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New generation fungicides in plant disease management

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Abstract
Worldwide plant pathogens cause yield losses of about 20% in the principal food and cash crops. Of the 100,000 described species of fungi in the world, approximately 20,000 produce one or more diseases in various plants. So the efficient management of plant diseases is essential in the modern agriculture. Fungicides which are the most reliable means of plant disease control at present. Fungicides are biocidal chemical compounds or biological organisms used to kill parasitic fungi or their spores. The introduction of new generation fungicides is an essential element to sustain control of major pathogen in agriculture. New generation fungicides can be discovered either within established mode of action (MoA) groups, ideally with low resistant risk (robust MoAs), or in areas with a novel MoA. Compounds having a novel MoA are of special interest, as they play a key role in resistance management strategies. Over the past few years, however, several truly novel compounds have been launched commercially and have reached an advanced stage of development, which include phenylpyrroles, anilinopyrimidines, strobilurin analogues etc with effects on respiration, cell membrane components, protein synthesis, signal transduction and cell mitosis. Many plant diseases which were not managed satisfactorily by the earlier traditional fungicides, can now be well controlled by the new generation which are mostly systemic in nature.

Keywords: fungicides and plant disease management

Introduction
Worldwide plant pathogens caused an estimated 20% loss. The value of plant diseases loss was calculated to be about 2,000 billion dollars per year (Pimentel, 2009). Fungicide is a compound which is toxic to fungi. They were developed after the great famines. Recently it has become increasingly difficult for growers to control crop diseases. With more intensive cropping, new diseases have arisen which are devastating if not controlled. In addition, new races and more aggressive pathotypes of pathogens have arisen. Genetic resistance of crops towards diseases has been in many cases short-lived, and GMOs have only limited success for disease control and acceptability. All these changes require the rapid development of chemical control measures - new generation fungicides. A chemical agent that prevents growth and multiplication of fungi without killing them called fungistatic. When they prevent penetration and infection, by forming a chemical barrier between host and the pathogen, the chemical are called protectant. When the chemical enter the plant and kill the pathogen inside the plant body, they are called therapeutant. When the chemical eradicate the dormant or active pathogen from the host known as Eradicant. Today, a wide range of fungicides is available, and new products are being introduced to the market at regular intervals

Classification of Fungicides
1. Mobility within plants- distribution: Contact and Systemic fungicides

2. By chemical nature: Copper fungicides, Inorganic sulfur, Acylalanines, Carbamates Dithiocarbomates, Chloronitriles, Benzimidazoles, Carboximides, Imidazoles, Pyridines, Strobilurins, Triazoles etc.

3. By mode of action: Mitocondrial electron transport inhibitors, Nucleic acid synthesis inhibitors, Mitosis and cell division inhibitors, protein synthesis inhibitors, Lipid and membrane synthesis inhibitors, Sterol biosynthesis inhibitors (SBIs), Glucan synthesis, Melanin synthesis in cell wall.

4. By general use- Seed protectants, Soil fungicides, Foliage and blossom protectants, fruit protectants, Eradicants, Tree wound dressing fungicides etc.

All fungicides are referred by a Chemical name, a Common name, and a Trade name:

- **Chemical name** is the scientific name of the active ingredient of the fungicide.
- **Common name** is a shortened version that everyone can recognize and pronounce.
- **Trade name** is used by companies to market the active ingredient.
- A single active ingredient can be marketed under more than one trade name by different companies or for different crops.

List of some important systemic fungicides registered in India (Thind, 2012)

Fungicide group	Name of fungicide	Mode of Action
1. Oxathins	Carboxin, Oxycarboxin	Mitochondrial electron transport inhibitors
2. Benzimidazole	Benomyl, Carbendazim	Mitosis & cell division inhibitors
3. Thiopanates	Thiophanate, Thiophanate- Methyl	Mitosis & cell division inhibitors
4. Dicarboxymides	Iprodione	Lipid & membrane synthesis inhibitors
5. Phenylamides	Metalaxyl, Metalxyl-m	Nucleic acid synthesis inhibitor
6. Triazoles	Propiconazole, Penconazole, Hexaconazole, Tebuconazole, Triadimefon	Sterol biosynthesis inhibitor
7. Morpholines	Tridemorph	Sterol biosynthesis inhibitor
8. Strobilurins (QoIs)	Azoxystrobin, Trifloxystrobin	Mitochondrial electron transport inhibitors

List of some important non-systemic (contact) fungicides registered in India (Thind, 2011)

Fungicide group	Name of fungicide
1. Copper	Bordeaux mixture, Bordeaux paste, Burgandy mixture
2. Inorganic Sulphur	Sulfex, lime sulphur
3. Dithiocarbamate	Thiram, Mancozeb, Maneb
4. Heterocyclic nitrogen compound	Captan

History of Fungicides

Year	Contributor (s)	Description
1637	Remnant	Mentioned the value of seed treatment with sodium chloride for the control of stinking smuts
1705	Homberg	Recommended mercuric chloride as a wood preservative
1761	Schulthess	First suggested the use of copper sulphate on wheat seed against stinking smut
1807	Prevost	Showed effectivity of copper sulphate in the control of stinking smut
1821	Robertson	Stated that sulphur is effective against peach mildew
1833	Kendrick	Proposed lime-sulphur preparation against grape mildew
1851	Grisson	Recommended boiled lime sulphur to control powdery mildew disease
1882	Millardet	Made his first report on the control of downy mildew of grapes with Bordeaux mixture.
1885	Ozanne	Was the first to try copper sulphate in India against sorghum smut before sowing and obtained fairly satisfactory results.
1887	Mason	Introduced Burgundy mixture in which quick lime of Bordeaux was substituted by sodium carbonate.
1897	Bolley	Was the first to use formaldehyde for wheat smut control.
1900	Selby	Recommended formaldehyde as a soil treatment for the control of onion smut.
1904	Lawrence	Used Bordeaux mixture for the first time in India against leaf spot of groundnut *(Cercospora* spp.).
1913	Reihm	Introduced organic mercuries for seed treatment of wheat for smut control.
1921	Bewley	Developed chestnut compound to control damping-off disease as a soil drench in nursery buds.
1934	Tisdale and williams	Reported the fungitoxic activity of dithiocar-bamates
1940	Cunningham and Sharvelle	Introduced Chloranil as a practical organic seed protectant
1942	Goldsworthy	Published the first field results on the fungicidal value of ferbam.
1942	Singh	Developed Chaubattia paste in Almora district (UP) as a wound dressing fungicide
1943	Dimond and his co-workers	Introduced the ethylene bisdithioar-bamates as fungicides.
1952	Kittleson	Developed first heterocyclic nitrogen compound Captan, commonly known as `Kittleson's Killer'
1966	Von Schmeling and Marshal Kulka	Discovered systemic fungicides Oxanthin
1968	Delp and Klopping	Reported systemic fungicidal properties of benomyl
1973	Ciba-Giegy company	Developed Metalaxyl fungicide which is effective against oomycetes (Peronosporales)
1974		Start the era of control of phycomycetes fungi with systemic fungicides (Prothiocarb and Propamocarb)
1978		Fosetyl-Al, a metal based systemic fungicide effective against phycomycetes with pronounced basipetal translocation was developed
1979		Introduced Bitertanol, a systemic fungicide against rust and powdery mildews
1981		Fungicide Resistance Action Committee (FRAC) constituted.
1996		First Strobilurins fungicide launched, which was isolated from wood-rotting mushroom fungi (*Strobilurus tenacellus*)

Development of Fungicides: During 18th & 19th century grower tried various chemicals like sulphur, lime sulphur, sodium chloride, copper sulphate, copper carbonate, ammonium sulphate, ammonium carbonate etc.The real

interest in the development and use of fungicides starting with the discovery of Bordeaux mixture by Millardet in 1885 for the control of grape downy mildew in France.

First generation fungicides: 1885-1965, Era of Contact Fungicides

Second generation fungicides: 1966-1976, Systemic and site specific fungicides

Third generation fungicides: 1977-1990, Systemic, site specific fungicides and broad spectrum.Development of Metalaxyl in 1977, Phenylamide, Trizoles and Phenylcarbamates.

New generation fungicides: Revolutions in Chemistry and Biochemistry leads to the development of novel and site specific chemicals. New generation fungicides have novel modes of action which had a significant impact on plant disease control. These are ecologically safer and are required in lower dose. These are Broad-Spectrum Fungicides and of site specific action & low phytotoxicity and safe for human. The specific fungicides with systemic properties were regarded as a true progress in crop protection. Their use has to be regulated as per FRAC guidelines to sustain their efficacy levels (Kramer *et al.*, 2012).

New generation fungicides- FRAC classification (Leadbeater, 2012)

Mode of action	Group	Examples	Disease/Pathogen controlled
1. Complex III inhibitors	Strobilurins and Other complex III inhibitors	Azoxystrobin, Pyraclostrobin, Famaxadone	DM, PM, Rust, Scab, blight, Blast
2. Succinate dehydrogenase (complex II) inhibitors	Anilides and Pyridinyl- Ethyl Benzamide	Boscalids, Penthiopyrad	*Rhizoctonia* spp
3. NADH inhibitors (complex I)	Aminoalkylpyrimidines	Diflumetorim	Rose PM, Chrysanthemum white rust
4. Uncouplers of Oxi. Phosphorylation	Dinitro phenol, Arylhydrazins, Diarylamines	Meptyldinocap, Drazoxolin, Fluazinam	PM, *Pyricularia oryzae*,
5. Signal transduction inhibitors	Phenylpyrroles and Dicarboximides.	Fluodioxinil	*Botrytis cinerea*
6. Cell division inhibitors	Benzamides	Zoxamide and Pencycuron	Late blight, DM, *Rhizoctonia* spp
7. SBI	SBI class I, II, III	Triazoles	PM and rust
8. Nucleic acid inhibitors	Phenylamide	Metalaxyl - M	Oomycetes

1. Fungicides acting on oxidative phosphorylation - Mitochondria is the power house of the cell. Essential organelle for all eukaryotes for complete oxidation. The inhibitors can be divided into three classes:

1. Inhibitors of electron transport
2. Inhibitors of phosphorylation
3. Uncouplers

Complex III inhibitors

It contains three highly conserved subunits: cytochrome b, the Rieske iron sulfur protein (ISP) and cytochrome c1. The complex catalyzes electron transfer from reduced UQ to cyt. C, coupled to the translocation of proton by a mechanism known as Q cycle. Strobilurin, Famoxadon and Myxothiazol bind close to heme b1 and influence its absorption spectrum (Chao *et al.*, 2011).

Example- Strobilurins (β- methoxyacrylates)

Strobilurins have became one of the most important classes of crop protection agents with a distributor sales value of US $ 3.8 billion, accounting 22.9 % of the total fungicides in 2016. Currently represent one fourth of the world fungicide market. At present, nine different strobilurins have been introduced into the world fungicide market. Effective against a diverse range of plant pathogens like Oomycetes, Ascomycetes, Basidiomycetes and Fungi imperfecti. Some resistance reports in PM and *Septoria tritici*, but have outstanding efficacy against a new fungal disease like soybean rust. They have unexpected beneficial influences on yield, stress tolerance and generally improve plant health. The strobilurins bind to one specific site in the mitochondria, the quinol oxidation (Qo) site (or ubiquinol site) of cytochrome b and thereby stop electron transfer between cytochrome b and cytochrome c,which halts reduced nicotinamide adenine dinucleotide (NADH) oxidation and adenosine triphosphate (ATP) synthesis (Dave *et al.*, 2002). This leads to the stopping of the energy production and the fungus will eventually die. Systemicity in plants is done by xylem transportation. Systemic acropetal transportation in the apoplastic xylem stream is possible, if foliar penetration of the active substance occurs. No phloem mobility is to be expected. It has beneficial influences on plant physiology, crop yield and Plant Defence: Effect and delay senescence that enable the plants to maintain their green leaf area until late in the season, thereby maximizing the grain filling period and yield. Altered CO_2 compensation point, reduced stomatal aperture and water consumption, better tolerance of oxidative stress, generation of nitric oxide. Pyraclostrobin seemed to be the most potent strobilurin in this respect.

Succinate Dehydrogenase (Complex II) Inhibitors

Anilides: Carboxin and Oxycarboxin are the early fungicides of this group (1976). The next generation of anilides consisted of the benzoic acid derivatives Mepronil and Flutolanil. The later generation of SDHIs inhibiting anilides consists of Boscalid (2003; BASF) and Penthiopyrad (2008; Mitsui). They are the most modern, broadly effective fungicide group available to farmers in their disease control programmes (Stammler *et al.*, 2015).

NADH inhibitors (Complex I)

Complex I inhibition is an important mode of action of pharmaceuticals and agrochemicals. Pyrimidinamines, which are considered to be the most interesting class of fungicides with a Complex I mode of action. Only one compound Diflumetorim trade name Pyricut, has been introduced into the market, with major fungicidal target on rose powdery mildew and chrysanthimum white rust. It is mainly used for the ornamentals disease control and has major fungicidal effect on powdery mildew of rose and white rust of chrysanthemum (Fujii *et al.*, 1998). Due to an unfavorable cost/activity relationship and also issues of high toxicity, they are not popular.

2. Uncouplers of Oxidative Phsphorylation

Uncouplers have the effects on ATP synthase. Various chemicals cause uncoupling by increasing the permeability of the membrane to protons and other small ions (Kramer *et al.*, 2012). One of the first uncouplers is Dinitrocresol (DNOC). Due to the lack of selectivity several commercial compounds are sold as pro- pesticides of the parent molecule. E.g.: Dinocap and Binapacryl. Uncouplers are classed by the FRAC as code 29 with a low resistance risk, and they are often used to control fungi that have developed resistance to other fungicides. The possibility of a single point mutation at the binding site giving rise to resistance does not exist. Various strategies have been employed to minimize the potential toxicity. Selectivity problem in some cases the lack of selectivity can be beneficial. For example, although the primary use of dinocap is as a fungicide for the control of powdery mildews, it also has acaricidal properties. One particular manifestation of a lack of selectivity is toxicity to humans.

Example: Arylhydrazones

Drazoxolon was commercialized by ICI under the trade name Milcol, used to control PM and other diseases. Further investigations resulted in the development of the pure Z-isomer, named Ferimzone. This compound was first commercialized by Sumitono in 1991 under the trade name Blasin. It is used for the control of a wide range of pathogens of rice including *Pyricularia oryzae, Helminthosporium oryzae.* Ferimzone has been shown to be fungistatic rather than fungicidal and providing curative as well as protectant activity. Ferimzone has a low acute toxicity compared to many typical uncouplers.

3. New Sterol Biosynthesis Inhibitors (SBI) group fungicides

SBI fungicides have been the most important group of specific fungicides worldwide. Fungi have specific sterols that differ from those in plants and animals. Fungal cell membranes are characterized by a common dominant sterol component, ergosterol. The SBI fungicides do not show any activity against Oomycetes. The main biosynthesis steps, involving 11 enzymes from Squalene to ergosterol. Lack of ergosterol impedes the synthesis of new membrane and leads to its deterioration. Plant growth regulatory effects have been noted with DMI fungicides. The resistance risk of SBI fungicides is generally regarded to be low to medium (Anonymous 2010)

SBI class 1: DMI (demethylation inhibitors) fungicides

1. Tetraconazole: It was the first Azole fungicide. Have good systemic action. In cereals used against PM and rust.

2. Epoxiconazole: It is a broad spectrum triazole fungicide with a pronounced strength against cereal leaf spots and rust fungi.

3. Triticonazole

It was presented as a new specific triazole for the control of cereal seed borne and foliar diseases.

4. Simeconazole

It's a new broad spectrum compound for seed treatment in cereals and rice. Show excellent results against *Ustilago* also shown to be effective against *Rhizoctonia*

4. Ipoconazole

systemic fungicide suitable for seed treatment in rice. It is particularly effective against Bakanae disease caused by *fusarium moniliforme, Helminthosporium* leaf spot and blast on rice.

The introduction of new compounds with a higher intrinsic activity has allowed maintenance of the efficacy of DMI fungicides on an economically highly competitive level for over 30 years (Kuck 2002).

SBI Class II: Amines

Spiroxamine

It was the first of the spiroketalamines. Spiroxamine was introduced in 1996. Similar to other amine fungicides, spiroxamine is applied in mixture with other fungicide for the control of powdery mildew in cereals under the trade name Input. It is also effective against cereal rusts and PM of Grapes (Dutzmann *et al.*, 1996). In grapes, spiroxamine is the only amine representative with a registration in all major vine producing countries, due to its favorable plant selectivity.

SBI Class III: Hydroxyanilides

Fenhexamide

It was the first of the Hydroxyanilides. It is one of the rare SBI fungicides with a quite narrow spectrum of biological activity. It shows excellent activity against *Botrytis* species. It is also effective against *Monilinia* and *Sclerotinia*. It also shows high-risk in resistance development.

5. Fungicides acting on signal transduction

Phenylpyrroles and Phenoxyquinolines comes under this group. Mode of action- They regulate high osmolarity glycerol pathway. Cause conidia and hyphal cells to swell and burst, the generation of a too high internal turgor pressure.

Example: Quinoxyfen

It belongs to a new chemical class of fungicides, the phenoxyquinolines Quinoxyfen was introduced in 1996 by Dow-Elanco. It is specifically active against powdery mildews on cereals and horticultural crops.

6. Fungicides acting on mitosis and cell division

Zoxamide: An Antitubulin Fungicide for the Control of Oomycete Pathogens- Zoxamide was discovered and commercialized by Rohm and Haas Company in 2001. The primary markets for zoxamide are late blight on potatoes and downy mildews on vines and vegetables.

Mechanism of action

It inhibit microtubule functions.

Resistance risk

Since its first commercial use in 2001, there have been no reports of any reduced pathogen sensitivity to zoxamide in the field.

Use in agriculture

These are sold primarily in mixtures with mancozeb under the trade names Gavel.

Host defence

In the natural environment, the defense reactions of plants are induced by a variety of factors. During the 1980s in parallel with the commercial success of Probenozole (PBZ) in the rice blast fungicide market of Japan, intensive research was

conducted worldwide into inducers of host defense systems. During the 1990s however, the rapid development of biochemical and molecular biological assays helps the development of the host defence inducers.

General mechanism of induced resistance

All plants possess an intrinsic capacity to defend themselves against attacks by pathogens. Induced resistance is typically a systemic response with long-lasting effects. Two major types of induced resistance have been identified: SAR, which depends on SA; and induced systemic resistance which requires JA and ethylene, but not SA. SAR is most efficient against biotrophic and hemibiotrophic pathogens and leads to the expression of pathogenesis related (PR) gene; in contrast, necrotrophic pathogens are generally controlled by ISR.

Market products

1. Probenazole (PBZ)

In 2010, a new granular formulation of PBZ in combination with insecticides was launched. On treating rice with PBZ, the induction of *PR* genes (*PBZ* 1 and *Os PR1*a) has been reported. Induction of SA signaling pathway.

2. Acibenzolar S methyl

Launched in 1996 for the treatment of cereals in Germany. ASM is the most widely investigated molecule as a positive marker of SAR in various species of plants. ASM directly activates the PR-1 gene and improves callose deposition

Metalaxyl M

New Generation Metalaxyl- Nucleic acid synthesis inhibitors. In 1996, Syngenta introduced metalaxyl-M (also known as Mefenoxam). Like metalaxyl, metalaxyl-M controls all pathogens of the Oomycetes**.** In all applications the outstanding level of control by Metalaxyl-M is achieved at up to half the rate of its predecessor metalaxyl. Major brand names are Ridomil Gold and Apron XL. A study conducted by Singh *et al.,* (2006); on the control of foot rot and root rot in citrus, shows that the slight herbicidal effect of metalaxyl was not present in Metalaxyl-M. The use of Metalaxyl-M is safe to the environment.

Indian scenario

Out of 52 fungicides presently registered in India, the fungicides (mancozeb, sulphur, COC, carbandazim and thiram) constitute 86.8% of the total fungicide used (Thind, 2007). Several of the modern fungicides of the groups like triazoles, Phenylamides are being used in India for controlling diseases on a number of crops. Two noval fungicides namely azoxystrobin and pencycuron have been registered for use against powdery and downy mildews in grape vine and rice sheath blight, respectively. Efficacy of three strobilurin fungicides i.e. azoxystrobin (Amistar), trifloxystrobin (Flint) and Kresoxim methyl (Stroby) have been studied. Monceren (Pencycuron; Bayer) has shown promising activity against *Rhizocotonia solani* and serve as a safe alternative to mercurial fungicides used in tuber dip treatment. Fluazinam found effective against late blight and against Oomycete pathogens, famoxadone and its combination with cymoxanil; fenamidone and its combination products with mancozeb etc. shows good results.

Conclusion

Fungicides are going to stay as important means of plant disease control in the foreseeable future. There has been a significant change in the development of fungicide from simple inorganic compounds in the early 20th century to the more potent present day organic compounds. Many of the important plant disease can be well managed by the new compounds which are mostly systemic in nature and they are effective at much lower doses. In view of the resistance risk associated with most of the systemic, site specific compounds, there is need to develop more classes of fungicides with novel target sites.

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