Antiprotozoal Drugs

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Protozoan parasites causing human diseases are widespread in underdeveloped tropical and subtropical regions due to inadequate sanitary conditions and vector control. Global travel has expanded the reach of protozoal diseases beyond specific geographic areas. Protozoal cells share metabolic processes with human hosts, making treatment more challenging compared to bacterial infections. Many antiprotozoal drugs have serious toxic effects, especially on highly metabolically active cells, and are generally unsafe for pregnant patients.

Chemotherapy for Amebiasis

Amebiasis (amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. E. histolytica is endemic in developing countries and is mainly transmitted via the fecal–oral route or through ingestion of contaminated food or water. Most infected individuals are asymptomatic but can exhibit varying degrees of illness depending on host factors and formation of trophozoites. The diagnosis is established by isolating E. histolytic from feces. Therapeutic agents for amebiasis are classified as luminal, systemic, or mixed amebicides according to the site of action.

A. Mixed amebicides (Metronidazole and Tinidazole)

1. Metronidazole:

Metronidazole, a nitroimidazole, is the preferred mixed amebicide for treating amebic infections. It is also utilized in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, anaerobic gram-negative bacilli (e.g., Bacteroides species), and anaerobic gram-positive bacilli (e.g., Clostridioides difficile).

Mechanism of action:

Amebas contain electron transport proteins with low-redox potential similar to ferredoxin. Metronidazole, through its nitro group, acts as an electron acceptor in amebas. This process leads to the formation of cytotoxic compounds that bind to proteins and DNA, causing the death of E. histolytica trophozoites.

Pharmacokinetic Metronidazole, when orally administered, is rapidly and completely absorbed, with widespread distribution in body tissues and fluids, including vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid. Metabolized in the liver, the drug accumulates in severe hepatic disease and is excreted in urine.

Adverse effects include nausea, vomiting, epigastric distress, abdominal cramps, and a metallic taste. It may lead to oral yeast infections and potentially prolong the QT interval, requiring caution when used with drugs that increase QT prolongation. Combining metronidazole with alcohol can trigger a disulfiram-like reaction.

2. Tinidazole:

Tinidazole, a second-generation nitroimidazole, shares a similar spectrum of activity and absorption with metronidazole. It is employed in treating amebiasis, amebic liver abscess, giardiasis, and trichomoniasis, demonstrating efficacy comparable to metronidazole but at a higher cost. Metabolized by CYP3A4, tinidazole concentrations can be influenced by strong inducers or inhibitors of this enzyme. Common adverse effects include gastrointestinal upset and a metallic taste, and alcohol consumption is advised against during therapy.

B. Luminal amebicides (luminal agent, such as *iodoquinol*, *diloxanide furoate*, or *paromomycin*,)

1. Iodoquinol:

Iodoquinol is an amebicidal medication effective against luminal trophozoite and cyst forms of E. histolytica. However, its use comes with potential adverse effects such as rash, diarrhea, and dose-related peripheral neuropathy, including rare optic neuritis. Due to these risks, long-term usage of iodoquinol is advised against.

2. Paromomycin:

Paromomycin, an aminoglycoside antibiotic, is specifically effective against luminal forms of E. histolytica as it is poorly absorbed from the gastrointestinal tract. Its direct amebicidal action and reduction of intestinal flora contribute to its anti amebic effects. The main adverse effects include gastrointestinal distress and diarrhea.

C. Systemic amebicides

Chloroquine, a systemic amebicide, is effective in treating extraintestinal amebiasis, including liver abscesses and intestinal wall infections caused by amebas. It is often combined with metronidazole or used as a substitute for nitroimidazoles in cases of intolerance to treat amebic liver abscesses. Chloroquine eliminates trophozoites in liver abscesses but is not effective against luminal amebiasis, necessitating follow-up with a luminal amebicide. Additionally, chloroquine is effective in treating malaria.

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *iodoquinol* or *paromomycin*
Amebic liver abscess	*Metronidazole* (or *tinidazole*) plus *iodoquinol* or *paromomycin*

Figure 1: Therapeutic options for the treatment of amebiasis.

Antimalarial drugs

Four species of plasmodium typically cause human malaria:

1. Plasmodium falciparum

2. P vivax.

3. P malariae.

4. P ovale.

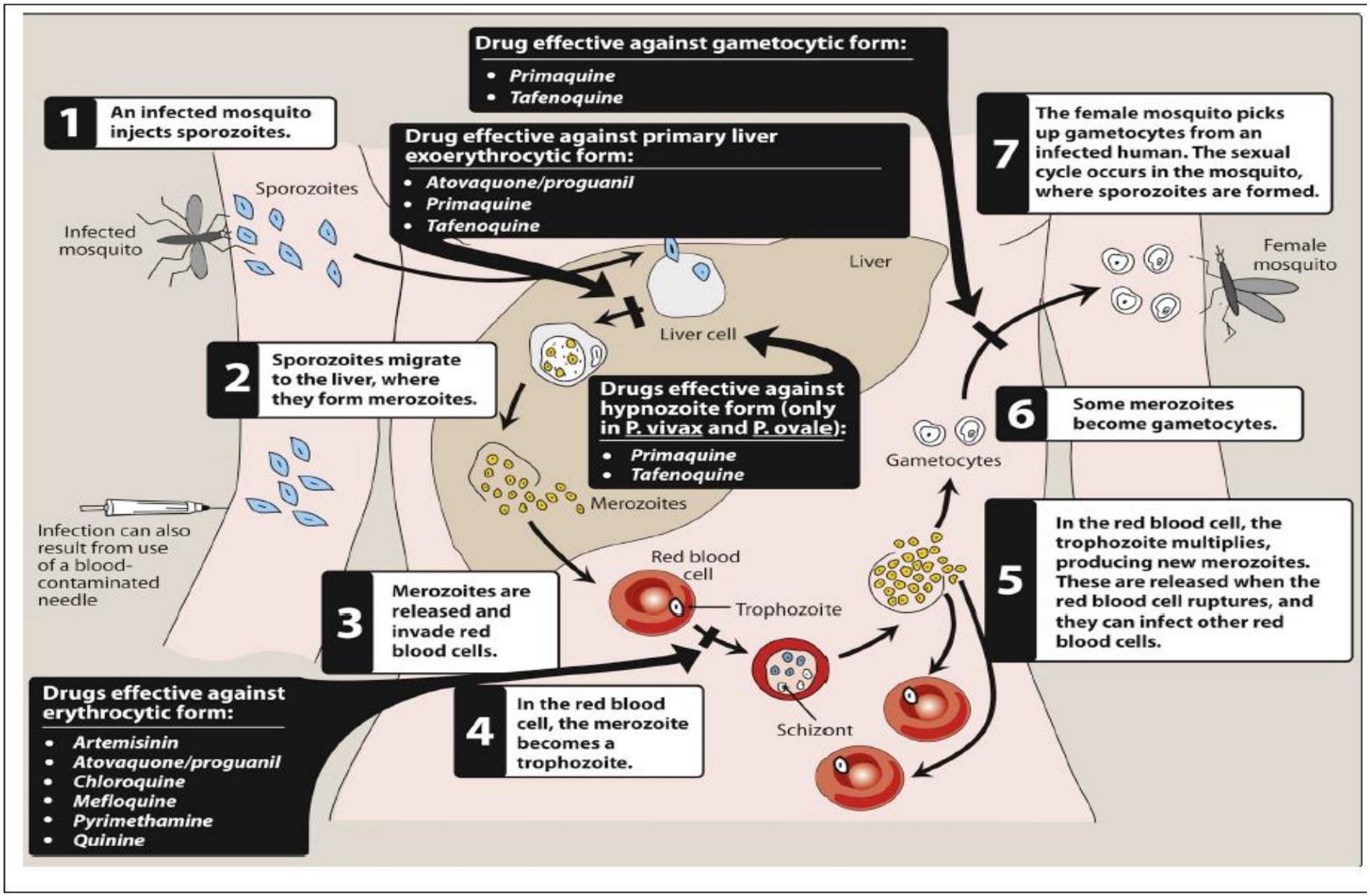


Figure 2: Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs

Classification of Drug

1. Tissue schizonticide

2. a blood schizonticide tissue schizonticide primaquine

• Eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale).

• Lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythrocytic form after the erythrocytic form of the disease is eliminated.

• The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thus interrupting the transmission of the disease.

Primaquine is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as chloroquine, quinine, mefloquine, or pyrimethamine.

Mechanism of action of primaquine

Metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.

Pharmacokinetics of Primaquine:

- Primaquine is well absorbed on oral administration
- It is rapidly oxidized to metabolites which appear in the urine

Adverse effects of Primaquine

- Hemolytic anemia (in patient's low levels of glucose-6- phosphate)
- Abdominal discomfort (with large doses) especially when administered in combination with chloroquine
- Methemoglobinemia
- Granulocytopenia (rarely)
- Primaquine is contraindicated during pregnancy.
- All Plasmodium species may develop resistance to primaquine

Blood schizonticide

Chloroquine

• The mainstay of antimalarial therapy, and it is the drug of choice in the treatment of erythrocytic P. falciparum malaria,

• Chloroquine is less effective against P. vivax malaria.

• It is highly specific for the asexual form of plasmodia.

• Chloroquine is also effective in the treatment of extraintestinal amebiasis

Pharmacokinetics of Chloroquine

Chloroquine is rapidly and completely absorbed following oral administration. 4 days of therapy suffice to cure the disease. The drug concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes.

Some metabolic products have antimalarial activity. The excretion by urine rate is enhanced as is acidified.

Adverse effect of Chloroquine

Higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurring of vision. Discoloration of the nail beds and mucous membranes may be seen on chronic administration. Electrocardiographic changes (because it has a quinidine-like effect). Dermatitis produced by gold or phenylbutazone therapy.

Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.

Mefloquine

An effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but like quinine, it can apparently damage the parasite's membrane, is absorbed well after oral administration and concentrates in the liver and lung, It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems., The drug undergoes extensive metabolism. Its major excretory route is the feces, Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Electrocardiographic abnormalities and cardiac arrest are possible if mefloquine is taken concurrently with quinine or quinidine.

Quinine and quinidine

Interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. For These drugs are reserved severe infestations and for malarial strains that are resistant to other agents, such as chloroquine.

Taken orally, quinine is well distributed throughout the body and can reach the fetus. Alkalinization of the urine decreases its excretion.

The major adverse effect of quinine

1. Cinchonism (syndrome causing nausea, vomiting, tinnitus, and vertigo).

2. Positive Coombs' test for hemolytic anemia occurs (Quinine)

3. Quinine is fetotoxic

Drug interactions of quinine

- Potentiation of neuromuscular-blocking agents
- Elevation of digoxin levels if taken concurrently with quinine
- Quinine absorption is retarded when the drug is taken with aluminum-containing antacids.

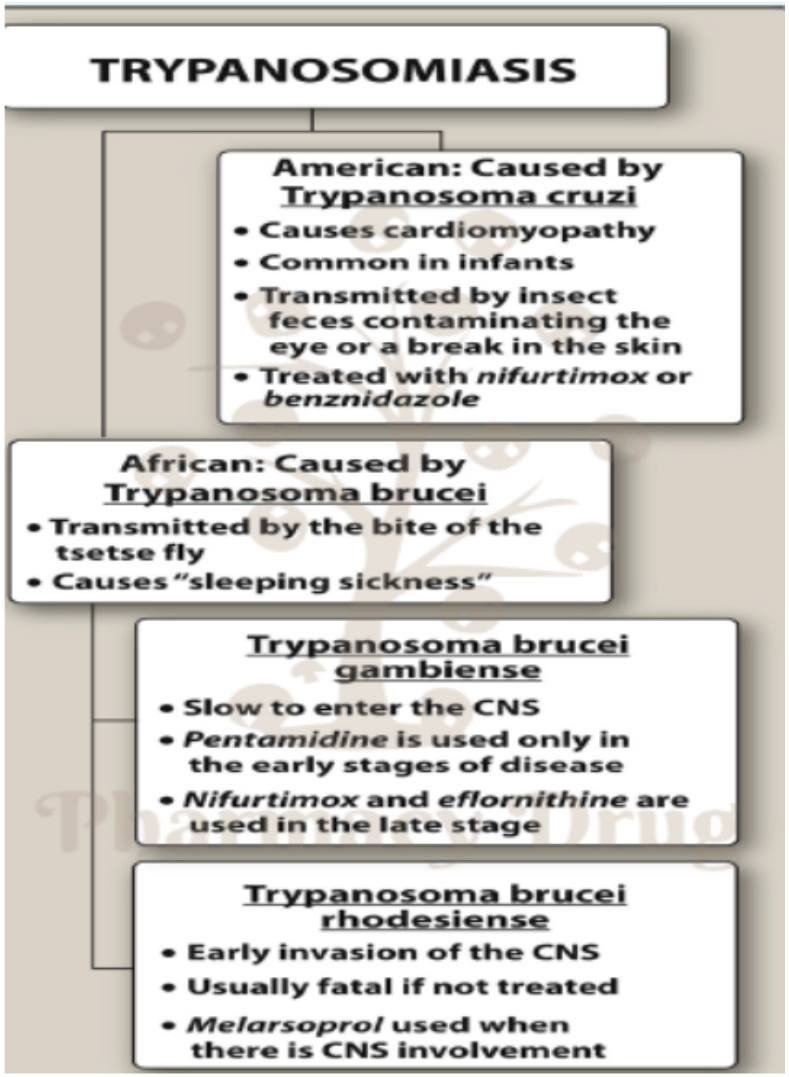
Pyrimethamine

- Inhibits plasmodial dihydrofolate reductase at much lower concentrations than those needed to inhibit the mammalian enzyme.
- The inhibition deprives the protozoan of tetrahydrofolate cofactor required in the de-novo biosynthesis of purines and pyrimidines
- It is also used against P. malariae and toxoplasma gondii.
- If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with leucovorin

Chemotherapy for Trypanosomiasis

Only four drugs are available for the chemotherapy of human African trypanosomiasis or sleeping sickness; Suramin, pentamidine, melarsoprol and eflornithine.

African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are two chronic and, eventually, fatal diseases caused by species of Trypanosoma. In African sleeping sickness, Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense initially live and grow in the blood. The parasite later invades the CNS, causing inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease is caused by Trypanosoma cruzi and is endemic in Central and South America



CNS = central nervous system

Figure-3- Summary of trypanosomiasis.

Pentamidine

Pentamidine is utilized to treat African trypanosomiasis caused by T. brucei gambiense in the early hemolymphatic stage without CNS involvement and is an alternative for preventing or treating infections caused by the atypical fungus P. jirovecii, especially in immunocompromised individuals. It is considered in cases where sulfonamides are contraindicated and is an alternative for treating leishmaniasis. The drug's mechanism of action involves concentration in T. brucei through an energy-dependent uptake system, potentially interfering with parasite synthesis of RNA, DNA, phospholipids, and proteins. Pentamidine is administered intravenously or intramuscularly for trypanosomiasis and P. jirovecii pneumonia. However, it carries risks of serious reversible renal dysfunction upon discontinuation, as well as adverse effects such as hyperkalemia, hypotension, pancreatitis, ventricular arrhythmias, and hyperglycemia. Monitoring plasma glucose is crucial due to the potential for life-threatening hypoglycemia.

Suramin

Suramin is primarily employed in the early stage of African trypanosomiasis caused by T. brucei rhodesiense, especially when there is no central nervous system (CNS) involvement. Its mechanism of action involves inhibiting various enzymes, particularly those related to energy metabolism, which contributes to its trypanocidal activity. Administered intravenously, suramin binds to plasma proteins, poorly penetrates the blood-brain barrier, and exhibits a prolonged elimination half-life (over 40 days), primarily excreted unchanged in urine. Adverse reactions, though rare, may encompass nausea, vomiting, shock, loss of consciousness, acute urticaria, blepharitis, and neurologic issues such as paresthesia, photophobia, and hyperesthesia of the hands and feet. Renal insufficiency, if present, tends to resolve upon discontinuation of treatment, and acute hypersensitivity reactions are also possible.

Melarsoprol

Melarsoprol, a trivalent arsenical compound, is the primary treatment for late-stage African trypanosome infections with CNS involvement from T. brucei rhodesiense. The drug interacts with sulfhydryl groups, affecting pyruvate kinase enzymes in both the organism and host. Administration through slow IV injection is crucial to reduce the risk of resistance, potentially associated with decreased transporter uptake. However, melarsoprol is associated with CNS toxicity, particularly reactive encephalopathy, resulting in a 10% fatality rate. Co-administration of corticosteroids can help mitigate the risk of encephalopathy. Adverse effects include peripheral neuropathy, hypertension, hepatotoxicity, albuminuria, hypersensitivity reactions, and febrile reactions post-injection. Individuals with glucose-6-phosphate dehydrogenase deficiency may experience hemolytic anemia as a side effect

Eflornithine

Eflornithine is a crucial component in the treatment of late-stage African trypanosomiasis when combined with nifurtimox. The intravenous form is used, but frequent dosing is required due to its short half-life. Additionally, topical eflornithine is employed to manage unwanted facial hair in women. Potential adverse reactions include anemia, thrombocytopenia, seizures, and temporary hearing loss.

Nifurtimox

The drug, when combined with eflornithine, is employed to treat advanced infections of T. brucei gambiense and T. cruzi (Chagas disease). Functioning as a nitroaromatic compound, it undergoes reduction, generating toxic oxygen radicals that are detrimental to T. cruzi. Administered orally, the drug excreted through urine. adverse effects including hypersensitivity reactions, gastrointestinal problems, and peripheral neuropathy.

Benznidazole

Benznidazole, a nitroimidazole derivative akin to nifurtimox, is the preferred treatment for Chagas disease due to its improved tolerability compared to nifurtimox. Adverse effects, such as dermatitis, peripheral neuropathy, insomnia, and anorexia, are common. Both benznidazole and nifurtimox are cautioned against during pregnancy due to the potential risk of harm to the fetus.

Chemotherapy for Leishmaniasis

Leishmaniasis, caused by various Leishmania species and transmitted by infected sand flies, presents in three forms: cutaneous, mucocutaneous, and visceral (potentially fatal if untreated). Treatments for visceral leishmaniasis include **amphotericin B,** pentavalent antimonials (**sodium stibogluconate or meglumine antimoniate**), pentamidine, and paromomycin. **Miltefosine**, an orally active agent, is also effective.

Sodium stibogluconate, administered parenterally, is a prodrug with an unknown mechanism of action, and resistance has developed. Miltefosine interferes with parasitic cell membrane components and induces apoptosis, but its use is cautioned during pregnancy due to teratogenic effects. Adverse reactions for both treatments include various side effects such as injection site pain, gastrointestinal upset, and cardiac arrhythmias.

Chemotherapy for Toxoplasmosis

Toxoplasmosis, a common human infection caused by the protozoan T. gondii, is transmitted through consumption of raw or undercooked infected meat, contaminated water, or accidental ingestion of oocysts from cat feces. Pregnant women can transmit the infection to their fetus, and immunocompromised patients may develop severe disseminated disease. Current treatments focus on the tachyzoite stage, with pyrimethamine, particularly in combination with sulfadiazine, being the most effective.

Leucovorin is often administered to prevent folate deficiency. Alternative treatments include pyrimethamine with clindamycin or trimethoprim/sulfamethoxazole. Prophylaxis against toxoplasmosis in immunocompromised patients involves the use of trimethoprim/sulfamethoxazole. Discontinuation of pyrimethamine is advised at the first sign of a rash due to potential severe hypersensitivity reactions.

Chemotherapy for Giardiasis

Giardia lamblia, the most commonly diagnosed intestinal parasite in the United States, is typically contracted through fecally contaminated water or food. Infections involve trophozoites in the small intestine, occasionally forming cysts passed in stools.

While some cases are asymptomatic, severe diarrhea, particularly in immunocompromised individuals, can occur. The preferred treatment is a single oral dose of tinidazole, with oral metronidazole as an alternative for 5 days. Nitazoxanide, approved for giardiasis and cryptosporidiosis, is administered as a 3-day oral therapy for giardiasis. Albendazole and paromomycin may also be effective, with paromomycin considered for pregnant patients.

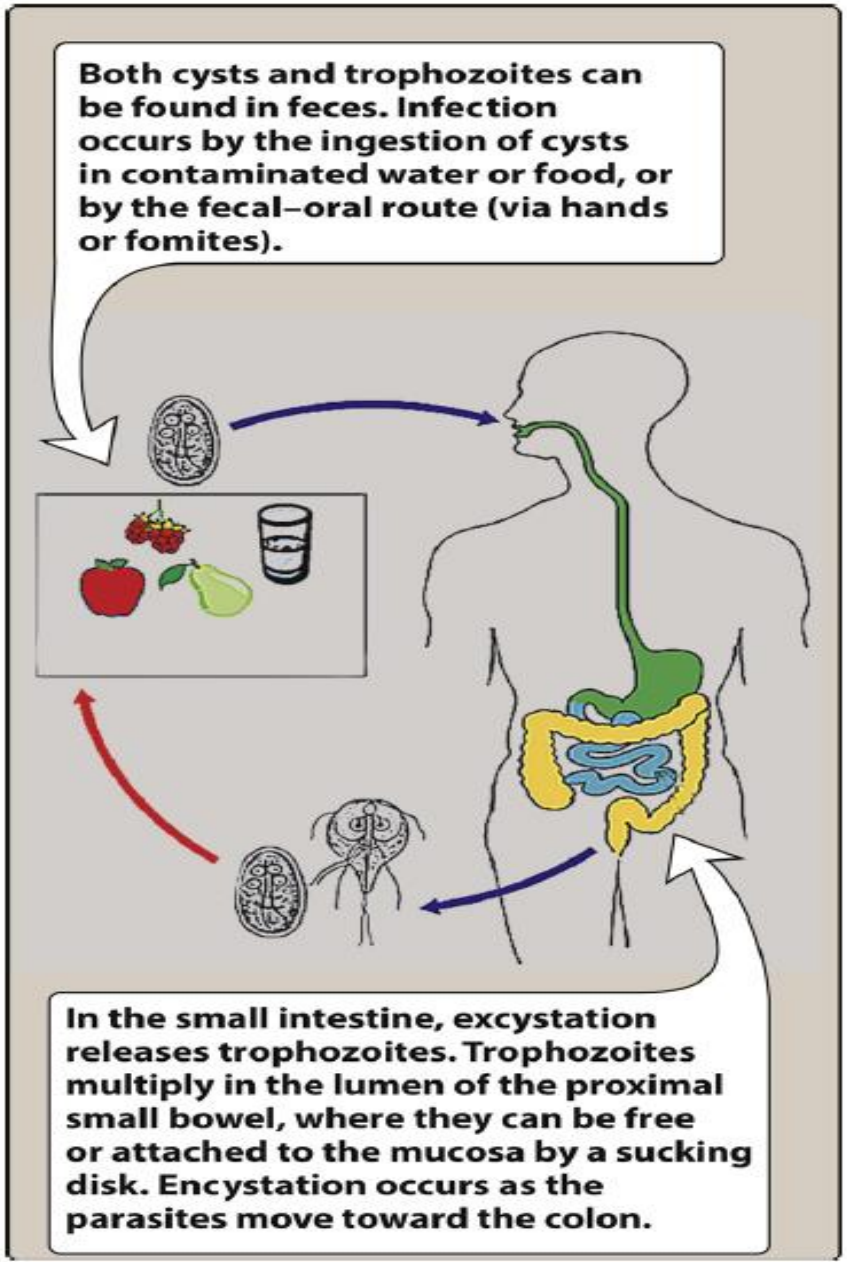


Figure: Life cycle of *Giardia lamblia*.