HLS

MODIFIED NO. 9

PHARMACOLOGY

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It's highly recommended to study microbiology lecture before pharmacology lecture.

Color code

- Slides
- Doctor
- Additional info
- Important

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*.**

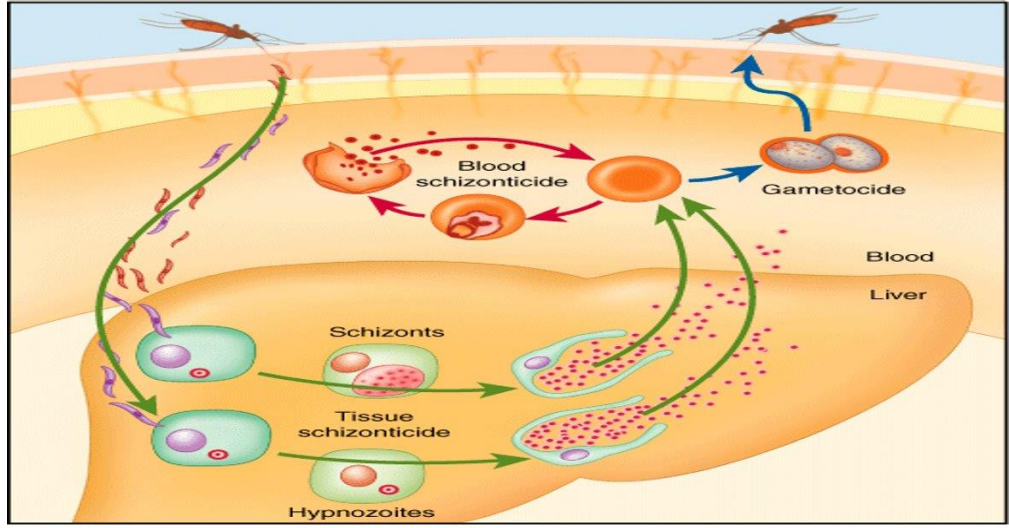
Malaria

- ***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.**

- Five type of Plasmodium species known to cause human malaria

Life cycle



Two Interdependent Life Cycles

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

Asexual cycle: two phases

- **<u>Exoerythrocytic phase:</u>** **occurs "outside" the erythrocyte**
- **<u>Erythrocytic phase:</u>** **occurs "inside" the erythrocyte**

Erythrocytes = RBCs

The life cycle of Plasmodium (recap from microbiology):

1. **Asexual Cycle (Human Host)**
   - Sporozoites Injection: The cycle begins when an infected female Anopheles mosquito bites a human, injecting sporozoites into the bloodstream.
   - Liver Stage (Exoerythrocytic Phase): Sporozoites travel to the liver, where they invade liver cells and develop into schizonts. These schizonts then rupture, releasing merozoites.
   - Blood Stage (Erythrocytic Phase): Merozoites enter red blood cells, where they multiply asexually, forming new merozoites. The infected red blood cells eventually burst, releasing merozoites that infect new red blood cells, leading to the characteristic symptoms of malaria (fever, chills).
   - Gametocyte Formation: Some merozoites develop into gametocytes (male and female forms) instead of continuing to multiply. Gametocytes are essential for the sexual cycle but remain inactive within the human host.
2. **Sexual Cycle (Mosquito Host)**
   - Gametocyte Ingestion: When a mosquito bites an infected person, it ingests gametocytes along with the blood meal.
   - Fertilization and Oocyst Formation
   - Sporozoite Development: Within the oocyst, sporozoites develop and are eventually released into the mosquito's body cavity, migrating to the salivary glands.
   - Transmission to Human Host: When the mosquito bites another human, the sporozoites are transmitted, starting the cycle again.

- This dual-phase life cycle, involving both asexual replication in humans and sexual reproduction in mosquitoes, is key to Plasmodium's spread and survival.
- Hypnozoites: dormant form of → P.ovale and vivax → can be reactivated into schizonts after some time of latency

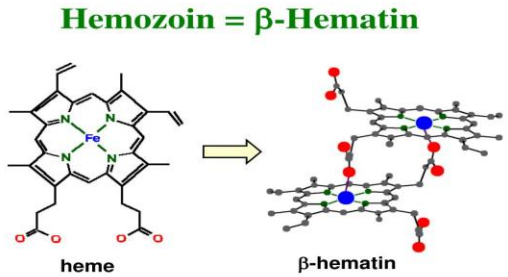
Anti-malarial agents

There is no drug targets all stages of malaria cycle

- 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.**
- **The two most likely mechanism of action:**

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

➢ **2. It also inhibits haem polymerase (heme detoxification enzyme) - the enzyme that polymerises toxic free haem(toxic to the parasite) to the innocuous(not harmful) haemozoin.**
(This mechanism is more favored by the doctor.**)**

- To survive, Plasmodium uses heme polymerase to convert toxic free heme into an inert form by crystallizing it into hemozoin.

Chloroquine

- **The drug of choice in the treatment of erythrocytic falciparum malaria, except in resistant strains.**
- **Its fully prophylactic toward malaria**
- **The main problem is the high resistant developed toward chloroquine**
- **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.(not teratogenic)

Chloroquine

- At high doses toxic effects occur,

  1.gastrointestinal upset

  2.pruritus

  3.headaches

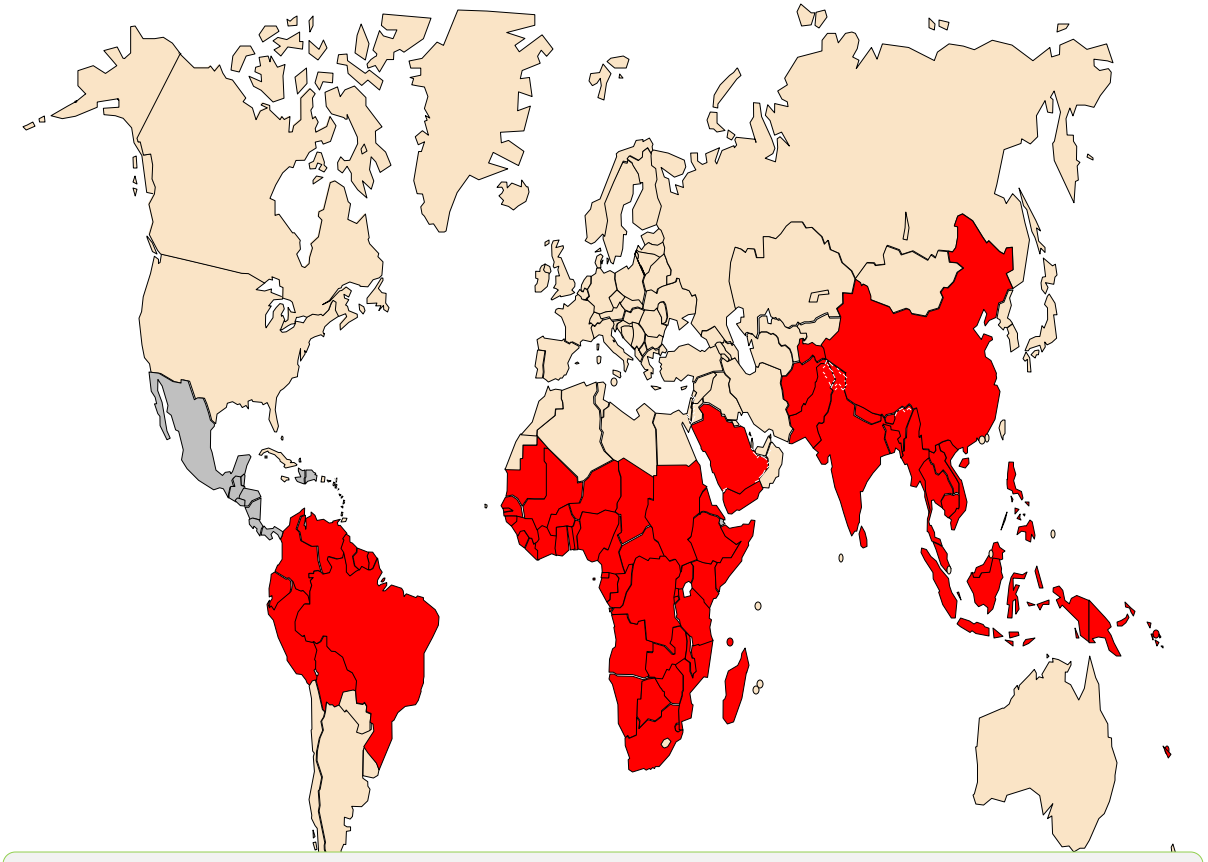
  4.visual disturbances (an ophthalmological examination should be routinely performed). (shared by Quinine and Quinidine)

- In parenteral administration under severe conditions, hypotension, cardiac arrhythmia (due to these drugs affecting heart conductivity), and convulsions may occur.
- (Parenteral: IV, intramuscular-IM, subcutaneous-SC, and intradermal-ID)
- Contraindication: psoriasis or porphyria

  →Increase the auto-immunity in the psoriasis or porphyria

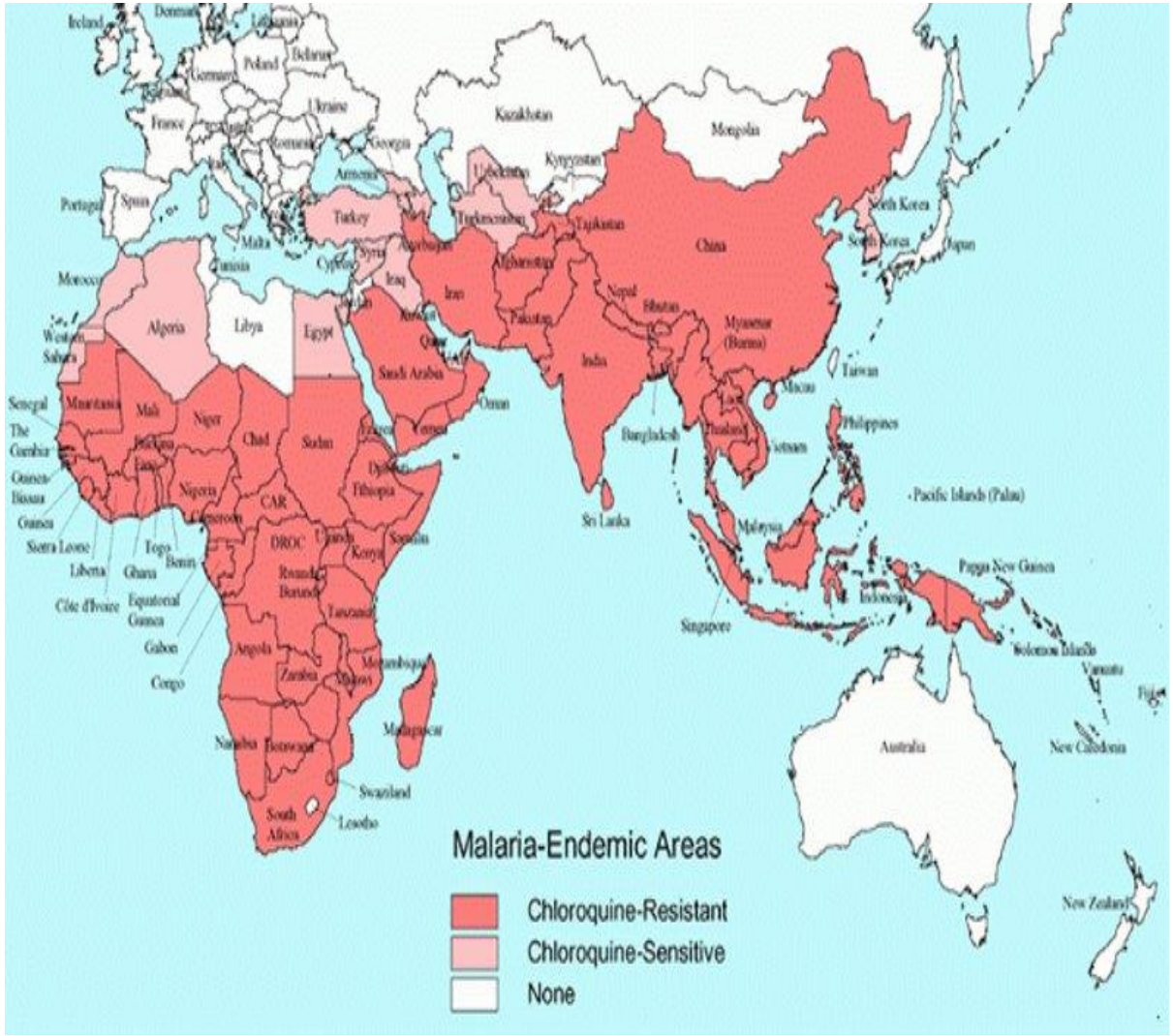
falciparum resistance to chloroquine

Source: WHO global database on drug resistance 1996-2004

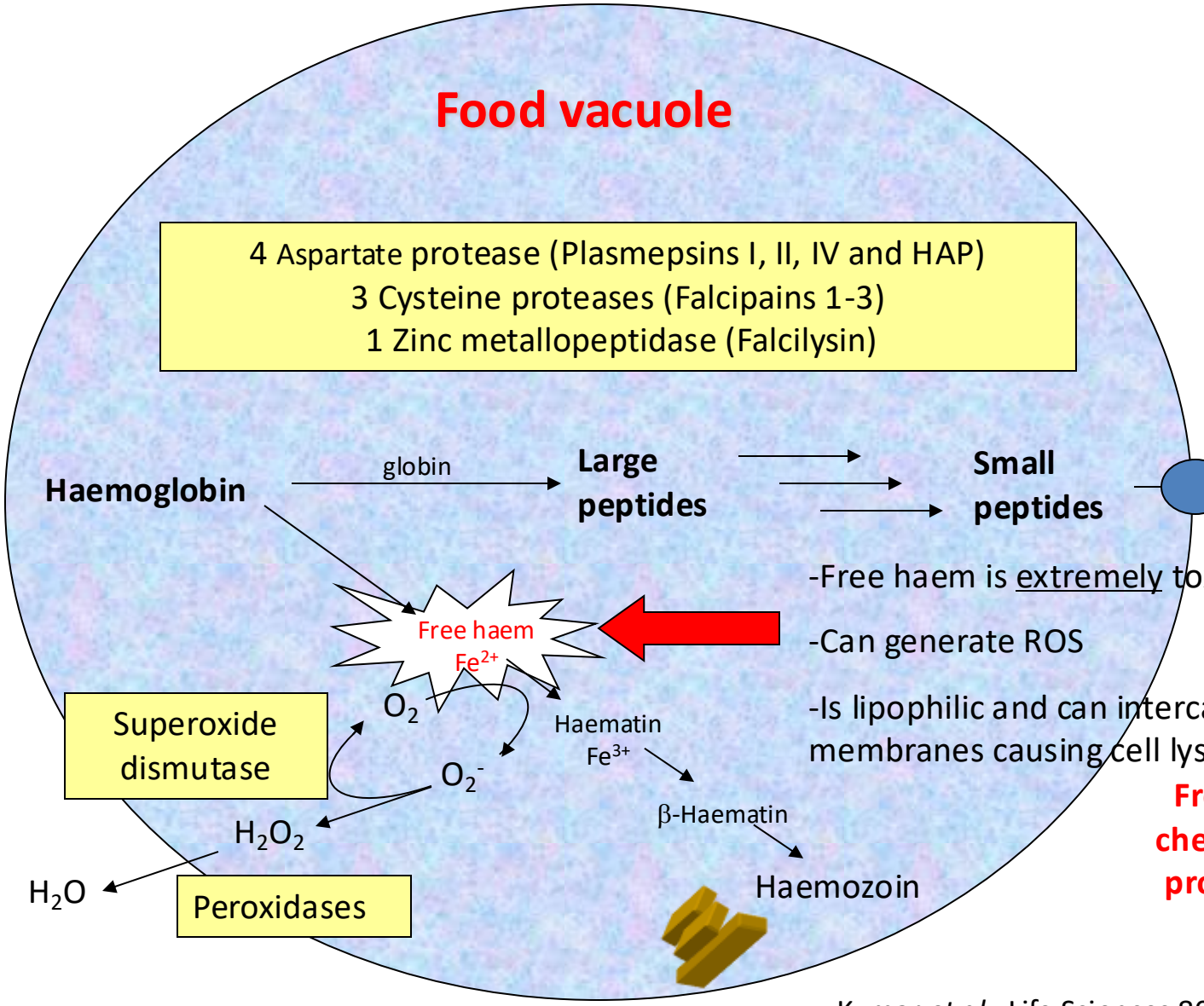


high resistant developed toward chloroquine worldwide

- Countries with at least one study indicating chloroquine total failure rate > 10%
- Chloroquine total failure rate < 10%
- No failure reported
- No recent data available



Haemoglobin degradation pathway



Cytoplasm

Amino-peptidases

Amino acids

-Free haem is extremely toxic

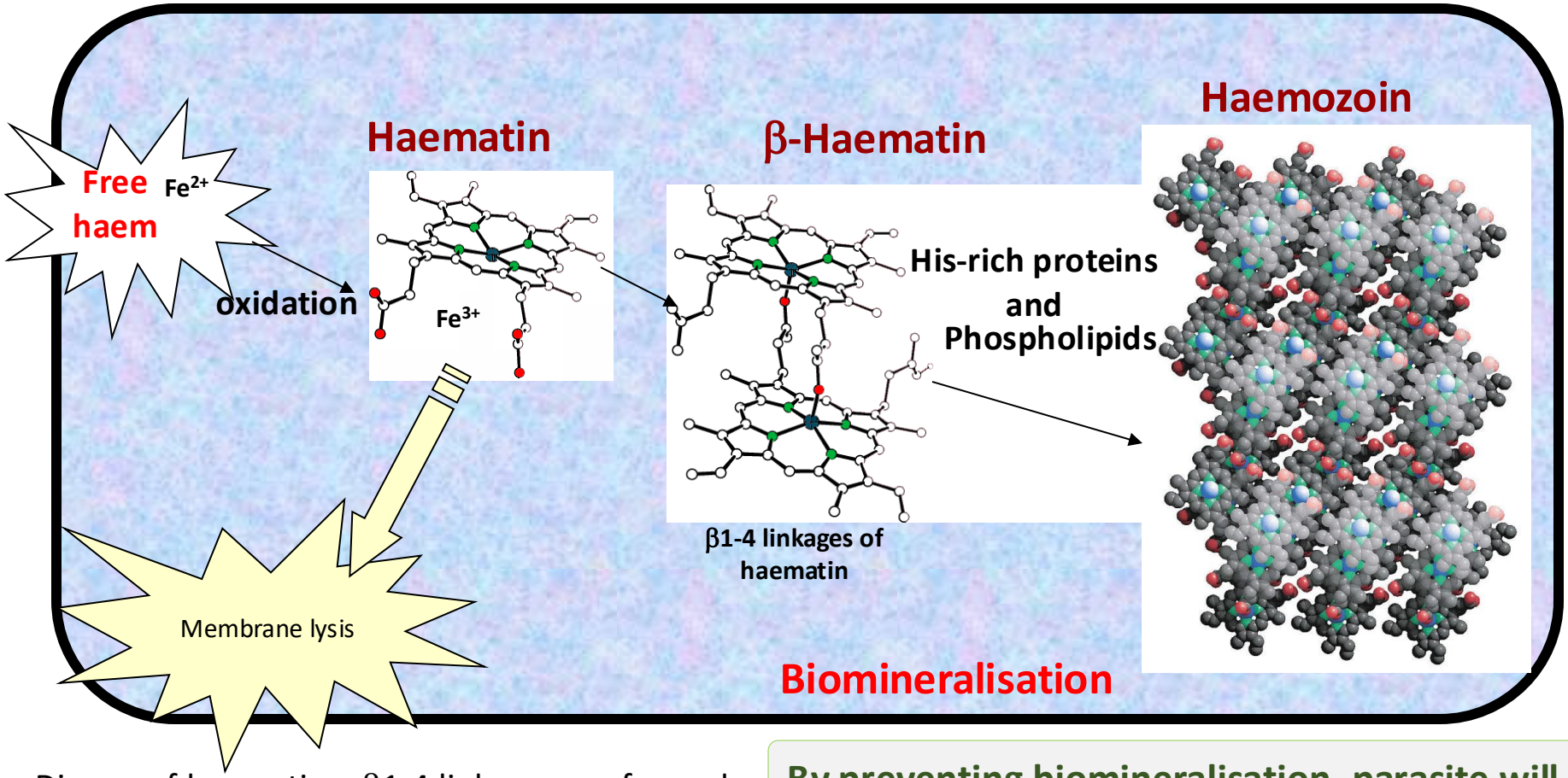
-Can generate ROS

-Is lipophilic and can intercalate into membranes causing cell lysis

Free haem metabolised to an inert chemical form called haemozoin by a process known as biomineralisation

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

Detoxification of Haematin into Inert Haemozoin



Dimers of haematin – β1-4 linkages are formed

By preventing biomineralisation, parasite will die.

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.**
- **Because of the high resistance to Chloroquine we use quinine(older drug) and quinidine, all are of the same family**
- **The drug is gametocidal against *P vivax* and *P ovale* but not *P falciparum.* It is not active against liver stage parasites.**
- **Which is better than Chloroquine by limiting the spread of P.vivax and P.ovale**
- **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.**

In severe, complicated and resistant cases → Quinine and quinidine
In susceptible cases (higher risk of contracting malaria) → Chloroquine

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 especially in (pregnant patients).** (unlike chloroquine which is safe for pregnant women)

- **Quinine can raise plasma levels of warfarin and digoxin (**inhibit cytochrome p450**)**

Proguanil (Chloroguanide)

- slow-acting erythrocytic schizontocide, also inhibits the preerythrocytic stage of P.falciparum.
- its activity is weak, it isn't administrated alone.
- Mechanism of action :
- It is cyclized in the body to cycloguanil which inhibits plasmodial DHFRase (dihydrofolate reductase) 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 pregnancy.

  Used as prophylaxis instead of drug, and is combined with chloroquine(both are safe in 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.**

  Although it's given once weekly because of its long duration of action its toxicity is a concern

- **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.**

  It also causes (not always):

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

- **is contraindicated (anything that is related to brain or cardiac conductivity) in a patient with a history of epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects**

Noted that we always discuss disturbances like behavioral changes and dizziness, but the good news is that mefloquine doesn't cause visual disturbances. However, it can affect cardiac conduction, especially in patients with pre-existing conduction defects.

Cardiac conduction refers to the process by which electrical impulses are generated and transmitted throughout the heart, leading to its rhythmic contractions. This conduction system is essential for maintaining a coordinated heartbeat and ensuring efficient blood flow throughout the body.

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)**.**

When treating patients with P. vivax or P. ovale infections, we administer primaquine (along with chloroquine, which acts as a blood schizontocide) either during or after the primary treatment.

To ensure the disease does not recur in these patients, we administer tissue schizonticidal drugs, such as primaquine, which act on the liver.

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

But it doesn't work on RBCs or erythrocytic stage of falciparum

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

Primaquine

This drug interferes with enzymes, including cytochrome P450 (CYP) enzymes, in both parasites and humans.
Explanation in the next slide 😁

- **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.→ increases side effects**
- **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**

How Primaquine Interacts with CYP Enzymes:

- In Parasites: Primaquine targets the parasite's CYP enzymes, specifically interfering with its ability to function normally. This disrupts essential processes in the parasite, which is particularly useful in treating malaria as it targets the parasite’s mitochondria and energy production.

- In Humans: Primaquine can also affect human CYP enzymes. In particular, the human CYP450 enzyme family helps process primaquine and other drugs, breaking them down into active or inactive forms. Primaquine’s interaction with these enzymes can sometimes lead to side effects or cause drug interactions, as it may alter how other drugs are metabolized in the body.

Why Primaquine is Risky in G6PD Deficiency:

- Primaquine generates oxidative stress in red blood cells as part of its action against malaria parasites. In people with G6PD deficiency, their red blood cells can't handle this added oxidative stress effectively, leading to **hemolysis** (the destruction of red blood cells). This can cause symptoms like jaundice, anemia, dark urine, and even serious complications if not carefully managed.

Artemisinin derivatives

Artemether / Arteether / Artesunate (the most used).

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

The mechanism of action of artemisinin depends on its ability to induce peroxidation, leading to free radical formation, and to form adducts that contribute to cellular damage. Explanation in the next slide

- Combination therapy. → never used alone because of recurrence during treatment
- Duration of action: **short** → one of the reasons why recurrence may occur
- **Recrudescence** rate is high
- When used alone in short courses
- Used **only** in **combination**

“The mechanism of action of artemisinin depends on its ability to induce peroxidation, leading to free radical formation, and to form adducts that contribute to cellular damage”

- Inducing Peroxidation: Artemisinin generates oxidative stress in malaria parasites, primarily through its reaction with iron, which leads to the formation of free radicals. This oxidative environment is critical for its antimalarial activity.

- Free Radical Formation: The free radicals produced from artemisinin’s action are highly reactive and cause significant damage to the parasite’s cellular structures, including membranes, proteins, and nucleic acids.

- Forming Adducts: The term "adducts" refers to the compounds formed when reactive species bind to cellular components (like proteins or DNA). Artemisinin can form adducts with biomolecules, contributing further to the parasite's damage and disrupting its vital functions.

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

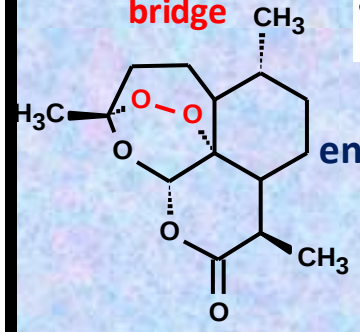
Youyou Tu
Nobel Prize – Medicine 2015

Haem and Mode of Action of Artemisinins

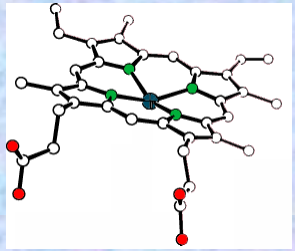
Doctor just read the slide quickly, but I will write in the next slide what he said 😬

Artemesinin accumulates in the FV

Endoperoxide bridge



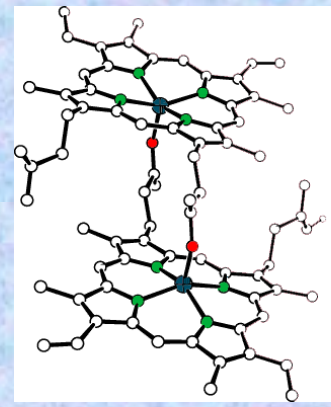
Haematin



Cleavage of endoperoxide bridge by haem

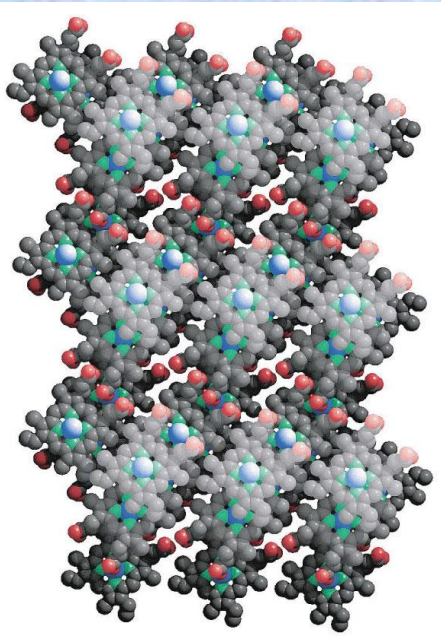
Carbon-centred free radicals generated

β-Haematin



haem-artemesinin adducts ("haemarts")

Haemozoin



Food Vacuole

Possible targets of artemisinin free radicals:
TCTP (translationally controlled tumour protein homolog)
SERCA (sarco/endoplasmic reticulum Ca^{2+} ATPase)
Cysteine proteases

- Artemisinin accumulates in the FV (Food Vacuole).
- It could form endoperoxide bridge.
- Artemisinin forms heme-artemisinin adducts, which disrupt the polymerization of heme into hemozoin, ultimately leading to cell death.

Pyrimethamine-sulphonamide and antibiotics

These Drugs are not required.

- **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	Use[2]	Adult Dosage[3]
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
Primaquine[4]	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

This table is not required too!!

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!