# ANTIMALARIAL DRUGS

- Malaria causes 900,000 deaths annually
- Resistance developed to chloroquine, mefloquine, quinine, atovaquone, pyrimethamine/sulfadoxin
- Chloroquine, primaquine,1946-1947
- Mefloquine, halofantrine, lumefantrine, 1967-1970
- **Cost To Develop One New Drug Is $2.6 Billion**

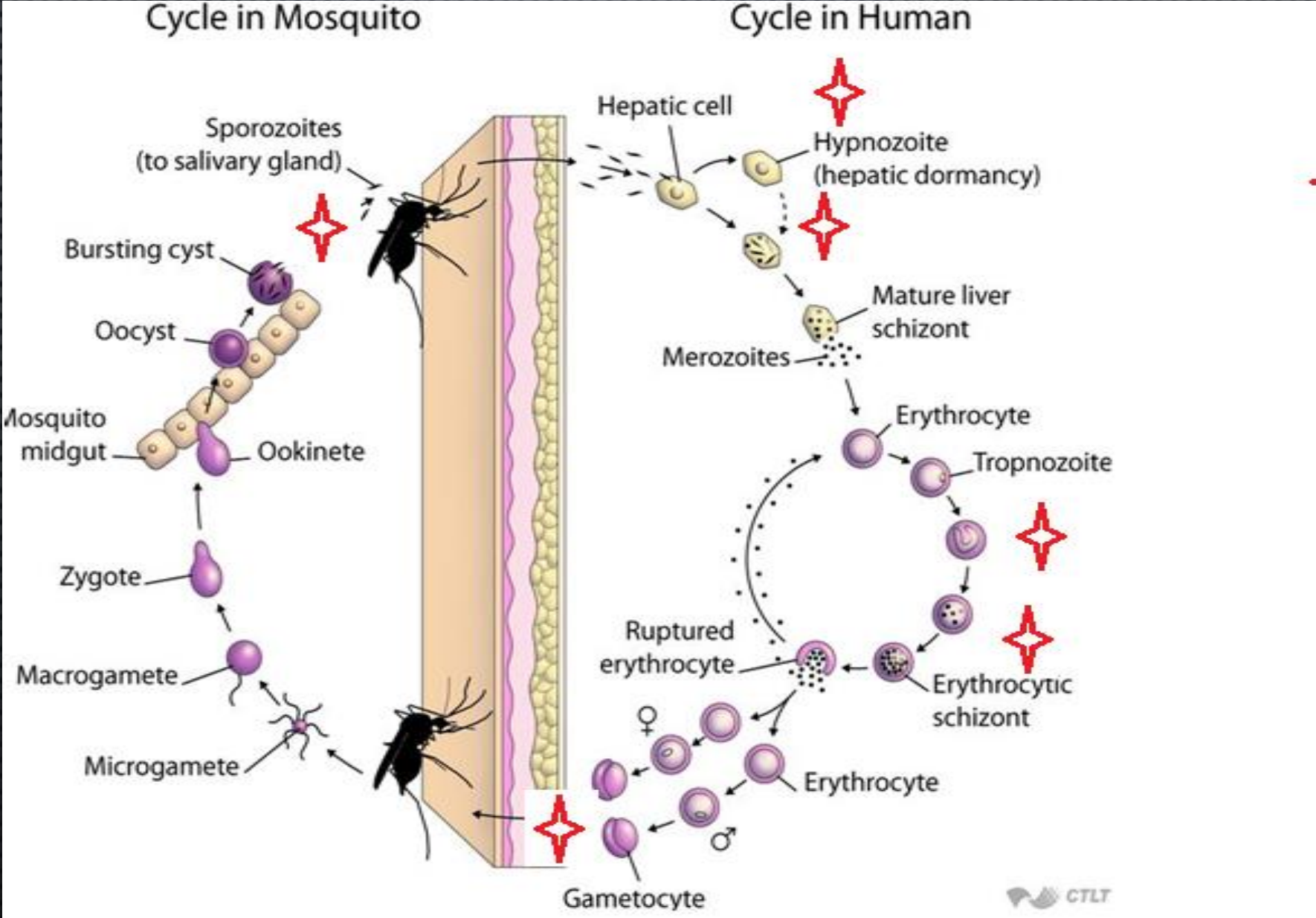
## VACCINATION?

# ANTIMALARIAL DRUGS

## ILOS

- Classify the main antimalarial drugs depending on their goal of therapy
- Detail the pharmacokinetics & dynamics of main drugs used to treat attack or prevent relapses
- State the WHO therapeutic strategy for treatment
- Hint on the CDC recommendations for prophylaxis in travelers to endemic areas

# Cycle & Drugs site of action



# ANTIMALARIAL DRUGS

## THERAPEUTIC CLASSIFICATION

| | | |
|---|---|---|
| Causal prophylaxis | Destroys parasite in liver cells & prevent invasion of erythrocytes | Primaquine |
| Supressive prophylaxis | Suppresses the erythrocytic phase & thus attack of malaria fever | Chloroquine, mefloquine, doxycycline |

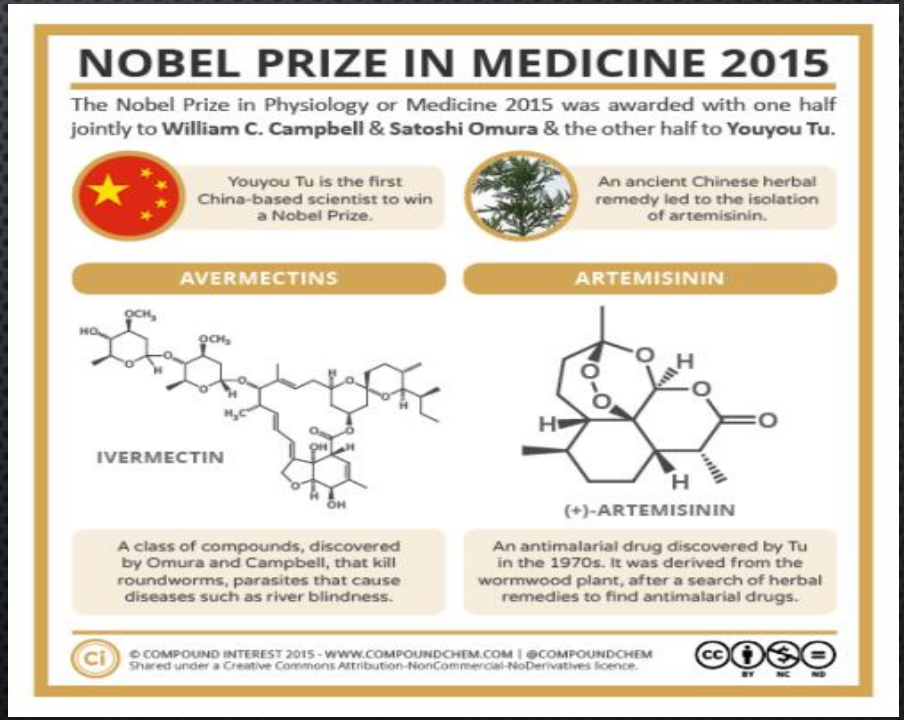
# ANTIMALARIAL DRUGS

## THERAPEUTIC CLASSIFICATION

| | | |
|---|---|---|
| Radical cure (erythrocytic schizonicide) | Eradicate all forms of vivax from the body | Suppressive drug + hypnozoitocidal |
| Gametocidal high efficacy | Destroys gametocytes & prevent transmission | Chloroquine, quinine against vivax |
| | | Primaquine, all species |
| Slow acting low efficacy | Destroys sporozoites | Proguanil, pyrimethamine |
| Sprozoitocides | | |

# ARTEMESININ

- Artemisinin is the active principle of the plant *Artemisia annua* **(qinghaosu)**
- Fast acting blood Schizontocide
- Affect all forms including multi-drug resistant *P. falciparum*
- Short duration of action
- High recrudescence rate
- Poorly soluble in water & oil, can only be used orally



# PHARMAOKINETICS

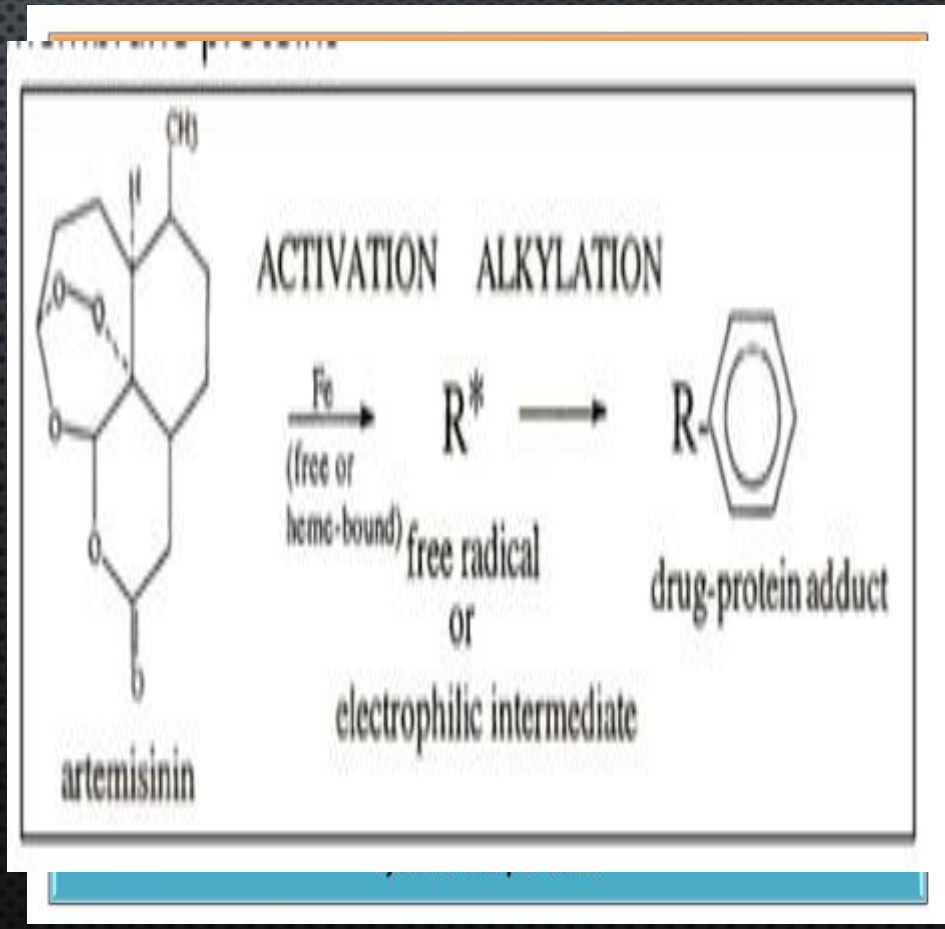
- Rapidly biotransformed in liver into dihydroartesiminin ➔ active metabolite
- Artemisinin ,artesunate, artemether are prodrugs
- Derivatives are rapidly absorbed orally
- Widely distributed
- t½ artemisinin ➔ 4hrs / artesunate ➔ 45min / artemether 4-11hrs
- Artesunate (water-soluble; oral, IV, IM, rectal administration)
- Artemether (lipid-soluble; oral, IM, and rectal administration)
- Dihydroartemisinin (water-soluble; oral administration)
- Induce its own CYP-mediated metabolism→ ↑ clearance 5 fold

# ARTEMESININ

## MECHANISM

They have endoperoxide bridges that are cleaved by haem iron to yield carbon- centered free radicals, that will➔

- Alkylate membranes of parasite's food vacuole and mitochondria➔ no energy
- Irreversibly bind & inhibit sarco-endoplasmic reticulum $Ca^{2+}$-ATPase of the parasite, thereby inhibiting its growth
- Inhibiting formation of transport vesicles ➔no food vacuoles



# ARTEMESININ

## ADRS

- Transient heart block
- ↓Neutrophil count
- Brief episodes of fever


Resistance ➔ was reported recently in Cambodia- Thailand border

# ARTEMESININ

## CLINICAL USES

- Because artemisinin derivatives have short t½ , **(1)** monotherapy should be extended beyond disappearance of parasite to prevent recrudescence or **(2)** by combining the drug with long- acting antimalarial drug

## PREPARATIONS

- Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24h) followed by complete course of ACT

# ARTEMESININ

## PREPARATIONS

- Artemisinin-based combination therapies (ACTs):
  - ➢Artemether + lumefantrine
  - ➢Artemether + amodiaquine
  - ➢Artemether + mefloquine
  - ➢Artemether + sulfadoxine- pyrimethamine

# ANTIMALARIAL DRUGS

## CHLOROQUINE

Potent blood Schizontocide

Active against all forms of the schizonts (*exception is chloroquine-resistant P.f. & P.v.)*

No activity against tissue schizonts

- Gametocide:-*Against all species except P. falciparum*

# CHLOROQUINE

## PHARMACOKINETICS

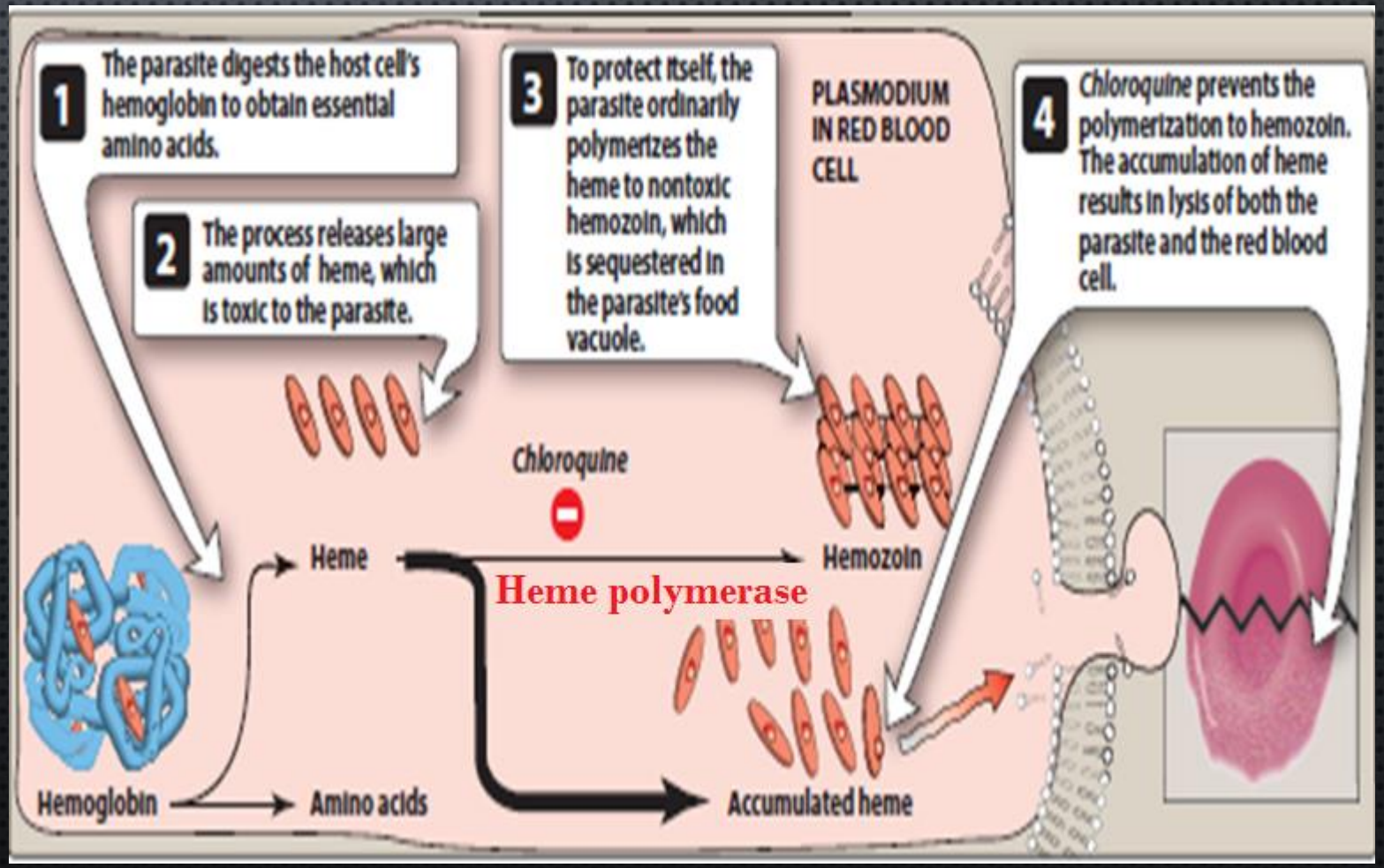
- Rapidly & completely absorbed from the GIT
- Has high volume of distribution(100-1000l/kg)
- Concentrated into parasitized RBCs
- Released slowly from tissues
- Metabolized in the **liver**
- Excreted in the urine 70% unchanged
- Initial t½ =2-3days & terminal t ½=1-2months

# CHLOROQUINE

## MECHANISM OF ACTION

Malaria Parasite digest host cell's Hb to obtain amino acids

Heme is released → Toxic
So parasite detoxifies it by *heme polymerase* → Hemozoin (NonToxic) & traps it in food vacuole



# CHLOROQUINE

## ADRS

1. Mild headache and visual disturbances

2. Gastro-intestinal upsets; Nausea, vomiting

3. Pruritus, urticaria.

***Prolonged therapy***

*Ocular toxicity: Loss of accommodation, lenticular opacity,* retinopathy

Ototoxicity

Weight loss

Bolus injection→ hypotension & dysrrhythmias

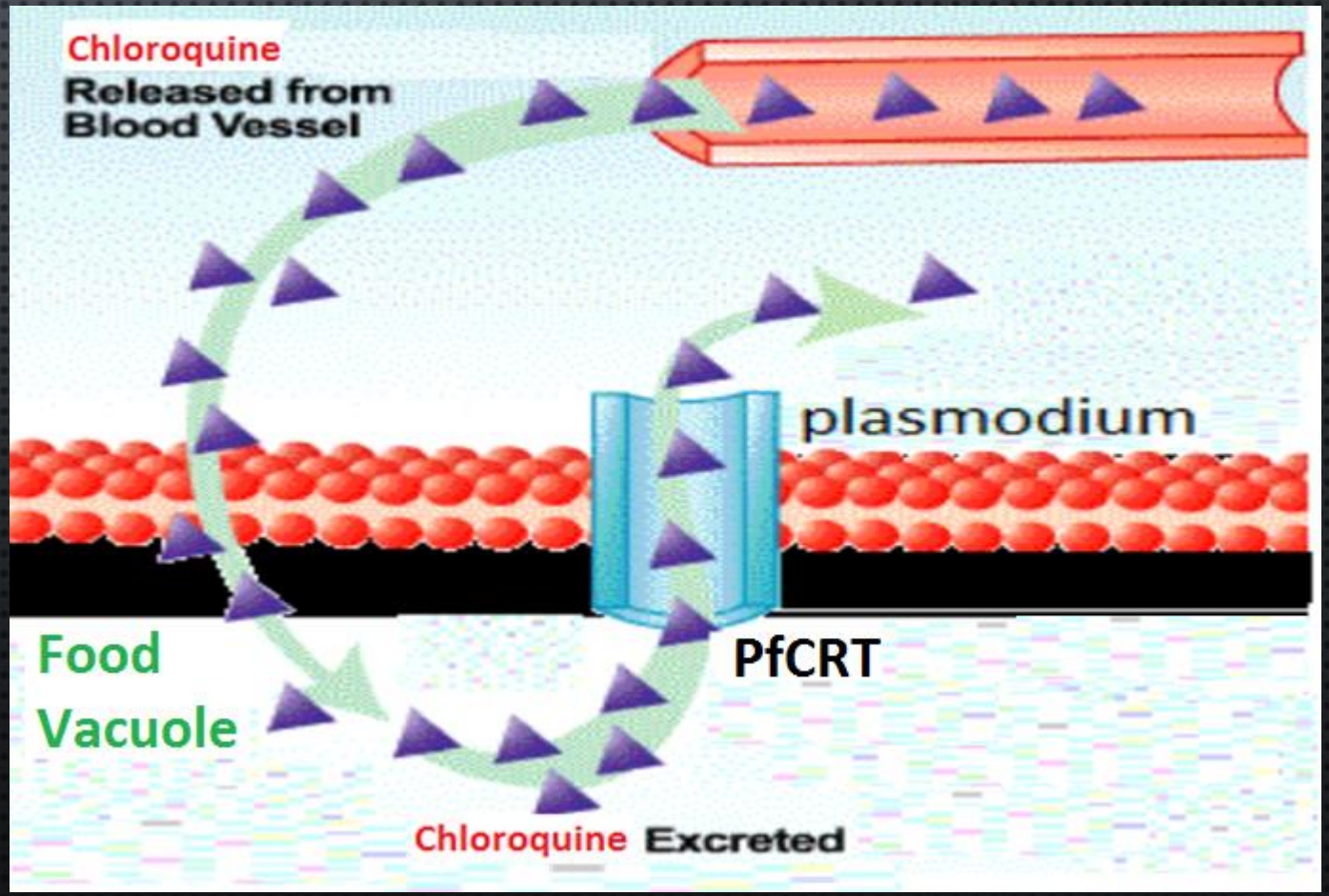
Safe in pregnancy

# CHLOROQUINE

## RESISTANCE

Resistance against the drug develops as a result of mutation of the chloroquine resistance transporter (PfCRT)

PfCRT enhances the efflux of chloroquine from the food vacuole



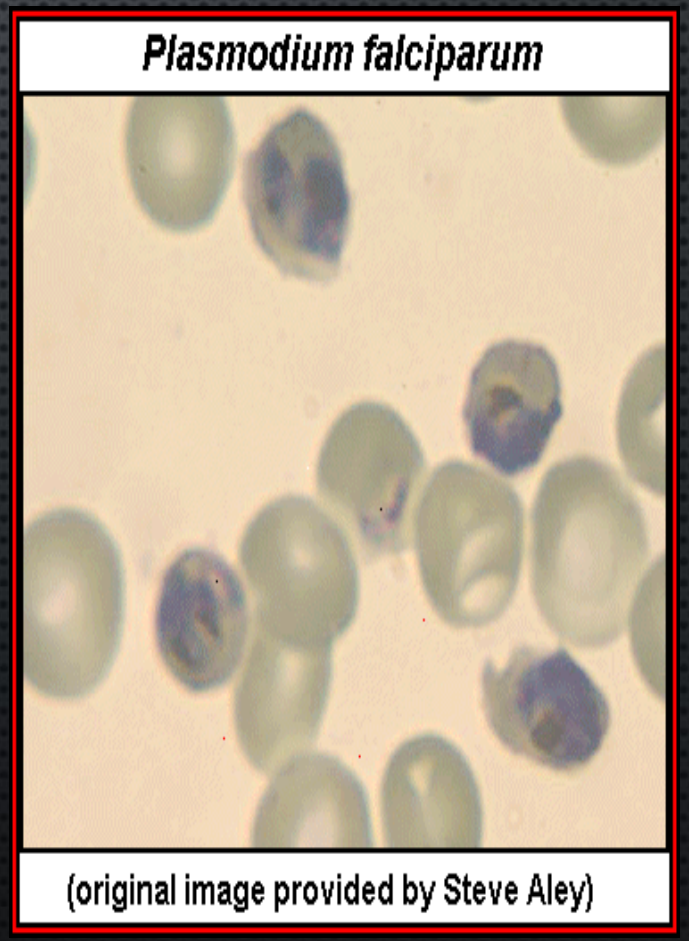
# CHLOROQUIN

## THERAPEUTIC USES

Used to eradicate blood schizonts of *Plasmodium*

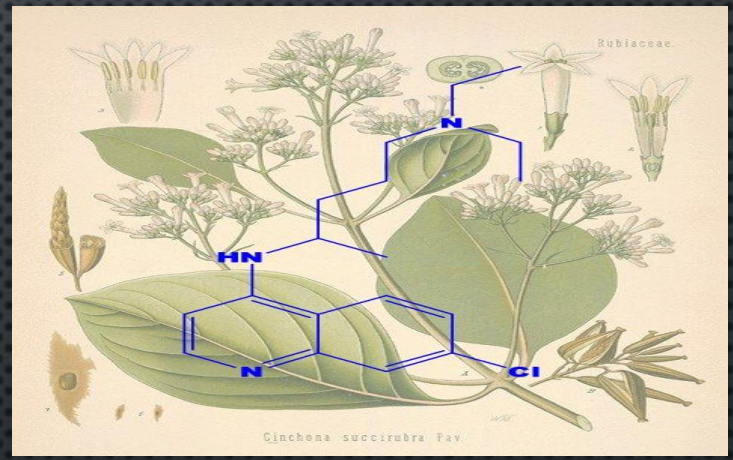
Hepatic amoebiasis

Rheumatoid arthritis



# QUININE

- The main alkaloid in cinchona bark




- Potent blood Schizontocide of all malarial parasites & weak gametocide for vivax & ovale

- Depresses the myocardium, reduce excitability & conductivity

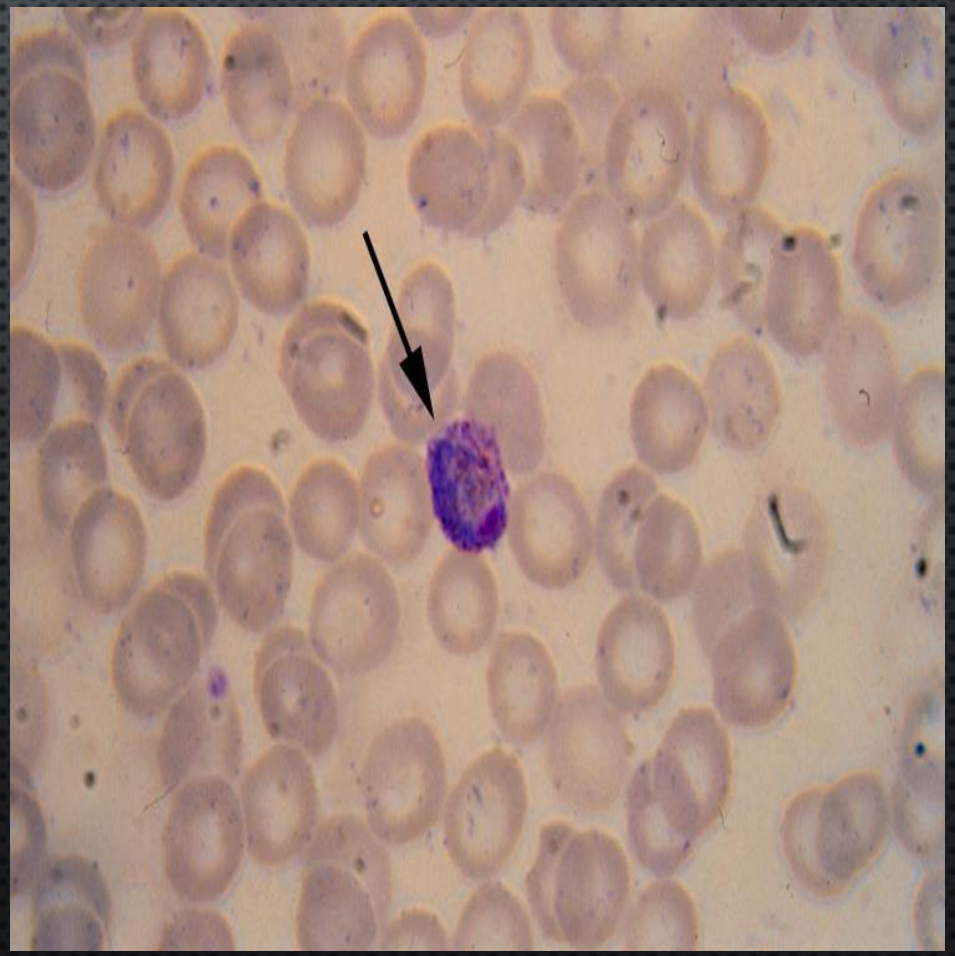
- Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curaremimetic effect

# QUININE

## PHARMACOKINETICS

- Rapidly & completely absorbed from the GIT
- Peaks after 1-3 hours
- Metabolized in the liver & excreted in urine
- 5-20% excreted in the urine unchanged
- $t_{1/2}$ = 10 hrs but longer in sever falciparum infection(18hrs)

Administered: orally in a 7 day course
or by slow IV for severe *P. falciparum* infection



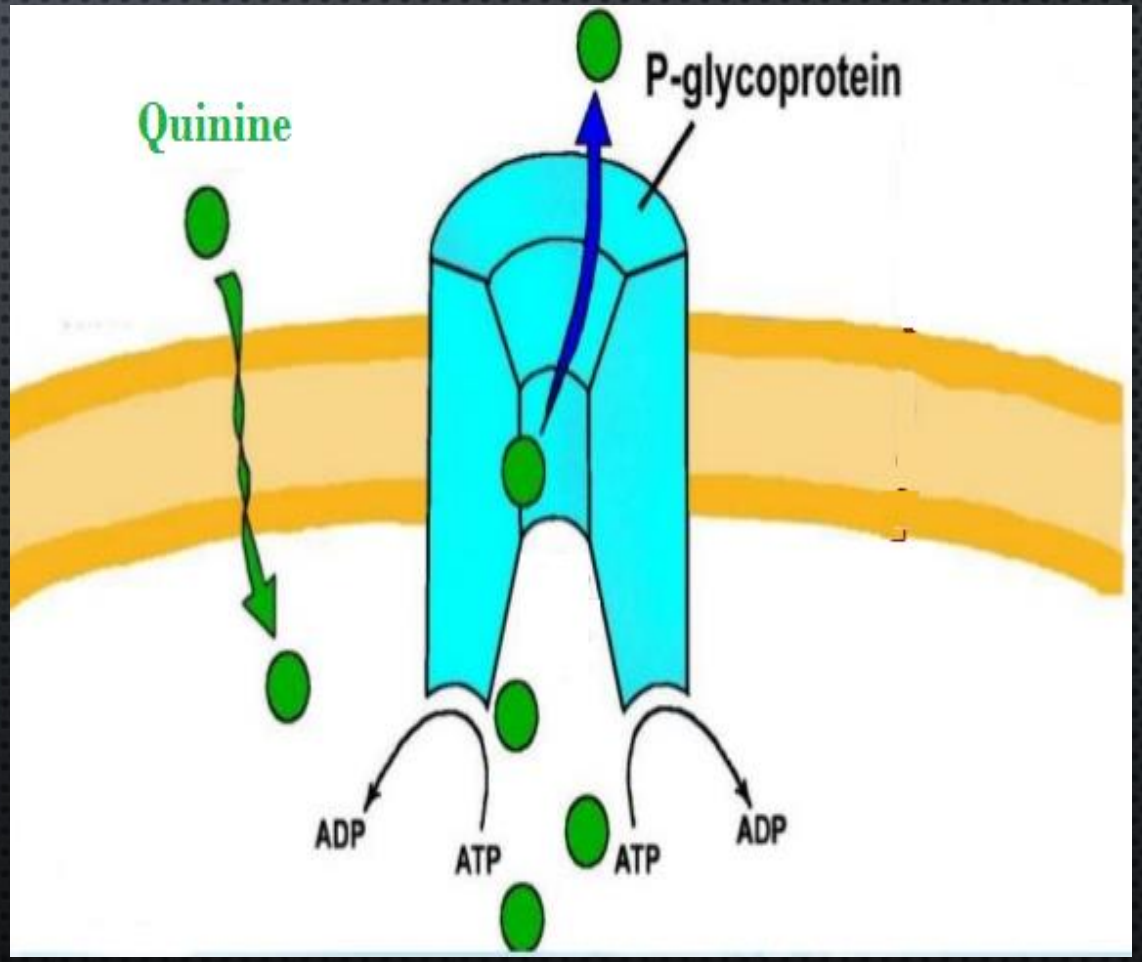
# QUININE

## MECHANISM

Same as chloroquine

## MECHANISM OF RESISTANCE

Like chloroquine by mutation of chloroquine resistance transporter, also increased expression of P-glycoprotein transporter



# QUININE

## ADRS

With therapeutic dose ➔ poor compliance ➔ bitter taste.

Higher doses ➔

- Cinchonism ➔ *(tinnitus, deafness, headaches, nausea & vis* *s)*
- Abdominal pain & diarrhea
- Hypotensio hypoglycemi
- Rashes, fever, hypersensitivity reactions
- Blood dyscarasis; anaemia, thrombocytopenic purpura & h *nia*
- Blackwater fever, a fatal condition in which acute haemolyti anaemia is associated with renal failure

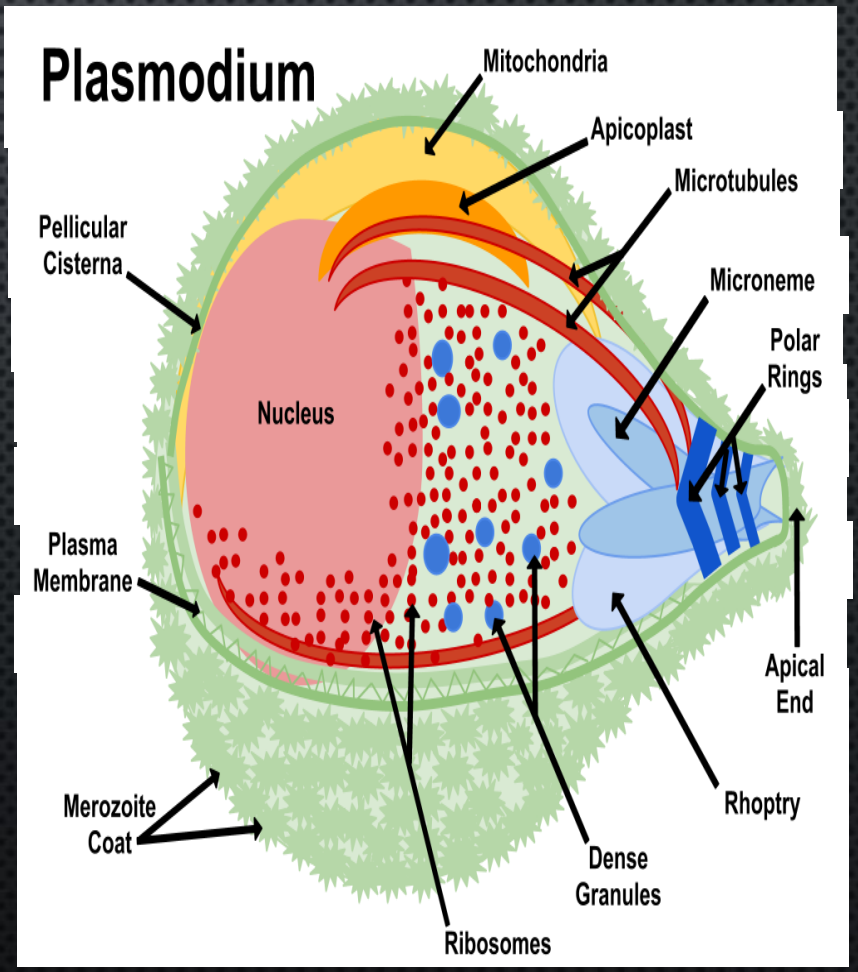
IV ➔ neurotoxicity ➔ tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma

Safe

# QUININE

## CONTRAINDICATIONS

- Prolonged QT Interval
- Glucose-6-Phosphate Dehydrogenase Deficiency
- Myasthenia Gravis
- Hypersensitivity
- Optic Neuritis, auditory problems
- Dose should be reduced in renal insufficiency



# QUININE

## CLINICAL USES

*Parenteral treatment of severe falciparum malaria*

*Oral treatment of falciparum malaria*

*Nocturnal leg cramps??*

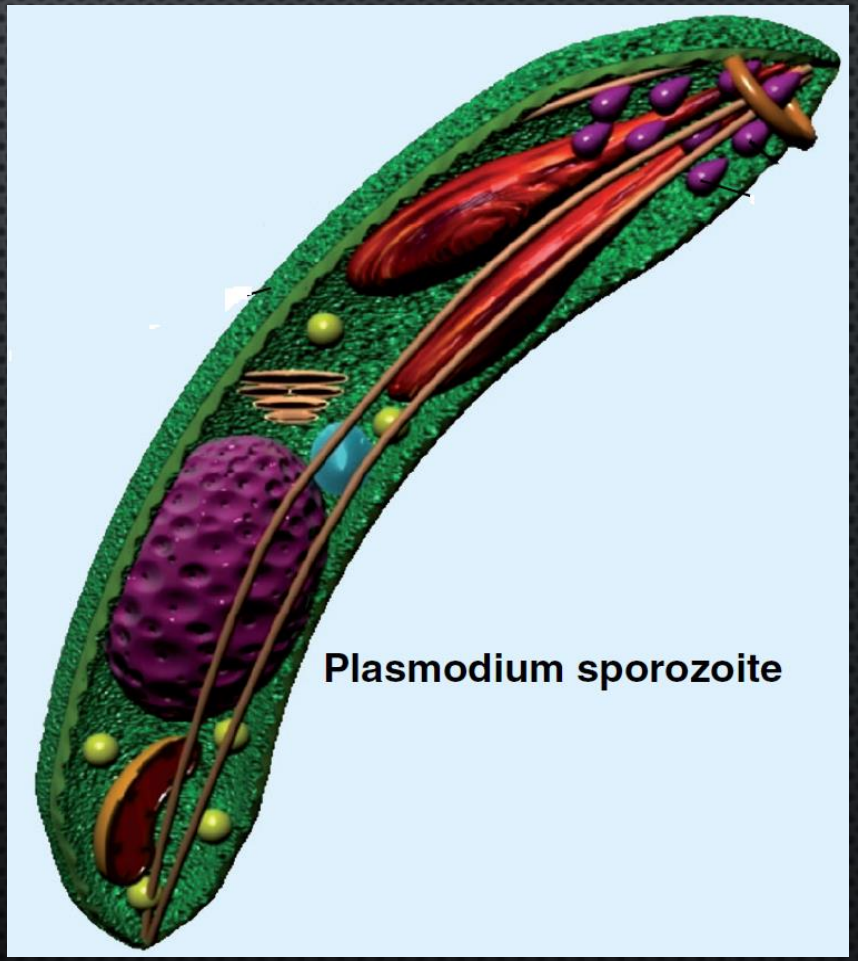
# QUININE

## DRUG INTERACTIONS

Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine

Mefloquine

Quinine can raise plasma levels of warfarin and digoxin



# PRIMAQUINE

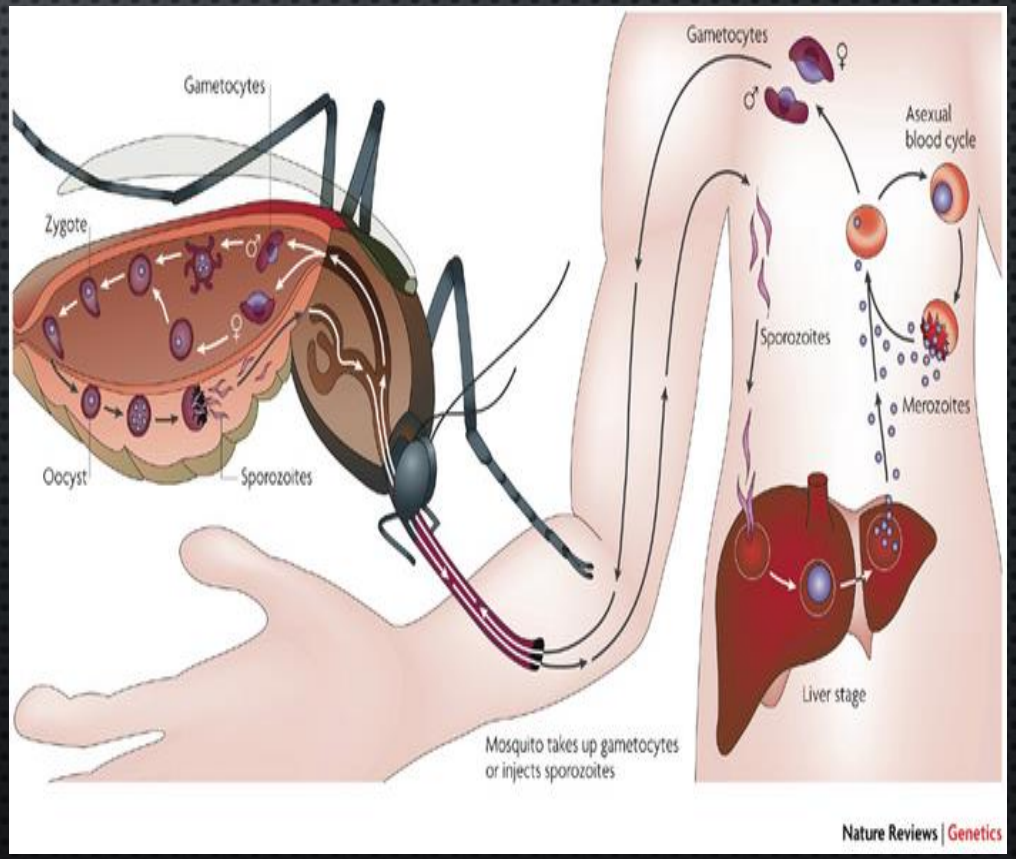
- Hypnozoitocides ➔ against liver hypnozoites & gametocytocide

*Radical cure of P. ovale & P. vivax*

*Prevent spread of all forms*

## PHARMACOKINETICS

- Well absorbed orally
- Rapidly metabolized to etaquine & tafenoquine ➔ more active
- t½ ➔ 3-6h



# PRIMAQUINE

## MECHANISM

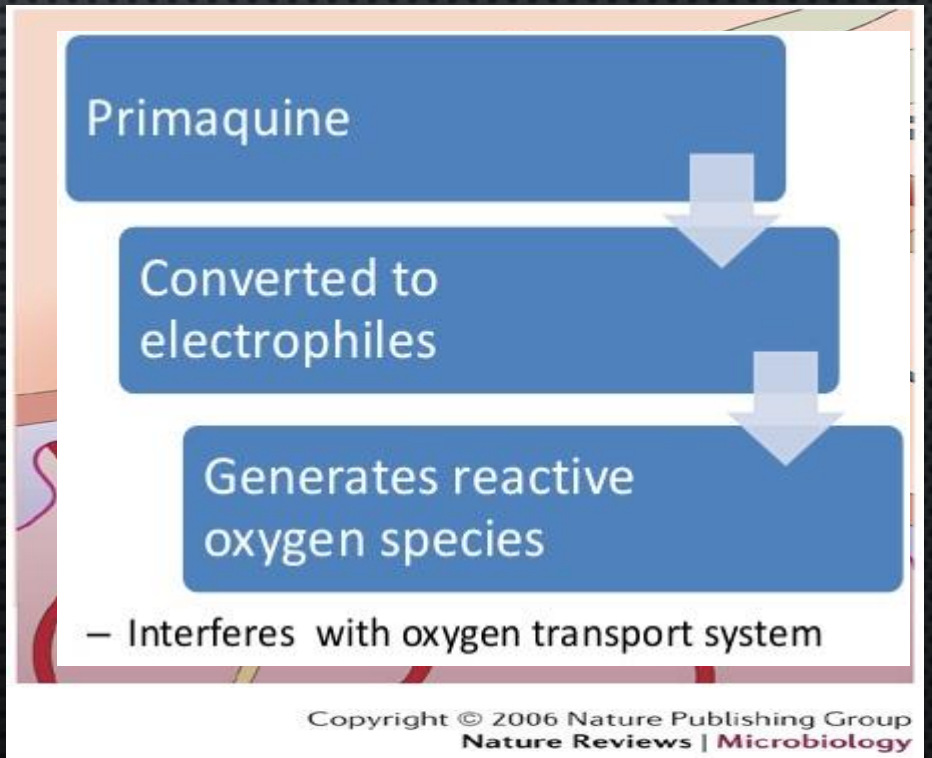
Not well understood. It may be acting by:-

- Generating ROS ➔ can damage lipids, proteins & nucleic acids

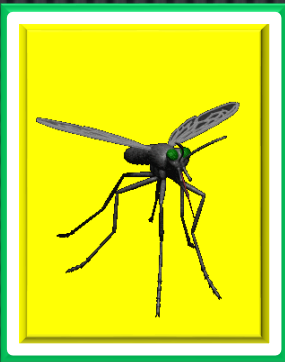
Interfering with the electron transport in the parasite ➔ no energy

Inhibiting formation of transport vesicles ➔ no food vacuoles

Resistance; ➔ Rare when primaquine & chloroquine are combined



# PRIMAQUINE



## ADRS

At regular doses ➔ patients with G-6-PD deficiency ➔ hemolytic anemia.

- Oxidation of primaqune produces free radicals
- Free radicals will cause oxidative damage of RBCs →Hemolysis
- $H_2O_2$ oxidizes GSH
- GSH
- Maintains integrity of RBCs

# PRIMAQUINE

## CLINICAL USES

Radical cure of relapsing malaria, 15mg/day for 14 days

In falciparum malaria: a single dose (45mg) to kill gametes & cut down transmission

| | |
|---|---|
| G-6-PD NORMAL | 15mg per day x 14 |
| G-6-PD deficiency (Mild African form) | 45mg per week for 8 |
| G-6-PD deficiency (More severe Mediterranean variety) | 30mg per week for 30 weeks |

Should be avoided in pregnancy(the fetus is relatively G6PD-deficient and thus at risk of hemolysis)& G6PD deficiency patients

# WHO TREATMENT GUIDELINES

## IN VIVAX

## IN FALICPARUM

All show Resistance

## UNCOMPLICATED

ACT

## RESISTANT

## COMPLICATED

IV Artesunate for 24 hrs followed by ACT
Or Artemether + [Clindamycin / doxycyline]
Or Quinine + [Clindamycin / doxycyline]

# WHO TREATMENT GUIDELINES

## IN FALICPARUM

## SPECIAL RISK GROUPS

| | |
|---|---|
| Pregnancy; 1st trimester | Quinine + Clindamycin (7 days) |
| Pregnancy; 2nd & 3rd trimester<br>Lactating women<br>Infants & young children | ACT |

# PROPHYLAXIS IN TRAVELLERS

## CDC RECOMENDATIONS

| | |
|---|---|
| Chloroquine | Areas without resistant *P falciparum* |
| Mefloquine | Areas with chloroquine-resistant *P falciparum* |
| Doxycycline | Areas with multidrug-resistant *P falciparum* |

Begin 1-2 weeks before departure (except for doxycycline 2 days) & continue for 4 weeks after leaving the endemic area