

# **Pharmacology of Adrenal Cortex**

**ROZAIMAH ZAIN-HAMID**

**Department of Pharmacology and Therapeutics**

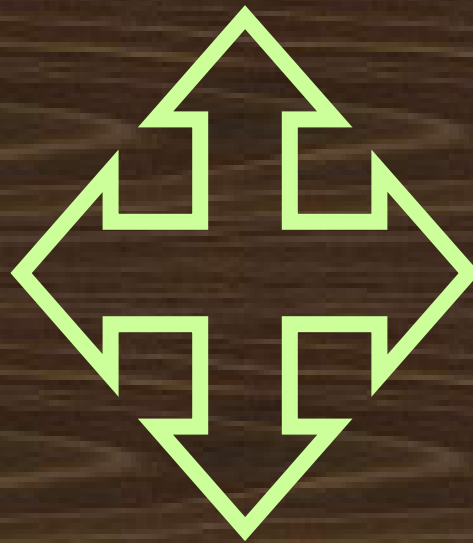
**Faculty of Medicine**

**Universitas Sumatera Utara**

**Medan, Indonesia**

# ADRENOCORTICOSTEROID

◆ **Glucocorticoid**  
(hydrocortisone)  
intermediate in  
metabolism  
process



◆ **Mineralocorticoid**  
(aldosterone)  
Na & water  
retention &  
Influenced by  
angiotensin

◆ **Testosterone &  
estrogen secretion**

# ADRENOCORTICOSTEROID



**DIAGNOSTIC:**  
**Adrenal gland dysfunction**

- THERAPY:**
- ◆ Inflammation process
  - ◆ Disturbancies of immunologic process
- 

# **PHARMACOKINETICS GLUCOCORTICOID**

# GLUCOCORTICOID

## Cortisol (hydrocortisone)

### *Pharmacokinetic:*

- ✿ Synthesized from cholesterol
- ✿ Cortisol is secreted 10-20 mg daily  
(“Circadian rhythm”)
- ✿ 75 % : Corticosteroid-binding globulin ( $\alpha_2$ -globulin)  
25 % : free form & 5 %: loosely bound to albumin  
(effect on target cells)

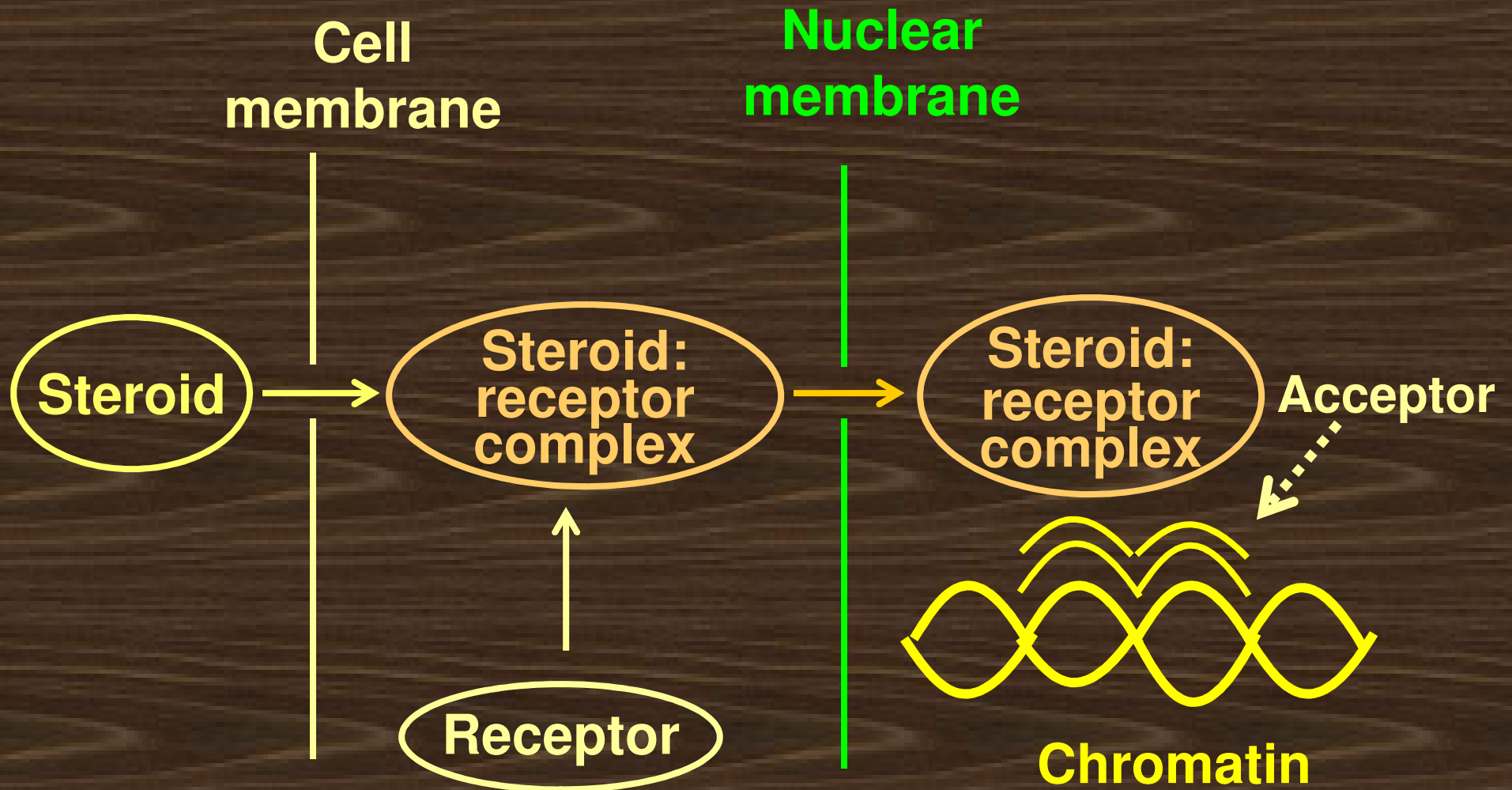
# GLUCOCORTICOID (Cortisol : hydrocortisone)

## *Pharmacokinetic*

- ✿ Synthetic corticosteroid (dexamethasone) :  
>>> bound to albumin
- ✿  $t_{1/2}$  : 60 – 90 minutes, could be longer :  
>>> cortisol administration,  
stress, hypothyroidism & liver disease
- ✿ Only 1 % of cortisol is secreted  
unchanged in the urine

# **PHARMACODYNAMICS GLUCOCORTICOID**

# Mechanism of action of steroid hormone





# GLUCOCORTICOID (Cortisol : hydrocortisone)

*Pharmacodynamic:*

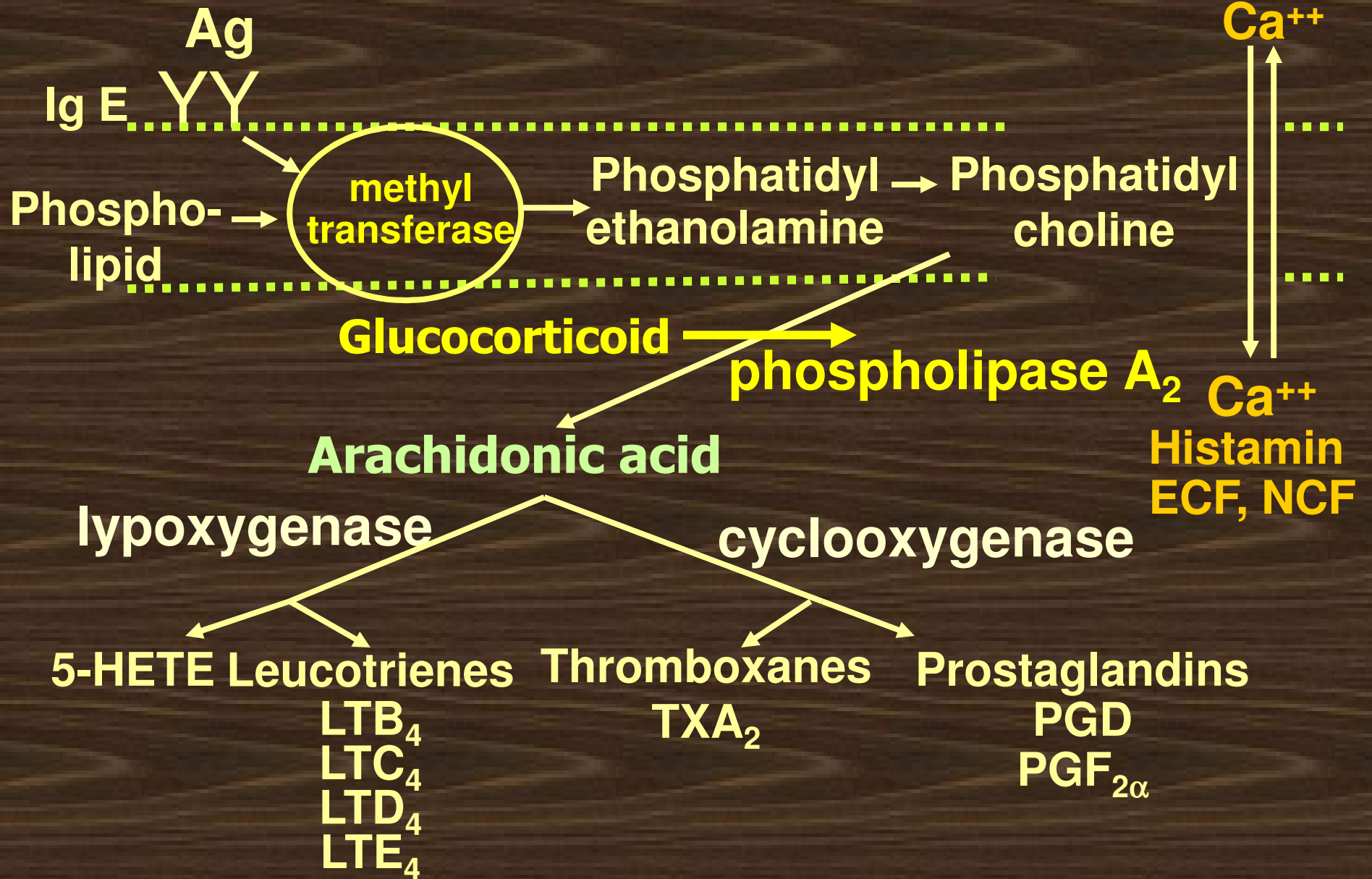
- ◆ Physiologic effects  
(homeostasis)
- ◆ Metabolic effects
- ◆ Catabolic effects

# GLUCOCORTICOID (Cortisol : hydrocortisone)

## *Pharmacodynamic:*

- ◆ **Anti-inflammatory**
- ◆ **Immunosuppresant**
- ◆ **Effects on the nervous system**
- ◆ **Increase platelets & red blood cells**
- ◆ **Effects on the development of the fetus**

# Cascade in inflammation reaction



**CLINICAL PHARMACOLOGY  
GLUCOCORTICOID**

# GLUCOCORTICOID

## *Clinical pharmacology*

- ❖ **Diagnosis & treatment of disturbed adrenal function**
- ❖ **Stimulation of lung maturation in the fetus**
- ❖ **Autoimmune disease :  
LE, rheumatoid arthritis etc**

# GLUCOCORTICOID

## *Clinical pharmacology*

- ❖ Inflammatory condition of bones & joint :  
arthritis, bursitis etc
- ❖ G.I.T diseases : Inflammatory bowel disease,  
subacute hepatic necrosis etc
- ❖ Pulmonary diseases : Asthma,  
aspiration pneumonia, prevention IRDS etc

# GLUCOCORTICOID

## *Clinical pharmacology*

- ❖ **Hematologic diseases : ITP, leukemia, acquired hemolytic anemia, etc**
- ❖ **Neurologic disease: Cerebral edema, multiple sclerosis**
- ❖ **Renal disease : Nephrotic syndrome**

# GLUCOCORTICOID

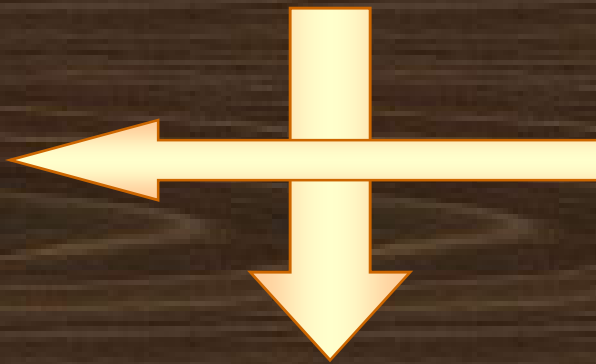
## *Clinical pharmacology*

- ❖ **Skin & eye diseases: Atopic dermatitis, seborrheic dermatitis, optic neuritis, allergic conjunctivitis, choroiditis, etc**
- ❖ **Organ transplantation:  
Prevention & treatment of rejection  
(immunosuppression)**



# Glucocorticosteroid cessation

Tapering-off



Withdrawal syndrome

# **NATURAL & SYNTHETIC GLUCOCORTICOIDS**

# SHORT TO MEDIUM ACTING GLUCOCORTICOIDS

Agent	Activity			Eq. oral dose (mg)	Forms available
	Anti-inflam.	Topical	Salt-retain.		
Cortisol	1	1	1	20	oral, inj, tpcl
Cortisone	0.8	0	0.8	25	oral, inj, tpcl
Prednisone	4	0	0.3	5	oral
Prednisolone	5	4	0.3	5	oral, inj, tpcl
Flurocortolone				5	oral, tpcl
M.prednisolone	5	5	0	4	oral, inj, tpcl
Meprednisone	5		0	4	oral, inj

# INTERMEDIATE - ACTING GLUCOCORTICOIDS

Agent	Activity			Eq. oral dose (mg)	Forms available
	Anti-inflam.	Topical	Salt-retain.		
Triamcinolone	5	5 <sup>3</sup>	0	4	oral, inj, tpcl
Paramethasone	10		0	2	oral, inj.
Fluprednisolone	15	7	0	1.5	oral

# LONG - ACTING GLUCOCORTICOIDS

Agent	Activity			Eq. oral dose (mg)	Forms available
	Anti-inflam.	Topical	Salt-retain.		
Betamethasone	25-40	10	0	0.6	oral, inj, tpcl
Dexamethasone	30	10	0	0.75	oral, inj, tpcl

**Bila hendak menuai yang baik, tanam yang baik**



# **TOXICITY GLUCOCORTICOIDS**

# GLUCOCORTICOID

## *Toxicity :*

- \* **Metabolic effect : Cushing's syndrome**
  - \* **Peptic ulcers & their complication**
    - \* **Myopathy (triamcinolone)**
- \* **Nausea, dizziness (methylprednisolone)**
  - \* **Psychosis**



# GLUCOCORTICOID

## *Toxicity :*

- \* **Post. subcapsular cataract & glaucoma**
  - \* **Intracranial hypertension**
- \* **Hypokalemic, hypochloremic & hypertension**
  - \* **Adrenal suppression**
    - \* **Osteoporosis**

**SPECIAL PRECAUTION  
GLUCOCORTICOID**

# GLUCOCORTICOID

*Special precaution:*

**Development of hyperglycemia, glycosuria, sodium retention with edema & hypertension, hypokalemia, peptic ulcer, osteoporosis, and hidden infection**

# **CONTRA-INDICATION GLUCOCORTICOID**

# GLUCOCORTICOID

*Contraindication:*

**Peptic ulcers, heart disease or hypertension with CHF, psychosis, diabetes, glaucoma, osteoporosis & herpes simplex infection**

# **ANTAGONIST OF GLUCOCORTICOIDS**

# ANTAGONIST OF GLUCOCORTICOID

**Mitotane, amphenone B, metyrapone,  
aminoglutethimide, ketoconazole,  
mifepristone (RU 486)**

# ANTAGONIST OF GLUCOCORTICOID

## Mitotane:

- ◆ orally in divided dose
- ◆ 1/3 adrenal carcinoma patient,  
↓ in tumor mass
- ◆ 2/3 of patients, ↓ steroid production
- ◆ Side effects: nausea, vomiting diarrhea,  
depression, skin problems



# ANTAGONIST OF GLUCOCORTICOID

## Amphenone B

- ◆ More potent inhibitor of synthesis than mitotane
  - ◆ Too toxic for use in human
  - ◆ Side effects: CNS depression, g.i.t & skin disorders, impairs liver & thyroid function

# ANTAGONIST OF GLUCOCORTICOID

## Metyrapone:

- ◆ More selective effect at lower dose than mitotane & amphenone B
- ◆ Inhibits 11-hydroxylation, interfering with cortisol & corticosterone synthesis & leading to secretion of 11-deoxycortisol
  - ◆ Most commonly used in test of adrenal function
  - ◆ Toxicity  $\ll$  the above agents, transient dizziness, g.i.t disturbances

# ANTAGONIST OF GLUCOCORTICOID

## Aminogluthetimide:

- ◆ Blocks convers. cholesterol → pregnonolone
- ◆ ↓ synthesis of all hormonally active steroids
  - ◆ Conjunction with dexamethasone to ↓ estrogen & androgen production in breast carcinoma
- ◆ Conjunction with ketoconazole to ↓ steroid secretion in Cushing's syndrome
  - ◆ ↑ metabolism of dexamethasone & ↓ its T<sub>1/2</sub> by an half

# ANTAGONIST OF GLUCOCORTICOID

## Ketoconazole:

- ◆ Potent & rather non-selective inhibitor of adrenal & gonadal steroid synthesis
- ◆ Inhibitory effects are seen only at high doses
- ◆ Treatment of Cushing's due to several causes

# ANTAGONIST OF GLUCOCORTICOID

## Mifepristone:

- ◆ May be useful in treatment of endometriosis, Cushing's syndrome, breast cancer & other neoplasma that contain glucocorticoid or progesterone receptors
- ◆ Has been used to terminate early pregnancy
- ◆ Side effects: vomiting, diarrhea, pain, vaginal bleeding requiring intervention

# **MINERALOCORTICOID**

# **MINERALOCORTICOID**

## **ALDOSTERONE :**

**Synthesized mainly in  
the zona glomerulosa  
of the adrenal cortex**

# **ALDOSTERONE :**

**◆ Act by binding to  
the mineralocorticoid receptor in  
the cytoplasm of target cell**



**collecting tubules of the kidney;  
specificity → by presence of the enzyme  
11  $\beta$  hydroxysteroid dehydrogenase**



# **ALDOSTERONE :**

**Metabolism is similar to that cortisol,  
appearing in the urine as conjugated  
tetrahydroaldosterone**

**&**

**small part is excreted free or  
as the 3-oxoglucoronide**

# ALDOSTERONE :

◆ Promote reabsorption of sodium from urine by distal renal tubule

◆ Overdosage of mineralocorticoid



hyponatremia, hypokalemia,  
metabolic alkalosis, ↑ plasma volume,  
hypertension.

◆ Antagonist of aldosterone → spironolactone

# MINERALOCORTICOIDS

Agent	Activity			Eq. oral dose (mg)	Forms available
	Anti-inflam.	Topical	Salt-retain.		
Fludrocortisone	10	10	250	2	oral. inj, tpcl
Desoxycortico-sterone	0	0	20		inj, pellets

# **MINERALOCORTICOID ANTAGONIST**

# MINERALOCORTICOID ANTAGONIST

## Spironolactone:

- ◆ May be useful in treatment of primary aldosteronism, hirsutism in women
  - ◆ Potassium-sparing diuretic
- ◆ Side effects: hyperkalemia, menstrual abnormalities, gynecomastia, sedation, headache, g.i.t disturbances, skin rash



**Like a solid rock is not shaken by the wind,  
so the wise are not moved by praise or  
blame (*Dhammapada*)**

Zain-Hamid, R; Faculty of Medicine, Universitas Sumatera Utara.



*THANK YOU*

Zain-Hamid, R; Faculty of Medicine, Universitas Sumatera Utara.