ANTIBIOTICS

SURENDER RAWAT

M. Sc. MICROBIAL BIOTECHNOLOGY

Chemotherapeutic Agents

- Used to treat infectious diseases
- Destroy pathogenic organisms or inhibit their growth at concentrations low enough to avoid undesirable damage to the host.
- ANTIBIOTICS : Anti – against & bios – life
- These are products of secondary metabolism
- 1904 - "MAGIC BULLET" by **Paul Ehrlich**
  - Found Tryptan red active against Trypanosome
  - With **Sahachiro Hata** found Arsphenamine effective against Syphilis
  - Later in 1910, Arsphenamine was sold under name of Salvarsan
- 1920- **Alexander Flemming** discovered Lysozyme in tears
- 1927- **Gerhard Domagk** discovered Prontosil red against streptococci and staphylococci
- 1928- Penicillin by **Alexander Flemming**
- 1939- Sulfa drugs by **Jaques and Therese**
- 1944- Streptomycin by **Selman Waksman**

ANTIBIOTICS

- Currently 8000 antibiotics are known
- Each year around 300 new antibiotically active compounds are detected, of which 30-35% are antibiotics
- Only 123 antibiotics of bacterial origin are produced by fermentation
- Only chloramphenicol, phosphonomycin and pyrrolnitrin are produced synthetically
- Significance for the strain is unclear

USES OF ANTIBIOTICS

- Antitumor antibiotics
- Antibiotics for plant pathology
- Antibiotics as food preservatives
- Antibiotics used as animal growth promoters and in veterinary medicine
- Antibiotics as tools in biochemistry and molecular biology

Antibiotics are classified in several ways

1.On the basis of mechanism of action

2.On the basis of spectrum of activity

On the basis of mechanism of action

- **Cell Wall Synthesis inhibitors:**

  Penicillins
  Cephalosporins
  Vancomycin

  Beta-lactamase Inhibitors
  Polymycin
  Bacitracin

- **Protein Synthesis Inhibitors**

- Inhibit 30s Subunit
  Aminoglycosides (gentamycin)
  Tetracyclines

- Inhibit 50s Subunit
  Macrolides
  Chloramphenicol
  Clindamycin
  Streptogramins

DNA Synthesis Inhibitors

Fluoroquinolones (ciprofloxacillin)
Metronidazole

- **RNA synthesis Inhibitors**

  Rifampin

- **Mycolic Acid synthesis inhibitors**

  Isoniazid

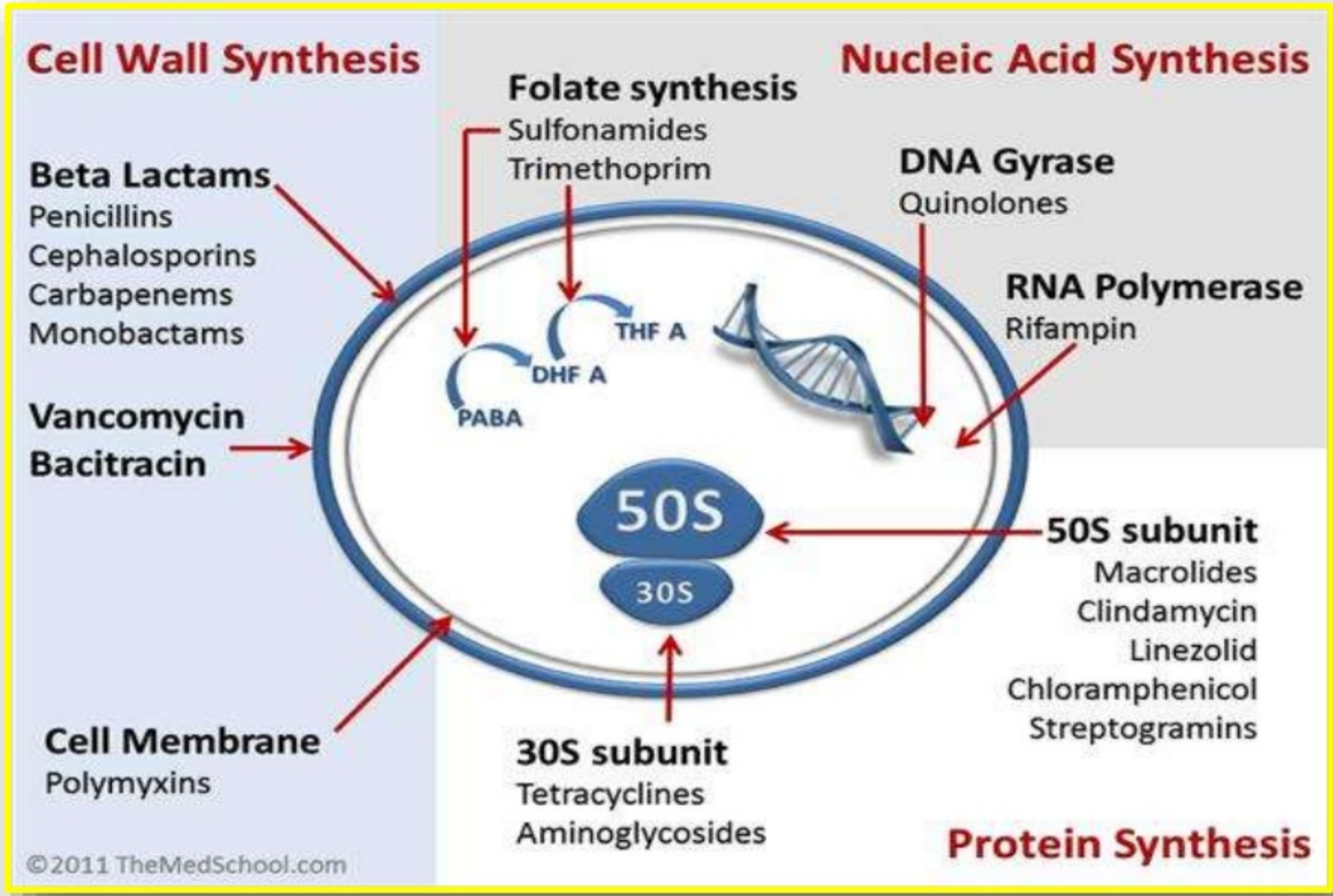
- **Folic Acid synthesis inhibitors**

  Sulfonamides
  Trimethoprim

Table 35.4 Mechanisms of Antibacterial Drug Action

Drug	Mechanism of Action
Cell Wall Synthesis Inhibition	
Penicillin Ampicillin Carbenicillin Methicillin Cephalosporins	Inhibit transpeptidation enzymes involved in the cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan. Activate cell wall lytic enzymes.
Vancomycin	Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation.
Bacitracin	Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.
Protein Synthesis Inhibition	
Streptomycin Gentamicin	Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.
Chloramphenicol	Binds to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.
Tetracyclines	Bind to the 30S ribosomal subunit and interfere with aminoacyl-tRNA binding.
Erythromycin and clindamycin	Bind to the 50S ribosomal subunit and inhibit peptide chain elongation.
Fusidic acid	Binds to EF-G and blocks translocation.
Nucleic Acid Synthesis Inhibition	
Ciprofloxacin and other quinolones	Inhibit bacterial DNA gyrase and thus interfere with DNA replication, transcription, and other activities involving DNA.
Rifampin	Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.
Cell Membrane Disruption	
Polymyxin B	Binds to the plasma membrane and disrupts its structure and permeability properties.
Metabolic Antagonism	
Sulfonamides	Inhibit folic acid synthesis by competition with *p*-aminobenzoic acid.
Trimethoprim	Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.
Dapsone	Interferes with folic acid synthesis.
Isoniazid	May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid "cord factor."

On the basis of mechanism of action:



On the basis of spectrum activity :

Broad spectrum antibiotics :

1. Amoxicillin
2. Tetracycline
3. Cephalosporin
4. Chloramphenicol
5. Erythromycin

Short spectrum antibiotics:

1. Penicillin –G
2. Cloxacillin
3. Vancomycin
4. Bacitracin
5. Fluxacillin

ON THE BASIS OF MODE OF ACTION:

Bacteriostatic antibiotics

- •Tetracycline
- Chloramphenicol
- •Erythromycin
- Lincomycin

Bacteriocidal antibiotics

- Cephalosporin
- Penicillin
- Erythromycin
- Aminoglycosides
- Cotrimoxazole

BETA LACTEM ANTIBIOTICS

- Broad class of antibiotics, consisting of all antibiotic agents that contains a β-lactam ring in their molecular structures.
- Examples include Penicillin, cephalosporin, monobactems, Nocardins.
- Most β-lactam antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism
- Bacteria often develop resistance to β-lactam antibiotics by synthesizing a β-lactamase, an enzyme that attacks the β-lactam ring. To overcome this resistance, β-lactam antibiotics are often given with β-lactamase inhibitors such as clavulanic acid.

Penicillin

- **Penicillin** is a group of antibiotics derived from *Penicillium* fungi, including penicillin G(intravenous use), penicillin V (oral use), procaine penicillin, and benzathine penicillin (intramuscular use).
- β-lactam antibiotics used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.
- Basic sturucture of penicillin is 6 aminopenicillinic acid
- Penicillin can be
  - Natural penicillins
  - Syntheic penicillins
  - Semicynthetic peniciliins
- Microorganisms used are
  - P. chrysogenum

PRODUCTION MEDIA

- Penicillin G and V are produced using submerged processes in 40,000-20,000 litre fermenters.

- Corn steep liquor(4-5% dry weight), an additional nitrogen source i.e. soy meal, yeast extract, whey a carbon source such as lactose, and various buffers.
- The pH is 6.5
- Phenyl acetic acid or phenoxy acetic acid is fed continuously as a precursor

PRODUCTION OF PENICILLIN

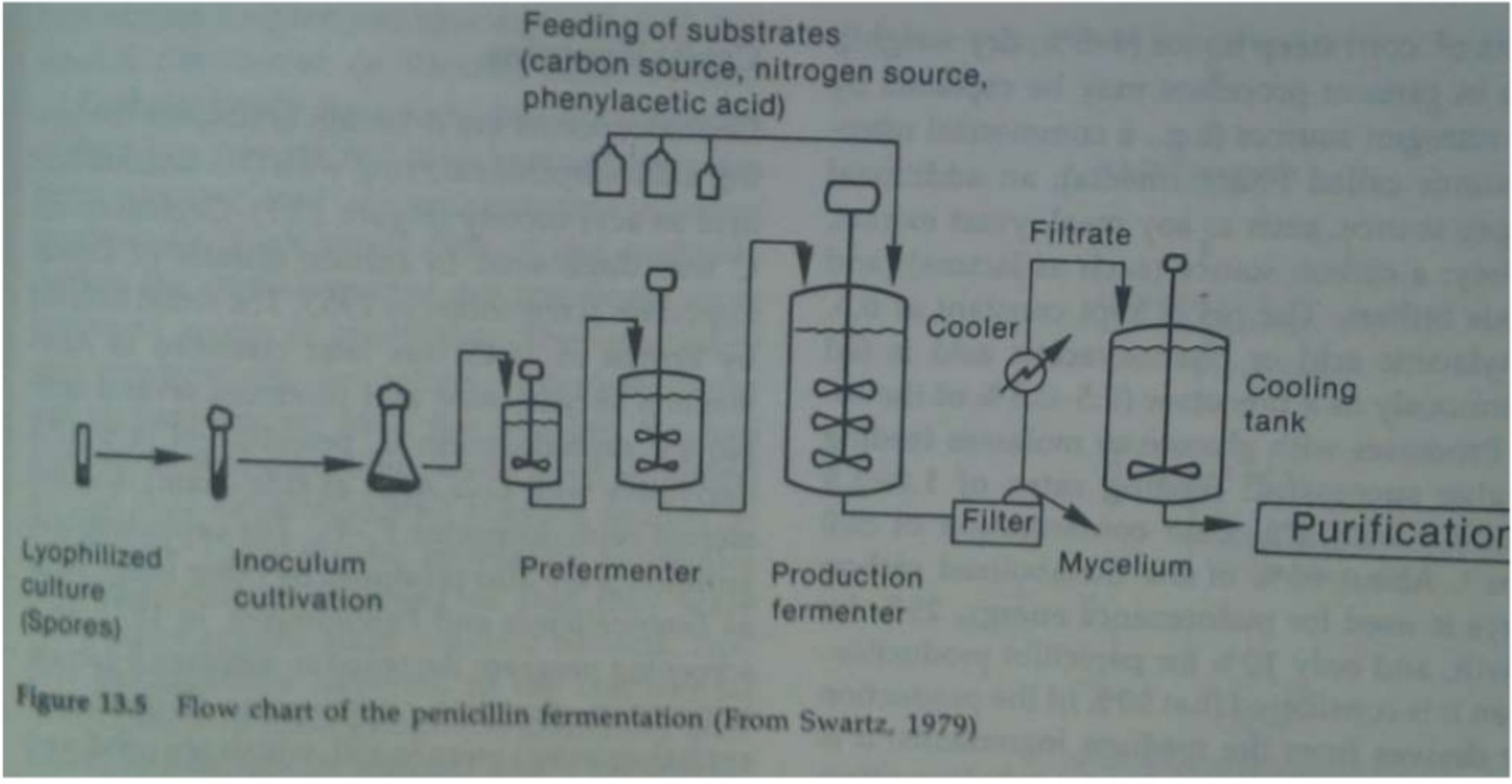


Figure 13.5 Flow chart of the penicillin fermentation (From Swartz, 1979)

CEPHALOSPORINS

- Any of various broad-spectrum beta- lactam antibiotics closely related to the Penicillins, that were originally derived from the fungus, ***Cephalosporium acremonium.***
- They contain a dihydrothiazinering with D aminoadipic acid as acyl moiety.
- It is also produced by *Emericellopsis* and *Paecilomyces.*

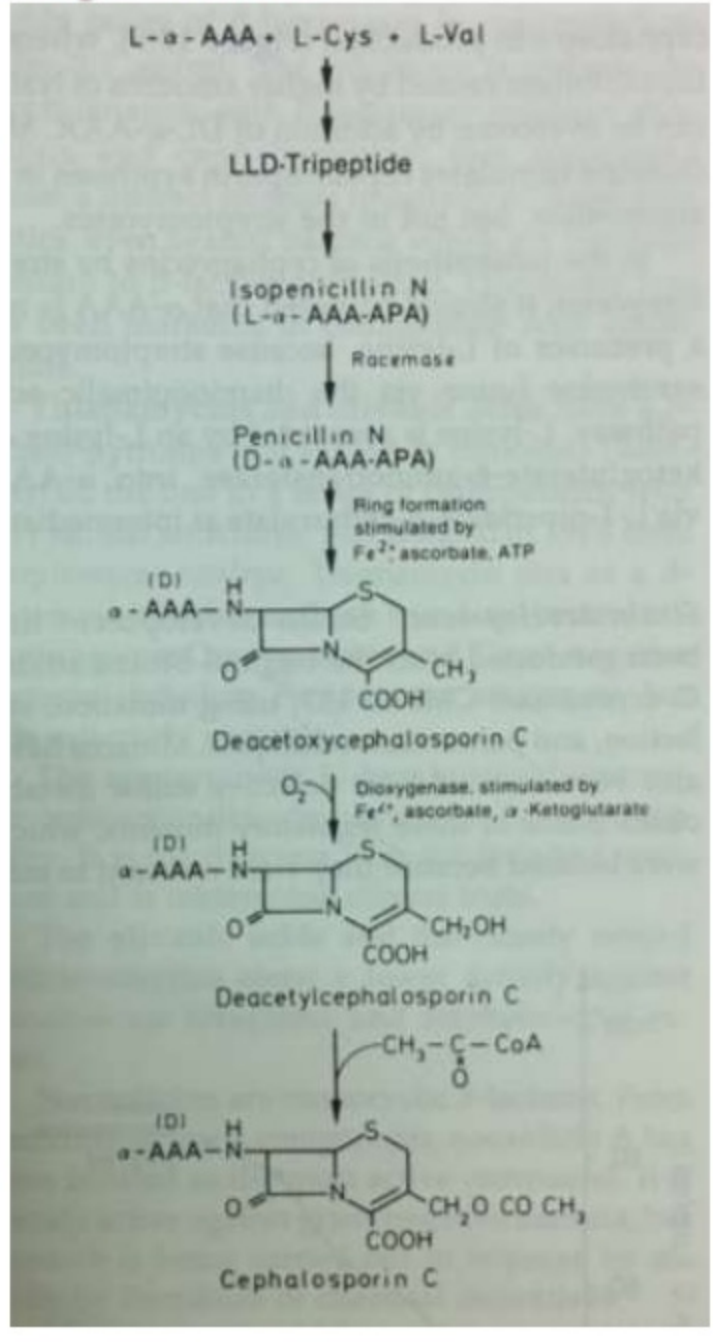
ACTION: Inhibitors of peptidoglycan synthesis, Activate cell wall lytic enzymes

COMMON USE: In surgical procedures- to reduce the risk of post- operative infections.

FIRST GENERATION - Cefazolin,Cephalexin
Spectrum: Most G (+)ve cocci (*Streptococcus, S. aureus*), *E. coli, proteus, Klebisella*
Use: *S. aureus infection,* surgical prophylaxis
SECOND GENERATION – Cefoxitin, Cefuroxime, Cefaclor, Cefprozil
Spectrum: Mainly effective gram negative bacteria, modest activity against gram positive bacteria
Use: Primarily for upper & lower respiratory tract infections
THIRD GENERATION – Ceftriaxone, Cefotaxime
Spectrum: enhanced G (–)ve activity
Use: Meningitis, highly resistant & multi drug resistant Streptococcus along with vancomycin
FOURTH GENERATION - Cefepime
Spectrum: Active against *Streptococcus, staphylococcus*, pseudomonas aeruginosa & aerobic G –ve

Production of Cephalosporins

- 13 therapeutically important semisynthetic cephalosporins are commercially produced.
- These have been synthesized by chemical splitting to form 7 aminocephalospioranic acid (7-ACA) with subsequent chemical acylation as well as by modification on the C-3 site.
- Complex media with Corn steep liquor, meat meal, sucrose, glucose and ammonium acetate are used in a fed batch system at ph 6-7 and temperature 24-28° C
- Recently chemical synthesis of cephalosporin by ring expansion of penicillin has been developed.
- Eg. Use of pennicillin V to produce oraspor, an orally active cephalosporin.



Peptide antibiotics :

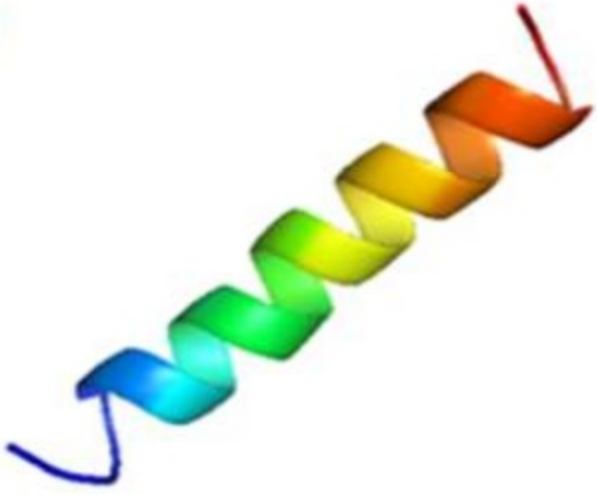
- Diverse class of natural products.
- Also known as natural antibiotics.
- key elements directly implicated in the innate immune response of their hosts.
- Response is fast , highly efficient and applicable to wide range of infective organisms.
- Some contain only amino acids joined by amide bonds, whereas others contain non amino acid constituents joined in ways other than conventional peptide linkage.
- The amino acids range from those commonly found in proteins to uncommon ones, with highly modified structures.
- The peptide array may be linear or cyclic or various combinations.

- Small molecules composed of less then 50amino acid residues mostly in common L configuration.
- Produced by all living organisms in a defense strategy against invading pathogens.
- Kill bacteria rapidly by acting on disrupting the bacterial membrane in a non-specific way.
- Potential replacement for antibiotics.
- Not affected by resistance mechanisms such as those witnessed for antibiotics.

CLASSES OF AMPS :

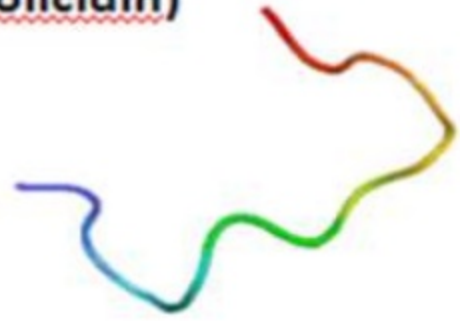
For Educational Use Only

α-helical
(Magainin)



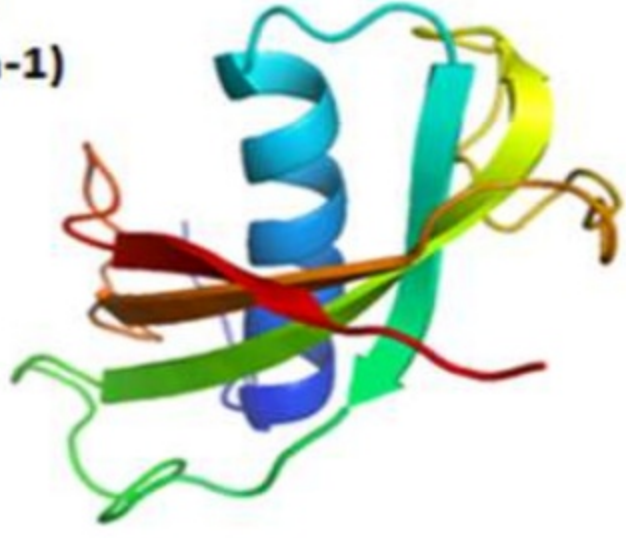
For Educational Use Only

Extended
(Indolicidin)



For Educational Use Only

Mixed
(Protegrin-1)



For Educational Use Only

B-sheet
(defensin.human)

MECHANISM OF ACTION

•Based on membrane disruption followed by pore formation on the nanometer scale and membrane depolarization.

•The following general model for the mechanism of action has been proposed:

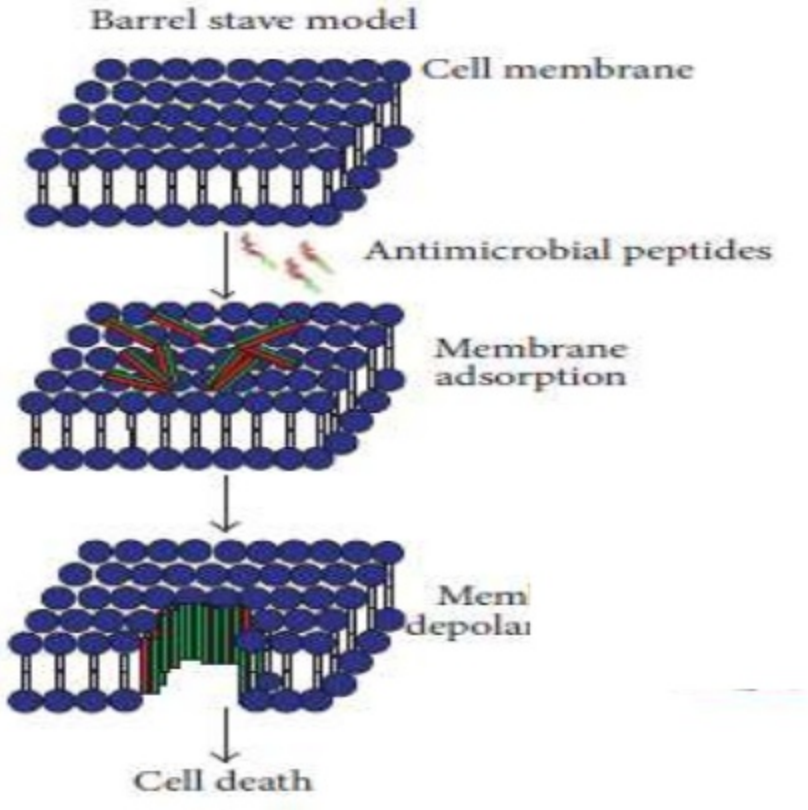
(i) AP-membrane attraction

(ii) attachment of the AP onto the membrane and

(iii) insertion of the AP into the membrane causing its disruption, leading to the leakage of ions and metabolites.

PERMEABILIZATION MECHANISM :

BARREL – STAVE MODEL



CARPET MODEL