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REVIEW ARTICLE

SECONDARY METABOLITES OF MICROBIALS AS POTENTIAL SOURCE OF AGROCHEMICALS

***Deepa James and Gleena Mary, C. F.**

Department of Plant Pathology, College of Horticulture, Kerala Agricultural University, Vellanikkara, India

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ABSTRACT

Microorganisms such as fungi, bacteria and viruses produce a mixture of structurally related compounds referred to as secondary metabolites which have no function in their physiological development. The natural products of microbial origin are categorized into insecticides, fungicides, bactericides, herbicides and nematicides. The major insecticides of microbial origin include avermectins, milbemectins and spinosyns isolated from actinomycetes. Bacteria such as *Bacillus thuringiensis* and *Photorhabdus luminescens* are considered to be potential insecticides. Fungicides and bactericides from microbes comprise of strobilurins, blasticidin, kasugamycin, and validamycin among which, strobilurins are the new generation fungicides effective against both higher as well as lower fungi. Different species of *Pseudomonas* and *Trichoderma* have emerged as potential biocontrol agents for the major diseases of commercial crops. Hence, several beneficial microorganisms have been found to be the active ingredients of a new generation of microbial pesticides or the basis for many natural products of microbial origin.

INTRODUCTION

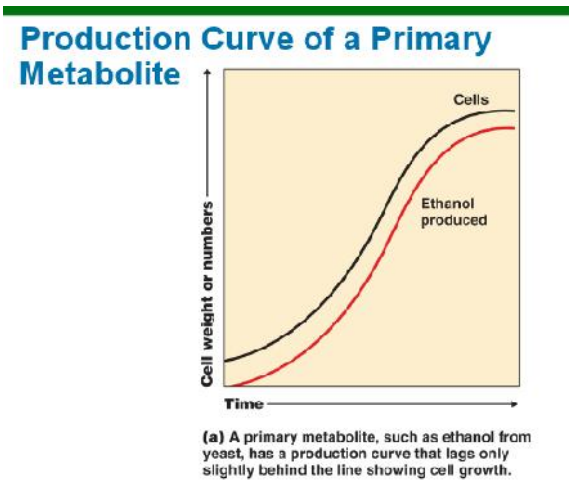
Agriculture has been a means of livelihood and a source of food since the dawn of human civilization. About one third of the total crop yield is lost due to insect pests, pathogens and weeds. The introduction of DDT in 1945 followed by the use of various other synthetic chemical pesticides has played a key role in the increase of agricultural productivity and protection of crops from pests and diseases. However, the indiscriminate use of synthetic pesticides leads to serious problems like pesticide residues in food products, environmental contamination and development of resistance in target organisms (Shelton *et al.*, 2002). Increased public concern about the potential adverse environmental effects associated with the heavy use of chemical pesticides has developed an urgent need to look for an alternative method for pest control. The use of microbial pesticides employing microorganisms or their byproducts seems to be one of the best alternatives.

Microbial pesticides-Advantages

Microbial pesticides comprise of microorganisms such as bacterium, fungus or virus as the combat weapon. The preference of using biopesticides over synthetic chemicals has been widely accepted for several reasons. They are degradable and their toxicity to non-target animals and humans is extremely low. Their ecological advantages are that they tend to be highly selective, infecting or killing a very narrow range of target pests. Another important advantage of bio-pesticides is their lower resistance in the target pest populations.

Primary vs secondary metabolites

The microorganisms produce a mixture of structurally related compounds, of which one or more are in relative abundance. They are classified as primary or secondary metabolites (Yamaguchi, 1996). Primary metabolites are produced during active cell growth of microorganisms ie. logarithmic phase (Fig.1).



(a) A primary metabolite, such as ethanol from yeast, has a production curve that lags only slightly behind the line showing cell growth.

Fig. 1.

Corresponding author: Deepa James,
Department of Plant Pathology, College of Horticulture, Kerala Agricultural University, Vellanikkara, India

In this production curve, ethanol is the primary metabolite from yeast which has a production curve that lags only slightly behind the line showing active cell growth. Secondary metabolites are produced near the onset of stationary phase (Fig. 2). The production curve shows that penicillin, the secondary metabolite from mold begins to be produced only after the logarithmic phase of the cell is completed. The main production of the secondary metabolite occurs during the stationary phase of cell growth.

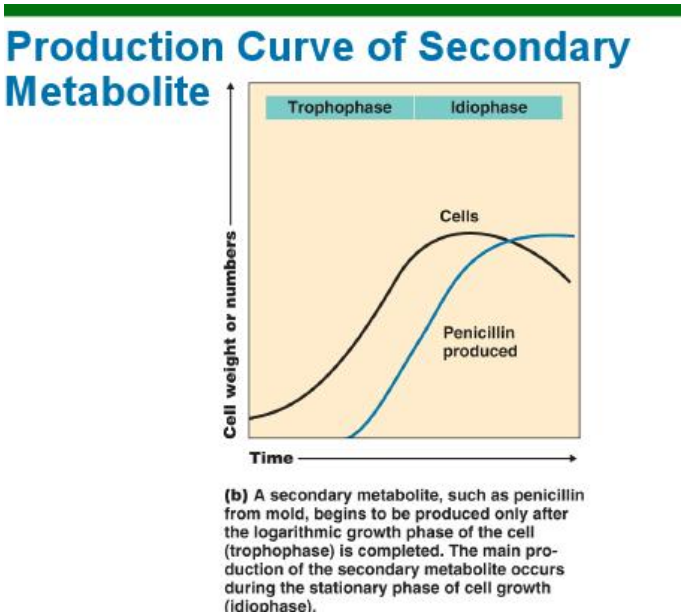


Fig. 2.

In the case of primary metabolites, extension of logarithmic phase is desirable for the production of primary metabolites. Examples are amino acids, proteins, vitamins, polysaccharides, ethanol, acetic acid, lactic acid etc. Primary metabolites are generally required for the organism's physiological development. These are produced in great abundance where as secondary metabolites which are produced in relatively less abundance have apparently no function in the physiological development of microbes. These are often derived from primary metabolites as a result of chemical adaptation to environment stress. These serve as chemical defense against pest infestation. The secondary metabolites are not involved either in cell metabolism or growth of microorganisms. These are produced in non-growing or slow growing cultures. The extension of stationary growth phase is desirable for the production of secondary metabolites and these are produced only when a nutrient is exhausted and balanced growth becomes impossible. Examples are antibiotics, growth promoters and therapeutic agents (Donidio and Monciardini, 2002).

Fermentation

Commercial preparation of the primary as well as secondary metabolites is by fermentation. A fermentation process is a biological process and, therefore, has requirements of sterility and use of cellular enzymatic reactions instead of chemical reactions aided by inanimate catalysts, sometimes operating at elevated temperature and pressure. A fermentor is a vessel containing some form of agitation and aeration to carry out fermentation. There are both heating and cooling mechanisms in it for temperature control. There are ports in it which hold the probes to measure pH, temperature, dissolved oxygen, redox potential etc (Fig.3). The basic fermentor design consists of a vertical cylindrical vessel which is fully baffled and contains a vertical shaft driven by turbine impellers for agitation. Air spargers are present at the bottom of the fermentor to provide aeration. The fermentor does have cooling coils and jackets for temperature control (Nigel *et al.*, 1992).

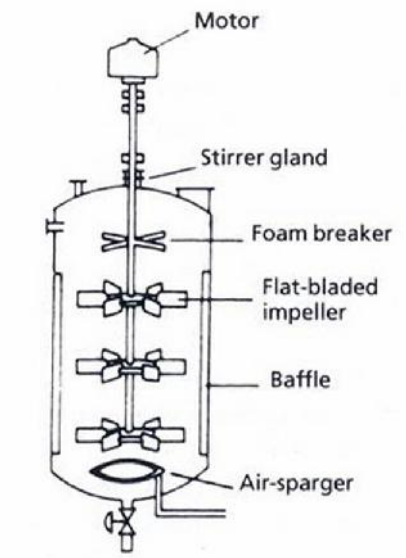


Fig. 3. Fermentor

Microbial pesticides

The microbial pesticides can be catagorized according to their main use as follows:

1. Microbial insecticides
2. Microbial fungicides
3. Bactericides/ antibiotics
4. Bioherbicides

Microbial insecticides

A large number of insecticides, either commercial or structural types are obtained from different microorganisms like actinomycetes, bacteria and fungi. Since these types of insecticides are species specific, several rounds of sprays are required to combat the insect pest population containing different species.

Actinomycetes

The important insecticides derived from actinomycetes available in the market are spinosyns, avermectins and milbemectins.

Spinosyns

The Spinosyns, a new class of highly active natural insecticides were discovered from a culture of soil actinomycete *Saccharopolyspora spinosa*. (Fig. 4)

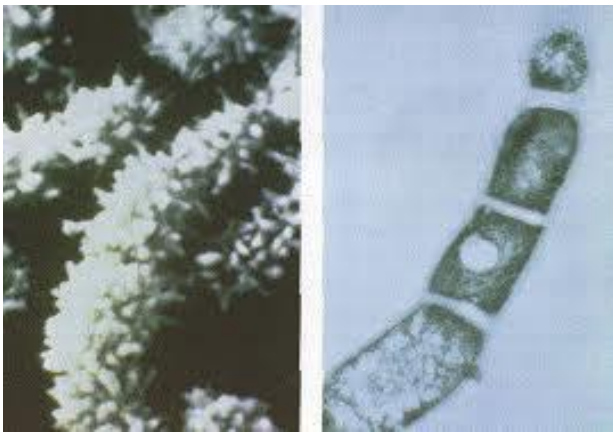


Fig.4. *Saccharopolyspora spinosa*

It is the producer of very effective insecticidal compounds and the commercial product is a mixture of spinosyn A and spinosyn D, hence the name spinosad (approximately 85% A and 15% D). The name "spinosad" originated from a contraction of the spinosyns "A" and "D".

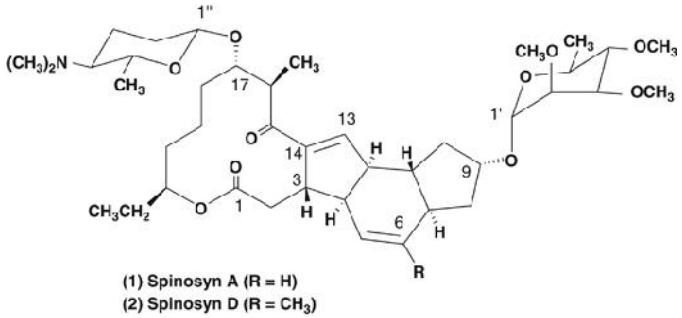


Fig. 5. Structure of Spinosyn A and D

Spinosad (Fig. 5) has a novel mode of action, with effects on target insects consistent with activation of the nicotinic acetylcholine receptor. It also affects GABA (g-aminobutyric acid) receptor. The compound causes rapid death of target phytophagous insects such as caterpillars, leaf miners, thrips and beetles. The important commercial formulations of spinosad available in the market are Naturalyte, Entrust, Conserve SC, and Spinosad. Spinosad is biologically active especially against lepidopteran insects like tobacco bud worm (*Helicoverpa virescens*), the cotton boll worm (*Helicoverpa zea*), American boll worm (*Helicoverpa armigera*), army worm (*Spodoptera litura*) etc (Thompson *et al.*, 1997).

Fig. 6. *Streptomyces avermitilis*

Avermectins

Avermectin was the natural product discovered *in vivo* screen involving fermentation broths of the naturally occurring soil actinomycetes *Streptomyces avermitilis*. (Fig. 6). It is a mixture of macrocyclic lactones *viz.*, avermectin B1a and avermectin B1b. The target for avermectin B1a involves g-aminobutyric acid (GABA) receptor in the peripheral nervous system. The compound stimulated the release of GABA from the nerve endings and enhanced the binding of GABA to receptor sites on the postsynaptic member of inhibitory motor neurons of the insects. The enhanced GABA binding resulted in an increased flow of chloride ions into the cells, with consequent hyper polarization and elimination of signal transduction resulting in inhibition of neurotransmission (Turner and Schaeffer, 1990). Avermectins are insecticides and acaricides with contact and stomach action. These are found very effective against mites and leaf miners. Commercial available products of avermectins are Avid, Agrimec, and Acramite.

Milbemectins

Milbemectins were isolated from the soil actinomycete *Streptomyces hygroscopicus* subsp. *Aureolacrimosus.* Milbemectins have same mode of action as avermectins but with a narrow spectrum of activity. Its mode of action involved opening the chloride channel in the plasma membrane of the nervous and neuromuscular systems. The mixture (milbemectins) has been used for the control of Tetranychidae on tea and brinjal. Milbemectin is available under trade name Milbeknock 1% EC.

Bacteria

The two important bacteria *viz.*, *Bacillus thuringiensis* and *Photorhabdus luminescens* are considered as good biocontrol agents with a diverse spectrum of activity.

Bacillus thuringiensis

Bacillus thuringiensis is a gram positive, spore forming bacterium (Fig. 7).

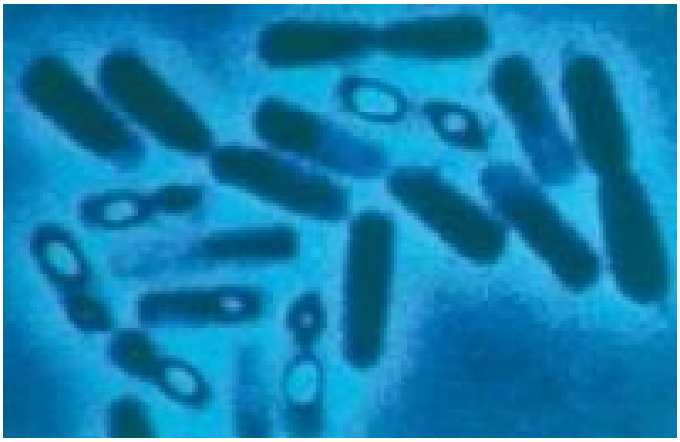


Fig. 7. *Bacillus thuringiensis*

There are several subspecies with a diverse spectrum of activity; for example, *B. kurstaki* attacks Lepidoptera; *B. israelensis* the aquatic Diptera; *B. tenebrionis* Coleoptera etc. The toxins produced by bacteria lyse the midgut cells, allowing it to penetrate the hemocoel and replicate. The four types of toxins include α–exotoxin, β-exotoxin, γ-exotoxin, and δ-endotoxin. The α–exotoxin is toxic to vertebrates and is produced by the subspecies *B. thuringiensis* and *B. aizawai*. It is effective against a broad range of insects including Lepidoptera, Diptera and Coleoptera. The β-exotoxin is a specific inhibitor of DNA-dependant RNA polymerase, thus interfering with RNA transcription and mitosis during molting and metamorphosis. The δ-endotoxin has been used for biocontrol purposes and is produced by Bt. During sporulation, Bt forms crystalline parasporal inclusion bodies which contain δ-endotoxin. After uptake by feeding, parasporal bodies dissolve in insect gut and the toxin is liberated. It then docks into epithelial cells and causes them to swell and burst which leads to death of the insect. Due to its highly insect specific mode of action, δ-endotoxin is not toxic to other living organisms. Bt has found to be very effective against Lepidoptera, Coleoptera and Diptera. Neema (2007) conducted bioassay studies with Bt and found effective against pumpkin caterpillar. Pathogenicity of Bt was studied and proved by Jyothi (2008) on lepidopteran caterpillar, *Spodoptera litura*. In the bioassay conducted by Sivaji (2010), it was found that Bt was very effective in controlling Dipteran insect *Drosophila melanogaster*. He selected four different isolates of Bt for bioassay study and a standard strain 4Q1 was used for standardizing the toxin dosage and comparing with toxicity of native isolates (Table 1).

Table 1. Mortality of Drosophila larvae at different spore concentrations of 4Q1

Sl. No.	Concentration (x 10^8 spores per ml)	Insect mortality (%)
1	1.1	6.7
2	3.3	24.4
3	5.5	45.6
4	8.8	73.4
5	11.0	88.0
6	13.2	100.0
7	16.5	100.0

Both liquid and granular formulations of Bt are available in the market as shown below. (Fig. 8)

Thuricide

Fig 8a. Bt liquid formulation

***Bacillus thuringiensis* 0.2% granule**

Fig. 8b. Bt granular formulation

Photorhabdus luminescens

Photorhabdus luminescens, a bacterium produces a family of insecticidal toxins that infects and kills insects with the help of a tiny worm or nematode. The toxins are active against a wide range of insects and are at least as potent as the insect-killing poisons produced by Bt. In nature, *Photorhabdus* bacteria live inside the guts of nematodes that invade insects. Once inside an insect host, the bacteria are released from the nematode and kill the insect. Moreover, the insect corpses left behind glow in the dark as the microbe produces luminescent proteins in addition to potent insecticides. The greatest potential application lies in transferring the toxin-producing genes from the bacteria to crop plants.

Fungi

Certain insecticides of commercial importance have been isolated from fungi. Destruxins, Bassianolide, and isarolides are some among these.

Destruxins

The first systematic study of toxin production by fungal entomopathogens *in vitro* was conducted on *Metarhizium anisopliae* and led to the discovery of destruxins A and B (Strasser *et al.*, 2000). Early experiment with destruxin A and B injected into *Bombyx Mori* fifth instars caused larval paralysis. Destruxin causes depolarization of muscle membranes, inhibition of ATPase, and inhibit acidification of cellular compartments.

Bassianolide

It has been isolated as the toxic principle from the mycelia of two entomopathogenic fungi *Beauveria bassiana* and *Verticillium lecanii*. Bassianolide was lethal to silkworm larvae (Suzuki *et al.*, 1977).

Isarolides

Isarins B, C and D were isolated from the fungus *Isaria felina*. These compounds were found effective against bright orange sponge *Jaspis sp* (Dumas *et al.*, 1994).

Microbial fungicides

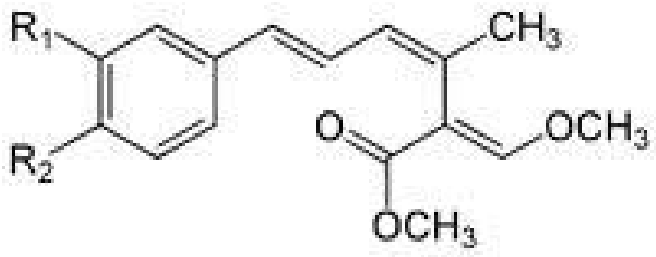
There are natural products and analogues from the cultures of actinomycetes and fungi which can be used as fungicides. The search for novel bio-control agents suitable for crop protection led to the development of useful antifungal natural products and analogues. Among these, the most important ones are strobilurins, blasticidin, kasugamycin, and validamycin.

Strobilurins

Strobilurins are the new generation fungicides available in the present market of pesticides. Anke *et al.* (1977) isolated strobilurin A and B from the wild mushroom *Strobilurus tenacellus* (Fig.9).

Fig. 9. *Strobilurus tenacellus*

The antifungal activity of strobilurin B *in vitro* and in the greenhouse against plant pathogens like *Venturia inaequalis*, *Cercospora arachidicola*, *Plasmopara viticola* and *Phytophthora infestans* was excellent. Strobilurins are found to be very effective against both higher and lower fungi. The structure of strobilurin A and B is shown below (Fig. 10).



Strobilurin A – R_1 = H, R_2= H
Strobilurin B – R_1 = OCH_3, R_2 = Cl

Fig. 10. Structure of strobilurin A and B

The strobilurins strongly inhibit mitochondrial respiration. The substructure responsible for the biological activity is beta – MAE (beta- methoxy acrylic ester). In field tests, the natural strobilurins were a failure, due to their inherent photoinstability. The half-life of strobilurin A in simulated sunlight was only 12 sec. The challenge to design photostable analogues of strobilurins with equal or even improved antifungal activity led to the development of azoxystrobin, trifloxystrobin, pyraclostrobin, kresoxim-methyl, picoxystrobin and fluoxastrobin.

Following are the commercial products available of different strobilurin fungicides.

Azoxystrobin- Quadris, Abound, Amistar, and Heritage
Trifloxystrobin - Flint, Stratego, Compass
Pyraclostrobin - Insignia, Cabrio, Headline
Kresoxim-methyl - Linkoon, Sovran, Cygnus
Picoxystrobin- Acanto
Fluoxastrobin-Disarm, Evito

The biological mode of action of strobilurins mainly involves translaminar activity. These exhibit *translaminar movement* (which means "across the lamina", or leaf blade). When these fungicides are applied, most of the active ingredient is initially held on or within the waxy cuticle of plant surfaces (for example, see Fig. 11). Some of the active ingredient "leaks" into the underlying plant cells. For those fungicides with an affinity for the waxy cuticle (such as trifloxystrobin and kresoxim methyl), active ingredient that "leaks" all the way through the lamina quickly rebinds to the cuticle on the far side of the leaf blade. Thus, the fungicide can be found on both leaf surfaces even if only one leaf surface was treated. Translaminar movement can take one to several days to be fully effective.

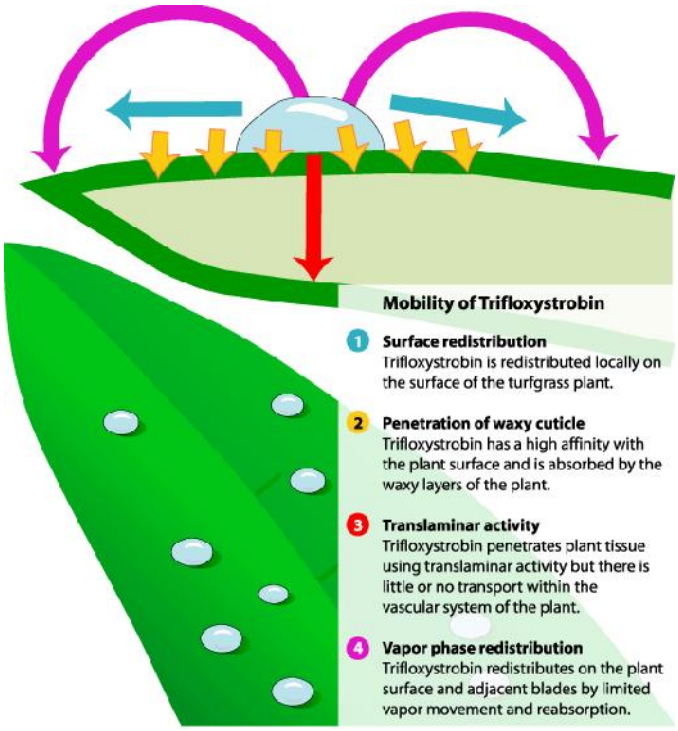


Fig. 11. Mobility of Trifloxystrobin

The fungicide azoxystrobin moves translaminarly as well as *systemically* (in the plant's vascular system, or "plumbing"). The fungicides kresoxim methyl and trifloxystrobin move translaminarly but not systemically. These latter fungicides, however, appear to move as a gas in the layer of still air adjacent to the leaf surface called the *boundary layer*. As they

move in the vapor phase, they readily re-bind to the cuticle. Fungicides such as kresoxim methyl and trifloxystrobin--which are not true systemics but which redistribute by these other mechanisms--have been referred to as "mesostemics", "quasi-systemics", or "surface systemics". The important diseases against which the strobilurins are active are shown below (Fig 12).

a. Powdery mildew of grapevine

b. Apple scab

c. Apple powdery mildew

d. Powdery mildew of cucurbits

Fig. 12. Important diseases against which strobilurins are effective

The following table shows different diseases against which these fungicides are effective with their causal pathogen (Table 2).

Table 2. Diseases against which strobilurins are effective

S.No	Crop	Disease	Pathogen	Qty (mg/ml)
1	Apple	Scab	*Venturia inaequalis*	1
2	Apple	Powdery mildew	*Podosphaera leucotricha*	1.25
3	Lettuce	Powdery mildew	*Erysiphae cichoracearum*	1.25
4	Cereals	Powdery mildew	*Erysiphae graminis*	2.5
5	Grape	Powdery mildew	*Uncinula necator*	10
6	Cucurbits	Powdery mildew	*Sphaerotheca fulgina*	100

Many studies were conducted with respect to the efficacy of strobilurin fungicides in controlling diseases. A comparative efficacy of strobilurin fungicides was made against downy mildew disease of pearl millet. Three commercial formulations of strobilurins, viz., azoxystrobin, kresoxim-methyl, and trifloxystrobin were evaluated for their efficacy against pearl millet downy mildew disease caused by *Sclerospora graminicola* (Fig. 13). Among the three fungicides, azoxystrobin proved to be the best by offering disease protection of 66%. Foliar spray alone provided significant increase in disease protection levels of 91, 79, and 59% in treatments of azoxystrobin, kresoxim-methyl, and trifloxystrobin, respectively. Disease curative activity of azoxystrobin was higher compared to trifloxystrobin and kresoxim-methyl (Sudisha *et al.*, 2004).

Blasticidin

It is obtained from the culture filtrate of *Streptomyces griseochromogenes* (Takeuchi *et al.*, 1958). It was discovered in Japan in 1958 to control rice blast *Pyricularia oryzae*, however, due to toxic and phytotoxic side effects, it has lost ground in the market to other performing products like kasugamycin.

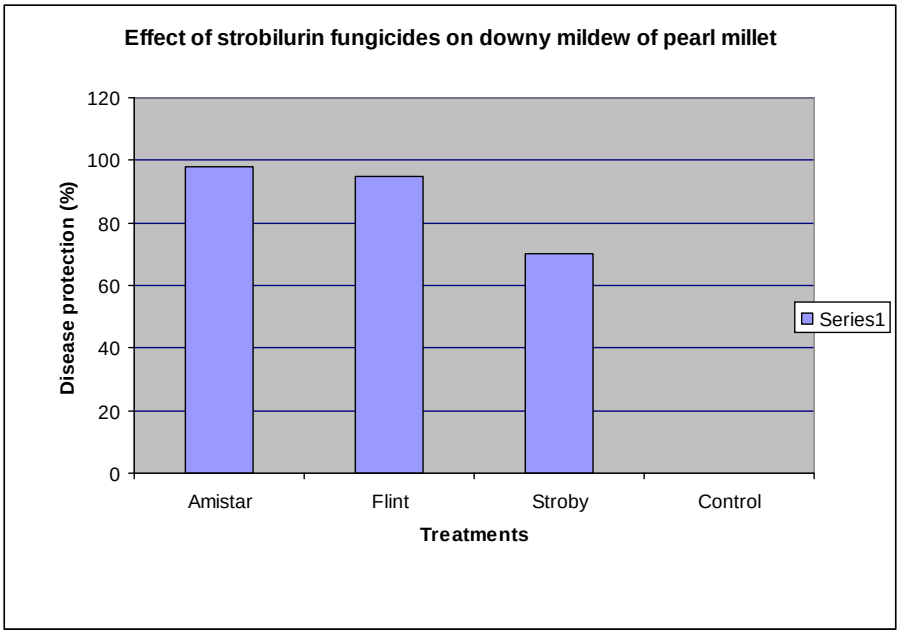


Fig. 13.

Kasugamycin

It is a bactericidal and fungicidal metabolite of *Streptomyces kasugaensis*. It acts as an inhibitor of protein biosynthesis in microorganisms and has excellent toxicological properties with systemic in action. It is used for the control of rice blast *Pyricularia oryzae* and bacterial diseases in several crops.

Validamycin

It is isolated from *Streptomyces hygroscopicus* var. *limoneus* and used for the control of rice sheath blight caused by *Rhizoctonia solani*. Validamycin is converted within the fungal cell to validoxylamine, a strong inhibitor of trehalase. This mode of action gives the metabolite a favorable biological selectivity, because vertebrates do not depend on hydrolysis of the disaccharide trehalose (Kameda *et al.*, 1987). The commercial products available are Validacin, Validamycin, and Sheathmar.

Other microbes which are having fungicidal effect and are now available in the market are:

1. *Trichoderma viride*. It is mainly used against the root rot disease of pulses and oilseeds.
2. *Pseudomonas fluorescens*. The major diseases against which *Pseudomonas* is effective are sheath blight and blast of paddy, wilt disease of red gram, chickpea and banana.
3. *Bacillus subtilis.* Mainly soil borne pathogens like *Macrophomina phaseolina*, *Rhizoctonia solani* and *Fusarium sp*. are controlled by this bacterium.

Bactericides/Antibiotics

Antibiotic is defined as a chemical substance produced by one microorganism which in low concentration can inhibit or even kill other microorganisms. They are specific in their action against plant pathogens like fungi, bacteria and phytoplasmas. Most of the antibiotics are the products of actinomycetes. The antibiotics are broadly grouped into two *viz.*, antibacterial and antifungal.

Antibacterial antibiotics

Streptomycin

It is an antibacterial antibiotic produced by the actinomycete, *Streptomyces griseus*. It is available under different trade names, Agrimycin-100, Agristep, Paushamycin, Plantomycin, Streptocycline etc. Streptomycin is effective against both Gram positive and Gram-negative bacterial plant pathogens, but they do not show any fungitoxicity against true fungi. It is mostly used as foliar spray at concentrations of 100-500 ppm. The important diseases controlled are fire blight of apple and pear (*Erwinia amylovora*), citrus canker (*Xanthomonas citri*), bacterial leaf spot of tomato and pepper (*Xanthomonas vesicatoria*) and soft rot of vegetables (*Erwinia carotovora*). Streptomycin acts as uncoupling agent and inhibit electron transport. It also inhibits protein synthesis.

Tetracyclines

These are broad spectrum antibiotics produced by *Streptomyces* sp. effective against both Gram positive and Gram negative bacteria. Examples are Oxytetracycline, Terramycin, Aureomycin etc. These are very effective against seed-borne diseases and phytoplasmal diseases. In general, tetracycline group of antibiotics are known to inhibit protein synthesis, amino acids and ribosomal proteins.

Antifungal antibiotics

Aureofungin

It is produced in submerged culture of *Streptoverticillium cinnamomum* var. *terricola*. The commercial product available

is Aureofungin-Sol. It causes disruption of fungal cell wall. It also changes the host physiology and makes it unfavourable to the pathogen. The major diseases against which Aureofungin-Sol is effective are citrus gummosis, powdery mildew of apple, apple scab, groundnut early and late leaf spots, downy mildew, powdery mildew and anthracnose of grapevine.

Griseofulvin

It was discovered as a metabolic product of *Penicillium griseofulvum*. It has no activity against bacteria and yeasts. It is commercially available as Fulvicin, Griseofulvin, and Grisovin. It is effective against powdery mildew of beans and roses, downy mildew of cucumber and powdery mildew of chrysanthemum. Griseofulvin inhibits chitin synthesis and protein synthesis in fungi.

Cycloheximide

It is produced by *Streptomyces griseus* and toxic to fungi, yeasts, algae and protozoa. It is commercially available as Actidione, Actidione-PM, and Actispray. Its use is limited because it is extremely phytotoxic. It is effective as foliar spray against rust diseases, powdery mildew of beans, powdery mildew of grapevine and cherry. It inhibits protein and nucleic acid synthesis.

Blasticidin

It is a product of *Streptomyces griseochromogenes.* It is a broadspectrum antibiotic inhibiting fungi, some Gram positive and Gram negative bacteria including *Pseudomonas*. It is used as a protectant fungicide against blast of rice. It is commercially sold as Bla-S. Blasticidin-S inhibits protein synthesis, ribosomal proteins and amino acids.

Nystatin

It is produced by *Streptomyces noursei* and is commercially marketed as Mycostatin and Fungicidin. It is used for the control of downy mildew of cucurbits and anthracnose diseases of banana and beans.

Validamycin

It is obtained from *Streptomyces hygroscopicus* and is sold as Validacin. It controls sheath blight of rice.

Bioherbicides

Bialaphos

Bialaphos produced by *Streptomyces hygroscopicus* is an alanylalanine amide of the biological acid phoshpinothricin and a potent irreversible inhibitor of glutamine synthase, causing ammonia accumulation and inhibition of photophosphorylation in photosynthesis (*Omura et al.*, 1984). It is used post emergence in vines, apples, brassicas, cucurbits and many other crops. Bialaphos is converted to phosphinothricin within the treated plants for herbicidal activity. It is found to be effective against a wide spectrum of monocot and dicot weeds.

Vulgamycin

The herbicidal activity of the metabolite from *Streptomyces chromofuscus* was detected and found to give excellent control of several weeds without damaging cotton, barley and maize. It induces apoptosis in the G2 phase of the cell cycle. It is a post emergent herbicide giving full control of weeds in the paddy field without impairing rice crop (Fushimi *et al.*, 1989). Among the bioherbicides, microbial plant pathogens are applied to target weeds and these are available in the market under trade names Collego, De Vine, Fumonisin B1 etc. Collego is the formulation of *Colletotrichum gloeosporioides* used for the control of Northern joint vetch in rice and soybean. Formulation of *Phytophthora palmivora* (De Vine) is used as a selective mycoherbicide for the control of milk weed in citrus. Bioherbicidal effect of fumonisin B1, a phytotoxic metabolite naturally produced by *Fusarium nygamai* was studied and found to be very effective against the parasitic weeds of the genus *Striga*. The herbicidal property of *Fusarium pallidoroseum* for the control of noxious aquatic weed, *Eichhornia crassipes* was studied by Nazeema *et al.* (1999). Abraham and Abraham (1999) reported that fungi like *Colletotrichum gloeosporioides*, *Alternaria alternata* and *Corynespora cassicola* are potential bioagents for the control of *Mikania micrantha*.

Conclusion

The unscrupulous use of chemical pesticides has led to widespread contamination of water, food and environment. Hence the use of microbial pesticides employing microbes or their by-products has found a potential role in the pesticide market. Microbes contain a virtually untapped reservoir of pesticides that can be used directly or as templates for synthetic pesticides. Several beneficial microorganisms have been found to be the active ingredients of a new generation of microbial pesticides or the basis of many natural products of microbial origin. Numerous factors have increased the interest of the pesticide industry and the pesticide market in this source of natural products as pesticides. The potential bioactivity evident from the overview on secondary metabolites of microbes presented above brings out clearly their potential for use in pest control. Being environment friendly and less toxic to non-target pests, these microbial pesticides emerge as a potential option for pest management and hence they can be exploited as a skeleton for the synthesis of new strategies.

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