ANTI MALARIA

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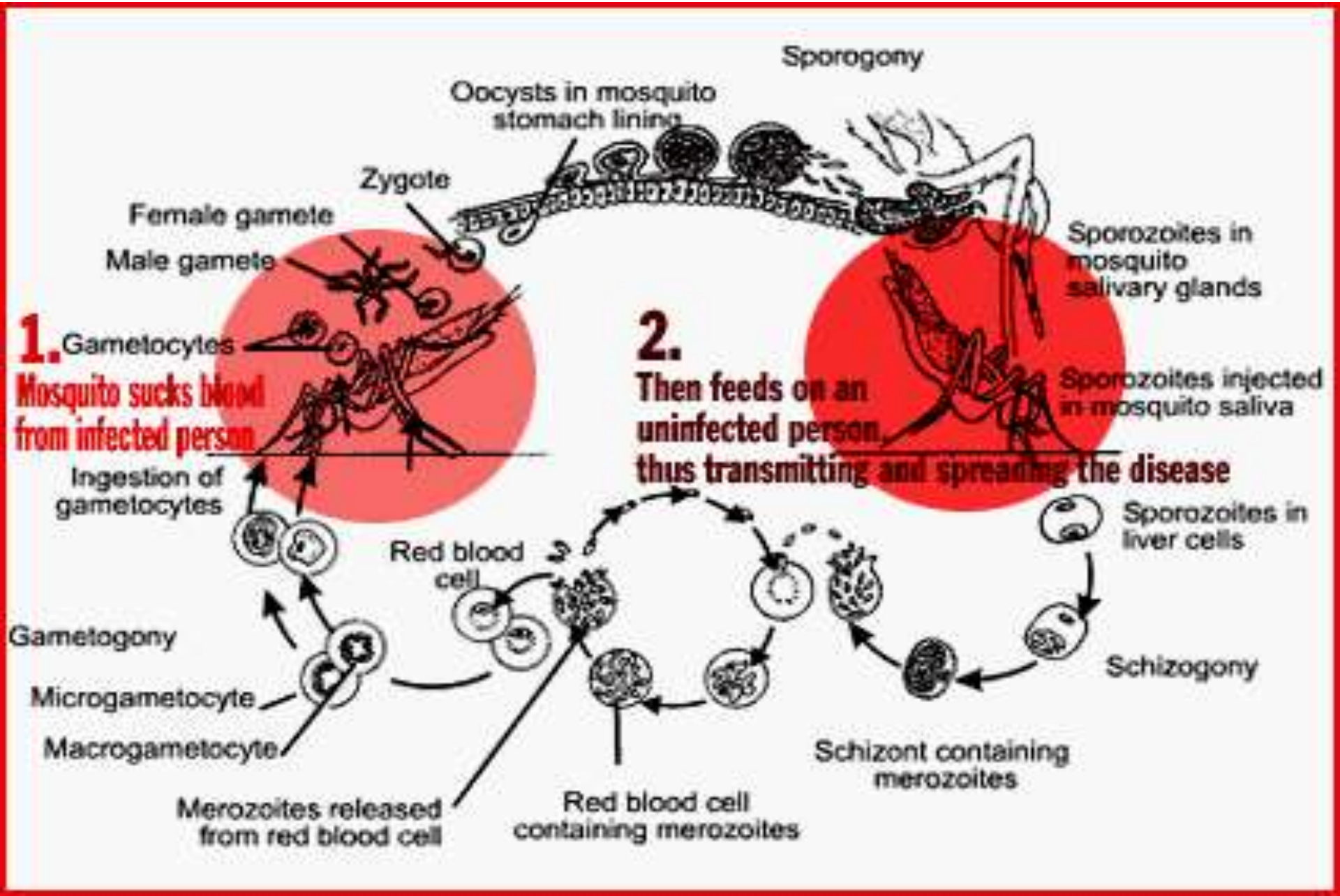
Penyebab Malaria

- Plasmodium falciparum
- Plasmodium malariae
- Plasmodium vivax
- Plasmodium ovale.

SIKLUS HIDUP



Sporozoit dalam kel.ludah nyamuk

↓

Fase Pre-Eritrosit : (sel parenkim hati)

Skizon jaringan

Merozoit (ke sirk.darah)

Fase Eritrosit: Eri + skizon matang pecah

Merozoit → ke-sirkulasi

→ mikro/makro gametosis

↓

Gamet→ zygot→ sporozoit (kel.ludah nyamuk)

Sikluas Hidup Malaria

Sporogony

Oocyst

Sporozoite

s

Mosquito
Salivary Gland

Zygote

Sporozoites

Hypnozoites
(for *P. vivax*
and *P. ovale*)

Gametocytes

Exo-
erythrocytic
(hepatic) cycle

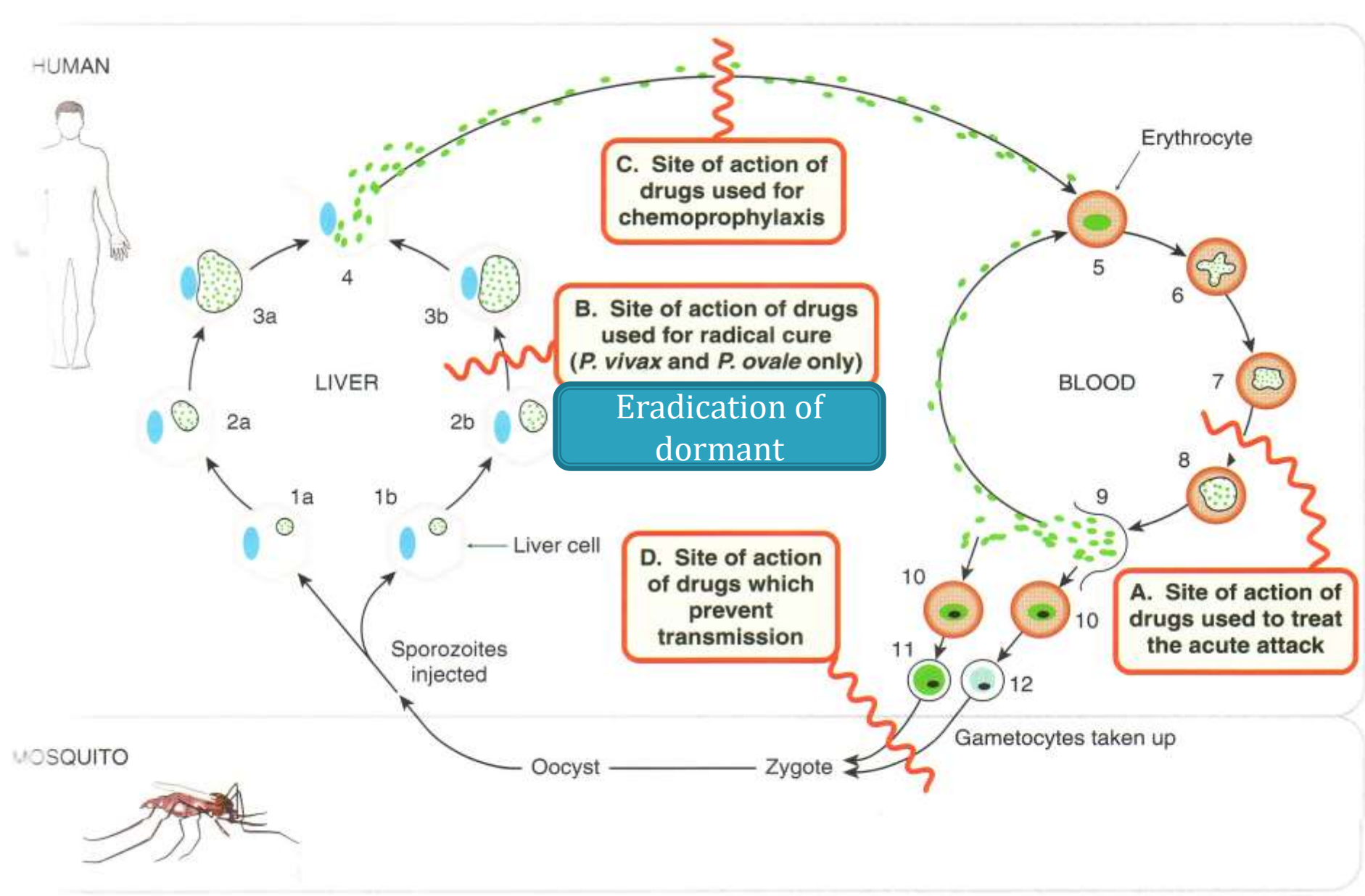
Merozoites

Erythrocytic
Cycle

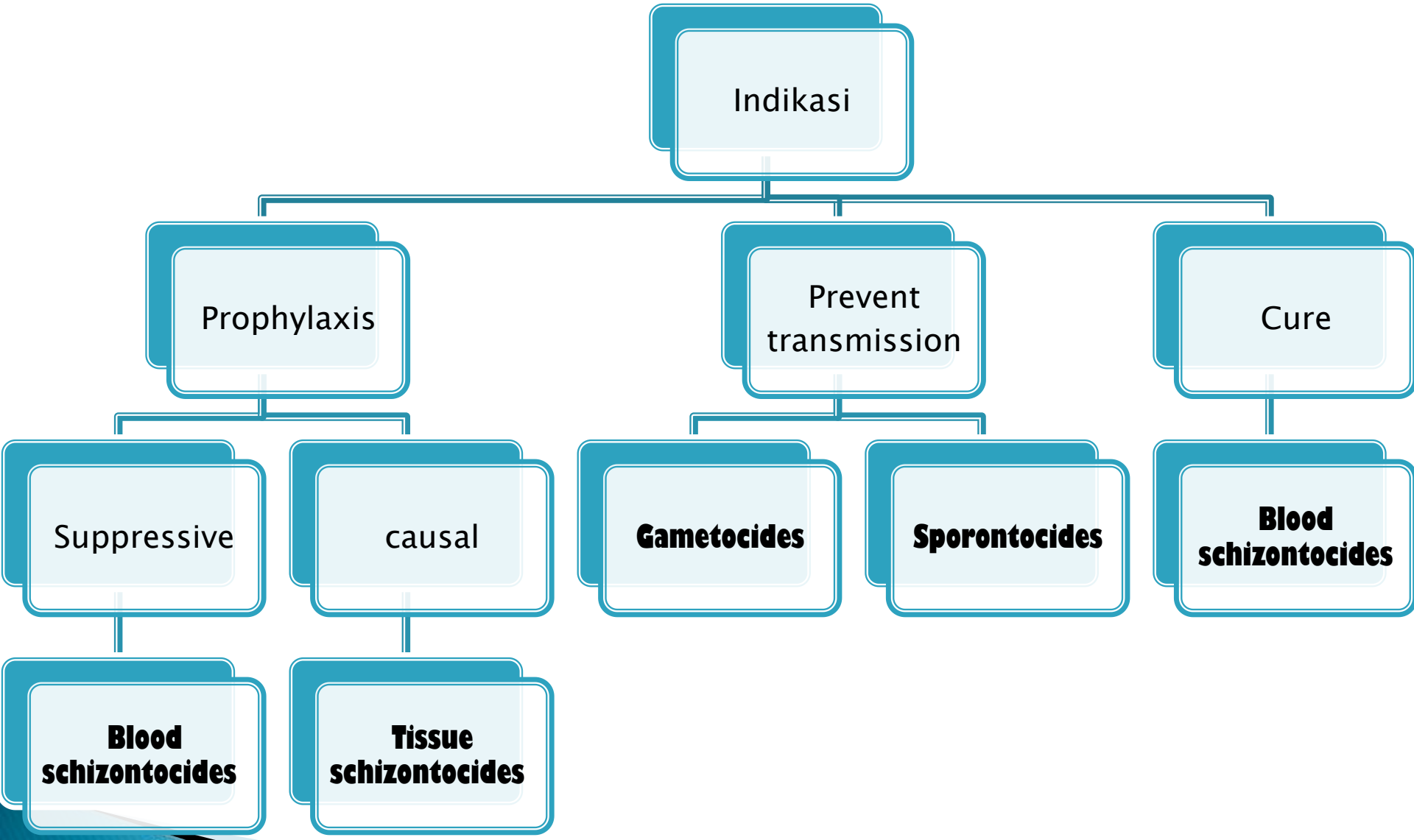
Merozoites

Schizogony

Target Kerja Anti Malaria



INDIKASI & KLASIFIKASI ANTI MALARIA



Indikasi Penggunaan

Profilaksis

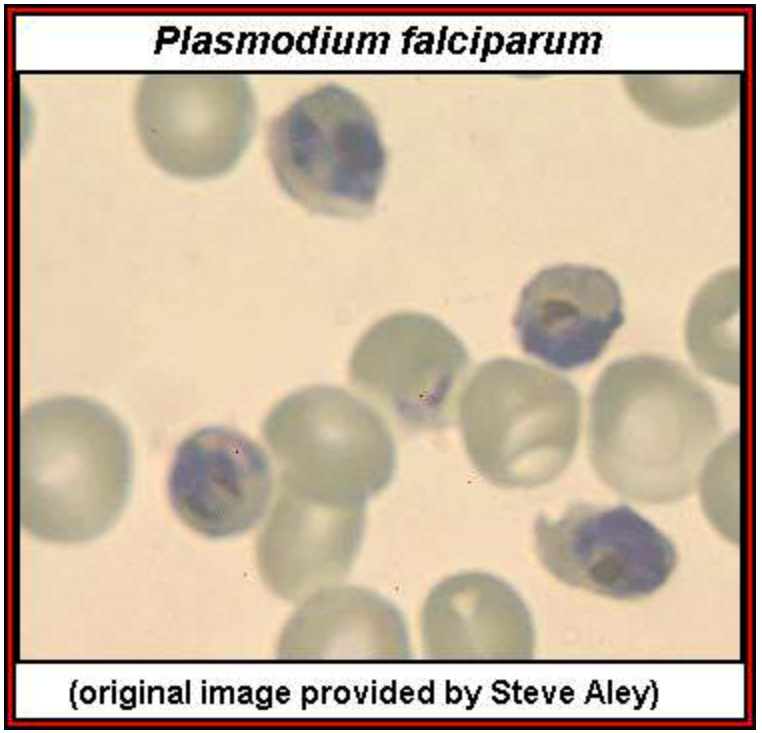
Untuk mencegah serangan klinis

Suppressive prophylaxis

blood schizontocides

Causal prophylaxis

tissue schizontocides – untuk mencegah parasit menetap di hepar



Kuratif

- terapi supresi serangan akut dg blood schizontocides →tdk terbentuk skizon baru →tdk terjadi lisis eritrosit→tdk muncul gx klinis.
- Terapi radikal dg kombinasi blood schizontocides dan tissue schizontocides

Mencegah transmisi

eradikasi infeksi pada nyamuk dg gametocytocides atau sporontocides.

Mencegah Relapse

Primaquine

P falciparum and P malariae

- invasi ke hepar hanya 1 siklus, infeksi sel hati berhenti spontan < 4 mgg, multiplikasi terbatas pd fase eritrositik sj
- terapi ditujukan utk mengeliminasi parasit fase eritrositik.

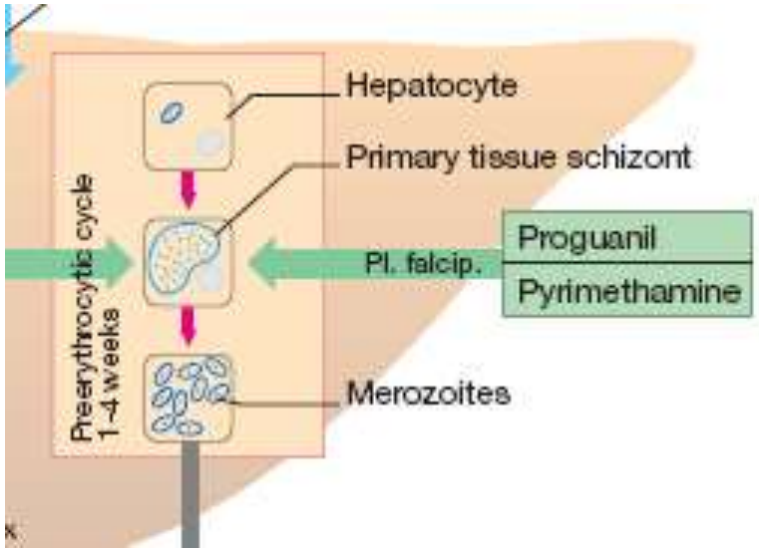
P vivax and P ovale

- merup *dormant parasites* di hepar → bisa terjadi relapse.
- Dibutuhkan obat untuk eradikasi parasit hepatis dan parasit eritrositik

KLASIFIKASI ANTI MALARIA

Tissue schizontocides

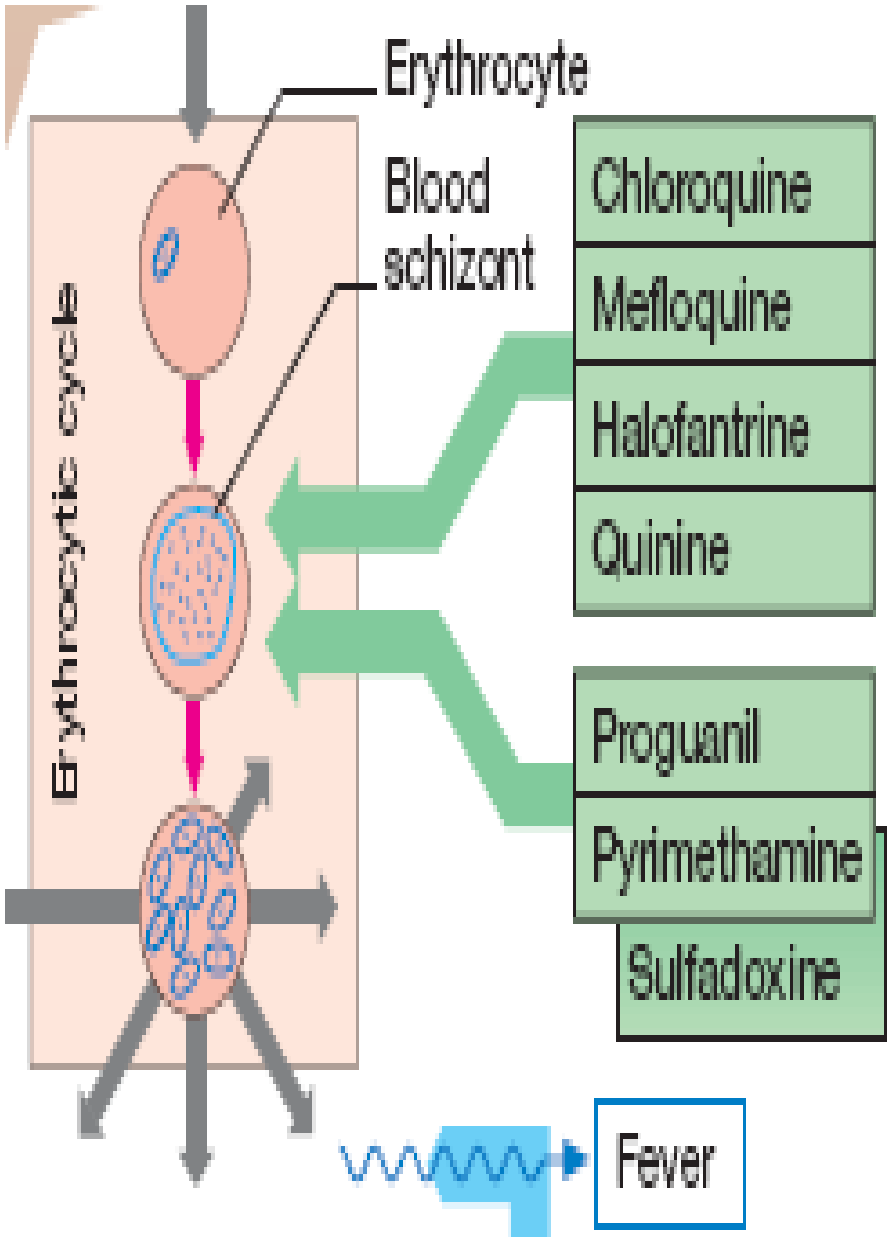
1. Proguanil (chlorguanide)
2. Pyrimethamine
3. Primaquine (relapse)



Blood-schizontocides

2 tipe :

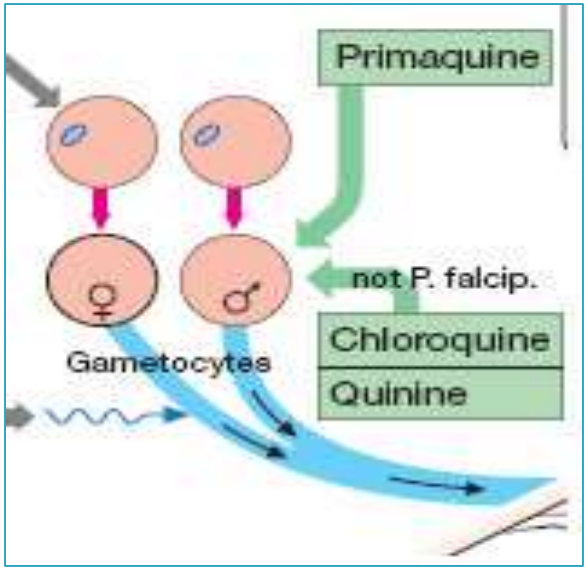
1. Chloroquine, Mefloquine, Halofantrine, & Quinine.
2. Proguanil, Pyrimethamine, & sulfadoxine.



Gametocides

Membunuh bentuk seksual dari parasit dan mencegah transmisi ke nyamuk.

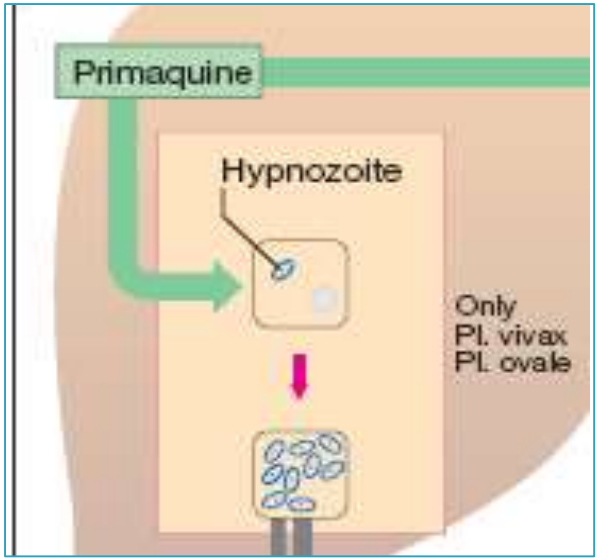
- P. vivax & ovale : Chloroquine, & Quinine.
- P. falciparum : Primaquine



Hypnozoitocides

Membunuh dormant hypnozoites dari *P. vivax* & *P. ovale* di hepar.

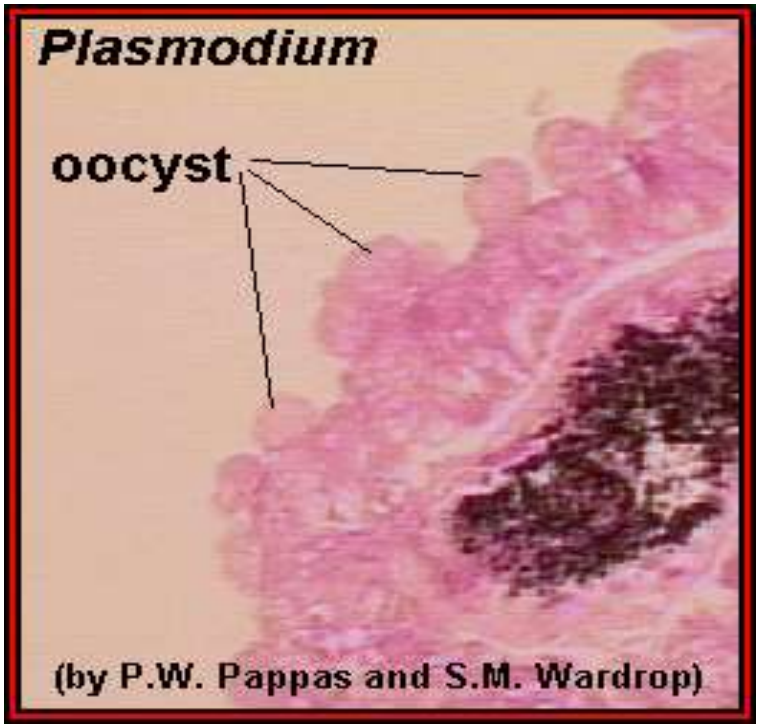
- Primaquine

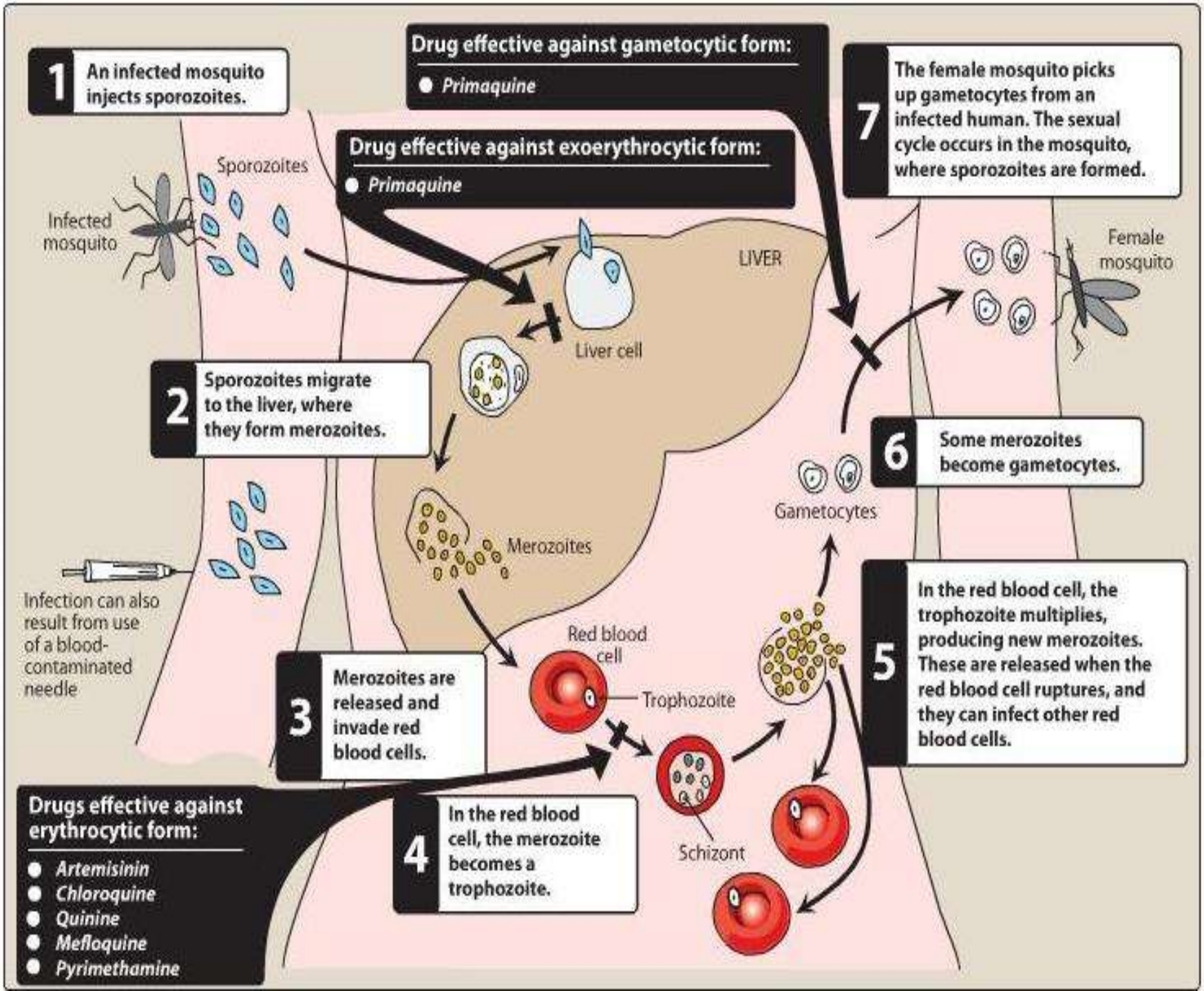


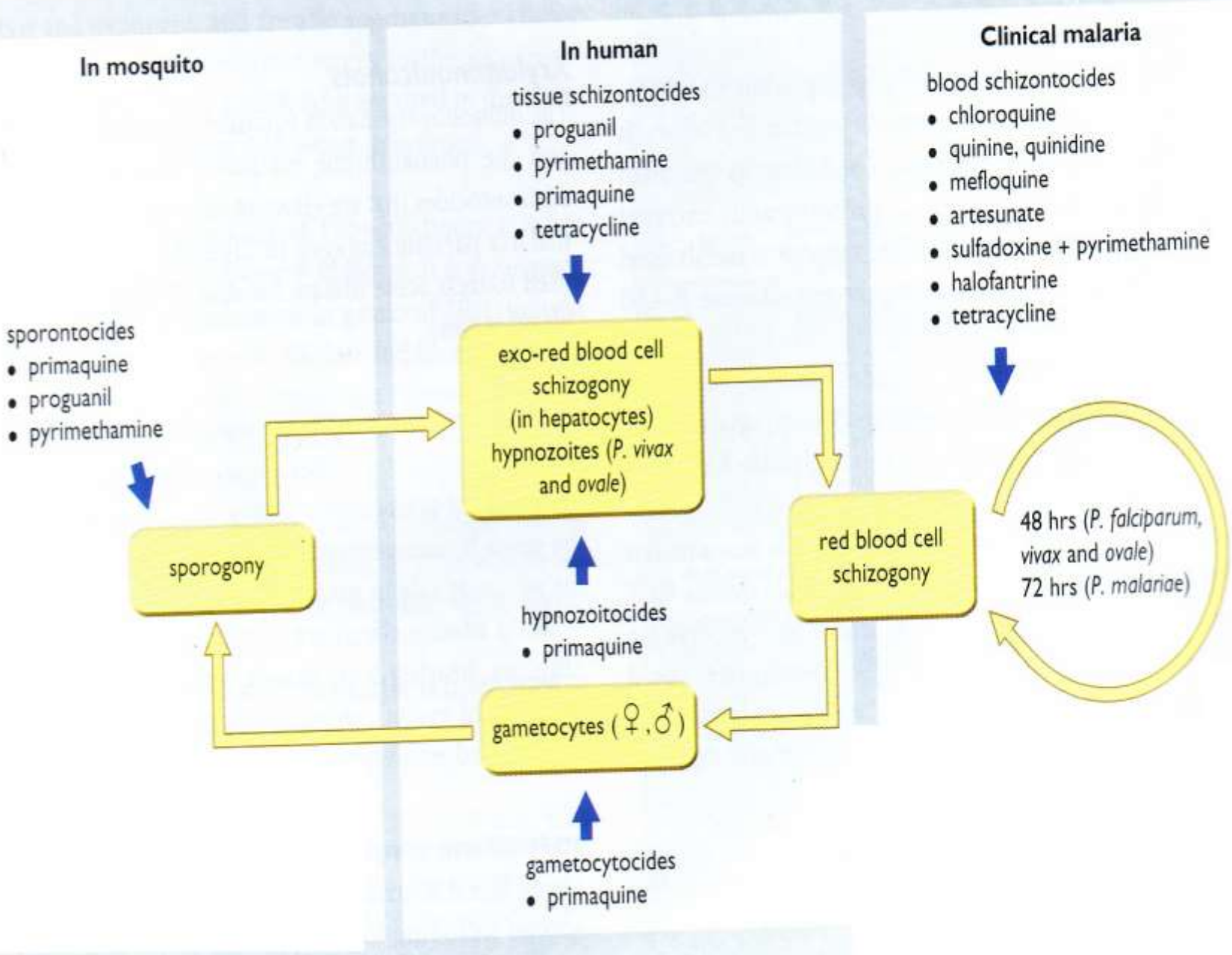
Sprontocides

Menghambat perkembangan fase sporogonia pada nyamuk

- Proguanil
- Pyrimethamine
- Primaquine

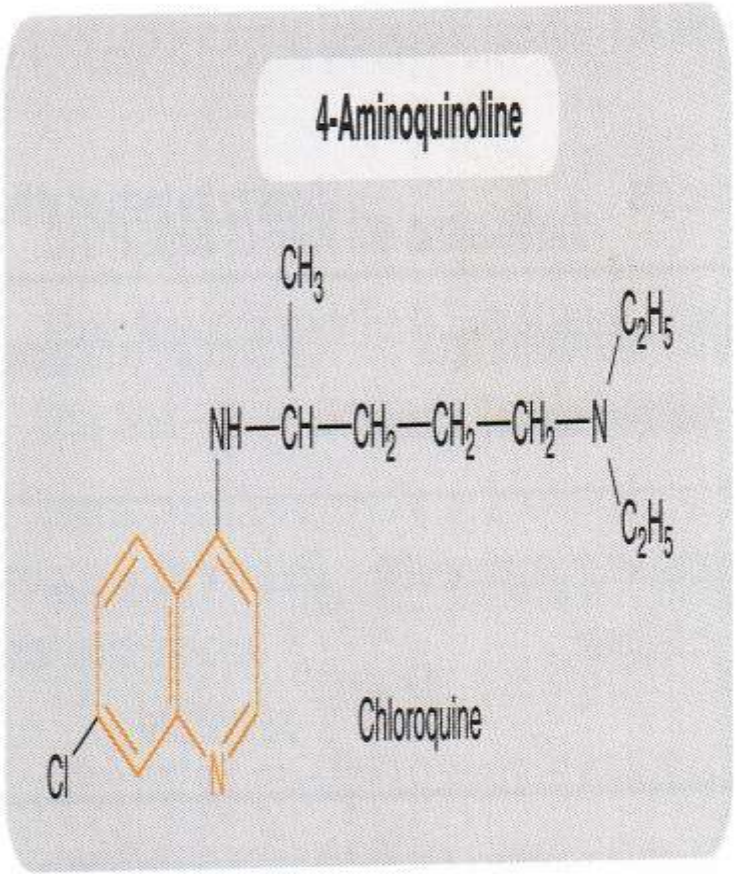



1 An infected mosquito injects sporozoites.
Drug effective against gametocytic form:
Primaquine
7 The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.
Drug effective against exoerythrocytic form:
Primaquine
Sporozoites
Infected mosquito
LIVER
Liver cell
Female mosquito
2 Sporozoites migrate to the liver, where they form merozoites.
6 Some merozoites become gametocytes.
Gametocytes
Merozoites
Infection can also result from use of a blood-contaminated needle
Red blood cell
Trophozoite
3 Merozoites are released and invade red blood cells.
5 In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells.
Drugs effective against erythrocytic form:
Artemisinin
Chloroquine
Quinine
Mefloquine
Pyrimethamine
4 In the red blood cell, the merozoite becomes a trophozoite.
Schizont

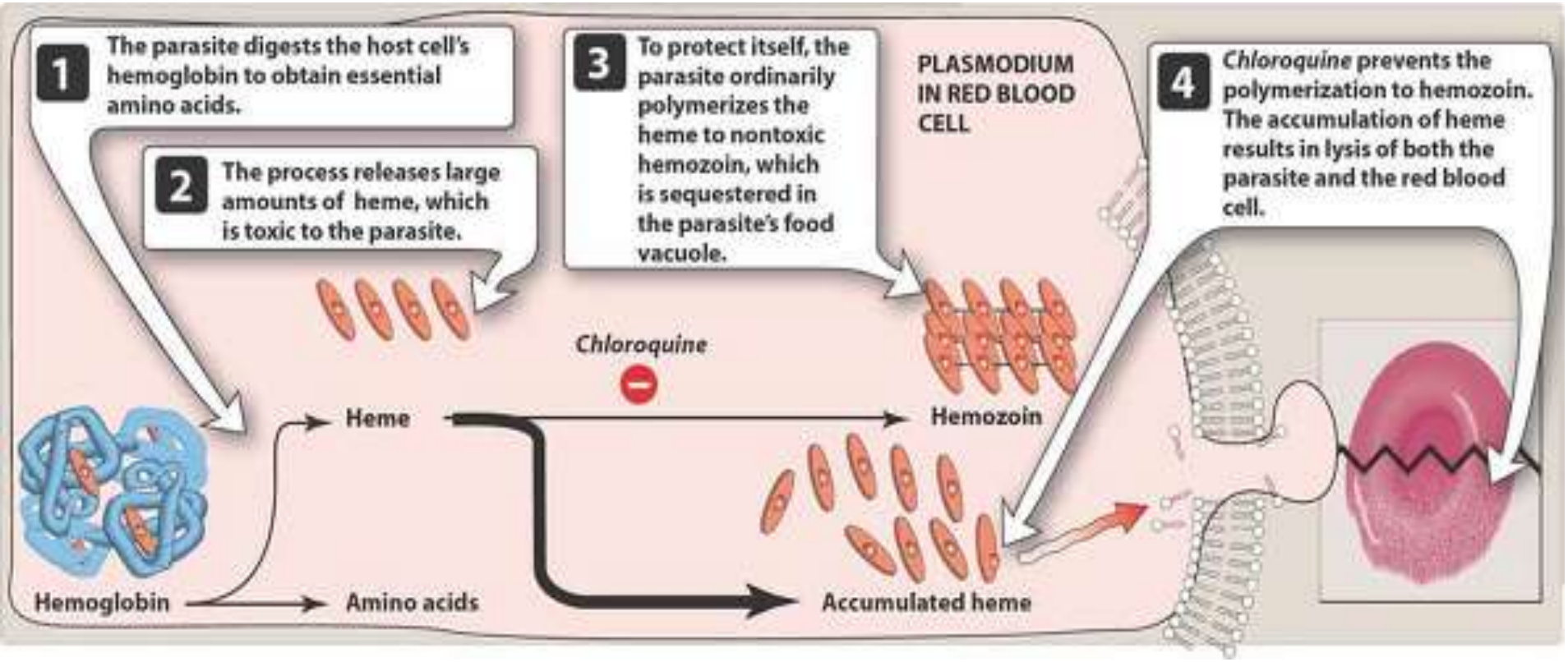

In mosquito
In human
Clinical malaria
tissue schizontocides
• proguanil
• pyrimethamine
• primaquine
• tetracycline
blood schizontocides
• chloroquine
• quinine, quinidine
• mefloquine
• artesunate
• sulfadoxine + pyrimethamine
• halofantrine
• tetracycline
sporontocides
• primaquine
• proguanil
• pyrimethamine
exo-red blood cell schizogony (in hepatocytes) hypnozoites (P. vivax and ovale)
sporogony
red blood cell schizogony
48 hrs (P. falciparum, vivax and ovale)
72 hrs (P. malariae)
hypnozoitocides
• primaquine
gametocytes (♀,♂)
gametocytocides
• primaquine

4-Aminoquinolines

- Mis. Chloroquine and amodiaquine
- potent blood schizontocide.
- Obat utama antimalaria sampai munculnya resisten P. Falcifarum
- Indikasi : malaria non-falciparum & sensitive falciparum



Mekanisme Kerja Amoquinoline

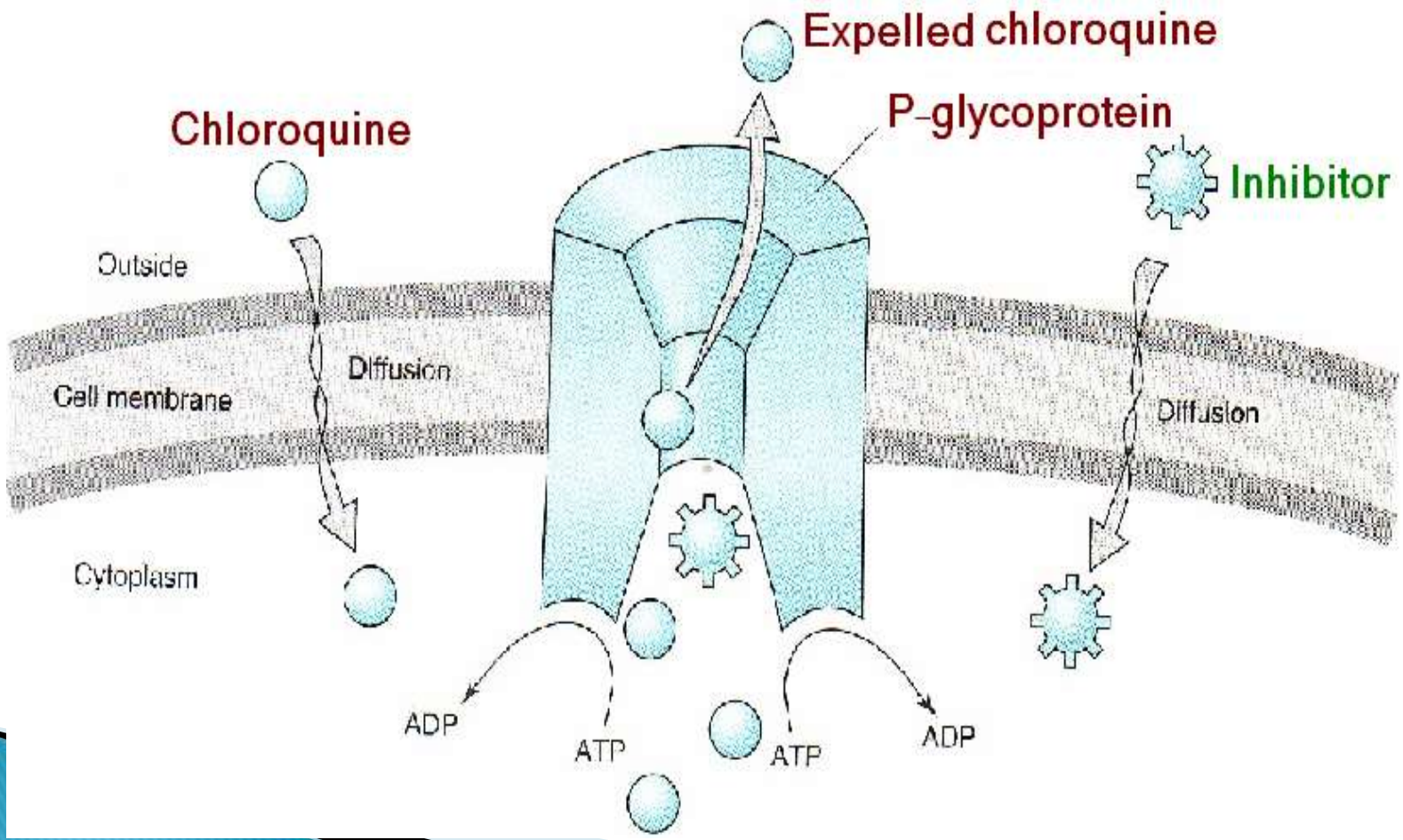


Parasit mencerna human hemoglobin (Hb) utk mendptkan asam amino , tp heme dari Hb bersifat toksik utk parasit
→ parasit mengembangkan enzyme utk polimerisasi heme.
→ membentuk insoluble crystals yg disebut 'hemozoin' , tersimpan dalam vacuola.

Chloroquine msk dlm sel parasit melalui difusi pasif.
→terjadi protonasi pd Chloroquine krn vakuola digestif bersifat asam (pH 4.7) → chloroquine tdk dpt keluar dr sel melalui difusi pasif →. Chloroquine menghambat polimerisasiheme→ akumulasi heme.

Chloroquine mengikat heme (or FP) membentuk FP-Chloroquine complex. Kompeks ini sangat toksik thd sel & merusak fungsi membran → cell lysis & sel parasit mengalami autodigestion.

- Resistansi : enhanced efflux of the parasite vesicle $\rightarrow\uparrow$expression of the human multi drug resistance transpoter P-glycoprotein.



- Absorbsi cepat dan lengkap di GIT,
- High volume of distribution(100-1000 L/kg).
- The drug is distributed into 2 compartments:

  The drug highly concentrated in tissues, thus low concentration in plasma
- Concentrated into parasitised RBCs.
- Administered as 1g loading dose, 6 hours later 0.5g as maintenance dose for 2-3 days

- Released slowly from tissues & metabolized in the liver, excreted in the urine 70% unchanged. Elimination is slow.
- Initial t½ =2-3days (for the first compartment, plasma, highly perfused tissues e.g. liver and spleen) & terminal t ½=1-2months (2nd compartment, in moderately perfused tissues e.g. muscle and bone).

ES :

- Nausea, vomiting, dizziness, blurring of vision, headache, urticaria
- Large doses→ retinopathy. (most serious , occurs with long time administration)
- Bolus injection→ hypotension & dysrrhythmias
- Safe for pregnant women.
- Used in acute attack

KI: Psoriasis atau prophyria, Visual field abnormalities or myopathy
hati-hati pd gangguan hepar, neurologi dan hematologi

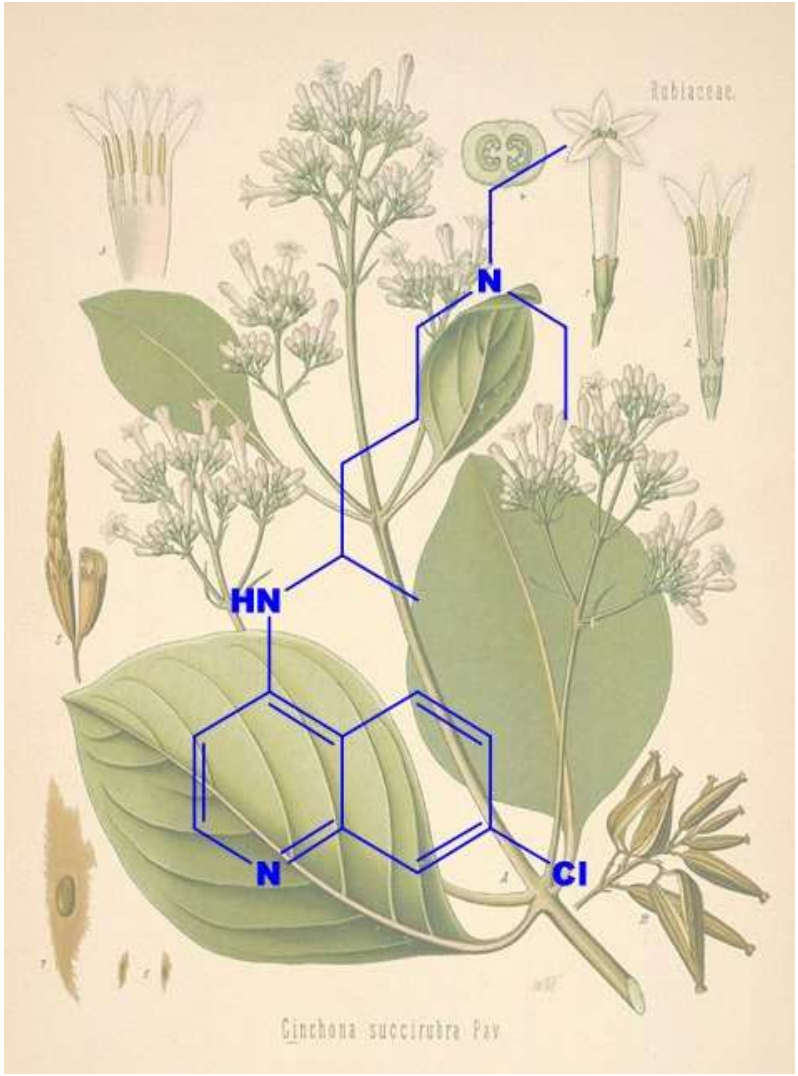
interaksi : antasida yg mengandung Ca & Mg mempengaruhi absorbsinya

Indikasi lain:

- Sbg DMARD (disease modifying antirheumatoid drug) :6-9 month
- SLE
- amebic liver abscess

Quinine

- Blood schizontocide
- Efektif utk semua jenis malaria.
- Dari kulit pohon kina
- FD : ↓ parasite's heme polymerase.
- ES : Depresi myocardium, krn strukturnya mirip dg quinidine, antiarrhythmic agent, as it is its d- isomer.



Indikasi:

- Blood schizonticide against all species.
- Gametocidal against *P vivax* and *P ovale*

FK:

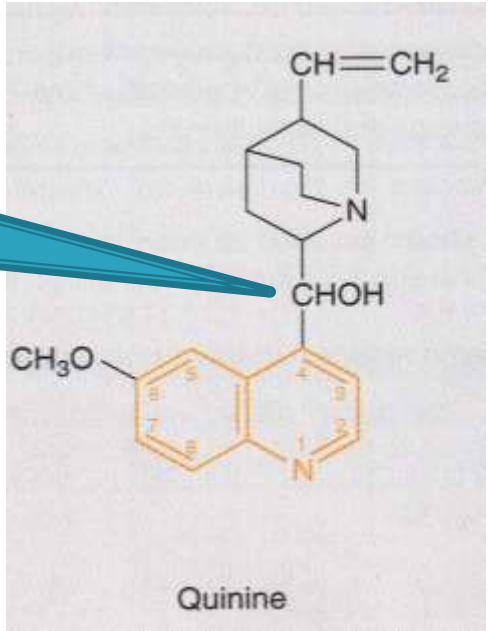
- Given orally in a 7-day course or by slow IV for severe *P. falciparum* infection,
- bitter taste →poor compliance,
- metabolized in the liver, short t½=10h.

ES:

- Mild oxytoxic (sever contraction) effects pregnant uterus, can cause abortion
- slight neuromuscular blocking action,
- weak antipyretic action.

- concentrations >30-60μmol/l→ cinchonism [nausea, dizziness, headache, tinnitus, blurring of vision].
- Higher doses can cause hypotension, cardiac arrhythmias, delirium, coma.
- Hypoglycaemia by influencing insulin's secretion, blood dyscrasias, hypersensitivity reactions
- Blackwater fever, a fatal condition in which acute hemolytic anemia is associated with renal failure.

Blackwater fever because of methanol group



Quinine

KI:

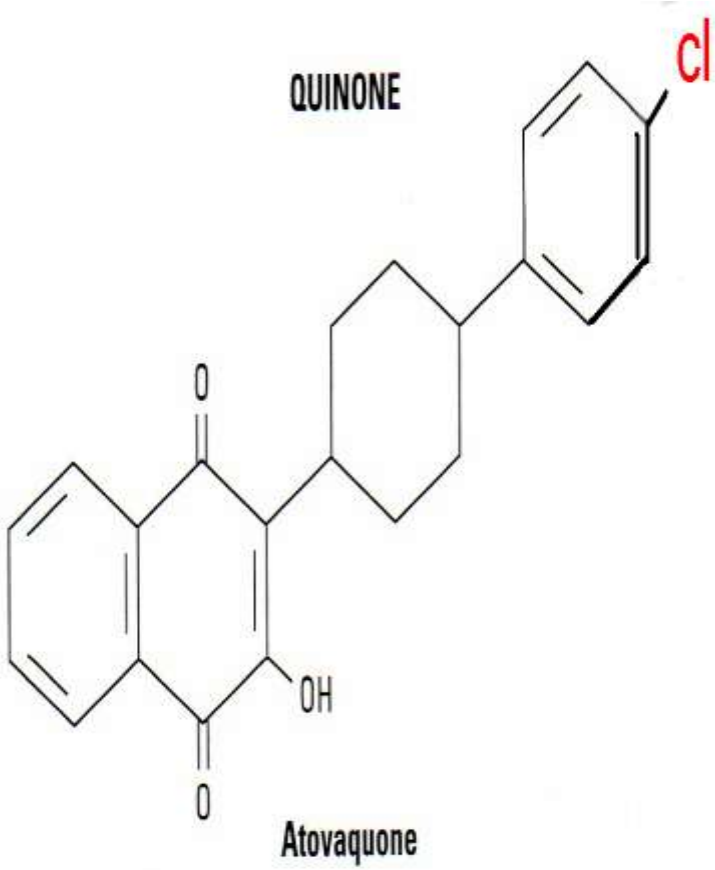
- Prolonged QT Interval
- Glucose-6-Phosphate Dehydrogenase Deficiency
- Myasthenia Gravis
- Hypersensitivity
- Optic Neuritis, auditory problems
- Dose should be reduced in renal insufficiency

Drug Interactions:-

- Antacids: Antacids containing aluminum and/or magnesium may delay or decrease absorption of quinine.
- Erythromycin, Cimetidine (CYP3A4 inhibitors) → ↑ concentration of quinine
- Mefloquine
- Quinine can raise plasma levels of warfarin and digoxin.

Hydroxynaphthoquinone

- Mis. Atovaquone:
- FD = ↓parasite's electron transport chain by mimicking the natural substrate ubiquinone
- Has synergistic effect with proguanil.



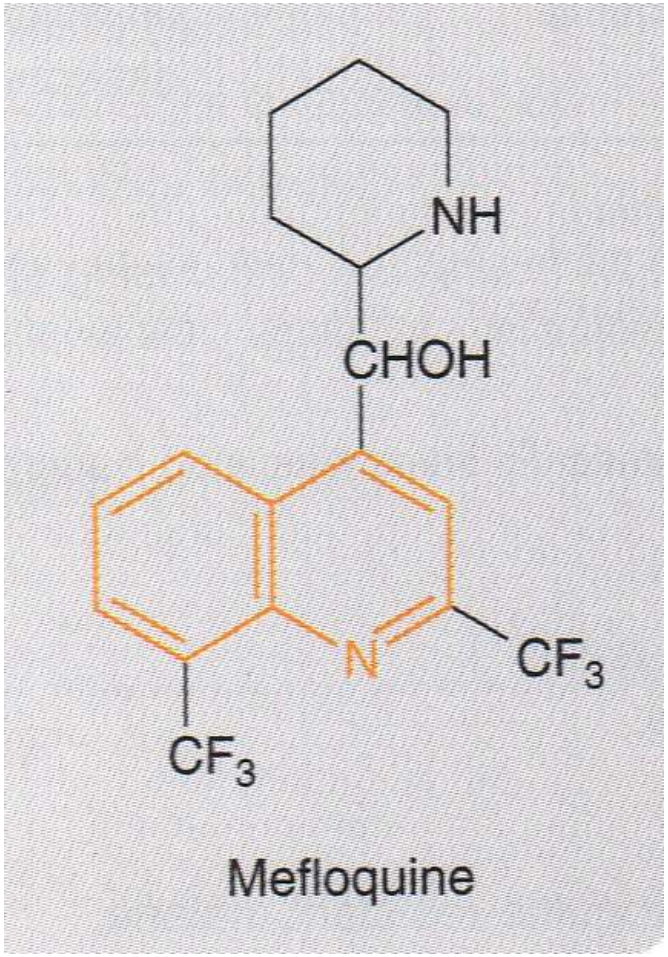
- Resistance to atovaquone is rapid, results from a single point mutation in the gene for cytochrome b. Thus, it should be used in combination with Proguanil
- Low bioavailability, slow, erratic absorption, yet ↑ by fatty food,
- highly protein- bound,
- t½ =2-3d, eliminated unchanged in feces.
- ADR:- fever, rash, Nausea, vomiting, & Diarrhoea, Insomnia
- Pregnant & breast feeding women should not use atovaquone.

Mefloquine

- Strong blood schizontocide active against *P.vivax & P.falciparum,* but does not affect hepatic forms of the parasite.

FD :

- Inhibits haem polymerase.
- Resistance has occurred in southeast Asia.



FK

- Given orally ,well absorbed, slow onset of action,
- high protein bound, extensive distribution
- t½= 30 day → enterohepatic recycling or tissue storage.

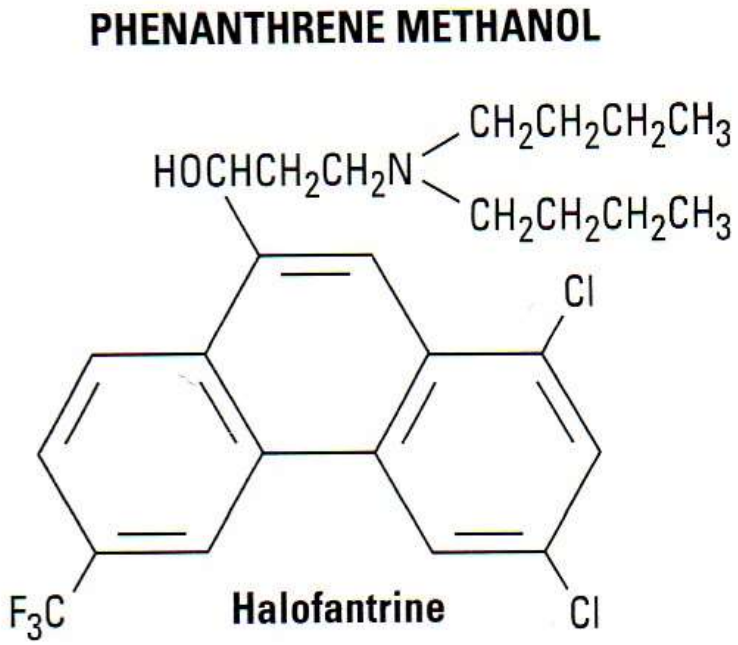
ES =

- GIT disturbances, leukocytosis, thrombocytopenia.
- Most common side effects are: transient CNS toxicity, confusion, Gidiness=dizziness, vertigo, dysphoria, insomnia. (contraindicated in CNS disease)
- May provoke neuropsychiatric disorder.

KI = pregnant women.

Halofantrine

- Blood schizontocide, active against strains resistant to chloroquine, pyrimethamine, quinine.
- Only in hospitalized pateint, t monitor their ECG
- Cross-resistance in falicparum infection occurred .
- Absorbed orally slowly , t½=11-12day
- Absorption ↑ with meals, elimination in feces.



ES :

-abdominal pain, headache, transient ↑in hepatic enzymes, cough, pruritus, lengthening of QT interval.

-May cause hemolytic anemia & convulsions.

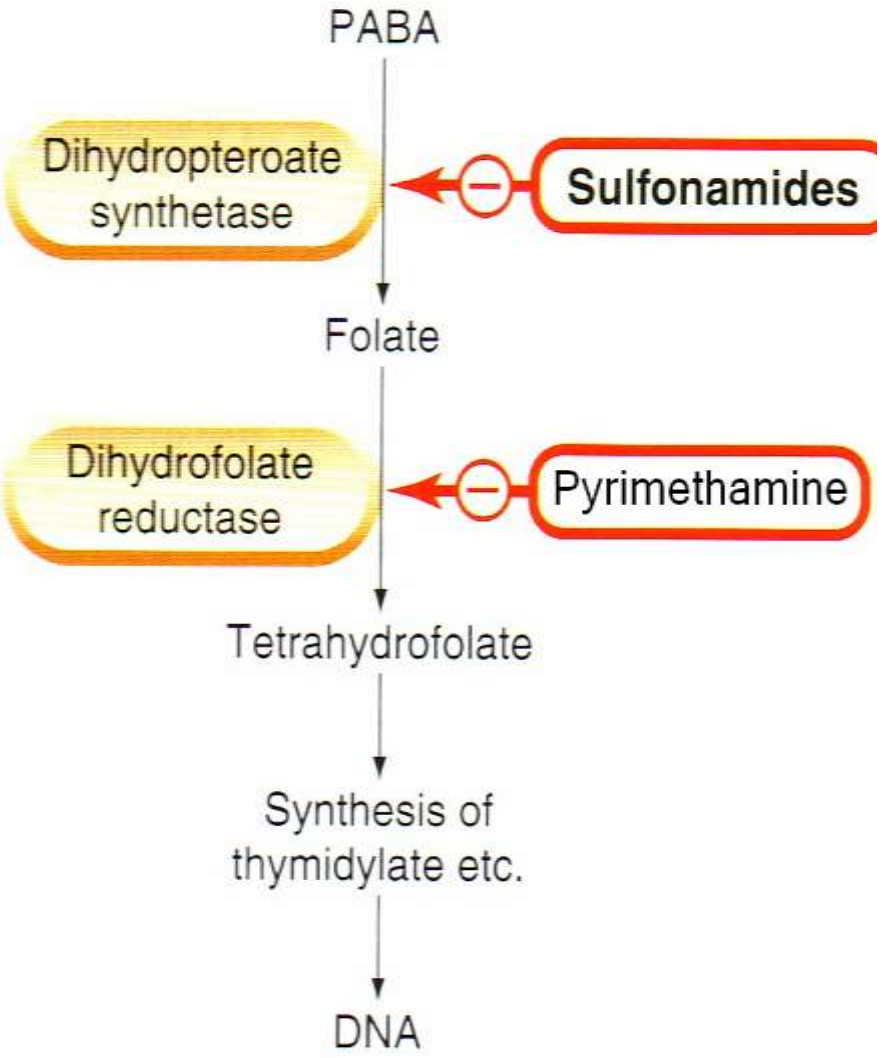
-Reserved for infection caused by resistant organisms.

KI :

- dg mefloquine.
- Pasien dg gangg konduksi jantung.
- Ibu hamil → embriotoxic in animals

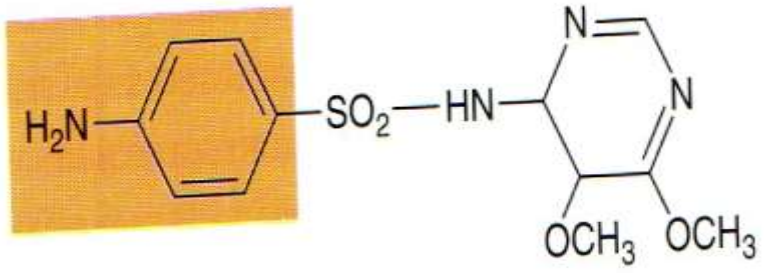
Antifolates

- Menghambat enzim dihidrofolat reduktase plasmodia → sintesis purin terhambat → skizon di hati gagal membelah.
- **Type 1** antifolates sulphonamides & sulphones , compete with PABA.
- **Type 2** ,pyrimethamine & proguanil→ inhibition of dihydrofolate reductase.



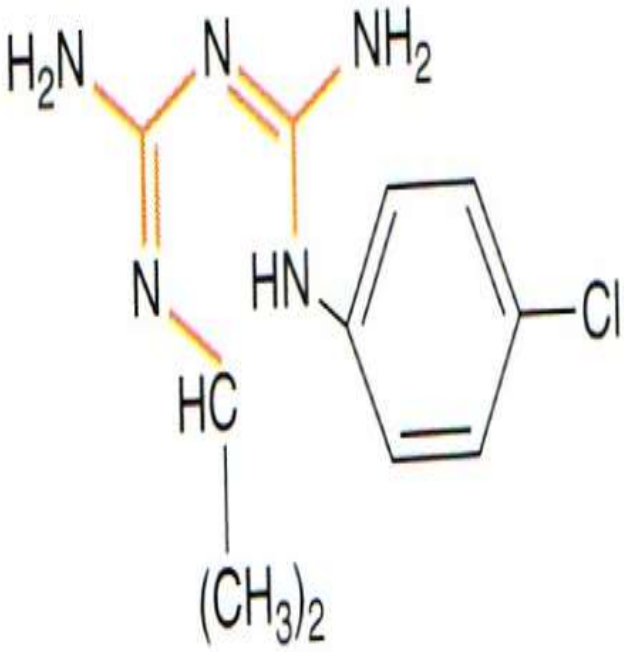
- Have slow action against the erythrocytic forms of the parasite.
- Pyrimethamine is used in combination with either dapsone or sulfadoxine
- High resistance

Pyrimethamine



Sulfadoxine

- Sulfonamides & sulfones are active against the erythrocytic forms of P.falciparum.
- Pyrimethamine –sulfodoxine (Fansidar) is used for chloroquine –resistant malaria.
- Pyrimethamine & proguanil are slowly orally absorbed.
- t½ of pyrimethamine =4d, proguanil=16h.
- Proguanil is metabolized to an active metabolite ,cycloguanil which is excreted in urine.

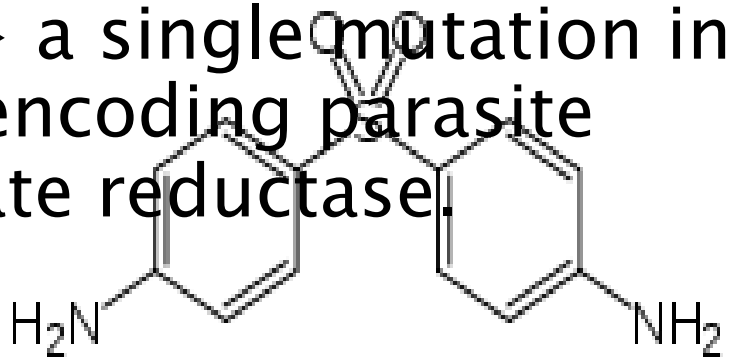


Proguanil

ES :

- large doses of pyrimethamine – dapsone combination causes haemolytic anaemia, agranulocytosis.
- In high doses pyrimethamine ↓mammalian dihydrofolate reductase→ megaloblastic anaemia.

Resistance → a single mutation in the genes encoding parasite dihydrofolate reductase.



Dapsone

Primaquine

- The only drug which is active against liver hypnozoites.
- FD : produces radical cure for parasites which have dormant stage in the liver [P.ovale & P.vivax].
- Has gametocidal action against **all** species. most effective for preventing transmission of the disease.
- Combined with chloroquine, mechanism unknown, resistance rare.

- FK= Given orally, rapidly metabolized to etaquine & tafenoquine which are more active and more oxidizing & slowly metabolized, t½=3-6h
- Indikasi = For radical cure of acute vivax and oval malaria":- chloroquine is given to eradicate erythrocytic forms and then primaquine(30mg daily for 14 days) to eradicate liver hypnozoites

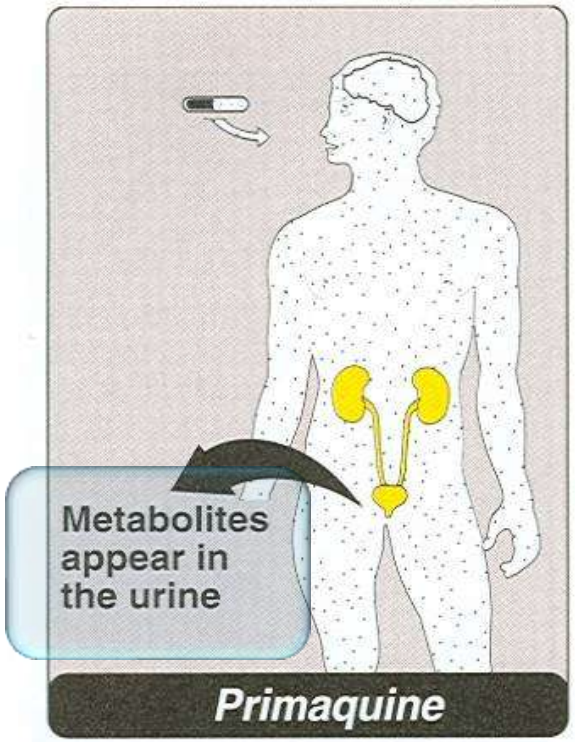


Figure 36.8
Administration and fate of *primaquine*.

ES:-

- GIT disturbances, in large doses → methemoglobinemia with cyanosis
- Causes hemolysis in G-6-P –dehdrogenase deficiency, metabolites have greater hemolytic activity

KI:

- Riwayat methemoglobinemi
- Pregnancy

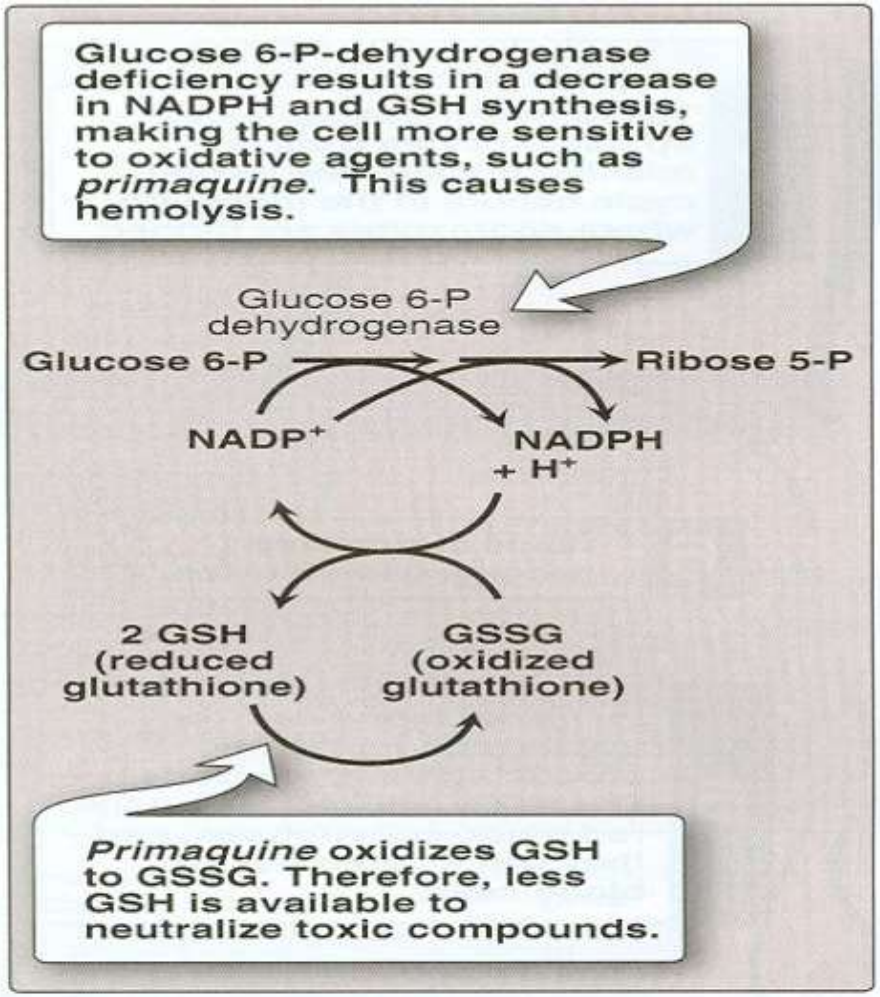


Figure 36.9
Mechanism of *primaquine*-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

Artemisinin

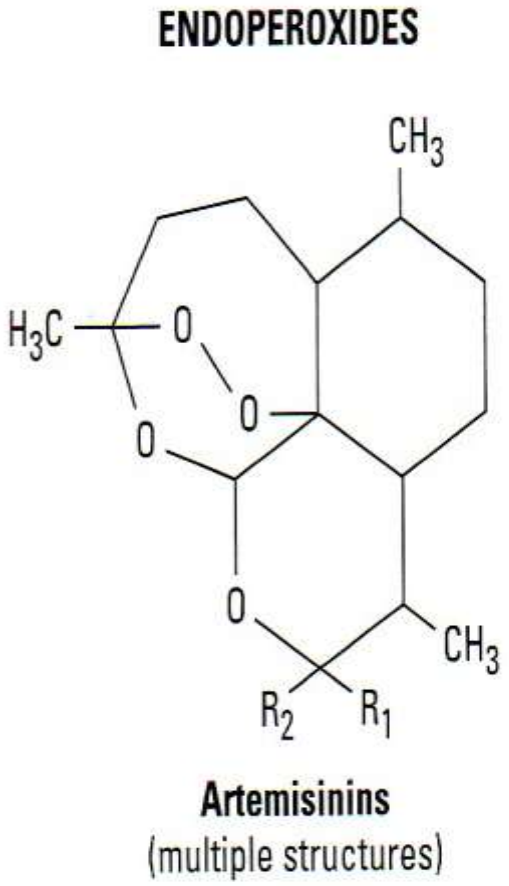
- Derived from the Chinese herb qinghaosu (Artemisia)
- Artemisinin is poorly soluble in water & a fast acting blood schizontocide.
- Effective in treating severe acute attacks, including chloroquine –resistant & cerebral malaria.

Artemesia annua

- Artesunate[a water- soluble derivative], artemether & artether [synthetic analogues] have higher activity & are better absorbed.
- FD= damages the parasite membrane by carbon-centered free radicals.
- FK = Used orally, Rapidly absorbed, widely distributed,

- Converted in the liver to the active metabolite dihydroartemisinin.
- t½ of artemisinin 4h,artesunate=45min, artemether 4-11h.
- No known resistance
- **ADR:-** transient heart block, ↓neutrophil count, brief episodes of fever.
- Neurotoxic in animal,

- No reported resistance



Antibiotics

- Doxycycline : active against ertythrocytic schizonts of all species

is used as a suppressive prophylactic in areas where mefloquine resistance is common.

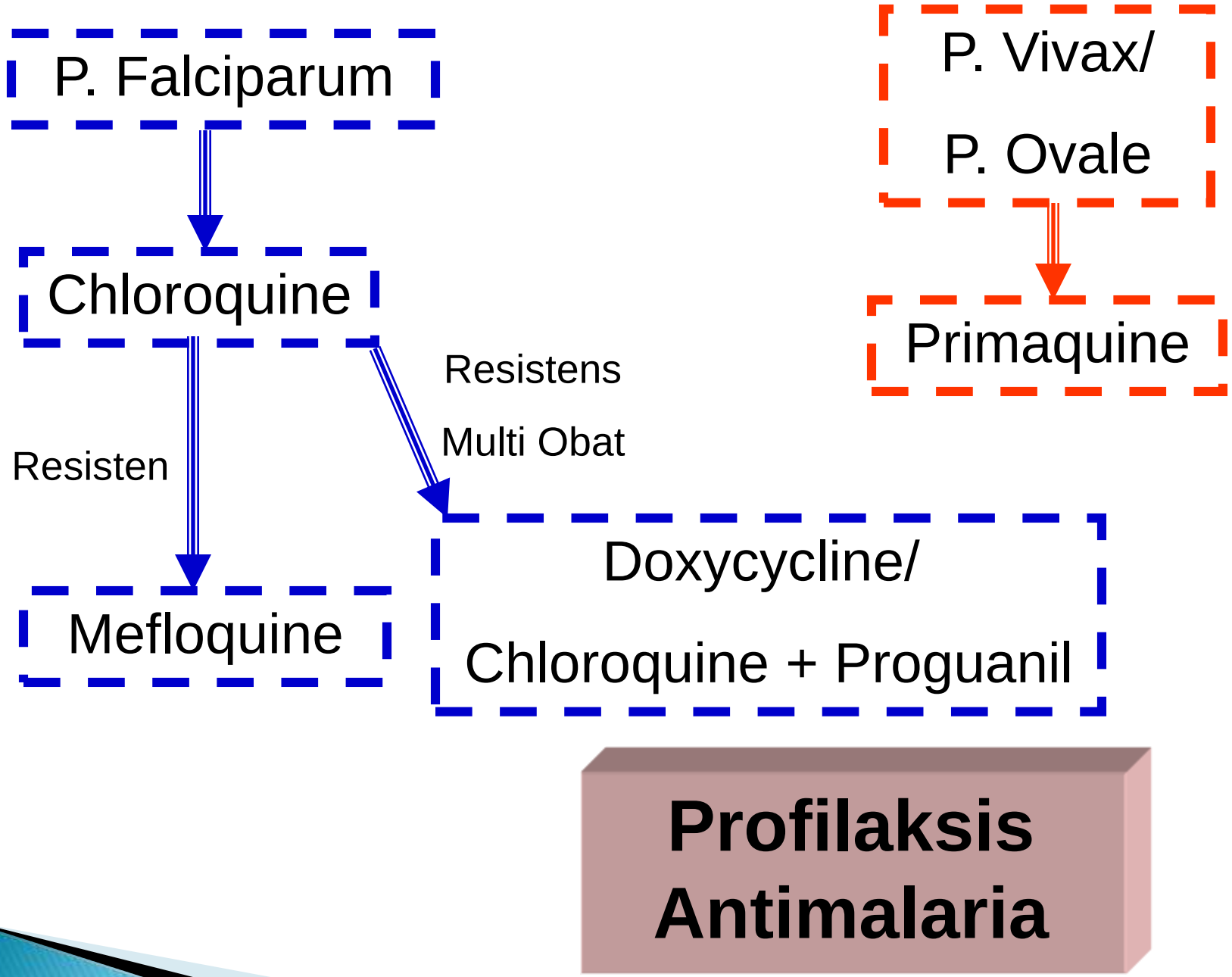
- Clindamycin has proved effective in the treatment of uncomplicated *falicparum* malaria, may be used in combination with quinine.

Drugs used in Malaria*

Drug	Use in acute attack?	Use for eradication of Liver Stage?	Use for prophylaxis?
Chloroquine	Yes	No	Yes, exept in region where P.falciparum is resistant.
Quinine, Mefloquine	Yes, in resistant P.falc	No	Yes, Mefloquine is used in region with Chloroquine-resistant P.falciparum.
Primaquine	No	Yes (P.vivax, P.ovale)	Yes, but only if exposed to P.vivax or P.ovale.
Antifolats	Yes, but only in resistant P.fal	No	Not usually advised.

Tx Prophylaxis

- Jarang utk *full-time residents of malaria-endemic areas* (biaya tinggi dan ES),
- Indikasi : short-term visitors & travelers to malarial regions.
- Jk tinggal sementara di dae endemik = Ox profilaksis 1-2 mgg sblm datang dan dilanjutkan samapai 4 mgg setelah meninggalkan daerah tsb.


P. Falciparum
Chloroquine
Resisten
Resistens
Multi Obat
Mefloquine
Doxycycline/
Chloroquine + Proguanil
P. Vivax/
P. Ovale
Primaquine
Profilaksis
Antimalaria

- Include mefloquine ,doxycycline, and the combination of atovaquone and proguanil (only needs be started 2 days prior and continued for 7 days afterwards).

Travelers to areas endemic for chloroquine-susceptible disease	Chloroquine
Travelers to areas endemic for chloroquine-resistant disease	Mefloquine

Tx Profilaksis Malaria pd Wisatawan

Obat	Penggunaan	Dosis dewasa
Chloroquine	Daerah tanpa P.falc resisten	500 mg setiap minggu
Mefloquine	Daerah dgn P.falc resisten-Chloroquine	250 mg setiap minggu
Doxycycline	Daerah dgn P.falc resisten-multi obat.	100 mg setiap hari
Chloroquine + Proguanil	Regimen alternatif menggantikan mefloquine	500 mg Chloroquine setiap minggu + 200 mg Proguanil setiap hari.
Primaquine	Profilaksis terminal infeksi P.vivax dan P.ovale.	26,3 mg setiap hari selama 14 hari setelah perjalanan.

Resistance

- About 90% of malaria deaths occur in sub Saharan Africa.
- The key factor contributing to↑malarial morbidity & mortality is ↑resistance of *P.falciparum* to chloroquine, sulfodoxin-pyrimethamin [SP] & amodiaquine.
- Artemisinin compounds produce a very rapid therapeutic response ,active against multi-drug resistant *P.falciparum,* well tolerated by the patient,↓gametocyte carriage, no resistance is detected.
- Artemisinins cure falciparum malaria in 7d, if combined with another drug in 3d.

WHO Recommendations

- WHO recommends that all countries experiencing resistance to conventional monotherapies should use combination therapy, preferably containing artemisinins [ACTs –artemisinin-based combination therapies].
- WHO recommends the following therapeutic options:-

1. Artemether/lumefantrine
2. Artesunate+amodiaquine
3. Artesunate+SP
4. Artesunate+ mefloquine [area with low to moderate transmission.
5. Amodiaquine+SP