بسم الله الرحمن الرحيم

Antiprotozoal and Antihelmentic drugs

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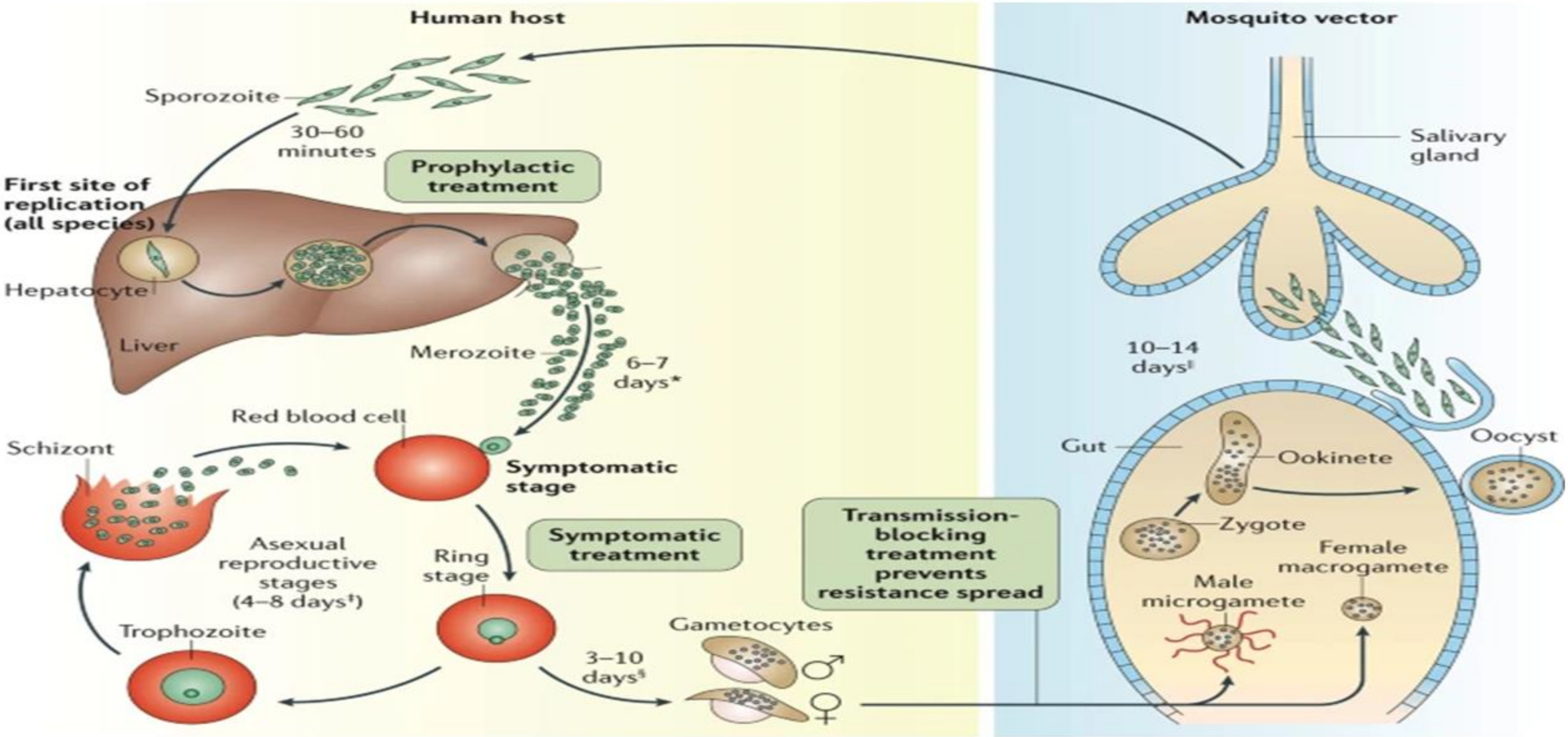
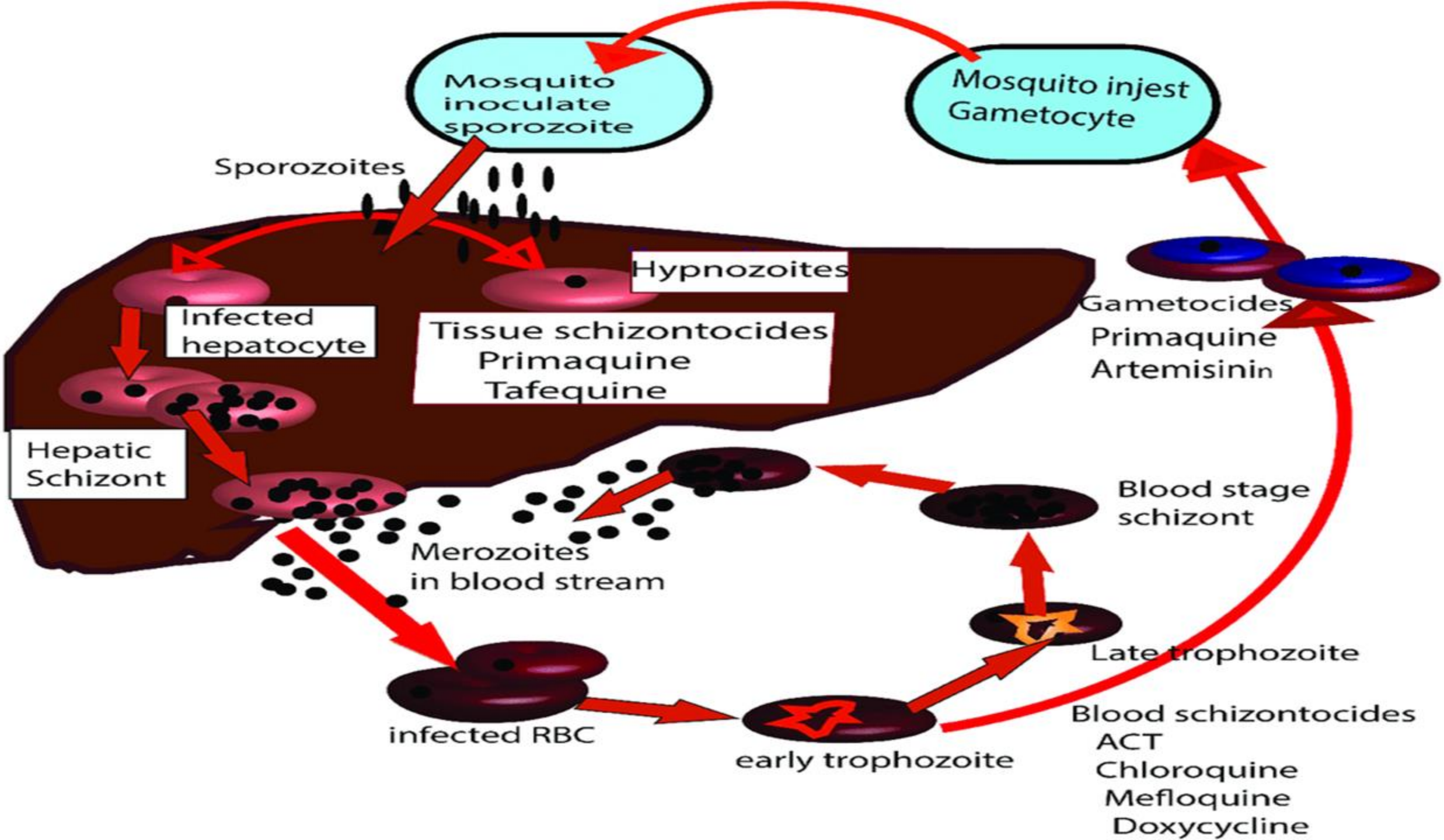
Malaria and its treatment




Mosquito inoculate sporozoite
Mosquito injest Gametocyte
Sporozoites
Hypnozoites
Infected hepatocyte
Tissue schizontocides
Primaquine
Tafequine
Gametocides
Primaquine
Artemisinin
Hepatic Schizont
Blood stage schizont
Merozoites in blood stream
Late trophozoite
infected RBC
early trophozoite
Blood schizontocides
ACT
Chloroquine
Mefloquine
Doxycycline

➢In P falciparum and P malaria infection, **only one cycle of liver** cell invasion and multiplication occurs, and liver infection ceases spontaneously in less than 4 weeks. Thus, treatment that eliminates erythrocytic parasites will cure these infections.

➢In **P vivax and P ovale** infections, **a dormant hepatic stage**, the hypnozoite, is not eradicated by most drugs, and relapses can occur after therapy directed against erythrocytic parasites. **Eradication of both erythrocytic and hepatic parasites** is required to cure these infections.

➢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.

Actions of antimalarial drugs

1- Tissue schizonticides

Primaquine, pyrimethamine, sulfonamides.

2- Blood schizonticides

- Type 1, quick onset: Chloroquine, mefloquine, quinine.
- Type 2, slow onset : Pyrimethamine, sulfonamides, doxycycline.

3- Gametocides

- Primaquine for Plasmodium falciparum.
- Quinine for P. vivax, P. malariae, P. ovale.

Prevention of malaria

1- Measures to prevent mosquito bites (eg, with insect repellents, insecticides, and bed nets), because parasites are increasingly resistant to multiple drugs and no chemoprophylactic regimen is fully protective.

2- Current recommendations: use chloroquine for chemoprophylaxis (in the few areas infested by only chloroquine-sensitive malaria parasites) and mefloquine, or doxycycline or other drugs for most other malarious areas.

3- Alternative chemoprophylactic drugs are primaquine and others.

- No single available agent can reliably effect a radical cure (eliminate both hepatic and erythrocytic stages).
- Most prophylactic drugs cannot prevent erythrocytic infection.
- However, **all effective chemoprophylactic agents kill erythrocytic parasites** before they increase sufficiently in number to cause clinical disease.

1- Chloroquine

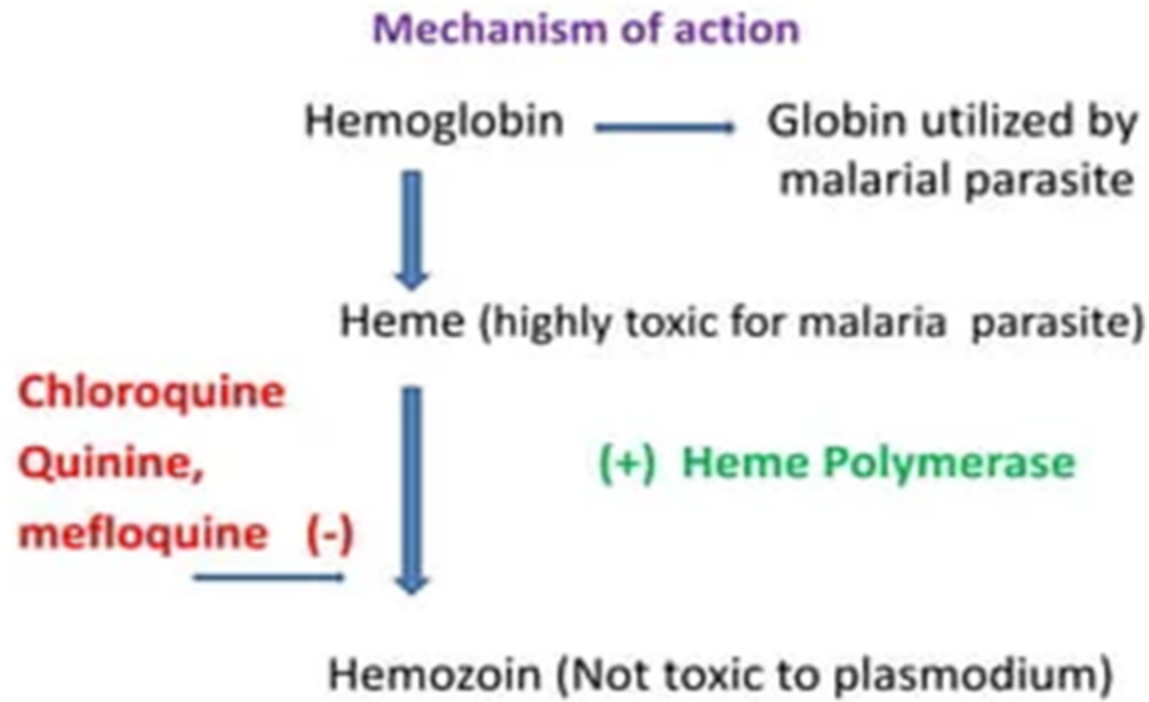
- Chloroquine has been a drug of choice for both treatment and chemo-prophylaxis of malaria since the 1940s, but drug resistance limits its usefulness against P falciparum.

- It is rapidly and almost completely absorbed from the gastrointestinal tract, reaches maximum plasma concentrations in about 3 hours, and is rapidly distributed to the tissues. It has a very large apparent volume of distribution of 100–1000 L/kg and is slowly released from tissues and metabolized in liver.
- Chloroquine is principally excreted in the urine

- When not limited by resistance, chloroquine is a highly effective blood schizonticide.
- Chloroquine is not reliably active against liver stage parasites or gametocytes.

- Chloroquine probably acts by concentrating in parasite food vacuoles, preventing the biocrystallization of the hemoglobin breakdown product (heme) into hemozoin, and thus eliciting parasite toxicity due to the free heme.

N.B. Chloroquine resistance can be reversed by certain agents, including verapamil, desipramine, and chlorpheniramine, but the clinical value of resistance-reversing drugs is not established.



Chloroquine is usually **very well tolerated**, even with prolonged use.

1- Common adverse effects include:

- **Pruritus** and urticaria: more common, primarily in Africans.
- Nausea, vomiting, abdominal pain, headache, anorexia, and malaise. **Dosing after meals may reduce some adverse effects.**

2 - Rare reactions include:

A- Hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons.

B-CNS toxicity: impaired hearing, confusion, psychosis, seizures.

C-Agranulocytosis, exfoliative dermatitis, alopecia, bleaching of hair.

D-Hypotension, and ECG changes with risk of arrythmias (occurs with injection).

3- The long-term administration of high doses of chloroquine for rheumatologic diseases (like systemic lupus or rheumatoid arthritis) can result in:

A. Hepatotoxicity.
B. Irreversible ototoxicity.
C. Retinopathy.
D. myopathy, and peripheral neuropathy.

but these are rarely seen with standard-dose weekly chemoprophylaxis.

- Chloroquine is contraindicated in patients with psoriasis or porphyria.
- Chloroquine should generally not be used in those with retinal or visual field abnormalities or myopathy.
- It should be used with caution in patients with liver, neurologic, or hematologic disorders.
- Chloroquine is considered **safe in pregnancy and for young children.**

2- Mefloquine

-It is used for treatment and prophylaxis of chloroquine-resistant P. falciparum.

-Side effects are GIT disturbance and CNS manifestations (dizziness, disorientation, hallucinations, depression and seizures).

3- Quinine

-Quinine acts mainly as a blood schizonticide.

-It acts also as gametocidal for P.vivax and P.malariae but not P .falciparum.

-It is more toxic and less effective than chloroquine, so chloroquine is the drug of choice in acute attacks. It is not active against liver stage parasites.

Quinine is derived from the bark of the cinchona tree.

Therapeutic uses:

1-The main indication for quinine is treatment of severe forms of P. falciparum infections whether sensitive or resistant to chloroquine, it is used as a lifesaving measure by I.V. infusion.

-If quinine is not available, parenteral quinidine is the alternative.

2-It is used with tetracyclines or fansidar in treatment of acute attacks of chloroquine-resistant P. falciparum (as these drugs as slow onset of action)

Side effects of quinine (cinchonism):

1. Headache, dizziness, tinnitus and visual disturbance, fever and skin rash.
2. Blood toxicity: hemolysis, thrombocytopenia and agranulocytosis.
3. **Cardiac toxicity.**
4. Deafness, marked visual abnormalities, vertigo, confusion and convulsion.

4- Primaquine

Therapeutic uses:

1-It is used with chloroquine to prevent relapse in cases of P. vivax & P. ovale, as it can destroy the persistent liver hypnozoites, so can cause radical cure.

2-It has a marked gametocytocidal activity (destroy gametocytes, so prevent transmission of malaria to the mosquito) against all types of malaria.

Adverse effects: Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.

5- Fansidar (Pyrimethamine + sulfadoxine)

Mechanism of action:

-Fansidar is a combination of pyrimethamine (inhibits dihydrofolate reductase) enzyme, and sulfadoxine (a long-acting sulphonamide).

-This combination has synergistic effect due to blocking of 2 sequential steps in folate pathway.

-Pyrimethamine is used in lower dose that does not affect the mammalian enzymes.

Therapeutic uses:

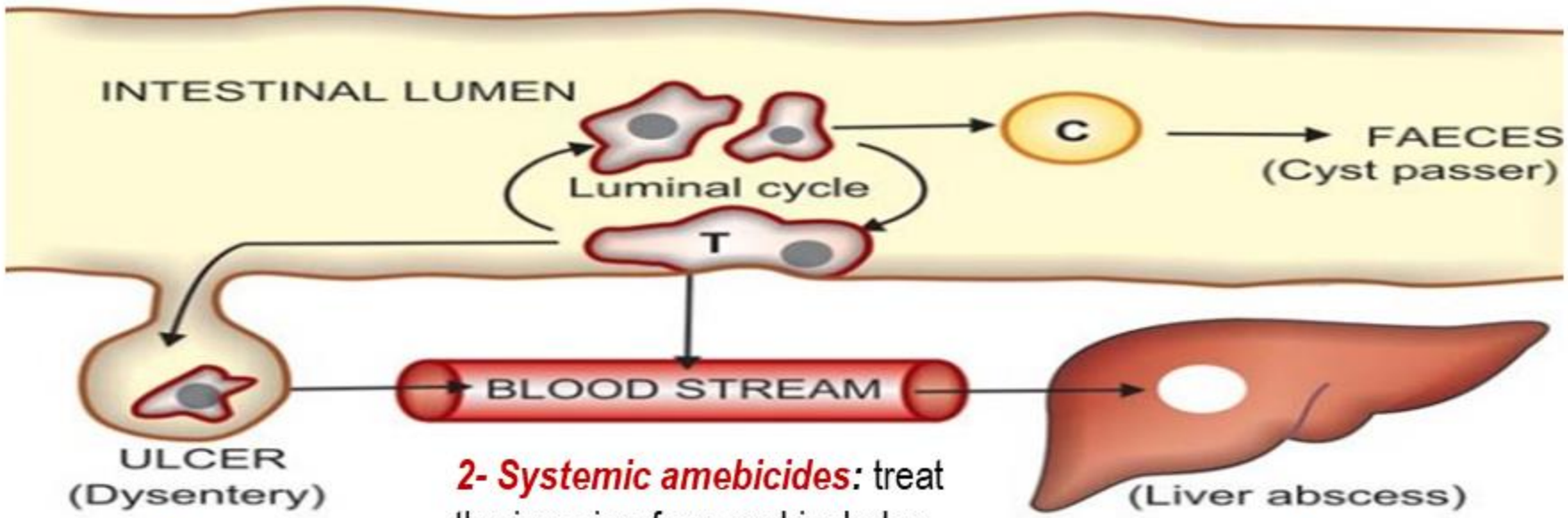
1-It is used mainly in treatment of acute attacks of chloroquine-resistant P. falciparum, but it has slow onset of action, so it is combined with quinine which has a faster onset.

-Now not used in prophylaxis due to risk of sulphonamide-induced allergy.

2-It is the **first choice in treatment of toxoplasmosis**

Treatment of amebiasis

1- Luminal amebicides: treat intestinal form as Diloxanide furoate.



2- Systemic amebicides: treat the invasive form and includes intestinal and extra- intestinal forms

a- Intestinal forms including Severe amebic dysentery: **dehydroemetine** but **metronidazole** is better

b-Hepatic abscess: **dehydroemetine** or **chloroquine** but metronidazole is better

1- Treatment of asymptomatic intestinal infections (cyst passer):

1- Diloxanide furoate:

-It is the drug of choice (used orally for 10 days) but ineffective in extra-intestinal cases.

It acts against trophozoites of E. histolytica that eventually form cysts.

Unknown mechanism, but structurally it is like chloramphenicol (suggesting inhibition of protein synthesis).

-It is **usually used with metronidazole** to produce a **cure of invasive and extraintestinal** amebiasis.

2- Diiodohydroxyquinoline (Clioquinol):

-It is alternative to diloxanide. It has antifungal and bacterioststic effects. Mechanism is not clear.

-It is widely used in treatment of **diarrhea** (one of **streptoquin** components).

- Large dose may cause optic neuropathy.

Streptoquin tablet is composed of the following active ingredients (salts)

1. Clioquinol
2. Homatropine Methyl bromide
3. Phthalyl Sulfathiazole
4. Streptomycin

Treatment of invasive intestinal infections (amebic dysentery):

1-Metronidazole is the drug of choice (but ineffective against cyst, so it is used in combination with one of the previously discussed drugs).

2-Emetine and **dehydroemetine** are effective, but highly toxic, used only if there is contraindication for metronidazole (dehydroemetine is safer than emetine).

3-Paromomycin (aminoglycoside), it causes direct kill of ameba.

4-Tetracyclines and **erythromycin** act by killing enteric flora essential for proliferation of pathogenic ameba.

Erythromycin is used in children and pregnancy.

c) Treatment of hepatic abscess and extra-intestinal infections

1-Metronidazole is the drug of choice.

2-If metronidazole is contraindicated. Emetine or Chloroquine could be used.

Treatment of giardiasis

1- Metronidazole is the preferred treatment.

2- Quinacrine: well absorbed rally even in severe diarrhea.

-Side effects: CNS manifestations (headache, dizziness, psychosis, ocular toxicity), exfoliative dermatitis and yellowish coloration of skin.

-It contraindicated in cases of psychosis and psoriasis.

3) Nitazoxinide.

Metronidazole (flagyl)

Mechanism of action:

-The nitro group of metronidazole is reduced leading to the formation of cytotoxic products that destroy the protozoal cells and anaerobic bacteria.

Pharmacokinetics:

-It is well absorbed after oral administration, can be used I.V. and rectally.

-10 % binds to plasma proteins and it is widely distributed to different tissues and fluids including saliva, milk and CSF (concentration in CSF as in plasma)

- **Half life is 8 hours**.

- It is metabolized in liver and excreted in urine as metabolites.

Therapeutic uses:

1. Treatment of all symptomatic cases of **amebiasis** including GIT infection and liver abscess, used orally 750 mg 3 times/ day for 5-10 days (but ineffective against E. histolytica cyst, so it is better to combined with diloxanide).
2. Treatment of trichomonas vaginalis.
3. Treatment of giardiasis.
4. Treatment of anaerobic mixed bacterial infection caused by B. fragilis (as in cases of abdominal, pelvic and brain abscess)
5. Treatment of pseudomembranous colitis caused by clostridium difficile.
6. Treatment of Helicobacter pylori infection (used with other drugs).

Side effects:

1- GIT: nausea, vomiting, diarrhea, dry mouth and ***metallic taste***.

2- CNS: headache, dizziness, vertigo and **paresthesia**.

3- Severe neurotoxicity: ataxia, seizures, encephalopathy.

4-Disulfiram-like reactions in alcoholics.

5-Carcinogenesis in animal and teratogenicity (not used during pregnancy, lactation)

5- Red brown coloration of urine.

6-Inhibits the metabolism of oral anticoagulants.

Tinidazole

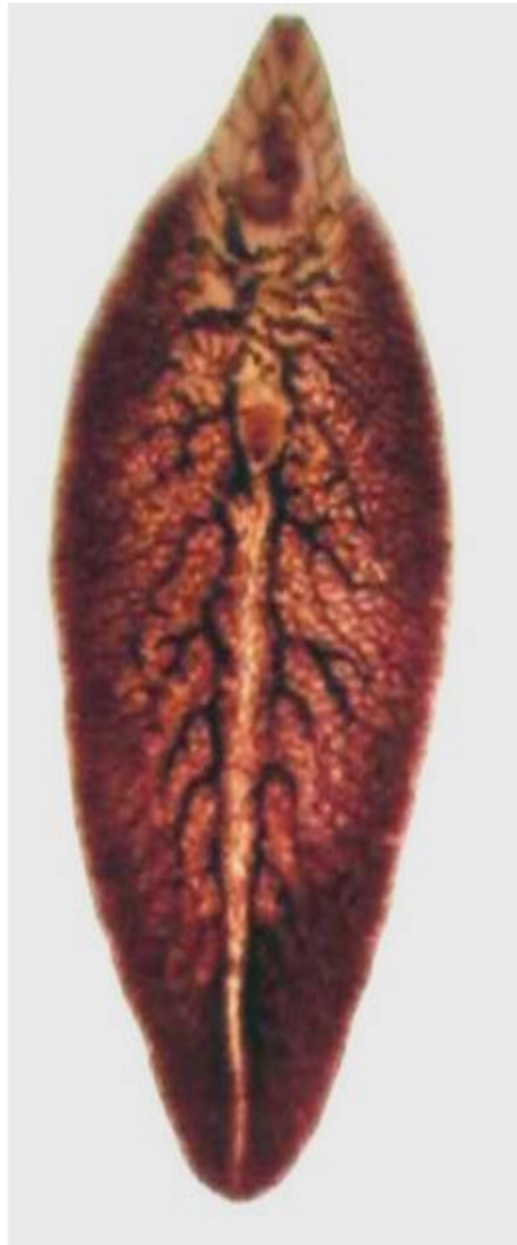
-As metronidazole, but it **has long $t_{1/2}$ (13 h.).**

-It can be used as a single oral dose which is effective as a course of metronidazole.

Treatment of trematodes (flukes)

Praziquantel

- Effective in ***all trematodes*** (S. haematobium, S. mansoni and H. heterophes) but not effective in Fasciola hepatica (**Bithional is effective**).
- It is also effective in ***all cestodes tapeworm*** *except* hydatid disease.
- It acts by increasing Ca^{++} influx causing marked **contraction** followed by spastic paralysis of worm musculature.
- In addition, it causes vacuolation and disintegration of the parasite and death follows. -- It can be used as a single dose orally.
- Praziquantel is contraindicated in ocular cysticercosis.



Treatment of cestodes (tapeworms)

1) Praziquantel: effective in all cestodes except hydatid disease.

2) Niclosamide:

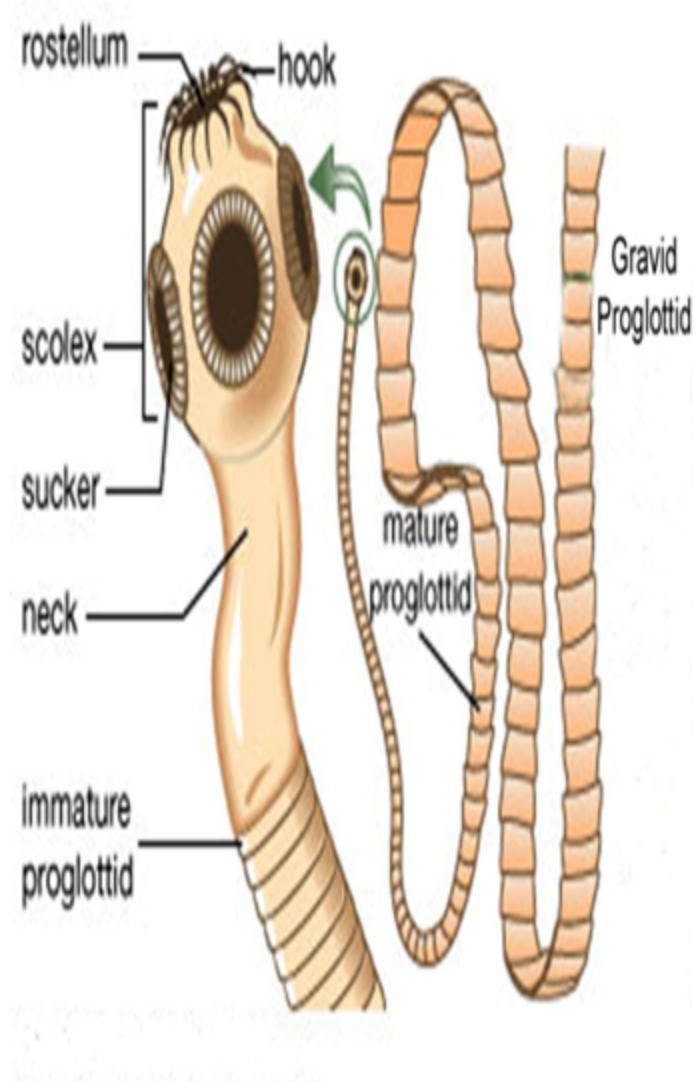
-**Effective in all cestodes except hydatid disease** and **cysticercosis** and considered as second choice after praziquantel.

-It acts by inhibition of oxidative phosphorylation of the parasite.

-There is release of viable ova into gut following digestion of segments that may cause cysticercosis, so in cases of Taenia solium purgative is given 3-4 h. after drug administration.

3) Albendazole: effective against hydatid disease, also it is used in cysticercosis.

4) Mebendazole: alternative to albendazole in treatment of hydatid disease



Treatment of nematodes (round worms

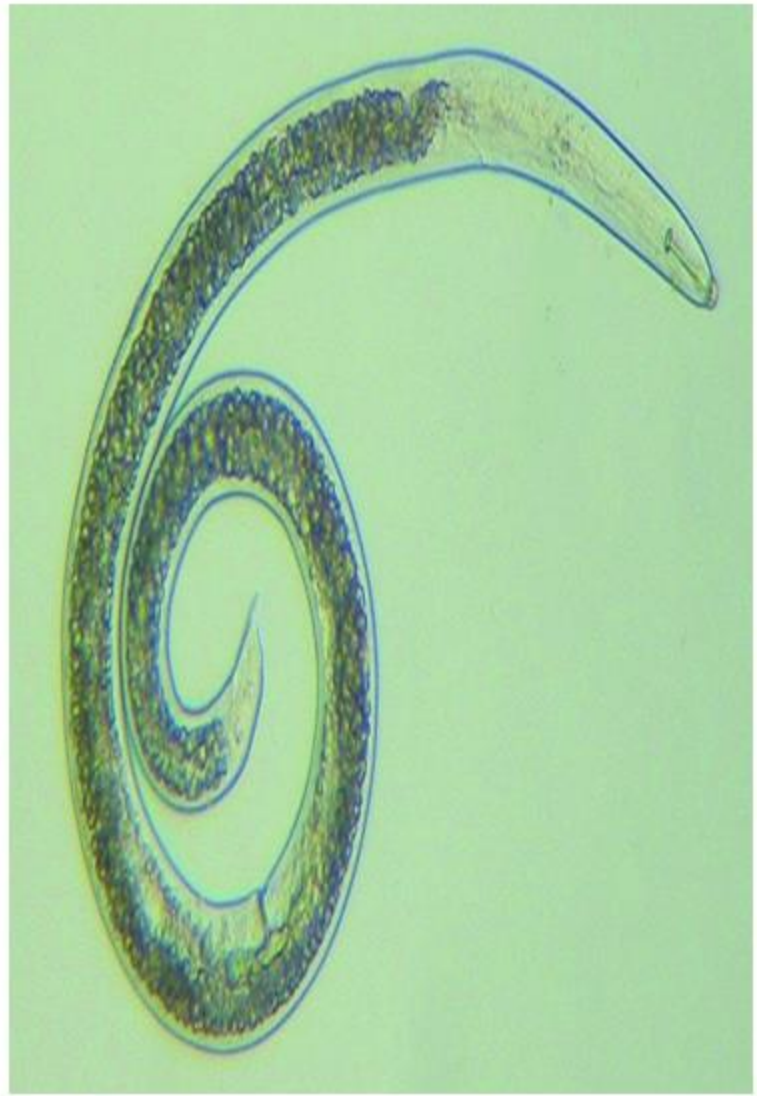
1) Benzimidazoles:

Mechanism of action:

-They act by **binding to tubulin**, so inhibit polymerization of microtubule causing immobilization and death of susceptible GIT parasites.

-The effect is slowly and may need several days after treatment for complete clearance of the parasite from GIT.

- Albendazole, Mebendazole and thiabendazole are examples.



Albendazole:

Pharmacokinetics:

-Irregular absorption after oral use and the absorption is increased by fatty meal .

-The drug can not be detected in the plasma due to rapid metabolism in the liver and intestine to the active albendazole sulfoxide.

-This active metabolite is widely distributed to different tissues including hydatid cysts.

Therapeutic uses:

a) Treatment of intestinal and tissue nematodes (ascaris, hook worm, enterobius…..)

b) Treatment of larval forms of certain cestodes as **cysticercosis** and **hydatid cysts**.

c) Control of lymphatic filarial

Side effects:

a) Mild if used for short term therapy as nausea, diarrhea, headache and dizziness.

b) Liver dysfunction if used for long term therapy.

Mebendazole:

-**Poorly absorbed orally**, so it does not cause significant systemic toxicity.

-Highly effective in GIT nematodes and more useful in mixed nematodal infections.

Thiabendazole:

-Rapidly absorbed orally, so rarely used now due to high toxicity and used mainly in:

a) Topically in cutaneous larva migrans of hookworm.

b) Orally in strongyloides infections.

2) Pyrantel pamoate:

-It causes depolarization of the neuromuscular junction of susceptible nematodes leading to ***spastic*** paralysis of the worm. It also inhibits cholinesterase enzyme.

-It is used in treatment of ascaris, enterobius and hookworm.

-It is used as **single oral dose.**

3) Ivermectin:

-It acts by causing tonic paralysis of the musculature of the nematode by acting on glutamate-gated chloride channels. It may bind to GABA receptors.

-It is used as **single oral dose** with wide safety margin.

-The drug of choice in treatment of strongyloides and filarial.

- Topical and systemic Ivermectin is used in treatment of **scabies**.

Side effects of most of anthelmintic drugs:

1-GIT manifestations: anorexia, nausea, vomiting, diarrhea and abdominal cramps.

2-Mild CNS manifestations: headache, dizziness and drowsiness.

3-Allergic reactions: fever, urticaria and elevation of serum transaminase.

4-Most of the drugs are contraindicated in pregnancy and lactation.


THANK YOU