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**CHEMOTHERAPY OF MALARIAL PARASITES**

1. **Classification of antimalarial agents**
2. **4-Aminoquinolines : Chloroquine, Amodiaquine**
3. **Quinoline; methanol mefloquine**
4. **Cinochona alkaloid: Quinine, Quinidine**
5. **Biguanides: proguanil (chloroguanide)**
6. **Diaminophyrimidine: Pyrimethamine**
7. **8-Aminoquinoline: primaquine ,Tefenoquine**
8. **Sulfonamides and sulfone : Sulfadoxine, Sulfamethopyrazine Dapsone**
9. **Antibiotics: Tetracyclins Doxycycline**
10. **Sesquiterpine lactose: Artesunate Artemether Areether**
11. **Amino alcohols: Halofantrine Lumefantrine**
12. **Napthyridine : Pyronaridine**
13. **Naphthoquinone : Atovaquone**

**1) Mechanism of action of 4-aminoquinolines**

**chloroquine**

* **It is actively concentrated by sensitive intra erythrocytic plasmodia by accumulating in the acidic vesicles of the parasite and weakly basic nature it raises the vesicular pH there by interferes with degradation of haemoglobin by parasitic lysosomes.**
* **Polymerization of toxic haeme to nontoxic parasite pigment hemozoin is inhibited by formation of chloroquine-hem complex.**
* **Haeme itself or its complex with chloroqine then damages the plasmodial membaranes. Clumping of pigment and changes in parasite membranes follow: death.**
* **Others related anti-malarials like amodiaquine quinine, mefloquine, lumefantrine act in a analogous manner.**

**2) Mechanism action of quinoline**

 **Mefloquine**

* **Active against chloroquines sensitive as well resistant P.vivax and falciparum**
* **Single dose: 15mg/kg controls fever and eliminates circulating paraddites (both P. vivax and Pf )**
* **Not used parentally**
* **Excreted in bile and urine**

**3) Mechanism of action of cinochona alkaloid**

**Quinine**

* **It is a weak base: gets concentrated in the acidic food vacuoles of sensitive plasmodia**
* **inhibits polymerization of haeme to hemozoin**
* **free haeme increases (toxic) or haeme –quinine complex damages parasite memebrane and kills it.**
* **After oral administration, quinine is rapidly absorbed, reaches peak plasma levels in 1-3 hours, and is widely distributed in body tissues.**
* **The use of a loading dose in severe malaria allows the achievement of peak levels within a few hours.**

**4) Mechanism of action of Biguanide**

 **Proguani (chloroguanide)**

* **It is cyclized in the body to cycloguanil which inhibits plasmodial DHFRase in preference to the mammalian enzyme.**
* **Resistance: due to mutational changes in the plasmodial DHFRase enzyme.**

**5) Mechanism of action of Diaminopyrimidine**

**Pyrimethamine**

* **In contrast to trimethoprim it has very poor action on bacterial DHFRase**
* **Pyrimethamine is a slowly acting erythrocytic schizontocide, but does not eliminate the pre-erythrocytic phase of P.Falciparum**
* **If use alone, resistance develops rather rapidly by Mutation in the DHFRase enzyme of the parasite.**
* **Used only in combination with a sulfonamide (s/p) or dapsone**
* **Addition of sulfonamide retards the development of resistance.**

**6) Mechanism of action of 8-Aminoquinolines**

**Primaquine**

* **primaquine bind to and alter the properties of protozoal DNA**
* **Primaquine is lethal to *P. vivax* and *P. ovale* in the liver stage, and also to *P. vivax* in the blood stage through its ability to do oxidative damage to the cell. However, the exact mechanism of action is not fully understood**

**7) Mechanism of action of sulfonamides and sulfone**

* **As an** [antibacterial](https://en.wikipedia.org/wiki/Antibacterial)**, dapsone inhibits** [bacterial](https://en.wikipedia.org/wiki/Bacteria) **synthesis of** [dihydrofolic acid](https://en.wikipedia.org/wiki/Dihydrofolic_acid)**, via competition with** [para-aminobenzoate](https://en.wikipedia.org/wiki/4-Aminobenzoic_acid) **for the active site of** [dihydropteroate synthase](https://en.wikipedia.org/wiki/Dihydropteroate_synthase)**, thereby inhibiting nucleic acid synthesis.**
* **As an** [anti-inflammatory](https://en.wikipedia.org/wiki/Anti-inflammatory)**, dapsone inhibits the myeloperoxidase-H2O2-halide-mediated cytotoxic system in polymorphonucleocytes**.
* **As part of the** [respiratory burst](https://en.wikipedia.org/wiki/Respiratory_burst) **that** [neutrophils](https://en.wikipedia.org/wiki/Neutrophil) **use to kill bacteria**, **myeloperoxidase converts hydrogen peroxide (H2O2) into** [hypochlorous acid](https://en.wikipedia.org/wiki/Hypochlorous_acid) **(HOCl).**
* **HOCl is the most potent oxidant generated by neutrophils, and can cause significant tissue damage during inflammation**

**8) Mechanism of action for antibiotics**

**Tetracycline**

* **They inhibit the initiation of translation in variety of ways by binding to the** [30S ribosomal subunit](https://en.wikipedia.org/wiki/30S_ribosomal_subunit), **which is made up of 16S rRNA and 21 proteins.**
* **They inhibit the binding of** [aminoacyl-tRNA](https://en.wikipedia.org/wiki/Aminoacyl-tRNA) **to the** [mRNA translation](https://en.wikipedia.org/wiki/MRNA_translation) **complex**.
* **It inhibits** [matrix metalloproteinases.](https://en.wikipedia.org/wiki/Matrix_metalloproteinases)
* **Tetracyclines are not only active against broad spectrum of bacteria, but also against viruses, protozoa that lack mitochondria and some noninfectious conditions**.
* **The binding of tetracyclines to cellular dsRNA (double stranded RNA) may be an explanation for their wide range of effect**.
* **It can also be attributed to the nature of ribosomal protein synthesis pathways among bacteria.**

**9) Mechanism of action for Sesquiterpine lactose**

**Artesunate**

* **It inhibits the essential** [*Plasmodium falciparum*](https://en.wikipedia.org/wiki/Plasmodium_falciparum) **exported protein 1 (EXP1), a membrane** [glutathione S-transferase](https://en.wikipedia.org/wiki/MAPEG).
* **It is hypothesized that the cleavage of endoperoxide bridge in the** [pharmacophore](https://en.wikipedia.org/wiki/Pharmacophore) **of DHA generates** [reactive oxygen species](https://en.wikipedia.org/wiki/Reactive_oxygen_species) **(ROS), which increases oxidative stress and causes malarial protein damage via** [alkylation](https://en.wikipedia.org/wiki/Alkylation).

**10) Mechanism of action for amino alcohols**

**Lumefantrine**

* **The exact mechanism by which lumefantrine exerts its antimalarial effect is unknown. However, available data suggest that lumefantrine inhibits the formation of β-hematin by forming a complex with hemin and inhibits nucleic acid and protein synthesis**.

**11)mechanism of action for Napthyridine**

**Pyronaridine**

* **It interfere with the food vacuole of the parasite**
* **In erythrocytic P. falciparum and P. berghei cultured in vitro in human erythrocytes, pyronaridine induced modifications to the food vacuoles followed by the rapid formation of multilameliate whorls in the pellicular complexes of trophozoites,**
* **pyronaridine targets haematin formation**
* **Pyronaridine inhibited β-haematin production with an IC50 similar to that of chloroquine (0.125 μM) and formed complexes with β-haematin with a 1:2 stoichiometry to enhance haematin-induced human blood cell lysis**
* **Pyronaridine has also been shown to inhibit glutathione-dependent haem degredation**
1. **Mechanism of naphthoquinone**

**Atovaquone**

* **inhibits the malarial cytochrome *bc*1 complex in the parasitic** [electron transport chain](https://en.wikipedia.org/wiki/Electron_transport_chain)**, collapsing the mitochondrial membrane potential.**
* **The malarial electron transport chain does not contribute significantly to ATP synthesis; thus, it is believed that parasite death is due to the indirect inhibition of dihydroorotate dehydrogenase, which requires transport chain function and is essential to pyrimidine biosynthesis.**[[](https://en.wikipedia.org/wiki/Atovaquone/proguanil#cite_note-15)