

PROSTAGLANDINS

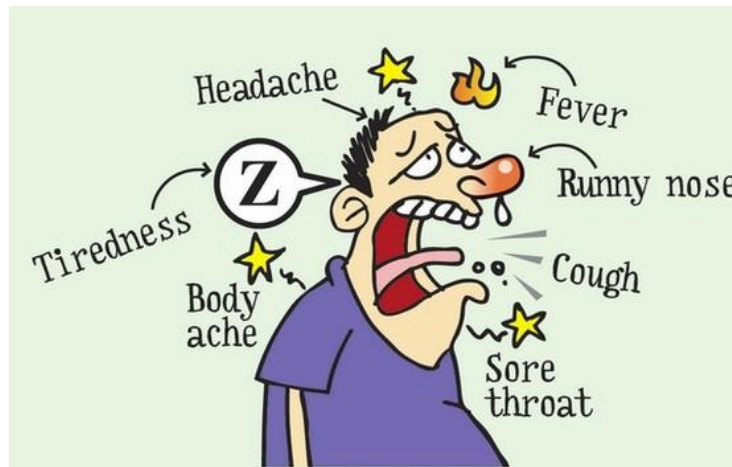


By Dr AyeshaJamil



# PROSTAGLANDINS

- Prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; “eicosa” refers to the 20 carbon atoms.]



# Prostaglandins as local mediators

- Prostaglandins and related compounds are produced in minute quantities by virtually all tissues.
- They act where they are produced and also metabolized there into inactive compounds.
- So their circulatory concentration is hardly significant.

# Synthesis of prostaglandins

- **Arachidonic acid**, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds.
- Arachidonic acid is present as a component of the phospholipids of cell membranes, primarily phosphatidylinositol and other complex lipids.
- Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A<sub>2</sub> and other acyl hydrolases via a process controlled by hormones and other stimuli.

# Pathways of synthesis of prostaglandins

- There are two major pathways in the synthesis of the eicosanoids from arachidonic acid.
- Cyclo-oxygenase pathway
- Lipoxygenase pathway

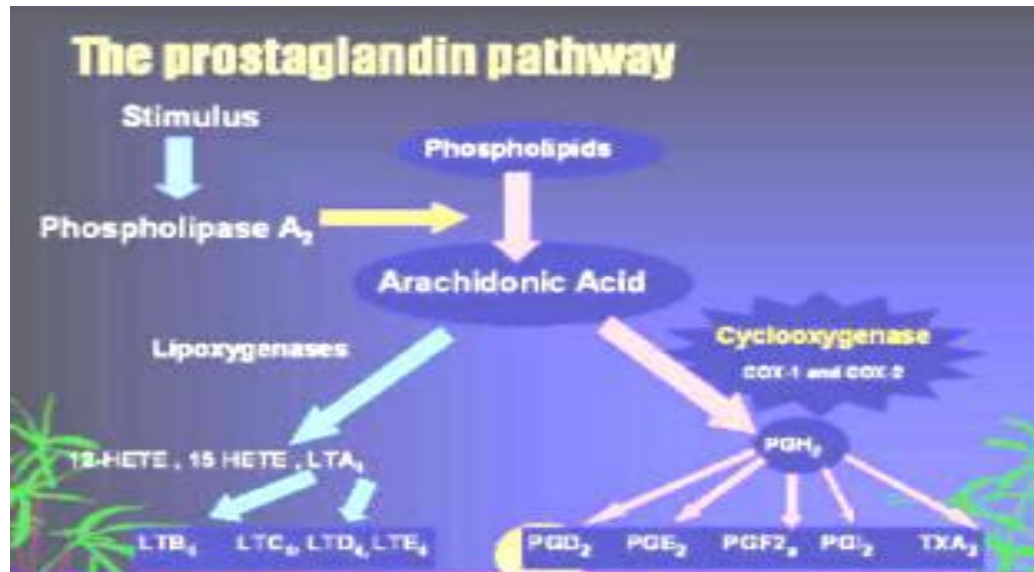
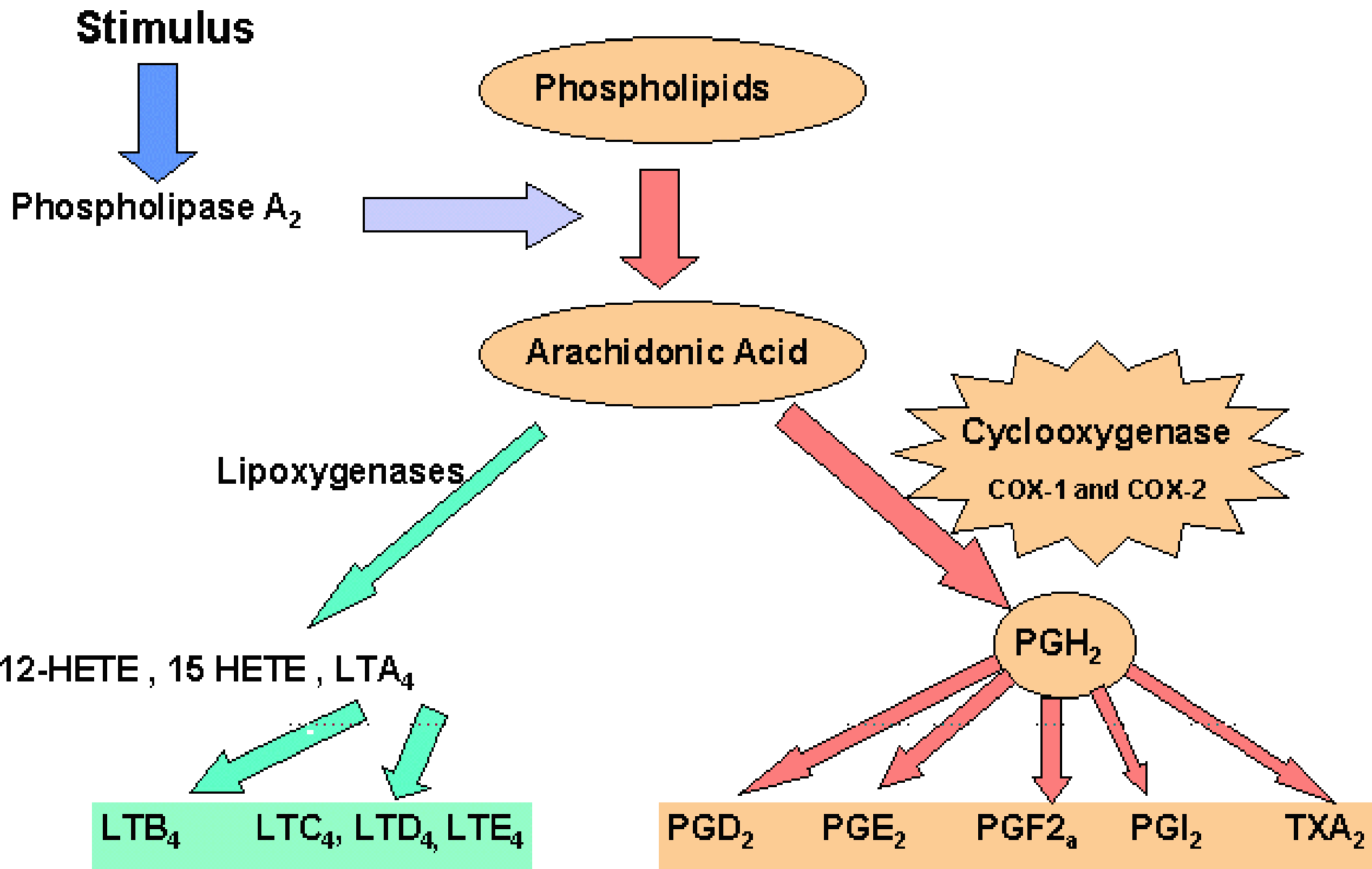


Figure 2 : Biosynthesis of eicosanoids



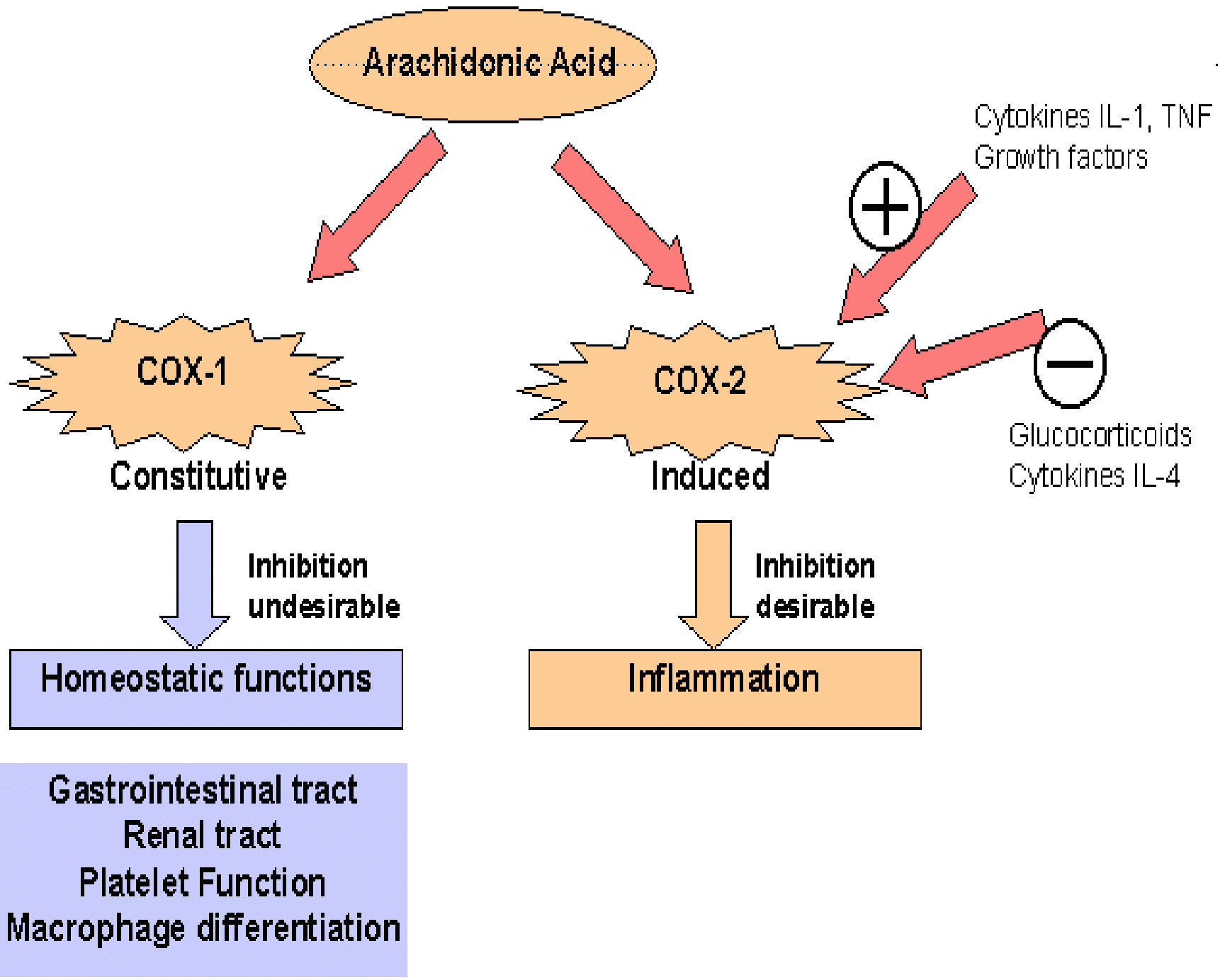
# Cyclooxygenase pathway

- All eicosanoids with ring structures (that is, *the prostaglandins, thromboxanes, and prostacyclins*) are synthesized via the cyclooxygenase pathway.
- Two related isoforms of the cyclooxygenase enzymes are present.
- **COX1 and COX2.**



# COX1&COX2

- **Cyclooxygenase-1 (COX-1)** : responsible for the physiologic production of prostanoids. It is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.
- **Cyclooxygenase-2 (COX-2)** : causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation. It is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. COX-2 is the expression induced by inflammatory mediators like TNF- $\alpha$  and IL-1, but can also be pharmacologically inhibited by glucocorticoids.



Arachidonic Acid

COX-1

Constitutive

COX-2

Induced

Inhibition  
undesirable

Inhibition  
desirable

Homeostatic functions

Inflammation

Cytokines IL-1, TNF  
Growth factors

Glucocorticoids  
Cytokines IL-4

Gastrointestinal tract  
Renal tract  
Platelet Function  
Macrophage differentiation

# Lipoxygenase pathway

- Lipoxygenases acts on arachidonic acid to form 5-HPETE, 12-HPETE, and 15-HPETE, which are unstable peroxidated derivatives that are converted to the corresponding hydroxylated derivatives (the HETEs) or to leukotrienes or lipoxins, depending on the tissue.
- Antileukotriene drugs, such as ***zileuton, zafirlukast, and montelukast***, are useful for the treatment of moderate to severe asthma

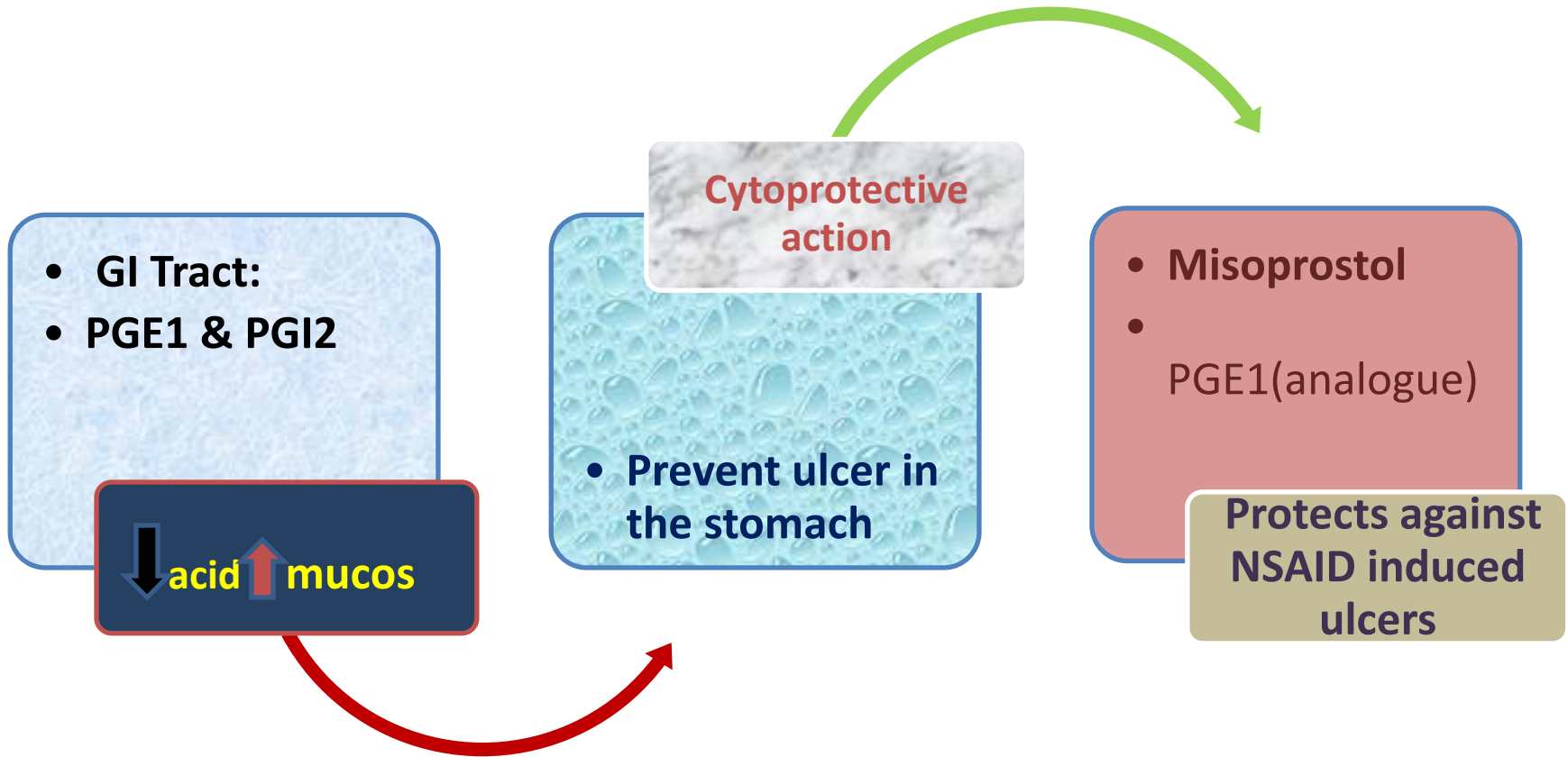
# Mechanism of action of prostaglandins

- Prostaglandins bind to a wide variety of distinct cell membrane receptors that operate via G proteins,
  - They activate or inhibit adenylyl cyclase or stimulate phospholipase C.
  - This causes an enhanced formation of diacylglycerol and inositol 1,4,5-trisphosphate.
  - Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site.
  - For example, the release of TXA<sub>2</sub> from platelets cause platelet aggregation (the first step in clot formation) as well as local vasoconstriction.
  - However, PGI<sub>2</sub>, produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation.
  - The net effect on platelets and blood vessels depends on the balance of these two prostaglandins.

- **PGI<sub>2</sub>** (prostacyclin) is located
- predominantly in vascular
- endothelium. Main effects:
  - vasodilatation
  - inhibition of platelet aggregation
- **TxA<sub>2</sub>** is found in the platelets.
- Main effects:
  - platelet aggregation
  - vasoconstriction

- **PGE<sub>2</sub>** causes:
  - inhibition of gastric acid secretion
  - contraction of pregnant uterus
  - contraction of GI smooth muscles
  
- **PGF<sub>2α</sub>** – main effects:
  - contraction of bronchi
  - contraction of miometrium

# Prostaglandins: Therapeutic uses



# Effect on CVS

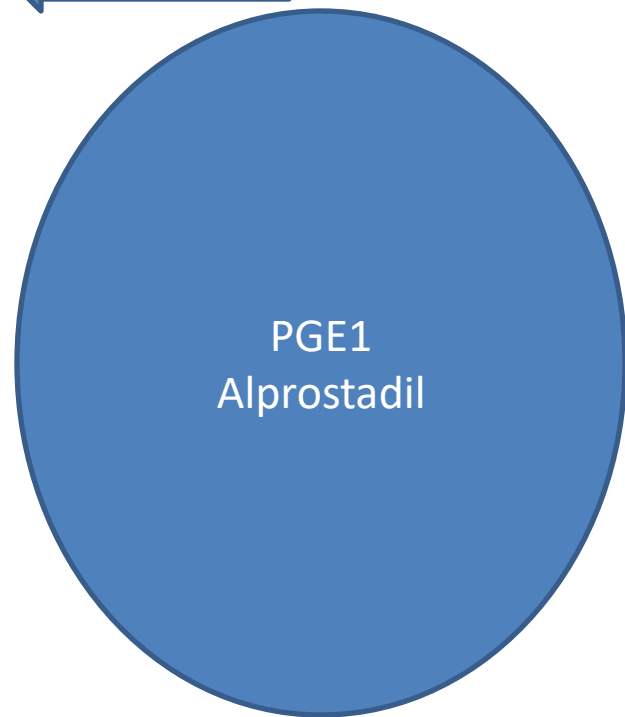
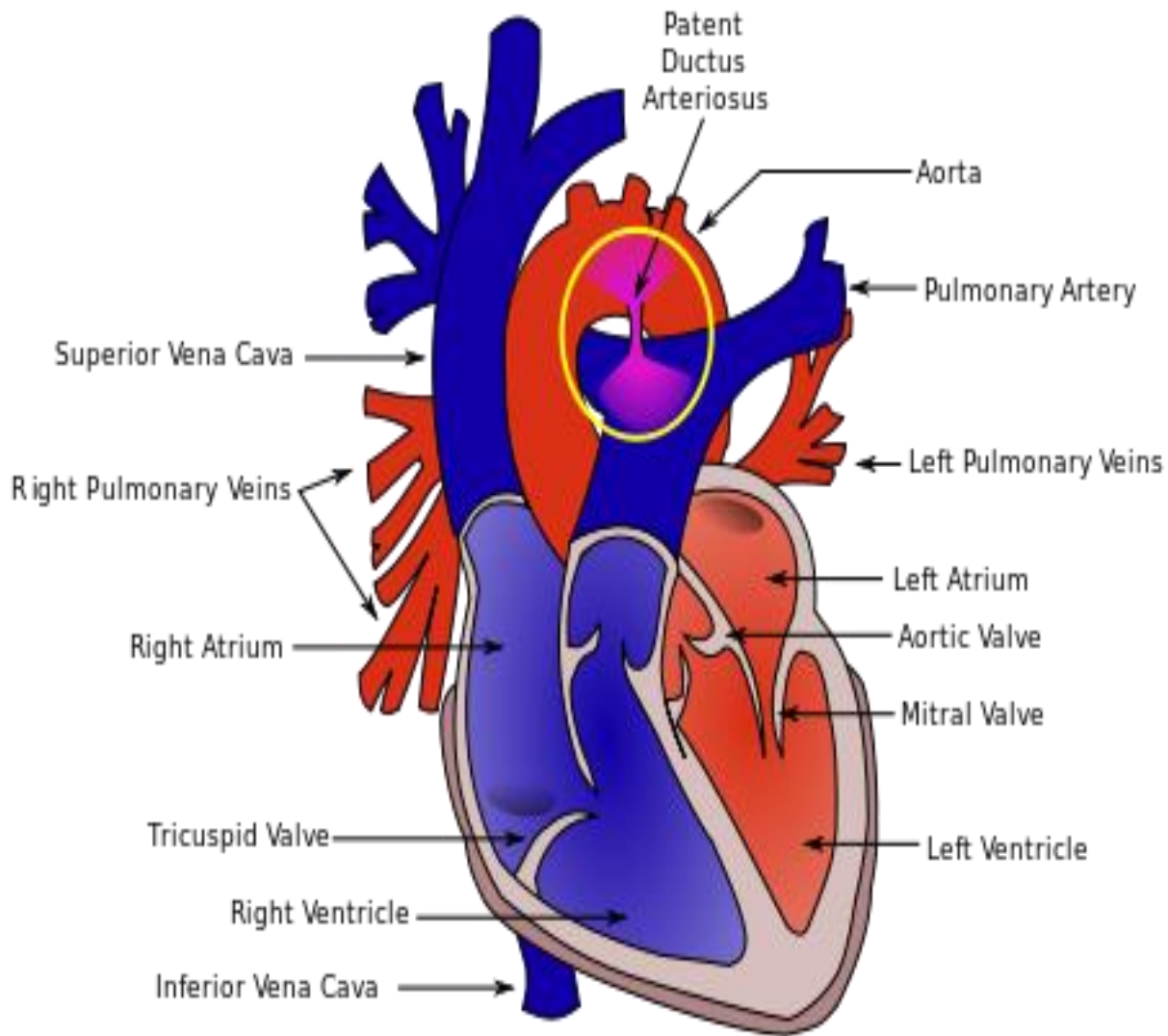
PGE1( alprostadil) for the patency of ductus arteriosus before surgery

PGI2 : (prostacyclin)vasodilator.  
Decreases peripheral, pulmonary & coronary HTN.

PGI2 (epoprostenol)  
For the treatment of pulmonary HTN

PGI2 inhibits platelet aggregation .





**Effects on eye  
PGF2 $\alpha$**

**Latanoprost  
Increases  
uveo-scleral  
outflow**



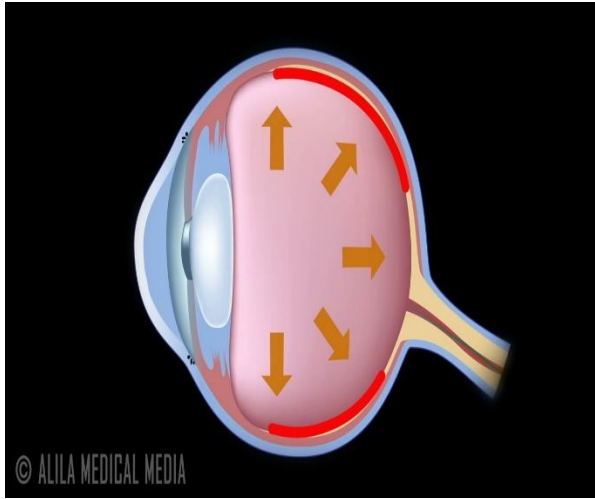
**Decreases  
intraocular tension**



**Latanoprost is  
used in glaucoma**

**Travoprost is a  
prodrug  
Decreases intraocular  
tension**

**Bimatoprost also reduces  
intraocular tension it also  
increase eye lash prominence  
& length**



# Effect on uterus

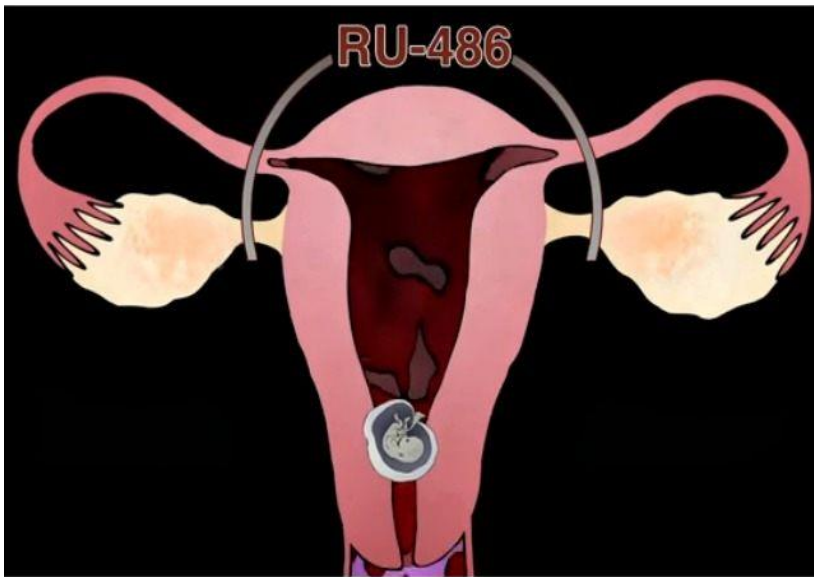
PGF2 & low doses of PGE2 contract uterus, so are **abortifacients**

PGE2 & PGF2 $\alpha$  are used for **labour induction** when oxytocin is not recommended

PGE2 is used for **cervical priming**.

**PPH:** PG"s increase Uterine tone & amplitude of contractions. Carboprost is used for this purpose.

**Erectile dysfunction (impotence):** PGE1 (alprostadil) is used for this purpose.



Abortifaciant  
PGF2 $\alpha$ , PGE2, PGE1



Contractions  
push the  
baby down ...

and pull the  
cervix open.

Induction of labour  
PGE2, PGF2 $\alpha$ ,

# Side effects



bachache



nausea



vomiting



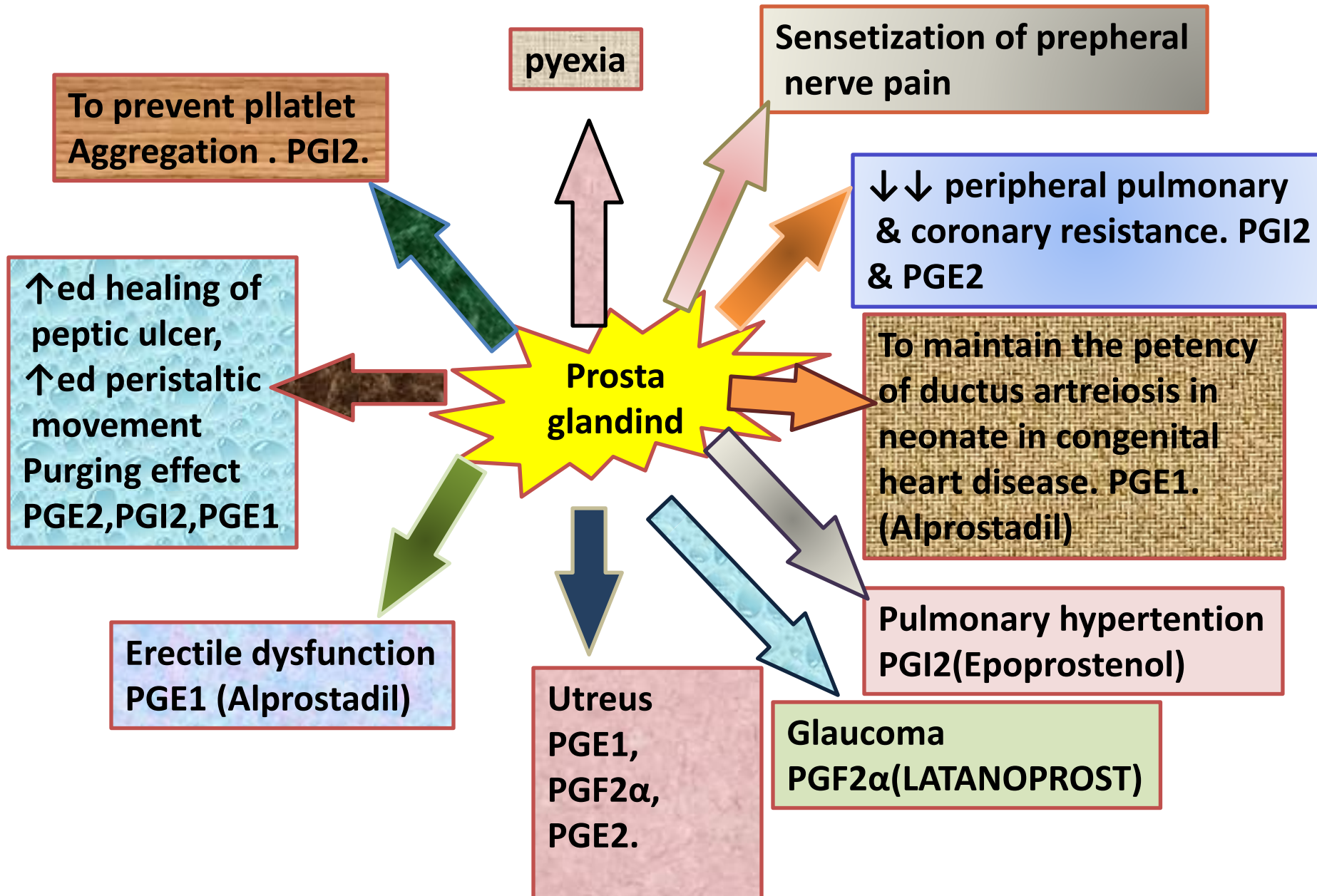
diarrhea



fever

# Therapeutic uses in obstetrics

- **First trimester:**
- **Gemetoprost(PGE1) , Dinoprostone(PGE2),:** They are used to soften the cervix for the surgical procedure.
- **Mefipristone (PGE1),** orally or locally is used for the termination of early pregnancy.
- **Second trimester:**
- **Dinoprostone(PGE2), Dinoprost(PGF2 $\alpha$ ) or Carboprost( 15-methyl PGF2 $\alpha$ )** are used for mid term abortions. They cause cervical softening and induce uterine contractions.
- **Third trimester :**
- **Gemetoprost(PGE1) or Dinoprostone(PGE2)** are used intravaginally. Usually the drug of choice for the induction of labour is oxytocin but when there are contraindications to this drug as in renal failure or eclampsia then PG's are the drug of choice as they are safe and associated with minimal systemic effects because they act locally.





# PG's

Sensitization  
of peripheral  
nerves pain.

↓↓  
peripheral  
pulmonary &  
coronary  
resistance  
(PGI<sub>2</sub>)

To maintain the  
petency of  
ductus  
arteriosus in  
neonates in  
CHD.  
(PGE<sub>1</sub>, Alprosta  
dil

Pulmonary  
HTN (PGI<sub>2</sub>, epo  
prostenol)

Glaucoma  
(PGF<sub>2</sub>α  
Latanoprost)

# PG's

**Uterus :  
abortion,  
Cervical  
ripening,  
induction of  
lab, PPH.**

**Erectile  
dysfunction  
PGE1  
Alprostadil.**

**GIT:  
Cytoprotective,  
Increase the  
peristaltic  
movments ,  
purpative  
effect(diarrhe(  
PGE2, PGI2)**

**pyrexia**

**THANK YOU**

