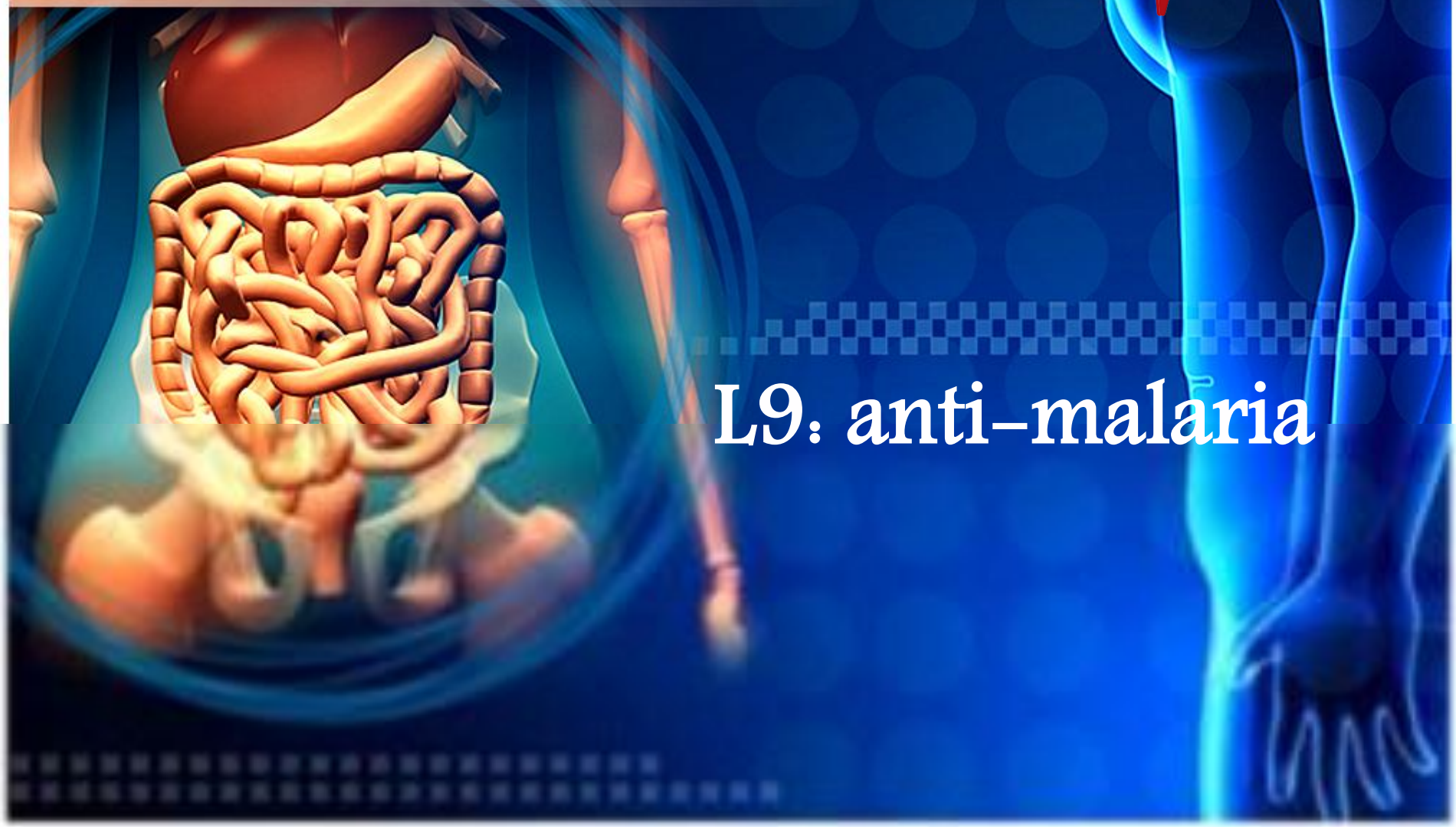
King Saud University
College of Medicine
2nd Year, 2nd Block

GIT BLOCK

PHARMACOLOGY 433

MED 433 Teams

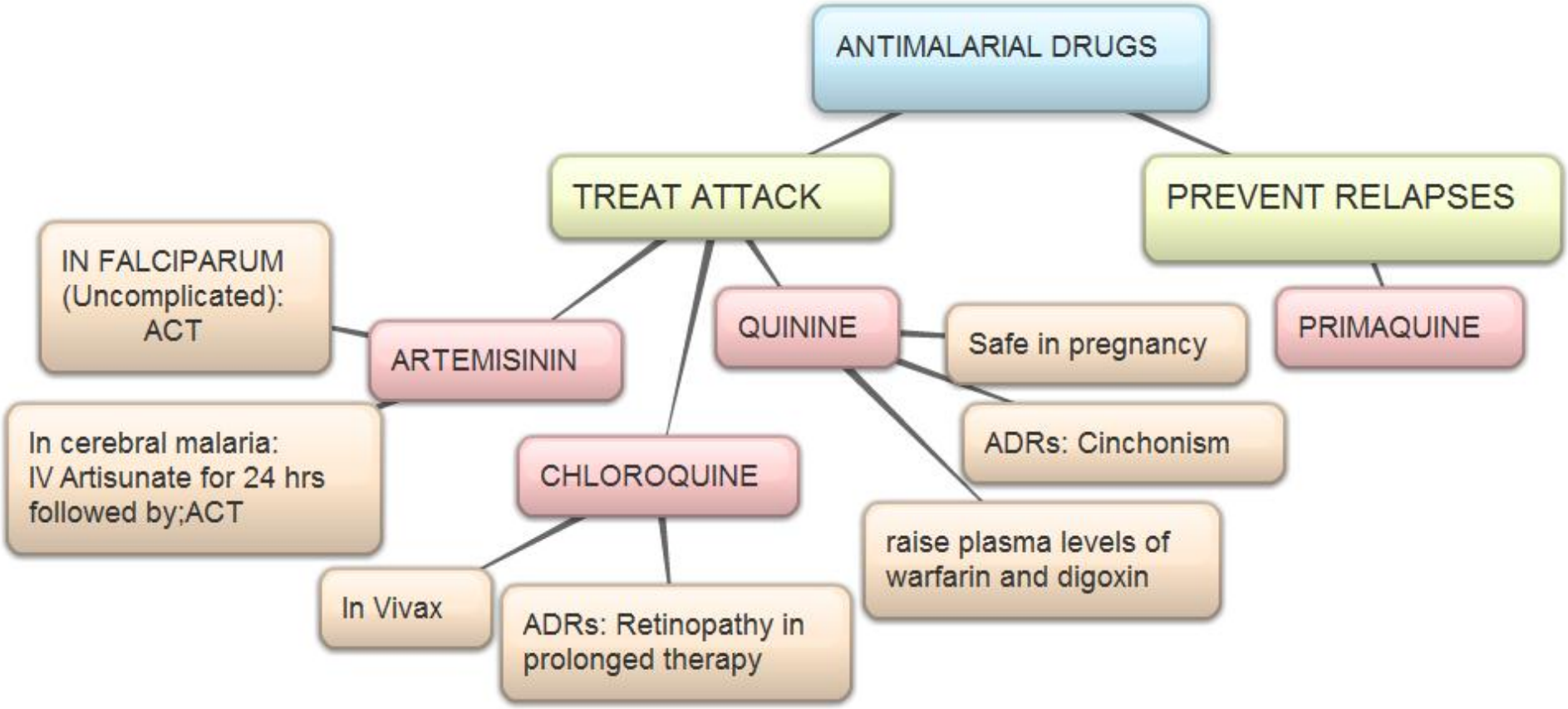


L9: anti-malaria

Objectives

- Classify the main antimalarial drugs depending on their target of action
- Detail the pharmacokinetics & dynamics of main drugs used to treat
  attack or prevent relapses
- Compare the mechanism and major ADRs of adjunctive drugs used in
  combinations
- State the WHO therapeutic strategy for treatment

Mind map


ANTIMALARIAL DRUGS
TREAT ATTACK
PREVENT RELAPSES
IN FALCIPARUM (Uncomplicated): ACT
ARTEMISININ
In cerebral malaria: IV Artisunate for 24 hrs followed by;ACT
QUININE
Safe in pregnancy
ADRs: Cinchonism
raise plasma levels of warfarin and digoxin
PRIMAQUINE
CHLOROQUINE
In Vivax
ADRs: Retinopathy in prolonged therapy

Target of the therapy

Blood schizontocidal drugs

To alleviate symptoms

- ✓ Artemisinin
- ✓ Chloroquine (in vivax only)
- ✓ Quinine (in pregnancy)

Tissue hypnotocidal (schizontocidal) drugs

To prevent relapses

- ✓ Primaquine

Gametocidal drugs

To prevent spread

- ✓ Primaquine

N.B. If patient has got infested by sporozoites ➔ we want to protect against progression to Tissue Shizontocides ➔ Primaquine

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1) ARTEMISININ and its derivatives (ARTENUSATE & ARTEMETHER)

*Affect all forms including multi-drug resistant *P. falciparum*

Action	**blood Schizontocide* (& rarely resistant except in Cambodia-Thailand border)**

Pharmaco kinetics

- Absorbed orally
- Biotransform in liver into Artenimol → active.
- Widely distributed
- Most used drug.

▪ t½	Artemisinin	Artesunate giving in acuteattack	Artemether
	4 hrs.	45 mins.	4-11 hrs.

Mechanism

Have endoperoxidase bridges→ cleaved by haem iorn →give free radicals →

- ✓ Alkylate membranes of parasite's food vacuole and mitochondria → no energy
- ✓ Irreversibly bind & inhibit sarco-ER Ca2+-ATPase of the parasite →inhibiting its growth
- ✓ Inhibiting formation of transport vesicles →no food vacuoles

ADR

1. Transient heart block
2. Decrease neutrophil count
3. Brief episodes of fever
4. Neuro, hepato and bone marrow toxicity (not given to a pregnant)

Preparations

- ✓ Should not be used as monotherapy
- ✓ IV or IM Artesunate in severe complicated cases as cerebral malaria (24h) followed by complete course of Artemisin-based combination therapies (ACTs)

Artemether + … (Artemisin-based combination therapies (ACTs)			
lumefantrine	amodiaquine	mefloquine	sulfadoxine-pyrimethamine

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DRUGS USED IN COMBINATIONS

(Artemisin-based combination therapies (ACTs))

DRUG	MECHANISM	ADRs
Lumefantrine	↓heme polymerase [like chloroquine]	Palpitation, dizziness,allergic reaction, hepatotoxicity
Amodiaquine		Nausea, vomiting, itching, stomach upset & headache.
Mefloquine		neuropsychiatric disorders
Sulfadoxine-pyrimethamine	Sequential block of dihydropteroate synthase & dihydrofolate reductase ↓ DNA synthesis	✓ Allergic skin reactions ✓ Agranulocytosis ✓ Aplastic anemia
Clindamycin	inhibits parasite apicoplast (needed for survival & successful host invasion)	✓ Skin rash ✓ Pseudo-membranous colitis
Doxycycline	Inhibit protein synthesis by binding to 30S subunit of ribosome	Yellowish discoloration of teeth, dental carries, bone deformity, vertigo, hypersensitivity

2) Chloroquine and Amodiaquine

*Safe in pregnancy

Action	✓ **Blood Schizontocide (except chloroquine-resistant plasmodium falciparum & viviax).** ✓ **Gametosidal .** ✓ **It is used also in rheumatoid artheritis, SLE.**
Mechanism	**Normally: Malaria Parasite digest host cell's Hb to obtain amino acids + Heme → Heme is released which is (Toxic) → parasite detoxifies it by heme polymerase to Hemozin (NonToxic) & traps it in food vacuole.** **CHLOROQUINE: work on the heme polymerase to prevent the conversion of heme to Hemozin & on the Peptides.**
Pharmaco kinetics	**-Rapidly & completely absorbed from the GIT.** **-Has high volume of distribution(100-1000l/kg) (it causes toxicity) .** **-Concentrated into parasitized RBCs.** **-Released slowly from tissues.** **-Metabolized in the liver.** **-Excreted in the urine 70% unchanged.** **-Initial t½ =2-3days & terminal t ½=1-2months.**
Therapeutic Use	**-Eradicate blood schizonts of Plasmodium vivax (plasmodium vivax resistance evolved in Indonesia, Peru and Oceania).** **-used also in rheumatoid artheritis, SLE.**

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2) Chloroquine and Amodiaquine

	Short – term	Prolonged therapy	Bolus injection
ADR	1-Mild headache and visual disturbances 2. Gastro-intestinal upsets; Nausea, vomiting 3. Pruritus, urticaria	1-Retinopathy, characterized by loss of central visual acuity, macular pigmentation and retinal artery constriction. Progressive visual loss is halted by stopping the drug. *Chloroquine concentrates in melanin containing tissues, e.g. the retina. 2. Lichenoid skin eruption, bleaching of hair (يرورح لون الشعر) 3-Weight loss	-hypotension - dysrrhythmias
Resistance	Why does resistance of this drug develop? as a result of enhanced efflux of parasite vesicle →↑expression of the human multi drug resistance transporter P-glycoprotein		

Why does Chloroquine concentrates in food vacuole of parasite?

1. Its protonation & ion trapping due to ↓ pH of vacuole
2. Its active uptake by a parasite transporters
3. Its binding to a specific receptor in the food vacuole.

3) QUININE * more effective than chloroquine

Action	• The main alkaloid in cinchona bark • Potent blood Schizontocide & weak Gametoside (Treat Attack)	
Pharmaco kinetics	✓ Rapidly & completely absorbed from the GIT ✓ Peaks after 1-3 hrs ✓ Metabolized in the liver	✓ t½ =10 hrs but longer in sever falciparum infection ✓ Administered orally in a 7 day course or by slow IV for severe P. finfection. ✓ Safe in pregnancy
Mechanism	▪ As ANTIMALARIAL → Same as chloroquine ▪ Other Actions: *Quinidine like action * Mild oxytoxic (Increase contraction of uterus) (effect on pregnant uterus in the last stage of pregnancy) *Slight neuromuscular blocking action * Weak antipyretic action	
ADR	**therapeutic**	poor compliance → bitter taste.
	Higher doses	✓ Cinchonism → (tinnitus, deafness, headaches, nausea & visual disturbances) ✓ Abdominal pain & diarrhea ✓ Rashes, fever, hypersensitivity reactions, Hypotension & arrhythmias ✓ Blood dyscarasis; anaemia, thrombocytopenic purpura & hypoprothrombinaemia ✓ Blackwater fever(a fatal condition in which acute haemolytic anaemia is associated with renal failure)
	IV → neurotoxicity→ tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma	

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3) QUININE * more effective than chloroquine

Resistence	like chloroquine by efflux through p-glycoprotein MDR transporter
Contra indications	-Prolonged QT Interval -Glucose-6-Phosphate Dehydrogenase Deficiency -Myasthenia Gravis -Hypersensitivity -Optic Neuritis, auditory problems -Dose should be reduced in renal insufficiency
Interactions	*Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine. *Erythromycin (CYP3A4 inhibitor): -Cimetidine. -Mefloquine. *Quinine can raise plasma levels of warfarin and digoxin.

4) 8-AMINOQUINOLINES → PRIMAQUINE (NOT USED ALONE)

Action	**Hypnozoitocides → against:** **1-liver hypnozoites (Radical cure of P. ovale & P. Vivax).** **2-gametocytocides (Prevent spread of all forms).**	
Pharmacokinetics *	✓ **Well absorbed orally.** *Not important. ✓ **Rapidly metabolized to etaquine & tafenoquine → more active .** ✓ **t½ → 3-6h.**	
Mechanism	**Not well understood. It may be acting by:** • **Generating ROS → can damage lipids, proteins & nucleic acids.** • **Interfering with the electron transport in the parasite → no energy.** • **Inhibiting formation of transport vesicles →no food vacuoles.**	
ADR	**Regular doses**	**patients with G-6-PD deficiency → hemolytic anemia.** **In G-6-PD deficiency → ↓NADPH, GSH synthesis. So RBCs become sensitive to oxidative agents → HEMOLYSIS** **Oxidizes GSH to GSSG → ↓ GSH → ↓ detoxification of toxic products**
	Larger doses :	✓ **Epigastric distress & abdominal cramps** ✓ **Mild anemia, cyanosis & methemoglobinemia** ✓ **Severe methemoglobinemia → rarely in patients with deficiency of NADH methemoglobin reductase** ✓ **Granulocytopenia & agranulocytosis → rare**

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IMPORTANT

WHO TREATMENT GUIDELINES

In VIVAX	Resistance	ACT (full course) followed by Primaquine for 14 days
	Sensitive	Chloroquine for 3 days followed by Primaquine for 14 days
In FALCIPARUM	All show Resistance	
	Uncomplicated	ACT
	Complicated	IV Artisunate for 24 hrs , Followed by ACT Or Artemether + [Clindamycin / doxycyline] Or Quinine + [Clindamycin / doxycyline]
	Special Risk Groups	-Pregnancy; 1st trimester → Quinine + Clindamycin (7 days) -Pregnancy; 2nd & 3rd trimester -Lactating women -Infants & young children → ACTs

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summary

Drug type :	Example of the drug:	General characters :	Uses :	ADRs :
LACTONE ENDOPEROXIDES	ARTEMISININ	Fast acting blood Schizontocide.	Affect all forms.	-Transient heart block - ↓neutrophil count - Brief episodes of fever - Neuro, hepato and bone marrow toxicity
4-AMINOQUINOLINES	CHLOROQUINE	Can be active against all forms of the schizonts (exception is chloroquine-resistant P.f. & P.v.)	eradicate blood schizonts of Plasmodium vivax	Short-term Pruritus, urticaria Prolonged therapy Retinopathy Lichenoid skin eruption, bleaching of hair
AMINOQUINOLINES DERIVATIVE	QUININE	Safe in pregnancy	Potent blood Schizontocide & weak Gametoside.	- Cinchonism - Blood dyscarasis IV → neurotoxicity - Blackwater fever
8-AMINOQUINOLINES	PRIMAQUINE	against liver hypnozoites & gametocytocides Prevent spread of all forms	Radical cure of P. ovale & P. vivax	-G-6-PD deficiency → hemolytic anemia. -Granulocytopenia & agranulocytosis

Quiz yourself

Ans: 1-D, 2-C, 3-D, 4-A, 5-A, 6-D, 7-A, 8-A, 9-A

1-Female pragenant patient came to the clinic with malaria infection which of the following is safe for her
A-artemisinin
B-cloroquine
C- quinie
D- B & C

2-Which one of the following antimalarial drugs has the fastest acting character :
A-quinine
B-chloroquinie
C-artemisinin
D-primaquine

3- Which one of the following drugs can cause neurotoxicity if injected IV as a side effect :
A-cloroquine
B-artemisinin
C-primaquine
D-quinine

4- G6PD Patient was using antimalarial drug he developed hemolytic anemia what is the most likely cause:
A- primaquine
B-quinine
C-chloroquine
D-artemisinin

5- Which of the drugs can act on the resistance form of P. falciparum:
A-artemisinin
B-chloroquine
C-primaquine
D-quinine

6- Which of the following can not be used as monotheraby:
A- primaquine
B-quinine
C-cloroquine
D-artemisinin

7- Which of the following drugs can not be used in patients using Cimetidine:
A-quinine
B-cloroquine
C-artemisinin
D-primaquine

8- Which one of the following can work against liver hypnozoites:
A-primaquine
B-quinine
C-artemisinin
D-chloroquine

9- Which one of the following antimalarial drugs can be used as prophylacsis :
A-primaquine
B-quinine
C-artemisinin
D-chloroquine

Done by

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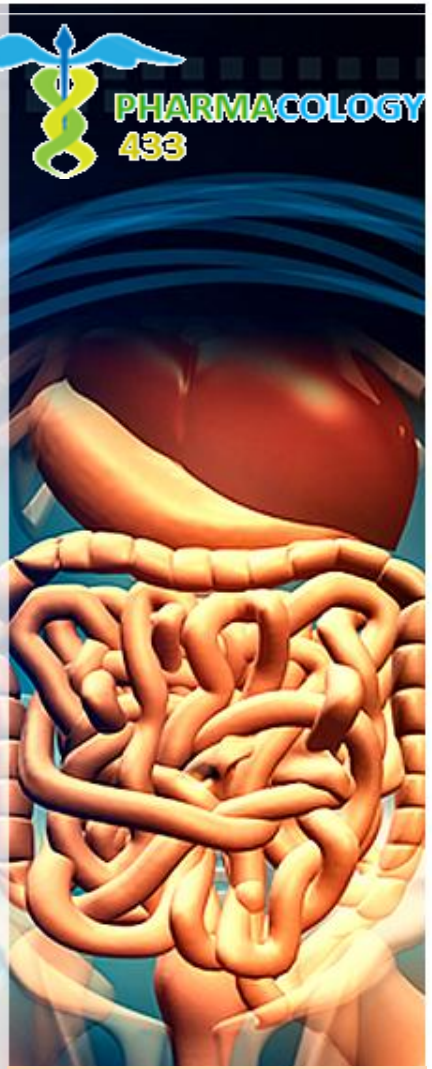
Nada bindawood	

It always seems impossible until it is done

BEST OF LUCK



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