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Metalaxyl resistance in *Phytophthora infestans*: An overview

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Abstract

Late blight is one of the major destructive diseases of two most important crops –potato and tomato. The disease is known to cause immense loss worldwide. The causal agent *Phytophthora infestans*, due to various reasons, developed resistance against Metalaxyl fungicide which was very effective against the pathogen, in its initial years of introduction. A number of possibilities have been estimated for the occurrence and development of resistance in the fungal pathogen isolates: existence of resistant isolates before the introduction of the fungicide, development of resistant mutants, presence of both the mating types A1 and A2 of pathogen in a locality leading to the possibilities of recombinants, migration of resistant isolates, excessive use of site specific fungicide etc. Since development of resistance in pathogen population against fungicide is an issue of serious concern and can pose a great threat to the potato and tomato production thus various anti resistance strategies need to be practiced.

Keywords: Late blight, *Phytophthora infestans*, metalaxyl resistance

Introduction

Late blight is one of the most serious diseases of potato and tomato and has been known to cause severe losses to the crop, worldwide. It is caused by a fungal pathogen *Phytophthora infestans*. In case of susceptible varieties, it is estimated to cause an approx yield loss ranging from 30–75% (Olanya *et al.* 2001) [70]. This disease has been highly studied and is the most devastating among all potato diseases (Jones, 1998) [45]. Plant diseases are now taking a severe form as there are many reports regarding the occurrence of fungicide resistance in various pathogens. The increased use of fungicides with increase in the incidence and severity of diseases in various parts of the world is one of the main reasons. This review deals with importance of the disease, major reasons for development of fungicide resistance in *Phytophthora infestans* and the alternate measures to minimise it.

Late blight is the major economic threat in many of the potato as well as tomato growing areas all over the world (Madden, 1983) [58]. The worldwide spread of the disease is probably through its association with seed of potato which is traded amongst the nations (Fry *et al.* 1993) [31]. The disease is considered as the main culprit of Irish famine (Nowicki *et al.*, 2011) [68] as it infected potato crop throughout Europe during 1840s. The disease led to a period of mass starvation, disease, and emigration from 1845 to 1849 in Ireland and is also called as the period of Great famine or Great hunger (Kinealy, 1994) [52]. The famine resulted in the death of millions of Irish people and many migrated (Bourke, 1993) [8]. The famine adversely affected the island's demography, culture and political situations, permanently spurring a century-long population decline (Kelly and Fotheringham, 2011) [50]. Since the disease has been responsible for such devastating famines in the past, humans might not be able to bear the cost of re-emergence of the disease due to development of fungicide resistance in pathogenic isolates in future, thus serious steps are needed to be taken in this regard.

Late blight disease symptoms appear in field initially as light to dark green coloured, small and circular or irregularly-shaped, water-soaked lesions (Kirk *et al.* 2013) [53]. The symptoms mainly occur on the lower leaves at first, where the humid microclimate is present (Martin *et al.* 1994) [60]. However, latter the symptoms appear on upper leaves under favourable weather conditions are favourable (Martin *et al.* 1994; Kirk *et al.* 2013) [60, 53]. In case of tuber infection white mycelial growth can be seen on surface of tubers (Fry and Grünwald, 2010) [32] degrading the quality of tubers.

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Phytophthora infestans, the name of fungal pathogen, is derived from Greek word 'Phyto' means 'plant' and 'pthora' means 'destroyer'. The pathogen in the earlier 1840s was named *Botrytis infestans* by M.J. Berkeley but was renamed as *Phytophthora infestans* by Anton de Bary in 1876 (Berkeley, 1846; de Bary, 1876) [3, 18]. The pathogen is considered as a major threat to food security, as the losses caused by late blight have been estimated to exceed \$5 billion annually, worldwide (Latijnhouwers *et al.* 2004) [56].

It is a member of the oomycetes, sometimes referred as "water molds". Oomycetes show close relation with brown algae and are not true fungi. The mycelium of the fungus is hyaline and coenocytic. *Phytophthora* shows a diploid life cycle and its first was given by Eva Sansome, a plant geneticist (Ristaino, 2007) [77]. It is classified under the Kingdom Stramenopila of the eukaryotes and family Peronosporaceae. Although Oomycetes shows similarity with many biological, ecological, and epidemiological characteristics with other fungal plant pathogens, they are not considered as the members of the Kingdom Fungi. *Phytophthora infestans* is considered to be the native of central Mexico (Goss *et al.*, 2014) [39].

The pathogen is known to reproduce both sexually and asexually. It produces sporangia during asexual reproduction. The sporangia germinate either directly by forming germ tube or indirectly by release of zoospore (Nowiki *et al.*, 2012). During sexual reproduction, the fusion between hyphae of A1 and A2 mating type leads to the production of antheridia and oogonia which combine to make an oospore. Oospores can tolerate unfavourable environmental conditions and can overwinter in soil thus are also called resting spores (Drenth *et al.*, 1995) [22]. Sporangia germinate by releasing zoospores if the temperature ranges from 12 to 15 °C, whereas above 15 °C temperature sporangia can germinate directly to produce a germ tube (Agrios, 2005) [1]. The zoospores produced, swim freely in water films and infect the plant. Zoospores encyst to infect leaves and penetrate the leaf surface with a germ tube, either through direct penetration or through stomata (Kirk, 2009) [53]. After penetration the mycelium grows profusely between the cells and forms haustoria into the cells. The pathogen survives in the living host tissue, like volunteer potatoes, seed tubers and left over potatoes that in the field (Shinners *et al.* 2003) [83], in the soil or on other solanaceous plants (Kirk *et al.* 2013) [54]. The growth and sporulation of the fungus is most abundant at 100% relative humidity and at temperature range of 15 to 25 °C (Agrios, 2005) [1]. Thus cool environmental conditions favours disease.

After various outbreaks of the disease in past years, several efforts were made in the direction of minimising the losses caused by the disease and subsequently in 1977, metalaxyl was developed against oomycetes and it proved very effective in controlling late blight of potato. But within 2 years of its introduction, in 1979 there were reports of development of resistance against metalaxyl (Carter *et al.*, 1982) [9]. Pathogenic strains with higher aggressivity were resistant to famous synthetic fungicides and thus created a challenge for people engaged in potato and tomato production (Powelson and Ingils 1998) [72].

Fungicide resistance is a serious emerging issue and can be defined as when a pathogen population changes from being sensitive to a fungicide, to one that is insensitive or less sensitive to a fungicide. Resistance may not always be complete. When resistance is not complete in a fungi it may be said to have reduced sensitivity to a fungicide. In many countries, *Phytophthora infestans* isolates showing resistance to Phenylamides, have steadily become an important part of

pathogen populations. However, Phenylamide component in various fungicide mixtures is still very effective for the control of late blight in potato.

Metalaxyl

Its chemical name is methyl N-(methoxyacetyl)-N-(2,6-xylyl)-DL-alaninate. It is an acylalanine systemic fungicide and is probably the most versatile of this group in terms of biological activity, systemic properties, and formulations (Davidse, 1987; Davidse *et al.*, 1991; Schwinn and Margot, 1991; Schwinn and Staub, 1987; Thomson, 1993) [13, 78, 90]. It was discovered by Ciba-Geigy, Basle, Switzerland under the code name CGA-48988 in the year 1973. Acylalanine belong to phenylamide group of fungicides. The phenylamide class of fungicides is highly active in controlling plant pathogens of the Oomycetes (the downy mildews caused by Peronosporales and Sclerosporales), and against most Pythiales (e.g. *Phytophthora* and *Pythium* spp.) (Gisi, 2002) [36]. They enter the plant tissue and are translocated acropetally within the plant. Metalaxyl, Furalaxyl and Benalaxyl are three important acylalanine fungicides. All three consist of 1,6-dimethylphenyl moiety and an alanine-methyl ester alkyl group. The high fungicidal activity is due to the alkyl group. For biological activity against oomycetes, the N-C(C)-C conformation with one asymmetric carbon atom is important. The imperial formula for Metalaxyl is C₁₅H₂₁NO₄ and the molecular weight is 279.33 g/mol. It is white to beige coloured crystalline substance which is slightly volatile in nature. It is readily soluble in most organic solvents. It has log P value 1.64 which indicates its medium lipophilicity (Nene and Thapaliyal, 1993) [67]. It has fungistatic mode of action and is highly specific to peronosporales. It is more effective in inhibiting fungus growth and sporulation rather than inhibiting germination of different fungal propagules (Bruck *et al.*, 1980; Davidse, 1987; Schwinn and Margot, 1991; Schwinn and Urech, 1986) [7, 13, 78, 80]. The primary mode of action of metalaxyl involves impaired biosynthesis of RNA so that mitosis is inhibited (Fisher and Hayes, 1982) [26]. Interference in the activity of the RNA polymerase I-template complex leads to selective inhibition of rRNA synthesis (Davidse, 1987, 1988; Davidse *et al.*, 1991; Schwinn and Urech, 1986) [13, 80].

Ridomil 2E, Apron 25 WP, Subdue 2E are famous trade names for Metalaxyl. It is also available in combination with folpet, mancozeb, captan etc. It is formulated as emulsifiable concentrate (EC), granule (G), wettable powder (WP) and seed dressing (SD).

Origin and Development of Metalaxyl Resistance

In 1979, the first Phenylamide-resistant isolate of *Pseudoperonospora cubensis* was isolated from the cucumber climbers cultivated in polyhouse in Israel and Phenylamide-resistant isolates of *Phytophthora infestans* were first reported in potatoes grown in the fields in Ireland in 1980 and in the Netherlands (Davidse *et al.*, 1981; Dowley and O'Sullivan, 1981) [16, 20]. Resistance to metalaxyl in *P. infestans* in India was first reported in Nilgiri hills by Arora *et al.* (1992) [2] and subsequently in Punjab State by Thind *et al.* (2001) [92]. The origin of resistance to Phenylamides is believed to begun from naturally resistant (insensitive) isolates which existed in minor section of the population even before exposure to fungicide. Daggett *et al.* (1993) [12] reported the existence of Phenylamide-resistant isolates in 1977 in the north of Berlin, before the use of metalaxyl in Germany. There were probably many cases of pre existing Phenylamide-resistant isolates all

over the world. In Europe, it is unknown that whether Phenylamide-resistance resulted from a number of simultaneous mutations at different sites or from the immigration of fungicide resistant genotypes. Random mutations in the absence of Phenylamide-fungicides might have lead to the development of these pre-existing resistant isolates; application of Phenylamide-fungicides does not alter the frequency of mutation. However, the selection pressure applied on the fungal population due to the use of Phenylamides resulted in increased number of resistant individuals which lead to formation of a resistant distinct subpopulation. Two different subpopulations with sensitive and resistant isolates were developed. Selection pressure imposed by the fungicide (i.e fungicide concentration and number of fungicide applications), and the comparative fitness of the resistant isolates (pathogen) plays a decisive role in the persistence and proportion of the resistant isolates.

Genetic studies conducted to determine the resistance to Metalaxyl have extensively worked up on crosses between isolates of various *Phytophthora* sp showing Metalaxyl sensitivity with those isolates which are Metalaxyl insensitive. Variations in the sensitivity levels were obtained in the progeny due to segregation (Gisi and Sierotzki, 2008; Gisi *et al.*, 2000)^[37, 36]. A number of genetic studies conducted in the past suggest that, one or two major MEX loci called MEX1 and MEX2 governs the Metalaxyl insensitivity in the pathogen. Some other genes have also been reported in contributing minor effects (Fabritius *et al.*, 1997; Judelson and Roberts, 1999; Lee *et al.*, 1999; Knapova *et al.*, 2002; Judelson and Senthil, 2006)^[25, 43, 57, 55, 44].

Use of [3H]uridine incorporation under biochemical assays, estimated a prime role of Metalaxyl in the RNA synthesis (Davidse *et al.*, 1983, 1988)^[14, 15], mainly, ribosomal RNA (rRNA) (Davidse *et al.*, 1983; Wollgiehn *et al.*, 1984)^[13, 95]. Less affect is observed on the formation of messenger (mRNA) and transfer RNAs (tRNA). This conveyed the role of RNA polymerase I (RNAPolI), which transcribes rRNA. The experiment also concluded that binding of RNA polymerase complex to DNA, exert the activity of Metalaxyl (Davidse *et al.*, 1983)^[15]. Topoisomerases and transcription factors are additional proteins which also may affect the activity of RNA polymerase (Drygin *et al.*, 2010)^[23]. All these reasons create difficulty in the exact confirmation of the attack of Mefenoxam on the specific subunit of RNA polymerase and the variation in the sequence which causes insensitivity.

Recent studies indicate that resistance in few isolates of *Phytophthora infestans* to metalaxyl is conferred by a single nucleotide polymorphism in gene encoding, the largest subunit of RNA polymerase I- RPA190. The 'resistant' allele of RPA190 when transferred to a sensitive isolate resulted in development of transgenic lines that showed resistance to Mefenoxam (Metalaxyl). The study concluded that variation in the sequence of RPA190 leads to insensitivity towards Mefenoxam (Metalaxyl) in *P. infestans* (Randall *et al.*, 2014)^[73]. The exact molecular mechanism of *Phytophthora infestans* showing insensitive to Phenylamides fungicides has been investigated but results have been inconclusive. Metalaxyl resistant isolates of *Phytophthora infestans* does not show cross resistance to novel action fungicides such as azoxystrobin, mandipropamid, benalaxyl, previcur, cymoxanil, fluopicolide and contact fungicides with multiple target sites (Matson *et al.* 2015)^[61].

Cause of development of metalaxyl resistance

A number of factors may be responsible for the development of resistance- pathogen factors (genetic diversity, shorter life cycle, higher multiplication rate etc.), fungicide factors (specific site of action, higher rate and frequency of application).The pathogen, *Phytophthora infestans*, has a heterothallic nature, that means it has two mating types: A1 and A2 (Erwin and Ribeiro, 1996)^[24]. Until 1984 there was no report of presence of A2 mating type isolates outside Central Mexico (Hohl and Iselin, 1984)^[42]. In 1988, there was first report of prevalence A2 mating type isolates in Brazil (Brommonschenkel, 1988)^[6]. Whereas, there is no evidence of recombination; even when both A1 and A2 mating types were present and the population of the fungal pathogen in Brazil comprised of two clonal lineages: US-1 and BR-1.

Through previous genetic analysis of *Phytophthora infestans* populations, limited number of clonal genotypes were identified out of which four (US1, US6, US7 and US8) were most common (Goodwin *et al.*, 1994)^[38]. The US-1 lineage was found to be responsible for late blight disease in tomato. The isolates of this lineage have the A1 mating type with Ib type restriction pattern of mitochondrial DNA (mtDNA). The other lineage, having A2 mating type with mtDNA IIa BR-1, was found to be linked with potato crops (Reis *et al.*, 2002, 2003)^[74, 75]. The presence of quantitative differences in the components of aggressivity in the clonal lineages contributed to the specificity of host (Suassuna *et al.*, 2004)^[89]. US-1 isolates of the pathogen are fitter on tomato plants compared to BR-1 isolates under higher temperatures (Maziero *et al.*, 2009)^[63].

There have been reports of greater genetic diversity in population of *P. infestans* across east to west within Central Mexico (Shakya *et al.*, 2018)^[81]. In case of *P. infestans*, it is crucial to understand whether the pathogenic isolates of tomato comprise only of A1 mating type or both mating types (A1 and A2). Presence of both mating types on the same host may lead to emergence of more virulent and fungicide resistant subpopulation. The pathogen population is governed by several evolutionary mechanisms. Some main evolutionary mechanisms are mutation; migration and recombination which are responsible for variation in genetic constitution of population of *P. infestans* (Fry, 2008).

Metalaxyl resistance occurrence, in more aggressive strains of *P. infestans*, increased the chances of association of metalaxyl resistance with pathogenic fitness (Cohen and Coffey, 1986; Kato *et al.*, 1997; Spielman *et al.*, 1991)^[11, 47, 87]. In Israel, Cohen and colleagues suggested that resistance to Metalaxyl was in association with some isolates of *Phytophthora* sp showing higher fitness (Bashan *et al.*, 1989; Kadish and Cohen, 1988; Kadish *et al.*, 1990)^[4, 48, 49]. However from the subsequent analysis of oospore progeny, it was observed that metalaxyl resistance and fitness were not linked (Gisi and Cohen, 1996).

In Brazil, the *P. infestans* population from tomatoes showed uniformity (Reis *et al.*, 2002)^[75], as recombination and migration does not occur within pathogenic population, the prime reason of variability may be mutation. Though, *P. infestans* population in Brazil has apparent genetic uniformity, mutation is the expected factor which can affect the management of disease, like insensitivity to fungicides and variability in virulence. Use of site- specific fungicides continuously and irrationally may be risky and may lead to development of resistant strains in the pathogen populations

(Dekker and Georgopoulos 1982)^[19]. There have been several reports of decreased effect of metalaxyl, in management of disease caused by the pathogen (Reis *et al.*, 2005)^[76].

The excessive utilisation of phenylamide group of fungicides has greatly enhanced the prevalence of insensitive isolates of the pathogen in Europe (Dowley and O'Sullivan, 1985)^[21] causing failures in management of disease (Bradshaw and Vaughan, 1996)^[5]. There have been many reports of emergence of fungicide-insensitive isolates in plant pathogenic populations due to repetitive use of systemic fungicides. A number of reports of metalaxyl resistance in *P. infestans* have been made in the past (Gisi and Cohen, 1996; Pérez *et al.*, 2009; Reis *et al.*, 2005)^[35, 71, 76]. Therefore, a regular monitoring of resistant pathogen populations, specifically to fungicides with systemic nature, is an eminent part of effective disease management strategy (Gisi and Cohen, 1996)^[35].

Over past 20 years, migrations of populations of *Phytophthora infestans* has led to the spread of both mating type A1 and A2 isolates in wider areas. The occurrence of phenylamide-sensitive and -resistant phenotypes is spread worldwide and majorly in all potato and tomato cultivated areas affected by late blight disease (Fry and Goodwin, 1995). Despite the prevalence of phenylamide-insensitive phenotypes of *P. infestans* (Shattock and Day, 1996)^[82], metalaxyl in combination with protectant fungicides, e.g. mancozeb, is successfully used for the management of late blight disease (Bradshaw and Vaughan, 1996)^[5].

A study conducted by Mazakova *et al.* (2006) revealed the prevalence and spread of A2 mating type of *P. infestans* when 199 isolates of *Phytophthora infestans* were collected from different regions of Czech Republic.

Apart from the cause of development of resistance, recent studies also focused on how the metalaxyl sensitive isolates differed from the non sensitive isolates of *Phytophthora infestans*. Mariduenza-Zavala (2017)^[59] did metabolomics-based characterization of fungicide(metalaxyl) resistant isolates of *P. infestans* collected from potato producing areas in Ecuador. The isolates which were resistance to metalaxyl were subjected to *in vitro* evaluation and the GC-MS metabolite profile. All isolates were examined at 0, 0.5 and 100 mg/L of metalaxyl. Mapping of all the isolates was carried out through potential pathways using KEGG pathway with *Pseudocercospora fijiensis* as the model organism. Amongst all the tested isolates only 30% showed sensitivity to the lower doses of metalaxyl and resistant isolates showed differential expression of 49 metabolites. The resistant isolates showed over expression of following metabolites: hexadecanoic and octadecanoic acids; proline, fructose, butanedioic, propionic acid, glucose and valine. Biosynthesis of the fatty acids and glycerophospholipid metabolism involved in maintaining membrane fluidity of the pathogen are greatly governed by resistance-related metabolic pathways. No residues of metalaxyl were found in resistant isolates, which reveals the inability of fungicide to enter the membrane of the fungal pathogen.

Strategies against resistance

Since Phenylamides are known to endure a great risk of resistance by the pathogen, to increase the durability of Phenylamide-fungicides, it is essential to develop and implement antiresistance strategies. Thus, PA-FRAC-Working Groups (Phenylamide fungicide resistance action committee) was started in 1982, in an international level and also as local basis for few countries, with many Phenylamide-

manufacturing companies as its members to draft recommendations for the efficient use of Phenylamides. The strategies included:

- Use of mixed formulation of Phenylamide fungicide with adequate rates of non Phenylamide compounds so that their different modes of action can counteract the pathogen in much efficient manner (Urech and Staub, 1985)^[94].
- Reducing the frequency of applications of fungicide in one crop and one season (2–4 treatments within 14-day intervals) to reduce excessive application of fungicides.
- Alternate use of contact and systemic fungicides or their mixtures (FRAC) greatly prevents the building up of selection pressure on pathogenic population.
- Following integrated disease management practices can enormously delay the development of fungicide resistance.

Metalaxyl resistance can be efficiently managed by application of fungicides with novel modes of action like Amistar 25 SC (azoxystrobin), Infinito 68.75 SC (fluopicolide+ propamocarb chloride), Acrobat 50 WP (dimethomorph), Curzate M-8 72 WP (cymoxanil + mancozeb) and Mandipropamid 250 SC (Thind, 2016)^[93]. Use of fungicides mixtures with components having different target sites slows down the development of resistance and will prove to be effective in sustainable management of disease.

Alternate methods of management of late blight of potato

The sole reliance on the use of fungicides for management of the disease is one of the main reasons for the development of resistance and is not an adequate management practice thus the concept of integrated disease management that includes cultural, biological, chemical and host resistance strategies can be utilized for effective management of disease and to reduce the losses caused by the disease (Kirk *et al.* 2013)^[54]. The integrated approach can greatly contribute in reducing the rate of development of fungicide resistance in plant pathogens and will also reduce the cost involved in fungicide sprays. Some of the measures for the management of late blight of potato are as under:

- Utilisation of old seed or seed saved from previous crops by the farmers increase the chances of late blight disease. Source of seed should be selected very carefully especially by keeping in view the new strains of the pathogen (Kirk, 2009)^[53]. Hilling at appropriate time with required quantity of soil and adequate management of nutrition requirements of plant (Garrett and Dendy, 2001)^[33] is effective.
- Weather conditions play an eminent role in the incidence and severity of late blight. (Hijmans, 2003)^[41]. Although, we cannot control the weather conditions, field selection and efficient management of irrigation can prevent availability of favourable environmental conditions for development of disease. Soils with good water infiltration capacity and drainage ability are suitable for potato planting.
- It is also essential to keep in mind the role of alternative host of late blight, like weeds that can greatly contribute to spread of disease under favourable conditions. Weeds if not hosts of late blight they may favour disease development by creating humid conditions. Heavy weed infestations may prevent the crop coverage at the time of fungicide spray (Kirk, 2009)^[53].

- It is important to remove the leftover potatoes which result from seed cutting or wasted during loading of the produce, before planting new crop in the season as these may support the production of inoculums (Agrios 2005) ^[1].
- Avoid excessive irrigation late in the season, as tubers may become infected with late blight as spore may wash off from infected leaves into the soil. Fertilizer applications late in the season should also be limited as it promotes green vines and tuber bulking, which makes the killing of green vines difficult. Immature tubers are more prone to infection at the time of harvest.
- Green vines also harbour pathogen propagules that may infect tubers at the time of harvest. Two weeks before harvest, vines with blight infection should be killed (Kirk *et al.* 2013) ^[54]. It reduces the chance of tubers getting contaminated. Tubers should be dried properly before keeping them in storage (Kirk, 2009) ^[53], and the air temperature and humidity in the storage should be optimised accordingly. To prevent the disease spread, frequent scouting and removal of diseased tubers from storage is required (Stone 2009) ^[88].
- Application of adequate and need based doses of fungicides can reduce the crop losses caused by disease. There are reports of better management of potato late blight with the use of reduced rates of Ridomil application with maximum marginal rate of return (Tsedaley *et al.* 2014) ^[91]. Use of fungicide along with genetic potential based on resistant cultivars is an important factor for management of disease (Namanda *et al.* 2004) ^[66]. Host resistance is an important component in management of late blight (Shtienberg *et al.* 1994) ^[84]. Variations in *P. infestans* population structure can be minimised by using late blight resistant varieties and also decreases the chances of development of resistance against fungicide (Hakiza 1999; Mukalazi *et al.* 2001) ^[40, 45, 60]. Selection of resistant varieties like Kufri Girdhari (Joseph *et al.*, 2011) ^[46], Kufri Neelima, Kufri Himsona etc. prevents disease. Area under disease progress curve (AUDPC) value is significantly lower in cultivars with polygenic resistance compared to susceptible ones (Fry, 1977) ^[28]. Specific resistance was discovered in the genes from *Solanum demissum* and the resistance genes are incorporated in new cultivars by potato breeders.
- The study of composition of *P. infestans* pathotypes provides essential details for breeding procedures of tomato which aims to produce disease resistant varieties. The resistance genes (Ph-1, Ph-2, and Ph-3) were incorporated in tomato plant from different attainment of *Solanum pimpinellifolium* (Moreau *et al.*, 1998) ^[64]. It was revealed later that accession L3708 of *S. pimpinellifolium* contains one other resistance gene along with the Ph-3 gene (Kim and Mutschler, 2005) ^[51]. It was named Ph-4 gene (Chen *et al.*, 2008) ^[10]. Knowledge about the dynamics of virulence genes in the population of pathogen which can overpower resistance genes can be of great help in the breeding programs for selecting parental plants with resistant genes and durability of resistance genes.

Efficient utilization of Late blight Disease Forecasting models such as Jhulsacast (Singh *et al.*, 2000) ^[85], Indoblighcast (Singh *et al.*, 2016) ^[86] based on daily maximum and minimum temperature and relative humidity for period of 7 days can detect the conditions favourable for occurrence of disease.

Predictive programs such as TOM-CAST and BLITECAST aid growers in scheduling fungicide application for crops (Gleason, *et al.* 1995; Krause *et al.*, 1975). These models can be of great help in management of disease as fungicide sprays can be scheduled on the basis of forecast. Number of sprays can be reduced on the basis of forecast thus unnecessary application of fungicide can be avoided which is not only money and effort saving but also reduces the load of chemical on environment.

Conclusion

Metalaxyl resistance in *Phytophthora infestans* emerged as one of the classical example of fungicide resistance in pathogen populations and potato and tomato being a staple food crops in many countries made it an issue of greater concern. Migration of resistant isolates of the pathogen, presence of the both the mating types of pathogen, more virulent strains of the pathogen, excessive and sole use of metalaxyl, development of mutants in pathogen population have been estimated to be the reasons for development of resistance. Metalaxyl being site specific fungicide (inhibiting RNA synthesis) is also a major reason for resistance development. Various anti resistance strategies have been developed to cope up with this serious issue of fungicide resistance such as use of combi product fungicides containing both, contact and systemic fungicides, alternate application of systemic and contact fungicides, reducing the sole reliance on fungicides that is utilising cultural, biological and chemical methods of disease management in the best possible manner through the integrated disease management approach. Incorporation of novel technology such as remote sensing, forecasting models, decision support systems and various system software programs in predicting disease and estimating the yield loss for better utilisation of resources in disease management can be practised.

Statement for declaration of conflict of interest

The authors of the manuscript entitled: Metalaxyl resistance in *Phytophthora infestans*: An Overview, hereby declare that there is no conflict of interest to declare.

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