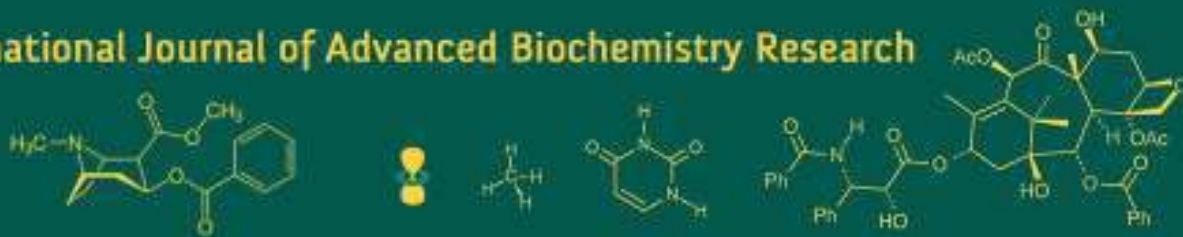


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## A review on mechanism of Bacteria resisting plant antibiotics

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### Abstract

Antibiotic resistance in plant pathogenic bacteria poses a significant threat to global agriculture and food security. With the discovery of penicillin in 1928, antibiotics have saved countless lives. However, there are now serious concerns of resistance acquired by bacteria due to their misuse and overuse. One major mechanism of antibiotic resistance in plant pathogenic bacteria involves the modification or degradation of antibiotics. Bacterial enzymes, such as beta-lactamases and aminoglycoside-modifying enzymes play a key role in breaking down the structure of antibiotics, rendering them ineffective, for instance, gene *aadA1* and *aadA2* encode enzyme aminoglycoside adenyltransferases helps in degradation of streptomycin and develop resistance against *Xanthomonas oryzae* pv. *oryzae*. Horizontal gene transfer is another significant contributor to antibiotic resistance, the *strA-strB* streptomycin-resistance genes found on the Tn5393 transposon in *Erwinia amylovora* and *X. campestris* have presumably been acquired from nonpathogenic epiphytic bacteria under antibiotic selection. Mobile genetic elements, such as plasmids and transposons, facilitate the transfer of resistance genes between bacteria, allowing for the rapid spread of antibiotic resistance within bacterial populations. Additionally, bacteria may possess efflux pumps that actively pump out antibiotics from the bacterial cell, preventing their accumulation at lethal concentrations. Furthermore, the adaptive nature of bacteria contributes to antibiotic resistance through the development of mutations in target genes. For example OA-resistant mutants showed reduced or negligible virulence in an immature apple, which highlight the role of *gyrA* mutations in pathogenesis or survival of *E. amylovora*. The complex interplay between these resistance mechanisms emphasizes the need for a multifaceted approach to address antibiotic resistance in plant pathogenic bacteria. Strategies such as the development of new antibiotics, the use of combination therapies, and the implementation of agricultural practices that minimize the need for antibiotics can all contribute to a more sustainable and effective management of bacterial infections in crops.

**Keywords:** Antibiotics, plant pathogenic bacteria, resistance, transposons

### Introduction

Antibiotic is a Greek word made up of two words “Anti” means fighting or killing and “bios” means life *i.e* it means ‘life killing’. According to Waksman's classical definition, an antibiotic is "a compound produced by a microbe with growth-inhibiting or killing activity against other microbes" (Davies and Davies, 2010) [13]. The majority of antibiotics currently in use have their origin in the phylum *Actinobacteria*, with soil-dwelling bacteria of the genus *Streptomyces* producing over 80% of actinobacterial-derived antibiotics (Barka *et al.*, 2016). Prior to the discovery of naturally occurring antibiotics, sulfa drugs, quinolones, salvarsan, and other synthetic chemicals were used as chemotherapy agents (Aminov, 2010). The most frequent ways that antibiotic resistance develops in bacteria are either by mutating a target-site protein, acquiring an antibiotic-resistance gene (ARG) that gives resistance by effluxing or inactivating the antibiotic, or synthesising a new target protein that is resistant to the antibiotic (Davis and Davis, 2010) [13]. Studies on antibiotic resistance in animal agriculture and human pathogens have yielded a wealth of information. The capacity of bacterial pathogens to obtain ARGs and combine them into transferable DNA blocks encoding multiple ARGs has led to important problems that have an impact on the efficaciousness of treatment interventions intended to address certain distinct human

infections. A swift evolutionary response to the millions of kilograms of antibiotics that human use annually has been sparked by basic mechanism of population dynamics and microbial ecology, which have contributed to the existing worldwide crisis of bacterial populations resistant to antibiotics. The fact that ARGs were already present in bacterial populations was not known when antibiotics were discovered and used in clinical medicine (Perry *et al.*, 2016) [42]. Furthermore, numerous sophisticated investigations determining the microbial antibiotic resistance have revealed information that was not known 70 years ago about the degree to which ARGs may be transferred from one bacterium to another, even between species that are phylogenetically different. The term "antibiotic resistome" refers to the entire microbial genome that contains all known ARGs (Wright, 2007) [65]. Conceptually, the most significant aspect of the antibiotic resistome is that individual ARGs may be accessed by all bacteria. Thus, this review has focused on the perspectives that can deal with the challenges that spring up by the spread of resistance among bacteria.

### History

In 1928, the fungus *Penicillium* inadvertently contaminated a culture plate in Alexander Fleming's laboratory which apparently led to the discovery of first naturally occurring antibiotic Penicillin. However, penicillin was not commercialised until the late 1930s as it prevented the formation of cell walls and proved highly effective against Gram-positive bacteria but on the other side, it was ineffective against Gram-negative bacteria (because of the outer membrane) and tubercle bacillus (because of its unusually thick cell wall). The next major finding was in 1943 with the discovery of streptomycin isolated by *Streptomyces griseus*. The major advantage of this discovery was that streptomycin was efficient against both tubercle bacillus and Gram-negative bacteria. It suppressed protein synthesis by binding to the 30S component of the bacterial ribosome (Hopwood, 2007) [21]. This was the golden period (1940-1990) for paving a way to antibiotic research and development that followed with the discovery of soil bacteria that produced chloramphenicol and tetracycline and revolutionised the field of antibiotics between years 1945 and 1955. After this period, researchers began examining the effects of antibiotics outside of the medical field based on their application. Brown and Boyle (1944) contributed to the plant disease management by effectively using penicillin to treat crown gall disease incited by multiple bacteria. Upjohn in 1946 from the United States discovered that cycloheximide had strong anti-fungal activity against plant infections. Following the use of these antibiotics, it was discovered that streptomycin and chloramphenicol had an effective influence on the management of bacterial and fungal infections (Clardy *et al.*, 2009) [10]. Out of the approximately 900 types of antibiotics whose chemical structures have been studied, just over ten types have been found to have a practical use in agriculture. Blasticidin was successfully developed by the Japanese company Hokko Chemical in 1955 followed by kasugamycin by 1963. These two antibiotics were used extensively to treat rice blast disease, which is caused by *Pyricularia grisea*. In 1972, Takeda Pharmaceutical Company created validamycin, a treatment for rice sheath blight (*Rhizoctonia solani*). The same pharmaceutical company created midiomycin by the

end of 1970 to successfully treat powdery mildew disease in significant crops. Along with Jinguangmycin, China was a major producer of the antibiotics blasticidin, kasugamycin, and polyoxin. In 1982, the Jilin Academy of Agricultural Sciences' Plant Protection Institute made significant progress in the development of gongzhulingmycin, primarily for the management of *Ustilagocrameri*, *Tilletiafoetida*, stinking bunt, and sorghum covered smut (Valarmathi, 2020) [61]. The first public sector pharmaceutical manufacturing company established by the Indian government is Hindustan Antibiotics Limited (HAL), with its headquarters located in Pimpri, India.

### Antibiotics use in plant agriculture

The huge amount of bacterial pathogen population on susceptible host with the scarcity of bactericides make treatment of plant diseases challenging but the antibiotics have proven to be the most effective alternative for bacterial disease control in many pathosystems when robust and lasting host disease resistance is lacking. This is because antibiotics reduce the size of the bacterial population and prevent disease outbreaks but the use was restrained by a number of factors, combining phytotoxicity problems at larger dosages and their lack of effectiveness at lower ones and higher cost when in comparison to other accessible techniques for preventing illness. Consequently, most common antibiotic used worldwide to control plant diseases is streptomycin, which targets pathogens like *X. campestris* causing bacterial spot on tomatoes and peppers, *Erwinia amylovora* causing fire blight on apple and pear and *P. syringae* infecting apple and pear trees, flowers and fruits. In certain disease control scenarios, such as the management of *X. arboricola* pv. *pruni*, the causal agent of bacterial spot on peaches and nectarine, oxytetracycline has been employed as the principal antibiotic (McManus *et al.*, 2002) [31]. Furthermore, in the United States, oxytetracycline has been employed as a supplementary antibiotic to address fire blight, particularly in cases where streptomycin resistance has been an issue. After the environment is exposed to the antibiotic solution, it is adversely affected by temperature, sunlight (both visible and UV), rainfall, and other particular elements of the phyllosphere that could impact adsorption, regardless of whether it reaches the target (Sundin and Wang, 2018) [60].

### Effect of antibiotic application on the microbiome

Most of the antibiotics are applied as spray on the plants. According to estimates, air blast sprayers lose between 44% and 71% of the spray solutions applied to the environment. If provided during the bloom phase, antibiotics that reach the target areas in the tree canopy have an effect on the microbiomes of the phyllosphere and flowers. The antibiotic may also be consumed by insects that are feeding in the tree canopy, which may have an effect on the gut microbiome of the insects. When applying antibiotic spray on trees, some of the spray may drift and not reach the target, or it may be lost to drainage from rain or spraying operations (Sundin and Wang, 2018) [60]. Following the release of the antibiotic solution into the surroundings, it is adversely affected by temperature, sunlight (both visible and UV), rainfall and other particular elements of the plant such as environment of leaf that could impact adsorption, regardless of whether it reaches the target. Some antibiotics drift to other plants and grasses which are grazed by animals and affect gut

microbiota of animals (Fig. 1). According to study conducted by Scherer *et al.* (2013) [52], it was recorded that the proportion of *E. coli* isolates resistant to streptomycin found in the feces of sheep grazing on a pasture sprayed with the antibiotic was found to rise (from 14.7% to 39.9% compared to 15.8% to 22.3% in a control group). Antibiotics

drifted from target can also affect phyllosphere and rhizosphere microbiome and develop resistance against antibiotics. Yashiro and McManus (2012) [67] observed that phyllosphere bacteria isolated from streptomycin sprayed orchard continuously for ten years exhibited less resistance than non-sprayed orchard against streptomycin.

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

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

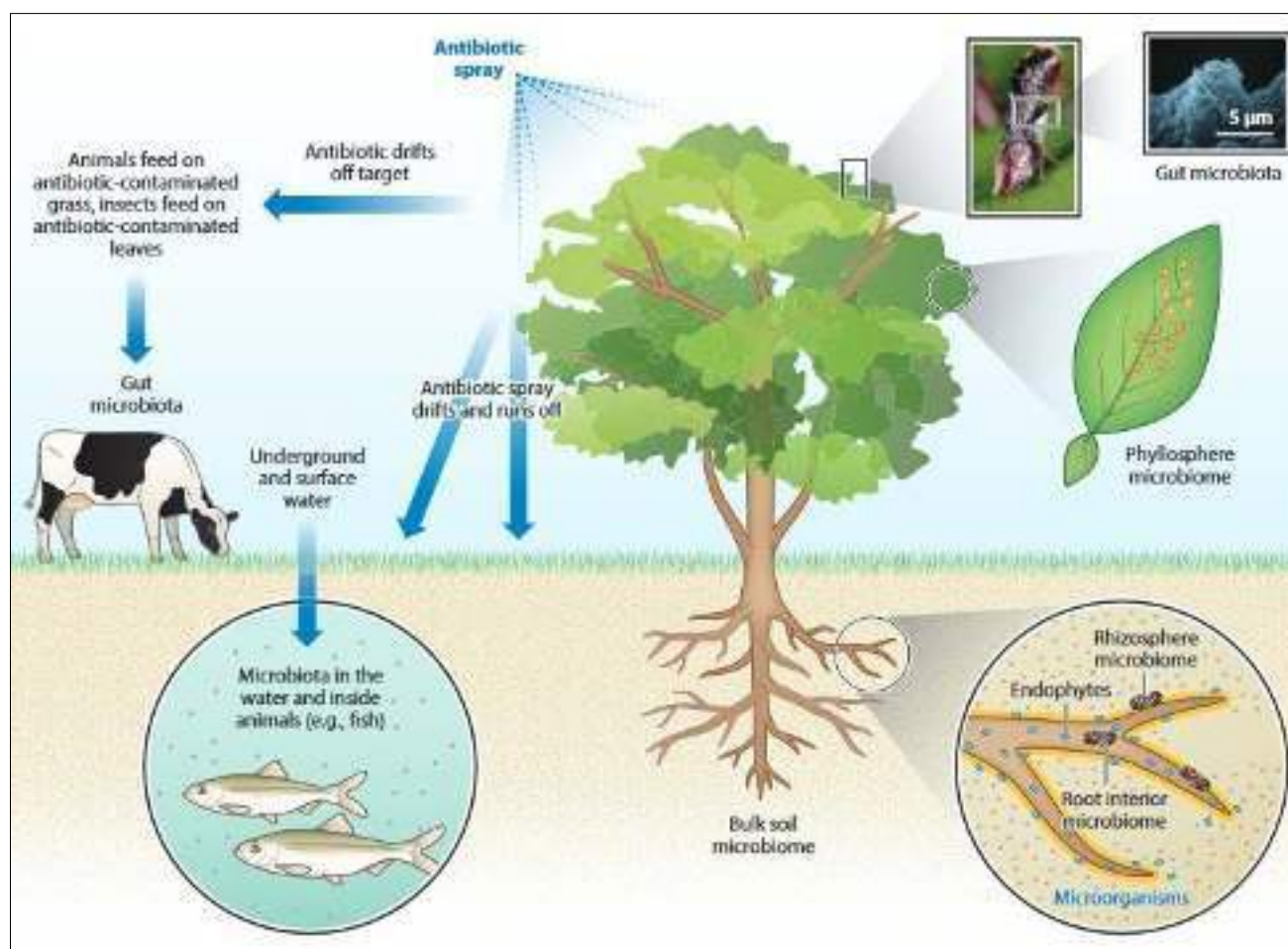
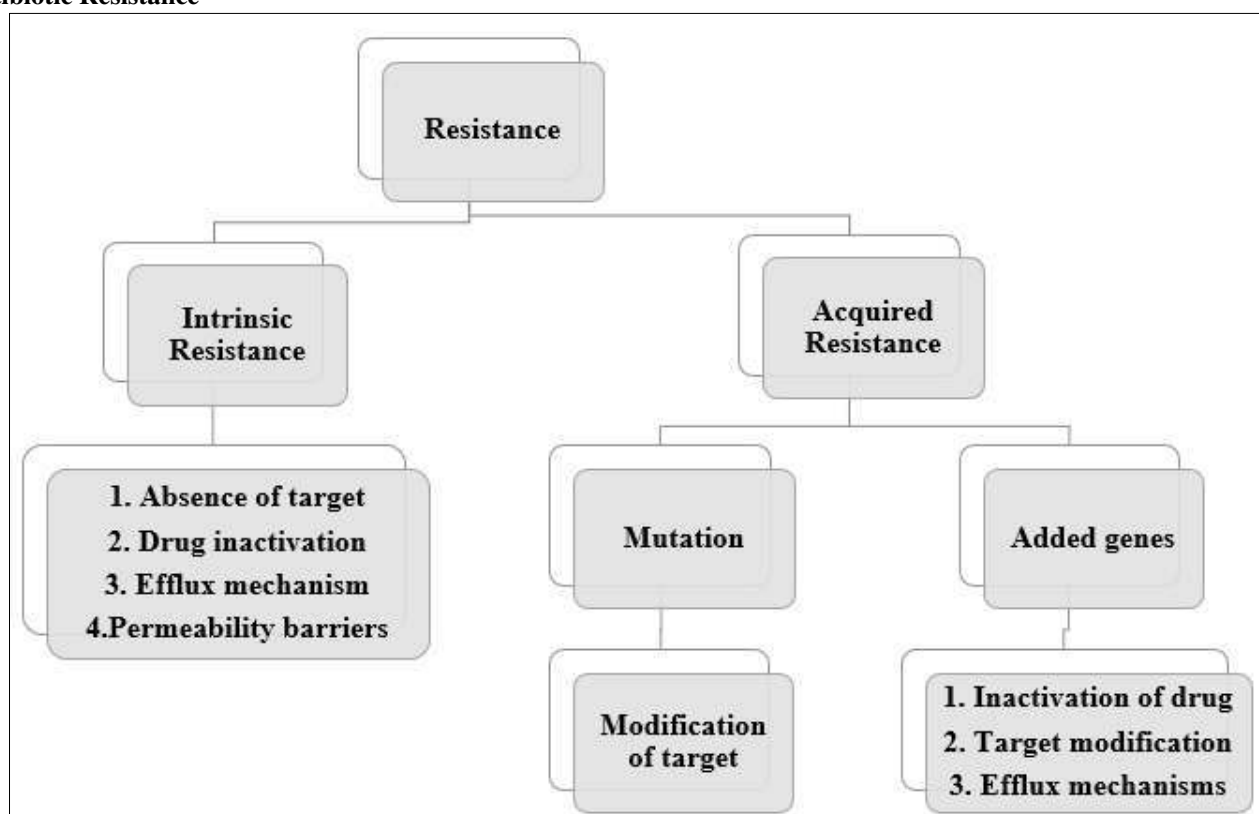


**Fig 1:** Impact of antibiotic use on plant orchard agriculture systems' microbiota (Wang *et al.*, 2017)

**Antibiotic Resistance****Table 2:** List of some antifungal antibiotics

| Chemical name | Sources                                                                                            | Effective against                                                                                                         |
|---------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Cycloheximide | <i>Streptomyces griseus</i>                                                                        | Mildew of beans, covered smut of oats, brown rot of peach                                                                 |
| Griseofulvin  | <i>Penicillium griseofulvin</i> , <i>P. patulum</i> , <i>P. digricans</i> and <i>P. janczewski</i> | Downy mildew of cucurbits, powdery mildew of rose, powdery mildew of beans, early blight of tomato and brown rot of apple |
| Blasticidins  | <i>S. griseochromogenes</i>                                                                        | Rice blast                                                                                                                |
| Aureofungin   | <i>S. cinnamomens</i> var. <i>terricola</i>                                                        | Downy mildew, powdery mildew and anthracnose of grapes, citrus gummosis                                                   |
| Antimycin     | <i>Streptomyces</i> sp. K01-0031.                                                                  | Early blight of tomato, seedling blight of oat and rice blast                                                             |
| Thiolutin     | <i>S. albus</i>                                                                                    | Potato late blight and broccoli downy mildew                                                                              |
| Mystatin      | <i>S. noursei</i>                                                                                  | Anthrachnose of beans and downy mildew of cucumber                                                                        |
| Bulbiformin   | <i>Bacillus subtilis</i>                                                                           | Wilt of pigeon pea.                                                                                                       |
| Validamycin A | <i>S. hygroscopicus</i>                                                                            | Sheath blight of rice and damping off of cucumbers                                                                        |

**Resistance: Acquired versus Intrinsic**

Antibiotic inactivating enzymes, permeability barriers, and non-specific efflux pumps—which most likely developed as a broad reaction to toxins to environmental—are examples of intrinsic antibiotic mechanisms (Fig 2), which are typically chromosome-encoded (Cox and Wright, 2013) <sup>[11]</sup>. The *E. coli* AcrAB/TolC efflux pump is a well-studied example of an intrinsic resistance mechanism. It can export different classes of antibiotics, detergents, dyes and disinfectants and has very broad substrate specificity (Nikaido and Takatsuka, 2009) <sup>[33]</sup>. Another instance of intrinsic resistance that results from the outer membrane's permeability barrier is

vancomycin resistance found in *E. coli* and other Gram-negative bacteria (Arthur and Courvalin, 1993) <sup>[2]</sup>.

Conversely, acquired resistance mechanisms are typically acquired through horizontal gene transfer (HGT). These mechanisms comprise enzymes which can alter antibiotic or its target, as well as plasmid-encoded specific efflux pumps (Fig 2), like *S. aureus* TetK and TetL (van Hoek *et al.*, 2011) <sup>[62]</sup>. An extensively recorded instance of this phenomenon is the mobilisation of the chromosomal  $\beta$ -lactamase gene *ampC* to a plasmid, which leads to its global spread (Dantas and Sommer, 2012) <sup>[12]</sup>.

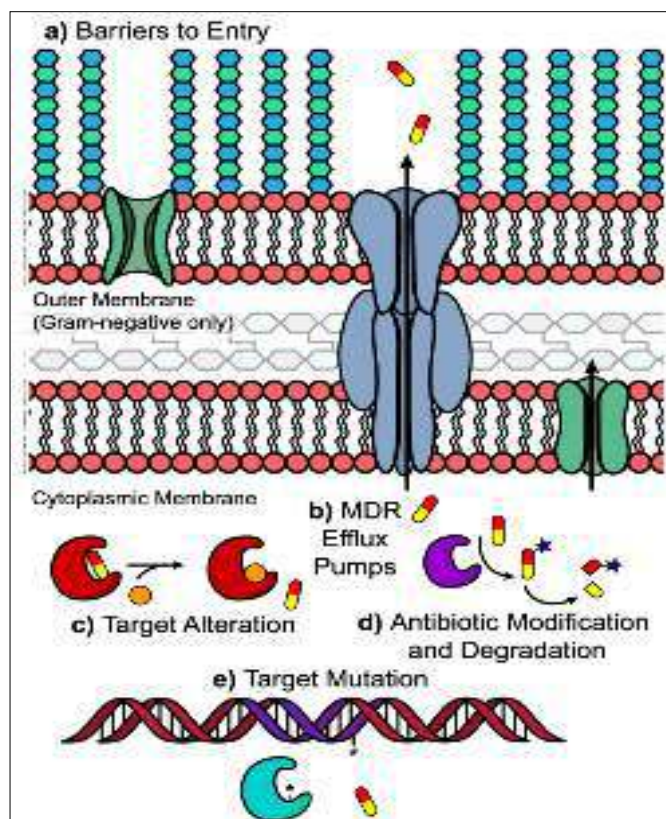


**Fig 2:** Intrinsic and acquired antibiotic resistance in bacteria

### Origin of antibiotic-resistant bacterial pathogens

The three main sources of antibiotic resistance that are currently known to exist in bacterial pathogens are mutations encoding target-site alterations, the existence of resistance genes within the microbiome, their eventual

transfer to pathogenic species subject to antibiotic selection, and the horizontal gene transfer mechanism used by antibiotic-producing microorganisms to release their naturally occurring resistance genes.

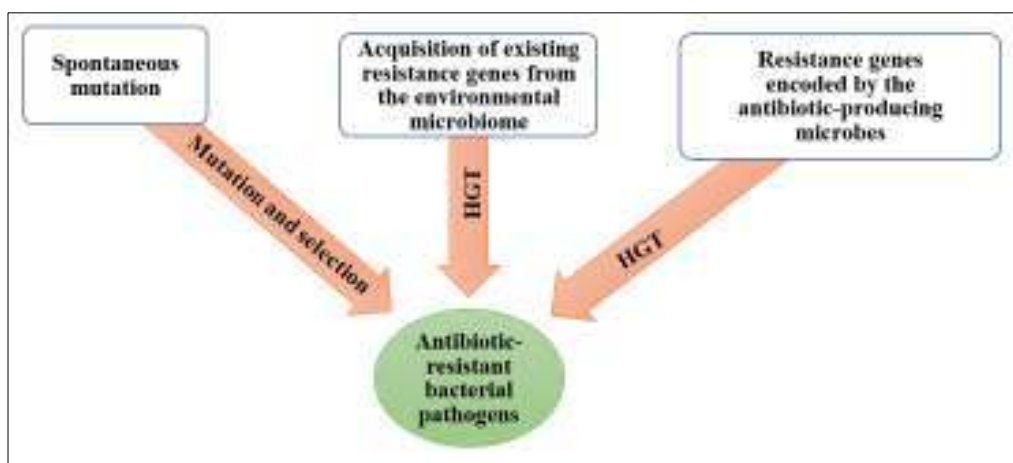


**Fig 3:** Origin of antibiotic-resistant bacterial pathogens

The majority of antibiotics used in medicine and agriculture today are either made by or derived from soil actinomycete bacteria. These organisms may have produced a variety of ARGs; naturally occurring ARGs are believed to have emerged billions of years ago and coevolved with the bacterial manufacture of antibiotics, which first functioned as a self-defense mechanism. (Bhullar *et al.*, 2012) <sup>[4]</sup>. For instance, it is known that *S. rimosus* carries several tetracycline-resistant determinants, such as *otrA*, *otrB*, and *otrC* (McMurtry and Levy, 1998) <sup>[32]</sup>. Antibiotic-modifying

enzymes that are known to exist today are thought to have their origins in the original escape of these naturally occurring ARGs. A study conducted on soil samples collected between 1940 and 2008 revealed a significant increase in the frequency of particular ARGs that confer resistance to erythromycins, tetracyclines, glycopeptides and  $\beta$ -lactams. One such ARG, tetracycline, was roughly 15 times greater in number in 2008 than they are in 1970s (Knapp *et al.*, 2010) <sup>[24]</sup>.

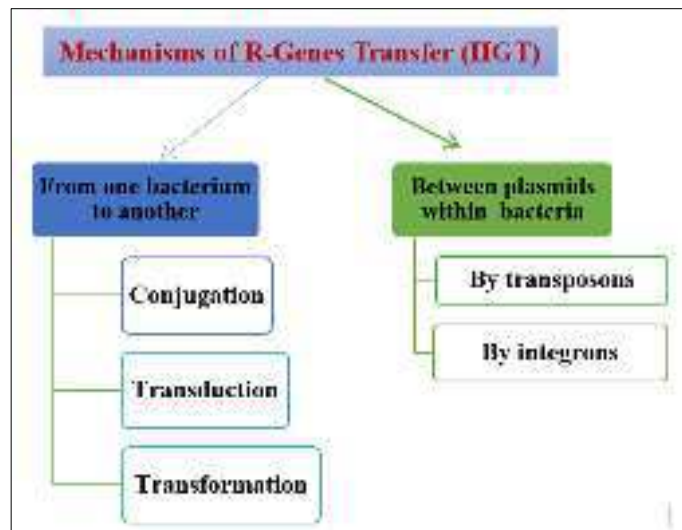


Fig 4: Mechanisms of R-gene transfer

R-genes can transfer from one bacterium to another through conjugation, transduction and transformation. In conjugation, R-genes transfer from one bacterium cell to another bacterium cell with help of conjugation tube or via

cell to cell contact. But in case of transduction, R-gene transfer is mediated by bacteriophage. A bacterium takes up a piece of DNA floating in its environment in case of transformation (Heuer and Smalla, 2007; Fig 4).

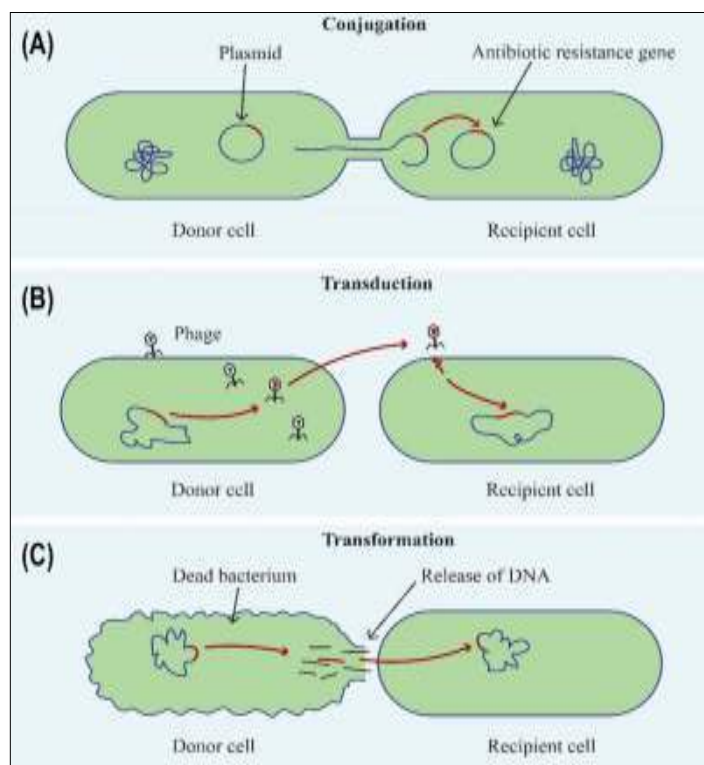


Fig 5: Mechanisms of HGT between Plant Pathogenic Bacteria

R-genes can also transfer from one plasmid to another plasmid within a bacterial cell with the help of transposons and integrons. Transposons or jumping genes are sequences of DNA that can move around different positions within the genome of single cell were first discovered by Barbara McClintock in maize during 1940s (Starlinger *et al.*, 1985)<sup>[56]</sup>, when donor plasmid carrying transposons co-integrate with recipient plasmid then these transposons can transfer from one plasmid to another plasmids. Integrons are large mobile DNA molecules packed with multiple gene cassettes each consisting of R-genes attached to a small recognition site were first discovered by Stokes and Hall in conjugative

plasmids, *Vibrio cholera* in 1989. The complete element consists of two conserved regions separated by a segment of variable length and sequence which includes inserted antibiotic resistance genes (Stokes and Hull, 1989)<sup>[57]</sup>. Numerous plasmids contain Tn5393. It was first identified on *E. amylovora*'s large conjugative plasmid pEa34 (34 kb) (Chiou and Jones, 1993)<sup>[81]</sup>. Thus, this conjugative plasmid may facilitate the HGT-mediated dissemination of genes resistance to streptomycin among *E. amylovora* or other bacteria, whether pathogenic or non pathogenic. Additionally, Tn5393 was discovered on the *E. amylovora* plasmid pEa29, where it can insert in multiple

places. Unlike pEa34, this 29-kb plasmid cannot be self-transferred to other strains and is unrelated to pEa34. Since pEa29 in *E. amylovora* is extremely stable, the integration of Tn5393 implies that the resistance has been steadily established in *E. amylovora* populations. Tn5393a, which lacks Tn5393's IS1133, was found in a number of strains of *Pseudomonas syringae* and *P. marginalis* (Han *et al.*, 2004). Additionally, it was found on the conjugative plasmid pEU30 in isolates of *E. amylovora* (Förster *et al.*, 2015) [15].

### Mechanisms of antibiotic resistance



#### Antibiotic modification or degradation

Antibiotic modification or degradation is a mechanism of antibiotic resistance in which bacteria possess enzymes or other mechanisms that can chemically modify or break down antibiotics, rendering them ineffective. This mechanism is not limited to plant pathogenic bacteria but can also be found in various types of pathogenic bacteria (Mann *et al.*, 2021). For instance, degradation of streptomycin by the bacterium *E. amylovora*, which causes fire blight in various fruit trees, including apple and pear trees. *E. amylovora* has developed resistance to streptomycin by producing an enzyme called streptomycin phosphotransferase (StrA). This enzyme phosphorylates (adds a phosphate group) to streptomycin, which changes the antibiotic's chemical structure. The modified streptomycin is no longer effective at inhibiting bacterial growth, allowing *E. amylovora* to continue its pathogenic activity (Forster *et al.*, 2015). Gene aadA1 and aadA2 encode enzyme aminoglycoside adenyltransferases that helps in inactivation of streptomycin that helps in development of streptomycin resistance against *X. oryzae* pv. *oryzae* (Xu *et al.*, 2013). strA-strB genes encode phosphotransferases that alter streptomycin into a nontoxic form which provides streptomycin resistance in *E. amylovora* (Forster *et al.*, 2015).

#### Antibiotics sequestering

Antibiotic sequestration is a mechanism of antibiotic resistance in which bacteria are capable of trapping or

sequestering antibiotics, preventing them from reaching their intended target sites and exerting their antibacterial effects. This mechanism can help plant pathogenic bacteria evade the harmful effects of antibiotics, enabling them to continue causing infections. According to Rudolf *et al.* (2015), the main antibiotic resistance mechanism is the sequestration of either the metal-free or metal-bound antibiotic by binding proteins ZbmA in *Streptomyces flavoviridis*.

#### Target Modification

Target modification is a mechanism of antibiotic resistance in which bacteria alter the target molecules or sites that antibiotics normally interact with, rendering the antibiotics ineffective. In plant pathogenic bacteria, this mechanism can enable them to continue causing infections without the antibiotics inhibiting their growth. An example of target modification in plant pathogenic bacteria is the modification of the ribosomal target site in response to streptomycin. In the case of *P. syringae* pv. *actinidiae* which causes bacterial canker of kiwi fruit, the bacteria modify a specific region on their ribosomes, called the S12 protein. This modified S12 protein no longer effectively binds to streptomycin. As a result, the antibiotic is unable to disrupt protein synthesis within the bacterial cell, rendering streptomycin antibiotic less effective or completely ineffective (Cameron and Sarojini, 2014). Streptomycin binds to protein S12, encoded by the rpsL gene of the 30S ribosomal subunit and inhibit protein synthesis. A change in nucleotides at codon 43 of the rpsL gene from AAA, which encodes lysine in streptomycin-sensitive *E. amylovora* strains, to AGA (arginine), AAT/C (asparagine), or ACA (threonine) conferred a resistance phenotype to the antibiotic observed that gyrA encoded the DNA gyrase subunit A which is target site for oxolinic acid mutation at GyrA helps to develop resistance against oxolinic acid in *Burkholderia glumae*.

#### Target Protection

Target protection is a mechanism of antibiotic resistance in which bacteria produce proteins or molecules that shield the target sites of antibiotics, preventing the antibiotics from binding and exerting their inhibitory effects. Tetracycline antibiotics work by binding to the ribosomes of bacteria, disrupting protein synthesis. In response to tetracycline exposure, certain plant pathogenic bacteria, such as *Agrobacterium tumefaciens* and *Agrobacterium vitis*, produce Tet proteins, including TetA and TetB, which are membrane transport proteins. These Tet proteins actively pump tetracycline out of the bacterial cells, reducing the intracellular concentration of the antibiotic. By expelling tetracycline from the cell, the Tet proteins protect the ribosomal target sites from the antibiotic. As a result, tetracycline is less effective at inhibiting protein synthesis in these bacteria, allowing them to continue growing and causing infections in plant tissues. Eliminating the antibiotic from the target site offers an additional line of defence against infection. DrrC in *S. peuceitius* removed intercalated daunorubicin/doxorubicin from DNA, enabling normal transcription and replication.

#### Target Bypass

Target bypass is a mechanism of antibiotic resistance in which bacteria evolve alternative biochemical pathways or

use alternative target molecules that circumvent the specific targets of antibiotics. This allows them to continue their growth and metabolic processes despite the presence of the antibiotics. While this resistance mechanism is more commonly associated with pathogenic bacteria in clinical settings, it can also occur in plant pathogenic bacteria. An example of target bypass in plant pathogenic bacteria involves the resistance of *Xanthomonas citri* subsp. *citri* to copper-based antibiotics. However, some strains of *X. citri* subsp. *citri* have developed resistance to copper antibiotics through target bypass. In this resistance mechanism, the bacteria utilize alternative copper-independent pathways for essential cellular processes, effectively bypassing the need for copper-dependent targets. This adaptation allows the bacteria to continue growing and causing disease in citrus trees, despite the presence of copper-based antibiotics. The production of an extra B subunit of DNA gyrase to confer resistance against novobiocin, an alternative resistant RNA polymerase to confer resistance against rifamycin, or an alternative fatty acid synthase to confer ability to withstand platensimycin.

### Antibiotic Efflux

Antibiotic efflux is a mechanism of antibiotic resistance in which bacteria actively pump antibiotics out of their cells, reducing the intracellular concentration of the drug. This mechanism is common in both clinical and plant pathogenic bacteria. According to Herbert *et al.* (2022) [19], TetC encodes ABC (ATP binding cascade) transporter that remove excessive amount of oxytetracycline and streptomycin from antibiotic efflux *Xanthomonas arboricola* pv. *pruni* cytosol to outside of the cell and reduce its concentration in cytosol that helps to develop resistance against these antibiotics. Antibiotic efflux is a significant challenge in the management of plant diseases, as it allows bacteria to expel antibiotics and maintain their virulence. It underscores the need for innovative strategies for plant disease control that are less susceptible to bacterial resistance mechanisms, such as efflux pumps. ABC (ATP binding cascade) transporters helps in efflux of oxytetracycline with the help of otrC and DrrAB efflux system in antibiotic producer bacteria as *S. rimosus* and *S. peuceitius*, respectively (Yu *et al.*, 2012; Mak *et al.*, 2014) [28].

**Table 3:** Mechanism of acquiring resistance against different antibiotics by plant pathogenic bacteria

| Antibiotic      | ARG(s) or gene modification leading to resistance     | Type of resistance      | Antibiotic resistance phenotype                                                                                                                                                                                                   | References                                                    |
|-----------------|-------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| Gentamicin      | aacA3                                                 | Antibiotic inactivation | aacA3 encodes the aminoglycoside 3'-N acetyltransferase which inactivates gentamicin                                                                                                                                              | Xu <i>et al.</i> (2013)                                       |
| Kasugamycin     | Aac(2')-IIa (acetyltransferase)                       | Antibiotic inactivation | Acetylation of the 2'-amino residue of kasugamycin, which inactivates the antibiotic                                                                                                                                              | Yoshii <i>et al.</i> (2015) [68]                              |
| Streptomycin    | StrA-strB                                             | Antibiotic modification | strA-strB encodes phosphotransferase that modify streptomycin into a non toxic form                                                                                                                                               | Forster <i>et al.</i> (2015)                                  |
|                 | aadA1, aadA2                                          | Antibiotic modification | aadA genes encodes aminoglycoside adenylyltransferases inactivating streptomycin                                                                                                                                                  | Xu <i>et al.</i> (2013)                                       |
| Oxolinic acid   | GyrA83 mutation                                       | Target modification     | gyrA encodes the DNA gyrase subunit A                                                                                                                                                                                             | Meada <i>et al.</i> (2007)                                    |
| Streptomycin    | rpsL                                                  | Target modification     | rpsL encodes the ribosomal protein S12. Point mutation occur at codon 43 ( <i>E. amylovora</i> ) or rarely at codon 88 or 128 ( <i>C. michingensis</i> ssp <i>michingensis</i> ), which prevent streptomycin to bind the ribosome | Forster <i>et al.</i> (2015); Valenzuela <i>et al.</i> (2019) |
| Oxytetracycline | tetC                                                  | Antibiotic efflux       | Efflux of the antibiotic through a pump                                                                                                                                                                                           | Herbert <i>et al.</i> (2022) [19]                             |
| Kasugamycin     | Deletion of <i>opp</i> and <i>dpp</i> (two permeases) | Reduced permeability    | Opp and Dpp are two major peptide ATP binding cassette transporter systems. When deleted, kasugamycin can't enter the cell                                                                                                        | Ge <i>et al.</i> (2018)                                       |

**Table 4:** Mechanisms of antibiotic self-resistance in bacteria that produce antibiotics

| Mechanisms of antibiotic resistance          | Examples                                                                                 | Location of Gene                                                                                     | References                                                                                          |
|----------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Antibiotic modification/degradation          | Aminoglycoside modifying enzymes (AME): AAC; APH; ANT Streptomycin-6-phosphotransferase  | Chromosome <i>S. griseus</i> (smk)                                                                   | Shinkawa <i>et al.</i> (1985) [55]; Mak <i>et al.</i> (2004) [28]                                   |
|                                              | $\beta$ -lactamase Class A, B, C                                                         | Chromosome <i>streptomyces</i> sp.                                                                   | Ogawara (2016) [36]                                                                                 |
| Antibiotic efflux                            | ABC transporter DrrAB (Dox) OtrC (oxytetracycline)                                       | Chromosome <i>S. peuceitius</i> (drrAB) <i>S. rimosus</i> (otrC)                                     | Yu <i>et al.</i> (2012); Li <i>et al.</i> (2014)                                                    |
|                                              | MFS transporter OtrB (oxytetracycline) Mfs1 (natamycin)                                  | Chromosome <i>S. rimosus</i> (otrB) <i>S. chattanoogensis</i> (mfs1)                                 | Ohnuki <i>et al.</i> (1985) [38]; Reynes <i>et al.</i> (1998); Wang <i>et al.</i> (2017) [63]       |
| Antibiotic sequestration by special proteins | Sequestration T1ma, B1ma, ZbmA (bleomycin)<br>Sequestration T1mA, B1mA, ZbmA (bleomycin) | Chromosome <i>S. hindustanus</i> (t1mA); <i>S. verticillus</i> (b1mA); <i>S. flavoviridis</i> (zbmA) | Gatignol <i>et al.</i> (1998) [16]; Sugiyama <i>et al.</i> (1994) [55]; Rudolf <i>et al.</i> (2015) |
| Antibiotic target modification               | Low affinity penicillin binding proteins (PBP) Class A Class B                           | Chromosome <i>Streptomyces</i> sp                                                                    | Ogqware (2015), 2016a                                                                               |
|                                              | Peptidoglycan remodeling                                                                 | Chromosome <i>S. toyocaensis</i> (VanHst,                                                            | Marshall <i>et al.</i> (1998) [29];                                                                 |

|                              |                                                                |                                                                                     |                                                                                                                       |
|------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
|                              | (Glycopeptides) VanHst, Dd1M, VanXst<br>VanHaov, Dd1N, VanXaov | dd1M, vanXst); <i>A. orientalis</i><br>(vanHaov, dd1N, vanXaov)                     | Binda <i>et al.</i> (2014) <sup>[5]</sup>                                                                             |
|                              | 23S rRNA methylation (MLS) Cfr, PikR1,<br>PikR2                | Chromosome <i>S. caelestis</i> (cfr); <i>S.</i><br><i>venezuelae</i> (pikR1, pikR2) | Calcutt and Cundliffe (1990) <sup>[6]</sup> ;<br>Almutairi <i>et al.</i> (2015) <sup>[1]</sup>                        |
|                              | 16S rRNA methylation<br>(Aminoglycosides) PCT, Sgm methylase   | Chromosome <i>S. pactum</i> (pct) <i>M.</i><br><i>zionsis</i> (sgm)                 | Ballesta and Cundliffe<br>(1991) <sup>[3]</sup> ; Kojic <i>et al.</i> (1992) <sup>[25]</sup>                          |
| Antibiotic target bypass     | DNA gyrase subunit B (novobiocin)                              | Chromosome <i>S. sphaeroides</i> (gyrBR)                                            | Schmutz <i>et al.</i> (2003) <sup>[53]</sup>                                                                          |
| Antibiotic target protection | Antibiotic removal DrrC (Dox) OtrA<br>(oxytetracycline)        | Chromosome <i>S. peucetius</i> (drrC) <i>S.</i><br><i>rimosus</i> (otrA)            | Doyle <i>et al.</i> (1991) <sup>[14]</sup> ; Mak<br><i>et al.</i> (2014) <sup>[28]</sup> ; Prija and<br>Prasad (2017) |

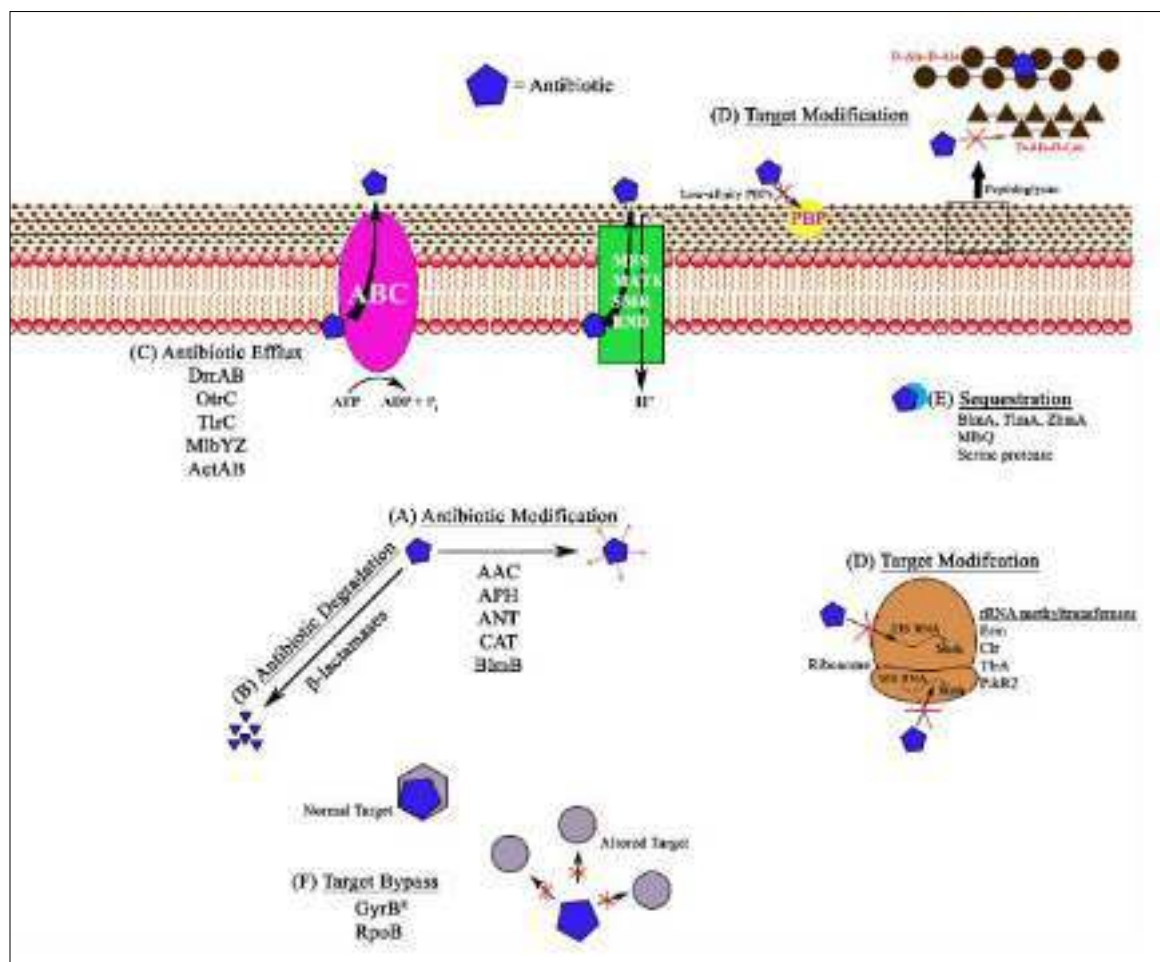


**Fig 6:** Diagram illustrating the several processes of antibiotic resistance in bacteria, along with examples (Peterson and Kaur, 2018)

**Table 5:** Reports of antibiotic resistance in plant-pathogenic bacteria

| Antibiotic    | Organism                                                                    | Location                           | Genetic mechanism                                                                  | Reference                                                                                                                                                              |
|---------------|-----------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kasugamycin   | <i>Acidovorax avenae</i> ssp. <i>Avenae</i> ,<br><i>Burkholderia glumae</i> | Japan                              | aac(2')-IIa                                                                        | Yoshii <i>et al.</i> (2012) <sup>[68]</sup>                                                                                                                            |
| Streptomycin  | <i>E. amylovora</i>                                                         | California, USA                    | Chromosomal mutation,<br>rpsL mutation,<br>strAB on plasmid RSF1010,<br>Tn5393a 32 | Schroth <i>et al.</i> (1979) <sup>[54]</sup><br>Chiou and Jones, (1995) <sup>[8]</sup> ;<br>Palmer <i>et al.</i> (1997) <sup>[39]</sup> ; Forster <i>et al.</i> (2015) |
|               | <i>Pseudomonas syringae</i>                                                 | Oregon, USA                        | strABa                                                                             | Scheck <i>et al.</i> (1996) <sup>[51]</sup>                                                                                                                            |
|               | <i>P. syringae</i> pv. <i>actinidiae</i>                                    | Japan                              | Tn5393a,<br>rpsL mutation                                                          | Han <i>et al.</i> (2004)                                                                                                                                               |
|               | <i>P. syringae</i> pv. <i>papulans</i>                                      | New York, USA and<br>Michigan, USA | strABb                                                                             | Norelli <i>et al.</i> (1991) <sup>[34]</sup>                                                                                                                           |
|               | <i>P. syringae</i> pv. <i>syringae</i>                                      | Oklahoma, USA                      | Tn5393a                                                                            | Sundin and Bender (1993) <sup>[58]</sup>                                                                                                                               |
|               | <i>Xanthomonas axonopodis</i> pv.<br><i>vesicatoria</i>                     | Argentina                          | Tn5393b                                                                            | Sundin and Bender (1995) <sup>[59]</sup>                                                                                                                               |
|               | <i>Xanthomonas citri</i> subsp. <i>citri</i>                                | Korea                              | strBc                                                                              | Hyun <i>et al.</i> (2012) <sup>[22]</sup>                                                                                                                              |
|               | <i>Xanthomonas oryzae</i> pv. <i>oryzae</i>                                 | China                              | aadA1                                                                              | Xu <i>et al.</i> (2013)                                                                                                                                                |
| Oxolinic acid | <i>Erwinia amylovora</i> , <i>Burkholderia glumae</i>                       | Israel                             | Probable chromosomal mutation                                                      | Kleitman <i>et al.</i> (2005) <sup>[23]</sup>                                                                                                                          |

## Conclusion

The emergence and spread of resistance against antibiotics in plant pathogenic bacteria pose significant challenges to agriculture and food production. The mechanisms underlying this resistance are diverse and interconnected, involving enzymatic degradation, active efflux, horizontal gene transfer, and adaptive mutations. The multifaceted nature of these resistance mechanisms underscores the complexity of addressing and mitigating antibiotic resistance in agricultural settings. Efforts to combat antibiotic resistance in plant pathogenic bacteria must be comprehensive and adaptive. Developing new antibiotics with different modes of action and exploring combination therapies can help overcome specific resistance mechanisms. Additionally, understanding the ecological and environmental factors that contribute to the dissemination of resistance genes is crucial for implementing targeted control strategies. The role of horizontal gene transfer in spreading antibiotic resistance highlights the necessity of monitoring and regulating the use of antibiotics in agriculture. Integrated pest management practices, crop rotation, and alternative disease control methods should be promoted to reduce reliance on antibiotics and minimize the selective pressure that drives the development of resistance. Collaboration between researchers, agricultural practitioners, and policymakers is essential to develop and implement effective strategies for managing antibiotic resistance in plant pathogenic bacteria. Continued surveillance and research efforts are crucial for staying ahead of evolving resistance patterns and identifying new potential targets for intervention. Ultimately, addressing antibiotic resistance in plant pathogenic bacteria is not only vital for safeguarding crop health and yield but also for preserving the long-term sustainability of agriculture. A holistic and proactive approach that combines scientific innovation, responsible antibiotic use, and sustainable agricultural practices will be key to mitigating the impact of antibiotic resistance on global food security.

## Future Aspects

- **Genomic Studies and Target Identification:** Continued advancements in genomics and bioinformatics will play a pivotal role in identifying specific genetic determinants associated with antibiotic resistance in plant pathogenic bacteria. Targeting these specific genes or pathways could lead to the development of novel and more effective antibacterial agents.
- **Antibiotic Alternatives:** Research into alternative methods for controlling bacterial infections in plants without relying on antibiotics will likely gain momentum. This could include the development of biopesticides, plant immune system enhancers, or bacteriophage-based therapies.
- **Precision Agriculture and Site-Specific Treatment:** Implementing precision agriculture techniques, such as sensor-based monitoring and automated delivery systems, can enable more targeted and efficient use of antibiotics. This approach minimizes unnecessary antibiotic exposure, reducing the risk of resistance development.
- **Microbiome Engineering:** Understanding the intricate relationships between plant microbiomes and pathogenic bacteria can lead to innovative strategies for

manipulating microbial communities to suppress pathogen growth. This may involve the use of probiotics or the engineering of plant microbiomes to enhance natural defenses.

- **Combination Therapies:** Exploring synergistic interactions between different antibiotics or combining antibiotics with other antimicrobial agents may enhance the effectiveness of treatment while minimizing the likelihood of resistance development.
- **Ecological Approaches:** Integrating ecological principles into agriculture, such as crop diversification and agroecological practices, can contribute to a healthier and more resilient plant ecosystem. This, in turn, may reduce the reliance on antibiotics and create an environment less conducive to the spread of antibiotic resistance.
- **Public Awareness and Policy Initiatives:** Increasing public awareness about the consequences of antibiotic misuse in agriculture and fostering a responsible use mindset among farmers will be critical. Policy initiatives and regulations that encourage sustainable agricultural practices and restrict the indiscriminate use of antibiotics are essential.
- **Surveillance and Monitoring Programs:** Establishing robust surveillance programs to monitor the prevalence and dynamics of antibiotic resistance in plant pathogenic bacteria will provide valuable data for early detection and intervention. This information can guide the development of targeted strategies to combat emerging resistance patterns.
- **Global Collaboration:** Since antibiotic resistance knows no borders, international collaboration is vital. Sharing knowledge, resources, and best practices on a global scale can accelerate progress in understanding and addressing antibiotic resistance in plant pathogenic bacteria.
- By embracing these future aspects, the scientific community, agricultural practitioners, and policymakers can work together to develop sustainable and effective solutions to the growing challenge of antibiotic resistance in plant pathogenic bacteria. This multidisciplinary approach is crucial for ensuring the long-term health and productivity of global agriculture.

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