UNIT : 2

Bacterial Antibiotics

An antibiotic is a type of antimicrobial substance active against bacteria and is the most important type of antibacterial agent for fighting bacterial infections. The term *antibiotic* which means "opposing life", based on Greek roots, anti: "against" and biotic: "life", is broadly used to refer to any substance used against microbes, but in the usual medical usage, antibiotics (such as penicillin) are those produced naturally whereas non antibiotic antibacterials (such as sulfonamides and antiseptics) are fully synthetic. However, both classes have the same goal of killing or preventing the growth of microorganisms, and both are included in antimicrobial chemotherapy.

Antibiotic medications are widely used in the treatment and prevention of such infections. They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess antiprotozoal activity. Antibiotics are not effective against viruses such as the common cold or influenzadrugs which inhibit viruses are termed antiviral drugs or antivirals rather than antibiotics.

"Antibacterials" include antiseptic drugs, antibacterial soaps, and chemical disinfectants, whereas antibiotics are an important class of antibacterials used more specifically in medicineand sometimes in livestock feed.

History :

Antibiotics have been used since ancient times. Many civilizations used topical application of mouldy bread, with many references to its beneficial effects arising from ancient Egypt, China, Serbia, Greece, and Rome. The first person to directly document the use of moulds to treat infections was John Parkinson (1567–1650). Antibiotics revolutionized medicine in the 20th century.

Alexander Fleming (1881–1955) discovered modern day penicillin in 1928, the widespread use of which proved significantly beneficial during wartime. However, the effectiveness and easy access to antibiotics have also led to their over use and some a bacteria have evolved resistance to them.

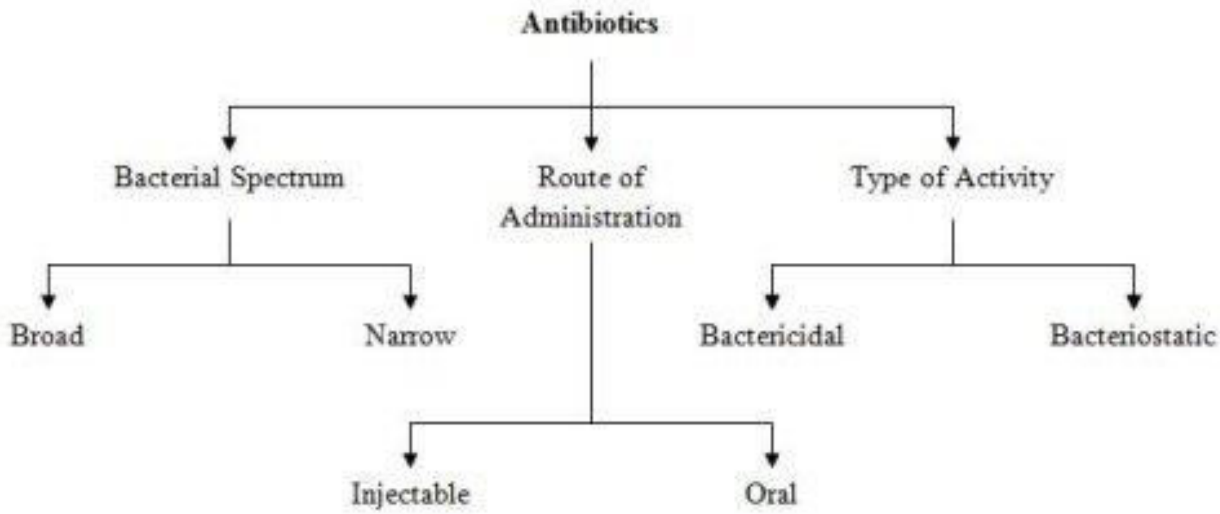
Classification :

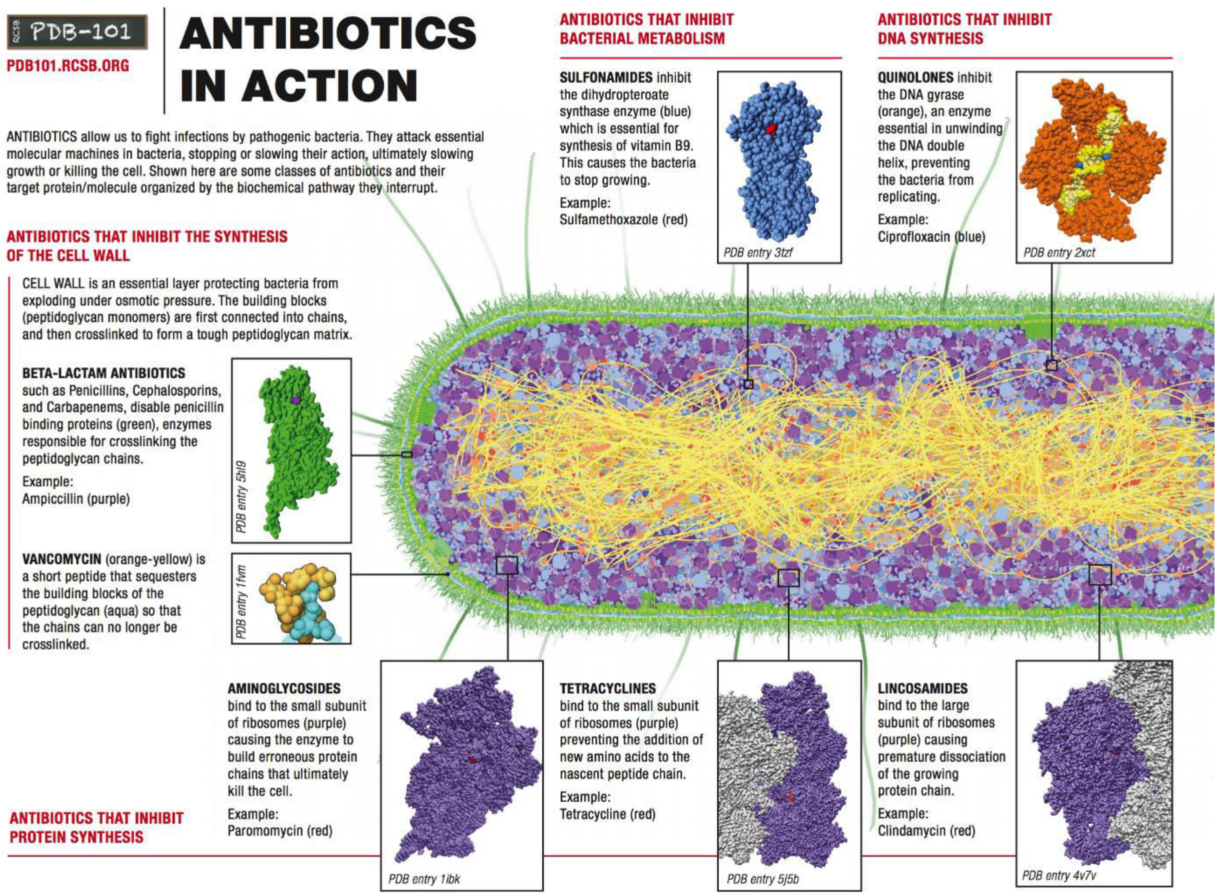
Antibiotics are commonly classified based on their mechanism of action, chemical structure, or spectrum of activity.

Most target bacterial functions or growth processes.Those that target the bacterial cell wall (penicillins and cephalosporins) or the cell membrane (polymyxins), or interfere with essential bacterial enzymes (rifamycins, lipiarmycins, quinolones, and sulfonamides) have bactericidal activities.

Protein synthesis inhibitors (macrolides, lincosamides, and tetracyclines) are usually bacteriostatic (with the exception of bactericidal aminoglycosides).

Further categorization is based on their target specificity. "Narrow-spectrum" antibiotics target specific types of bacteria, such as gram-negative or gram-positive, whereas broad-spectrum antibiotics affect a wide range of bacteria.





• Narrow spectrum	• Broad spectrum
- Penicilln	- Amoxicilln
- Cephalosporin (1st generation)	- Augmentin (Amoxicilln with clavulanic acid)
- Clindamycin	- Azythromycin - Tetracycline - Moxifloxacin

Antibiotics classification

Antibiotics are usually classified based on their structure,

Function and/or spectrum of activity

1Structure- molcular structure,

β-Lactams – Beta lactam ring

Aminoglycosides- vary only by side chains attached to basic structure

2Function – how the drug works, its mode of action.

5functioal groups

There are all components or function necessary for bacterial growth

Targets for antibiotics

- Inhibitions of cell wall synthesis
- Inhibitions of protein synthesis
- Inhibitions of membrane function
- Anti-metabolites
- Inhibitors of nucleic acid synthesis

3spectrum of activity:

- Narrow spectrum
- Broad spectrum

We will usually use functional classification

How do bacteria develop resistance to antibiotics?

'Antibiotic resistance' refers to a situation where a specific type of antibiotic drug is not effective at treating an infection caused by a specific bacterial species or strain.

Bacteria species: the huge genetic diversity of bacteria, make the species concept much less precise than for larger organisms. Broadly, it denotes a generic group of bacteria which all share a certain amount of genetic similarity (akin to that between humans and all primates) and so have similar functional characteristics.

Bacterial strain: in contrast to a species, a strain denotes a specific population of bacteria that share a very close genetic similarity. Strains are subtypes of a bacterial species existing in a specific context, which can have unique characteristics that differ from other bacteria of the same species.

This may happen for two reasons:

Intrinsic resistance: antibiotic resistance is a natural outcome of the bacteria's unique biology. In nature, antibiotic compounds are produced by many microorganisms to kill one another and discovering these compounds has formed the basis for most current antibiotic drugs. As a result, resistance to antibiotics has evolved and is found widely in natural settings, with some bacterial species having an intrinsic resistance to some types of antibiotic compounds.

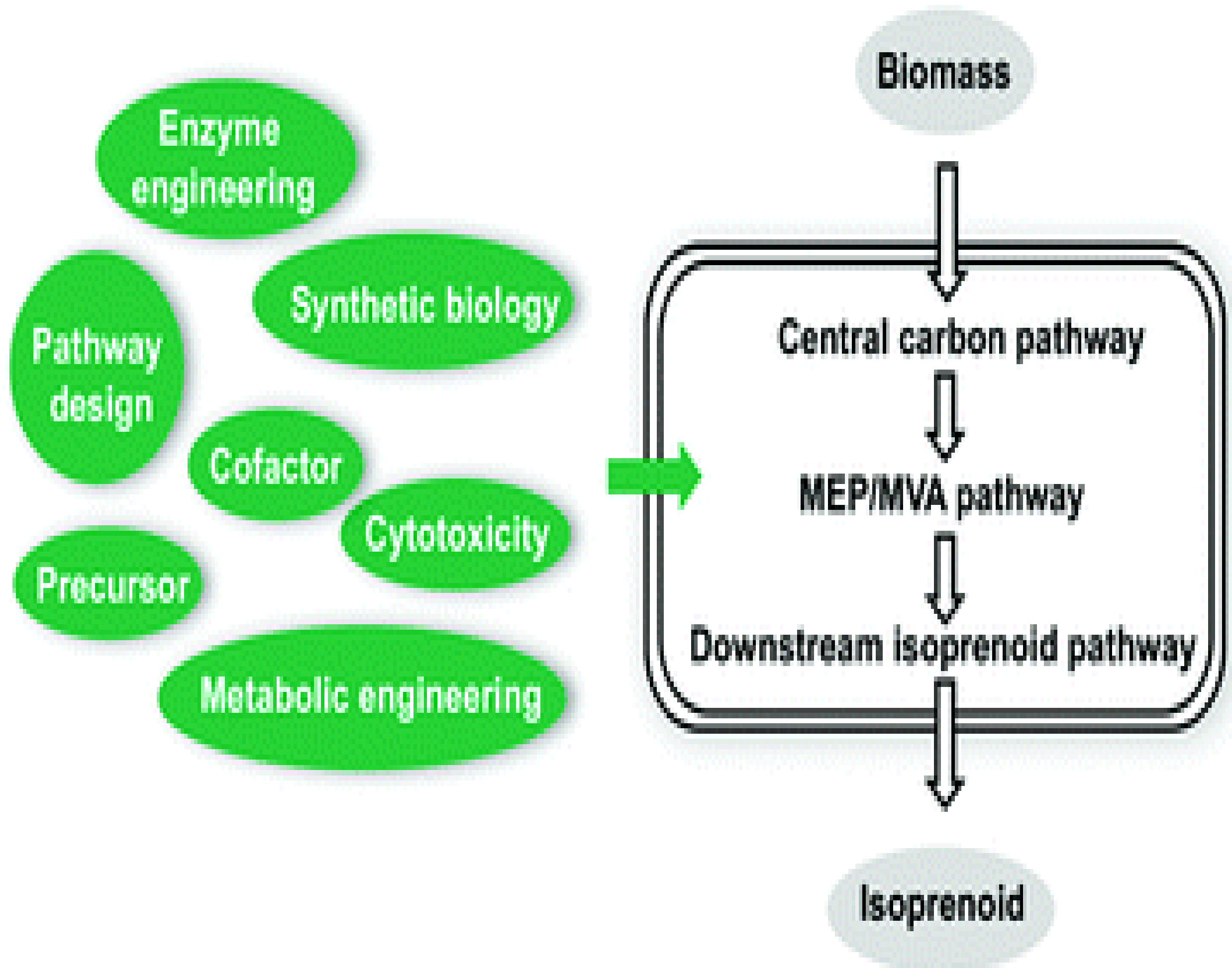
Acquired resistance: a specific population of bacterial cells that previously were sensitive to an antibiotic compound, may evolve by acquiring new genetic solutions and so biological capabilities, that enable it to disable the drug's ability to do them harm.

Metabolic Engineering of Microorganisms for the Production of Novel product of industry

- Natural products have been attracting much interest around the world for their diverse applications, especially in drug and food industries. Plants have been a major source of many different natural products. However, plants are affected by weather and environmental conditions and their successful extraction is rather limited. Chemical synthesis is inefficient due to the complexity of their chemical structures involving enantioselectivity and regioselectivity. For these reasons, an alternative means of overproducing valuable natural products using microorganisms has emerged.
- In recent years, various metabolic engineering strategies have been developed for the production of natural products by microorganisms. Here, the strategies taken to produce natural products are reviewed. For convenience, natural products are classified into four main categories: terpenoids, phenylpropanoids, polyketides, and alkaloids.
- For each product category, the strategies for establishing and rewiring the metabolic network for

heterologous natural product biosynthesis, systems approaches undertaken to optimize production hosts, and the strategies for fermentation optimization are reviewed. Taken together, metabolic engineering has enabled microorganisms to serve as a prominent platform for natural compounds production. Here we will examines both the conventional and novel strategies of metabolic engineering, providing general strategies for complex natural compound production through the development of robust microbial-cell factories.

- Metabolic engineering has been enabling development of high performance microbial strains for the efficient production of natural and non-natural compounds from renewable non-food biomass. Even though microbial production of various chemicals has successfully been conducted and commercialized, there are still numerous chemicals and materials that await their efficient bio-based production. Aromatic chemicals, which are typically derived from benzene, toluene and xylene in petroleum industry, have been used in large amounts in various industries. Over the last three decades, many metabolically engineered microorganisms have been developed for the bio-based production of aromatic chemicals, many of which are derived from aromatic amino acid pathways.



- Petroleum-derived chemicals have been essential in modern society because of their high demand in manufacturing fuels, solvents and materials among others. Aromatic chemicals are important in chemical, food, polymer and pharmaceutical industries since they serve various purposes. While bio-based processes for the production of a few aromatics have been commercialized, the majority of aromatic compounds are chemically synthesized due to the inefficiency of their biological production or even the lack of an appropriate bioproduction process.
- With the rapid advances in systems metabolic engineering tools and strategies, however, microbial production of aromatic compounds has seen a considerable progress over the past few years. By this approach, chemical processes for the synthesis of various aromatics using petroleum-derived benzene, toluene and xylene (BTX) as the starting materials can be replaced by bio-based sustainable and environmentally friendly processes.

Nonribosomal peptides (**NRP**) are a class of peptide secondary metabolites, usually produced by microorganisms like bacteria and fungi. Nonribosomal peptides are also found in higher organisms, such as nudibranchs, but are thought to be made by bacteria inside these organisms.

Nonribosomal peptides are synthesized by nonribosomal peptide synthetases, which, unlike the ribosomes, are independent of messenger RNA. Each nonribosomal peptide synthetase can synthesize only one type of peptide.

Nonribosomal peptides often have cyclic and/or branched structures, can contain non-proteinogenic amino acids including D-amino acids, carry modifications like *N*-methyl and *N*-formyl groups. Cyclization of amino acids against the peptide "backbone" is often performed, resulting in oxazolines and thiazolines; these can be further oxidized or reduced. On occasion, dehydration is performed on serines, resulting in dehydroalanine.

This is just a sampling of the various manipulations and variations that nonribosomal peptides can perform.

Nonribosomal peptides are often dimers or trimers of identical sequences chained together or cyclized, or even branched. Nonribosomal peptides are a very diverse family of natural products with an extremely broad range of biological activities and pharmacological properties. They are often toxins, siderophores, or pigments.

Nonribosomal peptide antibiotics, cytostatics, and immunosuppressants are in commercial use.

The biosynthesis of nonribosomal peptides shares characteristics with the polyketide and fatty acid biosynthesis. Due to these structural and mechanistic similarities, some nonribosomal peptide synthetases contain polyketide synthase modules for the insertion of acetate or propionate-derived subunits into the peptide chain.

Nonribosomal peptides (NRP), constructed on multimodular enzymatic assembly lines, often attain the conformations that establish biological activity by cyclization constraints introduced by tailoring enzymes. The dedicated tailoring enzymes are encoded by genes clustered with the assembly line genes for coordinated regulation. NRP heterocyclizations to thiazoles and oxazoles can occur on the elongating framework of acyl-S enzyme intermediates, whereas tandem cyclic PK polyether formation of furans and pyrans can be initiated by post-assembly line epoxidases.

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Nonribosomal peptides are synthesized by one or more specialized nonribosomal peptide-synthetase (NRPS) enzymes. The NRPS genes for a certain peptide are usually organized in one operon in bacteria and in gene clusters in eukaryotes. However the first fungal NRP to be found was ciclosporin. It is synthesized by a single 1.6MDa NRPS. The enzymes are organized in modules that are responsible for the introduction of one additional amino acid. Each module consists of several domains with defined functions, separated by short spacer regions of about 15 amino acids.

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Examples for bioactive compounds of nonribosomal origin