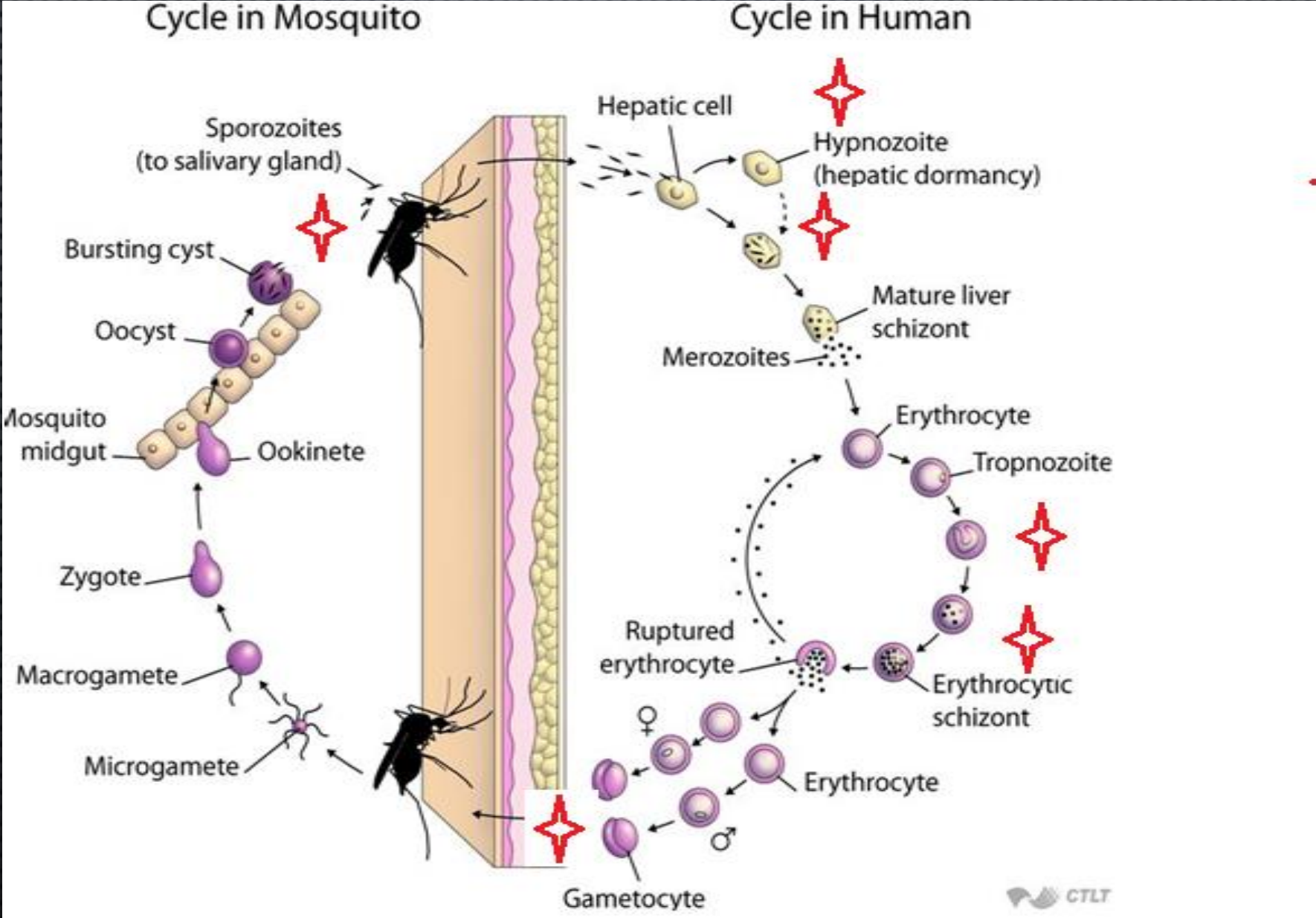
ANTIMALARIAL DRUGS

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

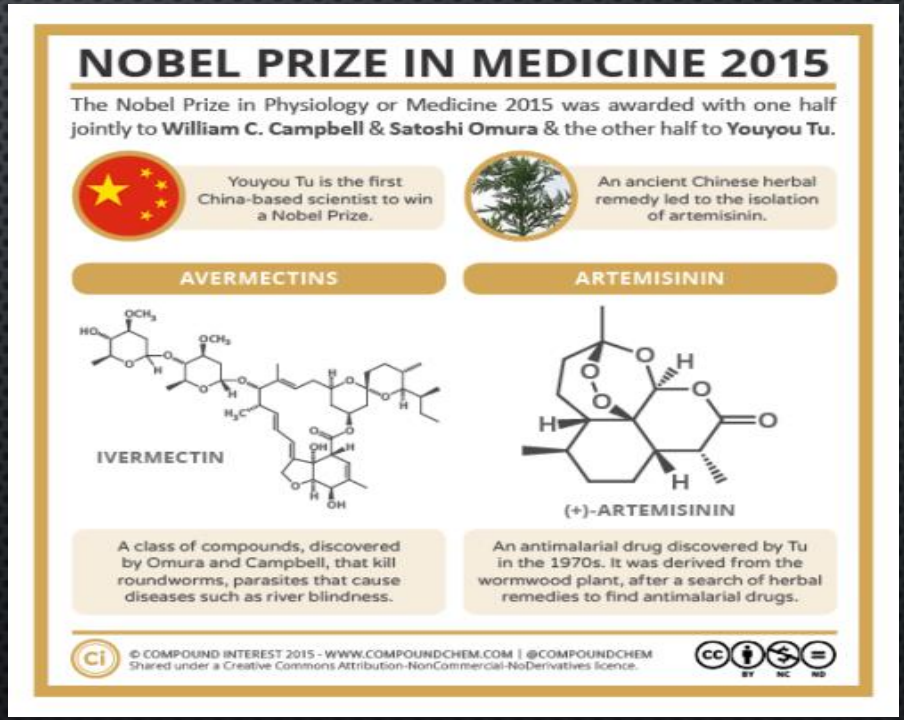
ANTIMALARIAL DRUGS

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 Sprozoitocides	Destroys sporozoites	Proguanil, pyrimethamine

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

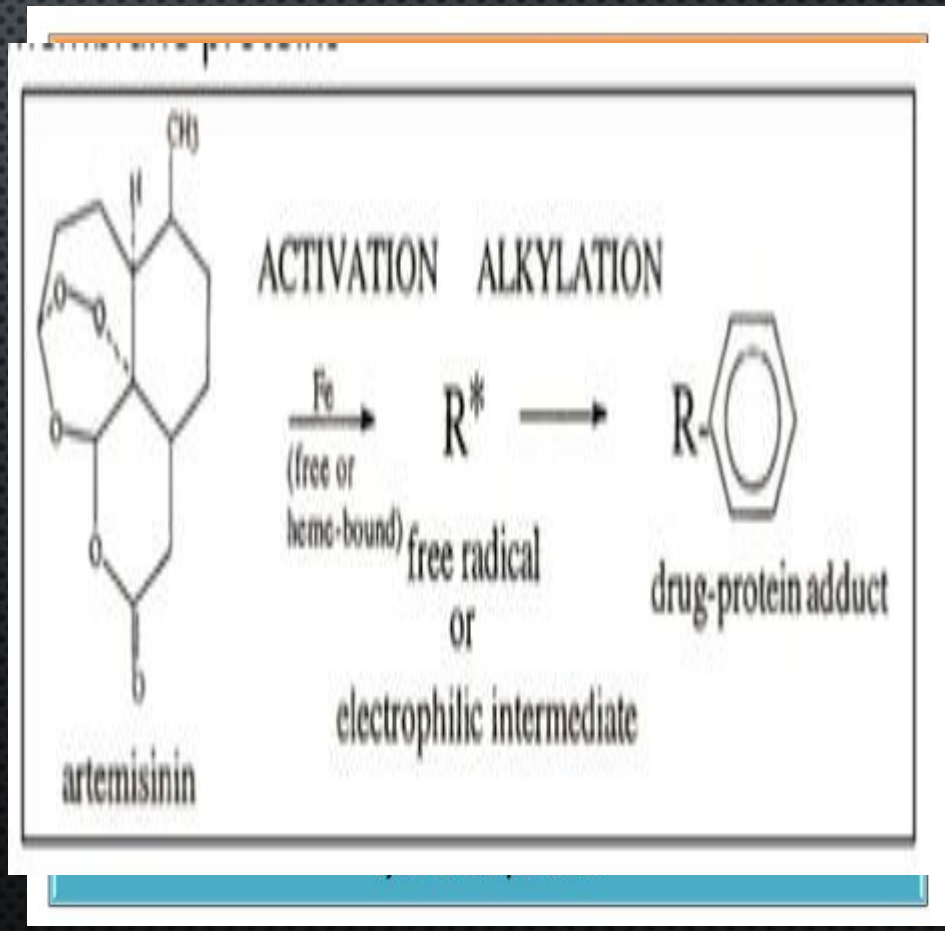
- Rapidly biotransformed in liver into dihydroartesiminin ➔ active metabolite
- Artemisinin ,artesunate, artemether are prodrugs
- Derivatives are rapidly absorbed orally
- Widely distributed
- t½ artemisinin ➔ 4hrs / artesunate ➔ 45min / artemether 4-11hrs
- Artesunate (water-soluble; oral, IV, IM, 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

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

ANTIMALARIAL DRUGS

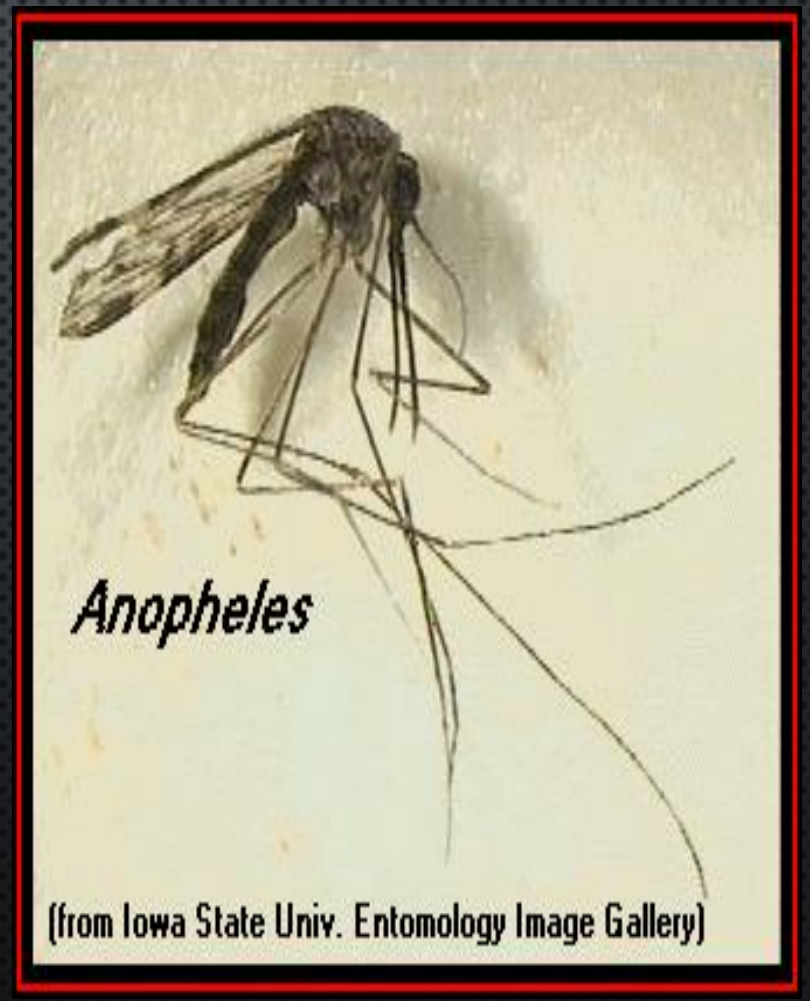
CHLOROQUINE

Potent blood Schizontocide

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

No activity against tissue shizonts

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



CHLOROQUINE

PHARMACOKINETICS

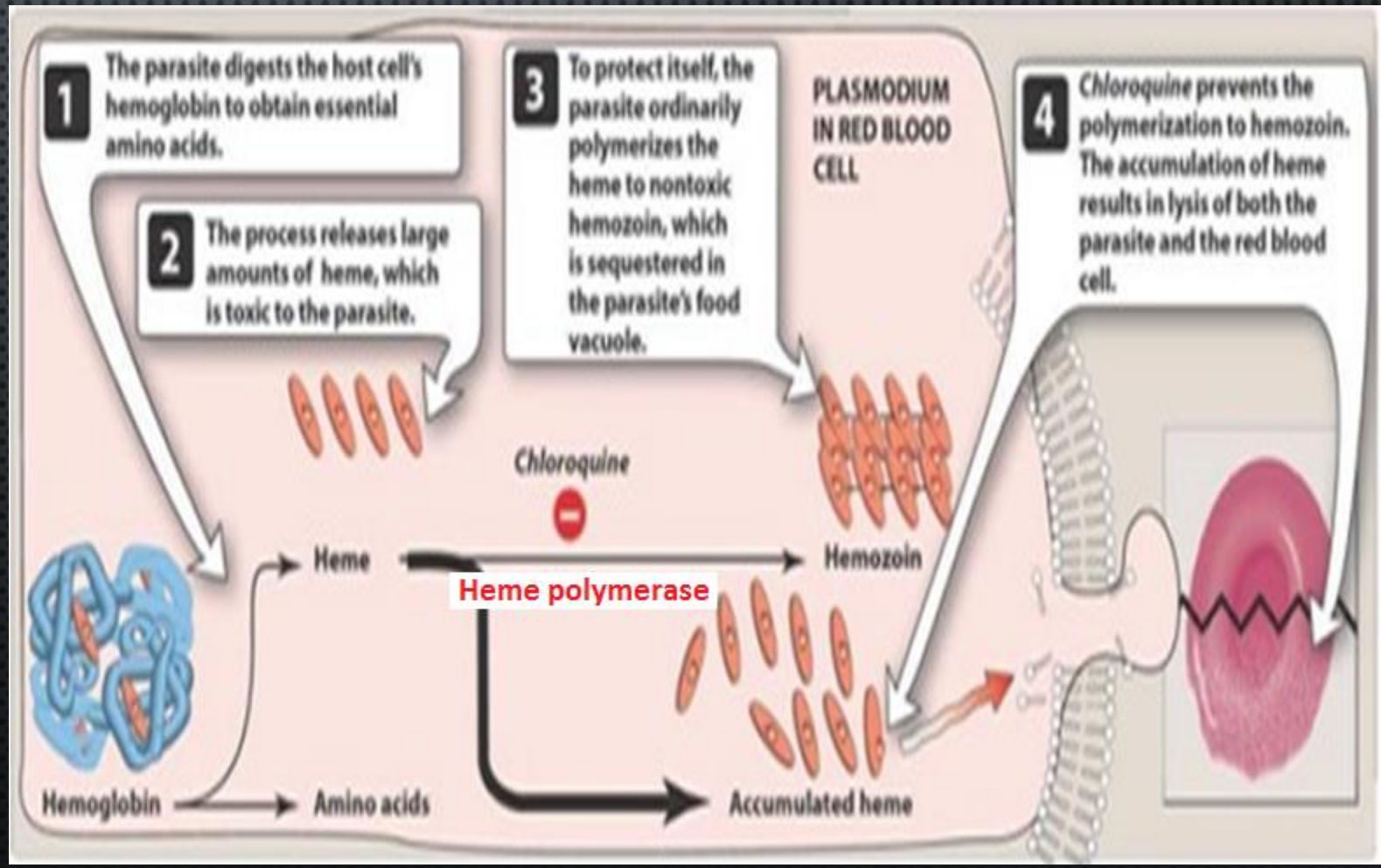
- Rapidly & completely absorbed from the GIT
- Has high volume of distribution(100-1000l/kg)
- Concentrated into parasitized RBCs
- Released slowly from tissues
- Metabolized in the **liver**
- Excreted in the urine 70% unchanged
- Initial t½ =2-3days & terminal t ½=1-2months

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

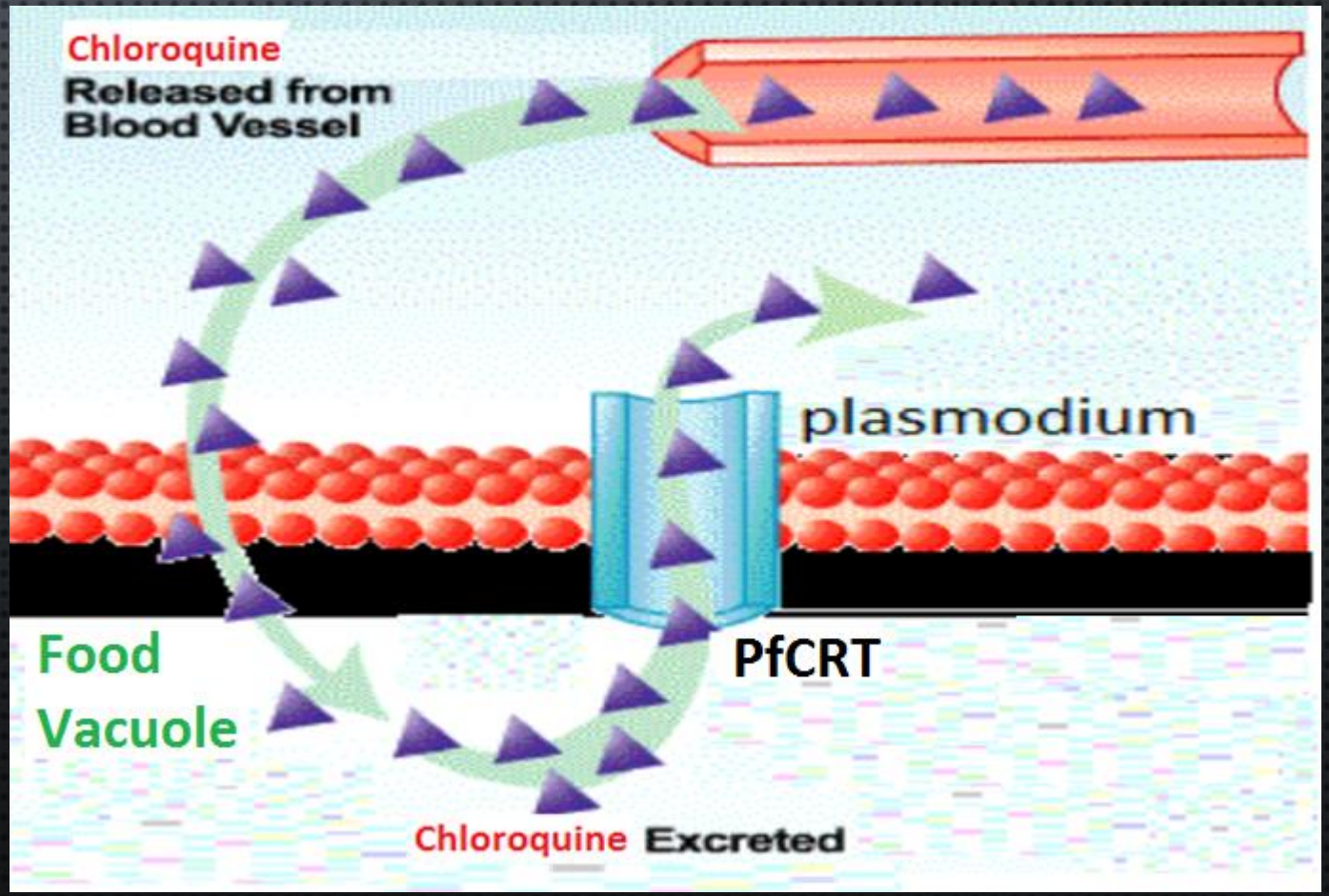
Safe in pregnancy

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



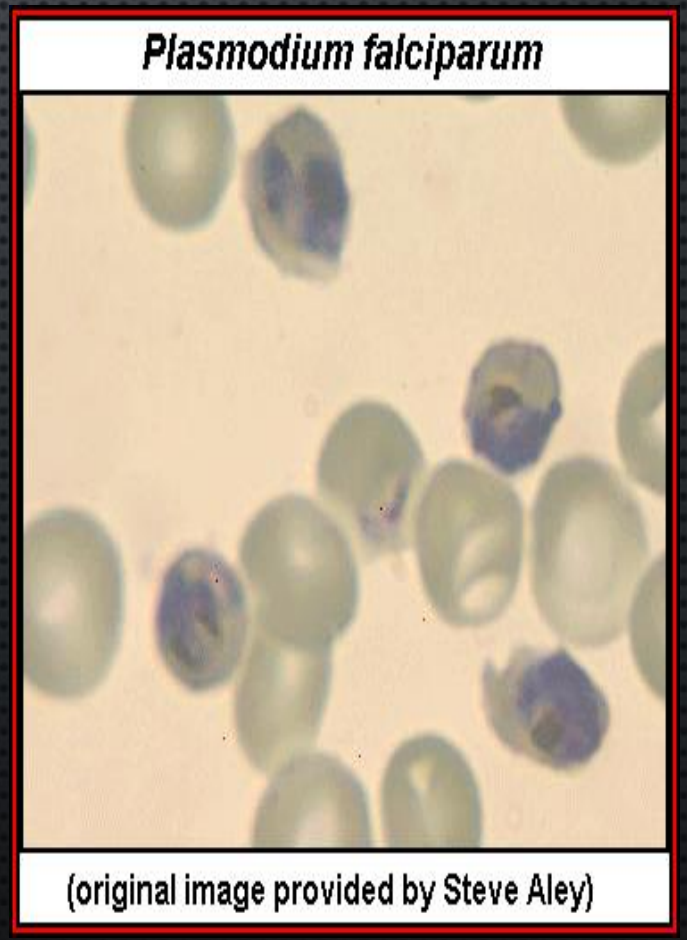
CHLOROQUIN

THERAPEUTIC USES

Used to eradicate blood schizonts of *Plasmodium*

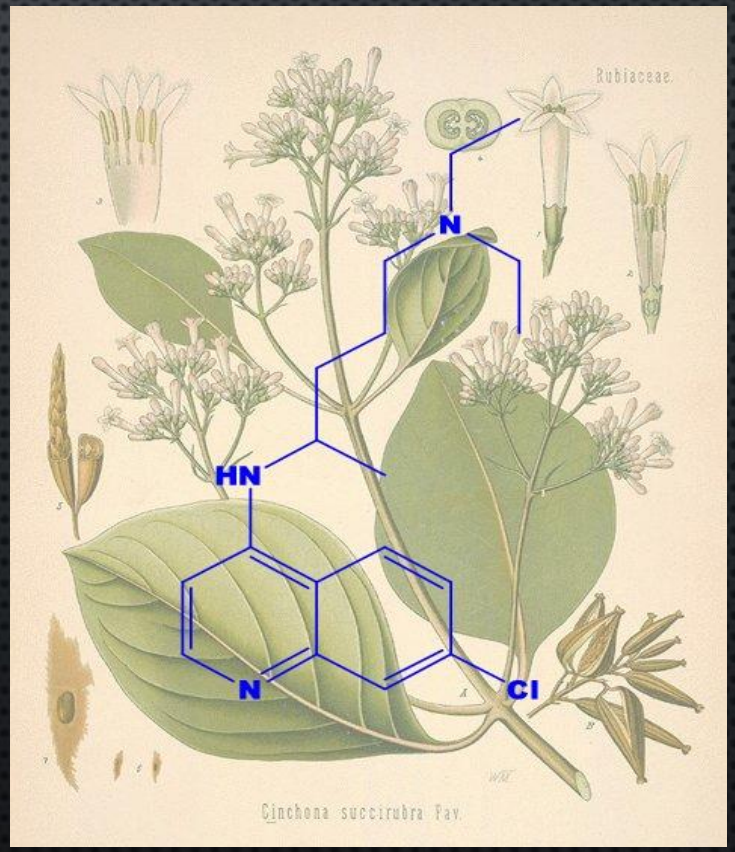
Hepatic amoebiasis

Rheumatoid arthritis



QUININE

- The main alkaloid in cinchona bark
- Potent blood Schizontocide of all malarial parasites & weak gametoside for vivax & ovale
- Depresses the myocardium, reduce excitability & conductivity
- Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curaremimetic effect

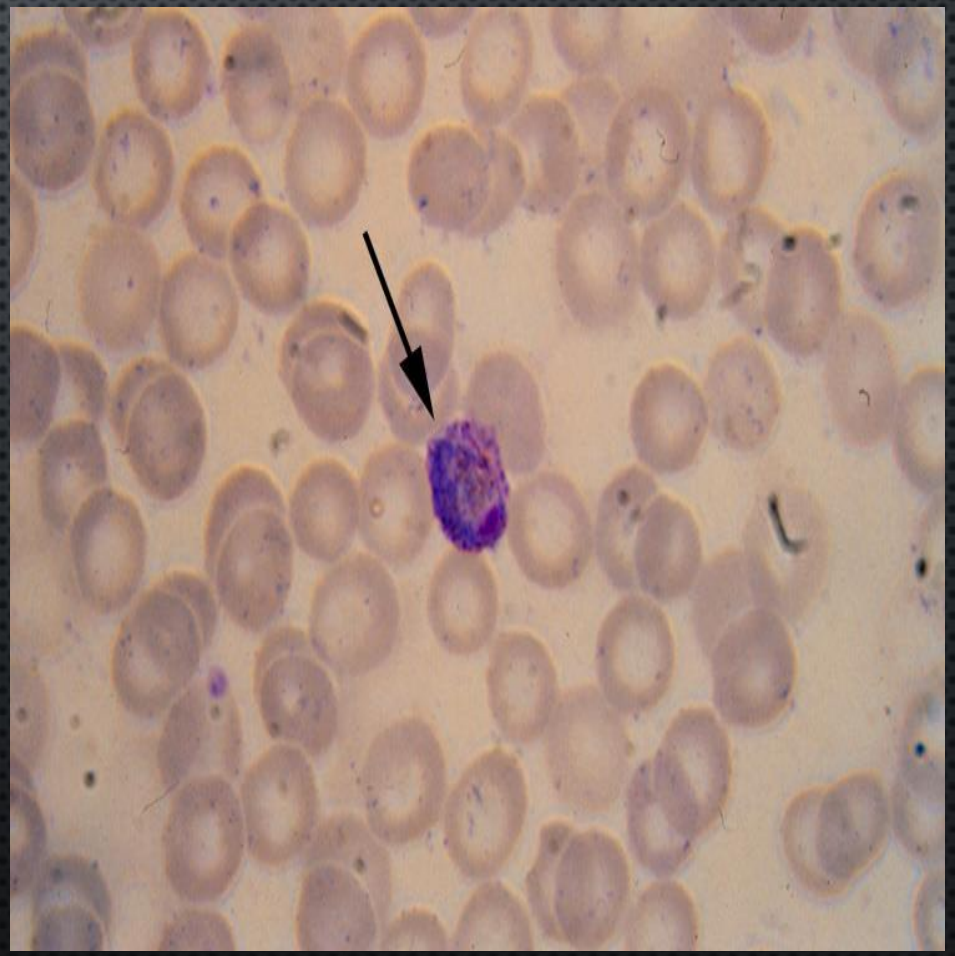


QUININE

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 & visual disturbances)*
- Abdominal pain & diarrhea
- Hypotension & arrhythmias, hypoglycemia
- Rashes, fever, hypersensitivity reactions
- Blood dyscarasis; anaemia, thrombocytopenic purpura & hypoprothrombinaemia
- Blackwater fever, a fatal condition in which acute haemolytic anaemia is associated with renal failure

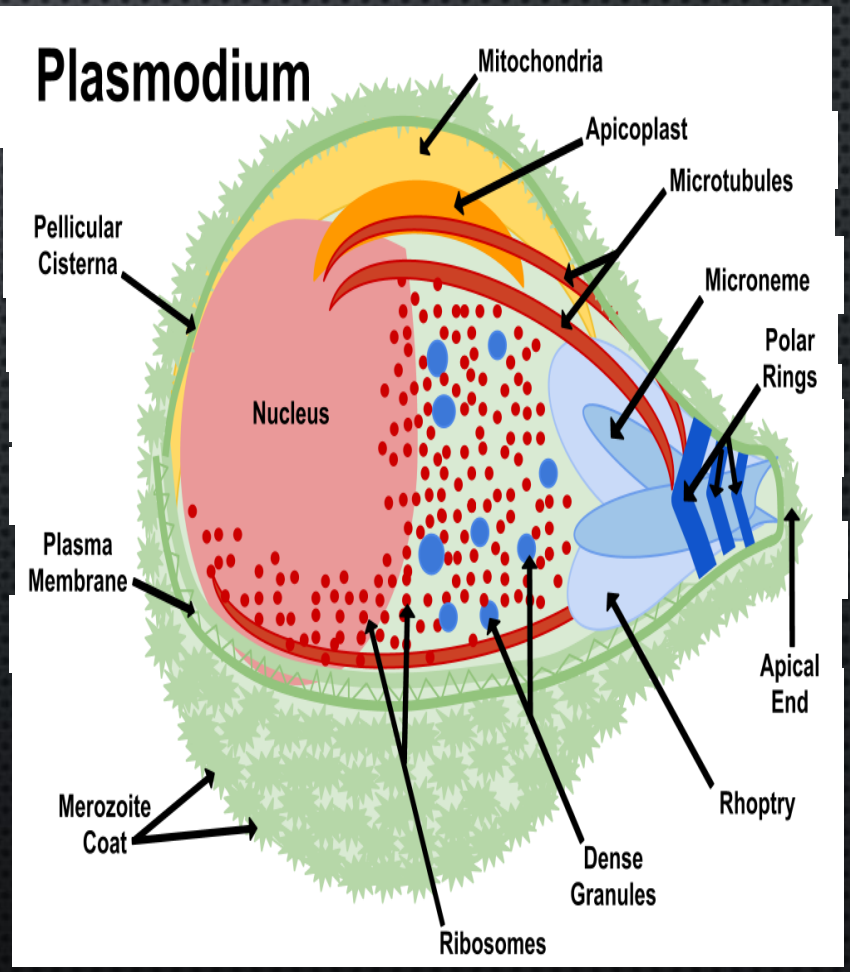
IV → neurotoxicity → tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma

Safe in pregnancy

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??

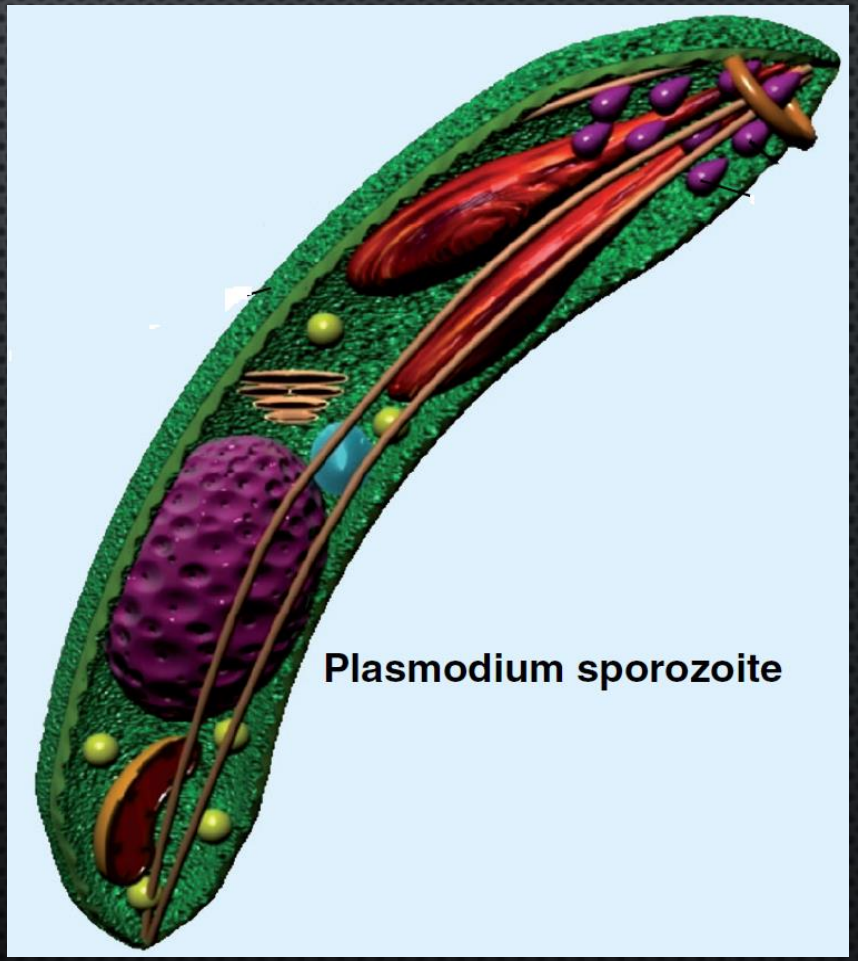
QUININE

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

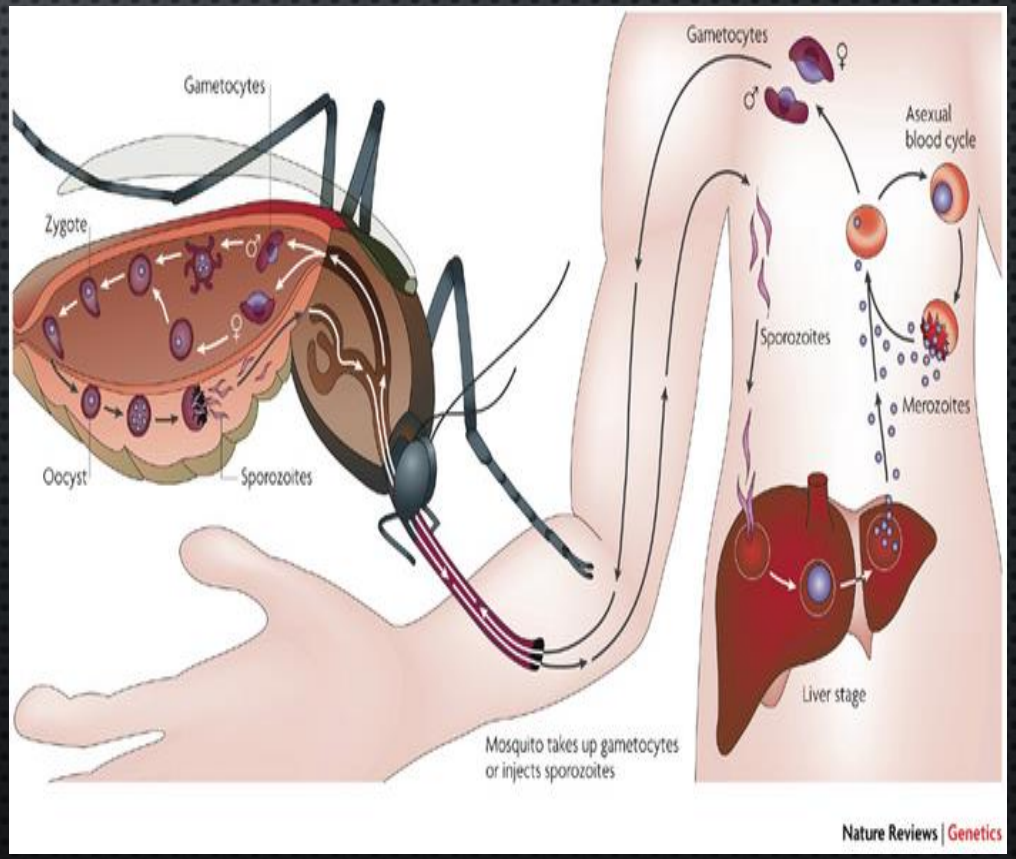
- Hypnozoitocides ➔ against liver hypnozoites & gametocytocides

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

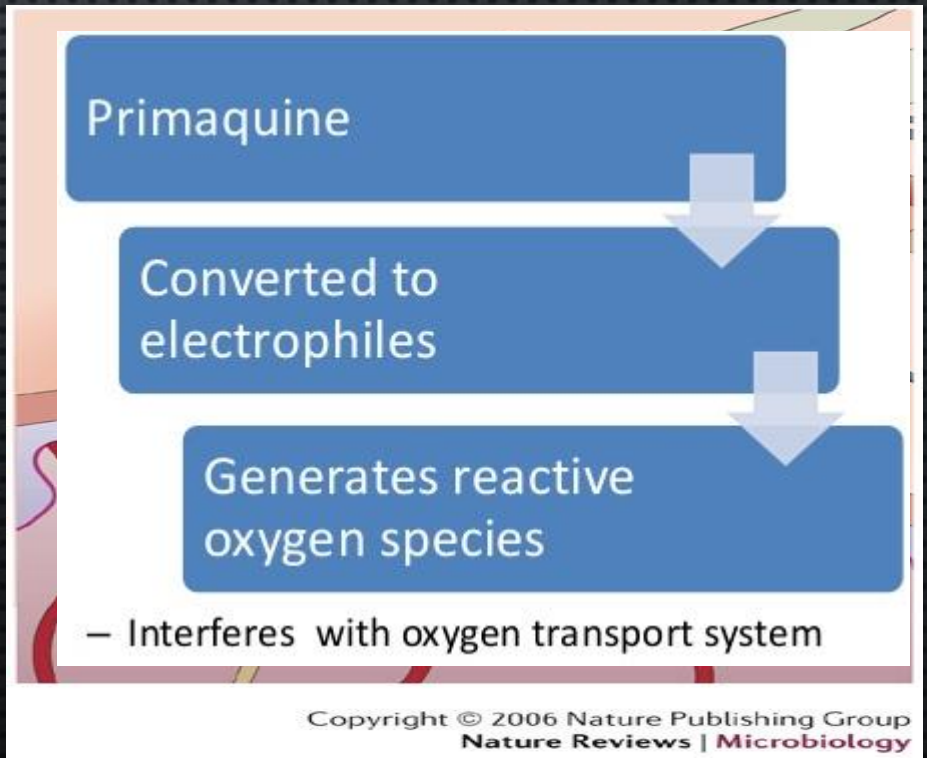
Not well understood. It may be acting by:-

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

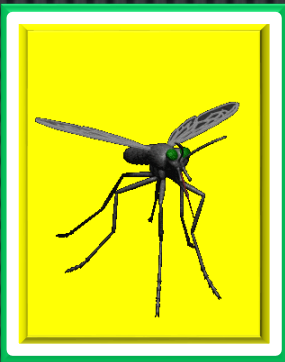
Interfering with the electron transport in the parasite ➔ no energy

Inhibiting formation of transport vesicles ➔ no food vacuoles

Resistance; ➔ Rare when primaquine & chloroquine are combined



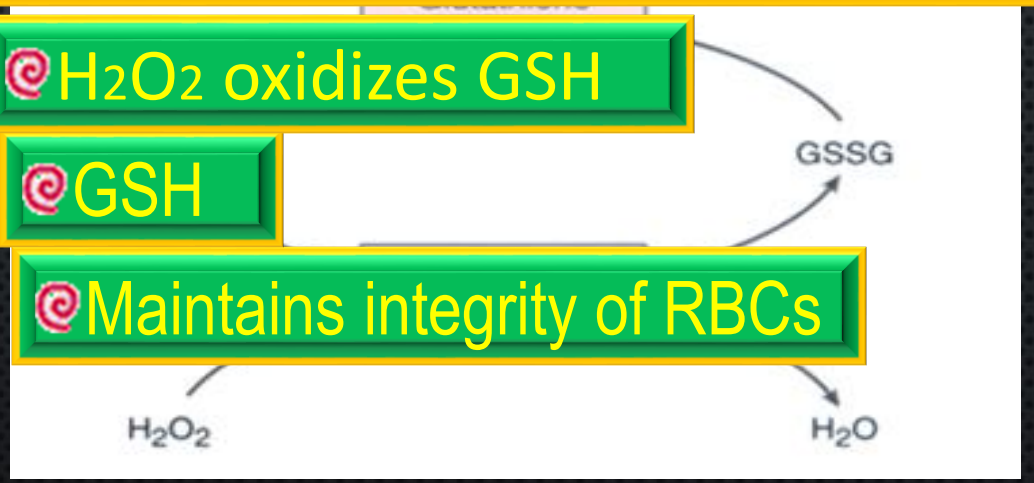
PRIMAQUINE



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 Lactating women 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