Chapter 23

PHARMACOLOGY

STUDENTS'LEARNING OUTCOMES

After studying this chapter, the students will be able to:

- Explain the drug discovery and development process.
- Define 4 classes of antibiotics (penecillins, Tetracyclins, Fluriquinolones and Sulfonamides) and describe their mode of action
- Define antivirals and antiretrovirals
- Describe advantages of monoclonal antibodies as compared to other drug classes.

Pharmacology is the branch of biology that deals with the study of drugs and their effects on living organisms. It includes the study of the sources, properties, composition, therapeutic uses, and effects of drugs on the body. Drugs are chemical substances used to diagnose, prevent, or treat diseases.

Drugs may be obtained from natural sources such as plants, animals, and microorganisms, or they may be synthesized in laboratories. Medicines prepared from plants are commonly used in traditional systems of treatment and are known as herbal medicines or Phytotherapy.

23.1- DRUG DISCOVERY AND DEVELOPMENT PROCESS

Drug discovery and drug development are important processes that help in the production of safe and effective medicines for the treatment of diseases. the process begins with the identification of disease-causing targets and the development of compounds that can interact with these targets. before a drug is approved for public use, it undergoes several stages of testing to evaluate its safety, efficacy, and quality. scientists, researchers, and regulatory authorities work together throughout this process to ensure that new medicines are beneficial and safe for human use.

23.1.1 STAGES OF DRUG DISCOVERY:

It is the initial stage of finding a new drug for any disease.There are following stages in the discovery of modern drugs;

1. Target Identification:

Scientists identify a specific molecule, such as a protein or enzyme, that is involved in causing a disease. This target is selected because it can be affected by a drug to treat the disease.

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2. Target Validation

Researchers confirm that the identified target plays an important role in the disease process. Experiments are carried out to ensure that acting on the target can produce therapeutic effects.

3. Lead Compound Identification

Scientists screen thousands of natural or synthetic compounds to find substances that can interact effectively with the target molecule. These promising substances are called lead compounds.

4. Lead Optimization:

These lead compounds are modified to improve their effectiveness, reduce toxicity, and enhance the drug-like properties.

23.1.2 DRUG DEVELOPMENTAL PROCESS:

It is the process of testing and preparing the discovered drug for public use. There are following stages to develop a new drug;

1. Preclinical Research:

Compounds are tested in *vitro* (cell-based culture) and in *vivo* (animal) to measure safety, toxicity, and efficacy before human trials.

2. Clinical Trials:

Drugs are tested on humans to ensure safety.

Phase 1: Testing in a small group (20–100) of healthy volunteers are taken to determine safety and dosage.

Phase 2: Testing in a larger group (100–300) of patients to test the effectiveness and side effects of drugs.

Phase 3: Large-scale trials (1,000–3,000) are taken to confirm the efficacy and monitor their adverse reactions in patients.

3. FDA Drug Review:

Regulatory agencies (FDA or EMA) thoroughly examine all data from clinical research trials to approve or reject the drugs before supply to market.

4. Manufacturing and Marketing

Once approved, the drug is produced on a large scale in pharmaceutical industries and made available for medical use.

5. Post-Marketing Surveillance

Even after release, the drug is continuously monitored for long-term effects and rare side effects to ensure ongoing safety in the population.

23.2- CLASSES OF ANTIBIOTIC:

Antibiotics are drugs that treat bacterial infection by killing bacteria or stopping their growth. Antibiotics are classified primarily by their mechanism of action and chemical

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structure. The major four classes are;

1. Penicillin
2. Tetracycline
3. Fluoroquinolones
4. Sulfonamides

23.2.1 Penicillin:

Penicillin is a group of bactericidal, antibiotics derived from *Penicillium* fungi, used to treat various bacterial infections by inhibiting bacterial cell wall synthesis. Alexander Fleming (1928), discover it, which is highly effective against gram-positive bacteria, including streptococcal and staphylococcal infections. Common side effects of penicillin antibiotics include nausea, vomiting, diarrhea, abdominal pain, and skin rashes.

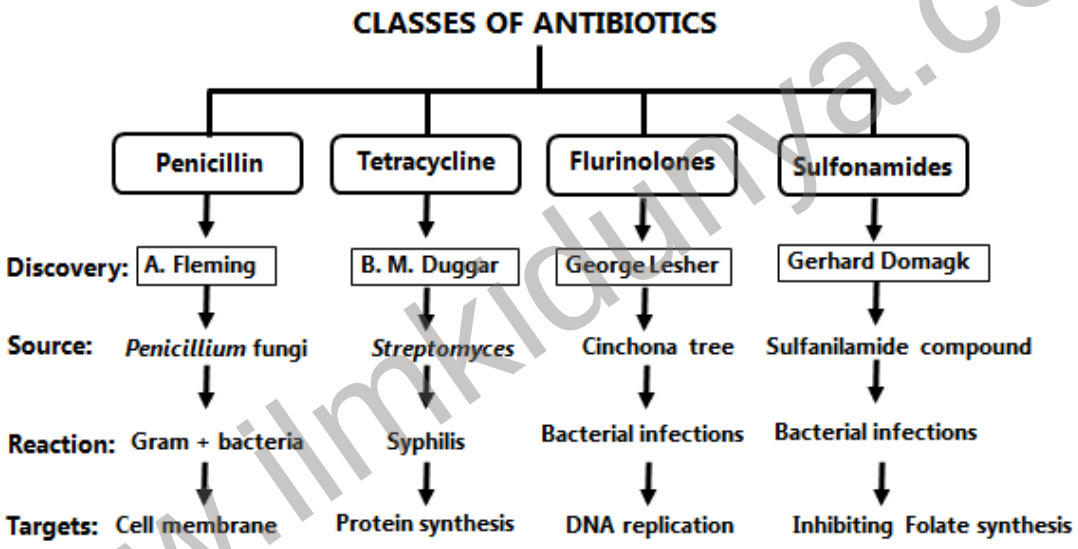

Fig: 23.1 Classification of Antibiotics

Mode of Penicillin Action:

Penicillin adopt following way to kill bacteria;

1. **Targeting Bacteria:** Penicillin target bacteria because animal cells lack the cell walls that are targeted by the drug.
2. **Cell Wall Inhibition:** It interrupt the cross-linking of peptidoglycan (murein) chains, stopping new cell wall synthesis of bacteria.
3. **Lysing bacterial Cell:** The bacterial cell wall can no longer maintain structural integrity and it may burst (lysis), after the attack of penicillin (kills rather than just inhibits growth).
4. **Resistance Mechanisms:** Some bacteria defend themselves by producing specific enzymes like beta-lactamases.

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23.2.2 Tetracycline:

Tetracycline antibiotic is derived from soil-dwelling bacteria of the genus *Streptomyces*, It is a bacteriostatic oral antibiotic used to treat bacterial infections like chlamydia and syphilis. It inhibits bacterial protein synthesis. It should not be taken with dairy or iron supplements. Common side effects include nausea, vomiting, diarrhea, and sun sensitivity.

Mode of Tetracycline Action:

1. **Bacteriostatic Effect:** They stop bacteria from growing and multiplying rather than killing them outright.
2. **Gram-Negative/Positive Action:** They are effective against both Gram-positive and Gram-negative bacteria.
3. **Targeting Ribosomes:** Tetracycline enter bacterial cells and it reversibly bind to the 30S ribosomal subunit of its target cell.
4. **Blocking Protein Production:** By binding to the 30S ribosome, they prevent aminoacyl-t RNA from binding to the acceptor site, to inhibit translation and protein synthesis.

23.2.3. Fluoroquinolones:

Fluoroquinolones are synthetic, antibacterial agents derived as a byproduct of chloroquine (quinine) synthesis. Chloroquine is a synthetic drug derived from structural modification of quinine, a natural alkaloid found in the bark of the South American Cinchona tree. Fluoroquinolones was discovered by George Lesher (1962), are a class of bactericidal antibiotics that treat bacterial infections by inhibiting bacterial DNA replication. They are also associated with significant, rare adverse side effects, including tendon ruptures, peripheral neuropathy, drug resistance and cardiac issues.

Mode of Fluoroquinolones Action:

1. **Bactericidal Effect:** Fluoroquinolones trap the enzymes involved in DNA replication, creating a complex that causes double-strand DNA breaks. This prevents the bacteria from multiplying and forces them to die, so it classified as bactericidal (kills bacteria).
2. **Targeting Topois omerases:** Fluoroquinolones enter the bacterial cells and inhibit their Type II topoisomerases.
3. **Targeting Topoisomerase IV:** Primarily targeted in Gram-positive bacteria, it stops the separation of replicated DNA.
4. **Targeting DNA Gyrase:** Primarily targeted in Gram-negative bacteria, it stopping the process of DNA uncoiling during replication.

23.2.4 Sulfonamides:

Sulfonamides are synthetic pharmaceutical compounds derived from sulfanilamide, discovered by Gerhard Domagk in 1932. These are antimicrobial drugs that can treat

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bacterial infections by inhibiting folate synthesis, primarily used for urinary tract infections and skin infections. It acts as competitive inhibitors and bacteriostatic antibiotics to inhibit bacterial synthesis of folic acid, which is essential for DNA synthesis and bacterial growth. These are often administered orally but have few side effects like rashes, nausea, photosensitivity and kidney damage.

Mode of Sulfonamides Action:

1. **Bacteriostatic Effect:** Sulfonamides do not kill bacteria immediately but inhibit their growth, allowing the body's immune system to destroy them.
2. **Selective Toxicity:** Sulfonamides are selectively toxic to bacteria because of how they handle folate. Bacteria must build this essential vitamin from scratch, whereas humans simply absorb it from food. This allows the drug to starve the bacteria of vital nutrients while leaving human cells untouched."
3. **Competitive Inhibition:** Sulfonamides bind to the enzyme responsible for creating folate, essentially taking para amino benzoic acid pathway (Folate metabolism).
4. **Combined Therapy:** They are often combined with other agents, like trimethoprim, to create a stronger bactericidal effect (killing bacteria).
5. **Broad Spectrum:** They are effective against both Gram-positive and Gram-negative bacteria, often used for urinary tract infections, acne, and respiratory infections.

23.3 ANTIVIRAL AND ANTIRETROVIRALS DRUGS

Antiviral drugs are used to treat viral infections. They prevent the growth and multiplication of viruses within the body. These medications can combat a wide range of viruses, including the hepatitis, influenza, and herpes viruses.

All Antiretroviral are Antiviral but all Antiviral are not Antiretroviral

Antiretroviral drugs are designed to treat illnesses brought on by retroviruses, including HIV (Human Immunodeficiency Virus). They aid in immune system defense and stop HIV from proliferating. Retroviruses are viruses that replicate by using enzyme reverse transcriptase and RNA as their genetic material.

23.4- MONOCLONAL ANTIBODIES:

These are artificially laboratory-produced molecules that enhance the immune system's ability to fight against pathogens. Monoclonal antibodies target specific antigens, making them effective for treating cancer, autoimmune disorders, and infectious diseases.

23.4.2- ADVANTAGES OF MONOCLONAL ANTIBODIES

Monoclonal antibodies are integral to personalized medicine, enabling tailored treatment approaches based on individual patient profiles. Continued innovation in

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these antibodies in design and production is critical to improve its effectiveness of therapies, ensuring they are better suited to each patient's unique biology.

Monoclonal antibodies have significant advantages as;

i. As compared to traditional drugs, they offer lower toxicity, potential for long-lasting effects.
ii. These have least side effects as compared to conventional chemotherapeutics.
iii. These have high specificity, binding to a single target with minimal variability.
iv. They provide targeted therapy in cancer, reducing damage to healthy tissues.
v. These are easily to prepare and used for research purpose.
vi. They reduced the risk of drug interactions.

These technologies enable the simultaneous testing of thousands of potential antibodies, reducing development timelines and enabling faster responses to urgent health challenges like infectious diseases and cancer.

EXERCISE

SECTION 1: MULTIPLE CHOICE QUESTIONS

1. The first step in drugs discovery is _____.
   (a) Lead optimization (b) Preclinical Testing
   (c) Target identification (d) Hit identification
2. Testing in a larger group about 100–300 patients to test the effectiveness and side effects of drugs indicate _____
   (a) Phase 1 (b) Phase 2
   (c) Phase 3 (d) Phase 4
3. Penicillin is highly effective against _____
   (a) Gram-positive bacteria (b) Gram-negative bacteria
   (c) *Streptomyces* (d) *Penicillium notatum*
4. The _____ antibiotic derived from soil-dwelling bacteria of the genus Streptomyces,
   (a) Penicillin (b) Fluoroquinolones
   (c) Sulfonamides (d) Tetracycline
5. The _____drugs are synthetic compounds derived from sulfanilamide,
   (a) Penicillin (b) Fluoroquinolones
   (c) Sulfonamides (d) Tetracycline
6. Monoclonal antibodies are considered highly affect because
   (a) have broad spectrum action (b) are highly specific to antigens
   (c) do not bind to any target (d) are non-biological in nature

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SECTION 2: SHORT QUESTIONS

1. Briefly describe Stages of Drug Developmental Process?
2. Write side effects of Penicillin?
3. Write a mode of Tetracycline action?
4. Differentiate between antiviral and antiretroviral drugs?
5. What are the advantages of monoclonal antibodies?

SECTION 3: LONG QUESTIONS

1. Describe the essential steps for the drug discovery and developmental process?
2. Explain different type of antibiotics. Describe their mode of action.
3. Describe the Monoclonal Antibodies and their advantages?

INQUISITIVE QUESTIONS

1. Predict the challenges the scientists may face during drug development process and propose possible solutions.
2. Assess the possible consequences of the misuse and overuse of antibiotics on human health.

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