



Review Article

ANTIBIOTICS - A MINI REVIEW

Dr. Shraavan Kumar<sup>1\*</sup>, D. Suchitra<sup>2</sup>, CH Sudha Bhargavi<sup>3</sup>, Swapna Vemireddy<sup>4</sup>

<sup>1</sup>Department of Pharmaceutics, Trinity College of pharmaceutical sciences, peddapalli, Karimnagar, Telangana, India.

<sup>2</sup>PhD Research scholar, University College of Technology, Osmania University.

<sup>3</sup>Assistant Professor, Department of Pharmacology, Sankara Academy of Vision, Bangalore, India.

<sup>4</sup>Assistant Professor, Department of Pharmaceutical Analysis and Quality Assurance, Chilkur Balaji College of Pharmacy, RVS Nagar, Aziz Nagar, Hyderabad, Telangana.

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**ABSTRACT**

Antibiotics (Greek anti, "against", bios "life") are chemical compounds used to kill or inhibit the growth of infectious organisms. The discovery of antibiotics in the twentieth century is a greatest boon to the mankind. Initially most of the antibiotics were discovered from natural sources mainly from Actinomycetes and few were synthesized taking lead from natural sources. However due to misuse and abuse of antibiotics, the microorganisms have developed resistance to the currently available antibiotics. In this article we present the history, discovery of antibiotics from natural sources, synthetic antibiotics and resistance by microorganisms to the currently available antibiotics, strategies to overcome the resistance to antibiotics.

**KEYWORDS:** Antibiotic resistance, Antibiotics, Actinomycetes and  $\beta$ -Lactam.

**INTRODUCTION:**

**1.1 Antibiotics and History**

Antibiotics (Greek anti, "against", bios "life") are chemical compounds used to kill or inhibit the growth of infectious organisms. The term antibiotic appeared as early as 1928 in the French microbiological literature on antibiosis [1]. This phenomenon of antagonism between living microorganisms was frequently observed ever since 1877, when Pasteur and Joubert noticed that aerobic bacteria antagonized the growth of Bacillus anthracis.

However, the word in its present restrictive meaning – "a chemical substance derived from microorganisms which has the capacity of inhibiting growth, and even destroying, other microorganisms in dilute solutions" – was introduced by Selman Waksman in 1942 [2]. In 1885, Babes was the first to interpret microbial antibiosis as

being due to production of an inhibitory chemical substance by the antagonistic organism. Some years after Babes' work, Bouchard, and Emmerich and Low, prepared an extract of Pseudomonas aeruginosa which they called "pyocyanase".

In high dilution, this compound was inhibitory to Corynebacterium diphtheriae, Salmonella typhi, and Pasteurella pestis as well as to pathogenic cocci. For approximately 20 years, pyocyanase was used in therapy in treating a variety of infectious diseases, but its toxicity prevented it from further extensive use. Many reports dealing with inhibitory effects of bacteria upon other microorganisms were written during this period [3].

In 1887, Louis Pasteur reported that when "common bacteria" (what he termed) were introduced into a pure culture of anthrax bacilli, the bacilli died, and that an injection of deadly anthrax bacilli into a laboratory animal was harmless if "common bacteria" were injected along with it. This did not always work, but it did lead to the appreciation of antibiosis, wherein two or more microorganisms competed with one another for survival.

The modern anti-infective era opened with the discovery of the sulfonamides in France and Germany in 1936 as an offshoot of Paul Ehrlich's earlier achievements in treating infections with organometallics and his theory of vital staining. The well-known observation of a clear zone of inhibition (lysis) in a bacterial colony surrounding a colony of contaminating air borne

**\*Corresponding Author:**

D. Suchitra,  
Professor,  
PhD Research scholar, University College of Technology,  
Osmania University, Hyderabad.  
E-mail: [suchirakhi@gmail.com](mailto:suchirakhi@gmail.com)  
DOI:

Penicillium mold by Alexander Flemming in 1929, and its subsequent purification of penicillin from it in late 1930s and early 1940s by Florey, Chain, Abraham, and Heatley, provided additional impetus<sup>[4]</sup>.

In rapid succession, deliberate searches of the metabolic products of wide variety of soil microbes lead to the discovery of tyrothricin (Rene Dubos 1939), streptomycin (Selman Waksman 1943), chloramphenicol (John Ehrich & Quentin Bartz 1947), chlortetracycline (Benjamin Duggar 1948), neomycin (Selman Waksman & H A Lechevalier 1949), and erythromycin (Robert Bunch & James McGuire 1952). These discoveries ushered in the age of so-called "miracle drugs".

Microbes of soil origin remain to this day the most fruitful sources of antibiotics, although the specific means employed for their discovery are infinitely more sophisticated today than those employed 50 years ago. Initially, extracts of fermentations were screened simply for their ability to kill pathogenic microorganisms in vitro. Those that did were pushed along through ever more complex pharmacological and toxicological tests in attempts to discover clinically useful agents<sup>[5]</sup>.

Most antibiotics are produced by microorganisms such as actinomycetes, bacteria, and fungi. But antibiotic compounds may also be obtained from many other living organisms such as higher plants, lichens, algae and animals. Among the microorganisms that produce chemotherapeutically useful antibiotics, actinomycetes are the important group of organisms. These organisms were first discovered by Ferdinand Cohn (1875) and Harz (1877) named them as actinomycetes.

It has been well established that microorganisms are a virtually unlimited source of natural products, many of which have potential therapeutic applications. Filamentous soil bacteria of the genus *Streptomyces* are remarkable, and merit special consideration with regard to the morphological and metabolic differentiation phenomena they manifest during later stages of development. Species of *Streptomyces* generally synthesize a sizable number of diverse natural secondary metabolites, the best known of which are antibiotics currently used worldwide as pharmaceutical and agrochemical products. Two-thirds of commercially available antibiotics and approximately 60% of those used in agricultural purposes were originally isolated from different *Streptomyces* species<sup>[6]</sup>. According to in depth analysis by Berdy<sup>[7]</sup> (2005) around 16,500 antibiotics had been discovered by 2002 of which 8,700 were produced by actinomycetes, 4900 by filamentous fungi and 2900 by bacteria.

## 1.2 Classification of Antibiotics

Antibiotics can be classified by several ways. The most common method classifies them according to their action against infecting organism<sup>[8]</sup>. Some antibiotics attack the cell wall; some disrupt

the cell membrane and a majority of them inhibit the synthesis of nucleic acids and proteins. Microbiologist prefers a classification according to the producing organism. Antibiotics are classified on the basis of chemical structure and are given in table 1.1.

**Table 1.1 Classifications of Antibiotics<sup>[9]</sup>**

Group	Antibiotics	Mechanism of Action
<b><math>\beta</math>-Lactum Antibiotics</b>	Penicillins, Cephalosporins Methicillin	Inhibition of bacterial cell wall, synthesis, specifically inhibition of the biosynthesis of the peptidoglycan. Interrupt the cell wall cross linking.
<b>Aminoglycosides</b>	Streptomycin Gentamycin, Amikacin, Neomycin.	Act directly on the bacterial ribosome to inhibit the initiation of protein synthesis and to interfere with the fidelity of translation of the genetic message.
<b>Tetracyclines</b>	Tetracycline	Inhibit protein synthesis by interaction with 30S and 50 ribosome subunits.
<b>Macrolides</b>	Erythromycin, Azithromycin	Binding to 50 S ribosome subunit to prevent translocation step of bacterial protein synthesis.
<b>Lincomycins</b>	Linomycin, Clindamycin	Binding to 50 S ribosome subunit to prevent translocation step of bacterial protein synthesis.
<b>Polypeptides</b>	Bacitracin  Vancomycin	Interfere with bacterial cell wall synthesis and are effective only against Gram-positive bacteria.  Inhibit the cell wall synthesis by preventing the synthesis of cell wall mucopeptide polymer.

	Daptomycin	Disruption of the bacterial membrane through the formation of transmembrane channels.
	Teixobactin	Teixobactin is an inhibitor of cell wall synthesis. It acts primarily by binding to lipid II, a precursor to peptidoglycan. In addition to inhibiting cell wall synthesis.
<b>Sulfonamides</b>	Sulfamethoxazole, Sulfadiazine	Block synthesis of tetrahydrofolic acid and cell-linked metabolic pathways.
<b>Trimethoprim</b>	Trimethoprim	Competitive inhibition of dihydrofolic acid reductase: blocks synthesis of tetrahydrofolic acid
<b>Quinolones</b>	Sparfloxacin, Norfloxacin, Ciprofloxacin	Inhibit enzymatic activity of Bacterial DNA-gyrase (DNA-Topoisomerase for introducing super helical twist into closed double stranded DNA)
<b>Miscellaneous</b>	Chloramphenicol	Inhibit protein synthesis by interaction with 50S ribosome subunits.
	Rifampin	Binds to bacterial RNA polymerase and blocks RNA synthesis.
	Linezolid	Inhibit protein synthesis by preventing the formation of translation initiation complex

Streptogramins A & B	Synergically Inhibit protein synthesis. Streptogramins A: Binds to 50S ribosomes causing conformational changes to 50S sub unit. Streptogramin B: Prevents elongation of protein chains and causes release of incomplete peptides.
Platensimycin	Inhibit $\beta$ -ketoacyl synthases I/II (FabF/B) which are key enzymes in the production of fatty acids required for bacterial cell membranes.

**Table 1.2 New antibacterial drugs launched since 2000 both Natural and synthetically derived [10].**

Year	Name	Class	Lead (Source)
<b>Natural Product-derived</b>			
2002	Biapenem	$\beta$ -Lactam (carbapenem)	Thienamycin (actinomycete)
2002	Ertapenem	$\beta$ -Lactam (carbapenem)	Thienamycin (actinomycete)
2005	Doripenem	$\beta$ -Lactam (carbapenem)	Thienamycin (actinomycete)
2009	Tebipenem pivoxil	$\beta$ -Lactam (carbapenem)	Thienamycin (actinomycete)
2008	Ceftobiprole medocaril	$\beta$ -Lactam (cephalosporin)	Cephalosporin (fungus)
2010	Ceftaroline fosamil	$\beta$ -Lactam (cephalosporin)	Cephalosporin (fungus)
2001	Telithromycin	Macrolide (ketolide)	Erythromycin (actinomycete)
2003	Daptomycin	Lipopeptide	Daptomycin (actinomycete)
2005	Tigecycline	Tetracycline	Tetracycline (actinomycete)
2007	Retapamulin	Pleuromutilin	Pleuromutilin (fungus)
2009	Telavancin	Glycopeptide	Vancomycin (actinomycete)
2015	Teixobactin	lipopeptide	Eleftheria terrae (Bacteria)

Synthetically-derived			
2000	Linezolid	Oxazolidinone	Oxazolidinone
2002	Prulifloxacin	Fluoroquinolone	Quinolone
2002	Pazufloxacin	Fluoroquinolone	Quinolone
2002	Balofloxacin	Fluoroquinolone	Quinolone
2004	Gemifloxacin	Fluoroquinolone	Quinolone
2007	Garenoxacin	Quinolone	Quinolone
2008	Sitafoxacin	Fluoroquinolone	Quinolone
2009	Antofloxacin	Fluoroquinolone	Quinolone Quinolone
2009	Besifloxacin	Fluoroquinolone	Quinolone

### 1.3 The problem of Antibiotic Resistance

Antibiotic resistance is the ability of a microorganism to withstand the effect of an antibiotic. Acquiring resistance to a specific antibiotic provides a clear benefit to the bacterium when exposed to that antibiotic. Thus, the acquisition of antibiotic resistance is commonly cited as an example of "evolutionary change," [11] referred to the development of antibiotic resistance as an example of evolutions "creative force." Some mutations, such as antibiotic resistance, can be beneficial since they may provide the organism an increased ability to survive under very specific environmental conditions [12].

#### Causes

Antimicrobial resistance occurs in viruses, bacteria, fungi, and parasites as a natural and unavoidable manifestation of their evolutionary capabilities. The decline in effectiveness of existing drugs is a consequence of a complex interaction among natural selection, environment, and patterns of drug use and misuse. In recent years, there has been a growing interest in biofilms, which are structured communities of microorganisms enclosed in a self-produced hydrated polymeric matrix attached to a living or inert surface. Although many infections manifest themselves as biofilms, most licensed antibiotics are not effective against them because of their sessile nature. As a result, antimicrobial resistance has developed into a global public health issue, as strains of a variety of pathogens have recently emerged that defy treatment with commonly available therapeutics [13].

#### Mechanisms

The various mechanisms by which microorganisms exhibit resistance to antimicrobial agents are:

1. Inactivation of the drug e.g., Staphylococcal resistance to penicillin is mediated by blaZ, the gene that encodes  $\beta$ -lactamase. This is predominantly extracellular enzyme, and is synthesized when Staphylococci are exposed to  $\beta$ -lactam antibiotics, this enzyme hydrolyzes the  $\beta$ -lactam ring, rendering the  $\beta$ -lactam antibiotics inactive [14].

2. Alteration of target site: PBP (Penicillin-binding proteins) is the target of beta-lactam antibiotics such as penicillin. Beta-lactam is a structural analogue of D-alanyl- D-alanine, and it binds covalently to the S. aureus PBP at its D-alanyl-D-alanine binding pocket. This inactivates the PBP and inhibits the cross-bridge formation step of peptidoglycan synthesis, causing the cell to rupture from the peptidoglycan mesh. However, MRSA produces a unique PBP, designated PBP2' (or PBP2A), which has an extremely lowbinding affinity to beta-lactam antibiotics. As a result, the PBP2' can keep on synthesising the peptidoglycan even in the presence of beta-lactam antibiotics. This is the basis of beta-lactam resistance of MRSA [15].

3. Modification of the permeability of the cell wall: The reduced susceptibility to vancomycin appears to result from changes in peptidoglycan biosynthesis. The Vancomycin-intermediate-resistant Staphylococcus aureus (VISA) strains are notable for the additional quantities of synthesized peptidoglycan that result in irregularly shaped, thickened cell walls. There is also decreased cross-linking of peptidoglycan strands, which leads to the exposure of more D-Ala-D-Ala residues. The altered cross-linking results from reduced amount of L-glutamine that is available for amidation of D-glutamate in the pentapeptide bridge. As a result, there are more D-Ala-D-Ala residues available to bind and trap vancomycin. The bound vancomycin then acts as a further impediment to drug molecules reaching their target on the cytoplasmic membrane [14].

4. Multiple Antibiotic Resistance (MAR) Efflux Pump: Several bacteria, including Escherichia coli, construct a multiple-antibiotic-resistance (MAR) efflux pump that provides the bacterium with resistance to multiple types of antibiotics, including erythromycin, tetracycline, ampicillin and nalidixic acid. This pump expels the antibiotic from the cell's cytoplasm, helping to maintain the intracellular levels below a lethal concentration [12].

5. Expression/ Loss of enzyme activity: The aminoglycoside antibiotics are cationic inhibitors of bacterial translation, and found clinical use for over half a century. Resistance to these antibiotics is primarily the result of expression of enzymes that covalently modify the antibiotics, either by acetylation, phosphorylation or adenylation (Wright G D, 2003). This modification interferes with binding to the target 16S rRNA in the decoding region of the A-site of the ribosome. Loss of enzymatic activity can result in metronidazole resistance. Intracellular metronidazole must be enzymatically activated before it can serve as an antimicrobial agent. This activation is achieved by the enzyme, NADPH nitroreductase. If the metronidazole is not activated it has no inhibitory effect on the bacterium. Thus, if NADPH nitroreductase activity is absent in the cell metronidazole remains inactive [12].

#### 1.4 Strategies to overcome the problem of antimicrobial resistance

The resistance problem demands that a renewed effort be made to seek antibacterial agents effective against pathogenic bacteria resistant to current antibiotics. An alternative approach to the problem of emerging resistance to current antibiotics is to seek structurally novel antibiotics that inhibit new molecular targets. Such agents are unlikely to be susceptible to existing mechanisms of resistance because of their structural novelty and unique mode of action.

New molecular targets involved in bacterial growth have been proposed. Nucleic acid, protein, and cell wall synthesis are already the targets of existing antibacterial agents. Nevertheless, the complexities of these processes provide a rationale for continuing to screen for inhibitors acting on new molecular targets within these pathways. Indeed, this position is supported by the discovery and current development of the oxazolidinones which inhibit bacterial protein synthesis by a novel mechanism. The antibiotic mupirocin inhibits bacterial isoleucyl-tRNA synthetase, which charges its cognate tRNA species with isoleucine. Mupirocin inhibits the formation of isoleucyl adenylate, the first step of this aminoacylation reaction, leading to depletion of charged tRNA. The resulting amino acid starvation not only leads to inhibition of protein synthesis but also has widespread effects on cellular metabolism through induction of the stringent response [16].

The efflux systems are potential targets for drug action that would lead to products containing an antibiotic and an inhibitor which prevent efflux of the drug from the cell. Further, efforts in this area are to be encouraged in view of the emergence of efflux-based resistance in clinical isolates [16].

The emergence of antibiotic resistance has led to the synthesis of analogues of existing antibiotics and their successful use against clinical isolates resistant to a number of antibiotics, including the tetracyclines,  $\beta$ -lactams, quinolones and glycopeptides. The chemical synthesis of analogues of these antibiotic classes has yielded new derivatives that bind to the refractory targets.

A combination of antimicrobials with different target sites and mechanisms of action can be beneficial in reducing resistance development. Some drug formulations in current use are already based on the concept of dual targets or mutual interference. For example, the combination of trimethoprim and sulphamethoxazole [17].

Chemical synthesis of antimicrobial agents can be used to make fundamentally new structures that might act at different bacterial targets to those already identified. Drugs arising from this approach include the oxazolidinones (Jones R N, 1996).

Another approach to combat the antimicrobial resistance is to discover new antibiotics from natural products. Plants have traditionally provided a source of hope for novel drug compounds, as plant herbal mixtures have made large contributions to human health and well-being owing to their popular use as remedies for many infectious diseases, searches for substances with antimicrobial activity in plants are frequent [17].

Soil, in particular, is an extensively exploited ecological habitat, the microorganisms of which produce many useful natural products, including some clinically important antibiotics [18].

#### Conclusion:

Antibiotics play a vital role in reducing mortality due to infections caused by pathogenic microorganisms. However these microorganisms are acquiring resistance to the currently available antibiotics by various mechanisms and rendering them useless and the need of the hour is to develop new antibiotics either from natural sources or synthetically.

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