Agri Articles
(e-Magazine for Agricultural Articles)
Volume: 03, Issue: 03 (MAY-JUNE, 2023)
Available online at http://www.agriarticles.com

Role of Antibiotics in Agriculture: Their Uses

(*Sushila Yadav[1], Asha Yadav[2], Deepak Yadav[3], Pinki Sharma[1] and Kiran Kumawat[1])
[1]Rajasthan College of Agriculture, MPUAT, Udaipur (Raj.), 313001
[2]Rajmata Vijayraje Scindia Krishi Vishwa Vidyalaya, Indore, Madhya Prades-474002
[3]RAK College of Agriculture, RVSKVV, Gwalior, Madhya Prades-474002
*Corresponding Author's email: ysushila46@gmail.com

Abstract
Antibiotics have been used since the 1950s to control certain bacterial diseases of high-value fruit, vegetable and ornamental plants, especially fire blight of pear and apple and bacterial spot of peach. Streptomycin antibiotic is used in several countries; the use of oxytetracycline, oxolinic acid and gentamicin is limited to only few countries. Antibiotics are applied when disease risk is high and consequently the majority of orchards are not treated annually. Today, the antibiotics most commonly used on plants are oxytetracycline and streptomycin. Resistance of plant pathogens to oxytetracycline is rare, but the emergence of streptomycin resistant strains of *Erwinia amylovora*, *Pseudomonas* spp. and *Xanthomonas campestris* has impeded the control of several important diseases. Antibiotics are widely used agricultural input and their application amount by humans. A wide range of antibiotics, having similar chemical properties with the antibiotics used for human therapeutics, are applied in animal husbandry, aquaculture and crop production. The present antibiotic era is threatened by the emergence of high level of antibiotic/antimicrobial resistance (AMR) of important pathogen with resistant strains (MRSA, VRE, etc.) against the commercial antibiotics causing challenging task to treat some life threatening diseases. A fraction of streptomycin-resistance genes in plant-associated bacteria are similar to those found in bacteria isolated from the humans, animals and soil, and are associated with transfer-proficient elements. However, the most common vehicles of streptomycin resistance genes in human and plant pathogens are genetically distinct. Nonetheless, the role of antibiotic use on plants in the antibiotic-resistance crisis in human medicine is the subject of debate.

Key words: Antibiotics, antibiotic resistance, agriculture, *Erwinia amylovora*, , streptomycin, tetracycline and Uses.

Introduction
The word 'antibiotic' is used in microbiology was derived from the French words antibiose and antibiotique, discovered by Vuillemin in the late 19th century (Vuillemin, and Antibiose, 1890). First antibiotic, penicillin, was discovered by Sir Alexander Fleming in 1928 and it was capable of killing gram-positive bacteria including gonorrhea, syphilis and puerperal infections. The term antibiotic was first used after discovery of streptomycin by Selman A. Waksman, Albert Schatz and Elizabeth Bugie at the New Jersey Agricultural Experiment Station at The State University of New Jersey, USA (Bennett, 2015). Selman A. Waksman in 1947 gave a scientific definition of antibiotic as: An antibiotic is a chemical substance, that produced by micro-organisms, which have a capacity to inhibit the growth and destroy the bacterial and other microorganisms population. The entire datasets for the 32 countries

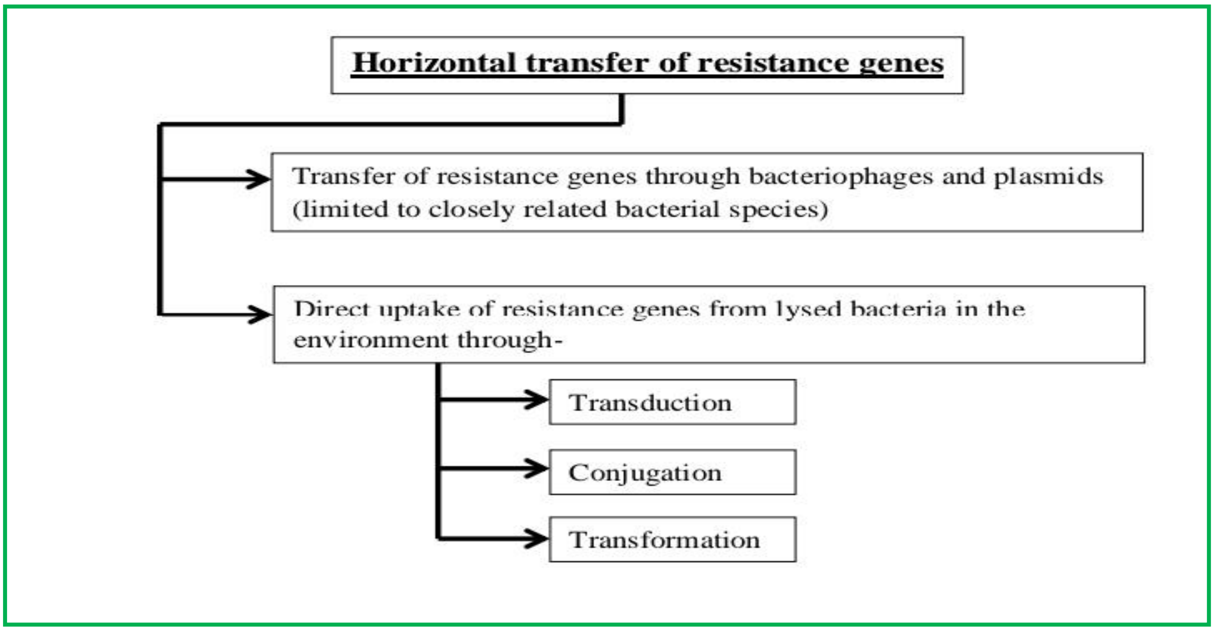
comprised 436,674 records, of these the proportion that contained a recommendation for an antibiotic accounted for just 0.38%. After excluding all countries that do not recommend antibiotics on crops the proportion of records containing an antibiotic increased to 0.66%. In ascending order, the recommendations of antibiotics, by proportion and absolute numbers were Eastern Mediterranean, Americas, Western Pacific and South East Asia (Taylor and Reeder, 2020). Bacterial diseases of plants are severe constraints to crop production and few materials are efficacious or available to mitigate crop loss. Antibiotics have different mechanism of action and based on mode of action and their chemical structure the common antibiotics are classified into major 17 classes. In livestock and poultry, antimicrobial are used to promote growth, prevent disease, and treat infection. Antibiotics for growth promotion and disease prevention are combined under the rubric "non-therapeutic uses." Therapeutic agents may be delivered to individual animals or to entire herds or flocks, depending on the disease, type of food animal, and type of production facility. The ability of antibiotics to cure victims of debilitating and fatal diseases was regarded as nothing short of astonishing. Plant pathologists quickly recognized the potential of antibiotics for the treatment of plant diseases, especially those caused by bacteria. During the 1950s, approximately 40 antibiotics of bacterial or fungal origin were screened for plant disease control (Goodman, R.N. 1959). Potency at low doses and negligible toxicity toward plants distinguished antibiotics from the metal-based bactericides available to farmers in the 1950s and 1960s. The primary targets of antibiotics were various bacterial diseases of vegetables and fire blight of apple and pear. First, great strides have been made in our understanding of the genetic mechanisms of antibiotic resistance in plant-associated bacteria. (Jones and Schnabel, 2000.). Second, over the past 12 years epidemics of fire blight of apple and pear, caused by the bacterium *Erwinia amylovora*, have also prompted surveillance for antibiotic-resistant strain, fostering new awareness of resistance. Third, the emergence of antibiotic resistance in the clinical setting has outpaced the development of new antibiotics. Our objectives in this review are to describe the current status of antibiotic use in plant agriculture, the nature of antibiotic-resistant plant pathogens and the ecology of antibiotic-resistance determinants in plant agricultural systems. We discuss the difficulties that have arisen as regulators, consumer advocates and growers attempt to weigh the repercussions of antibiotic use on plants on human health. Finally, we speculate on the future role of antibiotics in plant agriculture. The discovery of antibiotics, in the 1950s streptomycin was found to be an excellent chemical tool for the control of several bacterial diseases of plants (Loper *et al.*, 1991). Resistance of plant pathogenic bacteria to streptomycin resulted in: the use of streptomycin primarily for control of fire blight, a bacterial disease of pear and apple trees caused by *Erwinia amylovora* developing disease risk models based on environmental parameters to optimism the timing and reduce the number of antibiotic sprays in orchards and adding the antibiotics oxytetracycline, oxolinic acid or gentamicin for plant disease control in some countries. In clinical medicine, the development of antibiotic resistance in human pathogens has been widely publicized and is recognized as a major threat to the control of bacterial diseases and infections worldwide (Johnson and Stockwell, 2000). In the USA, antibiotics applied to plants account for less than 0.5% of total antibiotic use. However, the antibiotics streptomycin and oxytetracycline have been used on pear and apple orchards in the United States (USA) for over 50 years without any reports of adverse effects on humans (Schnabel and Jones, 1999). Nevertheless, the use of antibiotics on plants is a controversial practice.

The purpose of this review is to address the global use of antibiotics on plants. The mechanisms of resistance to each of the antibiotics and the fictitious risk factors for their use on plants will be discussed. Each of the antibiotics registered for use on crops is used primarily to control fire blight of pome fruits, caused by the plant pathogenic bacterium *E. amylovora*.

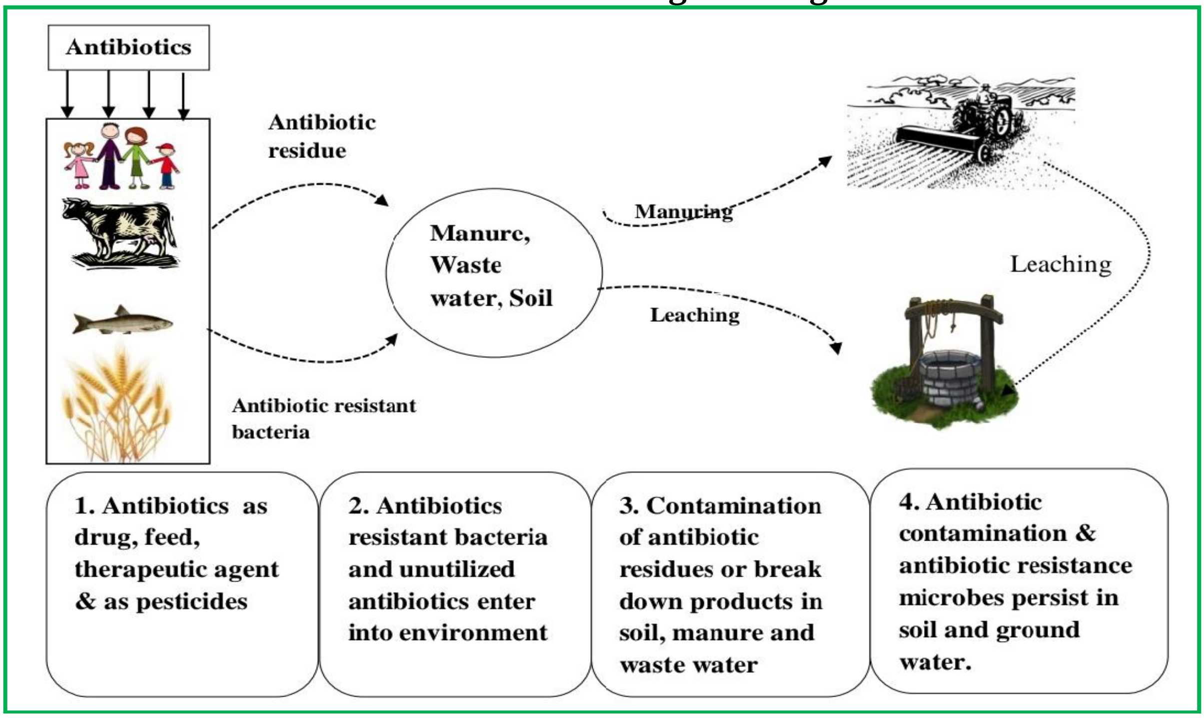
Method of horizontal transfer of antibiotic resistance genes

Bacterial resistance to antimicrobial is the evolutionary response of organisms in the presence of the selective pressure of antibiotic agents. The following 4 basic mechanisms of resistance have been documented (Zago *et al*. 2010):

1) Development of mechanisms that prevent antimicrobial access to the site of action by increasing efflux or decreasing influx through the cell membrane;
2) Development of enzymes that degrade or alter the antimicrobial agent;
3) Alteration of the site of antimicrobial action, rendering the drug ineffective; and
4) Development of site-of-action bypass mechanisms



Horizontal transfer of antibiotic resistant gene in agricultural environment



Classification of common antibiotics and their mode of action

Class	Antibiotics	Mode of action
β-lactams	Natural and semi-synthetic penicillins, natural and semi-synthetic cephalosporins and cephamycins, carbapenems, monobactams, and beta-lactamase inhibitors	Inhibition of action of peptidoglycan transpeptidases, essential for cell wall synthesis of bacteria
Aminoglycosides	Natural (streptomycin, tobramycin, kanamycin, neomycin, sisomicin, and gentamicin) products of soil bacterial of the genus *Streptomyces* and *Micromonospora* and their semi-synthetic products (amikacin, netilmicin and isepamicin)	Inaccuratetranslation/ misreading and premature termination of protein synthesis by irreversibly binding with 30S ribosomal subunit
Macrolides	Natural product (Erythromycin) of the actinomycete *Saccharopolyspora erythraea* and their semi-synthetic derivatives ("azalide''azithromycin and "ketolide'' telithromycin)	Blocks translation by reversibly binding with the 50S ribosome subunit
Lincosamides	Natural product (lincomycin) of *Streptomyces lincolnensis* and their semi-synthetic derivative (clindamycin)	Bind the 50S subunit of the bacterial ribosome
Streptogramins	Quinupristin (*Streptogramins B*), dalfopristin (Streptogramin A), virginiamycin Blocks translation by reversibly binding with the 50S ribosome subunit	Inhibits peptidyl transferal activity of the bacterial ribosome by binding to the 23S rRNA of the 50S ribosomal subunit
Tetracyclines	Natural products (chlortetracycline and oxytetracycline) from *Streptomyces aureofaciens*, *S. rimosus*) and semi-synthetic derivatives (minocycline, tigecycline or glycylcycline)	Inhibits protein synthesis by binding to the small ribosomal subunit
Glycopeptides	Vancomycin from *Amycolatopsis Orientalis* and teicoplanin, ramoplanin from *Actinoplanes* spp.; avoparcin, from *Streptomyces candidus*) and semi-synthetics (*e.g.*, telavancin, oritavancin).	Inhibit the synthesis of the cell wall of gram-positive bacteria
Rifamycins	Rifamycin from *Amycolatopsis rifamycinica* and its derivatives rifampicin or rifampin, rifabutin, rifapentine and rifaximin	Selectively inhibit bacterialRNA-polymerase
Oxazolidinones	Synthetically produced; linezolid, tedizolid, etc.	Block the initiation of protein synthesis by binding to the 23S unit of the 50S ribosomal subunit

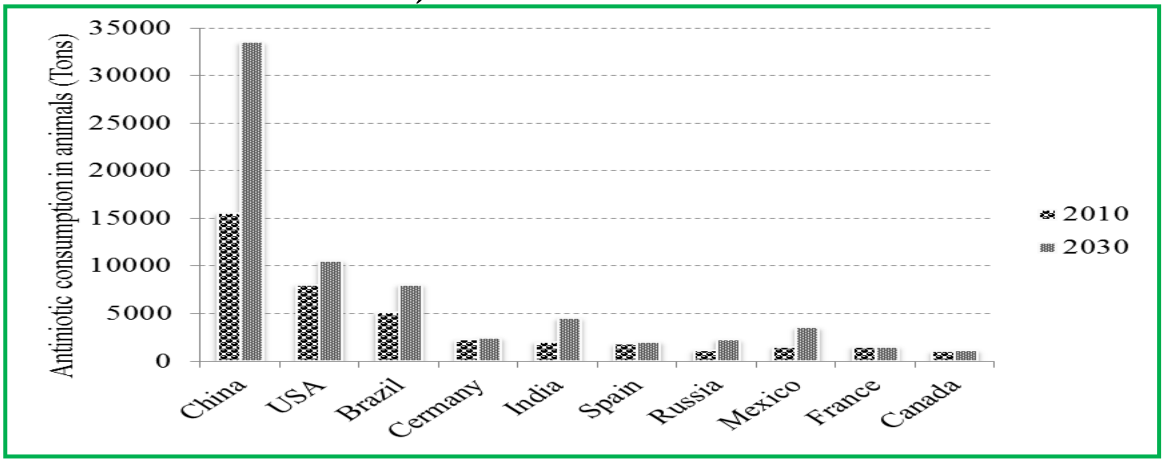
Key antibiotic classes shared by animals and humans

Antibiotic class	Used in animals	Used in humans
β-lactams	Amoxycillin	Penicillin G procaine
Macrolides	Tylosin, Azithromycin	Erythromycin, Azithromycin
Aminoglycosides	Neomycin, Gentamycin	Gentamycin
Fluroquinolones	Enrofloxacin, Ciprofloxacin, Levofloxacin, Ofloxacin	Ciprofloxacin, Levofloxacin, Ofloxacin
Tetracyclines	Oxytetracycline, Chlortetracycline	Doxycycline
Streptogramins	Virginiamycin	Quinpristine-dalphopristine
Glycopeptide	Avoparcin	Vancomycin
Phenicol	Florphenicol	Chloramphenicol
Cephalospoprins	Cephalexin	Ceftazidime, Cefexime
Polypeptides	Enramycin	Bacitracin
Pleuromultilin	Tiamulin	Retapamulin

Antibiotics use in Agriculture

Livestock: Antibiotics are used not only in humans but also to treat individual animals with bacterial infections and prevent infections in herds or flocks. Use of antibiotics as "growth promoter" in animal husbandry started accidentally in late 1940's while using by products of tetracycline synthesis as feed additives for chicken as substitute for vitamin B source (Amabile-Cuevas, 2016). Use of antibiotics to improve "feed efficiency" or the ability to grow animal faster was first approved by US Food and Drug Administration (FDA) in the early 1950s . Thus use of antibiotics in livestock can be classified into three sectors: 1. Therapeutic agents: An infected animal receives a high dose of antibiotics for a relatively short period of time for treatment of disease. 2. Prophylactic agents: An animal receives sub-therapeutic doses of antibiotics through the feed or drinking water for prevention of disease and 3. Growth promoters: An animal receives a very low dose of antibiotics on regular basis over the life time through feed to increase growth-rate and productivity. In animal husbandry, more than 63,000 tons of antibiotics were used worldwide in 2010 and but increase by two-thirds in 2030, to 105,600 tons, to meet the food protein demands of a projected 8.5 billion human population (Anonymous, 2015). The project increase of antibiotic consumption in animal is highest in China followed by USA > Brazil> India.

Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030) (source: Van Boeckel *et al*. 2015)



Around 30 different antibiotic classes are used in animal husbandry and most of them also used in humans in which top three classes used in animals are macrolides, penicillins and tetracyclines. According to Van Boeckel *et al.*, 2015 worldwide average yearly consumption of antibiotics is estimated at 172 mg/ kg of pig, 148 mg/kg of chicken and 45 mg/kg of cattle. There is also reports which indicates the decreasing efficiency of "growth promotion'' activity of antibiotics, in the 1950's, 5-10 ppm of tetracycline were used, while now 50-200 ppm are needed (Levy, 2002).

Aquaculture: FAO has estimated that fisheries and aquaculture supply around 110 million tons of fish per year (Anonymous, 2010) and providing a per capita supply of 16.7 kg of which 47 % is derived from aquaculture fish production. Food and Drug Administration (FDA) in the USA has approved oxytetracycline, florfenicol and Sulfadimethoxin /ormetoprim antibiotics for use in aquaculture (Romero, *et al*., 2012). Karunasagar *et al.*, 1994 reported use of cotrimoxazole, chloramphenicol, streptomycin, erythromycin as antibiotics in fish aquaculture in India. Antibiotics are delivered to fish through mixing them in specially formulated feed, but fish antibiotics and subsequently pass them largely in to environment through feces. It was estimated that around 75 percent of the antibiotics fed to fish are excreted into the water (Burridge *et al.*, 2010)

Crop protection: For crop protection use, streptomycin was the first antibiotic registered in the United States in 1959 and according to McManus *et al.*, 2002 in United States, antibiotic use in cop protection constitutes less than 0.5% of total antibiotic use and they are mainly used for controlling fire blight of pome fruits, caused by the enterobacterium *Erwinia amylovora*. First antibiotic selectively developed for crop protection is blasticidin S by Japan. Blasticidin S was isolated from culture filtrates of *Streptomyces griseochrogenes* and used for curative action against rice blast. Effective management of rice blast by blasticidin S inspired further researches on pesticides of microbial origin and led to development of commercial antifungal pesticides such as kasugamycin, validamycins etc. Aureofungin is a heptaene antibiotic and is extracted from *Streptomyces cinnamoseous* var. terricola. It is a broad spectrum systemic fungicide, effective against a wide variety of fungi. In India it is registered against gummosis in citrus.

Antimicrobials registered in India as fungicide and bactericide as per Insecticide act, 1968 (Anonymous, 2016).

Antimicrobials	Formulations	Effective against
Aureofungin	46.15% w/v. SP	Gummosis in citrus
Azoxystrobin	23% SC	Downy mildew& Powdery mildew in grape, Fruit rot & Powdery mildew in Chili, Anthracnose & Powdery mildew in mango, Early & Late blight in tomato, Downey mildew & Powdery mildew in cucumber, Late Blight in potato, Blight & Powdery mildew in cumin
Picoxystrobin	22.52% w/w SC	Rice blast; Downey Mildew & Powdery Mildew in grape
Pyraclostrobin	20% WG	Early blight in tomato; Frog eye leaf spot (cercospora) & Alternaria leaf spot in soybean; Alternaria Leaf blight in cotton; Tikka disease in ground nut
Kasugamycin	3% SL	Blast in rice
Kresoxim-methyl	44.3% SC	Blast & Sheath Blight in Paddy; Powdery mildew& Downey mildew in grapes
Streptomycin Sulphate + Tetracylin Hydrocloride	90% +10% SP	Fire blight in apple; Halo blight in beans; Citrus Canker in citrus; Black leg and soft rot, bacterial brown wilt or ring or the bangle disease of potato; Wild fire in tobacco; Bacterial leaf spot in tomato; Bacterial leaf blight in paddy; Blister Blight in tea
Validamycin	3% L	Sheath Blight in rice

References

1. Amabile-Cuevas, C.F., 2016. Antibiotics and Antibiotic Resistance in the Environment, CRC press, Leiden, The Netherlands,
2. Anonymous, 2015. World population prospects: key findings and advance tables, 2015 revision, Working Paper No. ESA/P/WP.241., Population Division. Department of Economic and Social Affairs, United Nations .
3. Anonymous, 2016. Major uses of pesticides (Fungicides) registered under the Insecticides Act, 1968, Directorate of Plant Protection, Quarantine & Storage Central Insecticide Board & Registration Committee, Department of Agriculture, Cooperation & Farmers Welfare, Ministry of Agriculture & Farmers Welfare, Government of India, http://cibrc.nic.in/mup.htm.
4. Anonymous, The state of world fisheries and aquaculture 2010, FAO Fisheries and Aquaculture Department, FAO of The United Nations, Rome.
5. Bennett, J.W. 2015. What is an Antibiotic? In: Antibiotics Current Innovations and Future Trends (Eds) Sánchez S. & Demain A. L. Caister Academic Press, Norfolk, UK, 2015.
6. Burridge, L., Weis, J. S., Cabello, F., Pizarro, J. and Bostick, K. 2010. Chemical use in salmon aquaculture: a review of current practices and possible environmental effects. *Aquaculture*, 306(**1**):7-23.
7. Goodman, R.N. 1959. The influence of antibiotics on plants and plant disease control. In *Antibiotics: Their Chemistry and Non-Medical Uses*, ed. HS Goldberg, pp. 322–448. Princeton: van Nostrand
8. Johnson, K.B. and Stockwell, V.O. 2000. Biological control of fire blight. See Ref. 86a, pp. 319–37.
9. Karunasagar, I., Pai, R., Malathi, G.R. and Karunasagar, I. 1994. Mass mortality of *Penaeusmonodon* larvae due to antibiotic-resistant *Vibrio harveyi* infection, *Aquaculture*, 1994, **128**(3–4):203-209.
10. Levy, S.B. 2002.The antibiotic paradox, 2nd ed., Cambridge MA, Perseus Publishing.
11. Loper, J.E., Henkels, M.D., Roberts, R.G., Grove, G.G, Willett, M.J. and Smith, T.J. 1991. Evaluation of streptomycin, oxytetracycline, and copper resistance in *Erwinia amylovora* isolated from pear orchards in Washington State. *Plant Diseases*,**75**:287-90.
12. McManus, P.S., Stockwell, V.O., Sundin, G.W. and Jones. A.L., 2002. Antibiotic use in plant agriculture. *Annual Review of Phytopathology*, **40:**443-465.
13. Romero, J., Feijoo, C.G. and Navarrete, P. Antibiotics in Aquaculture – Use, Abuse and Alternatives, In Health and Environment in Aquaculture, Carvalho, E.D., David, G. S. and Silva, R. J. ISBN 978-953-51-0497-1, 2012.
14. Schnabel, E.L. and Jones, A.L. 1999. Distribution of tetracycline resistance genes and
15. Taylor, P. and Reeder, R. 2020. Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. *CABI Agriculture and Bioscience*, **1**:1.
16. transposes among phylloplane bacteria in Michigan apple orchards. *Applied and Environmental Microbiology*, 65:4898-907
17. Van Boeckel, T.P., Brower, C., Gilbert, M., Grenfell, B.T., Levin, S.A., Robinson, T. P., Teillant, A. and Laxminarayan, R., 2015. Global trends in antimicrobial use in food animals. *Proceeding of the National Academy of Sciences of the USA*, **112**:5649-5654.
18. Vuillemin, P., Antibiose, S. 1890. Association Francaise pour L'avancement des Sciences. Compte Rendu de la 18ME Session, Seconde Partie, *Notes et Mémoires*, **11**, 525-543.
19. Zago, M., Huys, G. and Giraffa, G. 2010. Molecular basis and transfer-ability of tetracycline resistance in *Enterococcus italicus* LMG 22195 from fermented. *International Journal of Food Microbiology*, **142:**234-236.