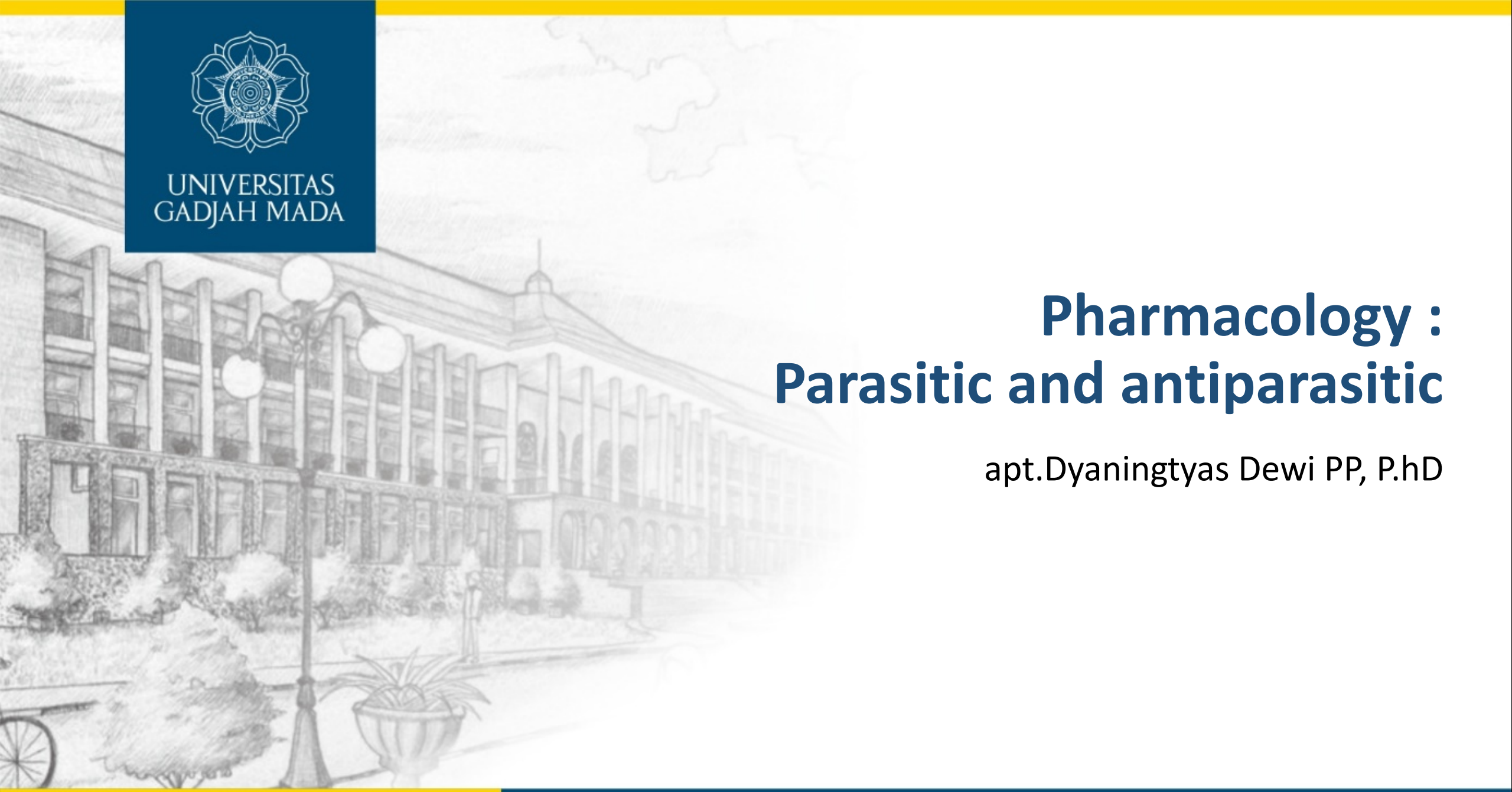


UNIVERSITAS
GADJAH MADA

Pharmacology : Parasitic and antiparasitic

apt.Dyaningtyas Dewi PP, P.hD

Introduction

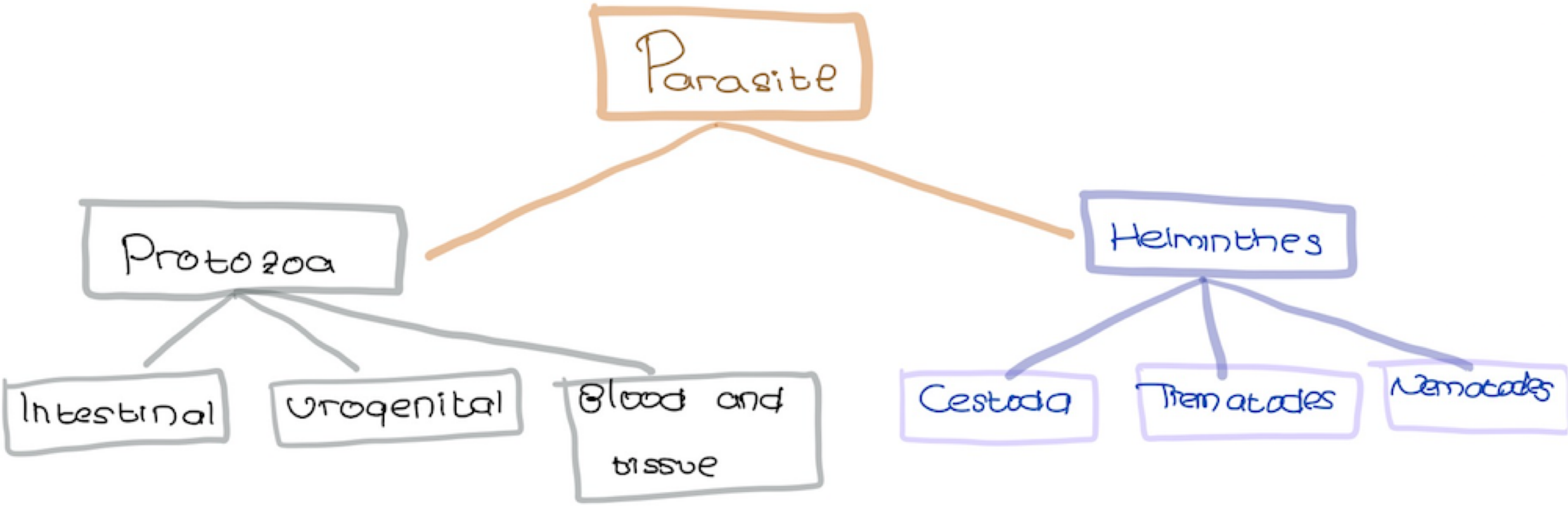
A parasite is an organism that lives on or inside another organism to the detriment of the host organism

The study of parasites is called **Parasitology.**

PARASITISM

- A form of symbiosis in which one organism (called parasite) benefits at the expense of another organism usually of different species(called host).

Classification



Protozoa

Intestinal

- Entamoeba histolytica
- Giardia lamblia
- Cryptosporidium

Urogenital

- Trichomonas vaginalis

Blood and tissue

- Malaria Toxoplasma
- Trypanosoma
- Leishmania .

Helminthes

Cestoda

Cystods (flat worms)

Taenia saginata
Tape like segmented,
Alimentary absent,
Coelom absent

Trematodes

Trematodes (fluks)

Bilharzia (Schistosomiasis)
Leaf like, hermaphrodite,
Coelom absent,

Nematodes

Nematodes (round worms)

Ascaris lumbricoides
(Roundworm)
Elongated, cylindrical, unsegmented,
Coelom present, sepearate sexes

COMMON PARASITIC DISEASES

- Amoebiasis: *Entamoeba histolitica*
- Giardiasis: *Giardia lamblia*
- Leishmaniasis: *Leishmania donovani*
- Malaria: *Plasmodium falciparum*
- Hook worm: *Ancylostoma duodenale*
- Round worm: *Ascaris lumbricoides*
- Echinococcosis: *Echinococcus granulosa* (tape worm)
- Pin worm: *Enterobious vermicularis*
- Scabies: *Sarcoptes scabiei*

Resume

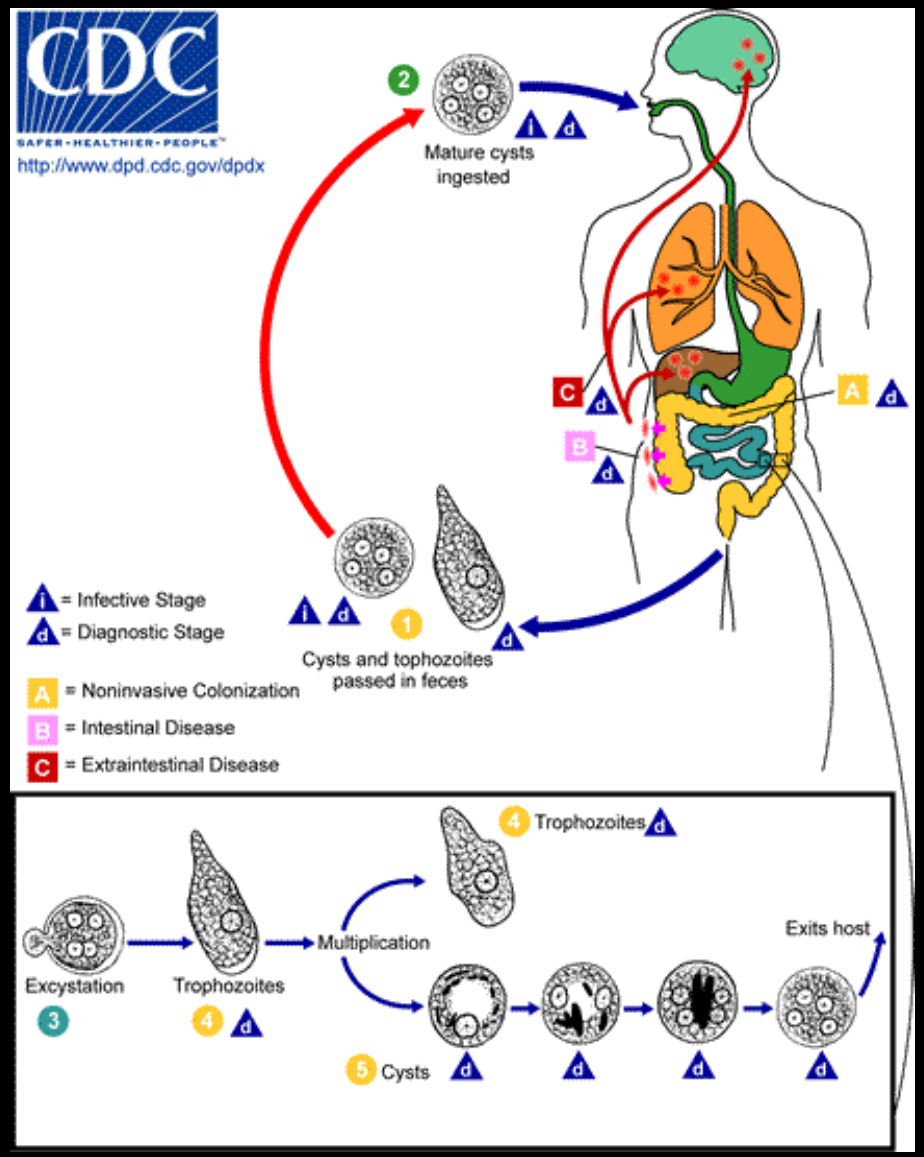
- Divisions of Parasitology:

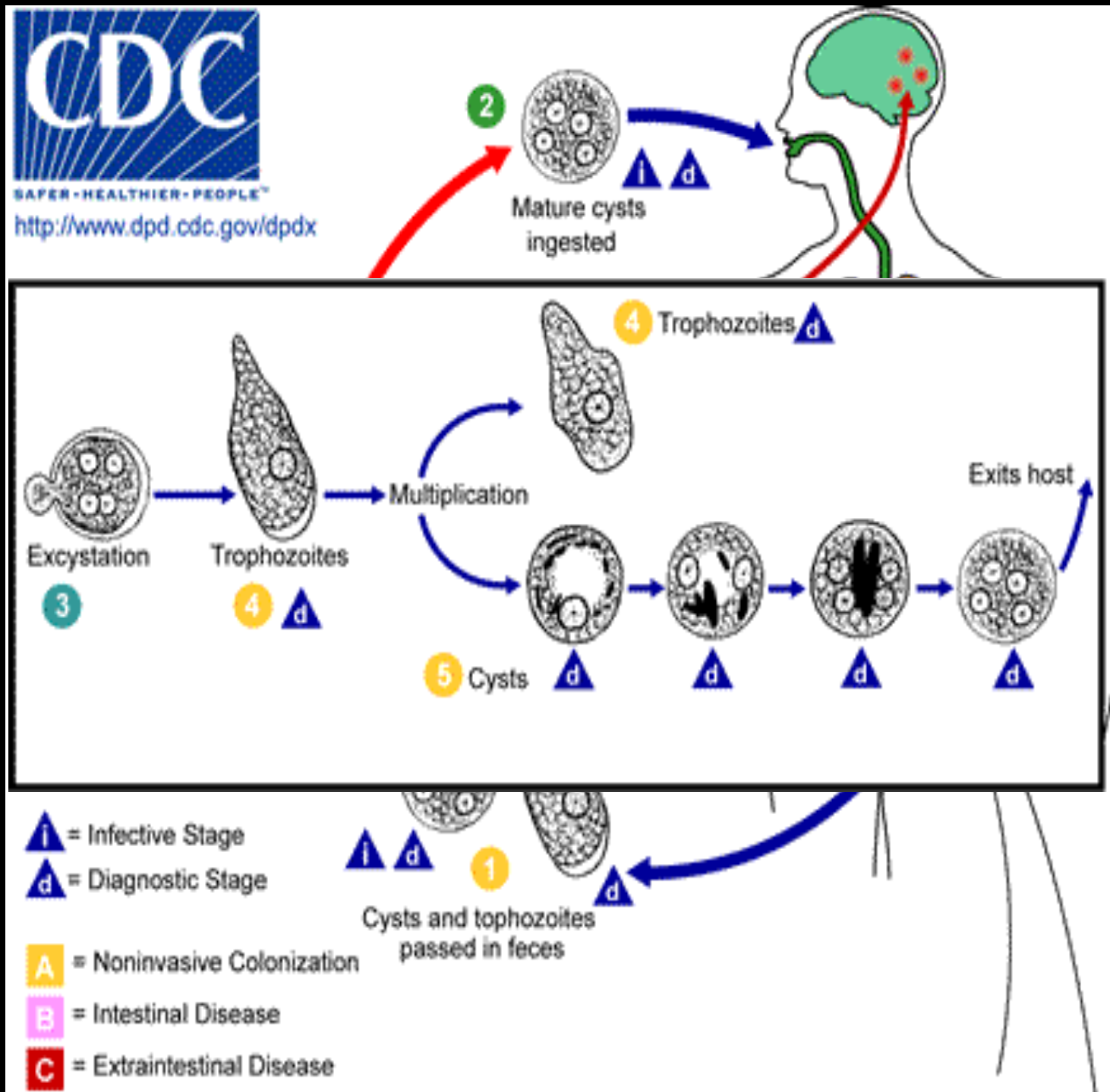
1. Protozoa
2. Helminths
    a. Roundworms (nematodes)
    b. Flatworms – Cestodes (tapeworm)
    c. Trematode (fluke)

Parasitism:

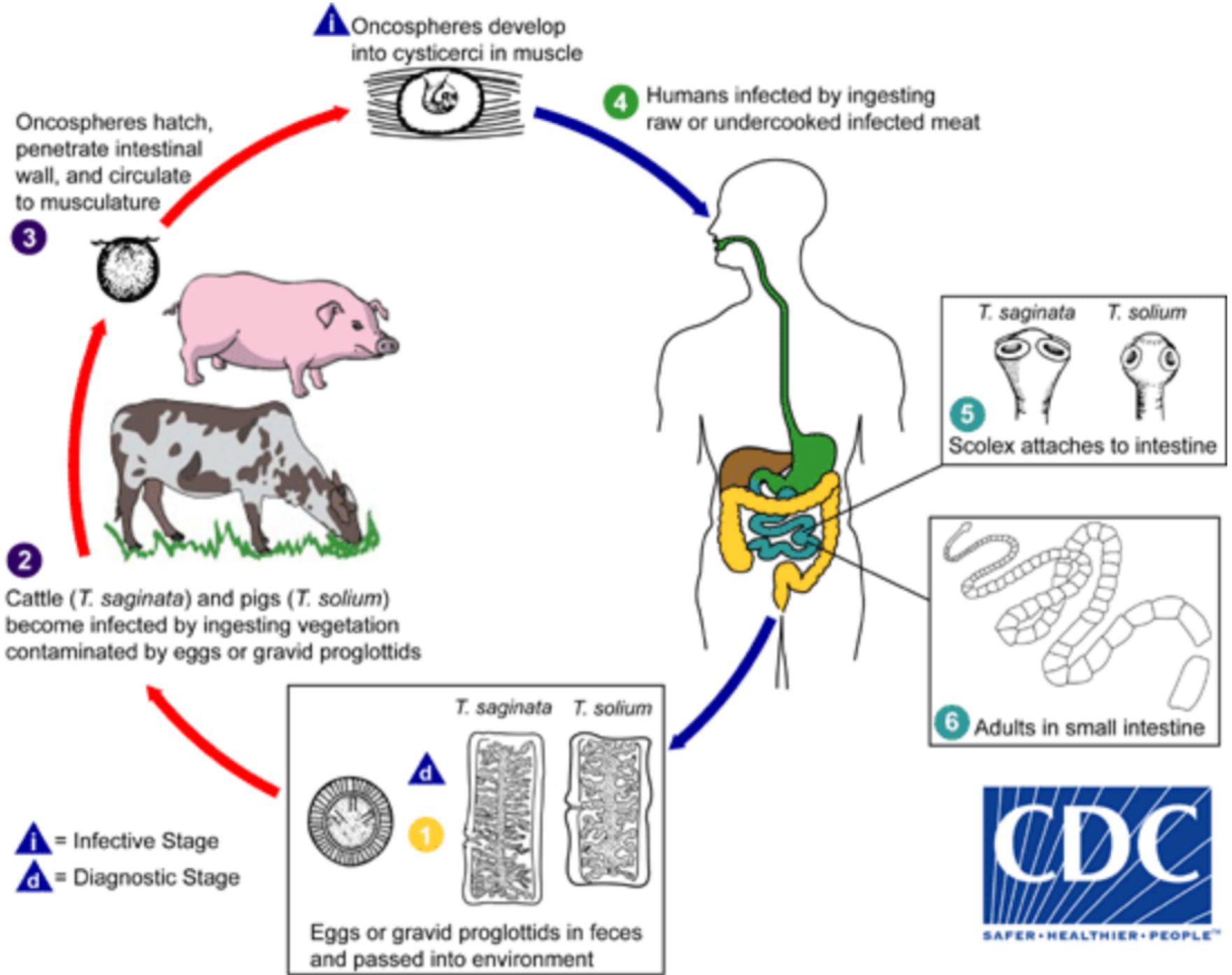
- organism depend upon another for living, one is living at the expense of the other and harmful, called Parasite, the other organism is called Host.

Life cycle-Direct





Life cycle-in Direct



Amoebiasis

- Clinical Presentation

- lumen of the intestine (“luminal amebiasis”).

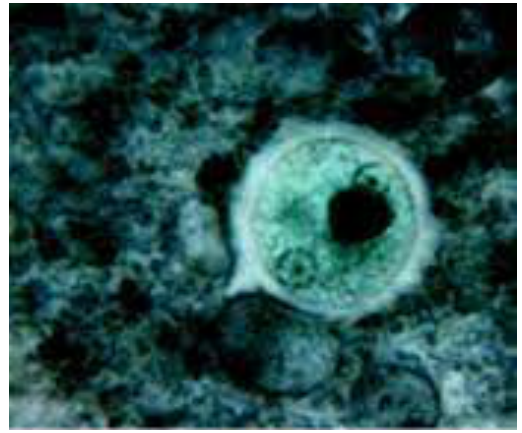
- Amebic colitis, or invasive **intestinal amebiasis → genus Entamoeba**

- Symptoms include

- severe dysentery.

- Severe chronic infections : complications such as peritonitis, perforations, and the formation of amebic granulomas (ameboma).

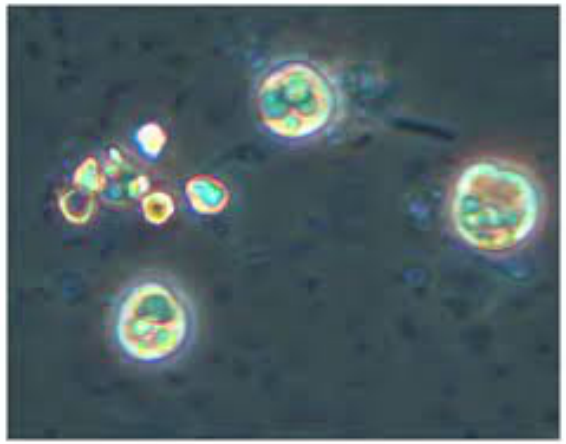
- **Amebic liver abscesses →** extraintestinal amebiasis. Pleuropulmonary abscess, brain abscess, and necrotic lesions on the perianal skin and genitalia have also been observed.



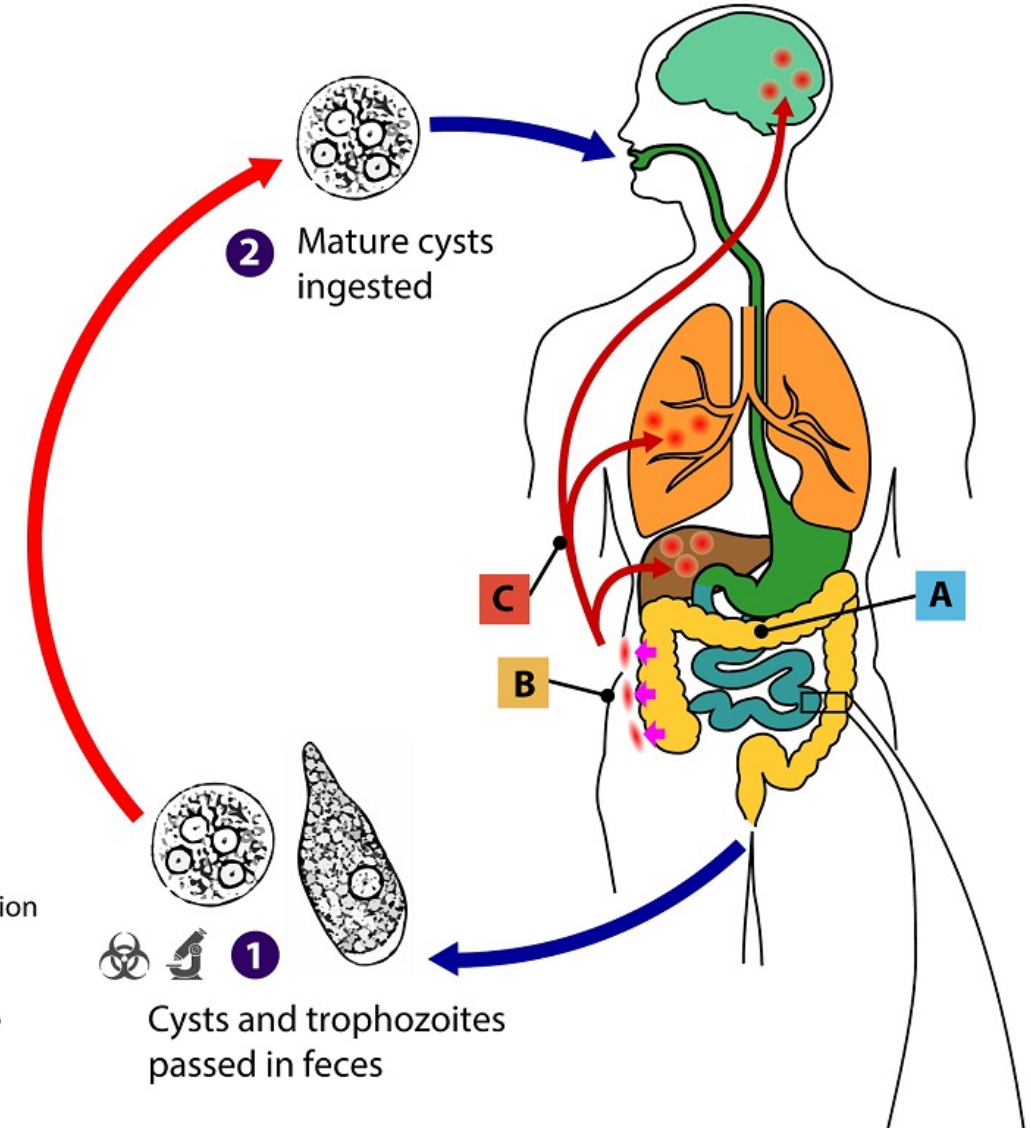
Amoebiasis

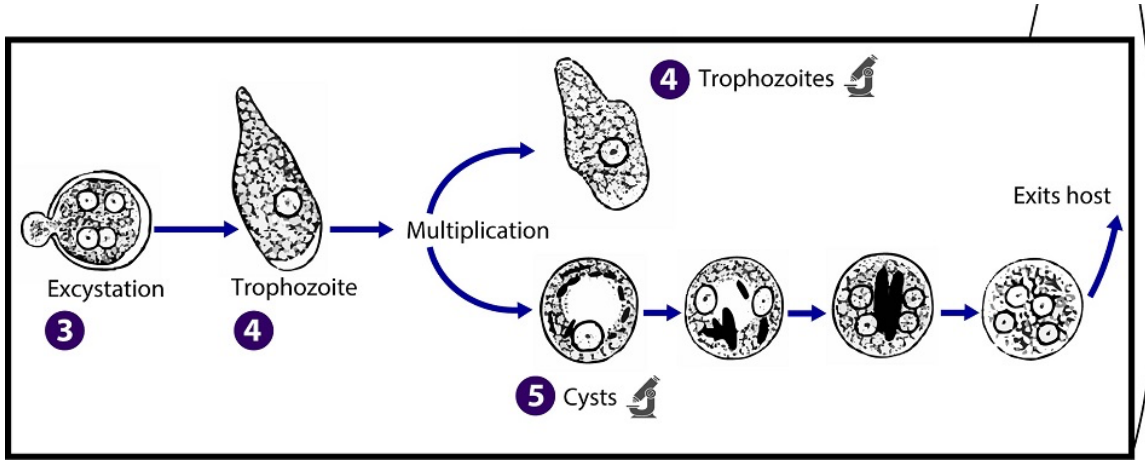
Four species

1. **Entamoeba hystolica**
2. Entamoeba dispar
3. Entamoeba moshkovskii
4. Entamoeba Bangladeshi



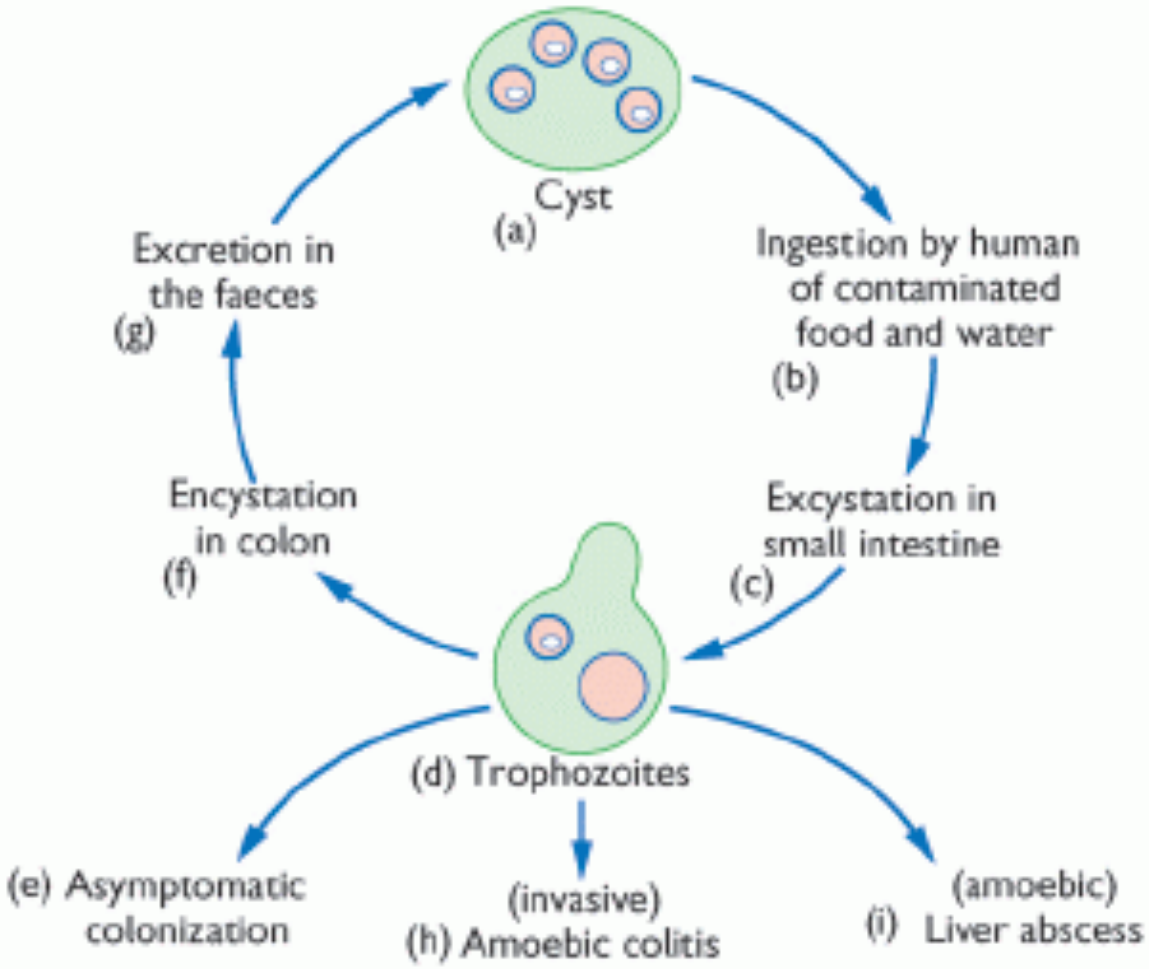
Amebiasis

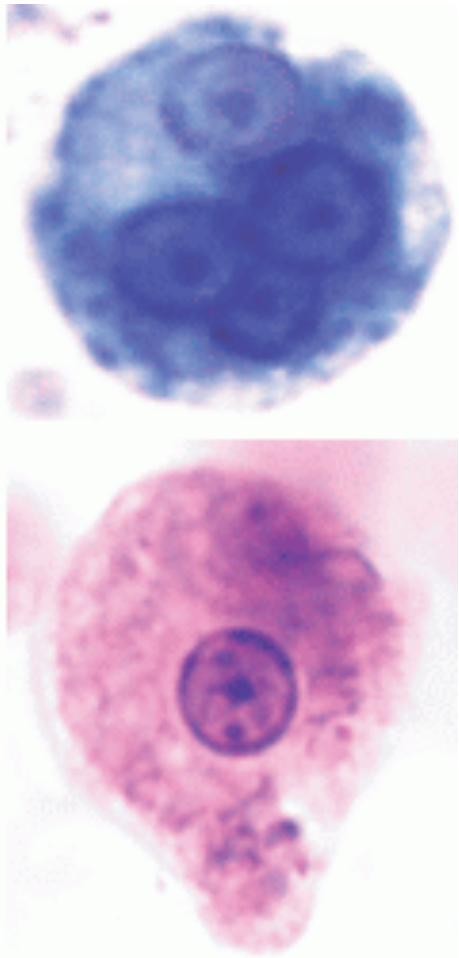

2 Mature cysts ingested
C
A
B
Infective stage
Diagnostic stage
A Noninvasive colonization
B Intestinal disease
C Extraintestinal disease
1
Cysts and trophozoites passed in feces


4 Trophozoites
Exits host
Multiplication
Excystation
3
Trophozoite
4
5 Cysts

The lifecycle of Entamoeba histolytica is in two stages: cysts and trophozoites

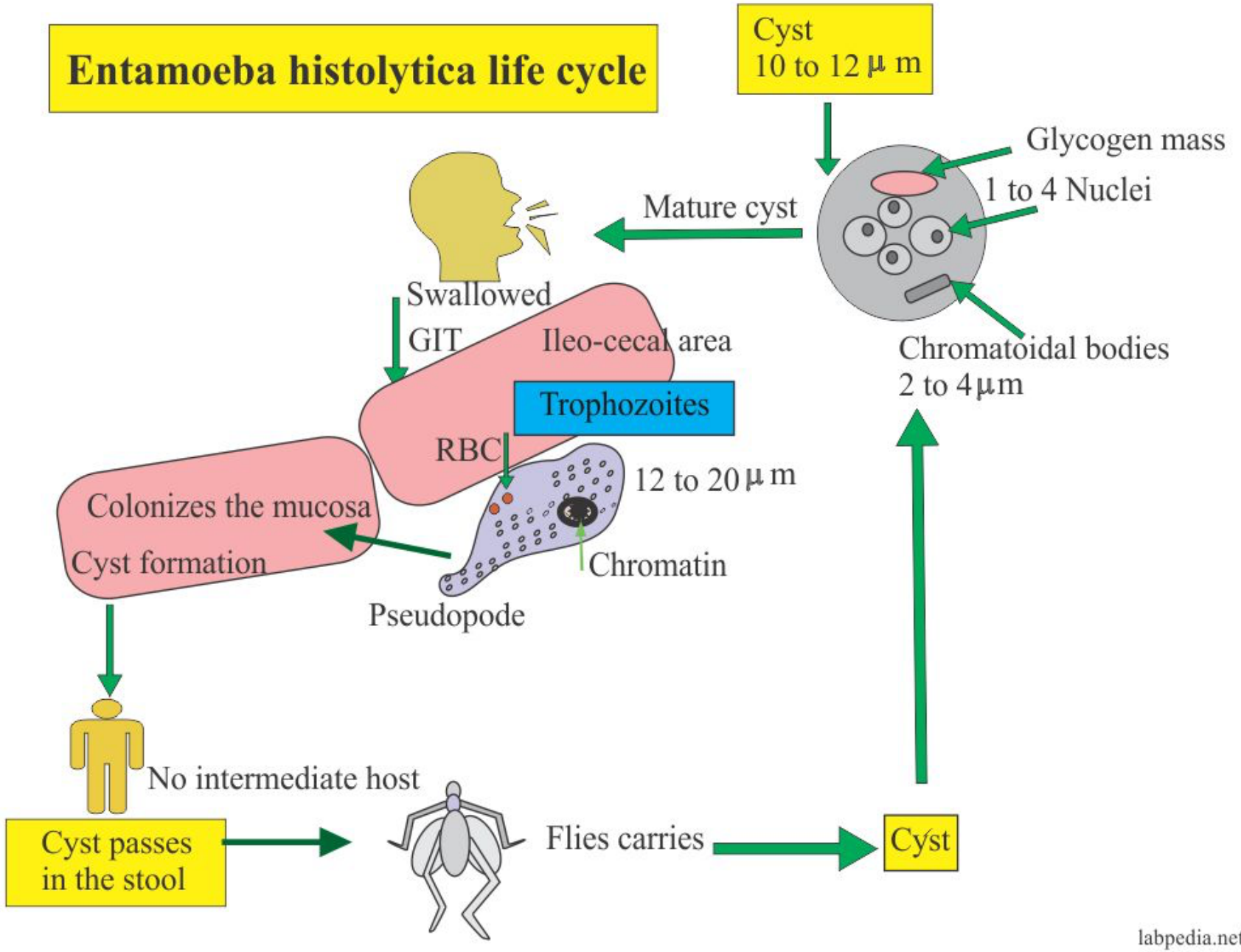
A



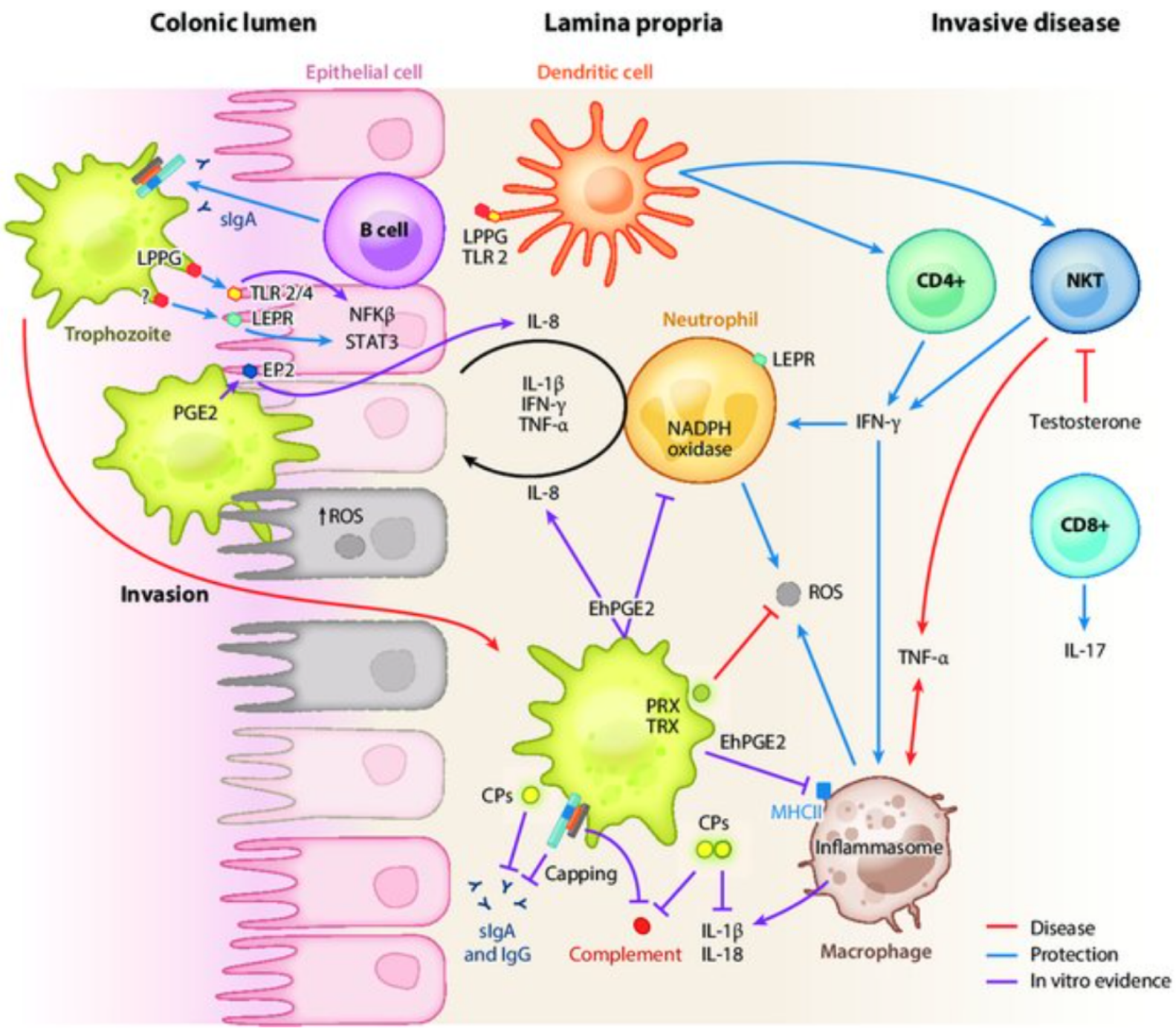


Huston CD, Haque R, Petri WA Jr. Expert Rev Mol Med. 1999

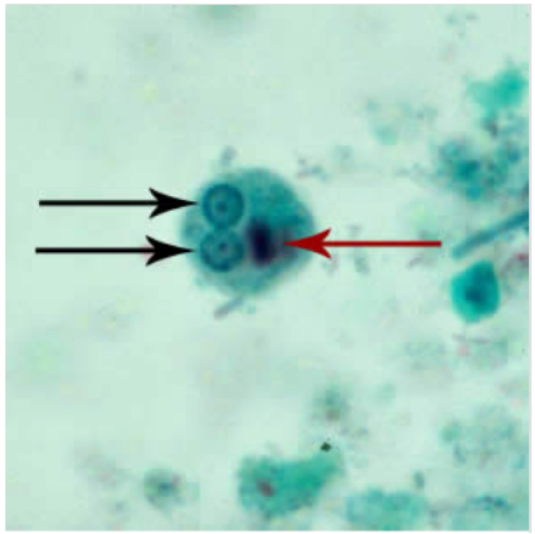
Entamoeba histolytica life cycle



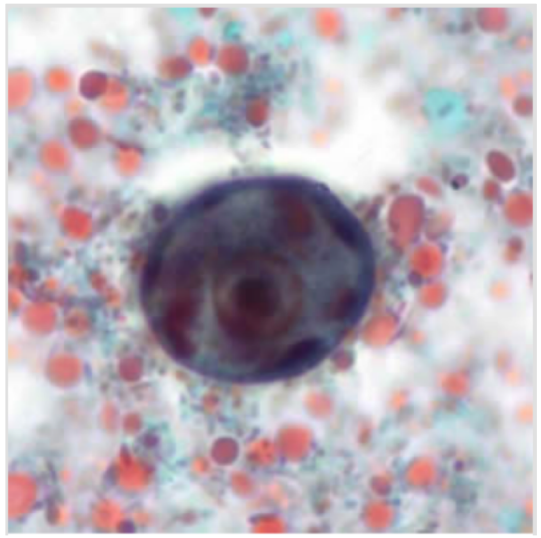
labpedia.net


Colonic lumen
Lamina propria
Invasive disease
Epithelial cell
Dendritic cell
sIgA
B cell
LPPG
TLR 2/4
LEPR
NFKβ
STAT3
Trophozoite
EP2
PGE2
IL-8
Neutrophil
LEPR
IL-1β
IFN-γ
TNF-α
NADPH oxidase
IL-8
LPPG
TLR 2
CD4+
NKT
IFN-γ
Testosterone
CD8+
IL-17
↑ROS
Invasion
EhPGE2
ROS
TNF-α
PRX
TRX
EhPGE2
CPs
MHCII
Inflammasome
CPs
Capping
sIgA
and IgG
Complement
IL-1β
IL-18
Macrophage
Disease
Protection
In vitro evidence

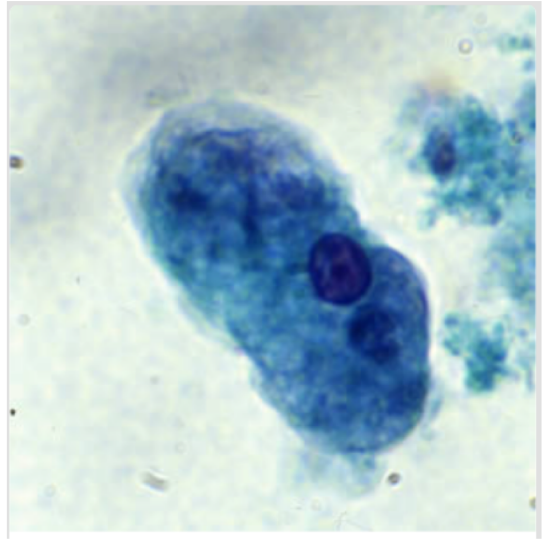
cysts



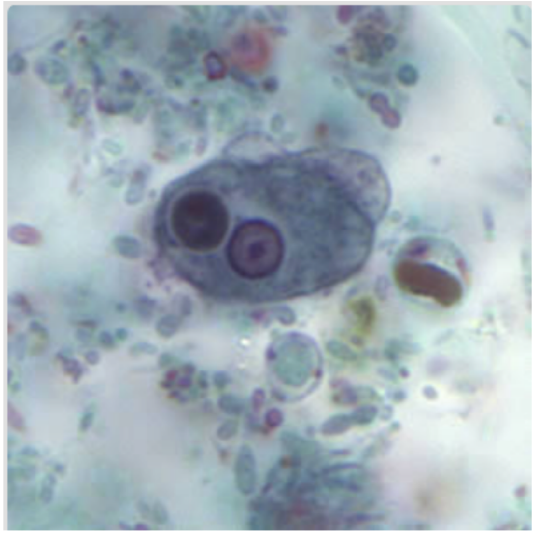
Immature cysts



Trophozoite



Trophozoites with ingested erythrocytes

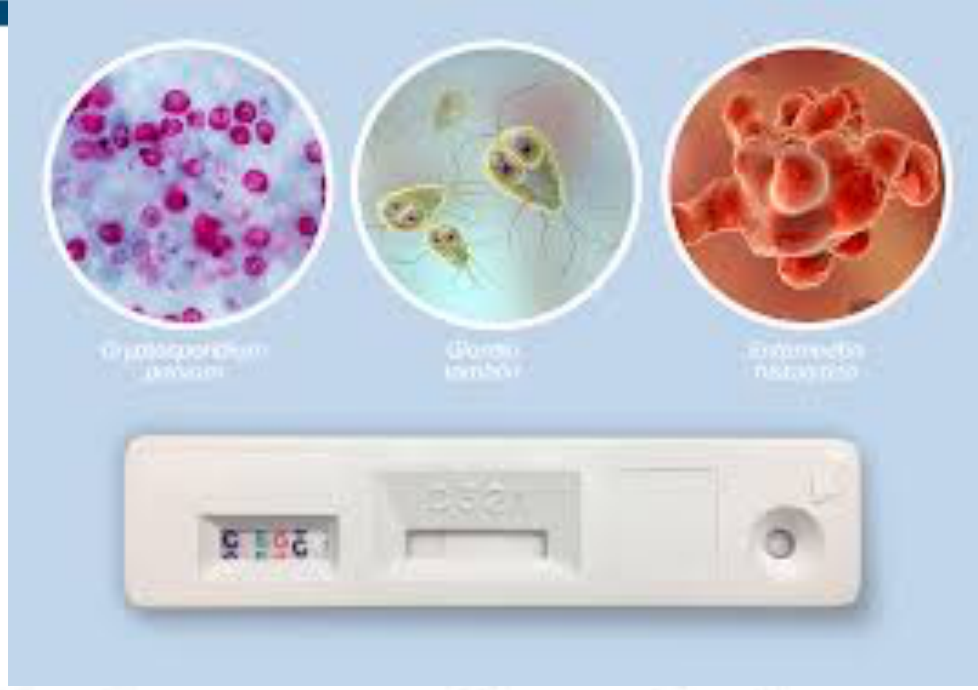


Laboratory Diagnosis

- Microscopic Detection
- Immunodiagnosis

1. Antibody detection

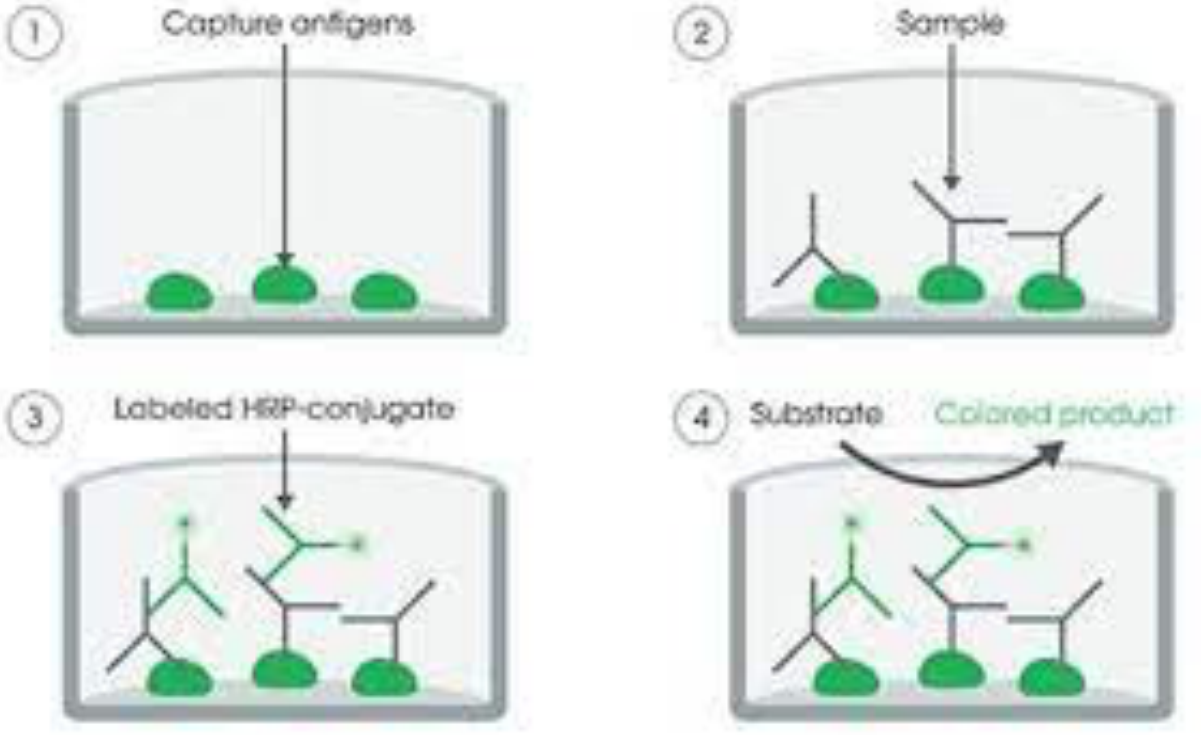
2. Antigen Detection

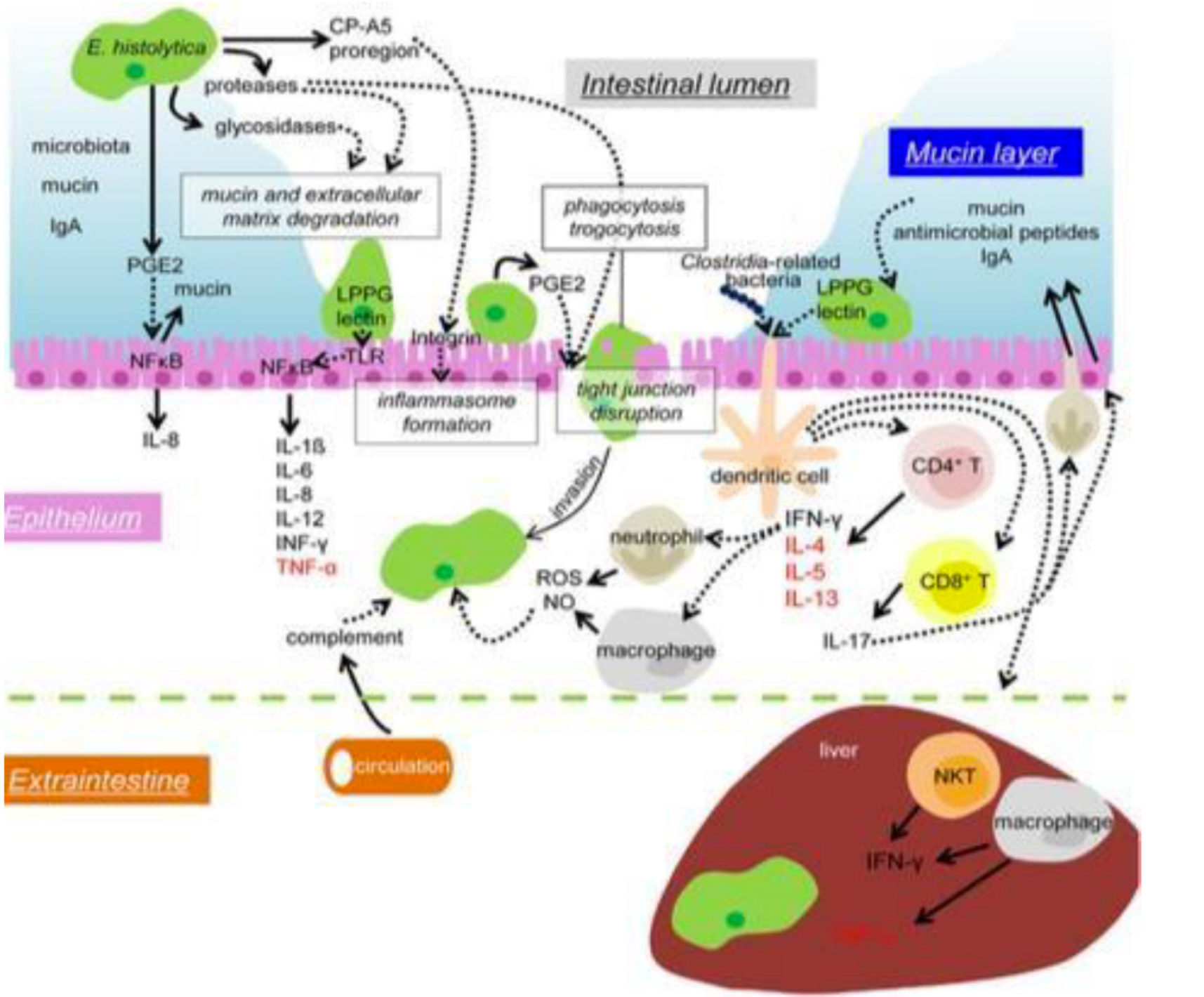


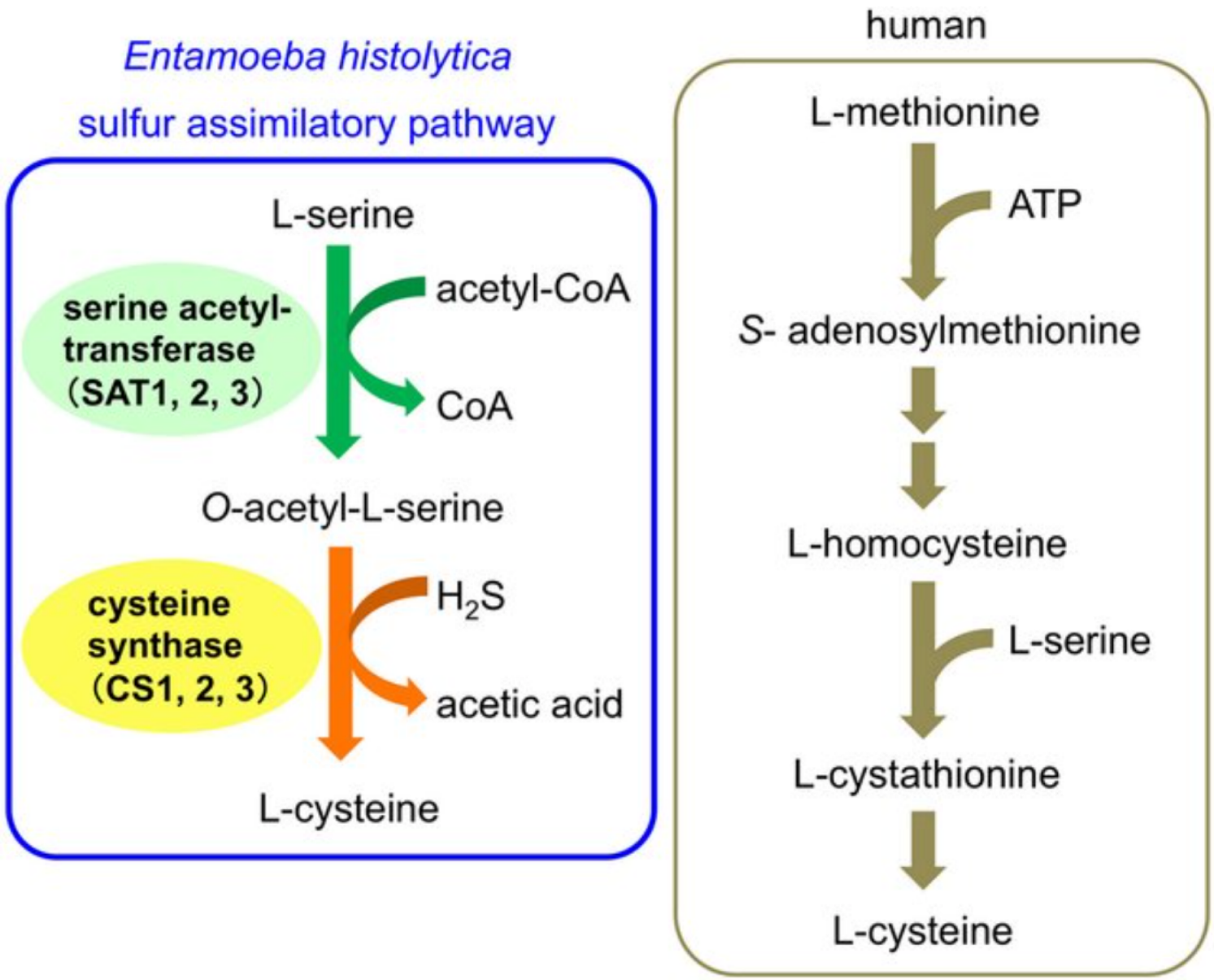
Molecular Diagnosis

- Conventional PCR

- Real-Time PCR

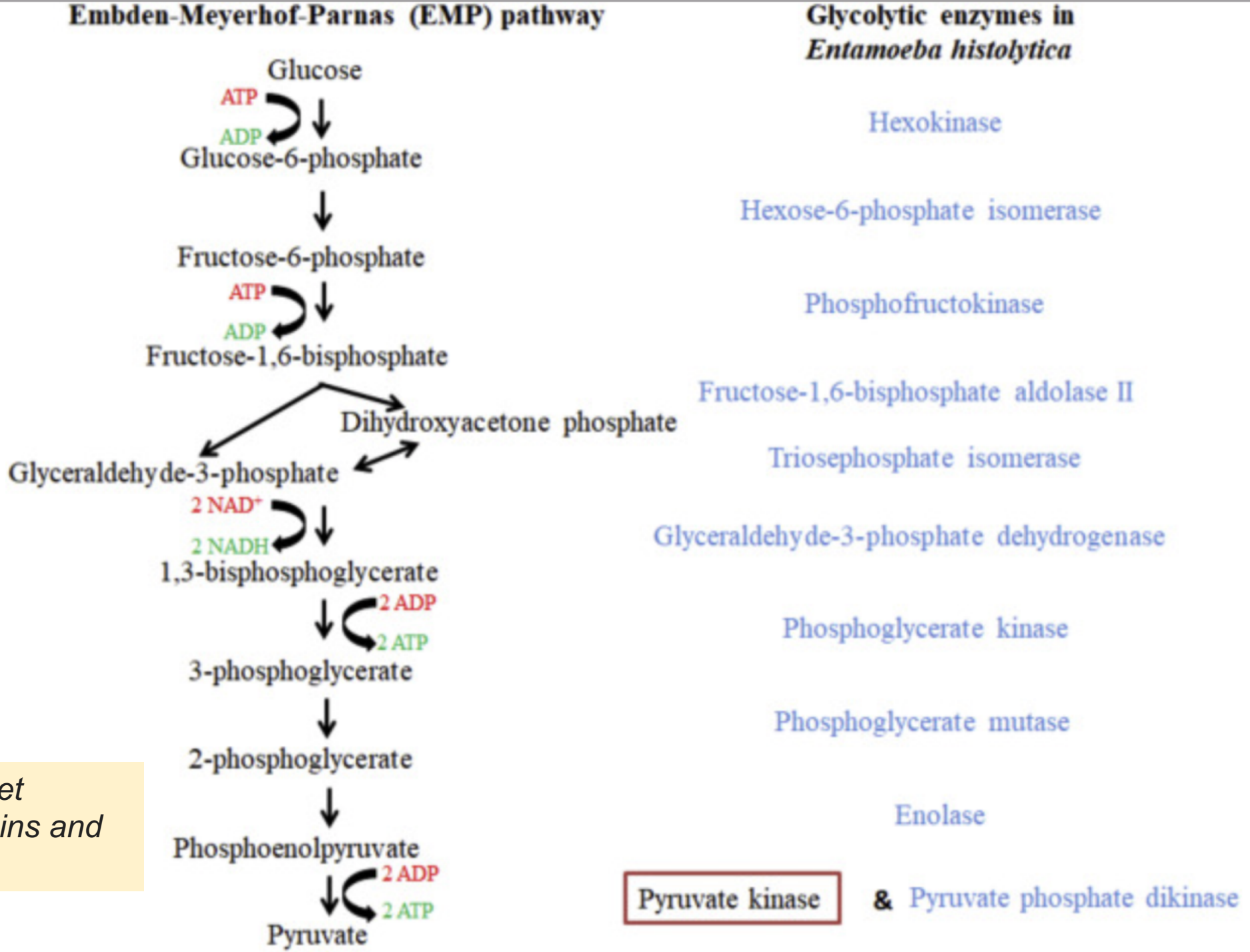



E. histolytica
CP-A5
proregion
proteases
glycosidases
Intestinal lumen
microbiota
mucin
IgA
mucin and extracellular
matrix degradation
phagocytosis
trogocytosis
Mucin layer
mucin
antimicrobial peptides
IgA
PGE2
mucin
LPPG
lectin
PGE2
Clostridia-related
bacteria
LPPG
lectin
Integrin
NFκB
NFκB
TLR
inflammasome
formation
tight junction
disruption
IL-8
IL-1ß
IL-6
IL-8
IL-12
INF-γ
TNF-α
dendritic cell
CD4+ T
Epithelium
invasion
neutrophil
IFN-γ
IL-4
IL-5
IL-13
ROS
NO
CD8+ T
complement
macrophage
IL-17
liver
NKT
macrophage
IFN-γ
Extraintestine
circulation



Mori, M., et.al., 2015.. *Frontiers in microbiology*,

The figure describes the **standard Embden-Meyerhof-Parnas glycolysis pathway** operating in *Entamoeba histolytica*



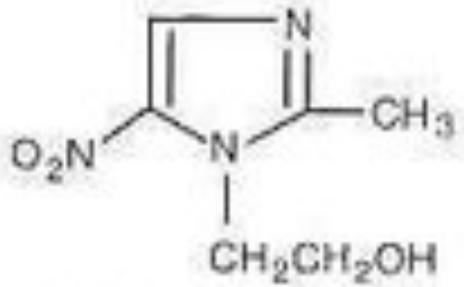
Kumari, P., et,al.,*Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, .

Therapy

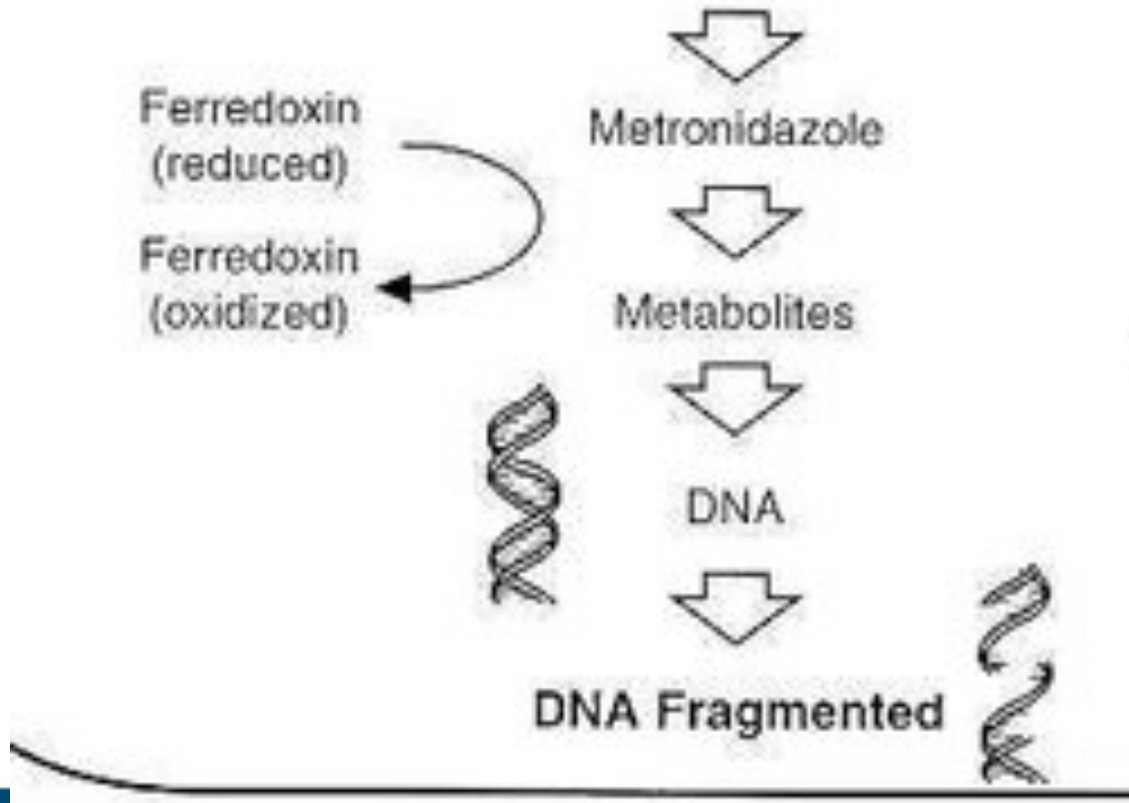
	Drug of Choice	Daily Dose	Duration, d	Alternatives
Tissue-active agent				
Amebic colitis[a]	Metronidazole or	750 mg po TID (35–50 mg/kg/d divided TID)	5–10	Nitazoxanide[b]
	Tinidazole	2 g po once daily (50 mg/kg once daily)	3–5	
Amebic liver abscess and disseminated amebic disease[a]	Metronidazole or	750 mg po TID (35–50 mg/kg/d divided TID)	10	-
	Tinidazole	2 g po once daily (50 mg/kg once daily)	5	
Luminal agent				
Asymptomatic carriage or following tissue-active agent	Paromomycin	25–35 mg/kg/d by mouth divided TID	7	Iodoquinol/diiodohydroxyquin diloxanide furoate[c]

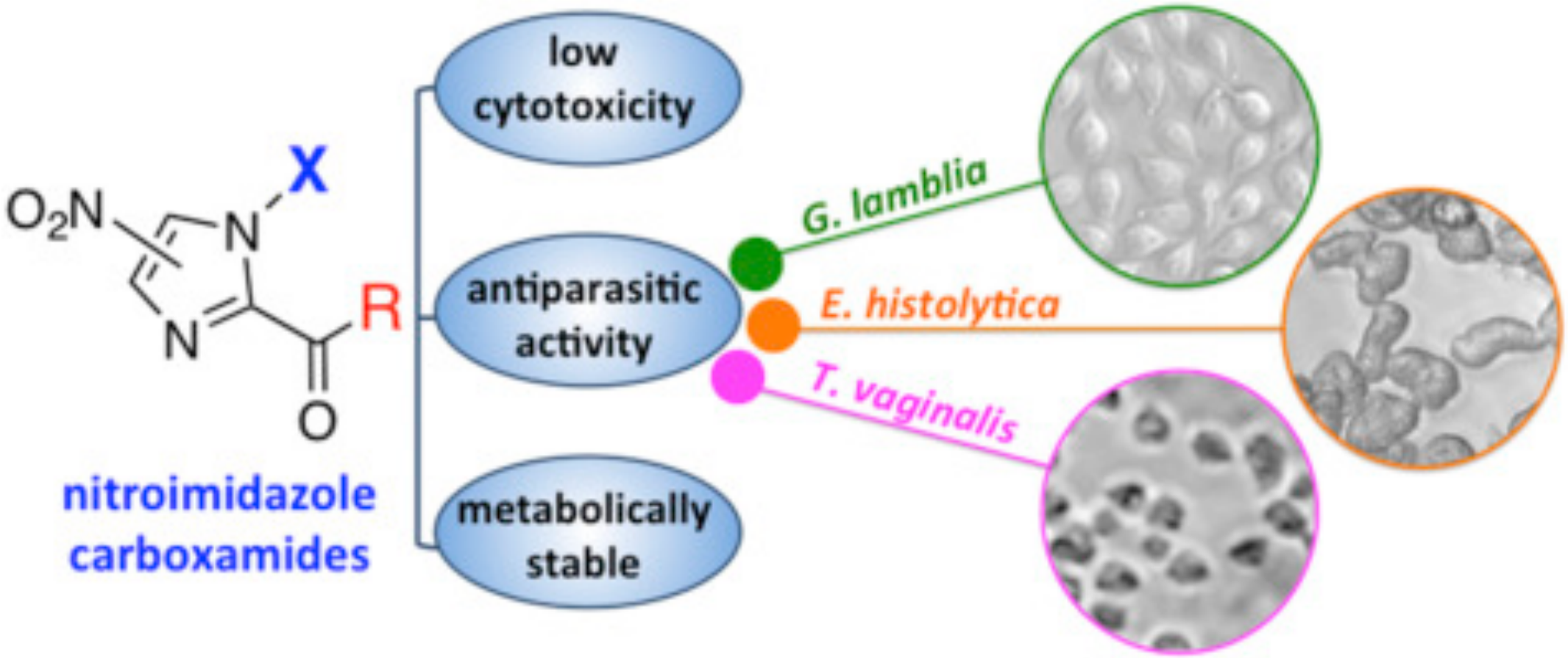
Metronidazole

- Metronidazole kills **trophozoites** of Entamoeba histolytica in intestines and tissue but does not eradicate cysts from intestines.
- It appears to be absorbed into cells.
- **Intermediate metabolized** compounds are formed and **bind DNA** and **inhibit protein synthesis**, causing cell death.
- Antimicrobial effect may be due to production of free radicals.
- Metronidazole is indicated for invasive amebiasis

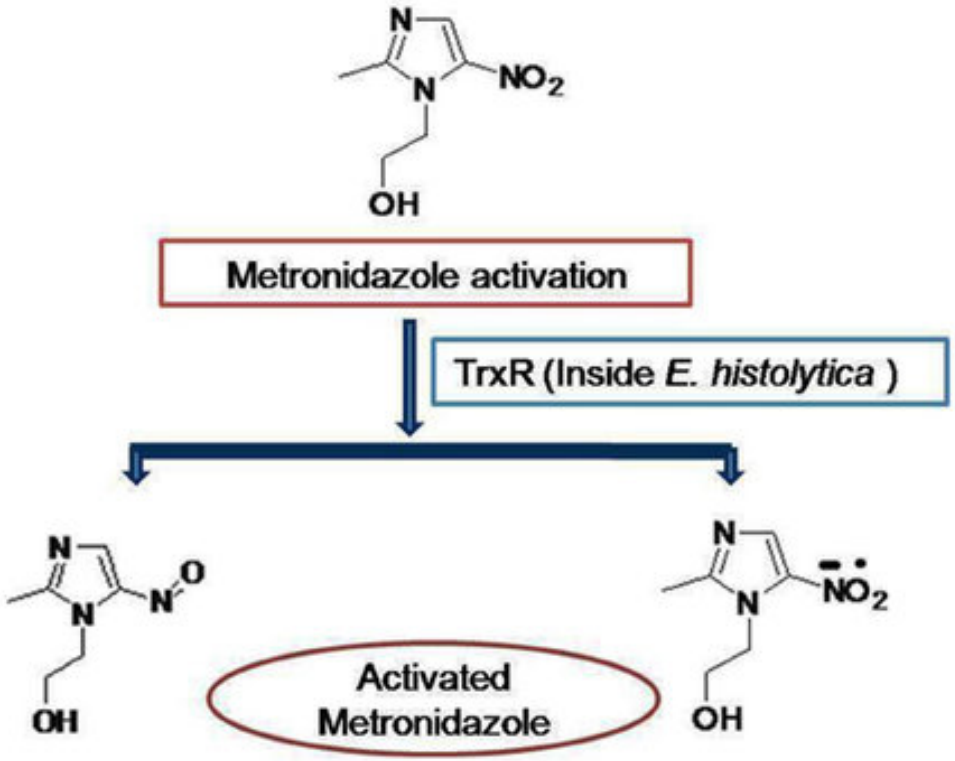


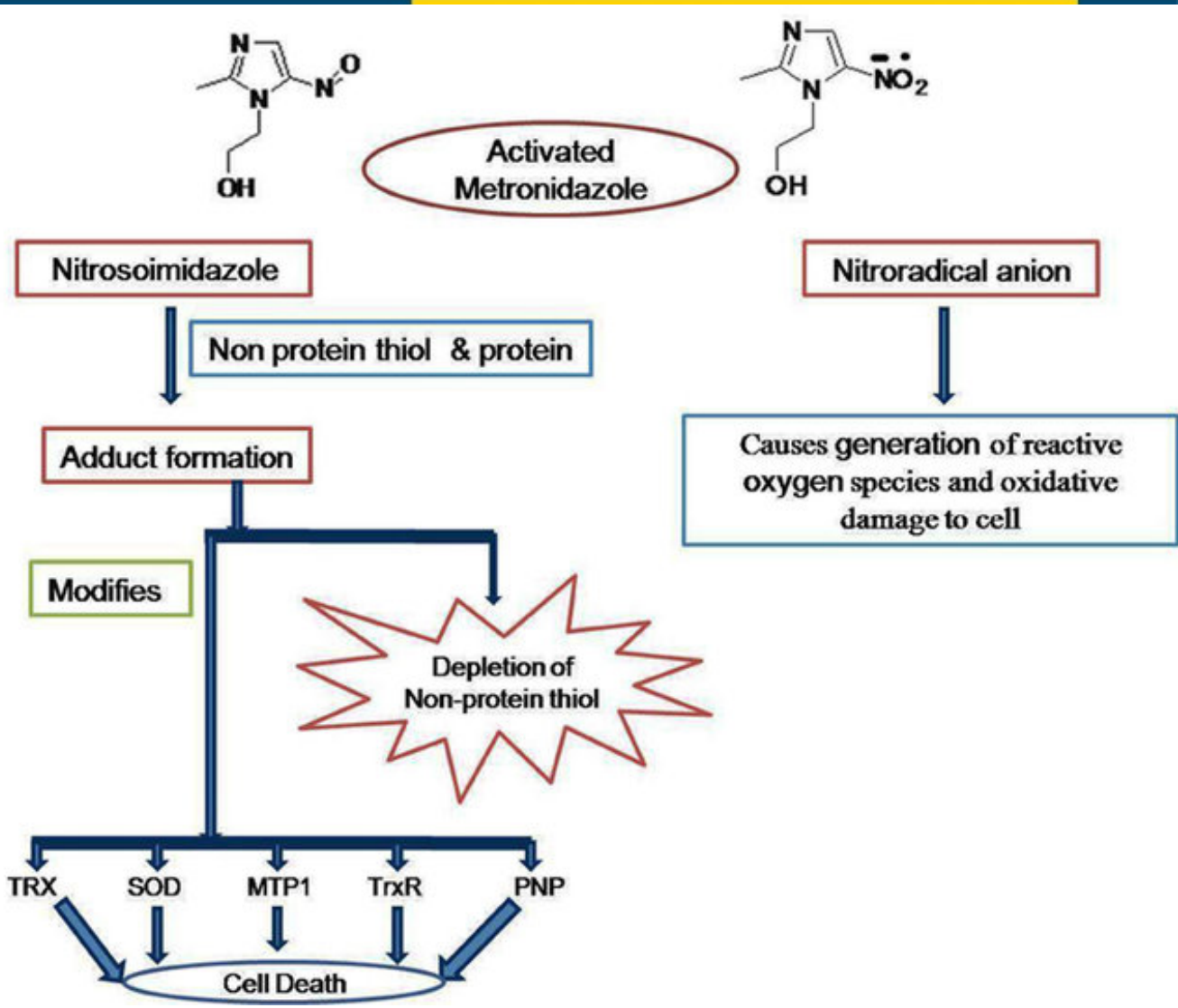
Metronidazole





Jarrad, A.M., etal., *European journal of medicinal chemistry*,



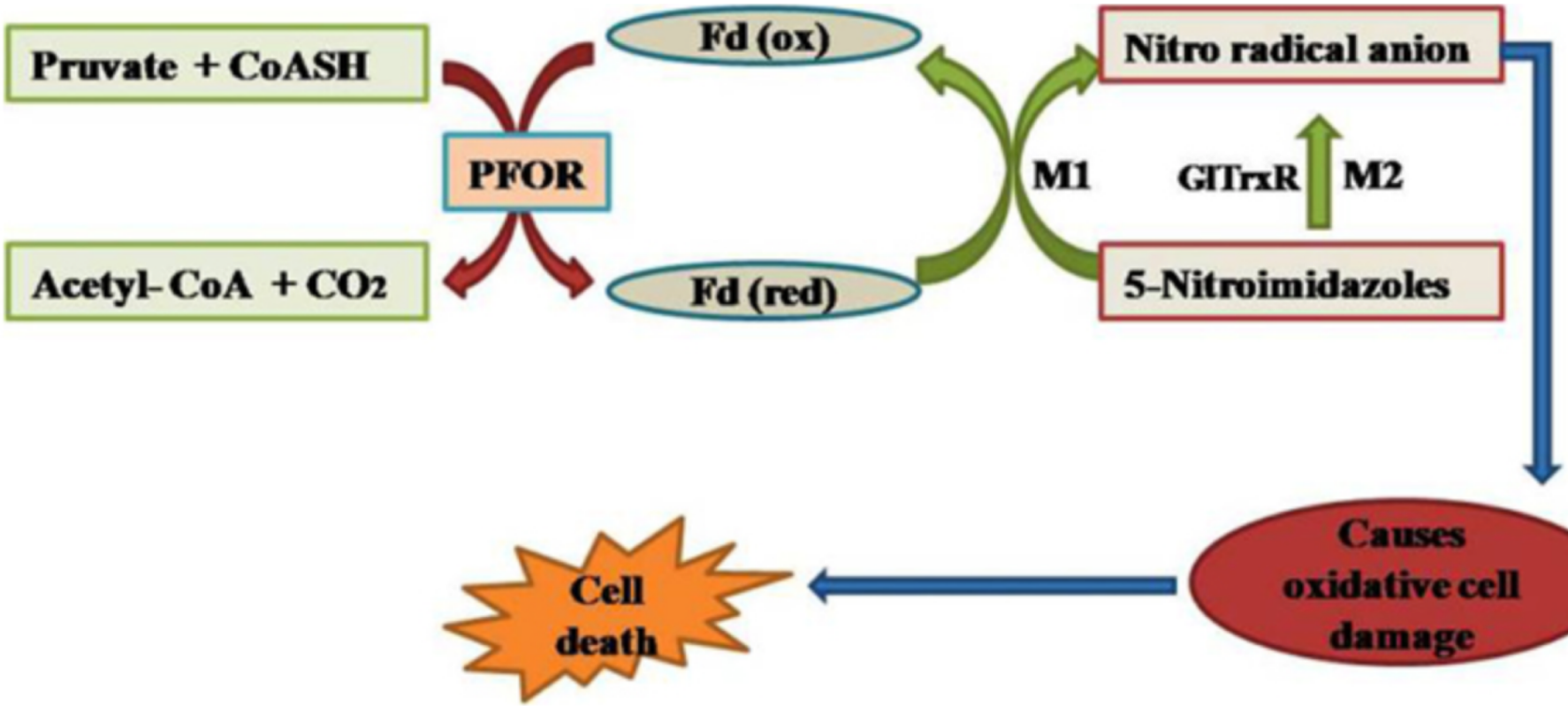


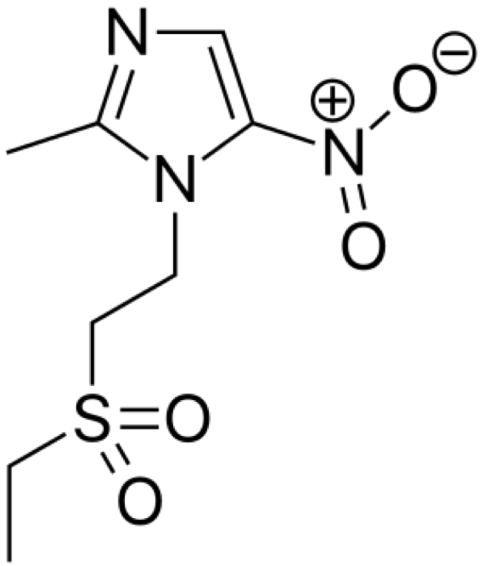
Azam, A., Peerzada, M.N. and Ahmad, K., 2015. *Frontiers in microbiology*, *6*, p.1183.

Tinidazole

Tinidazole is in a class of medications called nitroimidazole antimicrobials. trichomoniasis, giardiasis, amebiasis, and bacterial vaginosis.

It **works** by killing the organisms that can cause infection

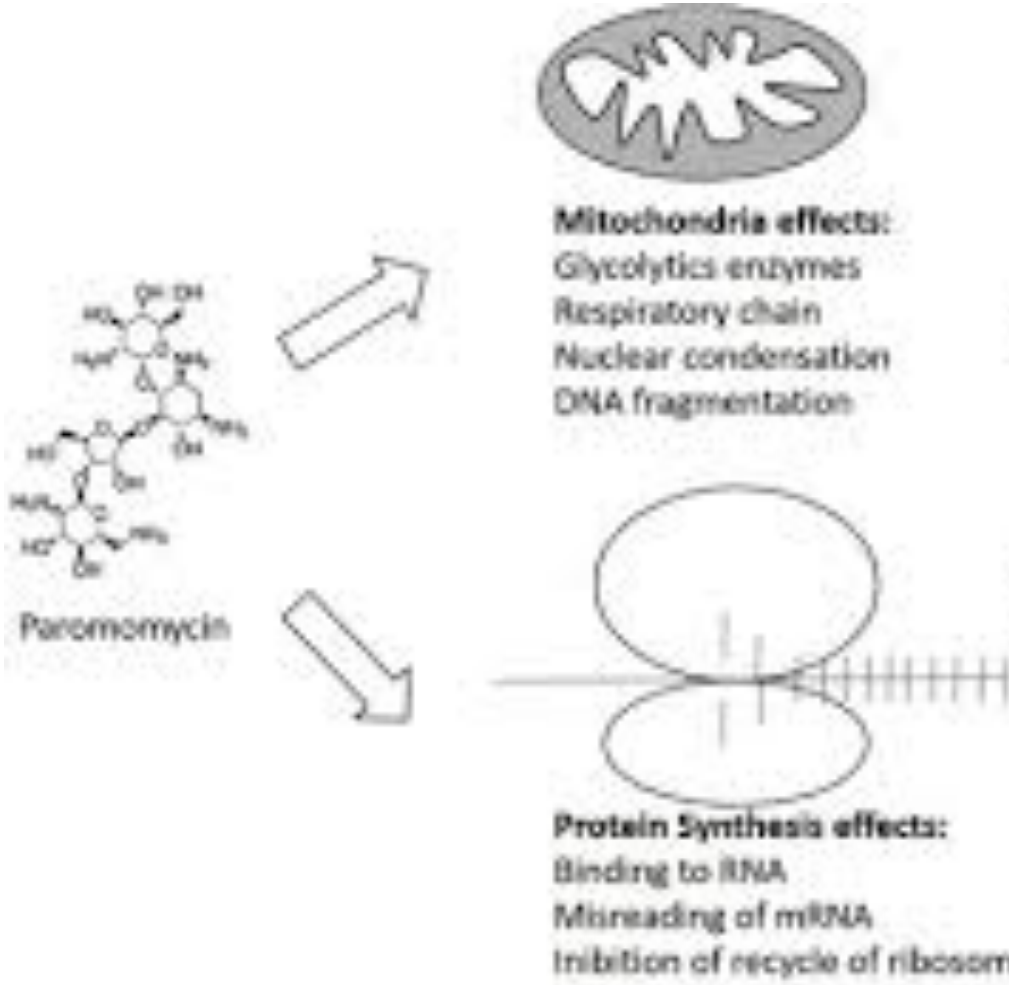




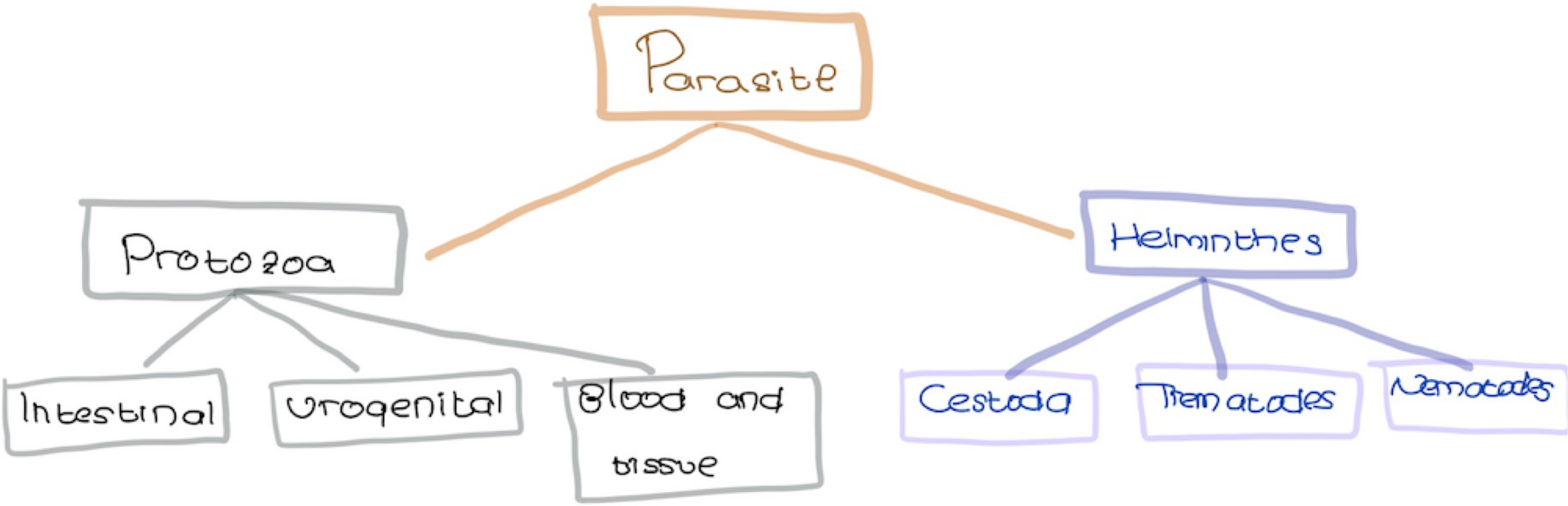
Paromomycin

- Paromomycin is an amebicidal and antibacterial aminoglycoside obtained from a strain of Streptomyces rimosus;
- Used to eradicate **cysts of E histolytica** after treatment with metronidazole or tinidazole for invasive disease

- **Paromomycin** inhibits protein synthesis by binding to 16S ribosomal RNA.



Classification



Protozoa

Intestinal

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- Giardia lamblia
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Urogenital

- Trichomonas vaginalis

Blood and tissue

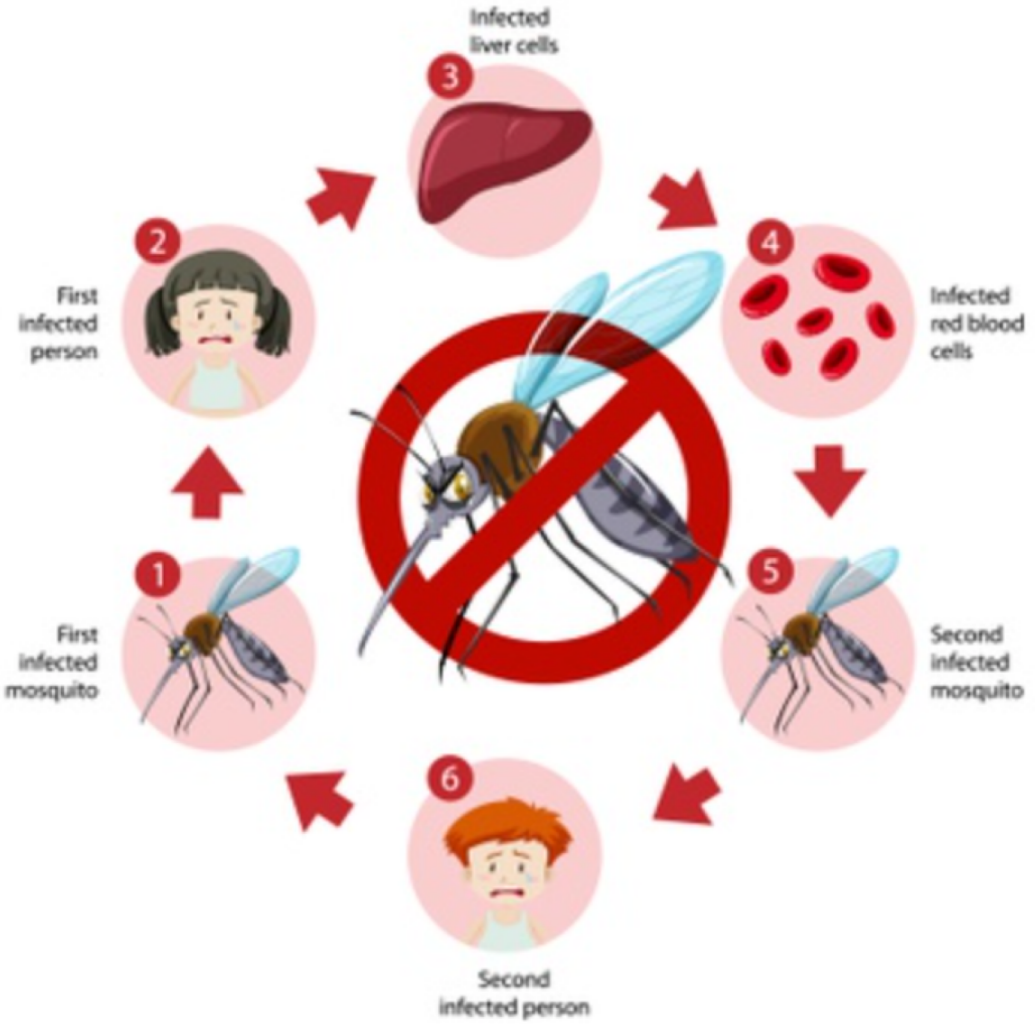
- Malaria Toxoplasma
- Trypanosoma
- Leishmania .

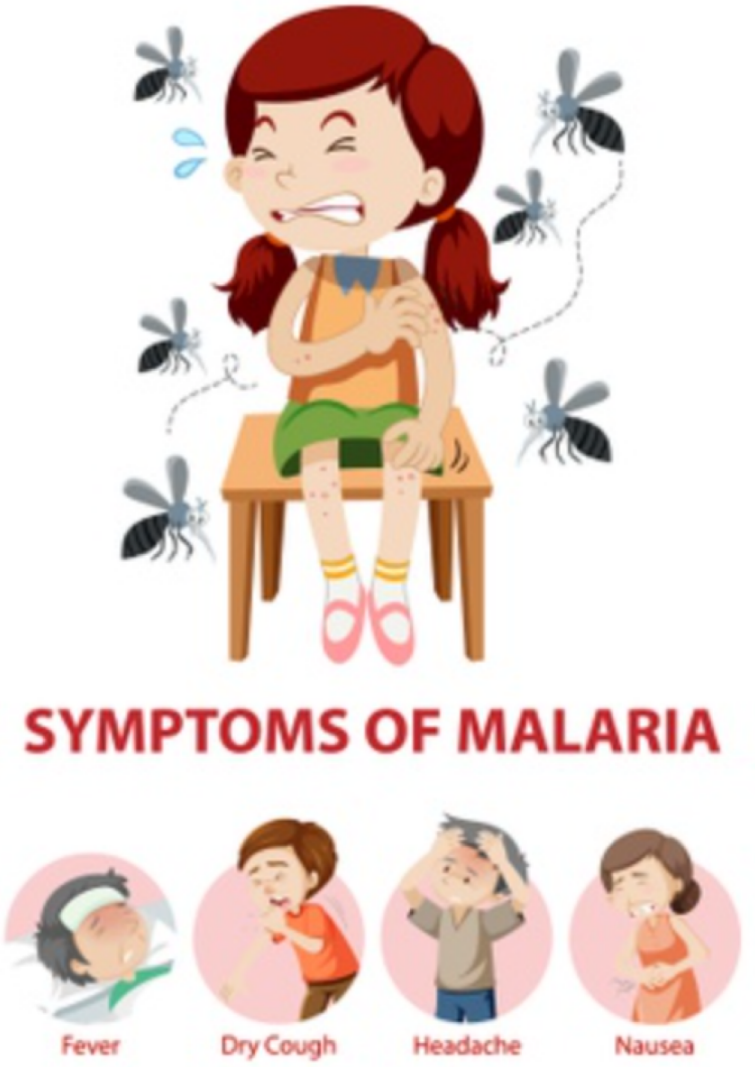
ANTIMALARIA

- Malaria:
  - Tropika ⇨ *P. falcifarum*
  - Tertiana ⇨ *P. vivax*
  - Kuartana ⇨ *P. malariae*
- Manusia ⇨ hospes tetap
- Nyamuk anopheles ⇨
  - Vektor
  - Hospes definitif/sementara

- ***Plasmodium falciparum*** merupakan penyebab malaria tropika. Plamodium ini mempunyai masa sporulasi (masa pembentukan spora) sekitar 1 hari (1 x 24 jam).
- ***Plasmodium vivax*** merupakan penyebab penyakit malaria tertiana. Masa sporulasinya setiap 2 x 24 jam.
- ***Plasmodium malariae*** merupakan penyebab penyakit malaria quartana. Masa sporulasinya setiap 3 x 24 jam.
- ***Plasmodium ovale*** merupakan penyebab penyakit limpa. Masa sporulasinya setiap 48 jam.

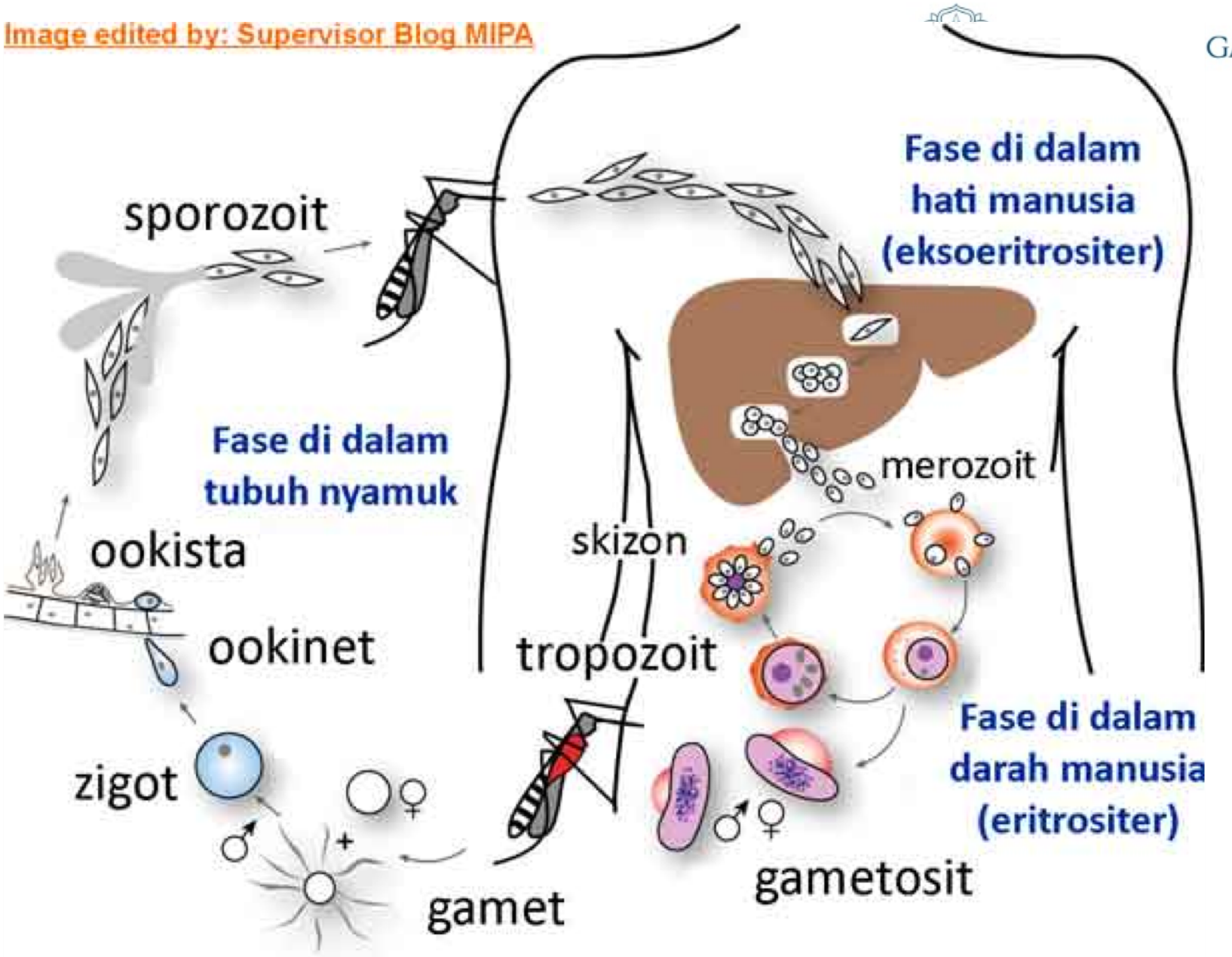
MALARIA TRANSMISSION CYCLE





https://www.freepik.com/free-vector/malaria-transmission-cycle-symptom-information-infographic_11206857.htm#&position=0

Tissue stage form plasmodia



Klasifikasi Antimalaria

1. Skizontosid jaringan dan darah
   - Bekerja thdp merozoit (fase eritrosit)
   - Tdk terbentuk skizon baru ⇨ tdk tjd penghancuran eritrosit ⇨ mengendalikan serangan klinik
   - Klorokuin, kuinin, meflokuin
   - Bekerja jg pd skizon yg br memasuki jar hati ⇨ Tahap infeksi eritrosit dpt dicegah ⇨ terapi kausal
     - Pirimetamin, primakuin
   - Skizontosid kerja cepat: Halofantrin

2. Gametosid
- Membunuh gametosid dlm eritrosit
- Klorokuin, kuinin, meflokuin ⇨ *P. vivax, P. malariae*
- Primakuin ⇨ *P. falcifarum*

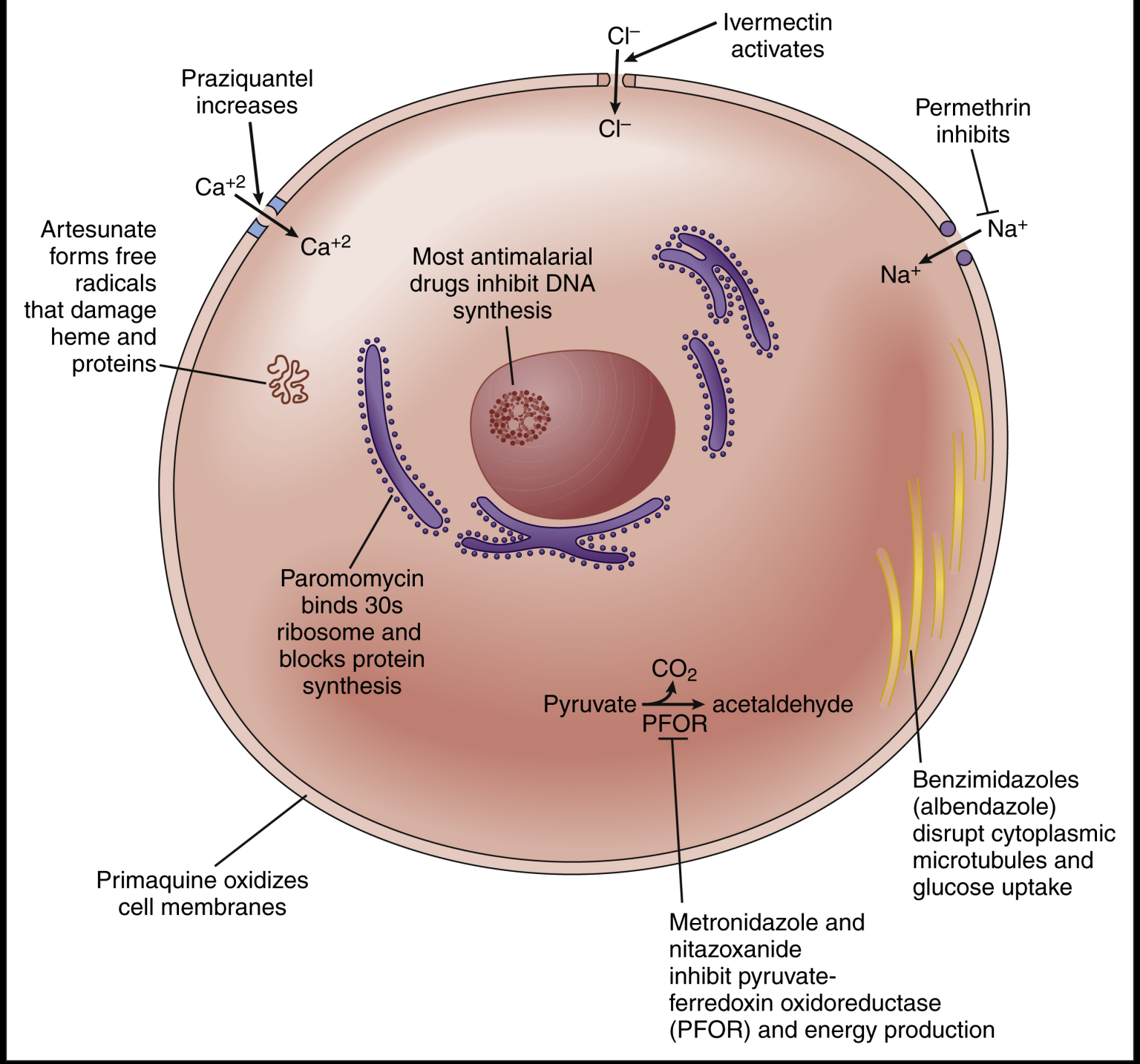
3. Sporontosid
- Menghambat perkembangan gametosit
- Rantai penularan terputus
- Primakuin, kloroguanid

Mekanisme

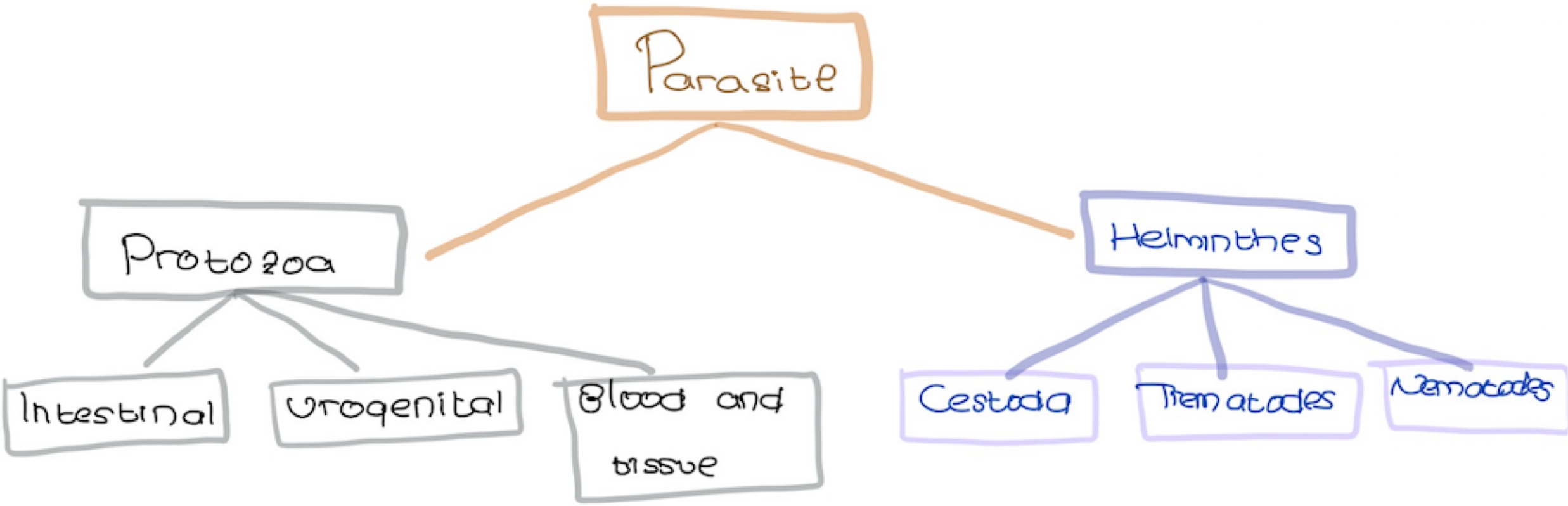
- Menghambat DNA-polimerase & RNA-polimerase
  - Berikatan dgn guanin rantai DNA
  - Obat terakumulasi pd eritrosit nyamuk *anopheles*
  - Klorokuin, primakuin, kuinin, meflokuin
- Menghambat enzim dihidrofolat reduktase plasmodia ⇨ pembelahan inti pd pertumbuhan skizon di hati terhambat krn sintesis DNA terhambat
  - Pirimetamin
- Menghancurkan *tissue stage form* plasmodia
  - Primakuin

- Mengikat folat dlm tubuh nyamuk
  - Proguanil, kloroguanid

- Menghambat sintesis protein dlm tubuh nyamuk: artemisinin


Cl⁻
Ivermectin activates
Cl⁻
Praziquantel increases
Ca+2
Ca+2
Permethrin inhibits
Na+
Na+
Artesunate forms free radicals that damage heme and proteins
Most antimalarial drugs inhibit DNA synthesis
Paromomycin binds 30s ribosome and blocks protein synthesis
CO2
Pyruvate
PFOR
acetaldehyde
Primaquine oxidizes cell membranes
Benzimidazoles (albendazole) disrupt cytoplasmic microtubules and glucose uptake
Metronidazole and nitazoxanide inhibit pyruvate-ferredoxin oxidoreductase (PFOR) and energy production

Classification



Antelmintik

- Pengertian
- Diagnosis
- Jenis & Mekanisme Antelmintik

Infestasi campuran c. tambang (*A. duodenale, A. lumbricoides*) & c. gelang (*N. americanus*)

- Befenium hidroksinaftoat
- Menyebabkan paralisis otot cacing krn kepekaannya thdp asetilkolin hilang
- Irreversibel
- Ccg keluar bersama tinja

- Levamisol
- Isomer dr tetramisol
- Menghambat transmisi neuromuskular ccg

- Paralisis otot ⇨ mati
- Ccg keluar bersama tinja

- Infestasi c. tambang (*A. lumbricoides*) & c. kremi (*E. vermicularis*)

- Piperazin
- Memblokade respon otot cacing thdp asetilkolin dgn mengganggu permeabilitas membran sel thdp asetilkolin & ion-ion yg berperan dlm kontraksi otot shg tjd paralisis
- Cacing mudah dikeluarkan oleh peristaltik usus
- Tdk perlu pencahar

- Infestasi c. tambang (*A. lumbricoides*), c. kremi (*E. vermicularis*) & c. gelang

- Pirantel pamoat
- Meningkatkan frekuensi impuls syaraf shg cacing mati dlm keadaan spasme

Filariasis (*W. bancrofti, B. malayi, Loa loa*)

- Dietilkarbamazepin
- Menyebabkan perub pd membran mikrofilaria
- Mudah dihancurkan proteolitik hospes
- Keluar dr peredaran drh

- Rx alergi dpt timbul sbg akibat dr matinya parasit/substansi yg dilepaskan oleh mikrofilaria yg hancur
- Alergi ringan – berat
- Kombinasi antihistamin- kortikosteroid

Infestasi c. pita (*T. saginata, T. solium*)

- Diklorofen
- Taeniasis kucing, anjing, manusia
- Segera sesdh obat diberikan, skoleks c. pita terlepas dr mukosa usus, ccg mati, dicerna usus

- Segmen ccg bercampur tinja ⇨ hsl terapi sukar ditentukan
- Pengobatan lanjutan

- Autoinfeksi dr telur yg dibebaskan oleh segmen ccg

Infestasi c. pita (*T. saginata, T. solium, Cestoda*)

- Niklosamid
- Menghambat fosforilasi anaerob ADP ⇨ ATP
- Tdk merusak telur dlm segmen

- Telur msk lumen usus
- Perlu pencahar

Infestasi *Cestoda & Trematoda*

- Prazikuantel
- Mekanisme:
  - Menyebabkan hilangnya ion Ca intrasel shg timbul paralisis yg bersifat reversibel
  - Menyebabkan tjd vesikulasi cacing shg tjd kehancuran cacing
- Efektif utk cacing dewasa (jantan-betina) & cacing imatur

Infestasi cacing campuran

- Mebendazol, Tiabendazol, Albendazol
- Antelmintik dgn spektrum paling luas
- C. gelang, c. kremi, c.pita, c. tambang, *T. trichiura*
- Mekanisme:
  - Menghambat masukan glukosa ke dlm sel ccg
  - Menghambat sekresi asetilkolin ccg
  - Menimbulkan sterilitas pd telur ccg
- Cacing mati perlahan, hasil terapi nampak sesdh 3 hr pemberian obat

ROLE OF VECTOR

Vector, a Latin word meaning "carrier“
Imp in transmission of parasite
No direct damage by vector
The *Anopheles* mosquito transmit Malaria,
Sandfly is vectors for Leishmaniasis
Domestic cats-vector of *Toxoplasma gondii, Echinococcus granulosis*

- Diagnosis of parasitic diseases depends on several laboratory methods, imaging techniques and endoscopy in addition to clinical picture and geographic location. Parasitic diseases may be presented by a wide variety of clinical manifestations according to the tissue invaded. Direct microscopy is based on detection of the parasite by examination of different specimens (stool, urine, blood, CSF and tissue biopsies).
- **Immunodiagnostic** techniques include antigen and antibody-detection assays.
- Molecular-based diagnostic approaches offer great sensitivity and specificity. Recently, nanotechnology can be applied as diagnostic procedures utilizing nanodevices. Control and prevention of parasitic diseases depend on the interactions among many factors
- such as the environment, the human behavior, and socio-cultural factors that determine transmission and persistence of parasites.

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TUGAS

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