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Life Without Antibiotics? - A Review on Increasing Threat of Antibiotic Resistance with A Broader Look on Agricultural aspect

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ABSTRACT

The discovery of antibiotic to combat bacterial infections, has been a lifesaving discovery. But, gradually due to more dependency and continuous use of antibiotics, instead of becoming a boon, it gradually tends more towards the negative aspect of development of antibiotic resistance. Eventually, the bacteria started developing resistance to the antibiotics. This has opened the door for researchers to learn more about how antibiotic resistance genes (ARG) evolve and lead to antibiotic resistance in bacteria. The present review focused on the use of two major antibiotics which are widely used now a days (Streptomycin and Oxytetracycline) emphasizing more on the mechanism of development of resistance in the bacteria and their impact on antibiotic resistance. Researchers are also trying continuously to develop some alternative antimicrobial drugs which will have minimum risk of antibiotic resistance. Antibiotic resistance is a risk that must be considered; else, a bleak future awaits.

Key words: *Antibiotics, Resistance, ARG, Plant pathology, Streptomycin, Oxytetracycline*

Introduction

Waksman referred an antibiotic as "a compound produced by a microbe with killing or growth-inhibiting activity against other microbes" (Waksman, 1973). Immediately after getting knowledge about the discovery of first antibiotic *i.e.* penicillin, this life saving antibiotic medicine has started to lead its responsibility for saving thousands and thousands of lives and has paved a way to control a broad group of microbes particularly bacteria. Within very short time some other antibiotic were also added in the list and they quickly occupied a major portion of the medicine industry. But very soon it was started to use in a broadly manner in veterinary, aquatic culture and sector of agriculture to protect all of them from different diseases. Gradually antibiotic has been started to call as "Silver bullet" for the harmful pathogens (Levy, 2002). But the sad but true fact is that this high dependency and irrational use of antibiotics has started to bring a new menace for us that has been proved as a bless for the pathogen *i.e.* the increasing threat of antibiotic resistance. Researchers were started to find out the answer that from where the antibiotic resistance gene (ARG) is getting developed and how the antibiotic resistant bacteria have been started to developed. The researches are still going on. Different way of acquiring resistance against antibiotic has been already discovered. But most of the research of antibiotic resistance was found to be very centralized to the clinical aspects only. In the agricultural field the two

most important antibiotic which are generally used in very wide manner *i.e.* streptomycin and oxytetracyclin.

The whole review centred on the three major topics, *i.e.* i) The mechanism of self-resistance in antibiotic producer plant pathogenic bacteria ii)The mechanism of development of antibiotic resistance in target microorganism and iii) Impact of antibiotic resistance. We tried to focus on the topic about how antibiotic resistance in plant pathogenic bacteria can harm the whole ecosystem, how it is already started to trapped us as we become very dependent on the antibiotics use for animal human and plant diseases and how it is leading us slowly to live a life where there will no antibiotic for curing the major and emerging diseases.

Use and availability of antibiotics in agriculture

As previously stated the discovery of antibiotic led to the dawn for the transformation of human health by saving lives, increasing life span and starting a revolutionary era in medical science. At the same time plant pathologists were also bothered from various severe bacterial plant diseases like Fire blight of apple which was creating havoc in the yield and production for the apple growers throughout the world. So, the plant pathologists quickly started to recognize the potentiality and effectivity of different antibiotics against different plant diseases. Up to the end of 1950s, almost 40 antibiotics were isolated from different bacterial and fungal sources and tested for its efficacy to be use against a wide range of plant pathogenic population. As an age old belief, initially antibiotics were only targeted to be used against only the different bacterial diseases (Goodman, 1959). This belief led to a misconception in the common people perception that antibiotics can be only targeted towards bacterial infections. But the fact is that, antibiotic like Kasugamycin is widely used to control the fungal disease like rice blast (Ishiyama, 1965). Validamycin is used mostly against *Rhizoctonia solani* and damping off diseases in seedlings of different vegetables, cotton, sugar beets and rice (Thomson, 1982; Meister, 1994). The two most important antibiotic that has been used mainly in agriculture aspects for controlling different diseases are Streptomycin and oxytetracyclin.

Streptomycin

Streptomycin is an aminoglycosidic antibiotic, generally formulated as Streptomycin sulfate or Streptomycin nitrate. It was the first registered antibiotic in USA (1959) and was widely used against *Erwinia amylovora* causing fire blight of apple and pear (McManus *et al.,* 2002). Since then the use of streptomycin for controlling the mentioned disease is widely adopted. Streptomycin can be used against a wide range of pathogen with high potentiality (Table 1).

Oxytetracyclin

Basically Oxytetracyclin is a tetracycline antibiotic, available in the formulation of Oxytetracyclin calcium complex and Oxytetracyclin hydrochloride. The use of Oxytetracyclin gained boom in those places where the use of Streptomycin was banned

Table 2. Oxytetracyclin can be used against control of wide range of pathogens

S.No.	Pathogen name	Disease	References
1	*Erwiniaa mylovora*	Soft rot of stone fruits	McManus *et al*., 2002
2	*Xanthomonasarboricola* pv. *Pruni*	bacterial spot of peach and nectarine	McMurry and Levy, 1998
3	*Phytoplasma*	Lethal yellows	McCoy, 1982

Table 1. Use of Streptomycin against wide range of pathogens

S. No.	Pathogen name	Disease	References
1	*Pectobacterium spp*. (formerly *Erwinia spp*.),	Softrot diseases of cut flowers and potato seed pieces	McManus *et al*.,2002
2	*Pseudomonas cichorii*	fruit-spotting or blossom-blast symptoms on apple, pear	McManus *et al*.,2002
3	*Xanthomonas campestrispv. vesicatoria*	Bacterial spot of pepper and tomato	McManus *et al*.,2002
4	*Agrobacterium tumefaciens*	Crown gall of rose.	McManus *et al*.,2002
5	*Pseudomonas syringae*	flower and fruit infection of stone fruits	McMurry and Levy, 1998
6	*Xanthomonas campestris*	bacterial spot of tomato and pepper	McMurry and Levy, 1998

due to antibiotic resistance and it responsibly acted as an alternative of Streptomycin.

Mode of action

Before knowing about this two particular antibiotic resistance and its impact first of all we have to know how it works on prokaryotes.

Streptomycin

Streptomycin was isolated first from *Streptomyces griseus,* an actinomycetes in 1944. (Schatz *et al*., 1944). Ever since its discovery, Streptomycin is still in controversy starting from the credit of discovery to its rapid resistance developing activity in microorganisms. Despite these controversies, Streptomycin occupies the most favourite place to be used against control of wide range of pathogens. It is a broad spectrum antibiotic effective against both gram-negative and gram-positive bacteria (Jan-Thorsten and Kee-Woei, 2004). Basically Streptomycin targets the most important and complex organelle *i.e.*, ribosome by interfering with its function resulting in inhibition of protein synthesis. If we study the mechanism of ribosome for protein synthesis it can be clear that how and where the streptomycin does its work. Prokaryotic ribosome (70S) haver two subunits *i.e.*, Larger subunit (50S) and smaller subunit (30S) mRNA controls the 50S subunit whereas the 30 S subunit reads the mRNA and matches it with tRNA which regulate the amino acid supply to ribosome. Streptomycin binds to the small 16S rRNAof the 30S subunit and hampers the normal binding process of formyl-methionyl-tRNA with the 30S subunit (Sharma *et al*., 2007). This results in mis-interpretation of codon resulting in frameshift mutation and formation of unnecessary or defective protein (Raymon, 2011). Streptomycin basically disturbs the molecular structure of the subunits by reducing the distance between the two helices which in turns disturbs the formation of decoding site and results in improper orientation and misinterpretation of the proteins (Demirci *et al*., 2013).

Oxytetracycline

Tetracycline is a broad spectrum antibiotic effective against a wide range of organisms like Gram-positive and gram-negative bacteria, spirochetes, obligate intracellular bacteria and protozoan. Chlorotetracyclin, a tetracycline based antibiotic was isolated from Streptomyces aureofaciens by Benjamin Duggar and was approved for clinical trials under the trade name of Aureomycin (Duggar, 1948). Within two years, scientists from Pfizer isolated another tetracycline group of antibiotic *i.e.*, Oxytetracycline and it got its approval in the trade name of Terramycin by U.S. Food and Drug Administration (FDA) (Finlay *et al*., 1950).

Basically tetracycline inhibits the bacterial protein synthesis by interacting with 16S ribosomal RNA (rRNA) targeting sites in the smaller sub unit of ribosome *i.e.*, 30S subunit by interrupting the aminoacyal transfer RNA or tRNA during helices elongation. (Maxwell, 1967; Brodersen *et al.*, 2000; Pioletti *et al*., 2001; Chopra *et al*., 1992; Schnappinger and Hillen, 1996). Tetracyclin are also well known for its bacteriostatic and as well as bactericidal activity(Norcia *et al*., 1999; Petersen *et al.,* 2007). The reason for its wider acceptability lies in its uptake by the membrane of the targeted organism and then ribosomal binding mechanism. Tetracycline are generally taken up by the gram negative enteric bacteria like *E.coli* through the outer membrane porinsOmpF and OmpC (Mortimer and Piddock, 1993; Thanassi *et al*., 1995). Here they produce positively charged cation (probably magnesium)-tetracycline chelate complexes (Chopra *et al*., 1992; Schnappinger and Hillen, 1996).Donnan potential across the outer membrane does it responsibility by accumulating the tetracycline molecule on the periplasm. On the next event the chelate formation with Mg^{2+} help the molecule to reach up to the ribosomal target site. Then passive diffusion, proton motive force, and phosphate bond hydrolysis produces that energy on which the uptake of tetracycline molecule partially depend (McMurry and Levy, 1978; Smith and Chopra, 1984; Yamaguchi *et al*., 1991). Crystallographic study of 30S ribosomal subunit of *Thermus thermophilus* proved that in 16S rRNA there is one high-occupancy tetracycline-binding site (Tet-1) and five other minor binding sites (Brodersen *et al*., 2000; Pioletti *et al*., 2001) and binding of this tetracycline to the ribosome results in structural change in 16 S rRNA Not only the structural changes due to the photo incorporation some tetracycline photoproducts are developed which may react further also with the ribosomes (Oehler *et al*., 1997).

Development of resistance

Discovery of antibiotics not only proved to be a blessing for human health but also paved a way for chemical management of different plant disease and

animal health issues. Despite of having different uncertainty factors like lack of knowledge of appropriate doses, phytotoxicity problems and comparatively high expenses, less availability; researchers were very hopeful about the starting of a new era of antibiotics in disease management. But gradually in less than a decade time commercialization and regular use of the antibiotic *i.e.*, streptomycin in the 1950s led to development of resistance in the pathogens (Jones and Schnabel, 2000; Moller *et al.*, 1981; Stall and Thayer, 1962). The development of resistance to antibiotics gradually led to the discovery of resistant strains of *Xanthomonas campestris*pv.*vesicatoria* in Florida in the early 1960s (Stall and Thayer, 1962). Resistance in *Erwinia amylovora* causing fire blight of apple and pear also added a new concern as Streptomycin was first used against that particular pathogen only (Johnson and Stockwell, 1998). The resistance to antibiotic was not only a concern for agriculture use, its widespread impact was spread over in all the sector. Understanding this concern the World Health Organization has termed antibiotic resistance as one of the three most important public health threats of the 21st century. Basically when we talk about bacterial resistance the first thing that comes in our mind is that if antibiotic is produced by the microorganism then how the microorganism save itself from the antibiotic effect? So, two types of resistance should be in lime light to discuss.

1) Self resistance mechanism by producer micro-organism itself
2) Resistance mechanism developed by target pathogen.

Self-resistance mechanism

The threat of antibiotic resistance is applicable for the producers as antibiotic is a toxic compound which can affect any other microorganism. For the need of outcome of this kind of threat antibiotic producing microorganism specifically bacteria adopt or developed different mechanism against their own produced antibiotics for self-defence. As a part of self-defence, the genes responsible for antibiotic biosynthesis and the genetic factor determining self-resistance are generally clustered together and express together in a co regulating manner (Mak *et al.*, 2014). Some self-resistance mechanism has been described briefly

a) **By modifying or degrading antibiotic**: The most common strategy for the self-defence by producer organism of antibiotic is the modification of antibiotic. Aminoglycosidic antibiotics when produced in the producer organism at the same time some aminoglycoside modification enzyme (AMEs) are also produce. Such enzyme was identified first in the clinical strains of Streptomyces species in early 1970s (Walker and Walker, 1970; Benveniste and Davies, 1973). A clear pathway of Streptomycin modification was seen in S.*griseus* where the streptomycin 6-phosphotrans-ferase (known as AMEs) generally converts the streptomycin into an inactive precursor streptomycin- 6-phosphate (Shinkawa *et al*., 1985). Some other scientists also claimed that the AMEs sometimes do not directly get involved in producing resistance in the producer organism, instead they perform some other metabolism activities in different biosynthetic pathways to bring about the resistance (Martinez, 2018).

b) **Antibiotic efflux:** Among the three most important mechanism of self-defence in producer bacteria or prokaryotes against the antibiotics, the antibiotic efflux is one of the most important pathway to bring about resistance. Generally, these kind of antibiotic efflux symbolizes a pump system that removes out the solutes from the cell. Basically the efflux pumps of microorganism make the cell internal environment safe by removing the different toxic compounds, even the antibiotics, which are generally produced by the pathogen itself (Pearson, 1999). This self-regulatory efflux pumps contains single component or multicomponent (Lee, 2000). Basically the Bacterial efflux pumps (EPs) are mainly the proteins which are generally located and embedded in the bacterial plasma membrane and are responsible to function not only as recognizer of toxic agents having potentiality to penetrate the cell protoplasm but also extrude them before reaching to the target point of cell (Amaral *et al*., 2008, 2010b, 2011b; Pagès and Amaral, 2009; Pagès *et al*., 2011). This EPs are so capable that they even can recognize the toxic metabolites of their own and somehow initiate the process of self-resistance by their own excretion(Li and Nikaido, 2009; Nikaido, 2011). For the functioning of this kind of EPs generally two source of energy needed: ATP (Marshall and Piddock, 1997; Lewis, 2001; Lorca *et al*., 2007; Moitra *et al*., 2011) and the proton motive force (PMF)

(Amaral *et al*., 2008, 2010b, 2011b; Li and Nikaido, 2009; Pagès and Amaral, 2009; Nikaido, 2011; Pagès *et al*., 2011; Spengler *et al*., 2012).

The self-resistance derived by antibiotic efflux has been described by researchers in some prokaryotes related to clinical drug production. Efflux of the antibiotics i.e., daunorubicin (DNR) and doxorubicin (Dox) in *Streptomyces peucetius* occurs by an ABC (ATP Binding Cassette) transporter DrrAB i.e., coded or regulated by *drrAB* genes and assembled by two protein subunit i.e., DrrA and the integral membrane protein DrrB; generally embedded within the gene cluster responsible for biosynthesis of these antibiotics (Guilfoile and Hutchinson, 1991). The DrrAB proteins carry out efflux of Dox in ATP or GTP dependent manner (Li *et al.,* 2014). Similarly, *Streptomyces rimosus* having two efflux proteins: OtrB (previously known as TetB) and OtrC located in the biosynthesis cluster, and are located outside the cluster respectively (Mak *et al*., 2014). OtrC protein that belongs to ABC family protein has similarity with the DrrAB on the basis of function *i.e*. resistance to multiple antibiotics (Yu *et al*., 2012; Mak *et al*., 2014).

2. Resistance mechanism developed by target pathogen

Antibiotic that was known as silver bullet for its widespread and very effective use on target organism have now a days become a serious concern only due to its rapid development of resistance. The mechanism of resistance is not same for every antibiotic or every organism. This can be varied by not only depending on the mode of action of the antibiotic compound but also the structural and bio chemical properties of its own. For example, in both the gram-negative and gram-positive bacteria involvement of the 28 different classes of efflux proteins can be seen for tetracycline resistance, but the same is not applicable for tetracycline resistance (Guillaume *et al.,* 2004). Antibiotic resistance of different antibiotic generally classified into some major division like modifications of the antimicrobial molecule or compound, mutation of a target site protein or alteration or modification of target protein and acquisition of an antibiotic-resistance gene (ARG) that confers resistance through efflux or inactivation of the antibiotic and by preventing the antibiotic from reaching its cellular target by reducing uptake. (Davies and Davies, 2010; Munita and Arias, 2016; Nguyen, 2014)

Antibiotic Resistance against Streptomycin

Immediately after the discovery of Streptomycin, it became very popular over a large geographic area to be used against a wide range of plant pathogenic bacteria. But no doubt this over and longer dependency already has invited the threat of resistance. The first streptomycin-resistant (SmR) plant-pathogenic bacteria was reported in strains of *E. amylovora* (McManus and Jones, 1994). Keeping in view the above explanation, the mechanism of streptomycin resistance can be understood as below.

Inactivation/modification of streptomycin and Horizontal gene transfer (HGT)

The two most known way of resistance are through the phosphorylation or adenylylation process that are directed by the encoding enzyme which confer resistance resulting in inactivation of the Streptomycin molecule (Shaw *et al*., 1993). The concept of inactivation of Streptomycin by the enzymatic process was initiated after the finding of phosphotransferase enzymes Aph(6)-Ia and Aph(6)-Ib from *S. griseus* and *Streptomyces glaucescens* respectively which has proper responsibility for the development of the self-resistance in the mentioned antibiotic producers (Shaw *et al.,* 1993). Comprehensive antibiotic resistance database (CARD) studies revealed that among the 40 tested protein sequences related to Streptomycin resistance 35 proteins are capable of inactivating Streptomycin. Streptomycin-6-phosphotransferase, an Aminoglycoside modifying enzyme (AME) was reported for antibiotic modification/ degradation (Shinkawa *et al*., 1985; Mak *et al*., 2014) in *S. griseus*.

Horizontal gene transfer (HGT) are known to be the most important and most effective way of evolution of antibiotic resistance (Benveniste and Davies, 1973). Transfer of the antibiotic determinants or the HGT mechanism in the bacterial population basically are the transformation, transduction and conjugation process which aims for the genetic exchange (Wright, 2007; Hu *et al*., 2017). One of the most important determinants of Streptomycin resistance are the *strAB* gene associated with transposon *Tn5393*, which transpose from one location to another and contribute in gene evolution and the related plasmids are pBP1 and RSF1010 having broad host range (Sundin and Bender, 1996). Streptomycin resistance mediated by Tn5393 or the presence of

strA and strB determinants, has been reported in *E. amylovora, P. syringae*, and *X. campestris* isolated from different parts of the world (Sundin and, Bender, 1996). Some other streptomycin resistance determinants which have been found till now are the *aadA* gene associated with integrons which have the capability of acquiring and adding additional resistance genes as cassets (Escudero *et al.,* 2015; Hall and collis,1995). *aad A*and variant alleles encodes Nucleotidyl transferase and are found in plant pathogenic bacteria like *Xanthomonas* (Wiener *et al*.,1998). Streptomycin-resistant *X. oryzae subsp. oryzae* from China indicated that four strains harboured the *aadA1* gene associated with class 1 integron sequences (Xu *et al*., 2013). Some other resistance determinant gene *aph(6)-1a* and *aph(6)-1b* both encodes Phosphotransferase enzyme in *Streptomyces* (Perreten *et al.,*1997; Projan *et al*., 1988).
Antibiotic Efflux

The second major mechanism of antibiotic resistance in different agricultural or clinical strains of Streptomyces involves decreased permeability and/or efflux of the antibiotic. Most of the plant pathogenic bacteria are gram negative in nature. In this gram negative bacteria decreased permeability is important due to the presence of the outer membrane resulting in formation of permeability barrier and protection against hydrophilic antibiotics and other antimicrobial agents (Nikaido, 2003). The ykkCD efflux pump belonging to a multidrug resistance family, has been identified to confer streptomycin and chloramphenicol resistance, although it was reported from *Bacillus spp* (Jack *et al*., 2001).

Mutational resistance to streptomycin

Mutational resistance although occurs in unpredictable manner but the frequency of their occurrence is not so called rare in different clinical as well as plant pathological bacteria. Generally, this type of mutational resistance modifies or alter the binding site in the bacterial ribosome where basically the Streptomycin works. Mutation in the *rrs*or *rpsL* genes results in the alteration of the binding site of streptomycin in the ribosome developed the resistance against it (Ozaki, 1969). This type of Mutational resistance occurs in *E. amylovora* (Moller, 1981)

Antibiotic Resistance Against Oxytetracycline (Tetracycline)

Tetracycline which is well known for both of its bacteriostatic and bactericidal effect have wide host range like gram-negative and gram-positive bacteria, spirochetes as well as protozoan parasites (Chopra and Roberts, 2001; Grossman,2016). Pfizer (New York) scientists isolated oxytetracycline,later approved by the U.S. Food and Drug Administration (FDA)in 1950 and marketed first as Terramycin (Finlay *et al.,* 1950). Mid 1950s majority bacteria were susceptible to tetracycline but later on resistance to tetracyclines has emerged in plant and fish pathogens as result of vast use of this antibiotics to control diseases (Levy, 1984). Tetracycline resistance was reported in plant-pathogenic bacteria like *P. syringae* (Hwang *et al.*, 2005) and tumer inducing bacteria *Agrobacterium tumefaciens* (Luo and Farrand, 1999). The followings are the different mechanisms of tetracycline resistance.

Antibiotic efflux

Efflux is one of the most important determinants for tetracycline resistance by preventing the reaching of the tetracycline in the target of the cell. More than 28 different classes of efflux proteins are involved in tetracycline resistance in different gram-negative and gram-positive bacteria against the tetracycline (Guillaume, 2004). Every efflux genes encodes for 46-kDa membrane-bound efflux protein that divided into six groups based on amino acid sequence (McMurry and levy, 2000; Tauch *et al*., 2000). Among them, *tetA* is the most widespread resistance determinant that majorly encodes tetracycline-resistance efflux in more than 1,000 bacteria. Although the basic function of all the *tet* efflux genes encode membrane-associated proteins which is responsible for exporting tetracycline molecule from the cell resulting in protecting the ribosomal target of cell by reducing the antibiotic concentration. As tetracyclines are hydrophilic so generally they use water-filled diffusion channels (porins) to cross the outer membrane (Pages *et al*., 2008). Not only that Mutation of the OmpFporin protein occurs in *E. coli* to reduce the uptake of tetracycline (Thanassi, 1995).

Inactivation of the tetracycline molecule

The first evidence of a tetracycline-modifying enzyme mechanism was first described in *E.coli,* which was encoded by Bacteroides plasmid, a flavin-dependent monooxygenase (Speer and Salyers 1988, 1989). The Two tetracycline-modifying monooxygenase genes, *tetX* and *tet37*, have been reported. This process of activation managed by the addition of a hydroxyl group to the C-11a position

located between the C and B rings of the tetracycline molecule core (Speer *et al*., 1991; Yang *et al*., 2004).

Ribosomal protection protein (RPPs)

Another mechanism of resistance determinant is the Ribosomal protection protein(RPPs) that have been identified from both gram-positive and gram-negative bacterial species by dislocating tetracycline from the ribosome and thus saving the ribosome from the inhibitory effects of tetracycline. The most common and best characterized RPPs are Tet(O) and Tet(M) which catalyses the GTP-dependent release of tetracycline from the ribosome (Connell *et al*., 2003ab). In the presence of the Tet(M) protein, tetracycline is apparently released from the ribosomes. In the presence of either the Tet(M) or the Tet(O) protein, tetracycline binding to the ribosomes is reduced in the presence of GTP (Trieber *et al*., 1998).

Impact of the antibiotic resistance

Since 1940s, the production of antibiotic in global sector annually has been increased so drastically that it has been estimated even up to 100–200 thousand tonnes. Significantly this huge production implies the over and irresponsible use and misuses in all the sectors like medical, veterinary and agriculture. And it is directly resulting in antibiotic excretion, deposition and environmental release and development of resistance in bacterial strain which is the key factor for the development of antibiotic-resistant bacteria (ARB) and ARG (antibiotic resistance genes) and this is increasing the risk of transmission of the environmental resistome to humans (Manaia *et al*., 2017). The pattern of antibiotic consumption in agricultural sector in different countries differs from each other as developed countries already banned the antibiotic use for its increasing resistance. (Moyane *et al*., 2013; Adebowale *et al*., 2016). According to a recent survey, this trend of antibiotic consumption will be doubled due to huge misuse and misleading consumption and unregulated supply in the BRICS countries consisting of Brazil, Russia, India, China and South Africa (Van Boeckel *et al*., 2015). The residues of the antibiotics, antibiotic-resistant bacteria and resistance genes has gradually achieved the place of potential pollutants which not only increases the human health risk by entering food chain but also the control of resistant bacteria have become more difficult and expensive with need of more amount of chemical to treat them. As a result, the soil and water environment or ecosystem are turning as reservoir for this excess amount of antibiotic and the situation is so much concerning that even the uncultured or non-pathogenic bacterias are also acquiring resistance gene (Riesenfeld *et al.,* 2004). And this is increasing the chance of the evolution among bacterial species that can be expressed as the emergence of new diseases or the major damage by different minor pathogens. So if Antimicrobials and their bioactive metabolites pollution in environment will not be checked then this antimicrobial resistance could lead to 10 million deaths per year by 2050 Whenever any spray solutions will be applied by air blast sprayers as a estimation of 44%–71% of spray solutions generally lost into the environment (Steiner, 1969). As an example when *oxytetracycline* used on the target plant generally its residues lost very rapidly from peach leaf surfaces (Christiano, 2010). Whatever if any antibiotic used on the plant surface generally by the drift and runoff the antibiotic residues may land on other plant surfaces which effect the phyllosphere or epiphytotic bacteria. An increase of streptomycin antibiotic resistance percentage (from 14.7% to 39.9%) was observed in *E. coli* that was found from faeces of sheep that feeds on a pasture that was sprayed with streptomycin (Scherer, 2013). Orchard epiphytes showed an increasing streptomycin resistance on trees with the increasing number of application of the antibiotic within one season (Tancos and Cox, 2017).

Soil is the base of our mother nature. It not only carries us but it is the inhabitant of uncountable microorganisms. So, the abundance of the ARB and ARG in the soil generally contributed by the antibiotic residues containing manure, residues in waste water that generally comes from pharmaceutical companies and the use of antibiotics to treat crop diseases (Finley *et al*., 2013). Antibiotic-resistant bacteria and resistance genes was discovered by different researchers from number of vegetables like lettuce, cabbage, radish, green corn, onion, carrot etc. which were grown by using manure and irrigated by the waste water (Marti *et al*., 2013; Oluyege *et al.*, 2015). Aquatic environment also added significant value by release, transformation, mobilisation and mixing of antibiotic residues resulting in persistence of ARB and ARG (Taylor *et al*., 2011). Antibiotic-resistant *Aeromonas* and *Pseudomonas* species were reported from surface and drinking water in Mafikeng, SouthAfrica (Mulamattathil *et al*.,2014). So the occurrence of antibiotic resistance became a

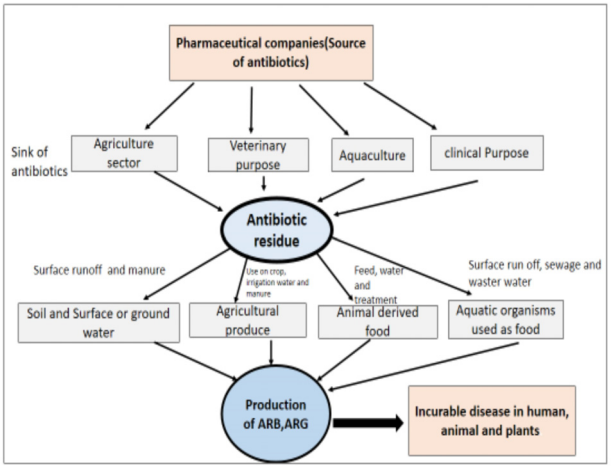

Fig. 1. Diagrammatic representation of antibiotic source, sink, residue and final destination.

serious threat for the human health as they would increase the risk of human exposure to antibiotic-resistant bacteria and resistance genes (Pavlov *et al*., 2004). Ground water also are polluting by this antibiotic residue. A report of Kummerer (2004), antibacterial agents were found in groundwater also but in low concentration. As a result of this consequences, some bacteria are getting so much resistant against different diseases that they are going beyond the treatment. Not only plant diseases, some human disease are also becoming very prevalent and causing much more damages. The current outbreaks of cholera in India were due to the constant change in biotypes of the strain *Vibrio cholera* which has developed the resistance against multiple antimicrobial medicine that were previously used in the treatment of the same cholera (Ramamurthy and Sharma, 2014).

Conclusion

An antibiotic resistance bacteria or development of antibiotic resistance gene is a serious matter of concern not only in a plant pathosystem but also with other relevant ecosystem also. Management of the antibiotic resistance may be difficult but not impossible. For this cooperative understating is needed. Although there is huge shortage of antibiotic of different mode of action which can really be a good management procedure for antibiotic resistance, but we can minimize the problem by limiting the frequency and amount of antibiotic application and that should also be in need based manner. Researchers are also trying continuously to develop some alternative antimicrobial drugs which will have minimum risk of antibiotic resistance. So if we think about post antibiotic era first we have to reduce the dependency on it and biological, cultural and other feasible methods of disease managements should be given priority. But as now we are helpless against some diseases without antibiotic, so this is a high time to think about the difficulties that we can face if we have no alternatives and if we are forced to lead a life without antibiotic as because all the organism till then can grow resistance against all known antibiotics. For a while knowledge about antibiotic residue, the proper use as per recommended quantity, proper disposal of antibiotic metabolites should come in limelight of discussion. Knowledge of farmer is foremost need as because due to the absence of proper knowledge they generally do irrational use of antibiotics. Even the government should impose proper check, and monitoring in case of the production, use and disposal of any antibiotics. Otherwise the day is not so far when there will be a life without antibiotics and we will struggle to control plant and animal diseases and as consequence will force to count the dead bodies because of double trouble, *i.e*. scarcity of food and incurable diseases.

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