Sumitomo Chemical is promoting development jointly with BASF in the EU, aiming to launch after 2022 (Anonymous 2020b).Metyltetraprole is highly effectiveagainst QoI-resistant strains of various pathogen species (Craig *et al.* 2019, Matsuzaki *et.al.,* 2019).

Six QoI fungicides with ISO common names are currently under development by Chinese companies: coumoxystrobin, enoxastrobin, fluf-enoxystrobin, triclopyricarb, and fenaminstrobin by Shanghai Research Institute of Chemical Industry (SRICI) and pyriminostrobin by Shenyang Sciencreat Chemicals (Fushikida, 2018). It is unclear whether they aim to obtain registrations around the world, as well as what characteristics each QoI has and how to segregate each product in the market.

As QiI fungicides, two compounds are currently under development. Fenpicoxamid (Meiji Seika Pharma, currently Corteva Agriscience), is a conversion product of UK-2A isolated from the culture broth of *Streptomyces* spp. by Ueki *et al.* (2020) at Osaka City University,and its action is inhibition of the mitochondrial electron transport system complex III. Meiji Seika Pharma introduced UK-2A from the university and subjected it to joint development with Dow after converting its structure into fenpicoxamid (Hiramatsu and Umetsu 2018). It is currently under development as an innovative fungicide for controlling key diseases in cereals, such as *Septoria tritici* and rust. It shows no cross-resistance to existing cereal fungicides (Hiramatsu and Umetsu 2018, Owen *et al*, 2017). Fenpicoxamid is a propesticide, since it is converted to UK-2A in crops. Florylpicoxamid (Corteva Agriscience) is a neopicolinamide fungicide under development and presumed to be a QiI, having the same mode of action as fenpicoxamid. Florylpicoxamid controls a wide range of pathogens including *Septoria* spp., powdery mildew, *Botrytis* spp., Anthracnose, *Alternaria*,scab and *Monilinia* sp. (Anonymous, 2018).

DMI fungicides

Currently, three DMIs are under development. Of these, mefentrifluconazole and pyrisoxazole should be noted. Mefentrifluconazole is the first isopropanol azole discovered and developed by BASF. Its registration was approved in the EU in 2019. It is highly effective against key fungal diseases in both row and specialty crops, including cereals, corn, soybeans, rice, grapevines, fruits, vegetables and turf (Semar *et.al*., 2019).

Pyrisoxazole, developed by SRICI, is a pyridine-type DMI that is effective against *Botrytis cinerea* and tomato leaf mold.

Mode of action is novel or unknown

Eight fungicides with a novel or unknown mode of action are marketed or under development since 2010 Fushikida (2018). Flutianil (OAT Agrio Co.) was registered during 2013 in Japan. Flutianil is chemically characterized as a cyanomethylenethiazolidine. It exhibits therapeutic and preventive effects against powdery mildew at a low dosage (Hayashi *et al*. 2020). The mode of action of this compound is yet to be reported.

Fenpyrazamine (Sumitomo Chemical) is a novel fungicide with an aminopyrazolinone structure that has shown high efficacy against gray mold, stem rot, and brown rot in field trials. The target enzyme of fenpyrazamine is the 3-keto reductase in the ergosterol biosynthetic pathway. Picarbutrazox (NipponSoda) was registered in June, 2017 in Japan. It belongs to the tetrazolyl oxime class, controlling oomycete diseases such as downy mildew and late blight. The mode of action of this compound is unknown, but it seems to have a new one, since the treatment of picarbutrazox causes swelling and hyperbranching of mycelia and inhibits zoospore formation, zoospore encystment and cystospore germination.

Tebufloquin (Meiji Seika Pharma) is used to control rice blast disease.The mode of action of this compound has not been clarified,but it is considered a respiratory inhibitor that acts on the mitochondrialelectron transport system.

Pyriofenone (Ishihara Sangyo Kaisha)is a novel fungicide with a benzoyl pyridine structure and was registered during 2013 in Japan. It is very effective against powdery mildew on wheat, cucumbers, strawberries and eggplants. It is of interest that pyriofenone is effective against QoI-and DMI resistant fungal plant pathogens. The mode of action of this compound was reported to be inhibition of the formation of appressoria and conidia and induction of morphological abnormality of the secondary appressorium and hyphae.

Oxathiapiprolin (Corteva Agriscience)is a new class of piperidinyl thiazole isoxazoline fungicide. The US EPA approved it in 2015 for use against several fungal diseases, including downy mildew and late blight on crops such as vegetables, ornamentals, and turf. Its mode of action involves binding to the oxysterol-binding protein in Oomycetes.Tolprocarb (Mitsui Chemicals Agro) is a rice blast fungicide which inhibited of the polyketide synthase in the melaninbiosynthesis pathway. In addition, tolprocarb induces systemic acquired resistance in *Arabidopsis thaliana* and rice. Owing to these double modes of action, tolprocarb can efficiently control not only rice blast but also bacterial diseases.Tolprocarb also provides long-term residual activity.Quinofumelin (Mitsui Chemicals Agro) has novel characteristics and effectively controls scabs, *Botrytis cinerea*, blast disease and anthracnose of fruits, vegetables, rape seeds, rice, etc. Mitsui Chemicals Agro signed a global license agreement with Bayer for its development and commercialization.

Others

Four other fungicides, are currently under development. Dichlobentiazox (KumiaiChemical) seems to be a plant defense activator created in the search for saccharin derivatives.It shows a stable effect against rice blast disease under various environmental conditions and treatment methods. It is safe for rice seedlings in nursery box treatment.Aminopyrifen (Agro-Kanesho) is a novel fungicide, and its synthesis and structure activity relationships were recently reported.It is reported that aminopyrifen inhibits the GWT-1protein in glycosylphosphatidylinositol-anchor biosynthesis. Dipymetitrone (Bayer) is a novel fungicide under developmentthat is effective against *Phytophthora* rot, downy mildew,scab, early blight and *Botrytis cinerea*. The mode of actionis unknown. Fluoxapiprolin (Bayer) effective against *Phytophthora* rot and downy mildew. It seems to be in the same group of fungicides as oxathiapiprolin.

Host Defense Inducers

Synthetic chemicals that have been defined as host defense inducers by the Fungicide Resistance Action Committee (FRAC) as code P1, are acibenzolar S methyl (ASM); code P2, such as probenazole (PBZ); and code P3, such as tiadinil and isotianil. According to the inducing agent involved and the subsequent molecular mechanism, two major types of induced resistance

have been identified: systemic acquired resistance (SAR) and induced systemic resistance (ISR). Transcription factors differentially regulate a number of genes involved in defense, leading ultimately to the production of defense proteins. In SAR expressing plants, the defense response occurs rapidly and/or efficiently on pathogen challenge. Isotianil, by itself, does not exhibit any activity against pathogens but rather protects plants against infection when applied at an early developmental stage.Bion, mimics the action of SA thereby inducing the same defense mechanisms as the biological induction. A battery of defense genes is activated in either case leading to a broad spectrum resistance against several fungal, bacterial and viral diseases. The influence of Bion-activated defense mechanisms in the life cycle of *Peronospora hyoscyami* f. sp.*tabacina* was examined after foliar spray application, by artificial inoculation and subsequent light microscopic analysis. Germination and appressorium formation of blue mold fungus in tobacco were not affected but both of the next steps, penetration and the formation of intra-epidermal vesicles were inhibited. In addition, deformed non-penetrating surface structures were found, a phenomenon which is known to occur in *P. hyoscyami* f. sp. *tabacina* on the resistant tobacco species *Nicotiana debneyi*. These observed effects together resulted in a reduced development of disease symptoms.

Role of FRAC in resistance management

The FRAC was founded as an organization designated to discuss resistance problems and to make cooperative efforts in the prevention and management of fungicide resistance. FRAC became incorporated within GIFAP, the International Group of National Associations of Manufacturers of Agrochemical Products. This organization evolved later on within an organization called Global Crop Protection Federation (GCPP) and then within CropLife International, the global federation representing the plant science industry.The purpose of FRAC is to provide guidelines for fungicide resistance management to prolong the effectiveness of “at risk” fungicides and to limit crop losses should resistance occur. In more detail the main aims of FRAC (http://www.frac info/frac/about) are to:

- Identify existing and potential resistance problems.
- Collate information on fungicide resistance and distribute it to those involved in research, development, distribution, registration and use of fungicides.
- Provide guidelines and advice on the use of fungicides to reduce the risk of resistance and to manage it should it occur.
- Recommend procedures for fungicide resistance studies.
- Stimulate open liaison and collaboration with universities, government agencies, advisors, extension workers, distributors, and farmers.

If molecules from different manufacturers have the same mode of action and if this mode of action bears at the same time a significant resistance risk, a FRAC working group (WG) can be established to analyze the resistance risk and to develop and publish common resistance management recommendations. There are currently FRAC WGs for SBIs,Qol fungicides, APs, SDHI fungicides, CAAS, AZN fungicides (formed in 2010), and most recently for the oxysterol-binding protein inhibitors (OSBPIs, U15, formed in 2016). The WGS meet regularly and publish annually updated reports on the resistance status and suitable resistance management recommendations. Task Forces (TF) may be analyzing the situation for new chemistries; they are expected to transition into WGs once established. For older modes of action for which regular monitoring programs are no longer performed (benzimidazoles, phenylamides, and dicarboximides), so called expert fora are available at the FRAC website (http://www.frac.info) to give advice and collect relevant literature on resistance monitoring methods and resistance management strategies.

CONCLUSION

The innovative nature of human beings has brought to the fore, a plethora of new generation fungicides and the search for more is on. The need of the hour is a multicide which will nullify the harmful effects of pests, pathogens and nematodes. Simultaneously, the chemicals should interact with the hosts in such a way, that resistance to pathogens is augmented. Invasive species of pathogen have thrown down the gauntlet in front of the plant pathologists and a fast track system of synthesis vis-à-vis registration of fungicides are

required. The changing paradigm of climate has also altered the status of pathogens and it is obligatory to walk that extra mile for production of safe food, devoid of any pathogen intervention. Possible? Not possible?

Let the answer be cradled in the arms of time.

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