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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Antibiotics**

  Historical background, Nomenclature, Stereochemistry, Structure activity

  relationship, Chemical degradation classification and important products of the following classes.

  Macrolide : Erythromycin Clarithromycin, Azithromycin.

  Miscellaneous : Chloramphenicol*, Clindamycin.

  Prodrugs : Basic concepts and application of prodrugs design.

- **Antimalarials :** Etiology of malaria.

  Quinolines : SAR, Quinine sulphate, Chloroquine*, Amodiaquine, Primaquine phosphate, Pamaquine*, Quinacrine hydrochloride, Mefloquine.

  Biguanides and dihydro triazines : Cycloguanil pamoate, Proguanil.

  Miscellaneous : Pyrimethamine, Artesunete, Artemether, Atovoquone.

Antimalarial Drugs

→ Antimalarial drugs are chemical agents used for the prevention and treatment of malaria, a protozoal disease caused by Plasmodium species and transmitted by the female Anopheles mosquito.

Causative Organisms

Malaria is caused by:

Plasmodium vivax
Plasmodium falciparum
Plasmodium malariae
Plasmodium ovale

Life Cycle of Plasmodium

- Sporozoites enter human blood through mosquito bite.
- They reach liver → form schizonts (hepatic stage).
- Merozoites released into blood → infect RBCs (erythrocytic stage).
- RBC rupture causes malarial fever.

Classification of Antimalarial Drugs

A. Tissue Schizonticides (Hepatic Stage)

- Primaquine
- Proguanil

B. Blood Schizonticides (Erythrocytic Stage)

1. Rapid Acting

- Chloroquine, Quinine, Mefloquine
- Artemisinin derivatives
  - Artesunate
  - Artemether

2. Slow Acting

- Pyrimethamine, Proguanil

C. Gametocidal Drugs

- Primaquine, Chloroquine (for *P. vivax*)

D. Sporontocidal Drugs

- Primaquine

- Proguanil

Mechanism of Action

A. Chloroquine

- Accumulates in parasite food vacuole
- Inhibits heme polymerization
- Toxic heme accumulates → parasite death

B. Quinine

- Interferes with DNA replication
- Inhibits heme detoxification

C. Artemisinin

- Produces free radicals inside parasite
- Damages parasite proteins

➡Very fast acting

Therapeutic Uses

⇨ Treatment of acute malaria
⇨ Radical cure of *P. vivax* and *P. ovale*
⇨ Severe falciparum malaria

Adverse Effects

Chloroquine

- Nausea, vomiting
- Headache
- Retinopathy (long-term)

Quinine

- Cinchonism (tinnitus, headache)
- Hypoglycemia
- Cardiac arrhythmias

Primaquine

- Hemolysis in G6PD deficiency
- GI upset

Resistance

- Resistance mainly seen with:

- Chloroquine
- Pyrimethamine

Etiology of Malaria

→ Malaria is a protozoal infectious disease characterized by periodic fever, chills, sweating, anemia, and splenomegaly. It is a major health problem in tropical and subtropical regions. Malaria is caused by Plasmodium parasites and transmitted to humans by the bite of an infected female Anopheles mosquito.

Meaning of Etiology

Etiology refers to the cause and origin of a disease.
The etiology of malaria includes:

- Causative organism
- Vector of transmission
- Mode of transmission
- Host factors contributing to disease development

Causative Organism

Malaria is caused by protozoan parasites of the genus ***Plasmodium*.**

Plasmodium Species Causing Human Malaria

- **Plasmodium vivax** – causes benign tertian malaria
- **Plasmodium falciparum** – causes malignant tertian malaria (most severe and fatal)
- **Plasmodium malariae** – causes quartan malaria
- **Plasmodium ovale** – causes mild tertian malaria
- **Plasmodium knowlesi** – causes zoonotic malaria with daily fever

➡*Plasmodium falciparum* is responsible for most complications, especially cerebral malaria.

Vector Responsible

→ The female Anopheles mosquito acts as the vector and definitive host.

→ Only female mosquitoes transmit malaria as they require blood for egg development.

Mode of Transmission

Malaria is transmitted by:

- Bite of infected female *Anopheles* mosquito
- Blood transfusion from infected donor (rare)
- Congenital transmission (mother to fetus)
- Sharing contaminated needles (very rare)

Infective Stage

⇨ The infective stage of Plasmodium for humans is the sporozoite.

⇨ Sporozoites are injected into the bloodstream during mosquito bite.

Host Involvement

Human – intermediate host (asexual multiplication in liver and RBCs)
Mosquito – definitive host (sexual reproduction of parasite)

Pathogenesis Related to Etiology

Sporozoites enter liver cells and multiply
Merozoites infect red blood cells
Rupture of RBCs releases toxins causing:
Fever and chills
Anemia
Jaundice
Splenomegaly

Factors Favoring Malaria

- Hot and humid climate

- Stagnant water and poor sanitation
- Lack of mosquito control measures
- Low immunity
- Drug resistance