Microbial metabolites in plant disease management: Review on biological approach

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Abstract
Biological control of plant diseases through microbial metabolites is an eco-friendly and effective means of reducing or mitigating crop losses. Among these microbial metabolites, antibiotics produced by different bacteria and fungi are now proving to be a new source of potential biopesticides. Various actinomycetes like Streptomyces, Actinoplanes, Actinomadura, Micromonospora, Streptosporangium, Streptoverticillium and Spirillospora, bacteria belonging to the genera Agrobacterium, Bacillus, Burkholderia, Enterobacter, Erwinia, Lysobacter, Pseudomonas, Serratia and a few fungal genera such as Ampelomyces, Aspergillus, Coniothyrium, Gliocladium, Laetisaria, Penicillium, Phlebiopsis, Sporodesmia, Talaromyces, Tilletiopsis, Trichoderma, Trichothecium and non-pathogenic Fusarium are prolific producers of secondary metabolites which at low concentrations are lethal to the growth or metabolic activities of other microorganisms. Phenazine-1-carboxylic acid, pyocyanin, 2,4-diacetylphloroglucinol, pyoluteorin, pyrrolnitrin, hydrogen cyanide, siderophores, zwittermicin a 14, kurstakin, azole compound, ammonia, wuyiencin, viridin, trichodermin, 6-pentyl-2H-pyran-2-one, gliovirin, gliotoxin, harzianopyridone, harzianolide, massoilactone and d-decanolactone, viridepyronone, koningins, t22 azaphilone, t39 butenolid, volatile compounds and trichothecin are some of the metabolites which have been used in plant disease control. These microbial metabolites can be used as a substitute for chemical fungicides and paved way for its use in sustainable agriculture as biopesticides.

Keywords: Secondary metabolites, plant disease, microbes, biopesticides and management

Introduction
Agriculture, the backbone of Indian economy, contributes to overall economic growth of the country and determines standard of living for more than 50 per cent of Indian population and contributes 14.4 per cent in GDP. Modern agriculture is evolving through agricultural innovations and farming practices and helping farmers to increase efficiency and reduce requirement of natural resources like water, land and energy necessary to meet world's food, fuel and fibre needs. In order to get higher yields, farmers practice monocropping and inadvertently make non-judicious use of chemical fertilizers resulting in pests and diseases outbreaks. Agrochemicals are invariably used to manage these diseases and posing threat to human health as well as causing widespread environmental damage. Non-judicious use of agrochemicals leads to development of fungicide resistance in pathogens. These environmental and consumer concerns have led the researchers to focus interest on of biological control agents development as an environment friendly and sustainable strategy for the protection of agricultural and horticultural crops against phytopathogens (Dunne et al., 1998) [30], as an alternative to the chemical fungicides (Ravikumar, 1998; Biju, 2000) [122, 18], thus gaining importance in modern agriculture.

Biological control is an eco-friendly and effective means of reducing or mitigating plant diseases through the use of natural enemies i.e., microorganisms. These microbe-based agro-agents are used as either whole organism or their metabolites. Interestingly, some of the microbial metabolites that are used in plant disease control programme are of great importance. Micro organisms produce a wide range of secondary metabolites like antibiotics, hormones, enzymes, pigments, mycotoxins etc. The discovery of penicillin, the first broad-spectrum antibiotic led researchers for the exploitation of microorganisms for secondary metabolite production, which revolutionized the field of microbiology (Keller et al., 2006).
Microbial secondary metabolites are low molecular bioactive compounds synthesized during a subsequent production stage (idiophase) of microbial growth. The secondary metabolite production is controlled by special regulatory mechanisms in microorganisms, as their production is generally repressed in logarithmic phase and depressed in stationary growth phases. It is commonly observed during microbial interaction of antagonistic microorganisms and pathogens. Among these microbial metabolites, antibiotics produced by different bacteria, actinomycetes and fungi is now proving to be a new source of potential biocides. Antibiotics are low molecular weight compounds produced by microorganisms which at low concentrations are lethal to the growth or metabolic activities of other microorganisms (Handelsman and Stabb, 1996) (100). In many biocontrol systems, one or more antibiotics have been shown to play a role in disease suppression and have been extensively emphasized by many researchers (Handelsman and Stabb, 1996; Yamaguchi, 1996; Fravel, 1988; Mathivanan et al., 2008) (100, 157, 39, 88). With the advent of new screening and isolation techniques, a variety of antibiotics have been identified. Hence, in the recent years, the use of secondary metabolites of microbial origin is gaining incentive in crop protection and such metabolites may become a supplement or an alternative to chemical control (Fravel, 1988; Prabavathy et al., 2006; Mathivanan et al., 2008) (19, 117, 88). Since these secondary metabolites are biologically synthesized, they are highly target oriented and hence, ecofriendly for beneficial organisms. Being biological origin, these metabolites are inherently biodegradable and often do not persist in nature and are safe to the environment (Suzni, 1992; Yamaguchi, 1996; Prabavathy et al., 2008) (138, 157, 117). The antibiotics produced by biological control agents are unique and advantageous over their competitors i.e., the chemical fungicides (Kim and Hwang, 2007) (71). These microbial metabolites can be used for the synthesis of plant protective chemicals as lead molecules, thus open up new vistas for entrepreneurs and industrialists (Jayaprakashvel and Mathivanan, 2011). Thus, worldwide interest in these have been renewed and presently several plant diseases are being managed by the use of microbial metabolites.

Source of secondary metabolites

1. Actinomycetes

Actinomycetes are potent producers of a wide variety of secondary metabolites with diverse biological activities, which include therapeutically and agriculturally important compounds (Tanaka and Omura, 1993) (142). Over 1,000 secondary metabolites from actinomycetes have been discovered during 1988–1992. Most of these compounds are produced by various species of the genus Streptomyces. In fact, about 60 per cent of the new insecticides and herbicides reported to be originated from Streptomyces (Tanaka and Omura, 1993) (142). Actinomycetes have produced various antibacterial, antifungal, nematocidal and herbicidal antibiotic compounds and many are used in agriculture. Several species of actinomycetes belonging to the genera Streptomyces, Actinoplanes, Actinomadura, Micromonospora, Streptosporangium, Streptovitiscillus and Spirillospora have been successfully used as potent antagonists against various phytopathogens.

Streptomyces is the dominant genera among actinomycetes known to produce numerous types of antibiotics, of which, many of them, for example, validamycin and kasugamycin have been commercialized as fungicides (Tanaka and Omura, 1993; Mathivanan et al., 2008) (142, 88). The tetracyclines, chloramphenicol, neomycin, erythromycin, vancomycin, kanamycin, cephalosporin and rifamycins, are few of the antibacterial antibiotics produced by actinomycetes (Prabavathy et al., 2008) (117).

2. Bacteria

In the prokaryotic group, bacteria belonging to the genera Agrobacterium, Bacillus, Burkholderia, Enterobacter, Erwinia, Lysobacter, Pseudomonas and Serratia have been successfully used as biological control agents against many plant diseases. Among these unicellular bacteria Bacillus and Pseudomonas is prolific producer of antibiotics.

a. Fluorescent Pseudomonads

Among various BCAs, fluorescent pseudomonads (FPs) are found to be the prolific producers of a wide variety of metabolites such as phenazines (Gurusiddaiah et al., 1986; Thomashow and Weller, 1988; Pierson and Thomashow, 1992; Chin-A-Woeng et al., 1998) (43, 145, 114, 21), phenolics (Keel et al., 1990, 1992; Vincent et al., 1991) (67, 150), pyrrole-type compounds (Homma and Suzui, 1989; Pfenfer et al., 1993) (52, 112), polyketides (Nowak-Thompson et al., 1994; Kraus and Loper, 1995) (104, 76), peptides (Nielsen et al., 1999; Sorensen et al., 2001) (103, 135), phosphogluconicins (Dwivedi and Johri 2003) (131), hydrogen cyanide (Castric 1981; Bagnoasco et al., 1998; Rodriguez and Fraga 1999; Siddiqui 2006) (131) and siderophores (Hamdan et al., 1991; Meyer et al., 2002).

b. Bacillus sp.

Antimicrobial metabolites of Bacillus spp. have been used against plant diseases (Kavitha et al., 2005) (166). Bacillus spp. are found to produce many antibiotics such as zwittermycin A (Smith et al., 1993) (134), bacillomycins, fungicin (Koumoutsi et al., 2004) (75), kanosamine, rhizoctin C, iturins (Paulitz and Belanger, 2001; Kloepper et al., 2004) (73, 111) and saltavalin and are also capable of producing thermostable antimicrobial peptides (Emmet and Handelsman, 1999; Kavitha et al., 2005; Leclere et al., 2005; Zhao et al., 2010) (34, 66, 78, 160). Bacteriocins are reported as biopreservatives in foods and beverages, and biocontrol agents in agriculture (Bais et al., 2004). Bacteriocins such as thuricin, thuricin 7, thuricin S, thuricin 19, thuricin 439A and thuricin 439B, bathuricin F4, tochicin, kurstakin 18 and entomocin to be the precursors of antibiotics (Sansinenea and Ortiz, 2011) (128). Other bacteria such as Agrobacterium radiobacter, Burkholderia cepacia, Pantoaea agglomerans and Lysobacter sp. have been reported to produce various antibiotic compounds such as agrocin 84 (Kerr, 1980) (68), pyrrolinitrin, pseudane (Homma et al., 1989) (52), herbiculin (Sandra et al., 2001) (127) and xanthobaccin A (Islam et al., 2005) (160) respectively.

3. Fungi

A number of fungal genera namely, Ampelomyces, Aspergillus, Coniothyrium, Gloecladium, Laetissia, Penicillium, Phlebiopsis, Sporodesmia, Talaromyces, Tilletiopsis, Trichoderma, Trichothecium and non-pathogenic Fusarium are known to produce biologically active secondary metabolites that are having potential in controlling plant pathogens (Dombou et al., 2002; Mathivanan and Manibhushanrao, 2004; El-Tarabily and Sivasithamparam, 2006; Mathivanan et al., 2006; Prabavathy et al., 2008; Ramesh, 2009) (27, 92, 33, 93, 117, 121). Other fungi like Aphanoacladium album, Acremonium obclavatum, Myrothecium verrucaria, Verticillium chlamydosporium,
Penicillium brevicompactum, Penicillium expansum, Penicillium pinophilum and Coniothyrium minitans were also reported to produce antimicrobial metabolites against plant pathogens. However, their potential have been inadequately explored in plant protection (Liu and Li, 2004; Mathivanan et al., 2008)[63, 68].

Among fungal BCAs, Trichoderma sp. is known to produces a wide range of volatile and non-volatile antibiotic secondary metabolites. Trichoderma species are free-living fungi which are highly interactive in root, soil and foliar environments. Anthraquinones are well-known metabolites of Trichoderma species. In 1967 a wild strain of T. viride have been isolated from soil and has been recorded to produce pachybasin, chrysophanol, trichodermol, emodin, 1,3,6,8-tetrahydroxyanthraquinone and 1-acetyl-2,4,5,7-tetrahydroxyanthraquinone. Trichoderma and Emodin possesses both monoamine oxidase inhibiting activity (Fujimoto et al., 1998) and tyrosine kinase (Jayasuriya et al., 1992; Kumar et al., 1998). T. viride, T. virens, T. harzianum and T. koningii are prolific producers of secondary metabolites such as trichodermin, viridol, peptaibols, pyrones, acarones, daucene, trichodermol, emodin, sterols, heterocyclic nitrogen compounds, sesquiterpenes, etc. (Weindling and Emerson, 1936; Sivasithamparam and Ghisalberti, 1998; Vyas and Mathur, 2002; Wiest et al., 2002; Mathivanan et al., 2008)[153, 133, 68]. Secretion of a variety of polysaccharide degrading enzymes including chitinases, glucanases, proteases and cellulases is a common feature of bacterial and fungal BCAs (Jan et al., 2011; Quecine et al., 2008)[61]. These enzymes are capable of degrading the cell walls of fungal (or oomycete) hyphae, chlamydospores, oospores, conidia, sporangia, and zoospores resulting in lysis and thus contribute to protection against Plant Disease.

Microbial secondary metabolites in plant disease management

Microbial metabolites of fungal, bacterial and actinomycetes antagonists have found capable of inhibiting the growth of various phytopathogens. Secondary metabolites produced by different microbes are as follows:

Phenazine-1-carboxylic acid (PCA)

It has been reported from P. fluorescens (Gurusiddaiah et al., 1986)[43], P. chlororaphis (Elander et al., 1968) [3] and P. putida (Pamtha et al., 2010)[110]. PCA has been reported to inhibit fungal pathogens such as Gaeumannomyces graminis var. tritici, Pythium sp., Rhizoctonia solani, Polyporus sp., Sarocladium oryzae, Macrophomina phaseolina, Pestalotia theae, various species of Colletotrichum etc. and bacterial pathogens, Actinomyces viscous, Bacillus subtilis and Erwinia amylovora etc. (Gurusiddaiah et al., 1986; Sakhthev and Gnanamanickam, 1987; Thomashow et al., 1990; Ayyadurai et al., 2007; Pamtha et al., 2010)[43, 146, 8, 110].

Pyocyanin (PCN)

Pyocyanin (1-hydroxy-5-methyl-phenazine) is predominantly produced by P. aeruginosa (Demange et al., 1987) [26]. This bluish coloured compound, is toxic to a wide range of fungi including Septoria tritici and bacteria (Hassan and Fridovich, 1980; Baron and Rowe, 1981; Flashman et al., 1990)[49, 11]. [138]. It is more stable than PCA and exhibits antifungal activities even in alkaline pH (Chin-A-Woeng et al., 1998)[21]. The broad-spectrum antifungal activity of PCN against Pythium, Fusarium oxysporum f.sp. radiiopersici, S. oryzae and R. solani have been documented (Chin-A-Woeng et al., 1998; Sunish Kumar et al., 2005)[21, 137].

2, 4-diacetylphloroglucinol (DAPG)

Production of 2, 4-diacetylphloroglucinol (DAPG), a phenolic antibiotic, has been reported from P. fluorescens strains such as Pf-5, CHA0, Q2-87, F113, Q8r1-96. DAPG-producing strains are effective against Pythium, causal organism of damping-off in cotton (Howell and Stipanovic, 1980)[155], soft rot of potato and take-all of wheat (Vincent et al., 1991; Fenton et al., 1992; Harrison et al., 1993; Pierson and Wellar, 1994; Rosales et al., 1995; Raajmakers and Weller, 1998)[158, 35, 113, 124, 119]. cyst nematode (Cronin et al., 1997)[24], black root rot of tobacco and root rot of tomato (Duffy and Defago, 1997)[29].

Pyoluteorin (PLT)

P. fluorescens strain Pf-5 produces an antibiotic pyoluteorin (PLT), a bichlorinated fatty acid metabolite of mixed polyketide/alpha acid origin (Maurhofer et al., 1992; Maurhofer et al., 1994; Kraus and Loper, 1995; Nowak-Thompson et al., 1997)[97, 95, 76] and is found to be more effective against the oomycete, P. ultimum causing damping-off disease (Maurhofer et al., 1992)[978]. Treatment of cotton seed with pyoluteorin or with P. fluorescens at the time of planting in P. ultimum-infested soil increased seedling survival from 33 to 65% and from 28 to 71%, respectively (Howell and Stipanovic, 1982)[52]. The mode of action is by the selective inhibition of bacterial isoleucyl-tRNA synthetase (Bennett et al., 1999)[177].

Pyrylnitrin (PRN)

Pyrylnitrin (PRN) has been reported from P. aureofaciens (Elander et al., 1968) [32] and P. fluorescens (Kimer et al., 1998)[72]. PRN has been found to be active against a wide range of fungi belonging deuteromycota, ascomycota and basidiomycota. Hence, PRN is widely used as fungicide in agriculture. PRN producing Burkholderia cepacia showed a broad-spectrum antifungal activity towards phytopathogenic fungi including R. solani (Cartwright et al., 1995)[20] and P. fluorescens BL915 has been reported as bacterial antagonists that suppress R. solani in cotton (Ligon et al., 2000)[81].

Hydrogen cyanide (HCN)

It is the most potent volatile compound produced by many soil bacteria. The HCN produced by antagonistic fluorescent pseudomonads (FPs) have been very well proved to have exemplary antifungal activity against phytopathogens. HCN in P. fluorescens CHA0 played an indispensable role in suppression of black root rot of tobacco caused by the fungus Thielaviopsis basicola (Voisard et al., 1981)[152] and take-all disease of wheat caused by G. graminis var. tritici. Siddiqui et al., (2003)[138] have clearly proved the protective nature of HCN produced by P. aeruginosa against Meloidogyne javanica, the root-knot nematode in tomato.

Siderophores

Siderophores, the iron-binding molecules produced by many rhizobacteria were responsible for inhibition of many phytopathogens. Examples of siderophores produced by BCAs are pyoverdin and pyochelin, which have been reported to contain antimicrobial activity on their own (Arora et al., 2001; Haas and Defago, 2005)[5, 44]. However, in most of the studies, the siderophores have been reported to inhibit the pathogens by iron competition only. Siderophore-mediated
biocontrol potential of *Rhizobium meliloti* against *Macrophomina phaseolina*, causal agent of charcoal rot of groundnut has been demonstrated (Arora et al., 2001) [5], Mercado-Blanco et al., (2004) [98] reported the siderophore-mediated suppression of Verticillium wilt by root-associated *Pseudomonas* sp. Bano and Musarrat, (2004) [10] have also demonstrated the role of siderophores produced by rhizobacteria for the control of *Fusarium* sp. Idris et al., (2007) [99] have reported that several rhizobacteria showed inhibitory activity toward *Pythium ultimum* by the production of antibiotic metabolites and siderophores. In iron deficient medium, the siderophores have resulted in the increased inhibition of mycelia growth of the pathogen (Jayaprakashv, 2008) [63].

Zwittermicin A 14
Zwittermicin A 14 produced by *B. thuringiensis* and *B. cereus* is a linear aminopolysaccharide antibiotic (Silo-Suh et al., 1998) [132]. It has ability to suppress damping-off disease incited by *Phytophthora medicaginis* in alfalfa.

Kurstakin
Peptides of Kurstakin 18 exhibits antifungal activity against *Stachybotrys chararum* produced by *Bacillus* sp. (Hathout et al., 2000) [80].

Azole compound
Recently, an azole compound produced by *B. licheniformis* MML2501 has been completely characterized for its disease control potential against *M. phaseolina*, the causative agent of dry root rot of groundnut. The purified azole compound has exceptional antifungal activity against many soil-borne fungal phytopathogens except *R. solani* (Prashanth, 2007) [118].

Ammonia
Howell and co-workers, (1988) [56] have reported that volatile compounds such as ammonia produced by *Enterobacter cloacae* has successfully suppressed *Pythium ultimum* induced damping-off of cotton. Kavitha et al., (2005) [66] have isolated and purified a thermostable antifungal protein from *Bacillus* sp. which retained antifungal activity against *M. grisea* even after autoclaving, thus demonstrating thermostability of the compound. Blasticidin (Takeuchi et al., 1958) [141], kasugamycin (Umezawa et al., 1965) [149], polyoxins (Suzuki et al., 1965) [139] and validamycins (Shibata et al., 1970) [129] are few of the commercially successful metabolites of actinomycetes that are used in plant disease control.

An antifungal protein from the marine bacterium, *Streptomyces* sp. strain AP77 has been found to be inhibitory against *Pythium porphyrae*, a causative agent of red rot disease in *Porphyra* spp. (Woo et al., 2002) [156]. Secondary metabolites viz., 5, 6-dimethoxy-4-p-methoxyphenylcoumarin and 5, 6-dimethoxy-4-phenylcoumarin produced by *S. aureofaciens* CMUAc 130 have effectively inhibited phytopathogenic fungi (Taechowisan et al., 2005b) [148].

Wuyiencin
Wuyiencin produced by *S. hygroscopicus* var. *wuyiensis* inhibits the germination of *Botrytis cinerea* conidia (Zhong et al., 2004). Wuyiencin has shown broad spectrum activity against other bacterial and fungal phytopathogens and effectively controlled gray mold, leaf mold and powdery mildew diseases (Cui et al., 2010) [25]. Two antifungal aliphatic compounds, SPM5C-1 and SPM5C-2 with a lactone and ketone carbonyl unit, respectively, have been obtained from *Streptomyces* sp. PM5 and evaluated under in-vitro and in-vivo conditions against major rice pathogens, *Pyricularia oryzae* and *R. solani* (Prabavathy et al., 2006) [118].

Several antimicrobial secondary metabolites of *Streptomyces* sp. MML1042 have been partially purified and demonstrated for the antifungal activity against many soil-borne fungal phytopathogens (Malarvizhi, 2006) [87]. Similarly, Ramesh, (2009) [125] has isolated and characterized bioactive compounds from *Streptomyces* MML1614 that has shown exceptional inhibitory activity against mycelial growth of *R. solani* and *A. alternata*. Metabolites such as 2,3-dihydroxy-5-(hydroxymethyl) benzaldehyde, 4-(4-hydroxyphenox) butan-2-one, acetic acid-2-hydroxy-6-(3-oxobutyl)-phenyl ester and 8-methyl decanoic acid effectively inhibited *Fusarium* wilt (Kavitha et al., 2010).

In-vivo antifungal activity of 5-hydroxyl-5-methyl-2-hexenoic acid from *Actinoplanes* sp. HBDN08 under greenhouse conditions has been demonstrated that metabolite could effectively control diseases caused by *Botrytis cinerea*, *Cladosporium cucumerinum* and *Cladosporium cassicola* with 71.42, 78.63 and 65.13%, respectively, at 350 mg/L. This strong antifungal activity is suggestive of 5-hydroxyl-5-methyl-2-hexenoic acid might be a promising candidate for new antifungal agents (Zhang et al., 2010).

Viridin
Viridin has been first described in 1945 as an antifungal metabolite of the fungus *Gliocladium virens* (Trichoderma virens) (Brian and McGowan, 1945). This compound has been detected in other *Trichoderma* species such as *T. koningii* (Beresteskii et al., 1976), *T. viride* (Golder and Watson, 1980) and *T. virens* (Singh et al., 2005) and prevents the germination of spores of *Botrytis allii*, *Colletotrichum lindenmayeri* and *Fusarium caeruleum* (MIC of 0.003–0.006 lg/ml), *Penicillium expansum*, *Aspergillus niger* and *Stachybotrys atra* (6 lg/ml) (Brian and McGowan, 1945; Ghisalberti, 2002). The related C-3 alcohol viridol has been obtained from *T. viride* and other *Gliocladium* species.

Trichodermin
Trichodermin has been first isolated in 1964 from a proposed *T. viride* strain (Gottfredsen and Vangedal, 1964). Subsequently, this compound has been obtained from *T. polysporum* and *T. sporalosum* (Adams and Hanson, 1972) and *T. reesei* (Watts et al., 1988).

6-pentyl-2H-pyran-2-one
The pyrone 6-pentyl-2H-pyran-2-one has been first identified by Collins and Halim, (1972) in culture broth of *T. viride*. Since then, it has been obtained from *T. harzianum* (Claydon et al., 1987) and *T. koningii* (Simon et al., 1988) and has been used in plate tests against *Rhizoctonia solani* and *Fusarium oxysporum* f. sp. *lycopersici* with the addition of 0.3 mg/ml of 6-pentyl-2H-pyran-2-one to agar medium and resulted in 69.6% growth reduction in *R. solani* and a 31.7% reduction in *F. oxysporum* after 2 days. When used in spore germination tests at the rate of 0.45 mg/ml has been found to completely inhibit the germination of *Fusarium* spores. The control of *Botrytis cinerea* rots in stored kiwi fruits has also been investigated by Poole et al., (1998) with the application of pyrone 6-pentyl-2H-pyran-2-one at rates from 0.4 to 4 mg, neat or diluted in oil, water or acetone, consistently reduced
the incidence of *B. cinerea* storage rots to low levels in both inoculated and naturally infected fruit.

**Gliovirin**
Gliovirin obtained from fungus *Trichoderma* has been found effective against *Pythium ultimum* (Howell and Stipanovic, 1983).

**Gliotoxin**
Strains producing gliotoxin has shown antagonistic activity against *Rhizoctonia solani* (Jones and Pettit, 1987)

**Harzianopyridone**
Racemic form of harzianopyridone has shown significant antifungal activity against *Botrytis cinerea, Rhizoctonia solani* (Dickinson et al., 1989) *Gaeumannomyces graminis* var. *tritici* and *Pythium ultimum* (Vinale et al., 2006).

**Harzianolide**
Harzianolide has been isolated from three different strains of *T. harzianum* (Almassi et al., 1991; Claydon et al., 1991; Ordentlich et al., 1992). In particular, harzianolide has been demonstrated to completely inhibit *G. graminis* var. *tritici* at the rate of 200 mg/ml and T39butenolide at 100 mg/ml. Furthermore, they inhibited the growth of *Rhizoctonia solani* and *Pythium ultimum* (Vinale et al., 2006).

**Massoilactone and d-decanolactone**
The hydro-derivatives massoilactone and d-decanolactone have been patented by Hill et al., (1995) for their ability to control a range of plant afflictions including, for example, those produced by *Botrytis* or *Phytophthora* species. In 1997, 5-hydroxyvertinolide a different butenolide of the vertinolide series has been isolated from the fungus *T. longibrachiatum* Rifai agr. which is antagonistic to the fungus *Mycena citricolor*, the agent responsible for American leaf spot disease of coffee (Andrade et al., 1992).

**Viridepyronone**
Viridepyronone has been isolated from a cultural filtrate of a strain of *T. viride*. This compound has been shown antagonistic activity under *in-vitro* against *Sclerotium rolfsii* at a MIC of 196 mg/ml (>90% inhibition) (Evidente et al., 2003).

**Koningins**
A series of complex pyranes named koninginins A–E and G have been discovered in some species of *Trichoderma*. Koninginin D has also affected growth of other soil-borne plant pathogens such as *Rhizoctonia solani, Phytophthora cinnamomii, Pythium middletonii, Fusarium oxysporum* and *Bipolaris sorokiniana*.

**T22azaphilone**
Two commercial strains of *T. harzianum* have been found to produce T22azaphilone which has shown a marked *in-vitro* inhibition of *Rhizoctonia solani, Pythium ultimum and Gaeumannomyces graminis* var. *tritici* (Vinale et al., 2006).

**T39 butenolide**
T39 butenolide has been isolated from a commercially available *T. harzianum* strain (Vinale et al., 2006). This compound has shown antagonism towards the growth of the take-all fungus *Gaeumannomyces graminis* var. *Tritici* (Almassi et al., 1991; Vinale et al., 2006).

**Volatile compounds**
Isolates of *Trichoderma viride* and *Trichoderma harzianum* has shown inhibition on the growth of *Fusarium moniliforme* and *Aspergillus flavus* by producing inhibitory volatile compounds (Calistru et al., 1997). The volatile secondary metabolites produced by *Trichoderma pseudokoningii*, *T. viride* and *Trichoderma aureoviride* have affected the mycelia growth and protein synthesis in two isolates of *Serpula lacrymans* in varying degrees (Humphris et al., 2002).

**Nonanoic acid**
I. Garret and Robinson, (1969) have isolated nonanoic acid from *Fusarium oxysporum*, which inhibited the spore germination of *Cunninghamella elegans*.

**Trichothechin**
II. Trichothechin has been used in cotton seeds and crop plants to prevent wilt diseases (Askarova and Ioffe, 1962). Recently, Jayaprakashavel et al., (2010) have successfully controlled the sheath blight disease of rice under greenhouse conditions with thermostable, photostable crude metabolites of *F. roseum* MML003. The toxic metabolites produced by *Fusarium chlamydosporum* have effectively inhibited groundnut rust pathogen, *Puccinia arachidis*, and successfully reduce the number of pustules (Mathivanan, 1995) [90]. Further, an antifungal metabolite of p-disubstituted aromatic nature isolated from the culture filtrate of *F. chlamydosporum* inhibited the uredospore germination at 30 mg/ml concentration (Mathivanan and Murugesan, 1999) [91].

**Fusapyrone and deoxyfusapyrone**
Two pyrones, viz., fusapyrone and deoxyfusapyrone from *Fusarium semitectum* have been highly active against *Alternaria alternata, Ascochyta rabiei, Aspergillus flavus, Botrytis cinerea, Colletotrichum cibicarium, Phoma tracheiphila* and *Penicillium verrucosum* while they were least active against *Fusarium spp.* (Altomare et al., 2000) [1].

**Lytic enzymes**
Manymicroorganisms produce and release *lytic enzymes* that can hydrolyze a wide variety of polymeric compounds, including chitin, proteins, cellulose, hemicellulose, and DNA. Expression and secretion of these enzymes by different microbes can sometimes result in the suppression of plant pathogen activities directly. For example, control of *Sclerotium rolfsii* by *Serratia marcescens* appeared to be mediated by chitinase expression (Ordentlich et al., 1988) [107]. And, a b-1,3-glucanase contributes significantly to biocontrol activities of *Lysobacter enzymogenes* strain C3 (Palumbo et al., 2005) [108].
| S. No. | Secondary metabolite | Source | Target pathogen/disease | References |
|-------|---------------------|--------|-------------------------|------------|
| 1.    | Phenazine-1-carboxylic Acid (PCA) | *Pseudomonas fluorescens*<br>*P. aeruginosa*<br>*P. chlororaphis*<br>*P. aeruginosa* | Gaeumannomyces graminis var. tritici<br>Fusarium oxysporum f.sp. radicislycopersici<br>Rhizoctonia solani | Pierson and Pierson, 1996; Thomashow et al., 1990 [13, 146] |
| 2.    | Phenazine-1-carboxamide | *Pseudomonas aeruginosa*<br>*P. chlororaphis*<br>*P. aeruginosa*<br>*P. aeruginosa*<br> | Septoria tritici<br>Pyricularia oryzae<br>Phytophthora capsici<br>Fusarium solani | Shanmugaiah et al., 2010 |
| 3.    | Pyocyanin (PCN) | *P. aeruginosa*<br> | Thieleniopsis basicola<br>Gaeumannomyces graminis var. tritici<br>Rhizoctonia solani<br>Meloidogyne javanica | Voisard et al., 1989, Jayaprakash et al., 2010, Siddiqui et al., 2003 [152, 64, 130] |
| 4.    | Anthranilate | *P. aeruginosa*<br> | Fusarium oxysporum f.sp. ciceris, Pythium | Anjaliath et al., 1998 [3] |
| 5.    | Pyrrolineitrin (PRN) | *P. fluorescens*<br> | Pythium ultimum<br>Gaeumannomyces graminis var. tritici | Howell and Stipanovic, 1980 [55] |
| 6.    | 2,4-Diacetylphloroglucinol (DAPG) | *Pseudomonas fluorescens*<br> | Gaeumannomyces graminis var. tritici<br>Rhizoctonia solani | Nowak-Thompson et al., 1994, Raaijmakers and Weller, 1998 [104, 119] |
| 7.    | Hydrogen cyanide (HCN) | *P. fluorescens*<br>*P. aeruginosa*<br> | Thieleniopsis basicola<br>Gaeumannomyces graminis var. tritici<br>Rhizoctonia solani<br>Meloidogyne javanica | Voisard et al., 1989, Jayaprakash et al., 2010, Siddiqui et al., 2003 [152, 64, 130] |
| 8.    | Ammonia | *P. fluorescens*<br>Enterobacter sp.<br> | Thieleniopsis basicola | Howell et al., 1988, Candole and Rothrock, 1997 [56] |
| 9.    | Cyclic lipopeptides like viscosinamide tensin, and amphisin | *P. fluorescens*<br>Burkholderia cepacia | Rhizoctonia solani | Thrane et al., 2000, Nielsen et al., (1999, 2002) [101, 102] |
| 10.   | Gluconic acid | *Pseudomonas strain AN5*<br> | Gaeumannomyces graminis var. tritici | Kaur et al., 2006 |
| 11.   | Volatile organic compound | *Pseudomonas spp.*, *Serratia spp.*, *Stenotrophomonas spp.*, etc | Many soil borne fungal pathogens | Dwivedi and Johri, 2003; Kai et al., 2007 [31] |
| 12.   | Oomycin A | *P. fluorescens*<br> | Pythium ultimum<br>Aspergillus flavus | Howie and Sulsow, 1991 [57] |
| 13.   | Siderophore | *Pseudomonas sp*.<br>*Rhizobium meliloti*<br> | Verticillium <br>Fusarium <br>Macrophomina phaseolina | Mercado-Blanco et al., 2004; Idris et al., 2007; Bano and Musarrat, 2004 [98, 59, 10] |
| 14.   | Bacillomycin, fengycin | Bacillus amyloliquefaciens FZB42 | Fusarium oxysporum<br>Fusarium graminearum, Alternaria alternata, Rhizoctonia solani, Cryphonectria parasitica and Phytophthora capsici<br>Aspergillus flavus | Koumoutsu et al., 2004 [73] |
| 15.   | Bacillomycin D | Bacillus vallismortis ZZ185 | Fusarium oxysporum<br>Fusarium graminearum, Alternaria alternata, Rhizoctonia solani, Cryphonectria parasitica and Phytophthora capsici<br>Aspergillus flavus | Zhao et al., 2010, Moyne et al., 2001 [160] |
| 16.   | Iturin A | *Bacillus subtilis*<br> | Colletotrichum gloeosporioides, B. cinerea and R. solani | Paulitz and Belanger, 2001; Kim et al., 2010 [111, 70] |
| 17.   | Mycosubtilin | *B. subtilis* BBG100 | Pythium ultimum<br>Fusarium oxysporum<br>Phytophthora medicaginis and P. aphanidermatum | Leclere et al., 2005 [78] |
| 18.   | Zwittermicin A | Bacillus cereus UW85 | Phytophthora medicaginis<br>Phytophthora medicaginis and P. aphanidermatum | Smith et al., 1993, Milner et al., 1996 [134, 100] |
| 19.   | Zwittermicin A 14 | *B. thurigiensis*<br>*B. cepacia* | Phytophthora medicaginis | Silo-Suh et al., 1998 [132] |
| 20.   | Wuyiencin | *S. hygroscopius* var. wuyiensis<br> | Botrytis cinerea<br>S. charatam | Zhong et al., 2004, Hathout et al., 2000 [50] |
| 21.   | Kurstakin 18 | *B. thuringiensis*<br> | S. charatam<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina | Paulitz and Belanger, 2001; Kim et al., 2010 [111, 70] |
| 22.   | Xanthobaccin A | *Lysobacter sp. strain SB-K88*<br> | Aphanomyces cochlioides<br>Phytophthora cinnamomi<br>Phytophthora parasitica<br>Fusarium oxysporum<br>P. ultimum<br>P. aeruginosa | Islam et al., 2005 [60] |
| 23.   | Herbicolin | Pantoea agglomerans C9-1<br> | Erwinia amylovora<br>Phytophthora cinnamomi<br>Phytophthora parasitica<br>Fusarium oxysporum<br>P. ultimum | Sandra et al., 2001 [127] |
| 24.   | Pyrrolnitrin, pseudane | Burkholderia cepacia<br> | R. solani and Pyricularia oryzae<br>Bacillus amyloliquefaciens<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina | Homma et al., 1989 [52] |
| 25.   | Agrocin 84 | Agrobacterium radiobacter<br> | A. tumefaciens<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina | Kerr, 1980 [64] |
| 26.   | Soraphen A | Sorangium cellulosum (A myxobacterium)<br> | Erysiphe sp.<br>R. solani<br>Fusarium oxysporum<br>P. ultimum<br>P. aeruginosa | Gerth et al., 1994, Khan et al., 2000 [50] |
| 27.   | Pyrone 6-pentyl-2H-pyran-2-one | *T. viride*, *T. harzianum*, *T. koningii*<br> | Rhizoctonia solani and Fusarium oxysporum f.sp. lycopersici.<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina | Claydon et al., 1987; Simon et al., 1988 |
| 28.   | Viridepyronone | *T. viride*<br> | Sclerotium rolfsii<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina | Evidente et al., 2003 |
| 29.   | Koningin D | *T. koningii*<br> | Rhizoctonia solani, Phytophthora cinnamomi, Pythium ultimum<br>Bacillus subtilis<br>Bacillus amyloliquefaciens<br>Verticillium <br>Fusarium <br>Macrophomina phaseolina |}
30. Viridin  Gliocladium virens (Trichoderma virens)  Botrytis allii, Colletotrichum lini, Fusarium caeruleum, Penicillium expansum, Aspergillus niger and Stachybotrys atrah  Brian and McGowan, 1945; Ghisalberti, 2002

31. Harzianopyridone  T. harzianum  Botrytis cinerea. Rhizoctonia solani  Gaumannomyces graminis var. Triticci and Pyhium ultimum  Dickinson et al., 1989; Vinale et al., 2006

32. T22azaphilone  T. harzianum  Rhizoctonia solani, Pythium ultimum and Gaumannomyces graminis var. tritici  Vinale et al., 2006

33. 5-hydroxyvertinolide  T. longibrachiatum  Mycena citricolor  Andrade et al., 1992

34. Gliotoxin  T. viride, T. hamatum  Rhizoctonia solani  Jones and Pettit, 1987

35. Gliovirin  Gliocladium virens (Trichoderma Virens)  Pythium ultimum  Howell and Stipanovic, 1983

36. Chitinase enzyme  Serratia marcescens  Sclerotium rolfsii  Ordentlich et al., 1988

Conclusions
It can be concluded that biological control of plant pathogens using the microbial metabolites produced by antagonistic microorganisms is an attractive substitute for chemically synthesized pesticides. Their specificity and non-persistence paved way for eco-friendly plant disease management and enables us to produce agricultural crops organically without posing threat to environment. Besides, use of these microbial metabolites as lead molecules for the synthesis of plant protective chemicals opens up new vistas for entrepreneurs and industrialists. Newer scientific approaches such as biocontrol and plant growth promotion approaches enable us to produce agricultural crops organically without any detrimental effects on humans.

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