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REVIEW ARTICLE

Changing trends in discovery of new fungicides: a perspective

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Abstract
Fungicides, despite certain limitations, continue to play a crucial role in the management of plant diseases. In their history of more than a century, several fungicide classes have been introduced starting from multi-site inorganic salts to organic compounds with protectant action and then to single-site systemic fungicides with curative activity. However, site-specific fungicides are regularly confronted with the problem of resistance. New compounds with novel modes of action are introduced to manage resistance to the existing fungicides and to provide more effective options for control of devastating diseases. Technological advances such as combinatorial chemistry, high throughput screening and bio-rational screen designs have revolutionized the synthesis and development of new fungicide active ingredients. However, stringent regulatory pressure has impacted the discovery of new active ingredients and this has led to the decline in introduction rate of new fungicides. In future, natural compounds hold promise to serve as new fungicide leads in place of more toxic synthetic compounds. This review will discuss technological advances and challenges in the discovery and development of new fungicides and future research needs for more ecofriendly disease management.

Keywords Combinatorial chemistry · Fungicide resistance · High throughput screening · Natural compounds · New fungicide leads · Regulatory norms

Introduction

Plant pathogens have the potential to cause significant crop losses in both pre- and post-harvest situations and fungicides remain a critical tool for protecting yield and quality. Fungicides play a significant role in our efforts to manage plant diseases caused by fungal pathogens, which have the potential to cause considerable crop losses before harvest as well as after harvest in transit and storage. These are considered as the second line of defense after host resistance in the fight against plant diseases. Their role assumes more importance when varietal resistance becomes ineffective to new pathogen races. In fact, these are the only hope for farmers once the disease starts appearing in the field. The past 100 years have seen the development of fungicides from a few simple inorganic compounds to several groups of organic compounds, and from the contact and multi-site fungicides to the systemic, site-specific fungicides with curative action (Morton and Staub 2008). The introduction of new fungicides is an essential element to provide sustained control of major crop diseases. The need for new and innovative fungicides is driven, among other factors, by resistance management, regulatory hurdles, and changing farmer's needs.

Over the years, fungicide research and development has transitioned from conventional approaches to more focused approaches using modern technologies keeping in view the changing needs in agriculture and environment safety. Discovery process of new fungicides has undergone significant changes both in terms of technology and perceived challenges of invading pathogens, fungicide resistance and environmental considerations. With more and more understanding of the biological processes both in fungal pathogens and host plants, development of selective fungicides with better disease control has increased, thereby replacing less specific conventional fungicides. With most of the fungicides introduced after 1970s having single-site mode of action, development of fungicide resistance in target pathogen has been a persistent problem. It has affected not only longevity of their use to control a plant disease but also caused financial losses to the developing company (Leadbeater 2015). Robotic machines with artificial intelligence and IT tools are now playing pivotal role in fungicide discovery

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right from synthesis to biological tests and elucidation of mode of action. More attention is being focused on environment safety, toxicological issues and human safety aspects of novel fungicide compounds. Significant changes have also occurred in formulation technologies. The focus has shifted from bulk powder formulations to low volume slow release formulations. This perspective addresses recent trends in discovery of new modes of action and various factors that impact research and development efforts for novel fungicides.

Fungicides scenario: past to present

Fungicides in the form of simple inorganic salts had been in use to protect agricultural crops since the ancient times. Interest in the chemical disease control started with the discovery of copper sulphate and lime based Bordeaux mixture in 1885 to control downy mildew in grapevine and other disease like late blight in potato. The discovery of Bordeaux mixture was followed by the development of fixed copper compounds and then mercury chloride and similar compounds for seed treatment and drenching. Until 1940s chemical disease control relied upon inorganic chemical preparations. These were frequently prepared by the users themselves from basic recipes (Russell 2005). Development of synthetic organic compounds started with the introduction of dithiocarbamates in 1934 and proprietary fungicide products soon became available. Between 1940 and 1960, several organic compounds other than dithiocarbamates, such as phthlamides, fentin compounds and guanidines were developed. These were multi-site contact fungicides with low biochemical specificity that were limited in their action to surface protection (Horsfall 1975).

The decade from 1960 to 1970 saw a rapid expansion of research and development with establishment of several agrochemical companies along with a rapid growth of the fungicide markets. In this decade, the most widely used protectant fungicides mancozeb (dithiocarbamates) and chlorothalonil (phthalonitriles) were introduced. This decade also gave us the first systemic fungicide carboxin belonging to carboxamides for smut control followed closely by other systemic fungicide classes viz. benzimidazoles, thiophanates and morpholines. From 1970 onwards, most of the fungicides of different chemical classes developed were systemic in nature with internal therapeutic action to eradicate established infections. These are site-specific in action and are used at low application rates. More prominent fungicide classes introduced between 1970 and 2000 are organophosphorus, phenylcarbamates, dicarboximides, sterol inhibiting fungicides—mostly demethylation inhibitors or DMIs (comprising seven sub-groups including widely used triazoles), phenylamides, cinnamic acid derivatives, melanin biosynthesis inhibitors, alkylphosphonates, phenylpyrroles, anilinopyrimidines, phenylpyazoles, aminopyridines, arylaminopyridines, strobilurins and quinolines. Some new classes of fungicides with novel properties have been developed during 2000–2020. Important among these are carboxanilides, benzamides, oxazolidinones, succinate dehydrogenase inhibitors (SDHI), carboxylic acid amides (CAA), benzophenones, quinazolinones, pyridinyl ethylbenzamides, piperidinyl thiazole isoxazolines, triazolo pyrimidines, tetrazolinones and oxysterol binding protein inhibitors (OSBPI). Among these groups, strobilurins, SDHI, DMI and CAA compounds are the most widely used fungicides against diverse plant diseases. Due to biochemical specificity in their mode of action, several of these fungicides can experience development of resistance in target pathogens (Thind 2011).

Several milestone fungicides have been developed since the discovery of Bordeaux mixture. Important fungicide discoveries from early 1900 s till 2020 are phenyl mercury chloride (1914), copper oxychloride (1916), thiram (1940), zineb (1943), captan (1952), dodine (1957), mancozeb (1962), chlorothalonil (1964), carboxin (1966), benlate (1968), copper hydroxide (1968), triadimefon (1973), imazalil (1973), iprodione (1974), metalaxyl (1977), fosetyl-Al (1977), cymoxanil (1979), propiconazole (1979), tebuconazole (1986), dimethomorph (1988), fluazinam (1992), fludioxonil (1993) pencycuron (1994), azoxystrobin (1996), quinoxyfen (1997), famoxadone (2001), pyraclostrobin (2001), fenamidome (2003), boscalid (2003), benthiovalicarb (2003), mefenoxam (2003), zoxamide (2004), proquinazid (2004), thifluzamide (2004), cyazofamid (2004), mandipropamid (2005), Fluoxastrobin (2005), metrafenone (2006), fluopicolide (2007), amisulbrom (2008), fluxapyroxad (2010), penflupen (2011), fluopyram (2012), ametoctradin (2015), oxathiapiprolin (2016), mefentrifluconazole (2016), pyraziflumid (2018), fluoxapiprolin (2018) and inpyrfluxam (2019) (Klittich 2008; Morton and Staub 2008; Leadbeater 2015; Umetsu and Shirai 2020). Recently in 2020, a new fungicide metyltetraprole belonging to class tetrazolinones has been developed to overcome QoI resistance (Matsuzaki et al. 2020). Most of the fungicides developed in the last four decades are site-specific in action and are generally used in combination with other modes of action, mostly multi-site inhibitors, to avoid resistance development.

Apart from direct action fungicides, few compounds that act indirectly against plant pathogens by activating host defense system have also been developed. More common defense activators are probenazole and acibenzolar-S methyl. A novel such compound called dichlobentiazox was introduced in 2020 (Food Safety Commission 2020). Currently, 231 fungicidal active ingredients from 59 modes of action groups, apart from biologicals, are registered for use in plant disease control (FRAC 2021), but all fungicide groups are

not equally in demand and the fungicide market by value is dominated by only a small number of modes of action.

Combinatorial synthesis of new chemistry

Earlier, traditional synthetic chemistry allowed only small number of molecules to be synthesized in a given time. With advances in synthetic organic chemistry using combinatorial chemistry allowing automated chemical synthesis, thousands of new molecules, referred to as a library, can be synthesized in the same period leading to more chances of discovering a new fungicide or pesticide.

Depending on set-up of the synthesis design, the compounds synthesized through combinatorial chemistry may be either biased or unbiased toward an intended target. Unbiased libraries provide maximum diversity among the compounds around a central core structure, each library generally containing 10,000–30,000 compounds. These large libraries are prepared by a combinatorial methodology known as mix-and-split design and the compounds are produced as mixtures with diverse structures. In contrast, biased libraries are generally smaller in size with compounds ranging from 100 to 2500 in number. Compounds in biased library are prepared using synthetic design that produces pools of discrete compounds (called parallel synthesis), each pool having 5–10 compounds. Structural motifs in the rationally designed compounds of biased libraries are considered advantageous for potential activity on the intended target on the bio-screens (Dan Hess et al. 2017).

High-throughput screening in fungicide discovery

High-throughput screening (HTS) is becoming increasingly important in the discovery of new fungicides and pesticides. This new technology of *in vitro* based miniaturized screening has been adopted from pharmaceutical industry and has greatly helped in maintaining a regular flow of novel fungicide products to the farmers. In the current process of fungicide discovery, synthesized compounds are subjected to a specific metabolic target on the bio-screens followed by efficacy evaluation, in contrast to the earlier system in which efficacy testing was proceeded by elucidation of mode of action.

HTS involves microtiter assay plates called bio-screens, each with 96–864 wells. High-density plates with 864 wells are preferred for *in vitro* assays that allow for testing more concentrations and helps in rapid identification of the active compounds. On the other hand, 96-well plates are preferred for *in vivo* assays. Using robotic pipetting, multiple beads are distributed into microtiter plates, while robot-controlled suction pipets help in distribution of single beads. After cleaving from beads, the compounds in a solvent are transferred to the assay plates and specific reagents are added to initiate the assay. Using microtiter plate assays, a wide range of *in vitro* screening for new fungicide leads can be performed. Such HTS bioassays also allow evaluating dose-response and structure-activity relationships (Drewes and Tietjen 2013). For discovering novel modes of action, target-based HTS technology provides a directed approach. The most crucial issue in this approach is selection of the best suited targets. In this regard, many essential genes are delivered as candidate genes by the genomic methods (Cools and Hammond-Kosak 2013).

Using HTS technology, miniaturized *in vivo* tests on whole real target organisms are now possible. *In vivo* screens form an integral part of new fungicide discovery, where young potted plants are treated with the test compounds and then inoculated with a pathogen causing a particular disease. The plants are transferred to a greenhouse or growth chamber where ideal disease conditions are maintained for symptom development. These are rated for the disease control efficacy, contact or systemic nature and also for phytotoxic effects.

Search for novel modes of action

Search for novel modes of action forms the basis for the discovery of new fungicides. Use of HTS involving target-based approach has facilitated the search for novel modes of action to a great extent. Genomic methods are lending a helping hand in selecting the best suited target.

It is very rare that all new modes of action discovered are developed into new fungicides as there are stringent parameters to fulfill before these are brought into the market. Normally the trend has been that if a particular mode of action fungicide becomes popular in controlling particular diseases, more fungicides are developed within the established mode of action group with minor differences. Such copycat modes of action have similar resistance risk as the original fungicide. This trend of proliferation of one mode of action to develop more similar group fungicides, as it has happened with the DMIs, QoIs, and SDHIs, results in fewer alternative modes of action and thus has an impact in terms of resistance management.

With high-throughput screening now commonly in use, there are ample chances of discovering fungicides with completely novel modes of action. On an average, 20 new active ingredients are discovered in a decade. Compounds exhibiting a novel mode of action are of special interest in resistance management strategies, along with other properties characteristics such as systemicity, curative activity and disease control potential. Advances in molecular genetics

and reactomics are likely to help explore the known modes of action in new ways (Glättli et al. 2011). But with implementation of more stringent legislation and escalating R & D costs, it is becoming difficult to introduce novel action fungicides (Leadbeater and Gisi 2010). It is easier to develop new fungicides around known modes of action as standard bioassays already exist for the known modes of action and their environmental risks and toxicity are well understood.

In the past 20 years, a diverse number of modes of action have led to discovery of successful fungicides against different diseases, and majority of the newly developed fungicides have lower risk of resistance development. As an example, a diverse number of modes of action (e.g. CAA group fungicides) have been introduced in the past two decades to control oomycete diseases. These provide a wide range of options to the growers for disease control as resistance to these fungicides, unlike phenylamides, is rarely known. New modes of action with the ability to control more number of diseases at a time are desperately required. Interestingly, a new oomycete fungicide ametoctradin blocks respiration at a step that is common to oomycetes and true fungi, and thus may help in controlling diverse diseases (Leadbeater 2015).

Leads for discovery of new fungicides

Generally, majority of the new leads for fungicide discoveries come from synthetic chemistry, notably combinatorial chemistry libraries. In the past, several successful fungicides have been developed from synthetic chemical leads and these have provided adequate control of some of the devastating plant diseases that were earlier difficult to control by conventional methods.

Because of the continual development of resistance, it is important to discover new fungicides with different modes of action from existing fungicides. For this, efforts are intensified to search for new lead compounds from a wide range of synthetic chemistry, for their further development as commercial fungicides. A recent example is the discovery of a new fungicide candidate for downy mildew control with different mode of action through lead optimization of a pyrimidinamine compound ic (Guan et al. 2017). However, novel modes of action too can succumb to the problem of resistance sooner or later due to their specific mode of action, although most of the newly developed fungicides after 2010 are rarely found to encounter resistance in practice. Hence, search for new fungicide leads with a different mode of action is a continual process.

Apart from synthetic chemistry compounds, a large number of bioactive compounds from plants and secondary metabolites of microbial origin are considered potential alternative source for new fungicide leads. Search for natural compounds is being strengthened as a new source of chemical diversity and also as compounds of lower toxicity to non-target species and acceptable levels of persistence in the environment. Both plants and microorganisms are storehouse of diverse bioactive compounds having anti-fungal activity. Several plant-derived metabolites such as cinnamaldehyde, gamma-aminobutyric acid, laminarin, phenolics, terpenoids, glycosides, phytoalexins, PR -proteins, glucosinolates, acetaldehyde and acetophenone from different plant species are known to have pronounced activity against many diseases (Martinez 2012; Ma et al. 2013). Likewise, secondary metabolites produced by certain bacteria, actinomycetes and fungi like pyrocyanin, pyrrolnitrin, trichodermin, viridian, siderophores, hydrogen cyanide, gliovirin, azole compounds, trichothecin, etc. have demonstrated potential activities against plant pathogens and hold promise as future bio-fungicide leads (Verma et al. 2020).

Natural compounds from these sources can either be used as such like fungicides or may be explored as leads for new fungicides. Somehow, their direct use as fungicides has not been quite successful as most of them are inherently unstable to sunlight and do not persist sufficiently in the field to deliver desirable effect against the disease. Hence natural products are mainly used as leads to design novel, synthetic compounds that with optimization via classical structure-activity relationship demonstrate desired biological, physical and environmental properties. Crop protection research has also introduced structure based design as an important facet of new molecule discovery (Kemmitt 2015).

Historically, plant-derived natural compounds have been largely explored as lead molecules for discovery of new insecticides and herbicides. In contrast, microbial metabolites from fungi and bacteria have been used as templates for the development of new fungicides for quite some time in the past (blasticidin, kasugamycin, validamycin) and continue to offer important leads in present times (Sparks et al. 2017). In mid-1990s, synthetic derivatives of strobilurins produced as metabolites by the wild mushroom *Strobilurus tenacellus* led to discovery of an important class of strobilurin fungicides such as azoxystrobin, kresoxim methyl and many more in later years. In the recent past, fenpiclonil and fludioxonil of phenylpyrrole group have been developed as chemical derivatives of pyrrolnitrin, a secondary metabolite produced by *Pseudomonas pyrrocinia* (Kim and Hwang 2007; Kilani and Fillinger 2016). Some plant and microbial metabolites have been found to protect plants through induction of systemic acquired resistance in host plants against invading pathogens.

Growing focus on biologicals

With increasing concerns on the use of synthetic fungicides (fungicide resistance, non-target effects, impact on environment), interest for the development of biological

fungicides (as for other biopesticides) is growing as these are considered relatively safer. They have multiple mode of action against a wide range of diseases, hence chances of resistance development are very rare. These are biodegradable and have no toxicity. A good number of plant derived products and microbial formulations are used as bioweapons against plant diseases. While some have been developed for direct use against plant diseases, others elicit defense response in host plants.

Plant derived fungicide preparations are generally composed of extracts and oils from different plant parts. These botanical fungicides act by disrupting cell membrane with multiple effects on ion membrane transporters. Some examples of plant based commercial fungicides that are registered for use in Europe and USA are CitroBio (citrus seeds extract), extract from *Melaleuca alternifolia* (tea tree oil) and plant oils (eugenol, geraniol, thymol), extract from lupine cotyledons having polypeptide lectin. Milsana, derived from extract of *Reynoutria sachalinensis* (giant knotweed), acts by inducing host defense through anthraquinone elicitors. Laminarin, a polysaccharide found in brown algae, is another example of natural product that acts as elicitor of induced resistance. Extract from *Swinglea glutinosa* has been developed into an elicitor bio-fungicide and activates defense mechanism in host plants through its constituents comprising of phenols and sesquiteepenes (Martinez 2012; FRAC 2021).

Bio-fungicides in the form of microbial formulations have been in use over the years. They are mainly derived from certain pseudomonads, Bacillus, Streptomyces and fungal species. Some commercial microbial fungicides include preparations from living microbes, extracts or metabolites of *Bacillus amyloliquefaciens, B. subtilis*, *Pseudomonas chlororaphis*, *Streptomyces griseovirides*, *S. natalensis*, *Trichoderma atroviride*, *T. asperellum*, *T. harzianum*, *Gliocladium catenulatum*, *Coniothyrium minitans*, *Talaromyces flavus*, *Saccharomyces cerevisae*, etc. These biological act against the pathogens through competition, mycoparasitism, antibiosis, membrane disruption by fungicidal lipopeptides or lytic enzymes. Some microbial antifungals act through induction of systemic acquired resistance. Examples include Messenger (derived from harpin protein secreted by pathogenic bacteria), Serenade (a microbial protectant derived from *Bacillus subtilis*), Sonata (based on a unique strain of *Bacillus pumilus*), and preparations from strains of *Bacillus mycoides* and *Saccharomyces cerevisiae* (FRAC 2021). As elicitors generally lack innate antifungal activity, hence they will not appear active in most current high throughput screening assays. A trend is in the offing to promote combination of biocontrol agents with conventional fungicides with skillful use of adjuvants and co-formulants.

Advances in formulation technology

Research is focused on developing safer, eco-friendly and better performing formulations of fungicides that offer better redispersibility and flow properties of the active ingredient. We are slowly moving away from bulk volume spray tank application. Among different formulation types, SC (suspension concentrate) formulations for fungicides have become relatively more preferred as compared to WP (wettable powder) and WG (water dispersible granule) formulations which are still in ample use and have high active ingredient strength. It is followed next by EC (emulsifiable concentrate) formulations. As SC formulations are water based, this type is a preferred choice while developing a new active ingredient, which should also have low water stability and melting point greater than room temperature. SC formulations are also prepared with blends of two or more actives. Choice and level of dispersant is important factor for developing a stable formulation. Controlled release granular formulations for combined application of fungicide and insecticide in rice fields have also been developed. Among several seed treatment formulations, DS (dry powder), WS (water dispersible powder), LS (liquid solution) and FS (flowable solution) have been developed with many advantages of safety, coverage and surface redistribution. Research is also focused on developing combined formulations of microbial and synthetic actives. Innovations are being made to develop new formulants (e.g. polymers, fillers, rheology modifiers) and encapsulation of actives (Bullock and Calvert 2020).

Slow release nanoformulations of fungicides are also being developed that help in reducing the number of applications. Encapsulated nanoformulations of few commonly used dithiocarbamate fungicides mancozeb and zineb have been prepared using polyethylene glycol and hyperbranched poly citric acid as capping agents. Using nanotechnology, hexaconazole has been encapsulated into chitosan nanoparticles so as to develop a fungicide nanodelivery system for effective transport to the target pathogen cells (Maluin et al. 2019). Lignin-based nanocarriers have proved to be promising biodegradable fungicide delivery platform, and these are recently reported to enhance pyraclostrobin efficacy to control esca in grapevine after application of its nanoformulation (Machado et al. 2020).

The nano-emulsions containing essential oils of cinnamon, thyme, manuka, and tea tree oil have been recently obtained by using high-energy emulsification methods (ultrasonification) which could increase biological activity of essential oils (Miastkowska et al. 2020).

Despite several potential advantages associated with the use of nanoformulations, not many nanoparticle-based

fungicides have been commercialized in plant disease control. More studies are required for assessing toxicity and environmental impact of nanoformulations (microcapsules) after release as well as their redistribution within plants after absorption (Tleuova et al. 2020). Regulatory considerations and restrictions including prohibition on using certain formulants have to be considered at all stages of the formulation process. Radical changes in formulation technology are being effected towards developing smaller volumes and robust, concentrated formulations with more precision.

Desirable features of new fungicides

New fungicides after discovery are optimized during development in a way that they have least harmful effects on and application in the field as also during manufacturing and handling. They should possess excellent field efficacy against a plant disease at an extremely low dosage and should have high level of crop selectivity. They ought to have increased systemicity and effective redistribution on or inside the crop plant and enhanced curative activity.

The new compound should have the least chances of resistance development with novel mode of action. In fact, the search for novel action fungicides is driven by the need to manage resistance, hence compounds having new mode of action are of special interest. The new compound should have optimal compatibility and miscibility with other mode of action compound in the combination fungicide formulation for resistance management and wide spectrum of disease control.

The toxicological parameters are quite important in development of new fungicides which should be readily degradable and less persistent in the environment. They should leave least residue in the agricultural produce. There is a need to develop selective toxic compound which should be safe to the crop and do not have any adverse non-target effects including safety concerns for the applicator. Additional desirable features include synthetically accessible structure allowing its manufacturing at scale cost and physiochemical properties allowing formulation flexibility. They should be stable in storage. Likewise, microbial fungicides must retain their fungicidal properties during storage and should be able to establish ideally in the crop environment after application for reliable efficacy to control diseases.

Challenges in new fungicide discovery

Agricultural crops are continually confronted with the onslaught of ravaging diseases and there is urgent need to develop novel fungicides having improved effectiveness and safety. However, there are some challenges facing discovery and development of new fungicides.

Regulatory pressure

In early period of crop protection chemicals, concerns for the impact of fungicides on the environment and humans including applicators were largely non-existent. However, with increasing awareness and concerns for human and wild life, regulatory measures were put in place and the guidelines are revised with need of the time.

The increasing regulation for human and environment safety has made the introduction of new fungicides and other pesticides quite challenging. This is more so in EU countries where registration procedure takes into account hazard rather than risk from a new compound. Due to stringent regulation for safety margin, identification and introduction of new fungicide active molecules, which have otherwise high chances of being registered for use in disease control, has become highly difficult. Even some important existing fungicides like triazoles are facing uncertainty about their future in some developed countries. With increasing regulatory measures, cost of development of new fungicides continues to escalate and so is the maintenance of already registered fungicides.

Fungicide resistance: a continuing challenge

Development of fungicide resistance in plant pathogens continues to pose a serious challenge in disease management ever since the introduction of systemic, highly effective but site-specific fungicides since 1970s (Ishii and Hollomon 2015). Rapid emergence of benomyl resistant strains of *Venturia inaequalis* (apple scab) and metalaxyl resistant strains of *Phytophthora infestans* (potato late blight) in 2–3 years after their introduction are classical examples of fungicide resistance development in plant pathogens (Wicks 1974; Davidse et al. 1981). Among different groups of fungicides, benzimidazoles, dicarboximides, phenylamides and strobilurins carry high risk of resistance development (Morton and Staub 2008). It still remains a major challenge to some of the new generation fungicides. Hence, it warrants discovery of new fungicides with different modes of action to manage resistance. The need for novel action compounds is particularly felt in the context of potential loss of some key fungicides in future due to regulatory pressure. This will further limit the number of effective modes of action that are available to the farmers for resistance management strategies.

The future focus in fungicide discovery is the likely development of multiple activity anti-fungal compounds. Recently, mono-alkyl lipophilic cations (MALCs) have been developed that inhibit oxidative phosphorylation by

affecting NADH oxidation and also induce production of reactive oxygen species at the level of respiratory complex I in target fungal pathogens. These MALCs could prove as effective agricultural fungicides with least chances of resistance development (Steinberg et al. 2020).

Increased focus on alternative technologies

Increasing regulatory requirements and rising costs in development of new fungicides have led to agrochemical companies contemplating alternative technologies for crop protection. These include genetically modified (GM crops), biological, bio-stimulants, microbiome exploitation etc. Several agrochemical companies are diverting their R&D budgets away from new chemistry toward GM trait development. This has led to decline in development of new active ingredients and their subsequent introduction into the market. Availability of older fungicides is also getting affected by re-registration requirements, particularly in EU and the USA. Diversion of focus toward alternative technologies and decreased interest in crop protection innovation have led to the merger of many agrochemical companies which has considerably affected the competitive environment to discover and develop new chemistries.

Impact of changing climate

It is now well established that climate change can influence prevalence and severity of plant diseases. As an example, wheat and oats have become more susceptible to rusts with increased temperature due to climate change. Some minor diseases are likely to become more severe with the changing climate and assume regional importance. This will affect management of diseases with regard to application timing, efficacy and preference of fungicides. The impact of climate change on plant diseases has the potential to shape the future landscape of fungicides development.

Fungicide activity is a major determinant in the effective management of plant diseases. Changes in climate, apart from impacting plant diseases, may also affect fungicide efficiency. In the event of elevated temperature and CO_2, erratic rainfall and higher intensity sunshine, efficiency of fungicides is adversely affected (Choudhury and Saha 2020). Climatic aberrations like highly frequent rainfalls can greatly affect efficiency of surface protectants, as frequent rainfall can wash off contact fungicides from plant surface and thus render them less effective. Surface residues of systemic fungicides after application are also likely to be impacted, though plants with higher metabolic rates have rapid intake of fungicides and are less affected by rainfall (Zayan 2019). Under increased sunshine, some fungicides can undergo extensive photodegradation (Thind and Bala 2017). With rise in temperature and moisture, fungicides applied to the soil can degrade at faster rate owing to increased microbial activities. This will require repeated application of fungicides at higher use rate.

Thus climate change can impact prolonged use of new fungicides which are developed at the huge expense of time and resources. This requires to discover and develop such fungicide compounds and their formulations that can withstand the onslaught of changes occurring in the climate.

Future of fungicide research and development

Even after more than a century of fungicide research and development, quest to discover new fungicide compounds driven by the need to manage plant diseases more effectively is still continuing and is likely to continue further in the foreseeable future. Emerging plant diseases require viable solutions in terms of efficiency, economics and ecology. Despite preference for resistant crop varieties, fungicides offer immediate, short term remedy for disease management and search for new, more effective new fungicides goes on continually.

It is foreseen that dependence on fungicides may be moderated in the coming years by further development in crop biotechnology that is focusing more on GM crops, new fungicide development will continue for efficient and timely control of plant diseases. Available genome sequences of the ravaging fungal and oomycete pathogens will prove handy in discovering new modes of action and bring new opportunities in chemical disease control. Whole genome research has not yet been amply exploited in discovering new fungicide compounds. However, with further improvements in molecular biology, transcriptomics, computational analysis and chemical genetics, discovery and development of new fungicides in future will be greatly facilitated.

It is a fact that the number of new active ingredients has declined in recent years. It is attributed to high costs of R & D budgets which are being diverted to alternative crop protection technologies such as GM crops, biological, RNAi (gene silencing) and CRISPER (gene editing). Despite all this, new innovations in fungicide discovery are reported every year. New proteomic based strategies are being explored as disease control agents. Peptide sequences (aptamers) that have the ability to disrupt fungal development or strengthen plant defense are likely to offer new fungicide designs in future. In a recent study, molecular docking has been used to search promising phytofungal proteins for fungicidal activity that could be used as lead molecules for development of new fungicides (Acero et al. 2011; Mishra et al. 2019).

Fungicide resistance is a continual challenge and the new fungicide discovery is derived by the need to manage

this problem by discovering novel modes of action. In this endeavour, new antifungal compounds with multiple modes of action, such as mono-alkyl lipophilic anions, are being investigated as new fungicide options that are able to control multiple diseases with minimum chances of resistance development (Steinberg and Gurr 2020).

In the near future, random screening will play important role in identification of new active ingredients and natural products will represent a major source of fungicide leads. Progress is underway for the development of high-throughput screens that comprise of target enzymes or cell-based assays. These advanced techniques will improve chances of discovering new compounds. Apart from improved fungicidal efficiency, human and animal safety and environmental protection will remain important criteria for development of new fungicides.

It is believed that use of fungicides in combination with alternative technologies is likely to provide a more sustainable solution in plant disease management. With increase in awareness to minimize crop losses due to diseases, fungicide market is expected to grow in developing countries like India in the near future. It is envisaged that search for new active gradients of fungicides will continue in the near future as they can help achieve desirable crop yields by effectively managing serious plant diseases.

Conclusions

Despite certain drawbacks, fungicides continue to play important role in our efforts to manage plant diseases. Scenario of fungicides discovery and development has undergone much transformation with introduction of several classes of fungicides during the past over 100 years. With advancements in synthesis and screening technologies, several fungicides with new modes of action and improved features have been developed that provide much needed control of some devastating diseases which were difficult to control with earlier fungicides. However, fungicide resistance remains a challenging problem with most of the new fungicides, which is generally attributed to the specificity in their modes of action. The need for new active ingredients is mainly derived from the increasing impact of pathogen resistance to existing fungicides rendering them ineffective to manage plant diseases of concern. Thus, discovery of novel action fungicides is considered as an important strategy for resistance management. Several major classes of fungicides such as strobilurins and SDHIs were introduced as a part of resistance management in the previous categories of fungicides. In the last two decades, new modes of action seem to be discovered more frequently for the control of oomycete pathogens.

Over the years, several technological advances have taken place that has given impetus to the discovery and development of new fungicides. Good progress has been made in the development of high-throughput screens that are generally comprised of target enzyme sites or cell-based assays. These improved screens will improve the chances of new fungicide discoveries. Research efforts are directed towards identification of natural products from plants or microbes as suitable leads for new fungicides. Once the leads are identified, biorational design is used to optimize specific properties of the intended new fungicide. Glasshouse assays and field evaluation trials are likely to remain reliable methods for determining disease control efficacy of new fungicides. Further, new compounds are expected to have low toxicity to humans and wild life, low impact on the environment and low residues in food and feed. They should be compatible with other components of IPM programmes. It is envisaged that for effective and environment friendly management of plant diseases, natural products derived synthetic lead compounds, knowledge of host-pathogen interactions and fungal cell biology and eco-toxicological norms will lead the way for the discovery of new fungicides. Likewise, innovations are taking place for the development of slow release, low volume active ingredient formulations of fungicides.

There is no denying the fact that fungicides with novel modes of action continue to be discovered by the agrochemical companies, but their introduction rate is declining. Despite the available technology for discovery and development of new active ingredients, increasing regulatory pressure and thereby escalation of R & D costs make the discovery and introduction of new fungicides increasingly slow and difficult. The number of older fungicides is also declining due to the impact of re-registration requirements.

With changes in agricultural practices and the climate, disease scenario is also changing. New pathogens and their strains are frequently invading the crops. New fungicides can be of much help in managing emerging diseases. There is a need to continue innovating user friendly fungicides to provide better disease control options. Nevertheless, human safety and environment protection have to be kept on priority list while developing new fungicides.

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Declarations

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References

Acero FJF, Carbú M, Rabie El-Akhal M, Garrido C, González-Rodríguez VE, Cantoral JM (2011) Development of proteomics-based fungicides: new strategies for environmentally friendly control of fungal plant diseases. Int J Mol Sci 12:795–816

Bullock J, Calvert D (2020) Crop science formulations 2020. iFormulate Ltd. http://www.iformulate.biz

Choudhury PP, Saha S (2020) Dynamics of pesticides under changing climatic scenario. Environ Monit Assess 192:814. https://doi.org/10.1007/s10661-020-08719-y

Cools HJ, Hammond-Kosak KE (2013) Exploitation of genomics in fungicide research: current status and future perspectives. Mol Plant Pathol 14:197–210

Dan Hess F, Anderson RJ, Reagan JD (2017) High throughput synthesis and screening: the partner of genomics for discovery of new chemicals for agriculture. Cambridge University Press, London

Davidse LC, Lovijen D, Turkensteen LJ, Van der Wal D (1981) Occurrence of metalaxyl resistant strains of *Phytophthora infestans* in Dutch potato fields. Neth J Plant Pathol 87:65–68

Drewes M, Tietjen K (2013) High-throughput screening in agrochemical research. Comb Chem High Throughput Screen 8:1–20

Food Safety Commission (2020) Dichlobentiazox (pesticides). Food Saf 8(1):6–7

FRAC (2021) FRAC Code List – 2021: fungal control agents sorted by cross resistance pattern and mode of action. Crop Life International, Brussels

Glättli A, Grotel T, Stammler G (2011) SDH-inhibitors: history, biological performance and molecular mode of action. In: Dehne H-W, Deising HB, Gisi U, Kuck KH, Russell PE, Lyr H (eds) Modern fungicides and antifungal compounds VI. DPG-Verlag, Braunschweig, pp 159–170

Guan A, Wang M, Yang J, Wang L, Xie Y, Lan J, Liu C (2017) Discovery of a new fungicide candidate through lead optimization of pyrimidinamine derivatives and its activity against cucumber downy mildew. J Agric Food Chem 65:10829–10835

Horsfall JG (1975) Fungi and fungicides: the story of a nonconformist. Ann Rev Phytopathol 13:1–14

Ishii H, Hollomon DW (2015) Fungicide resistance in plant pathogens: principles and a guide to practical management. Springer, Tokyo

Kemmitt GM (2015) Fungicide development for the 21st century. Plant Pathol J 97:S13

Kilani J, Fillinger S (2016) Phenylpyrroles: 30 years, two molecules and (nearly) no resistance. Front Microbiol. https://doi.org/10.3389/fmicb.2016.02014

Kim BS, Hwang BK (2007) Microbial fungicides in the control of plant diseases. J Phytopathol 155:641–653

Klittich CJ (2008) Milestones in fungicide discovery: chemistry that changed agriculture. Plant Health Prog. https://doi.org/10.1094/PHP-2008-0418-01-RV

Leadbeater A (2015) Recent developments and challenges in chemical disease control. Plant Prot Sci 51:163–169

Leadbeater A, Gisi U (2010) The challenges of chemical control of plant diseases. In: Gisi U, Chet I, Gullino ML (eds) Recent developments in management of plant diseases - plant pathology in the 21th century, vol 1. Springer Science, Dordrecht, pp 3–17

Ma Y, Fan H, Gao Y, Li H, Zhang A, Gao J (2013) Natural products as sources of new fungicides (I): synthesis and antifungal activity of acetophenone derivatives against phytopathogenic fungi. Chem Biol Drug Des 81:545–552

Machado TO, Beckers SJ, Fischer J, Müller B, Sayer C, De Araújo PHH, Landfester K, Wurm FR (2020) Bio-based lignin nanocarriers loaded with fungicides as a versatile platform for drug delivery in plants. Biomacromolecules 21:2755–2763

Maluin FJ, Hussein MZ, Yusof NA, Fakurazi S, Idris AS, Hilmi NHZ, Daim LDJ (2019) Preparation of chitosan–hexaconazole nanoparticles as fungicide nanodelivery system for combating Ganoderma disease in oil palm. Molecules 24:2498

Martinez JA (2012) Natural fungicides obtained from plants. In: Dhanasekaran D (ed) Fungicides for plant and animal diseases. InTech Publishers, Croatia

Matsuzaki Y, Yoshimoto Y, Arimori S, Kiguchi S, Harada T, Iwahashi F (2020) Discovery of metyltetraprole: identification of tetrazolinone pharmacophore to overcome QoI resistance. Bioorg Med Chem Lett. https://doi.org/10.1016/j.bmc.2019.115211

Miastkowska M, Michalczyk A, Figacz K, Sikora E (2020) Nanoformulations as a modern form of biofungicide. J Environ Health Sci Eng 18:119 – 128

Mishra P, Eswaran M, Raman NM, Kaul T (2019) Probing of phytofungal proteins for fungicidal activity by molecular docking. J Proteomics Bioinform 12:79–84

Morton V, Staub T (2008) A short history of fungicides. Online, APSnet Features. https://doi.org/10.1094/APSnetFeature-2008-0308

Russell PE (2005) A century of fungicide evolution. J Agric Sci 143:11–25

Sparks TC, Hahn DR, Garizi NV (2017) Natural products, their derivatives, mimics and synthetic equivalents: role in agrochemical discovery. Pest Manag Sci 73:700–715

Steinberg G, Gurr S (2020) Fungi, fungicide discovery and global food security. Fungal Genet Biol. https://doi.org/10.1016/j.fgb.2020.103476

Steinberg G, Schuster M, Gurr SJ, Schrader TA, Schrader M, Wood M, Early M, Kilaru S (2020) A lipophilic cation protects crops against fungal pathogens by multiple modes of action. Nat Commun 11:1608. https://doi.org/10.1038/s41467-020-14949-y

Thind TS (2011) Fungicide resistance in crop protection: risk and management. CABI, Wallingford

Thind TS, Bala A (2017) Photodegradation of fungicides: an appraisal. Plant Dis Res 32:153–160

Tleuova AB, Wielogorska B, Prasad VSSL, František T, Christopher S, Elliott T, Grigoriev DO (2020) Recent advances and remaining barriers to producing novel formulations of fungicides for safe and sustainable agriculture. J Control Release 326:468–481

Umetsu N, Shirai Y (2020) Development of novel pesticides in the 21st century. J Pestic Sci 45:54–74

Verma C, Jandaik S, Gupta BK, Kashyap N, Suryaprakash VS, Kashyap S, Kerketta A (2020) Microbial metabolites in plant disease management: review on biological approach. Int J Chem Stud 8:2570–2581

Wicks T (1974) Tolerance of the apple scab fungus to benzimidazole fungicides. Plant Dis Report 58:886–889

Zayan ZA (2019) Impact of climate change on plant diseases and IPM strategies. In: Snježana T-P (ed) Plant diseases - current threats and management trends. IntechOpen, London. https://doi.org/10.5772/intechopen.87055