Chapter 4
Synthetic Chemicals: Major Component of Plant Disease Management

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Abstract Direct protection using synthetic chemicals is one of the basic principles of plant disease management. Historical perspectives of using chemicals for plant diseases control Include application of effective methods for controlling plant diseases. Fungicides, Bactericides and Nematicides are applied through different methods such foliar, slurry, drench, paste etc.). Fungicides or Fungistatics, can be classified based on mode of action, usage and composition. Limitations of pesticide usage occur in plant disease management, due to health hazards and pesticide impact on the environment. Insurgence of fungicidal resistance in plant pathogens is also a significant threat. Efficacy of chemicals compounds is also affected by climate changes. Recent trends in the development and use of synthetic chemicals (broad spectrum and new chemistry fungicides) in plant disease control Consider a comparison between pesticides and alternative plant disease control methods, fungicide marketing policies and procedures.

Keywords Foliar fungicides · Synthetic fungicides · Viricides · Fungicidal resistance

4.1 Historical Prospective of Chemicals for Plant Disease Control

A number of chemicals that we are using today are being applied by farmers since 100 years ago, against pests causing serious losses in food productions (Rhoades 1963). It is hypothesized that organized agriculture started with wheat and barley cultivation about 5000 years BC, in the Middle East (Behrens 1957). It is likely and

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possible that these crops were infected with plant pathogens already in the same era. However, the cause of plant diseases remained a mystery for several millennia. Damage to plants was (and still is) closely associated with natural phenomena. It is believed that the first management attempts focused on weather conditions around the year, and that they continued in this way for centuries. This practice resulted in naming the disorders and diseases as Blight, Blast and Mildews by the majority of people. Rapid destruction of plants was termed as Blast/Blight while a slow and more visible growth appearance of the pathogen on the plant surface were termed as "mildews". Local farmers are still using these terminology (Mildew and Blight) for any disease that they experience in their fields or orchards. In the early ages of organized agriculture, people began to focus only to those diseases and disorders that were directly related to their interest as they directly affected them. Let's have a look at the commercial development of chemicals for crop protection from these humble beginnings until the modern era.

About 500 AD people in India used fumigants, obtained by animal (dog, cow) bones and cat excretions, on cucumbers. In the seventeenth century, microorganisms (fungi, bacteria) were already detected on diseased plants. However, their role in causing plant diseases remained unknown. In 1761, the role of copper sulphate in the reduction of bunt disease was observed by Schulthess. In 1807, it was assured that wheat bunt was caused by a fungus and copper sulphate was used for its control (Prevost 1807). This attempt resulted in suppression of fungal structures but was not accepted by the majority of people. When Irish famine (1845–1849) occurred, people named bunt as a cause but later on the epidemic was identified as due to attacks of a fungus, which at that time was termed *Botrytis infestans* (actually *Phytophthora* infestans). Attempts were made to control this disease by soil application of copper sulphate, lime and salt mixtures. However, these attempts failed. Unfortunately, foliar applications of these chemicals were not adopted. Meanwhile the concept of seed treatment against smut and bunt diseases was introduced. Later on, arsenic and copper sulphate were tried. In the eighteenth century adding lime addition was considered to reduce the phytotoxicity of copper sulphate on cereal seeds. Various products were developed and tested as fungicides. In nineteenth century, several attempts were made to exactly identify what may be considered as a true fungicide. First fungicides started with the application of elemental sulphur for the management of fruit crops diseases such as powdery mildews and few other diseases of grapevines.

In mid nineteenth century lime-sulphur solutions were used against powdery mildew of vines by Kenrick. The development of synthetic fungicides progressed rapidly in 1930s. In 1942, thiram, zineb and nabam (introduced in 1943) were followed by maneb (in 1955). In 1961 mancozeb (manganese and zinc) was introduced (Agrios 2005). Major chemical classes i.e. (phthalimides, guanidines, methyl benzimidazole carbamates, SBI morpholines and 2-aminopyrimidines) were introduced from 1945 to 1970, in an era dominated by the crop protection industry. During this period ornamental, vegetable and fruit diseases were focused. Experiments were conducted by foliar applications of newly introduced fungicides (maneb, ethirimol, benomyl and tridemorph) to control powdery mildew of barley throughout Europe (Russell 2005).

4.2 Basic Principles of Plant Disease Management with Synthetic Chemicals

The excessive use of synthetic chemicals in agriculture has been initiated in the last few decades and the major groups of chemicals were developed in the last 60 years (Martínez 2012). The role of synthetic chemicals in food security and safety has become more prominent as they promised economic and social benefits for global economy. Hence, these chemicals have become an important component of the global agrochemical business.

Losses caused by plant pathogens are the main issue in management of field crops and during postharvest storage. The use of chemicals is one of the most effective methods of controlling plant diseases, either in field or during storage, transportation and marketing. This includes the application of chemicals that directly inhibit the pathogens' growth, either upon plant surfaces or within host plant tissues. These chemicals either have adverse effect on the pathogens' life cycle or are completely injurious to them. This approach has been widely adopted due to its effectiveness in controlling the plant diseases.

Synthetic fungicides played a major role in crop protection by controlling fungal diseases across the world. This has been the most appropriate and quick method to control fungal diseases, particularly post-harvest diseases. In ancient times, most farmers were unable to assess the losses caused by fungi but in the changing scenarios of growing world population the losses have become unacceptable. That's why producers are still dependent on synthetic chemicals for managing fungal diseases. However, the need for selectivity, systemic and therapeutic properties in new fungicides has been increased. Fungicides penetration into host plant is necessary, either to eradicate established infections and to be redistributed throughout the plant. Therefore, they show selectivity towards pathogen.

Another approach considers the use of chemicals that do not target a given pathogen but the disease itself.

Depending on the kind of pathogen they affect, the chemicals are called fungicides, bactericides, antibiotics, nematicides, viricides.

Fungicides: used for killing fungi.
Bactericides: used for killing of bacteria.
Antibiotics: substances that are produced by one microorganism and used to kill or inhibit other microorganisms particularly bacteria, at low concentrations (Madigan et al. 2008).
Nematicides: used for killing nematodes.
Viricides: used for an antagonistic action towards viruses.

4.2.1 Fungicides

Although chemicals are applied to control a wide range of plant pathogens or managing stress sources, their role in controlling fungal diseases has been more prominent. Fungicides are broadly classified based on their chemical nature, their mode of action and usage. Since their discovery in 1807, fungicides are successfully used for disease management in agricultural crops (Leadbeater 2015), to control foliage diseases, for disinfection of bulbs, seeds, tubers, and soil or to eliminate the established infection within the vegetative plant material. Some chemicals are used for wound treatment, protection of fruits and vegetables while others are applied to control insect vectors, that spread diseases. The majority of chemicals are only effective before infection starts. They are effective only in those parts of the plant where they have been applied, and are unable to translocate or to be absorbed by the plants. In their majority they are used as foliar sprays or as dusting. Their effectiveness largely depends upon the ability to be absorbed by and act on the pathogen. However, they must have ability to be insoluble to avoid rain depletion, for a longer protection of the treated plant tissues. Fungicides must be capable to cover and protect the whole infected area and have good adhering ability, so their effect will lasts for a longer time. Moreover, they must be toxic to the pathogen but not to the plants and consumers. As they are used as protectant and not as curative, their application must precede the pathogen arrival or at least be performed before the establishment and germination of the pathogen into the host tissues. Fungicides are also infused or injected into high economic value tree species, such as elm trees, to reduce severity. These chemicals, however, need periodic applications for effective and long term prevention.

Fungicides inhibiting demethylation and sterol biosynthesis are of much importance, but must diffuse into the plant tissues to eliminate recently established infections. Earliest fungicides were inorganic compounds, which were based on simple elements or metallic molecules. Organic products (i.e. thiram and captan), developed and introduced into the market in early-mid-1900s, had a broad spectrum and were used either as protectant or contact fungicides. Protectant fungicides are effective against a wide range of fungal pathogens and protect the plant parts to which they are applied. In the early 1960s, systemic fungicides began to be developed. They have the ability to be absorbed by the plant surfaces without causing any damage to it, and to be transported to the infection site where they eradicate or control the infection. However, most of them are not fully systemic, as they have only one way of action. At present, only one fungicide, fosetyl aluminium, is truly systemic, being characterized by an upward and downward distribution.

4.2.2 Antibiotics

The role of antibiotics in plant disease management is very prominent. About 40 antibiotics of fungal or bacterial origin were screened during the 1950s for the control of plant pathogens (Goodman 1959). Since 1950, antibiotic have been in prac-

tice to control bacterial diseases of important ornamental plants, fruits and vegetables (McManus et al. 2002). However, they have limited applications in the management of bacterial and fungal diseases, as fungi and bacteria have ability to develop resistance against these chemicals. Historically, antibiotics have been widely used for the control of apple and peach fire blight disease (McManus and Stockwell 2001).

Actually, only a few antibiotics are commonly in use, or permitted, to control plant diseases. Since its introduction as a plant protectant in 1955, streptomycin is the most commonly used antibiotic, effectively applied against bacterial canker, bacterial spot of stone fruit, bacterial speck of tomato, and fire blight of apple and pear (McManus et al. 2002). It is also effective as seed dressing on cotton, tomatoes and beans. However, due to phytotoxicity its application, particularly on beans, has made its use limited. This antibiotic has been successfully used in the treatment of stem rot of *Dieffenbachia* cuttings, and in the control of other diseases (lethal yellowing of palms and pear decline) caused by phytoplasmas. Also oxytetracycline is considered as one of the most important antibiotics, as development of resistance by plant pathogens to this chemical is rare. It is used against bacterial pathogens (*Pseudomonas* spp., *E. amylovora* and *Xanthomonas* spp.) of apple, pear and various vegetables. Additionally, it is also effective in the suppression of lethal yellowing of elm trees and palms (McCoy 1982).

Gentamycin is used, in some Latin American countries, to control bacterial diseases of fruits and vegetables caused by *Ralstonia*, *Pectobacterium*, *Erwinia*, *Xanthomonas* and *Pseudomonas* spp. (McManus et al. 2002). In Israel, oxolinic acid is commercially used to control fire blights of fruits and other related plants (Shtienberg et al. 2001). Most of the commercially available antibiotics are fungitoxic. In Japan several fungi toxic antibiotics against bacterial (bacterial leaf blight) and fungal (rice blast) diseases of rice, fruits and vegetable crops, have been developed. Some antifungal compounds (cyloheximide and blatomycin-s) have been classified as antibiotics and are used against rice blast and some fungal diseases. Cycloheximide is used as a protectant or eradicant fungicide against powdery mildew and rust diseases, on various crops. However it is more suitable for woody plants as compared to herbaceous ones, due to its phytotoxic effects. In Europe, a less toxic antibiotic, griseofulvin, has been widely used to control powdery mildews and *Botrytis* sp. on greenhouse vegetables. Antibiotics used in agriculture are usually formulated as a powder, having 17–20% active ingredient, by dissolved or suspended in water to an adjusted final concentration of 50–300 ppm.

4.2.3 Nematicides

Nematicides are highly toxic and expensive and are used mostly on high return crops. They are fumigant or non-volatile compounds. Various nematicides are available for effective control of nematode pests of annual crops, but their use is justifiable only on high-value economic crops (Gowen 1997). Since their discovery about 50–60 years ago, several formulations and products have been available worldwide. However, the nematicide industry progressed slowly perhaps due to a lack of knowl-

edge and awareness about nematode pests among farmers' communities, and the few reports available in the past on the economic losses caused by nematodes (Hague and Gowen 1987).

Development and use of nematicides can be divided into 3 periods, basically an ancient (1854–tile World War-I), a median (1919–1942) and a modern (1943 to onward) eras (Taylor 2003). In the second half of the nineteenth century, carbon disulphide was discovered as first synthetic chemical having nematicidal activity. The sugarbeet nematode *Heterodera schachtii* was reported in 1859 and attempts were made for its control by carbon bisulphide applications (Schacht 1859). This ancient period was dominated by carbon bisulphide (an insecticide acting against soil pests). Chloropicrin was also used as a nematicide after World War I. In England, chloropicrin was successfully used against soil pathogens including nematodes (Mathews 1919). In Hawaii, it minimized RKN densities in pineapple fields (Johnson and Godfrey 1932; Godfrey 1935). D-D (a mixture of dichloropropane-dichloropropene) was discovered in 1940s as effective in controlling soil populations of most plant parasitic nematodes (Sikora and Hartwig 1991). This discovery laid the foundation of the development of other nematicides. In 1943, the D-D mixture was used as a soil nematicide n pineapple crops (Carter 1943). In 1944, ethylene dibromide was evaluated as soil nematicide (Thorne and Jensen 1946).

In 1946, nematicides got a quick popularity on a commercial scale and their filed applications increased rapidly. McBeth and Bergeson (1955), reported the nematicidal activity of 1, 2-dibromo-3-chloropropane (DBCP). Furthermore, this chemical was less toxic and effective against nematodes of living trees, grape vines and citrus which can be applied before and after planting. In 1956, Vapam (sodium N-methyl dithiocarbomate dihydrate) was introduced in the market as a herbicide, fungicide and nematicide. The next nematicidal chemical in this series introduced in 1957 was V-C 13 (0–2, 4-dichlorophenyl 0, 0-diethyl phosphoro-thioate). In 1960s, a new generation nematicides such as organophosphates and carbamates was discovered, acting as contact nematicides. Many of them are systemic within plants. Oxamyl is the only systemic nematicide available as a commercial product. Other nematicidal soil fumigants developed were halogenated hydrocarbons and volatile compounds. Since 1960, nematicides got much popularity as their application was easy, and most of the formulations were granular. A high concentration of nematicides is essential for effective control of nematodes on the plant roots. However, it becomes more difficult to control nematodes through chemicals once they penetrate the host roots (Taylor 2003).

4.2.4 Viricides

Some viruses are important plant pathogens causing major economic losses in agricultural and horticultural crops. Chemotherapy against plant viruses has been developed about 50 years ago as a result of a series of incidental observations (Dawson 1984). In 1925, it was found that application of various plant extracts was useful in

the inhibition of TMV. Several other chemicals, dyes, plant extracts, analogs azaguanuine and thiouracil were subsequently found effective in virus biosynthesis inhibition (Duggar and Armstrong 1925). In 1961, Quak work laid the foundation of applied chemotherapy against plant viruses. He applied thiouracil on virus infected leaves as a foliar application, and found that these chemicals were not only effective in the reduction of the virus infection, but could also prevent their replication without inhibiting cell metabolism (Quak 1961). In the mid 1960s the first antiviral drug was identified (Galasso 1984). It was proved that plant virus chemotherapy could only be possible if the system became non-infective through the process of aging. However, the role of chemotherapy is mostly curative rather than preventive, and these chemicals can be applied to systemically infected plants. As most crop viruses are seed borne, only seed chemical treatments can be suitable for protection and management. The chemicals used vs plant viruses are toxic and may act either as fumigants or disinfectants (Hansen and Stace-Smith 1989).

4.3 Application of Chemicals

Plant diseases have been of much importance from ancient times as they badly affected the global economy of the countries and have changed the fate of many nations. In this regard Irish famine due to late blight of potato, Bengal famine due to brown leaf spot of rice, chestnut blight and southern leaf blight of corn are the most prominent, as they resulted in severe economic and social losses. They have been responsible of losses not only in field crops and storage commodities, but also on landscape.

The core objective of chemicals application is to reduce losses caused by plant pathogens below a given threshold level, traditionally known as plant disease control. However, this term has been replaced by “plant disease management” and “integrated plant disease management”. Correct and true identification of the disease and pathogen is necessary for the development of any management strategic plan. Application of chemicals is called chemotherapy, and is an integral part of crop disease management, worldwide. Some toxic chemicals are used as fumigants, sterilants and disinfectants for eradication of pathogenic organisms, as well as control of diseases that have an economic importance.

Over the years various chemicals have been in practice to control pathogens or diseases, formulated to target one or more organisms. These chemicals must be applied to such sites where they can come into contact with the pathogen, or from where they can be absorbed and translocate to the whole plant tissues, such as seeds, foliage or growing parts. Seeds can be treated with liquid or solid chemicals such as dusts to suppress or kill the mycoflora and nematodes, or limit the eggs hatching, either on the seed surface or in the surrounding soil. They are also used for seed dressings or pelleting. Liquid sprays are most commonly used for the foliage of growing plants. Application of chemical dusts is most common in dry areas.

The exposed plant surfaces (after mechanical operations) can be painted with suitable chemicals to restrict pathogen entry into the tissues. Dipping of propagative materials in the chemical solution is also a common practice. Internal tree infections can be treated by injecting chemicals into internal host tissue, by a hole in the stem.

4.4 Human Civilization and Fungicides

Human civilization and crop cultivation are linked together. Both have been threatened many times in the course of centuries, by severe plant disease epidemics as recorded in Biblical and early Greek and Roman times. Most recently, plant disease epidemic outbreaks such as the Irish (1846–1850) and Bengal famine (1943), left long-lasting and significant impacts on society and economy, with loss of about 5.5 million lives (Kislev 1982; Deising et al. 2002). With an ever increasing world population and a finite, decreasing per capita agricultural land area, the increasing pace in crop yields should continue exponentially. However, this trend has been constantly challenged by many biotic and abiotic stressors (Cleland 2013; Yildiz 2017). Plant pathogens induced crop decrease was estimated to reach 16–20% of yield. This food is lost and could be attained in case of pathogens exclusion. Losses due to fungi have the highest share, that may reach up to 80% (Savary et al. 2006; Moore et al. 2011). Plant diseases have severe detrimental impact on yields in almost any crop, and this situation could be worsen under favorable conditions if no control is applied. This is especially true in developing countries, having limited resources to manage crops. Human intervention is indispensable to get the desired yields by controlling disease and keeping their effect on yield potential at a minimum level (Shurtleff et al. 2018).

Human civilization has faced disease issues and acknowledged its importance since primitive times and had used more spiritual than practical, maybe not knowingly, methods of disease control. But starting from nineteenth to twentieth century more practical methods and chemicals were developed and used extensively. Simple plant protective agents, copper and sulfur, laid the foundation of today's billion dollar vast growing pesticide industry, based on complex chemistries with various mode of actions against different groups of fungi (Hewitt 2000; Deising et al. 2002). Fungicides may control a disease during the developmental crop stages of and increase its productivity. They may also increases its market value by saving the produce from spots and blemishes, in field and storage conditions (McGrath 2004). Fungicides as pesticidal agents may be chemical or biological, and are marketed to kill or inhibit the fungal growth or spore germination. Modern fungicides instead of killing, inhibit fungal development for a specific period of time by interfering with routine metabolic processes.

4.5 Classification of Fungicides

Fungicides can be classified into different classes/groups on the basis of their chemical structure, mode of action, type of crop, mode of application, method of absorption/mobility etc.

4.5.1 Mode of Action

To delay resistance against fungicides and to avoid detrimental impacts on plant growth, it is effective to use specific fungicide or mixture of fungicides, with diverse mode of actions. These may target fungal growth by inhibiting spore germination, colonization, reproduction, at any or all stages of disease development. Various biochemical processes or structures of target fungi are suppressed or disturbed by fungicides. Various unknown and known modes affect cell membranes, cell division, synthesis of proteins, respiration, signaling etc. (Hewitt 2000; Mueller et al. 2008; Yang et al. 2011).

(a) **Cell membrane components**

Organization and function of porous cell membrane in fungi is similar to that of higher eukaryotes, including: selectivity to ionic conductivity and organic molecules, signaling, adhesion, shape maintenance, protection of cell contents from noxious substances etc. Ergosterol (ERG), a special sterol membrane lipid and an important component of the cell membrane biogenesis, derived its name from ergot, the common name of *Claviceps* spp., with a critical role in the fluidity and permeability of the fungal cell membrane (Alberts et al. 2002; Iwaki et al. 2008). Being a special fungal membrane component, alternative to cholesterol in animals, ergosterol serves as an effective and important target for fungicides, disintegrating plasma membrane or disturbing ERG biosynthesis. Sterol inhibitors are the most effective and broadest used fungicides, that can act as protectant as well as suppressers of fungal growth by affecting various developmental stages. Even after decades from their discovery, sterol biosynthesis inhibitors account for a 1/fifth share in global market, due to their broad spectrum and mobility within plant. Among them, triazole acts by dismantling the integrity of the cell membrane with an ergosterol-specific site of action. Due to its reserve in spore, ERG specific fungicides have no effect on germination and germ tube development of spores. Aromatic hydrocarbon (AH) fungicides, supposedly, disturb mycelial growth by interfering with the biogenesis of lipids in the cell membrane, whereas De Methylation Inhibitors (DMI) disturb different reactions in the ERG production pathway, by inhibiting the enzyme demethylase, necessary for ergosterol biosynthesis, eventually killing the fungus (Hewitt 2000. Fishel 2005; Mueller et al. 2008; Vagi et al. 2013; Yang et al. 2015).

When treated with AH fungicides such as dicloran and etridiazole, lysis of fungal cell membrane occurs by destruction of the membrane linoleic acid and by phos-

pholipids hydrolysis, respectively (Radzuhn and Lyr 1984). Apart from impact on plasma membrane, certain fungicides, such as acriflavine, affect intracellular membranes such as the mitochondrial membrane, by reducing its permeability. This causes an imbalance of the proton gradient across the membrane, which results in the reduction of ATP synthesis and ultimately in the fungal cell death (Kawai and Yamagishi 2009).

(b) **Signal transduction**

In fungi, cellular signaling is mainly mediated by the Mitogen Activated Protein (MAP) kinase pathway, necessary for responding to environmental stimuli and intracellular signal transmission. Fungicides affecting osmotic signaling retard growth and differentiation in fungi by interfering with spore germination and mycelial growth (Yoshimi et al. 2005). Fungicides affecting cell membrane and its components also disturb signal transduction pathways, which take place on the cytoplasm and plasma membrane interface (Yang et al. 2011). Two group of fungicides, phenylpyrroles (PP) and dicarboximides, although characterized by a different structure, target the same osmotic signal transduction pathway in fungi. Due to their effectiveness, they have been used worldwide against a range of phytopathogenic fungi (Tanaka and Izumitsu 2010). PP fungicide fludioxonil interferes with the osmoregulatory signaling in *Botrytis* spp. by inhibiting spore germination and germ tube extension (Kim et al. 2007; Rosslenbroich and Stuebler 2000). Iprodione, a dicarboximide group fungicide, causes malfunctions during the sterol biosynthesis, lowers growth rate, mycelium elongation and disturbs hexoses and chitin productions (Ochiai et al. 2002). Both groups primarily target the histidine kinase pathway, in which improper signaling finally causes abnormal phosphorylation of MAP kinase. This is involved in the expression of genes responsible for hyperosmotic environmental adaptations (Hagiwara et al. 2007; Vargas-Pérez et al. 2007).

(c) **Respiration**

Fungal respiration is inhibited by various groups of fungicides having different modes of actions. In fungi, the mitochondrial respiratory complex I transports electrons to ubiquinone from the reduced form of NADH (Joseph-Horne et al. 2001). Complex I inhibitors disturb respiration by retarding NADH oxidation-reduction activity. Diflumetorim, an effective C1 fungicide, control powdery mildew and rust disease pathogens in ornamental plants by targeting an oxido-reductase (Fujii and Takamura 1998; Tomlin 2006). Oxidation of succinate and its further coupling with ubiquinone is carried out by respiratory complex II system, which is translated by a complex of four SDH genes (Bullis and Lemire 1994; Daignan-Fornier et al. 1994; Joseph-Horne et al. 2001). When targeted by commonly used complex II inhibitors such as boscalid, carboxin and flutolanil, SDH function in electron transport and tricarboxylic (TC) cycle are disabled, which causes reduced respiration and fungal growth (Motoba et al. 1988; Matsson and Hederstedt 2001; Spiegel and Stammler 2006). SDH inhibitors effectiveness against diseases is testified by tremendous yield increase reported (Smith et al. 2008; Bittencourt et al. 2007).

Compex III of mitochondrial respiration is inhibited by fungicides by inactivating cytochrome bc1 at Quonine outside and inside (Qo and Qi) sites (Gisi et al. 2002). Qo and Qi inhibitor fungicides share the same target enzyme, but have distinct binding sites as name indicates. These fungicides hinder the energy producing potential of the fungus by limiting respiration, which results in death (Hewitt 1998; Mueller et al. 2008). Newest, widely used and important strobilurin fungicides belong to QoI family (Vincelli 2002).

While most fungicides under the umbrella of respiration mode of action target enzyme complexes, some hinder respiration process through other targets of energy conversion as uncoupling and ATP synthase, by upsetting oxidative phosphorylation. Fluazinam has an unusual uncoupling activity by joining with glutathione, interrupting ATP synthesis and disturbing a number of metabolic pathways (Guo et al. 1991; Brandt et al. 1992).

(d) **Amino acid and protein synthesis**

Proteins are synthesized by long or short chains of amino acids which perform many vital roles in cell functioning. Functions of fungal proteins in fungi include cell wall strengthening and structure, sensing changes in local environment, signal transduction, biochemical reactions etc. Cell wall synthesis enzymes of fungi are specific and are used as target for fungicides (Lodish et al. 2000; Hall et al. 2013). Fungicides affect protein synthesis on various stages i.e. initiation, elongation, and termination steps of protein synthesis or by disturbing genes of methionine biosynthesis, as in anilino-pyrimidines (AP) fungicides. Streptomycin, having both fungicide and bactericide properties, affect synthesis of amino acids, translation process and also disturbs the 70S ribosome in *E. coli*, by adding isoleucine in polypeptide chains. Oxytetracycline disturbs amino-acyl complexes of tRNAs on the ribosome and ultimately retards bacterial community by affecting ectoenzyme activity (Old and Gorini 1965; Halling-Sørensen et al. 2002; Carr et al. 2005).

(e) **Mitosis and cell division**

Cell division is imperative for continuation of life, necessary for growth and reproduction in multicellular and for reproduction in unicellular organisms. Different groups of fungicides cause death of fungal pathogens by interrupting cell division and mitosis, at various steps (Seiler 1975; McCarroll et al. 2002). Methyl benzimidazole carbamates inhibit processes in which tubulin monomers react together to form microtubule polymers (Gupta et al. 2004; Davidse 1986; Koo et al. 2009). Three compounds of benzimidazoles, namely carbendazim, benomyl and thiabendazole, inhibit polymerization and proliferation by targeting recombinant β_2 tubulin up to 93.5%, 92.6% and 81.6% respectively. They are known for inhibiting mitosis in *Fusarium* spp. Benzimidazole targets the microtubules forming process and is ineffective against polymerized cytoskeleton or spindle microtubules (Zhou et al. 2016). Cytoskeleton microtubules perform vital functions in the cell, whereas spindle microtubules arrange chromosomes at the metaphase plate in a linear fashion. Applications also cause chromatid loss due to instability between spindles and kinetochore connections (Rathinasamy and Panda 2006).

(f) **Nucleic acid synthesis**

Among fungicides affecting nucleic acid metabolism and synthesis, phenylamides (PA) group include several effective fungicides with RNA polymerase I as action site. Metalaxyl affects the RNA chain, inhibiting the uridine incorporation. RNA synthesis is more affected than DNA (Fisher and Hayes 1982; Sukul and Spiteller 2000). Interference in systemic activity of RNA transferase occurs during the nucleic acid synthesis, by affecting the uridine transcription process. Activity of the enzyme adenosine deaminase is inhibited by ethirimol, belonging to hdroxypyrimidine group. It inhibits the activity of nucleotides as adenine and metabolic agents as inosine (Hollomon and Chamberlain 1981). Ethrimol also disturbs the nucleotide pool balance by increasing the adenine salvage pathway enzyme phospho-ribosyl-transferase. It also inhibits the activity of adenosine deaminase, which results in ceased inosine synthesis and impaired nucleic acids production (Brown and Simpson 1994). DNA/RNA synthesis is inhibited by fungicide of the heteroaromatic group such as hymexazol. When applied it reduces the thymidine incorporation ratio as compared to uridine in RNA, reducing colony growth by targeting DNA synthesis (Kamimura et al. 1976).

(g) **Multisite activity**

Multi-target fungicides are widely used in agriculture but may have detrimental impact on other non-target organisms. Chlorothalonil, due to its multi biochemical action sites, is considered as a successful fungicide, reducing enzymatic activity and blocking the transformation of glutathione into its various structures (Chen et al. 2001). Another broadly used fungicide, mancozeb, shows a multisite activity inhibiting metabolism of targeted cells (Cycoń et al. 2010). Other examples of multisite fungicides are thiram, captan, propineb, maneb and many copper-based compounds (Milenkovski et al. 2010).

4.5.2 Classification Based on General Uses

(a) **Seed and planting material**

Discovery of carboxin, first systemic fungicide, was a milestone in the control of seed borne diseases. It is effective against surface and deeply penetrating pathogens, especially in controlling loose smut, a major disease of wheat and barley. Due to its active redistribution ability within the plant, carboxin replaced less effective products previously applied in seed treatments such as the organomercurial fungicides (Kulka and Von Schmeling 1987; Maude 1996; Klittich 2008). Systemic fungicides protect plants in its early, tender age by reducing the spread of fungal compounds toxic to young plant parts such as cotyledons, leaves and seedlings. Systemic fungicides are widely used in the seed treatment market and are more effective in controlling seed borne diseases in comparison to non-systemic fungicides. The latter are still used as successful protectants. Seed treatments with captan and diathane M-45

increased the germination and reduced the seed associated mycoflora effectively, as compared to control (Mahal 2014). Protectant fungicides i.e. iprodione and vinclozin, can also effectively eradicate seed borne pathogens such as *Sclerotinia* sp. from infected sunflower seeds, equally to systemic fungicide such as benomyl (Herd and Phillips 1988). The effectiveness of protectants, equivalent to that of systemic fungicides, is due to the location of the seed borne pathogens spores or mycelium, that may be mostly found on the seed surface, in superficial tissues and/or in the pericarp. Only few pathogens reside in the inner seed parts as endospore or in the embryo.

Pathogens which develop close to the seed surface, such as *Sclerotinia*, *Fusarium*, *Alternaria* etc., are controlled by both protectants and systemic fungicides. For protectants to be effective it is needed an ability to reach the internal seed tissues (Maude 1996). The chemotherapeutic effects on treated seeds is maximum as the seed and inoculum volumes are minimal, as compared to other plant parts. Due to these concentration factors the active ingredient remains at high levels for a long period of time, and ultimately increases the chances to eradicate the seed borne pathogens. Planting materials such as cuttings, bulbs, tubers etc., that also are infected by severe pathogens, may remain symptomless for a longer period of time. This makes it difficult to formulate a disease-free crop. Processes and factors in the control of planting material pathogens are similar to those applied for seed borne pathogens, except the increased volume as compared to seed, the higher inoculum amounts, and the higher concentration and exposure time required bu. the fungicide for pathogen control (Ivic 2010). Treatments of *Phytophthora*-infected potato tubers with the systemic fungicide thiophanate methyl plus mancozeb as a preventive measure before infection, increased plants emergence (Inglis et al. 1999). Similarly, a reduced effect of the fungal pathogen *Phaeomoniella* sp. was observed in benomyl-treated grapevine cuttings, when compared with control. Fungicide treatment is also effective for planting material. Myclobutanil-treated chrysanthemum cuttings showed no symptoms of white rust as compared to the 90% prevalence found in control (Bonde et al. 1995). Strawberry seedlings infected with *Colletotrichum* when treated with prochloraz, propiconazole and difenconazole treatment, showed lower mortalities in comparison to the 80% rate found in the control (Freeman et al. 1997).

(b) **Soil fungicides**

Soil borne pathogens show their presence through aboveground symptoms, that become visible long after the infection occurs. This causes considerable losses to root or crown parts. Symptoms of soil borne pathogens are complex and nonspecific, difficult to diagnose accurately and are challenging for control through fungicides. Few systemic fungicides show the ability of downward translocation, such as fosetyl-Al, that effectively controls the stem canker of avocado caused by *Phytophthora* spp., when soil drenched. Exact doses for soil treatments are difficult to calculate, as plants uptake small amounts of the fungicide, as compared to the foliar application.

Fungicides can be used before and after cultivation begins. Most of the time they are preventive but may also be curative. The amounts of a.i. applied with soil treatments is relatively high, because of the crop biomass that usually already develops, prior the aboveground symptoms are visible (El-Hamalawi et al. 1995; Ivic 2010). For example, Phytophthora root and crown rot of apples in plants early developmental stages were controlled by matalaxyl soil drenching. Soil drenched apple trees remained alive as compared to control trees which died due to the rot (Utkhede 1987). Carbendazim, a benzimidazole fungicide, when used as soil drench recovered 15–20 years old apples trees from *Rosellinia* root rot (Gupta 1977). Pre- and post-sowing soil drenching with carbendazim, carboxin and thiram was investigated against wilt and rot diseases of cotton. Pre-sowing drenching was most effective as compared to post-planting (Chauhan et al. 1988). Tridemorph when applied as a soil drench gave promising results against *Rosellinia* rot of rubber, cocoa and mulberry (Mappes and Hiepko 1984). *Phytophthora* root rot has been studied extensively as compared to other similar diseases. However, high efficacy of fluazinam was also observed on *Rosellinia* white root rot of grapevine, after soil drench at different concentrations, even when the soil was highly infested (Kanadani et al. 1998; Hoopen and Krauss 2006). Three fungicides, azoxystrobin, trifloxystrobin and kresoxim methyl, were tested for their root uptake ability, in pearl millet against downy mildew. Azoxystrobin showed a systemic activity to some extents, while the other two lacked root uptake, being not systemic (Sudisha et al. 2005).

Methyl bromide (MeBr) has been used extensively, until its ban, in strawberry nurseries for soil borne pathogens such as *Phytophthora*, *Pythium*, *Rhizoctonia*, *Fusarium* and *Verticillium* spp. in Mediterranean countries, such as Italy and Spain. Chloropicrin, dazomet and metam sodium are newer soil fumigants being used and found to be effective (De Cal et al. 2005). Di-nitrogen tetraoxide, as compared to methyl bromide, is not phytotoxic and is less dispersed in the atmosphere. These properties and its effectiveness in killing all fungi present in infested soil within 10–20 min in pre-planting soil fumigation make it a better alternative to MeBr (Tadmor et al. 2005). Paraformaldehyde when also used as a substitute for MeBr, reducing soil pathogens from 4000 to 40 colony forming units/g increasing seed germination (Al-Khatib et al. 2017). Treatments of infested soil and potting media with metam sodium at the high concentration of 1.0 ml/L eliminated all pathogens including *Phytophthora*, *Pythium*, *Thielaviopsis* and *Cylindrocladium* spp. effectively (Linderman and Davis 2008).

(c) **Foliar fungicides**

Fungicides are efficient in controlling diseases if applied prior to pathogen establishment in host or before symptoms appear. Systemic fungicides having curative effect can eradicate the pathogen even after its establishment in the host tissue. However, as for seed treatments, the time of application after pathogenesis is very critical, in order to control foliar diseases, especially when the mycelium grows deeper in tissues and reaches high densities (Ivic 2010). Effectiveness of strobilurin and trifloxystrobin, decreased from 89 to 60% when applied 24 and 96 h after

tomato inoculation with *Cladosporium fulvum*, respectively. The decrease of the tomato leaf mold disease was also significant at various concentration of trifloxystrobin (Veloukas et al. 2007). Effectiveness of myclobutanil as foliar treatment against white rust of chrysanthemum was evaluated at different periods of post infection. Susceptible plants resulted in few pustules as compared to the untreated control, when exposed to the inoculum and sprayed with myclobutanil after 10, 15 and 20 days. Sprays applied 5 days before inoculation reduced the infection, but did not prevent it (Bonde et al. 1995). High level of pathogen inoculum reduce the ability of the fungicide to control a disease, especially in post infection, when the pathogen development and sporulation are relatively high, due to favorable environmental conditions.

In an experiment to control blossom blight caused by *Monilinia* fructicola in sour cherry, nine different fungicides were tested. Four of them namely: tebuconazole, propiconazole, iprodione and vinclozoline were effective when sprayed at inoculum concentration of 5×10^3 conidia/ml, 48 hours after infection. When the inoculum concentration was increased to 5×10^4, the disease reduction was less, as compared to control (Wilcox 1990). An inoculum dependence was also observed in black rot of grapes, when inoculum concentration increased to 1×10^6 from 2×10^4 conidia/ml, showing a much reduced effectiveness of azoxystrobin (Hoffman and Wilcox 2003). Foliar efficacy of three strobilurins were evaluated against downy mildew of pearl millet. Although all three a.i. were highly significant, only azoxystrobin appeared the most effective, with a 91% disease reduction, as compared to control (Sudisha et al. 2005). Azoxystrobin and pyraclostrobin were evaluated against strawberry leather rot disease. Protectant and curative effects of both fungicides were tested and found to be at same level, when plants were inoculated with 10^5 zoospores/ml of *Ph. cactorum* (Rebollar-Alviter et al. 2007).

(d) **Injection**

Vascular wilts, wood rot and cankers are difficult to control, due to the same reasons given for root and crown rot diseases. In case of vascular wilt, the pathogens can be present in various plant parts through the xylem vessels. Wood rotting fungi could cause serious damages to lignin and cellulose before the trees start to show symptoms. Due to the various ways of entry of vascular wilt and wood rotting fungi, such as through soil, wounds or insect vectors etc., their penetration period is hard to determine. These disease are difficult and expensive to control as can develop throughout the year, in particular cankers which are, however, easier to detect. With development of systemic fungicides and new method of use these disease can be managed, as shown by trunk injections (Ivic 2010). Cocoa stem canker caused by *Ph. palmivora* was effectively controlled by trunk injection with potassium phosphonate, as compared to ridomil spraying application and control (Guest et al. 1994). When metalaxyl and fosetyl Al were used as trunk paints, they effectively reduced *Phytophthora* trunk rot in peach (Taylor and Washington 1984). Thiabendazole injected in trunk was effective in managing Dutch elm disease. Thiabendazole and propiconazole are also effective in controlling the disease, but

only when it is not too severe (Lanier 1987; Scheffer et al. 2008). Propiconazole injected in oak trees showed reduction in crown losses, as compared to control, Disease prevalence was reduced from 100 to 41%, and the results were more effective when plants were treated prior to symptoms appearance (Appel and Kurdyla 1992). Vines injected with cyproconazole against trunk disease esca showed a significant control of the disease, and increased production (Calzarano et al. 2004). Symptoms of esca were reduced when the trunk was injected with thiabendazole, propiconazole and difenoconazole (Dula et al. 2007). A similar control was observed when tetraconazole, penconazole and flusilazole were used (Di Marco et al. 2000). Apple trees trunk injected with prohexadione carboxylic acid against fire blight disease, caused by *Erwinia amylovora*, showed a reduced primary infection at blossom (Düker and Kubiak 2011). Ash dieback, a serious forest problem, was effectively controlled by thiabendazole and allicin trunk injections, which reduced necrosis (Dal Maso et al. 2014). Single injection of phosphites against apple scab showed significant and effective result as compared to propiconazole and penthiopyrad (VanWoerkom et al. 2014).

4.6 Recent Trends in Development of Synthetic Chemicals

Synthetic fungicide with novel site of action with low risk of resistance development have a key role in controlling well established plant pathogens. Important fungicides are those which can reduce disease spread in modern agriculture, when the same variety is grown on a large area with a high risk of epidemics development. Fungicides with systemic, curative, known mode of action and long term control are preferred. Chemicals which have a major share in the global fungicide market are at medium to high risk as concerns resistance development. Focus is those which are environment-friendly and effective at low doses. Trend shifted from multisite and site-specific chemicals to novel fungicides of various classes which are ecofriendly, due to low doses as compared to earlier products (Kumar and Gupta 2012). Fungicides with various chemistries and modes of action against a broad range of diseases have been introduced. These new generation of chemicals are safer and selective, mostly having a specific, single action site, with high potency of disease control (Leadbeater 2012). Focus is on the development of efficient chemicals with improved formulations that are environmentally safe, proceed from a natural source, with a low dosage and a reduced number of treatments (Nabi et al. 2017). As pathogens can resist to different chemicals having the same mode of action, they can be effectively controlled by compounds targeting a different action site. Focus is on finding different mode of actions. For control of ascomycetes nine mode of actions have been made available, which ensures plant disease control with a minimum risk of resistance development (Hollomon 2015a, b).

4.7 Broad Spectrum and New Chemistry Fungicides in Plant Disease Control

In spite of the broad range of fungicides available on the market, innovative chemicals having novel and robust modes of actions are needed. New chemistry fungicides discovered with available or new mode of actions are necessary especially for *Pythium* and *Fusarium* soil borne diseases, and bacterial and, possibly, viral diseases as these are a continuous challenge for crops. As discussed earlier, resistance management and control of adapted plant pathogens is effectively performed by fungicides having novel mode of actions, which are important because of their systemic and curative capability, and longevity (Leadbeater 2015). Among the 57 mode of action groups known thus far, the major market share, almost 70%, belongs to few groups. Among them, some fungicides with a high to medium induced resistance risk have more share, as compared to low resistance risk fungicides (McDougall 2014). This shows that there is great need for a continued availability of diverse and effective mode of actions in the market for resistance management and effective plant disease control.

Contact or systemic fungicides are simultaneously effective against a range of pathogens belonging to different classes of ascomycetes, basidiomycetes, oomycetes etc. When they also act on different hosts they are called "broad spectrum fungicides". These can manage disease when the causal organism is uncertain or when it derives from a complex of pathogens, involved in its development. Mancozeb, a dithio-carbamate introduced in 1962, is an important broad spectrum fungicide registered and used in more than 120 countries worldwide. Introduced in late 1970s and still playing major role in fungicide market, in 2004 it was the primary active ingredient with a maximum sale. Even in 2007 mancozeb was second with 500 million US dollar sale after tebuconazole, another important fungicide. Mancozeb development, commercialization and use on different crops and diseases resulted in various formulations. If co-formulations are included, used to further broaden its spectrum, then this sale figure in 2007 reached 740 million US dollars (AgroSciences 2008). Mancozeb is under review in the EU due to reproductive and developmental toxicity (Runkle et al. 2017).

In agriculture, azoxystrobin, a model broad spectrum member of the strobilurin group, played a significant role with registration on more than 80 crops, in various countries. Key for such appreciation and popularity is its effective action against four major fungal classes of ascomycetes, basidiomycetes, deuteromycetes and oomycetes. Almost all strobilurin members, i.e. trifloxystrobin, kresoxim methyl and metominostrobin, have a broad spectrum activity with varying levels of control. Trifloxystrobin and kresoxim methyl provide a moderate and a poor to moderate control against oomycete and basidiomycete diseases, respectively. However, metominostrobin is exclusive against oomycete diseases on rice and turf hosts (Bartett et al. 2001, 2002). Benzovindiflupyr, a broad spectrum chemical, is effective against apple, grapes and strawberry diseases, applied alone or in combination with other fungicides (Ishii et al. 2016). When compared to boscalid against *Botrytis*

and *Alternaria* spp., it was found to be promising in reducing conidia germination, and was also effective against *Colletotrichum* spp. (Vega and Dewdney 2015). Strobilurins outperform all other fungicides in the market share except DMI. Data indicate that fungicides belonging to new chemistries with an excellent performance in disease control are demanded and accepted by farmers all over the world, at least where it was registered. This is also due to the reduced performance of previously applied fungicides and resistance development (Morton and Staub 2008).

4.8 Fungicide Market, Policies and Procedures

The world population growth is increasing the demand of fungicide and of disease-free crop productions and food security. These are driving force increasing the fungicides demand globally (McDougall 2018a, b). Introduction of novel compounds targeting respiration, cell and cell membrane components, signal transduction etc. have effectively managed plant diseases threatening many crop productions. Despite the effectiveness of old fungicides, there is a need to develop more classes of fungicides, as site-specific and systemic novel compounds, in order to tackle resistance risks (Nabi et al. 2017). Introduction of new chemistries in the market is necessary for a better and continuous management of diseases. This is a lengthy process involving various time-requiring steps, including research, formulation, trials, registration etc. all requiring huge economic efforts.

In 2010, the time required from new product development to first sale was almost 10 years, involving around 260 million USD. This effort, powered by extensive studies, is required for: (i) research and science to find an active ingredient, (ii) formulation, (iii) safety to humans, other organisms and environment, (iv) optimization of production so that a newly introduced chemical can maintain itself in the market for longer period of time, ensuring safety to consumers. In recent times focus has been given to chemicals which are highly effective at low doses and to development of new application methods. Finding a new active ingredient is not the only requirement to develop a new fungicide. In general, one a.i. out of ten is accepted, the others being rejected due to many obstacles on the way to marketing. Over the past few years many products have been introduced in the world market, some of them, such as DMI and stobilurin-type, are confined to local markets (McDougall 2010; Leadbeater 2015). Cost requirement of a new product increased by 55%, from 184 to 286 million USD, since the start of this century. This increase is due to shifts of priorities since 1960s. Initially the focus was on yield increases and disease control, now it is on the fungicide efficacy, prior to marketing. Recently, much focus has been given to human and environment which are at risk, due to unsafe chemicals. Extensive research and development, strict registration policies and other regulatory decisions increased time requirement from 8.3 to 11.3 years (Carson 1962; McDougall 2018a, b).

The sale of crop protection chemicals in 2014 was 56.7 billion USD, corresponding to almost 73% of total agribusiness. Share of fungicides in crop protection sales

was 25.9%, with 14.7 billion USD. In 2017, crop protection sale was 57.7 billion USD which is expected to increase with a compound annual sale growth (CAGR) of 5% to 77.3 billion USD within 5 years (McDougall 2014; Research and Market 2018). Fungicide sale showed an increasing market trend and is expected to reach 17.58 billion USD from 2017 to 2022 (List 2018). According to Statista (2016), fungicide market in 2023 will reach 21 billion USD. Almost 90% of the global agribusiness sale is achieved by 10 leading industrial companies. Agribusiness, especially the crop protection market, is facing various challenges, ranging from increasing food demand to resistant risk, which are faced by various existing popular chemicals worldwide. These can be tackled by heavy investment in research and development departments of the pesticide industry. Outcome of this heavy investment in RD will be the invention of new sustainable chemistries, with less environmental impact (Maienfisch and Stevenson 2015).

The first comprehensive law regarding pesticide distribution in USA was passed in 1947 (Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA). It required labelling and product registration with USDA, and was mostly concerned about a chemical effectiveness, rather than its harmful impact on humans or the environment (Rohrman 1968). The present act is still known as FIFRA, although there have been major changes in the law since then, especially with the FEPCA amendments in 1972. For convenience, we will refer to the pre-1972 version as the "Old FIFRA". This law in its original form was just a formality. In 1964 few revisions in the registration process were added to authorize the Secretary to cancel the registration of new or existing chemicals. In the late 1960smany environmental groups were active against over use of harmful agricultural chemicals such as DDT, Aldrin, Mirex etc. (Case et al. 2011; Schierow and Esworthy 2004). Main purpose of FIFRA is the registration of chemicals, from manufacturing to import. A pesticide has to be registered with the U.S. Environmental Protection Agency (EPA), that requires data from a many years study, which needs a significant economic investment, as discussed earlier. Registration was given for a limited period of 5 years. After that period additional data had to be provided for further sale and marketing of the product. This timing was extended in 1996 to 15 years, however products registered earlier had to face new strict standards which, according to the pesticide industry, discourage RD and new chemistries research (Miller 2014).

USA shifted regulatory pesticide powers from USDA to EPA in the 1970s, during the transition towards a socially derived regulatory model. Brazil, in 1990s adopted a new and unique model of pesticide regulation, by forming a troika of agriculture, health and environmental ministries with predominant economic interests rather than checking socio-environmental issues. A pesticide regulation framework was adopted recently in 2011 is by the EU, which has prevalent concern of socio-environment regulations (Pelaez et al. 2013). Different countries impose different pesticide regulations, including limits of residues in food, prerequisites for product registration and restrictions on usage. In USA, there is a specific limit of pesticide residues allowed in a given crop which are properly regulated. This means that the amounts of pesticide to apply may vary from country to country, for the same crop. Food or other organic commodities imported are subject to pesticide

regulations of the accepting country. For USA any pesticide or chemical, subject to import or export, must be registered with EPA, and an EPA approved label is required before export. Chemicals manufactured in the USA, but only for export purposes, may not be registered with EPA, but for sale and use within the country it has to go through state laws more stringent than federal regulations (NPIC 2018).

4.9 Fungicide Resistance and Plant Pathogens

As discussed previously, earlier inorganic fungicides such as those based on sulphur and copper, (most popular among them was the Bordeaux mixture), were used extensively until the discovery between 1940s and 1970 of organic fungicides, that were mostly multisites, with a broad spectrum (Bernard and Gordon 2000; Morton and Staub 2008). Site-specific fungicides, benzimidazoles, were discovered in late 1960s. A few years after their discovery resistant plant pathogens were observed, along with a decreased fungicidal activity. *Botrytis cinerea* was the first plant pathogen for which resistance to fungicides was described, raising increasing awareness on this major issue.

Chemistry and MOA of fungicides, along with biology and mode of fungus reproduction, are the main factors involved in the insurgence of resistance (Brent and Hollomon 1998). Short life-cycle and abundant sporulation of *B. cinerea* make it a high risk resistant pathogen. Risk increases when the conditions are favorable for grey mold and fungicide applications are frequently repeated (Brent and Hollomon 1995). *Botrytis cinerea* as model organism developed both target site-specific and efflux transport resistance. As a result, strains having multi-resistance have been observed. This erosion of efficacy is a major threat to *B. cinerea* management. The same phenomenon of resistance development can be also observed in other fungal pathogens (Hahn 2014). If a favourable mutation occurs in the encoding gene of a fungicide target protein, it will help the fungal cell to survive. Target site resistance is most important, as it is observed in all site specific fungicides. This leads mostly to cross resistance, towards fungicides having the same MOA (Cools and Fraaije 2008).

Product having MOA of the same type may interact differently from each other if particular changes occur at specific sites of action. The outcome may be a range of resistance levels with a further evolution. Different mutations at the target sites, alone or in combinations, will result in different patterns of resistance towards the same group of fungicides (Parker et al. 2011). Overexpression of target gene, as in the citrus and apple scab pathogen, and of fungicide efflux transporters are other major resistance types found in fungi (Ma and Michailides 2005). Each fungicide class has a specific resistance risk behavior. Phthalimides, copper-based fungicides, dithiocarbamates, mancozeb, thiram etc. have rarely faced the risk of resistance insurgence. On the contrary strobilurin, benzimidazoles such as benomyl, metalaxyl, pyraclostrobin etc., face high resistance risks after 2–10 years of market introduction. Cross-resistance correlates with all QoI fungicides, targeting Qo center,

which supports the idea that resistance occurs when changes occur at the target site or the metabolic pathway related to it. A site which has resistance against a specific MOA will then show resistance against all fungicides having that same mode of action, either in use fungicide or new The risk of resistance development is in effect higher for site-specific fungicides, as compared to multi-site fungicides (Brent and Hollomon 2007a, b).

Contrary to the site-specific type, fungi can develop efflux transport resistance against different groups of fungicides having different MOA. Efflux transporters have a key role in fungicide cross resistance of (Reimann and Deising 2005). The behavior of efflux mechanism resistance towards several fungicide groups is also known as MDR (multi-drug resistance) and has been mostly observed in laboratory assays (Kretschmer 2012). Pathogen exposure to the fungicide significantly enhances the resistance risk, at a dose of chemical applied which should be sufficient to kill or inhibit the pathogen wild type. When the pathogen is exposed to higher doses, especially when these are applied for eradication, it starts a survival competition favoring the fittest within the population and increasing the overall resistance risk. To manage this threat to fungicide efficacy, low dose rates with a steady use for long period of time appear effective (Ishii and Holloman 2015).

Despite the significant understanding of various resistance development processes, and of their implication of management strategies, problem may always occur. Previously established anti-resistance strategies, with the exploration of new mode of actions within the legislation umbrella, may allow a success if new and old strategies are combined successfully as in IDM systems. Activation of host resistance through systemic acquired resistance (SAR) is a new trend in IDM, as was observed for probenazole in the rice blast case. IDM systems always imply a judicious use of all available options, including synthetic chemicals, bio-fungicides, SAR, conventional breeding and GM technology (Hollomon 2015a, b).

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