REVIEW ARTICLE Agricultural Reviews, Volume 41 Issue 1: 43-50 (March 2020)

Antibiotics- Miracle Drugs as Crop Protectants: A Review

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10.18805/ag.R-1941

ABSTRACT

Antibiotics known as the drugs of wonder seem to have long run since olden times as significant in its application towards agriculture. Antibiotics have its application to control bacterial, fungal, viral and phytoplasmal diseases of high valued tree crops and plants of ornamental in nature. The laws of drug in various countries differ distress over use of antibiotics as crop protectants. The main concern related to use of antibiotics is appropriate and hence more information is needed over the effectiveness and safety use of antibiotics in controlling plant diseases. Development of antibiotic resistance in plant-pathogenic bacteria alarmed problem in the agro pathosystems where it have been used for many years in disease control programs. The efficacy of antibiotics to control plant diseases has been diminished due to the emergence of antibiotic-resistant strains for the particular pathogens. Inspite of negative aspect, the antibiotics seems to continue important tools for the management of the important devastating plant diseases.

Key words: Antibiotics, *Erwinia amylovora*, Human health, Oxytetracycline, Streptomycin, Streptomycin resistance.

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How to cite this article: Valarmathi, P. (2020). Antibiotics- Miracle Drugs as Crop Protectants: A Review. Agricultural Reviews. 41(1): 43-50.

Submitted: 13-09-2019 **Accepted**: 24-02-2020 **Published**: 18-03-2020

The plant diseases are attempted to control by the use of antibiotics by plant pathologists all over the world since the discovery of penicillin. Foremost necessities in the world seem to be the production of food for billions of people. Such food production is enhanced by the inclusion of pesticides; but its use generates the possibility of environmental pollution. Due to application of agricultural antibiotics at very low concentrations, the quantity used in a unit area is far less than of other conventional pesticide chemicals. The term antibiotics used to refer secondary metabolites produced by microorganism resulting in inhibition over the growth of another microorganism. Secondary metabolites are those compounds which are not essential for the growth of the microorganism and not involved in primary metabolic processes like formation of cell wall and pathways of energy production. The use of the antibiotics in the management of plant diseases, with particular references to the disease caused by bacteria, mycoplasma and ricketsia is well demonstrated (Mondal, 2011). The effective mode of action bound towards control of the causal agents without any harmful effect for the infected host. Several antibiotics and other organic substances move systemically in plants and studies in this direction have led to the application of some antibiotics in the control of certain bacterial and fungal pathogens for which no other effective remedy is known. Due to its high specificity against plant pathogens, with relatively low phytotoxicity, absorption by the foliage with systemic translocation and activity at low concentrations, antibiotics needs special attention for consideration. During the past five decades numerous of the known and new antibiotics have been tested for use in plant disease control. In recent years, agricultural antibiotics have gained a tremendous amount of attention from the media. In determining how much antibiotic use is too much, we must turn to the things we do not know. From the proportion of antibiotics by weight used in agriculture as opposed to human medicine, it does not follow that the majority of selective pressure on human pathogens, let alone the majority of human health impact of antibiotic resistance, results from agricultural uses. To establish such a causal mechanism requires quantifying the relationship between quantity of antibiotics used, selection exerted and human health impact. We also have limited knowledge of the consumption of antibiotics in different animal species and similarly limited surveillance programs to monitor and trace the emergence of resistance in animals. The greatest value of reducing agricultural antibiotic use now may be in maintaining a status quo that, while far from ideal, is greatly preferable to the alternative. This article mainly emphasis over the sources and mode of action of antibiotics, role of antibiotics in plant disease control, development of resistance pathogens against antibiotics and concern of its use on human health.

Discovery of antibiotics to exploit in Agriculture

The application of antibiotics for medical purpose started in the year 1928 when Alexander Fleming from The United Kingdom discovered the miracle drug penicillin antibiotics. Since the antibiotic penicillin show excellent effect on killing a few bacteria in the human body, people started to search dynamically for antibiotics with new mode of action for other purposes. With immediate effect discovery of other antibiotics like chloramphenicol, chlorotetracycline and streptomycin fetches importance. Selman Waksman in 1941

first used the word antibiotic to describe any small molecule produced by a microbe that antagonizes the growth of other microbes. From the year 1945-1955 the development of penicillin, which is produced by a fungus, along with streptomycin, chloramphenicol and tetracycline, which are produced by soil bacteria, made revolution in the era of antibiotics. During the year 1940, based on the application of antibiotics, researchers started to study its impact other than the medical field. By the year 1944, Brown and Boyle had practical application of penicillin to effectively control the crown gall disease caused by several bacteria. Further in 1946, Upjohn from United States found that the antibiotic cycloheximide possessed high anti-fungal activity against fungal infection on plants. Followed by these antibiotics, streptomycin and chloramphenicol showed effective impact over control of bacterial and fungal diseases which made to realize even antibiotics can be used to treat plant diseases (Clardy *et al*. 2009).

Although there are about 900 kind of antibiotic where the chemical structures have been studied, only more than 10 types of antibiotics possessed practical application towards agriculture. The reason may be due to the instable nature of antibiotic, high cost, high toxicity on warm-blooded animal and toxic effects on plants. Japan had made significant progress in the era of antibiotics for its use in agriculture. The antibiotic blasticidin was first discovered in 1955 and later by 1963 kasugamycin had successfully been developed by Hokko chemical industry in Japan. These two antibiotics had been used in large scale for the control of blast disease of rice caused by *Pyricularia grisea.* In Japan, Blasticidin (Bla-S) and Kasugamycin (Kasumin) are two of the antibiotics which are widely used to control blast disease of rice. By the year 1972, Takeda Pharmaceutical Company developed validamycin which can be used to control sheath blight (*Rhizoctonia solani*) disease of rice. By the end of 1970, the same pharmaceutical company developed midiomycin for its effective control of powdery mildew disease for important crops successfully. China also played a major role in the production of antibiotics namely blasticidin, kasugamycin and polyoxin as well as Jinggangmycin. In 1982, the plant protection institute of Jilin Academy of Agricultural Sciences had further successfully developed gongzhulingmycin, mainly for the control of sorghum covered smut, *Tilletia foetida*, stinking bunt and *Ustilago crameri.* Thus the antibiotics which are produced in huge quantity with its wide application for agricultural purposes had been established significantly (https://www.chemicalbook.com/ProductCatalog_EN/141624.html).

Nature and use of antibiotics in plants

The number of antibiotics used in plant agriculture seems relatively less over its applications in human and veterinary medicine, where more than 30 different drugs from at least 14 distinct classes are used alone in the USA. Agricultural antibiotics are usually formulated as powders with 17% to 20% active ingredient. The powder formulation are dissolved or suspended in water to get concentrations of 50 to 300 ppm with its suitable application as a fine mist to the target plant parts. Due to its expensive in nature, antibiotics are used primarily on high-valued fruit and vegetable crops and ornamental plants where their cost of use can be regained. Of the myriad antibiotics application in agriculture, streptomycin and oxytetracycline, two of them are used effectively for control of plant diseases (Fig 1) (McManus and Stockwell, 2001).

Streptomycin

Streptomycin is an aminoglycoside antibiotic formulated either as streptomycin sulfate or streptomycin nitrate. The different trade names include Agrept, Agri-mycin, Agri-strep, Fructocin and Plantomycin. The primary mechanism of action of streptomycin is binding irreversibly to bacterial ribosomes and wherein inhibition of protein synthesis. In the U.S. application of streptomycin is registered for its use over 12 plant species, but the primary uses was on apple, pear and related ornamental trees to control of fire blight caused by *Erwinia amylovora*. Its negligible application includes flower crops, seed treatment and certain vegetable seedlings in the greenhouse and/or field. Streptomycin causes phytotoxic effect with high concentration to plants and hence applied to the surface of plants without injection (McManus and Stockwell, 2001).

Oxytetracycline

Oxytetracycline belongs to member of the tetracycline antibiotics formulated either as an oxytetracycline calcium complex or oxytetracycline hydrochloride. It is marketed under the trade names Biostat, Glomycin, Mycoshield, Terrafungine and Terramycin. Tetracyclines inhibit protein synthesis by binding reversibly to bacterial ribosomes. This antibiotic is used primarily on peach, nectarine and pear. Oxytetracycline is also used as an emergency basis on apple in specific regions where streptomycin-resistant strains of *E. amylovora* have been observed. Tetracycline derivatives are the only antibiotics registered for internal use in plants. A negligible amount of oxytetracycline is injected into the trunks of palm and elm trees to mitigate symptoms of lethal yellows phytolasmal diseases. Oxytetracycline significantly controlled fire blight on apple using trunk injection of the antibiotics (Acimovic *et al*. 2013).

Sources and mode of action of antibiotics

The agricultural antibiotics have various kinds of mechanism of action which can be generally divided into three categories as i) Suppression of energy production, ii) Interfering with the biosynthesis and iii) Destruction of cell structure (Stockwell and Duffy, 2012). The mode of action of the antibiotics varies depending on the site of action which in turn determines their specificity towards a given target host. The sensitivity of the antibiotics varies with their structure and mode of action. Streptomycin, oxytetracycline and chlortetracycline results in the inhibition of the biological oxidation function, interfering with the respiration of pathogens which leads to deficiency to sustain its life. Cycloheximide and blasticidin interferes with the binding of

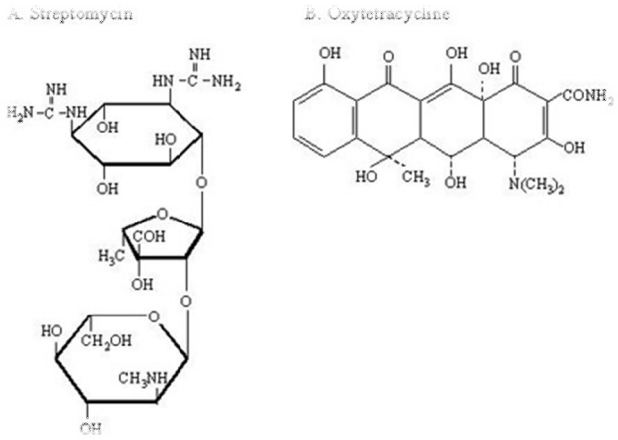


Fig 1: Chemical structure of (A) Streptomycin and (B) Oxytetracycline (McManus and Stockwell, 2001).

RNA to amino acids which results in inhibition of protein synthesis. Polyoxin inhibit the activity of the uridine phosphate-N-acetylglucosamine transferase resulting the glucosamine unable to enter the cell wall for chitin biosynthesis. Jinggangmycin causes abnormal mycelium branching. Occasionally the mixtures of antibiotics employed to manage in reducing the diseases or delay resulting in emergence of resistance development against a particular antibiotic by the causal agent.

The beta (β)-lactam antibiotics constitute one of the oldest classes of antibacterial agents. β-lactam antibiotics are a broad class of antibiotics. They consist of all antibiotic agents that contain a β-lactam ring in their molecular structure. This includes penicillin derivatives (penams), cephalosporins (cephems), monobactams and carbapenems (Holten and Onusko, 2000). They act as an irreversible inhibitor of the enzyme transpeptidase, an enzyme used by bacteria to make their cell walls. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by transpeptidase knows as penicillin binding proteins (PBPs). PBPs bind to the D-Ala-D-Ala at the end of muropeptides, the peptidoglycan precursors to crosslink the peptidoglycan. β-lactam antibiotics mimic the site and competitively inhibit PBP crosslinking of peptidoglycan (Vollmer *et al.* 2008).

The aminopenicillins are a group of antibiotics in the penicillin family. Like other penicillin's this group is characterised by its four-membrane, nitrogen-containing β-lactam ring at the core of its structure, which is crucial to antibacterial activity of this group of antibiotics. Ampicillin and amoxicillin and clavulanic acid are examples of two aminopenicillins. Amoxicillin is sometimes combined with clavulanic acid, a β-lactamase inhibitor. This combination increases the spectrum of action against microorganisms and aids in overcoming bacterial antibiotic resistance mediated through β-lactamase production. Clavulanic acid is a suicide inhibitor of bacterial β-lactamase enzyme from *Streptomyces clavuligerus* (Doran *et al.* 1990). When administered alone, it only has weak antibacterial activity against most organisms, but when given in combination with β-lactam antibiotics prevents antimicrobial inactivation by microbial lactamase. It does this by binding and irreversibly inhibiting the β-lactamase, this results in a restoration of the antimicrobial activity of β-lactam antibiotics against lactamase-secreting-resistant bacteria. Moreover by inactivating β-lactamase, the accompanying penicillin may be made more potent (Bush, 1989).

Tetracycline antibiotics were isolated from various species of *Streptomyces* in the late 1940s and early 1950s. Since the 1950s many semisynthetic structural modifications have been made on the tetracycline molecule to yield other tetracycline molecules with different pharmacokinetic properties and antimicrobial activities. Tetracycline encapsulates the related compounds oxy- and chlortetracycline, doxycycline and minocycline. Oxytetracycline and chlortetracycline were discovered in 1948, tetracycline in 1953 and doxycycline in 1967 and minocycline in 1972 (Nelson and Levy, 2011). Of these chlortetracycline and oxytetracycline are natural products while the others are semisynthetic. Tetracyclines possess antibacterial activity by binding to the 30S ribosomal subunit of a susceptible organism. Following ribosomal binding the tetracycline interferes with the binding of aminoacyl-tRNA to the messenger RNA molecule/ribosome complex; this disrupts the bacterial protein synthesis (Chopra and Roberts, 2001). Tetracycline binds with the 70S ribosomes found in mitochondria and can also inhibit protein synthesis in mitochondria (Eliopoulos and Roberts, 2003). Tetracyclines are bacteriostatic and illustrate great affectivity against multiplying bacteria. Tetracycline is a broad-spectrum antimicrobial and used for a wide variety of Gram-positive and Gram-negative bacterial infections.

Formulations of antibiotics

Among the different formulations available in the market, eight antibiotics are considered to have importance. These include 1. Agrimycin 100 (15 per cent streptomycin sulphate and 1.5 per cent terramycin), 2. Agromycin 500 (1.755 per cent streptomycin sulphate and 0.176 per cent terramycin and 42.4 per cent metallic copper), 3. Agristrep (37 per cent streptomycin sulphate), 4. Phytomycin (20 per cent streptomycin nitrate in liquid form), 5. Accostreptoycin (45 per cent streptomycin sulphate), 6. Actidione (2.26 per cent cycloheximide), 7. Actidione R2 (5 per cent cycloheximide and 75 per cent pentachloronitrobenzene) and 8. Actispray (7.7 per cent cycloheximide in tablet form). Most of the above preparations are used to control plant diseases in the United States and a few in Europe (https://www.chemicalbook.com/ProductCatalog_EN/141624.html).

Antibiotics for crop disease control

The widely used known antibiotics available are from the actinomycetes and some are from fungi and bacteria. Streptomycin used to control citrus canker, hollow blight of french bean and fire blight of apples and pears. It is also used as a dip for potato seeds against various bacterial rots of tubers and as a seed disinfectant in bacterial pathogens

of beans, cotton, crucifers, cereals, etc. It is also effective against halo blight, citrus canker, seedling blight, leaf spot and black arm disease of cotton. Other targeted pathogens and their hosts include *Pectobacterium spp*. causing soft rot diseases of cut flowers and potato seed pieces; *Pseudomonas cichorii*, which causes bacterial blight of celery; various pathovars of *Pseudomonas syringae*, causing fruit-spotting or blossom-blast symptoms on apple, pear and related landscape trees; *Xanthomonas campestris pv. vesicatoria* causing bacterial spot of pepper and tomato and *Agrobacterium tumefaciens* causing crown gall of rose (McManus *et al*. 2002). Sources of antibiotics and modes of action are given in the Table 1.

Cycloheximide is known as actidion, actispray, actidione PM, actidione RZ and use to control mildew of beans, covered smut of oats, brown rot of peach. Griseofulvin is produced by *Penicillium griseofulvin*, *P. patulum, P.digricans* and *P. jancyewski.* It is found to be effective against downy mildew of cucurbits, powdery mildew of rose, powdery mildew of beans, early blight of tomato and brown rot of apple. The dosage of foliar spray varies from 100-1000 ppm. Blasticidins is produced by *Streptomyces griseochromogenes* and active against both bacteria and fungi with selective in its activity. Aureofungin, possess high activity against a large number of phytopathogens and its absorption and translation in living plants. Spraying of this antibiotics control downy mildew, powdery mildew and anthrancnose of grapes. Seed treatment of rice controls *Bipolaris oryzae*, *Pyricularia oryzae* of rice, mango *Diplodia*, tomato *Alternaria* rot, peach *Sclerotinia* rot, cucurbits *Pythium* rot. Tetracyclines are produced by a number of species of streptomyces and effective against crown gall and fire blight of apples. This antibiotic can also been employed to control phytoplasma. Antimycin is effective against early blight of tomato, seedling blight of oat and rice blast (http://agropedia.iitk.ac.in/category/tags-agroblog/antibiotics/2012).

Thiolutin is water soluble antibiotic produced by *Streptomyces albus* and used for controlling potato late blight and broccoli downy mildew in limited scale. Mystatin, an antifungus antibiotic produced by *Streptomyces noursei* and effective against anthracnose of beans and downy mildew of cucumber. Bulbiforrmin is an antifungal antibiotic

Table 1: Sources of antibiotics and modes of action (Obtained from Mondal, 2011).

Chemical name	Group	Sources	Mode of action	Effective against
Penicillins	β- lactams	*Penicillium sp*	Inhibition of synthesis of mureins. Breakage of murein cross linkage	Prokaryotes
Cephalosporins	β- lactams	*Cephalosporium spp.*	Inhibition of synthesis of mureins. Breakage of murein cross linkage	Prokaryotes
Erythromycin	Macrolides	*Streptomyces erythraeus*	Inhibition of translocation by binding to the 50S ribosome	Prokaryotes
Carbomycin	Macrolides	*S. halstedii*	-do-	Prokaryotes
Streptomycin	Aminoglycosides	*S.griseus*	Cause aberrant inhibition complex by binding to protein S12 of 30S ribosome	Prokaryotes
Neomycin	Aminoglycosides	*S.fradiae*	Prevention of translation by misreading of codon on mRNA and affect 30S ribosomal subunit	Prokaryotes
Kanamycin	Aminoglycosides	*S. kanamyceticus*	Prevention of translation by misreading of codon	Prokaryotes
Rifampicin/ Rifampin	Rifamycins	*Amycolatopsis rifamycinica*	Prevent transcription to RNA by inhibiting DNA dependent RNA polymerase and translation to proteins	Prokaryotes
Chlorotetracycline	Tetracyclines	*S. aureofaciens*	Inhibition in binding of aminoacyl t-RNA to A site of 30 S ribosomes	Prokaryotes
Oxytetracycline	Tetracyclines	*S.riomosus*	Inhibition in binding of aminoacyl t-RNA to A site of 30 S ribosomes	Prokaryotes
Polymixin G	Polypeptides	*Bacillus polymyxa*	Destruction of cytoplasmic membrane	Prokaryotes
Bacitracin	Polypeptides	*B.subtilis*	Inhibition of murein biosynthesis	Prokaryotes
Chloramphenicol	Polyenes	*S. venezuelae*	Affect translation step of 70S ribosome function. Inhibition of peptidyl transferase activity of 50S ribosome.	Prokaryotes
Aureofungin	Polyenes	*Streptoverticillium cinnamoneus var terricola*	Inactivation of membrane containing sterols by making pore through which small molecules Kions to pass	Eukaryotes
Nystatin	Polyenes	*S. nouresii*	Inactivation of membrane containing sterols by making pore through which small molecules Kions to pass	Eukaryotes

produced by *Bacillus subtilis* and controls wilt of pigeon pea. Validamycin A, commercially used agricultural antibiotic produced by *Strepomyces hygroscopicus* with aminocyclitol compound used as a control agent for sheath blight of rice and damping off of cucumbers (http://agropedia.iitk.ac.in/category/tags-agroblog/antibiotics/2012).

In India, streptochlor, a mixture of streptomycin and chloromycetin, has been tried to control bacterial blight of rice caused by *Xanthomonas oryzae pv. oryzae*. The use of antibiotics to control post harvest diseases emerges to be significant in India. The antibiotics, aureofungin produced by *Streptomyces cinnamomens* var. *terricola,* Cycloheximide (Actidione) produced by *S. griseus* and Griseofulvin produced *by Penicillium griseofulvum* have systemic action against fungal diseases of plants. Citrus gummosis (*Phytophthora citrophthora*) can be controlled by the application of Aureofungin at 20µg/ml. In order to control fruit rots of mango and tomato, fruits dip in 100 ppm of Aureofungin solution has been recommended. It is also used to control seed-borne infection and seedlings blight of rice and in the control of mildews and anthracnose of grapevine (Rangaswami and Mahadevan, 2014).

Streptocycline, antibiotic preparation containing 9 parts of streptomycin and one part of tetracycline most useful antibiotic mixture available in India has been reported to be effective against 17 different plant pathogenic strains of *Xanthomonas* which includes and two of *Pseudomonas* under *in-vitro* conditions. This preparation with concentration of 0.3 % has been recommended to control different foliar bacterial diseases and at higher concentrations to eliminate infections with seed-borne nature. There are also several antibiotics which are reported to be effective against plant pathogens under *in-vitro* conditions, yet to be developed for its field application (Rangaswami and Mahadevan 2014). Streptocycline was used effectively to control bacterial blight of rice (*Xanthomonas oryzae pv. oryzae*), Bacterial blight of pomegranate (*X. axonopodis pv punicae*), Black spot of mango (*X. citri pv. mangiferae indicae*) and Bacterial blight of cotton (*X. axonopodis pv. malvacearum*) (Mondal, 2011).

Hindustan Antibiotics Limited (HAL), based in Pimpri, India, is the first public sector drug manufacturing companies set up by the Government of India. It was the first company in India to launch a recombinant DNA product, rHU-Erythropoietin (Hemax) in 1993. Aureofungin (anti-fungal used in preservation of the fruits and vegetables) and Streptocycline (antibacterial for effective control of diseases in plants) are the antibiotics used in agriculture.

Development of antibiotic resistance by plant pathogenic bacteria

The development of antibiotic resistance occurs when the target bacteria changes its site of action through reduction or elimination of the effectiveness of chemicals specific for its use to control. The bacterium starts to survive and continue to multiply causing resistance against the target antibiotics. Even though the amount of antibiotics used on plants is small compared to medical and veterinary, the emergence of resistant plant pathogens against streptomycin further complicate the control of bacterial diseases of plants. Antibiotic resistance in plant-pathogenic bacteria emerges to be a problem in agro pathosystems since the use of these antibiotics started to initiate resistant strains. Observation for antibiotic-resistant plant pathogens has been less frequent and usually undertaken when the used antibiotic failed to control the disease. However, the development of antibiotic resistance in targeted plant pathogenic bacteria is a real concern for the long-term and sustainable use of antibiotics over crop disease management (Stockwell and Duffy, 2012). Most of the surveys showed that development of streptomycin-resistant strains of *Erwinia amylovora* in apple and pear, *Pseudomonas cichorii* in celery, *Pseudomonas syringae* in apple, pear and ornamentals and *Xanthomonas campestris* in tomato and pepper (Jones and Schnabel, 2000).

In *Erwinia amylovora*, two distinct types of streptomycin resistance have been described elaborately by Chiou and Jones, 1995 a, b. The development of resistance includes a mutation in the chromosomal gene rpsL which prevents streptomycin from binding to its ribosomal target and inactivation of streptomycin by an enzyme encoded by strA and strB (Jones and Schnabel 2000). The level of resistance conferred to the bacterium resulted from the chromosomal mutation renders the cell insensitive to the antibiotic, inspite of production of the enzyme which inactivates streptomycin. However the level of resistance conferred by the enzyme is still about five times greater than the concentration of use of streptomycin in field. The genetic basis for resistance has been examined, antibiotic resistance in plant pathogens has most often evolved through the acquisition of a resistance determinant through horizontal gene transfer (Sundin and Wang, 2018). Streptomycin resistance in most strains of *E. amylovora* has been attributed to chromosomal mutation because the majority of resistant isolates obtained from different locations does not harbor strA-strB. Molecular studies show that the chromosomal mechanism of resistance has been arisen independently over many times in the pathogen (Sundin and Wang, 2018). For example, the strAB streptomycin-resistance genes occur in *Erwinia amylovora, Pseudomonas syringae* and *Xanthomonas campestris* and these genes have presumably been acquired from nonpathogenic epiphytic bacteria colocated on plant hosts under antibiotic selection (Sundin and Wang, 2018). Kasugamycin (Ks) found to be substitute for the use of streptomycin and effective to control fire blight of apple. On the other hand, there remains a concern that Ks application in orchards select Ks resistance that could be linked with other resistance genes which are active against antibiotics used in human medicine. To observe for antibiotic resistance, the effect of the use of Ks (Kasumin 2L) in orchard systems on the level of resistance to Ks and five other antibiotics (streptomycin, ampicillin, gentamicin, cefotaxime and tetracycline) were assessed. Although the bacterial population sizes were larger on Ks-amended medium from soil compared to leaf samples, there were no differences in

populations from Ks treated vs. non-treated sites. Similarly, there was no difference in levels of resistance to the tested five antibiotics between Ks-treated and non-treated places (Gebben *et al.* 2016).

The investigation of the impacts of increasing streptomycin and kasugamycin applications on bacterial epiphyte community composition and antibiotic resistance in the phyllosphere apple plantings in 2014 and 2015 (Tancos and Cox, 2017). The majority of isolated epiphytic bacteria were identified as *Pantoea agglomerans* and fluorescent *Pseudomonas spp.,* whereas *Erwinia amylovora* was rarely found. Increased application of kasugamycin reduced the overall number and percentage of streptomycin-resistant epiphytes in the phyllosphere, which has important implications regarding the use of kasugamycin in orchards where streptomycin resistance is a concern. Thus the influence of antibiotic applications on the community structure of plant-associated bacteria and their antibiotic resistance profile is considered to be minor and short-lived (McManus, 2014). The duration of effect of antibiotics over the plant tissues found to be transitory. Antibiotics inhibit the growth of antibiotic-sensitive bacteria on flower and leaf surfaces for less than five days over its application (Stockwell *et al*. 2008). The degradation of antibiotics resulted due to its exposure to sunlight and rainfall do reduce its concentrations over the plant tissues (Christiano *et al.* 2010). Soil particles do absorb and inactivate the tetracyclines antibiotics (Subbiah *et al.* 2011).

Risk of human health for over use of antibiotics

The classes of drugs that are more widely used in agriculture at the global level, which are of growing scientific concern with regards to their potential adverse effects and risk management steps, include the tetracyclines, aminoglycosides, β-lactams, lincosamides,macrolides, pleuromutilins and sulphonamides. The indiscriminate and abusive use of antibiotics can result in higher concentrations of antibiotics in the environment, which can be termed as antibiotic pollution. The significance of antibiotics use in agriculture resulted in the emergence and spread of clinical antibiotic resistance is real concern of current discussion and controversy, with one prominent statement that 'farming practices are largely to blame for the rise of antibiotic-resistant strains' (Kennedy, 2013). If so ever the use of antibiotics in agriculture contributes for the spread of resistance, then immediate steps to be taken in order to limit its source to human as well as animal. However, the magnitude of the threat arising from the agricultural issues is less concern for multiple reasons (Chang *et al.* 2014). The greatest concern who oppose to use antibiotic on plants is that spraying of antibiotics in the open environment and over physically large expanses of land might increase the frequency of antibiotic resistance genes; rather than the presence of streptomycin and tetracycline resistance genes but also any other resistance genes that might be carried on the same plasmid, thereby increasing the risk of these genes to find their entry to cause resistance for medically important bacteria (Kennedy, 2013). This would require the transfer of resistance genes from plant- and soil-borne bacteria to bacteria which exist in humans. The transfer would have to occur when the sprayed antibiotics in the orchard came in contact with the human skin or gut, in an environment sufficiently favorable to both the gene donor and the recipient. In addition to transfer of resistance genes from environmental bacteria to "human" bacteria, the genes would have to be functional in their new bacterial host in order to inflict devastation. The streptomycin and tetracycline resistance genes were often carried on the same large plasmid in orchard bacteria, but when the plasmid was transferred into *E. coli*, the new host was resistant only to tetracycline and not to streptomycin or other antibiotics (Schnabel and Jones, 1999). At this point, streptomycin and oxytetracycline have been used on crop plants for the past 45 years and 25 years, respectively, without any reports of adverse effects on humans. The efficacy of these silver bullets for control of plant diseases has been diminished in some regions due to the emergence of antibiotic-resistant strains of pathogens. However, until effective and economic alternatives become available, antibiotics will remain important tools for the management of some of the most devastating plant diseases (Stockwell and Duffy, 2012).

Antibiotic use for essentially non-medical or non-therapeutic purposes in agricultural settings that are at subtherapeutic levels over an extended period is observed as a major route for the advent of antibiotic resistance and antibiotic-resistant bacteria and resistance genes have been reported to be transferred to humans (Duro and Cook, 2014). Irrational or non-prudent use of antibiotics in food-producing animals have resulted in antibiotic residues in animal-derived products. Therefore, antimicrobial stewardship is equally implemented to ensure prudent antibiotic use in agriculture, in order to conserve and maintain the effectiveness of available antibiotics, as well as curb the problem of antibiotic resistance and residues in food products derived from animal (Moudgil *et al*. 2017). The National Farmed Animal Health and Welfare Council pointed out that the implementation of antimicrobial stewardship in agriculture can be approached from the following perspectives, including clinical microbiology, infection control (biosecurity), regulations, surveillance on antibiotic use and resistance, animal management, husbandry and alternatives to antibiotics. A coordinated network of actions from the veterinarians, livestock producers, pharmacists, veterinary pharmaceutical industries and regulatory authorities are relevant to enforce prudent antibiotic use. Following the Global Action Plan on antimicrobial resistance and the Global principles for the containment of antibiotic resistance in animals intended for food presented by WHO, nations are expected to implement measures that are in line with the key actions highlighted for the combat of antimicrobial resistance. The Ministry of Health and Family Welfare in India amended the Drugs and Cosmetics regulations, 1945 and set withdrawal limits for drugs used in animal farming and agricultural use. The ministry further emphasized that drug producing companies

should equally imprint the withdrawal periods on the containers of drugs meant for animal consumption; however, if not provided, a withdrawal period of not less than 28 days should be considered (Manyi-Loh *et al.* 2018).

Future scope of antibiotics usage

If usage of antibiotics were withdrawn from plant disease management programs, the production of most crops will remain unaffected since only few bacterial and phytoplasmal diseases are managed with antibiotics. Even important fruit crops such as apple, peach and pear where streptomycin and oxytetracycline are applied, only few hectares of land gets treated. This suggests that alternatives to antibiotics are available and practically feasible to less extent. In fact bacterial disease management in most cropping systems is based on the integration of genetic resistance of the host, sanitation and cultural practices that create an unfavorable environment for multiplication of pathogens. Indeed the application of copper compounds found to be effective in population reduction of some bacterial plant pathogens, although several species have become resistant to copper (Christiano *et al.* 2010) where the most of tree-fruit crops are sensitive to copper injury.

In addition to conducting routine surveillance programs for resistance, many farmers apply combinations of antibiotics or alternate antibiotics to reduce the selection pressure for antibiotic-resistant isolates of the target pathogen. Most of the farmers employed biological control agents along with use of antibiotics in their disease-management programs. Such successful example includes improved control of fire blight over suppressive populations of the biocontrol agent *Pseudomonas fluorescens* strain A506 on apples flowers during early bloom, followed by a single application of an antibiotic where the disease pressure is high (Stockwell *et al*. 2008). This type of 'probiotic-like' approach may further reduce the usage of antibiotics to crops and results in delay of the emergence of antibiotic-resistant pathogens. In the case of fire blight, *E. amylovora* becomes systemic in trees, the complete removal of infected tissues became problematic. Even sanitation efforts get hindered by the introduction of bacterial pathogens on nursery stock (Sundin and Wang, 2018). Hence the application of antibiotics continues to remain significant in the management of certain bacterial diseases of fruits and ornamental trees especially of economic importance.

CONCLUSION

At present, we lack the knowledge of the effect of the microbiome structure of organisms on the potential of plant pathogens to evolve antibiotic resistance. Such knowledge contributes significantly over the development of robust resistance management strategies to ensure the safe and effective, continued use of antibiotics as crop protectants. There is need for better studies which combine the quality surveillance with good data on antibiotic usage in agriculture. Overall, antibiotics have been requisite for crop protection for more than 60 years without any reports of adverse effects on human health or the environment. The cautious use of antibiotics in agriculture contributes to the long-term efficacy of these important tolls for the management of bacterial diseases of plants and mitigates potential undesirable effects on the environment. Research should focus on the impact of oxytetracycline, kasugamycin and combinations of antibiotics over the control of plant diseases and presence of resistance genes in orchard environments. Further the involvement of disease forecasting systems helps to limit the usage of antibiotics as crop protectants. Moreover the farmers are more aware of the presence of resistance management strategies and to reduce the application of antibiotics in efficient crop management programmes.

REFERENCES

Acimovic G.S., Zeng Q., McGhee G.C., Wise J.C. and Sundin G.W. (2013). Control of fire blight (*Erwinia amylovora*) with trunk injection of the maximum seasonally allowed doses of SAR inducers and antibiotics in apple trees. In: Pest and Disease Management on Apple, The American Phytopathological Society, USA. www.apsnet.org/online/feature/antibiotics.

Bush, K. (1989). Characterization of beta-lactamases. Antimicrobial Agents and Chemotherapy. 33(3): 259-263.

Chang Q., Wang W., Yochay G.R., Lipsitch M. and Hanage P.W. (2014). Antibiotics in agriculture and the risk to human health: how worried should we be? Evolutionary Application. doi:10.1111/eva.12185.

Chiou C.S. and Jones A.L. (1995a). Expression and identification of the strA-strBgene pair from streptomycin-resistant. Erwinia amylovora. Gene. 152: 47-51.

Chiou C.S. and Jones A.L. (1995b). Molecular analysis of high-level streptomycin resistance in *Erwinia amylovora*. Phytopathology. 85: 324-328

Chopra, I. and Roberts, M. (2001). Tetracycline antibiotics: mode of action, applications, molecular biology and epidemiology of bacterial resistance. Microbiol. Molecule. Biology Reviews. 65(2): 232-260.

Christiano R.S.C., Reilly C.C., Miller W.P. and Scherm H. (2010). Oxytetracycline dynamics on peach leaves in relation to temperature, sunlight and simulated rain. Plant Dis. 94: 1213-1218.

Clardy J., Fischbach M. and Currie C. (2009). The natural history of antibiotics. Current Biology. 19(11): R437-R441. doi: 10.1016/j.cub.2009.04.001.

Doran, J. L., Leskiw, B. K., Aippersbach, S., Jensen, S. E. (1990). Isolation and characterization of a beta-lactamase-inhibitory protein from *Streptomyces clavuligerus* and cloning and analysis of the corresponding gene. J. Bacteriol. 172(9): 4909-4918.

Duro, L.M. and Cook, K.L. Impact of antibiotics use IJN agriculture. (2014). What are the benefits and risks? Curr. Opin. Microbiol. 19: 37-44.

Eliopoulos, G. M. and Roberts, M. C. (2003). Tetracycline therapy: update. Clinical Infectious Dis. 36(4): 462-467.

Gebben S., McGhee G.C and Sundin G.W. (2016). Effect of kasugamycin application on bacterial resistance to kasugamycin and cross resistance with other antibiotics. In: Biology and Disease Management: Chemical Control. The American

Phytopathological Society, USA. www.apsnet.org/online/feature/antibiotics.

Holten, K. B and Onusko, E. M. (2000). Appropriate prescribing of oral beta-lactam antibiotics. American Family Physician. 62(3): 611-620.

http://agropedia.iitk.ac.in/category/tags-agroblog/antibiotics/2012

https://www.chemicalbook.com/ProductCatalog_EN/141624.html

Jones A.L and Schnabel E.L. (2000). The development of streptomycin -resistant strains of *Erwinia amylovora*. *In:* Fire Blight: the Disease and its Causative Agent *Erwinia amylovora. J Vanneste* (ed.) CAB International. 235-251.

Kennedy D. (2013). Time to deal with antibiotics. Science. 342: 777.

Manyi-Loh, C., Mamphweli, S., Meyer, E. and Okoh, A. (2018). Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. Molecules. 23: 795.

McManus P.S. (2014). Does a drop in the bucket make a splash? Assessing the impact of antibiotic use on plants. Curr. Opin. Microbiol. 19: 76-82.

McManus P.S. and Stockwell V.O. (2001). Antibiotic use for plant disease management in the United States. Plant Health Prog. DOI: 10.1094/PHP-2001-0327-01-RV. http://www.Planthealthprogress.org/Current/reviews/antibiotic/top.htm

McManus P.S., Stockwell V.O., Sundin G.W. and Jones A.L. (2002). Antibiotic use in plant agriculture. Ann. Rev. Phytopathol. 40: 443-65.

Mondal K.K. (2011). Antibiotics and their mode of action. In: Plant Bacteriology. Kalyani Publishers, New Delhi, 190pp.

Moudgil, P. Bedi, J.S., Moudgil, A.D., Gill, J.P.S. and Aulakh, R.S. (2017). Emerging issue of antibiotic resistance from food producing animals in India: Perspective and legal framework. Food Rev. Int. 34(5): 447-462.

Nelson, M. L. and Levy, S. B. (2011). The history of the tetracyclines. Annals of the New York Academy of Sciences. 1241 (1): 17-32.

Rangaswami G. and Mahadevan A. (2014). Principles of Plant disease control. In: Diseases of Crop Plants in India. Prentice Hall of India Publishers, 548pp.

Schnabel E.L. and Jones A.L. (1999). Distribution of tetracycline resistance genes and transposons among phylloplane bacteria in Michigan apple orchards. Appl. Environ. Microbiol. 65: 4898-4907.

Stockwell V.O. and Duffy B. (2012). Use of antibiotics in plant agriculture. In Antibiotic Resistance in Animal and Public Health [G. Moulin and J.F. Acar, (eds)]. Rev. Sci. Tech. Off. Int. Epiz. 31 (1): 199-210.

Stockwell V.O., Temple T.N., Johnson K.B. and Loper J.E. (2008). Integrated control of fire blight with antagonists and oxytetracycline. Acta Horticulture. 793: 383-390.

Subbiah M., Mitchell S.M., Ullman J.L. and Call D.R. (2011). β-lactams and florfenicol antibiotics remain bioactive in soils while ciprofloxacin, neomycin and tetracycline are neutralized. Appl. Environ. Microbiol. 77: 7255-7260.

Sundin G.W. and Wang N. (2018). Antibiotic Resistance in Plant-Pathogenic Bacteria. Ann. Rev. Phytopathol. 56: 161-180.

Tancos K.A. and Cox K.D. (2017). Effects of consecutive Streptomycin and Kasugamycin applications on Epiphytic Bacteria in the apple phyllosphere. Plant Disease. 101: 158-164. http://dx.doi.org/10.1094.

Vollmer, W., Blanot, D. and De Pedro, M. A. (2008). Peptidoglycan structure and architecture. FEMS Microbiol. Reviews. 32(2): 149-167.