Malaria

- **is a mosquito-born disease causing about 3 million deaths a year world-wide. Many are children under the age of 5.**

- **The parasite is transmitted by bites from the female anopheles mosquito.**

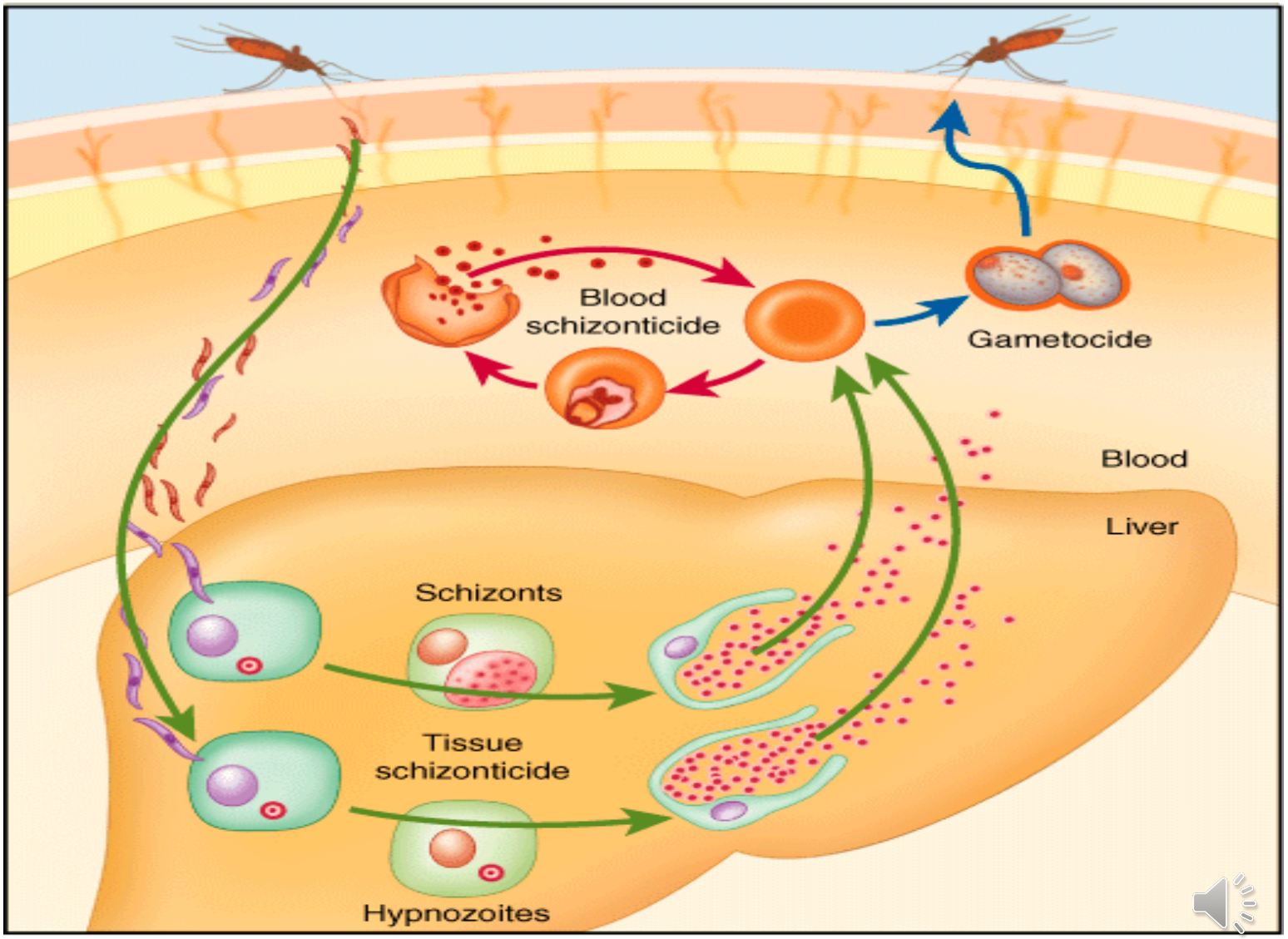
- **Currently, there are over 300 million new infections annually.**

- **The disease is caused by several species of the *Plasmodium* parasite. The two most important are *P. falciparum* and *P. vivax*.**

Malaria

- ***P. falciparum*** **causes "malignant tertian malaria". "Malignant" because it is the most severe form of malaria and can be fatal. "Tertian" because it is said to produce fever every third day.**

- ***P. vivax*** **produces "benign tertian malaria". "Benign" because it is less severe than falciparum and is seldom fatal.**


Blood schizonticide
Gametocide
Blood
Liver
Schizonts
Tissue schizonticide
Hypnozoites

Life cycle

Two Interdependent Life Cycles

- **Sexual cycle: in the mosquito**
- **Asexual cycle: in the human**
  - **Knowledge of the life cycles is essential in understanding antimalarial drug treatment.**
  - **Drugs are only effective during the asexual cycle.**

Asexual cycle: two phases

- **Exoerythrocytic phase: occurs "outside" the erythrocyte**
- **Erythrocytic phase: occurs "inside" the erythrocyte**

Erythrocytes = RBCs

Anti-malarial agents

- Drugs that eliminate developing or dormant liver forms are called **tissue schizonticides;**

- those that act on erythrocytic parasites are **blood schizonticides;**

- and those that kill sexual stages and prevent transmission to mosquitoes are **gametocides.**

- No single available agent can reliably effect a **radical cure,** ie, eliminate both hepatic and erythrocytic stages.

Chloroquine

- **It is a potent blood schizontocidal drug effective against all four types of clinically important plasmodium species.**

- **Its mechanism of action is complex and not fully understood.**

➢ **It is accumulated in parasite lysosomes. Chloroquine inhibits digestion of haemoglobin by the parasite and thus helps reduce its supply of amino acids.**

➢ **It also inhibits haem polymerase - the enzyme that polymerises toxic free haem to the innocuous haemozoin.**

Chloroquine

- **The drug of choice in the treatment of erythrocytic falciparum malaria, except in resistant strains.**
- **Chloroquine is less effective against vivax malaria.**
- **It is also effective in the treatment of extraintestinal amebiasis.**
- It is used for the treatment of malaria in pregnancy.

Chloroquine

- **At high doses toxic effects occur,**

  gastrointestinal upset, pruritus, headaches, and

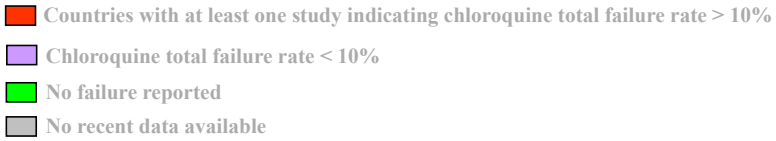
  visual disturbances (an ophthalmological examination should be routinely performed).

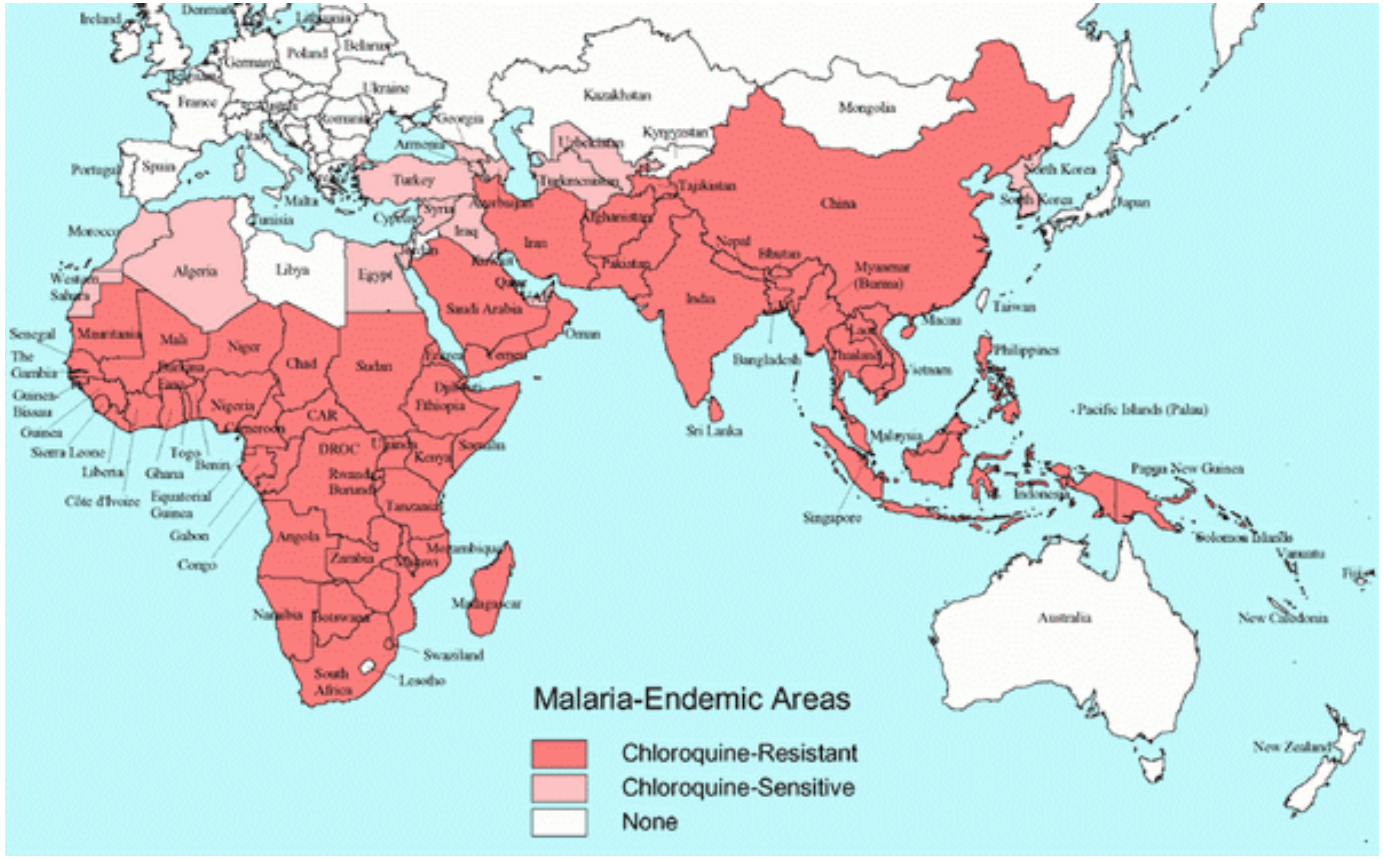
- **Parenteral administration – hypotension and cardiac arrhythmia, convulsions.**

- **Contraindication: psoriasis or porphyria**

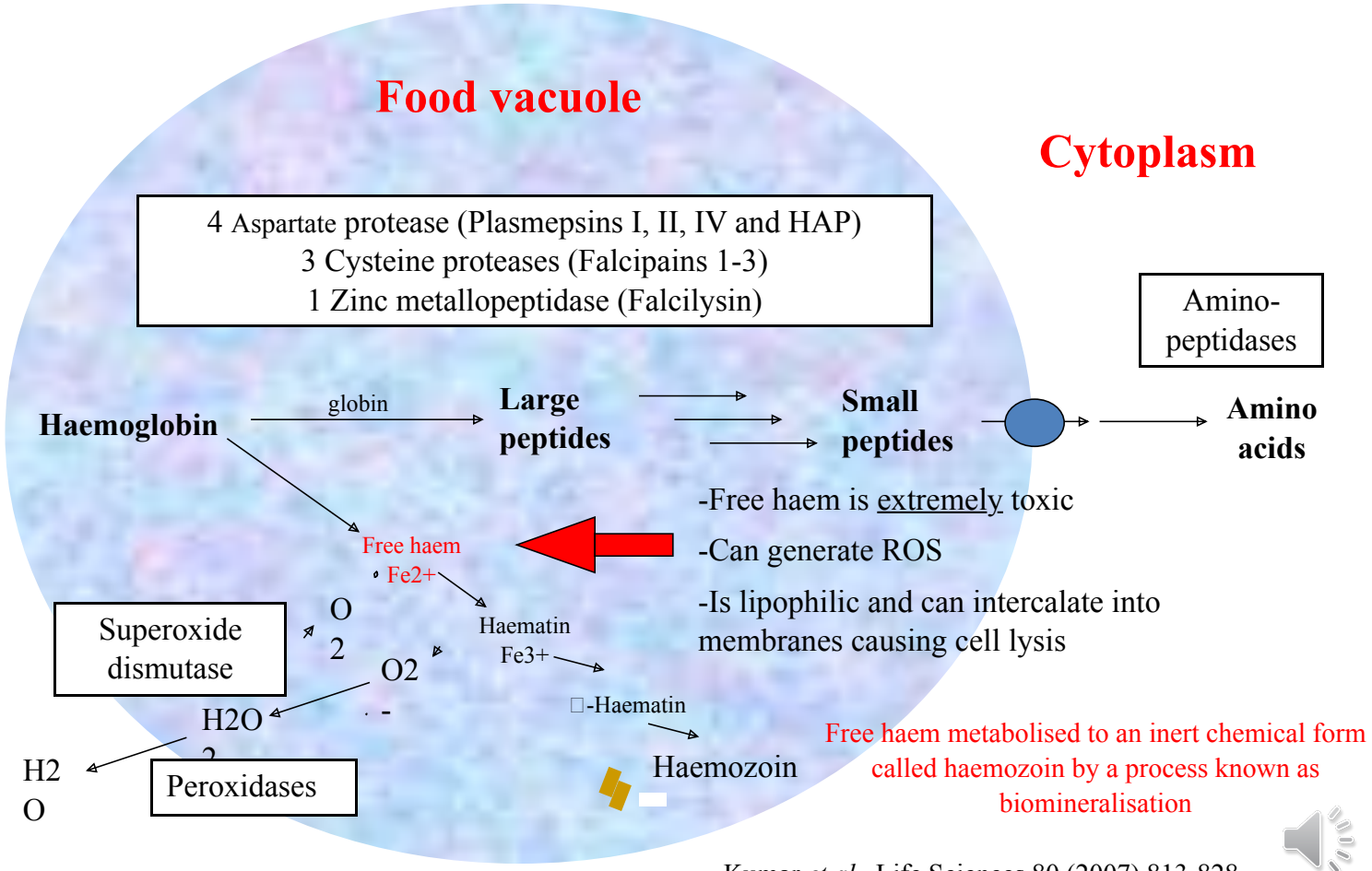
P- falciparum resistance to chloroquine

Source: WHO global database on drug resistance 1996-2004



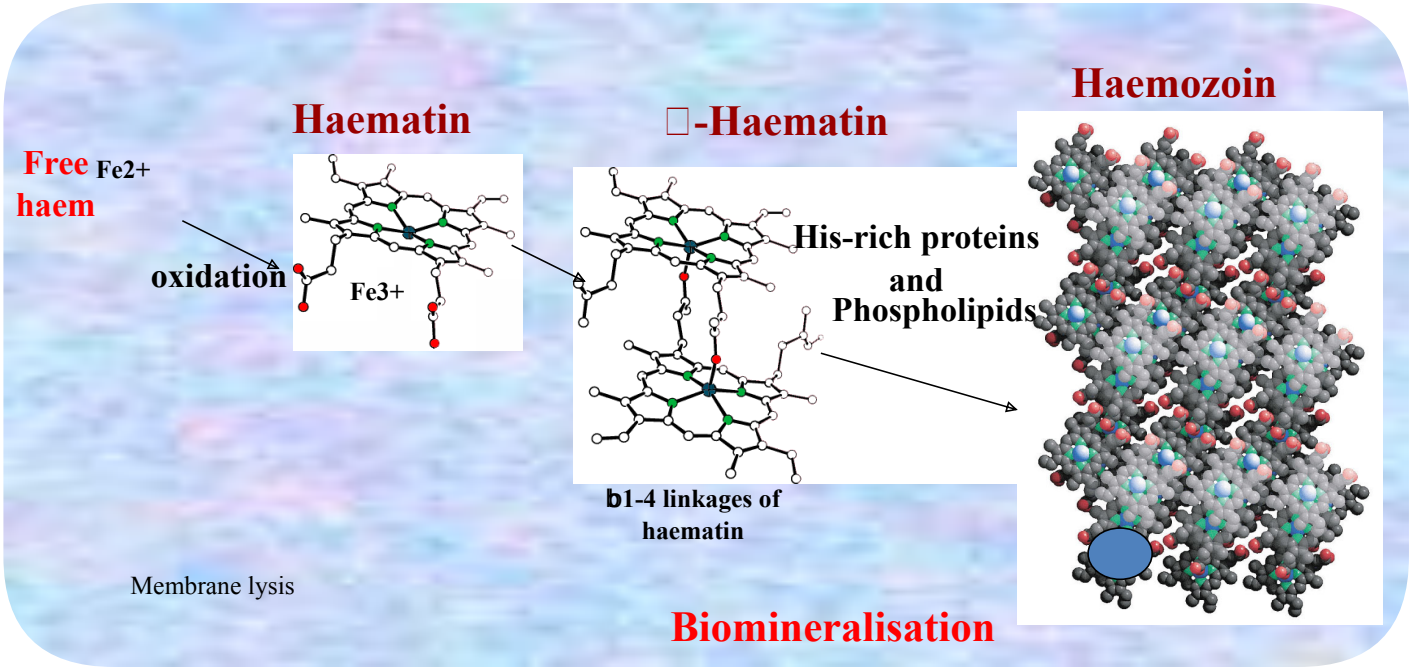

Malaria-Endemic Areas
Chloroquine-Resistant
Chloroquine-Sensitive
None
Ireland
Denmark
Lithuania
Poland
Belarus
Germany
France
Ukraine
Kazakhstan
Mongolia
Georgia
Armenia
Kyrgyzstan
Portugal
Spain
Turkey
Tajikistan
China
South Korea
Japan
Malta
Tunisia
Cyprus
Syria
Azerbaijan
Afghanistan
Morocco
Iraq
Iran
Nepal
Bhutan
Pakistan
Algeria
Libya
Egypt
Myanmar (Burma)
India
Western Sahara
Saudi Arabia
Taiwan
Macau
Laos
Philippines
Senegal
Mauritania
Mali
Niger
Chad
Sudan
Oman
Yemen
Bangladesh
Thailand
Vietnam
The Gambia
Guinea-Bissau
Guinea
Nigeria
CAR
Ethiopia
Pacific Islands (Palau)
Sri Lanka
Malaysia
Sierra Leone
Liberia
Togo
Ghana
Benin
DROC
Uganda
Kenya
Somalia
Rwanda
Burundi
Papua New Guinea
Indonesia
Côte d'Ivoire
Equatorial Guinea
Tanzania
Singapore
Gabon
Angola
Zambia
Malawi
Mozambique
Solomon Islands
Vanuatu
Fiji
Congo
Madagascar
Australia
New Caledonia
Namibia
Botswana
Swaziland
South Africa
Lesotho
New Zealand

Haemoglobin degradation pathway



Kumar *et al.*, Life Sciences 80 (2007) 813-828

Detoxification of Haematin into Inert Haemozoin



Dimers of haematin – b1-4 linkages are formed

Dimers then begin to crystallise in a process known as biomineralisation to generate haemozoin

Process not fully understood but is thought to be promoted by several factors including – the low pH of the food vacuole, association of haematin with histidine-rich proteins and phospholipids

Ultimately haemozoin crystals are formed which are chemically inert and a safe storage mechanism for the parasite

Quinine and Quinidine

- **is a rapid-acting, highly effective blood schizonticide against the four species of human malaria parasites.**

- **The drug is gametocidal against *P vivax* and *P ovale* but not *P falciparum*. It is not active against liver stage parasites.**

- **Quinine and quinidine remain first-line therapies for falciparum malaria—especially severe disease—although toxicity may complicate therapy.**

- **Quinine is more toxic and less effective than chloroquine against malarial parasites susceptible to both drugs.**

Quinine and Quinidine

- **Therapeutic dosages of quinine and quinidine commonly cause tinnitus, headache, nausea, dizziness, flushing, and visual disturbances, a collection of symptoms termed cinchonism.**

- **Therapeutic doses may cause hypoglycemia through stimulation of insulin release (pregnant patients).**

- **Quinine can raise plasma levels of warfarin and digoxin**

Proguanil (Chloroguanide)

- **slow-acting erythrocytic schizontocide,also inhibits the preerythrocytic stage of P.F alciparum.**

- **Mechanism of action :**
- **It is cyclized in the body to cycloguanil which inhibits plasmodial DHFRase in preference to the mammalian enzyme.**
- **Current use of proguanil is restricted to prophylaxis of malaria in combination with chloroquine in areas of low level chloroquine resistance among P. falciparum. Safe during during pregnancy.**

Mefloquine

- **Mefloquine is effective therapy for many chloroquine-resistant strains of *P falciparum* and against other species.**

- **Although toxicity is a concern, mefloquine is one of the recommended chemoprophylactic drugs for use in most malaria-endemic regions with chloroquine-resistant strains.**

- **Its mechanism of action appears to be associated with inhibition of the haem polymerase.**

Mefloquine

- **Weekly dosing with mefloquine for chemoprophylaxis may cause nausea, vomiting, dizziness, sleep and behavioral disturbances, epigastric pain, diarrhea, abdominal pain, headache, rash, and dizziness.**

- **Neuropsychiatric toxicities ??????????????**

- **is contraindicated in a patient with a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects**

Primaquine

- **destroys primary and latent hepatic stages of *P. vivax* and *P. ovale***

- **thus has great clinical value for preventing relapses of *P. vivax* or *P. ovale* malaria (**Standard therapy**).**

- **exert a marked gametocidal effect against all four species of plasmodia that infect humans, especially *P. falciparum*.**

- **Because of its lack of activity against the erythrocytic schizonts, primaquine is often used in conjunction with a blood schizonticide.**

Primaquine

- **induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase.**

- **Patients should be tested for G6PD deficiency before primaquine is prescribed.**

- **causes nausea, epigastric pain, abdominal cramps, and headache, and these symptoms are more common with higher dosages and when the drug is taken on an empty stomach.**

- **Primaquine should be avoided in patients with a history of granulocytopenia or methemoglobinemia, in those receiving potentially myelosuppressive drugs (eg, quinidine),**

- **Avoided in pregnancy & G6PD**

Artemisinin derivatives

Artemether / Arteether / Artesunate

- It is a potent and rapidly acting blood schizontocide and have peroxide configuration – responsible for its action.

- Combination therapy.
- Duration of action: **short**
- **Recrudescence** rate is high
- When used alone in short courses
- Used **only** in **combination**

Artemisinin Combination Therapy (ACT)
current frontline therapy

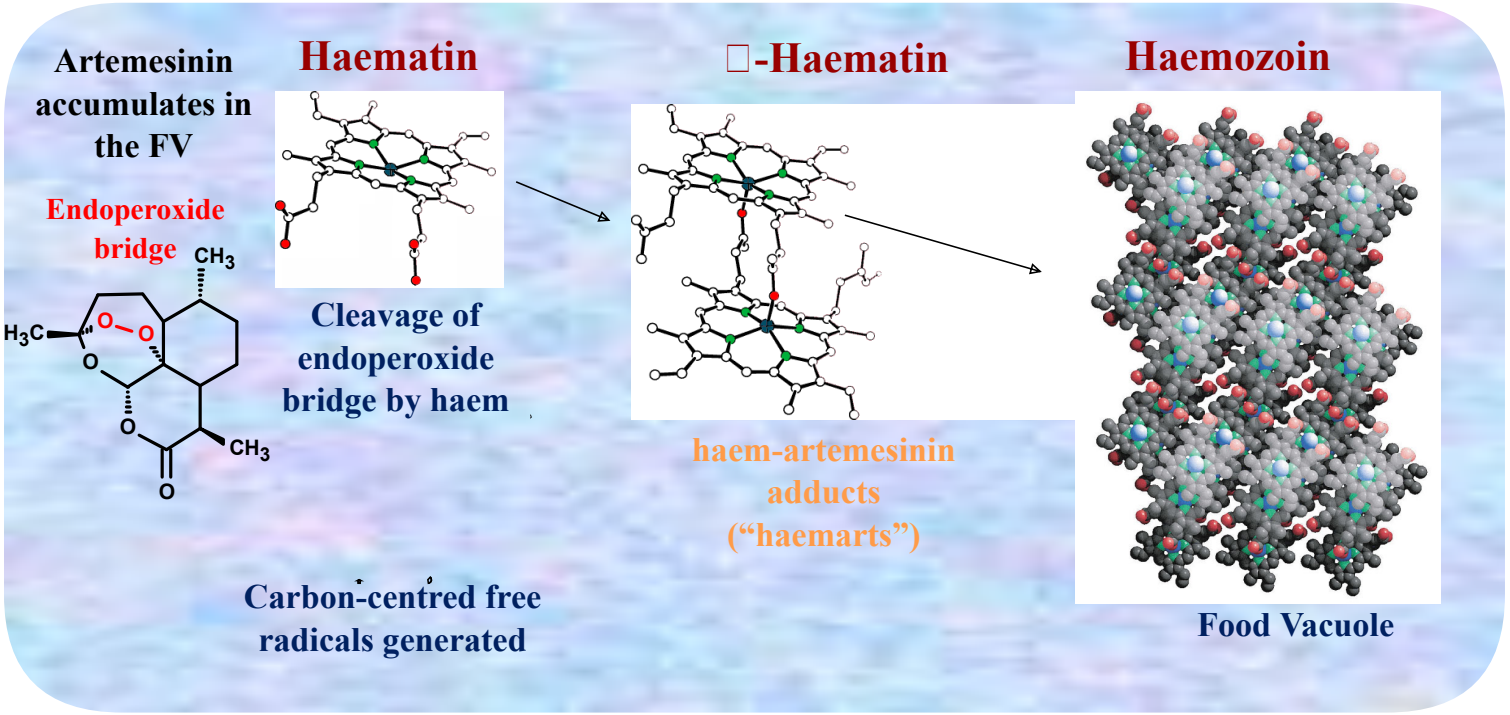
- **Artemisinins reduce parasite burden rapidly**

- **Used in combination with other drugs to protect emergence of resistance to partner drug (ACT)**

Artemisia annua – sweet wormwood

Youyou Tu
Nobel Prize – Medicine 2015

Haem and Mode of Action of Artemisinins



Possible targets of artemisinin free radicals:
TCTP (translationally controlled tumour protein homolog)
SERCA (sarco/endoplasmic reticulum Ca2+-ATPase)
Cysteine proteases

Pyrimethamine-sulphonamide and antibiotics

- **Pyrimethamine inhibits plasmodial dihydrofolate reductase at much lower concentrations than those that inhibit the mammalian enzyme. …… sulfa….**

- **Tetracycline and doxycycline are active against erythrocytic schizonts of all human malaria parasites. They are not active against liver stages.**

- **Doxycycline is used in the treatment of falciparum malaria in conjunction with quinine, allowing a shorter and better-tolerated course of that drug.**

Drug	Use2	Adult Dosage3
Chloroquine	Areas without resistant P falciparum	500 mg weekly
Atovaquone-proguanil (Malarone)	Areas with chloroquine-resistant P falciparum	1 tablet (250 mg atovaquone/100 mg proguanil) daily
Mefloquine	Areas with chloroquine-resistant P falciparum	250 mg weekly
Doxycycline	Areas with multidrug-resistant P falciparum	100 mg daily
Primaquine4	Terminal prophylaxis of P vivax and P ovale infections; alternative for primary prevention	52.6 mg (30 mg base) daily for 14 days after travel; for primary prevention 52.6 mg (30 mg base) daily