

# Chapter 6: Acetate – Malonate Pathway

## Acetate-derived Natural Products

Acetate formed from carbohydrate via pyruvic acid

Acetate is precursor for large no. of important natural products (flavonoids, anthraquinones, macrolides, terpenes & steroids)

2 main routes originate with acetate pathway:

1. Acetate – Malonate Pathway leading to FA & polyketides

2. Mevalonic acid pathway producing terpenes & steroids

# Acetate malonate pathway

double bond



acetyl acetyl acetyl

The biogenesis of naturally occurring acetylenic substances is very closely related to the synthesis of unsaturated fatty acids.

liquid

In the Plant Kingdom, fatty acids are used to form of triglycerides to produce oils.

The natural sequence of the fatty acids (even-numbered fatty acids) starts with Palmitic acid (16 carbons), Stearic acid (18 carbons) and then Arachidonic acid (20 carbons). Palmitic acid and stearic acid are important in plants' oils,

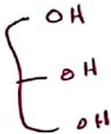
no double bond

oils are composed of three fatty acids connected to glycerol. If glycerol is connected to 3 saturated fatty acids, the product is a solid substance called fat, and its found primarily in animal kingdom (mammals especially).

When at least two of the hydroxyl groups in the glycerol are connected to unsaturated fatty acids, the product is termed as Oil, because of its liquid consistency.

esterification  
two of this hydroxyl group

Oils are mainly found in plants, but there are some exceptions (like coconut oil, which is solid).

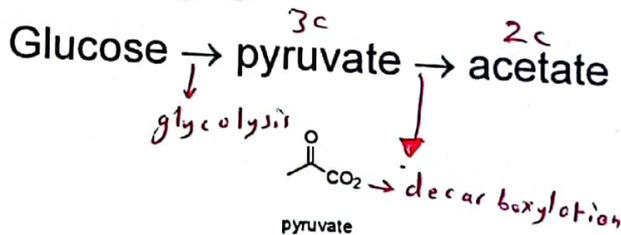


## Lipids in plant kingdom include

- fatty acids and waxes
- essential oils
- many vitamins like lipophilic vitamin
- hormones (non-peptide)
- components of cell membranes (non-peptide) like phospholipid

Lipids are Hydrophobic (non-polar, soluble in organic solvent), typically of low molecular compound or organic origin

Share a common biosynthesis that ultimately derives their carbon source from glucose (glycolysis)



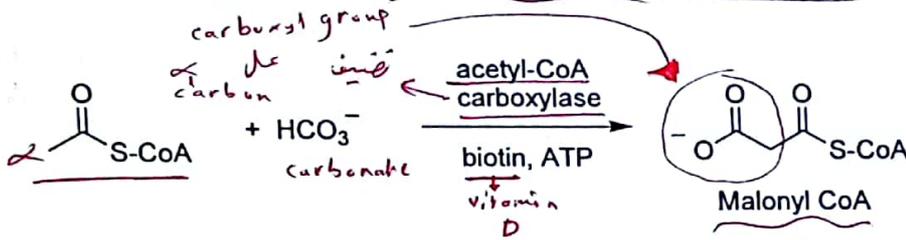
Acetate-malonate pathway and Mevalonic acid pathway start their biogenetic role with acetyl CoA.

starting compound/material

#

<sup>2C</sup> Acetyl CoA is a very important building block of two carbons compound, it is needed in the degradation of carbohydrates and the synthesis of fatty acids, and appears in Krebs cycle and in the breakdown process of fatty acids.

Acetate Malonate + Mevalonic acid pathways



Acetate Malonate pathway

46:30

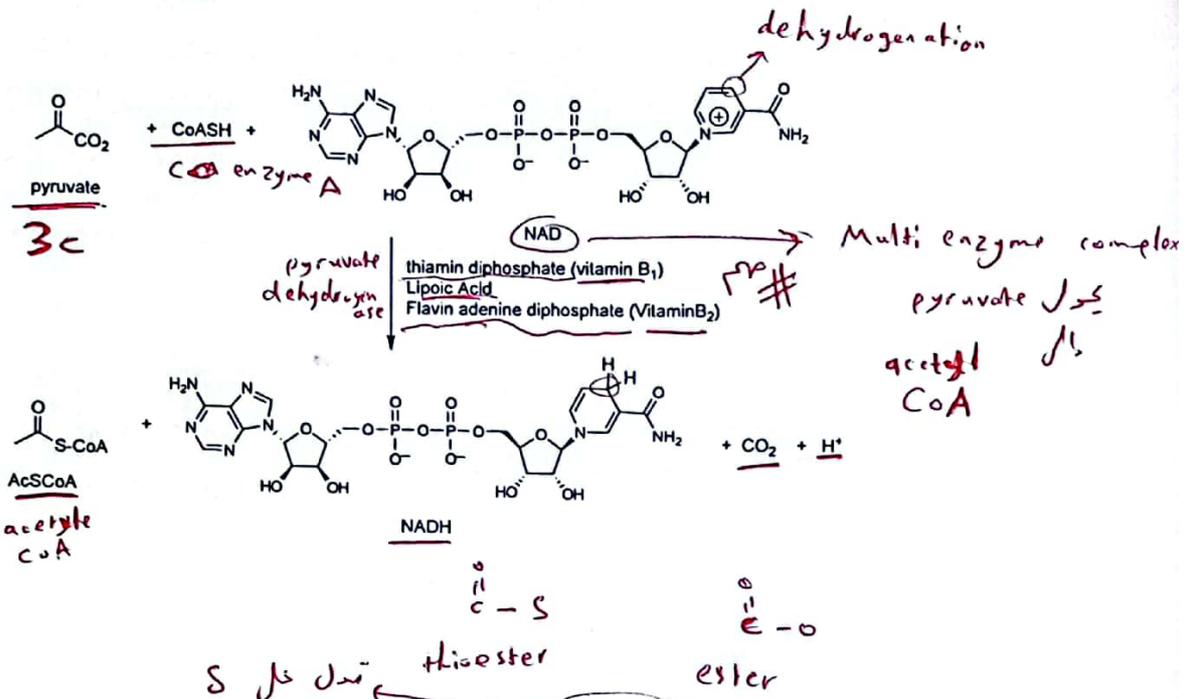
Now we will start with acetate-malonate pathway, and specifically with non-aromatic (aliphatic) derivatives.

None-aromatic derivatives in the acetate-malonate pathway polyacetylenic or polyynes, compounds having several unsaturated bonds.

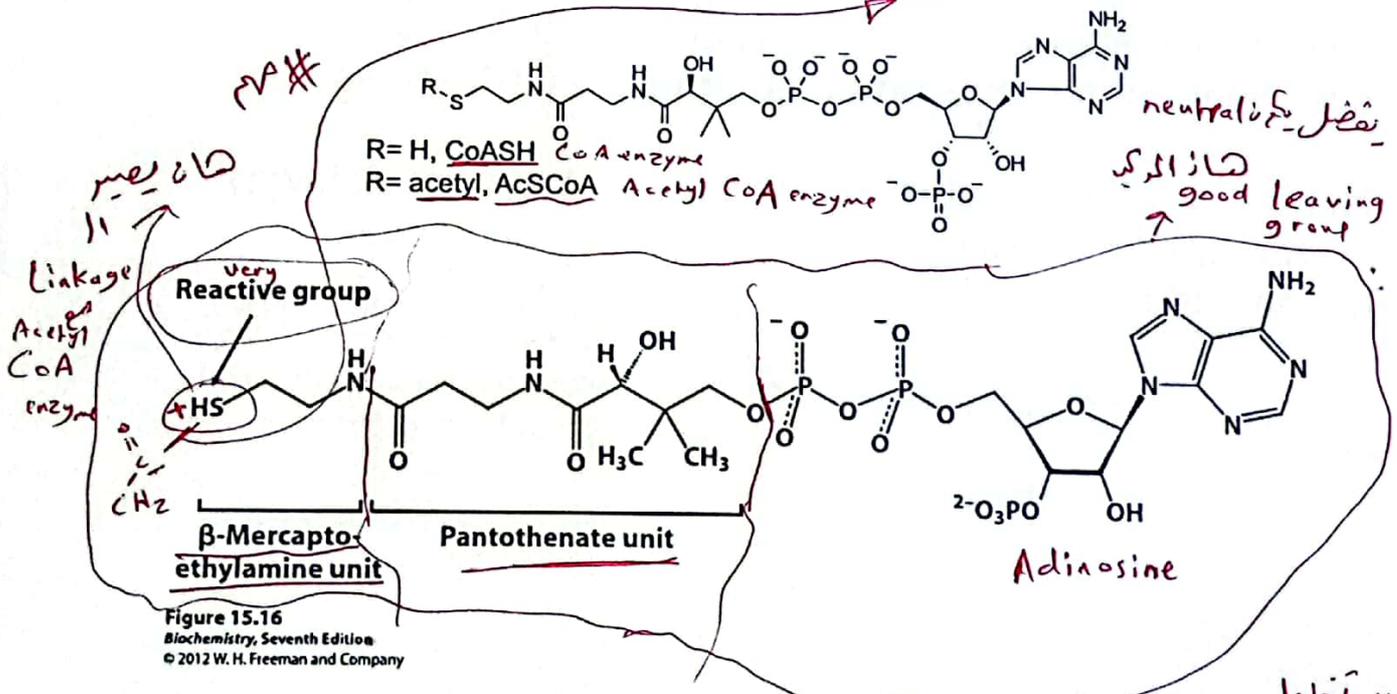
multiple double bond  
double bond + double bond + double bond ...

acetyl + acetyl + acetyl ...  
cis

Pyruvate dehydrogenase: Multi-enzyme complex that converts pyruvate to AcSCoA (most important step in Acetate-malonate pathway).

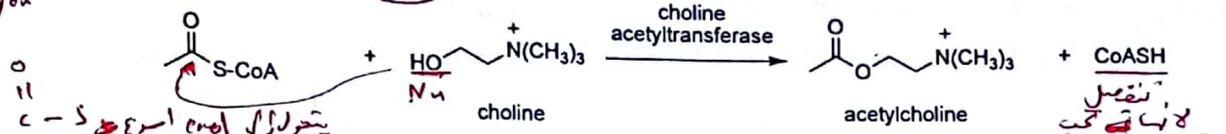
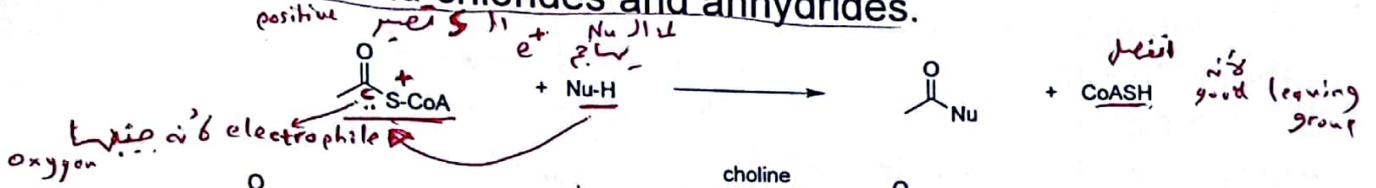


Acetyl Coenzyme A. AcSCoA is a thioester

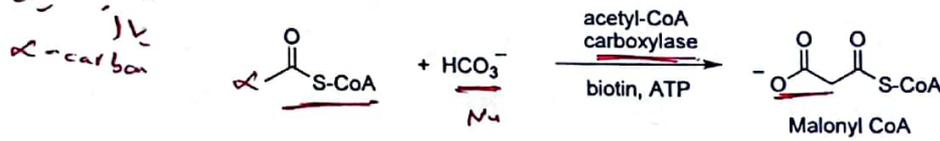
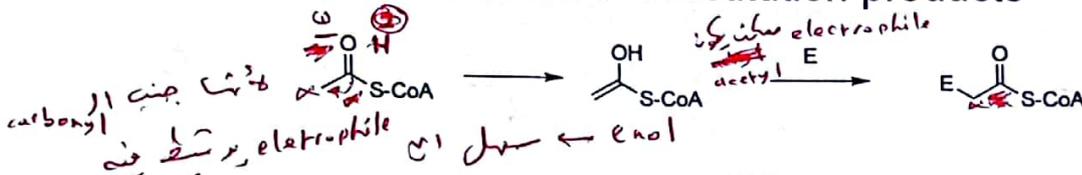


~~CoA Adenosine~~  
 $\text{CH}_2 \text{---} \text{C} \text{---}$   
 positive charge  
 electron deficient  
 electrophile  
 carbonyl carbon  
 positive charge  
 متفاعل بين  
 س  
 س  
 س

Acetyl CoA is a thioester. Thioesters are more reactive toward nucleophilic acyl substitution than esters, but considerably less reactive than acid chlorides and anhydrides.

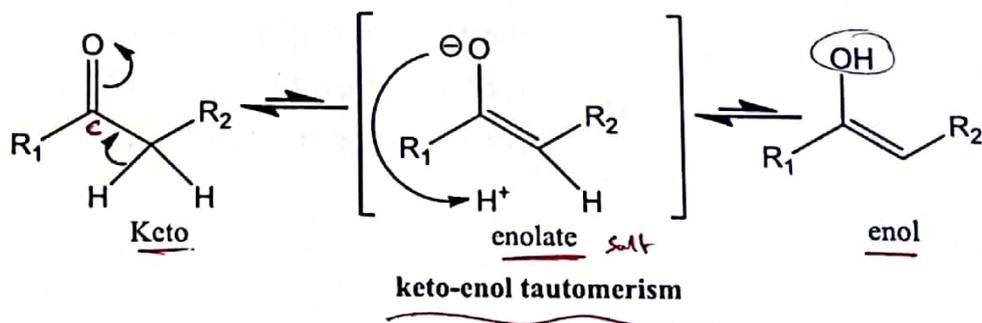


Thioester enolize more readily than esters. The enol can react with electrophile to afford  $\alpha$ -substitution products



$\alpha$ -carbon of carboxyl group

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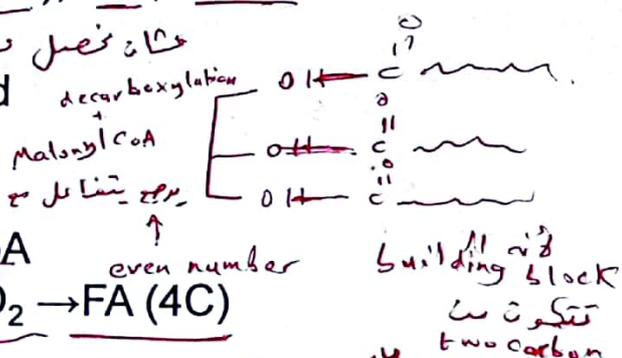
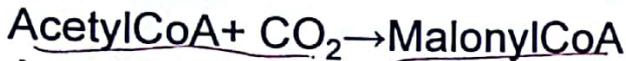


# Fatty acids (FA), fats, waxes

Fatty acid

- FA: saturated or unsaturated
- Biosynthesis:

**Saturated:** single bond



Butyric (4C), Caproic, Caprylic, Capric, Lauric, Myristic, Palmitic, Stearic, Arachidic (20C)

**Unsaturated:** by dehydrogenation of saturated FA

Oleic acid 18:1 (9c) Linoleic acid 18:2 (9c, 12c) omega 6

α-Linolenic acid 18:3 (9c, 12c, 15c) omega 3

γ-Linolenic acid 18:3 (6c, 12c, 15c)

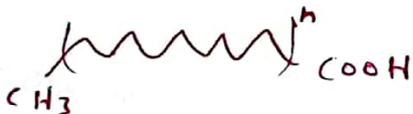
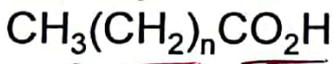
Arachidonic acid 20:4 (5c, 8c, 11c, 14c) omega 6

Eicosapentaenoic acid [EPA] 20:5 (5c, 8c, 11c, 14c, 17c) omega 3

Eicosanide derivative

**Fats, Oils, and Fatty Acids.** *Fatty acids:* refers to long, straight-chain saturated and unsaturated acids, typically from C<sub>12</sub> - C<sub>20</sub> (Table 26.1, p. 1069).

saturated fatty acids:



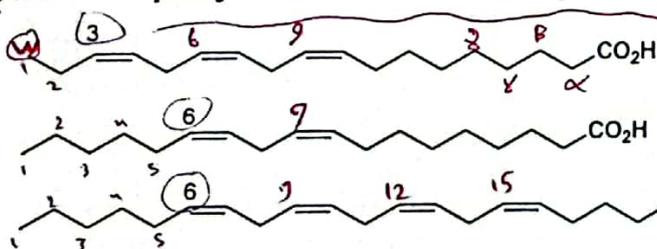
- n=10, lauric acid (C<sub>12</sub>)
- n=12, myristic acid (C<sub>14</sub>)
- n=14, palmitic acid (C<sub>16</sub>)
- n=16, stearic acid (C<sub>18</sub>)

unsaturated fatty acid



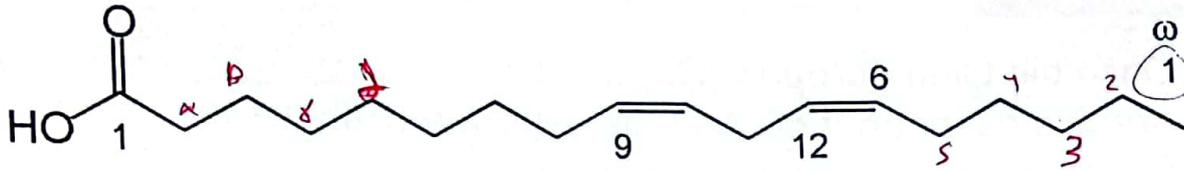
C<sub>18</sub>, oleic acid

polyunsaturated fatty acids (PUFA)



- C<sub>18</sub>, linolenic acid (Omega 3) 18:3 (3, 6, 9)
- C<sub>18</sub>, linoleic acid (Omega 6) 18:2 (6, 9)
- C<sub>20</sub>, arachidonic acid (Omega 6) 20:4 (6, 9, 12, 15)

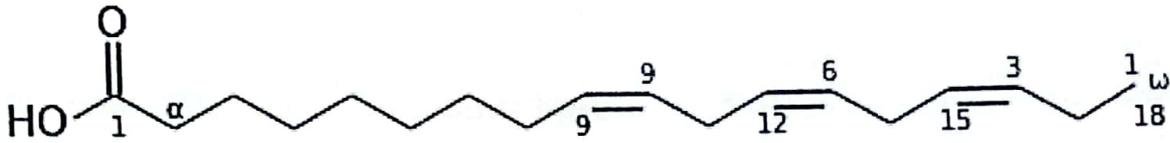
Linoleic acid  
is a polyunsaturated omega-6 fatty acid



alpha-Linolenic acid

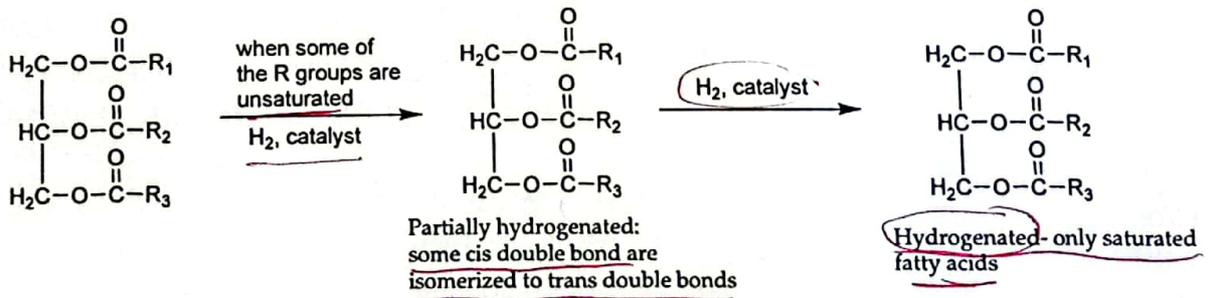
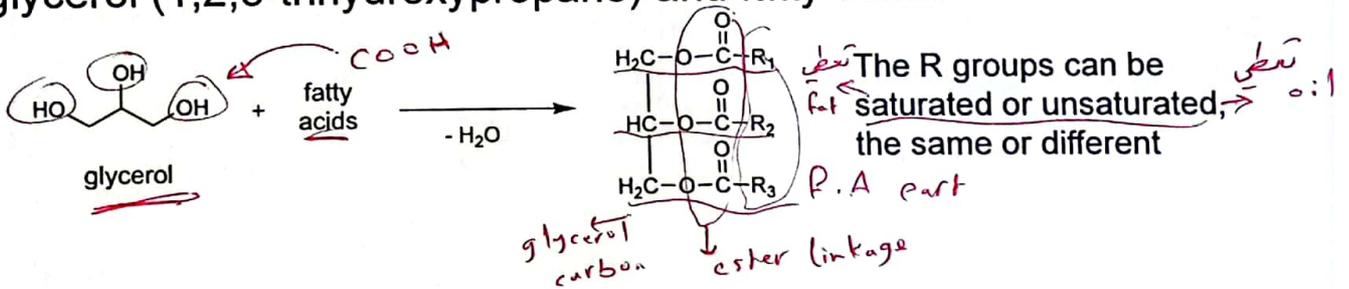
(ALA) is an  $n-3$  fatty acid, it is one of two essential fatty acids (EFAs), so called because they are necessary for health, and they cannot be produced within the human body. They must be acquired through diet.

ALA is an omega-3 fatty acid (9c, 12c, 15c)



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Fats and Oils: Triglycerides (triacylglycerols) are tri-esters of glycerol (1,2,3-trihydroxypropane) and fatty acids.



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## Some important oils/fats/waxes



+ حفظ

- Olive oil: *Olea europea* (Oleaceae)
- Arachis oil, peanut oil: *Arachis hypogea* (Fabaceae)
- Sesame oil: *Sesamum indicum* (Pedaliaceae)
- Almond oil: *Prunus amygdalus* (Rosaceae)
- Cottonseed oil: *Gossypium herbaceum* (Malvaceae)
- Soya bean oil: *Glycine max* (Fabaceae)
- Castor oil: *Ricinus communis* (Euphorbiaceae)
- Cocoa butter: *Theobroma cacao* (Sterculiaceae)
- Beeswax : *Cera flava*
- Spermaceti; *Physeter macrocephalus*

Spermaceti (from Latin *sperma* meaning "semen", and *ceti* meaning "whale") is a waxy substance found in the head cavities of the sperm whale

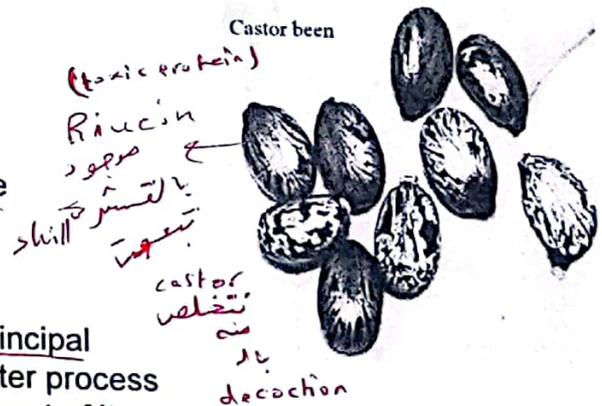
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### Castor Bean, Castor Oil Plant:

( بذور الخروع - زيت بذور الخروع )

*Ricinus communis* L. Family: Euphorbiaceae

- Castor bean Oil: ricinoleic acid
- Oil from the castor bean seeds:
- The oil is obtained from the seeds by two principal methods - expression and decoction. The latter process is largely used in India, where the oil on account of its cheapness and abundance, is extensively employed for illuminating, as well as for other domestic and medicinal purposes.



### Castor :

is a triglyceride, comprised of fatty acids, 90% of which is ricinoleic acid, 7% oleic, 3% linoleic, 2% palmitic, 1% stearic, and trace amounts of dihydroxystearic.

major component

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## Medicinal Uses

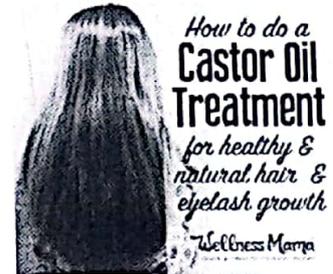
Where can I find Castor oil in the pharmacy?



1. Castor oil is used to treat Constipation it is Laxative & purgative.
2. Castor oil can be used to treat Skin Problems such as sunburn, abrasions, acne, dry skin warts.
3. Castor oil is used in hair treatment: Castor oil protects the scalp and hair from microbial and fungal infections due to the presence ricinoleic acid which has germicidal, insecticidal and fungicidal properties
4. Castor oil is used in as anti-wrinkle Treatment

### Contradictions: *ممنوع استعماله*

- Castor oil is contraindicated in intestinal obstruction and during pregnancy and nursing. *= Feeding*
- The drug can't be administered to children under 12 years

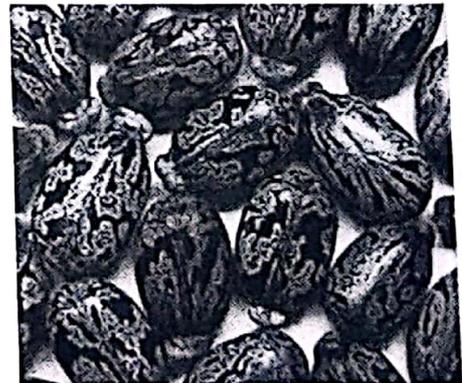


**Toxic Part in castor : The toxin Ricin is found within the hard, water-impermeable coat of the seeds. The toxin is not released unless the seed coats are broken (e.g., chewed) and the contents digested.**

### Symptoms of Poisoning

Variations in the severity of toxicity may be related to the degree to which seeds are chewed. Effects begin as nausea, *قيء*, *قيء*, *قيء* vomiting, abdominal cramping, diarrhea, and dehydration. *جفاف*

- One castor bean contains enough ricin to kill a child



# Omega 3 fats

Omega-3 fats are a key family of polyunsaturated fats. There are three main omega-3s:

1. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) come mainly from fish, so they are sometimes called marine omega-3s.  
*20:5* *22:6*  
*أكثر شيوعاً*  
*السمك* *#*
2. Alpha-linolenic acid (ALA), the most common omega-3 fatty acid in most Western diets, is found in vegetable oils and nuts (especially walnuts), flax seeds and flaxseed oil, leafy vegetables, and some animal fat, especially in grass-fed animals. The human body generally uses ALA for energy, and conversion into EPA and DHA is very limited.  
*الأكثر شيوعاً*

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## Why do we need Omega 3?

*دليل*

Alpha-linolenic acid (ALA), is found in vegetable oils and nuts (especially walnuts), flax seeds and flaxseed oil, leafy vegetables, and some animal fat, especially in grass-fed animals. The human body generally uses ALA for energy.  
*الدهون النورية*

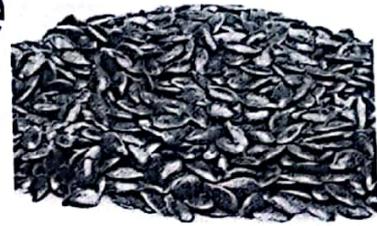
The strongest evidence for a beneficial effect of omega-3 fats has to do with heart disease. Omega-3 fats lower blood pressure and heart rate, improve blood vessel function, and, at higher doses, lower triglycerides and may ease inflammation, which plays a role in the development of atherosclerosis.  
*تصلب الشرايين*

Several large trials have evaluated the effect of fish or fish oils on heart disease. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (known as the GISSI Prevention Trial), heart attack survivors who took a 1-gram capsule of omega-3 fats every day for three years were less likely to have a repeat heart attack, stroke, or die of sudden death than those who took a placebo.  
*تكرار*

There have also been promising results from studies looking at omega-3 for cancer, depression, and attention-deficit hyperactivity disorder (ADHD). Due to these potential health benefits, fish oil, which is rich in omega-3 fatty acids, has become a popular supplement.  
*مقرباً الكوليسترول*

There is evidence that recommended amounts of DHA and EPA, taken as fish or fish oil supplements, may lower triglycerides and reduce the risk of heart attack, abnormal heartbeat, and stroke in people who have heart disorders. DHA and EPA may also benefit people who have hardening of the arteries or high blood pressure. Similar effects have been found for ALA, but more evidence is needed to support its potential benefits.

# Linseed- Flax seed بذر الكتان



- Linum usitatissimum L. Family: Linaceae.
- They're the best plant source of omega-3 fatty acids.
- Flaxseeds are also a powerful source of fiber, protein, magnesium, iron, and potassium.
- Flaxseeds are also the leading source of a class of compounds called (lignans) which are phyto-estrogens, or plant estrogens. Lignans influence the balance of estrogens in the body and help protect against breast cancer.
- The seeds must be ground, as the nutrients are difficult to absorb from the whole seeds. Since the oil in flaxseed spoils quickly, it's best to grind them as needed. Some people use a grinder dedicated to flaxseeds, grind them in small amounts, and keep the ground portion in the fridge in a small glass jar.
- Sprinkle ground flaxseeds on oat-meal, cereal, and yogurt, and use it in smoothies, pancakes, muffins, and quick breads. One to two tablespoons of ground flaxseed a day is all you need.

For post menopause women

side chain from acial esters  
dimer from phenyl propanoic derivative  
C6C7C6

معلنة كبيرة

# Linseed- Flax seed بذر الكتان



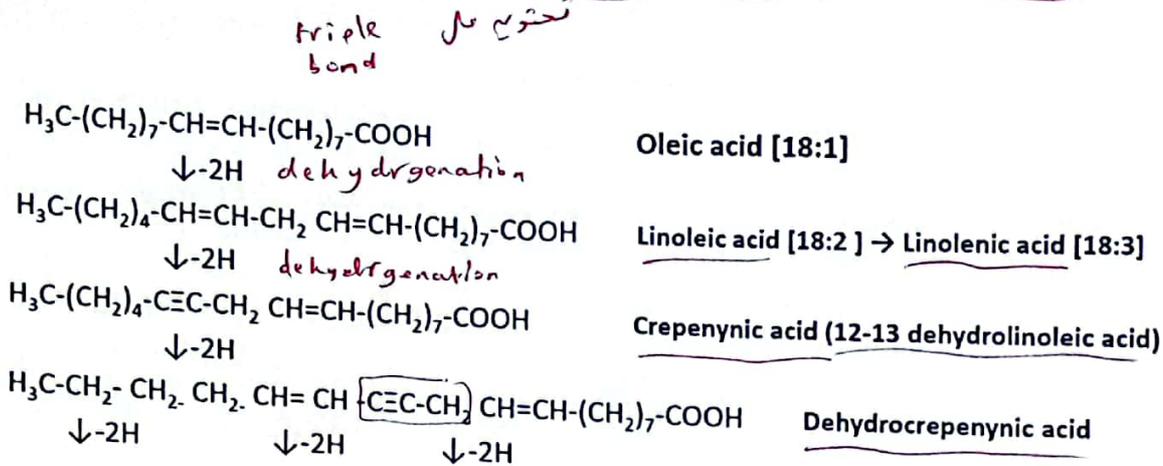
- **Active constituents:**
- Mucilages: including arabinoxylans, galactans, rhamnogalacturonans.
- Cyanogenic glycosides: Linamarin, linustatin, neolinustatin (yielding under optimal conditions 30-50 mg HCN per 100 gm).
- Linamarin (may play a role in cancer treatment)
- Fatty oil (30-45%): chief fatty acids linolenic acid, linoleic acid, oleic acid.
- Proteins.
- Gluten: Flax is gluten-free.
- Lignans: secoisolariciresinol-diglucoside
- lignans: Flax is a very rich source of a lignan called secoisolariciresinol diglucoside (SDG), which is found in amounts ranging from 1 mg/g of seed to nearly 26 mg/g of seed.
- lignans are natural antioxidants that may reduce the activity of cell-damaging free radicals, slow the aging process, and increase overall wellness.
- Besides acting as antioxidants, lignans are phytoestrogens
- Lignans are especially important for women as studies have shown them to decrease the risk of breast cancer. In addition, lignans have been proven to reduce breast cancer symptoms and reduce the spread and growth of breast cancer after diagnosis.

gally  
cyanide  
C≡N

ما صيب gluten

# Biogenesis of natural acetylenes

The precursor of the acetylenic substances is oleic acid



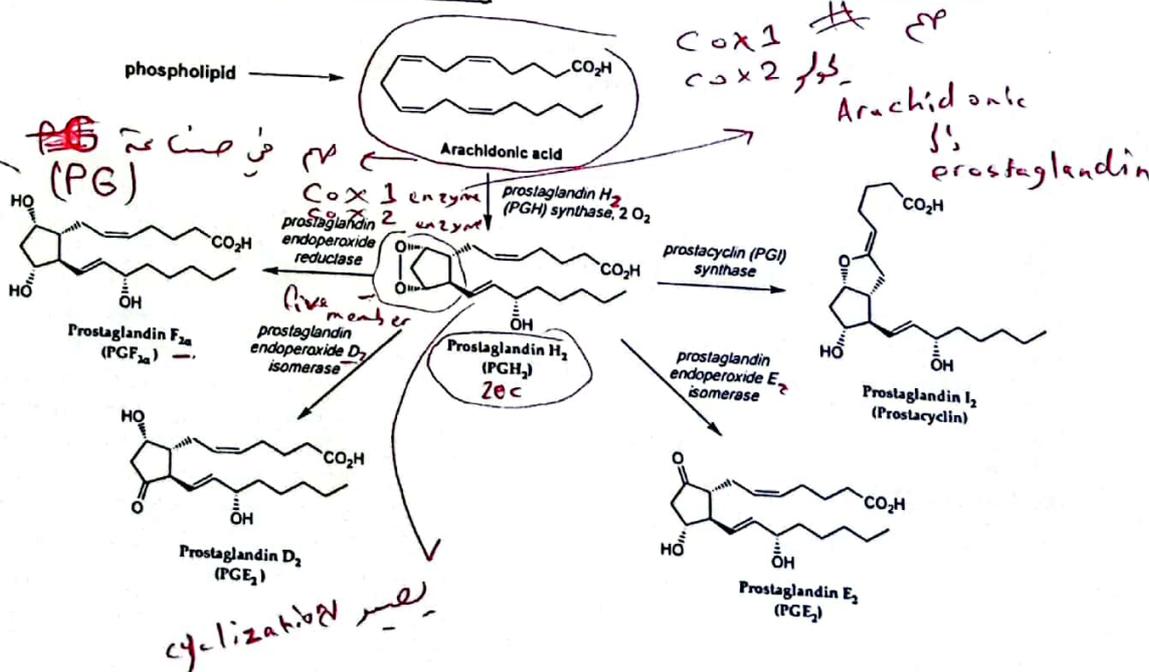
triple bond      يحتوي على triple bond  
 double bond      يحتوي على double bond  
 acetylenic substances      و هي التي تحصل على

Ref.:  
 Prof. Sulaiman Khalil

## Prostaglandin

production  
 injury  
 inflammation

The prostaglandins (PG) are a group of physiologically active lipid compounds having diverse hormone-like effects in animals. Prostaglandins have been found in almost every tissue in humans and other animals. They are derived enzymatically from fatty acid (Arachidonic acid). Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring

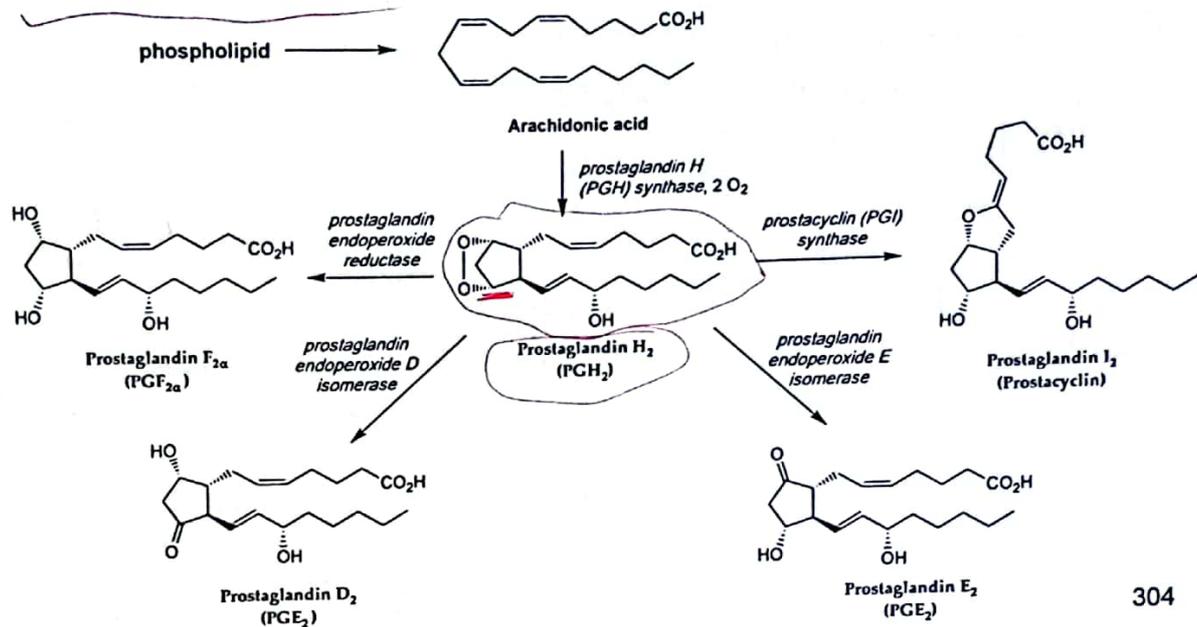


**Prostaglandins. (eicosanoids) C<sub>20</sub> compounds derived from arachidonic acid and related fatty acids**

latino name 20

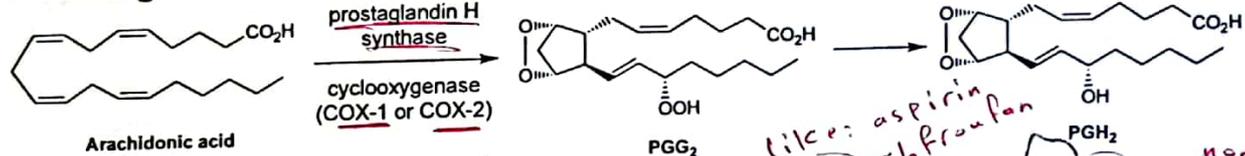
سر ادر كيميائيه ناتاقه

**hormone:** (Greek, *horman*, to set in motion) chemical messengers from one cell to another, that acts as a signal for a biochemical event.

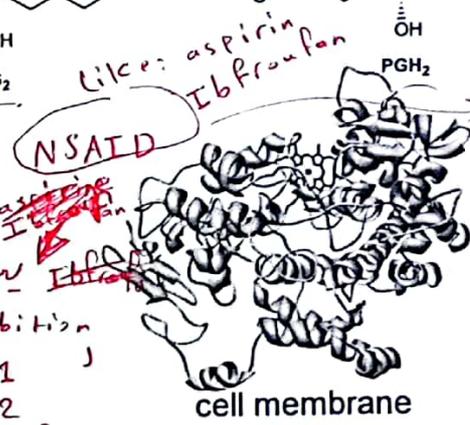


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**Prostaglandin biosynthesis**



COX-2



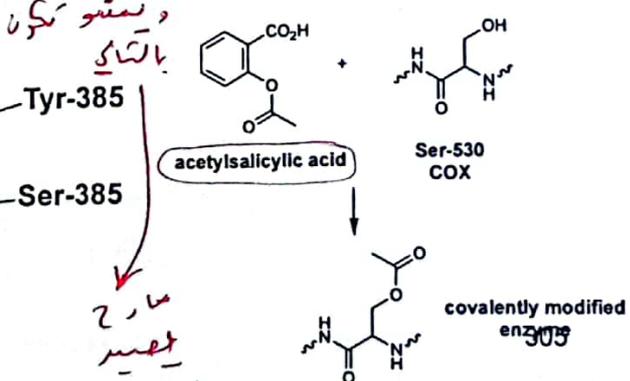
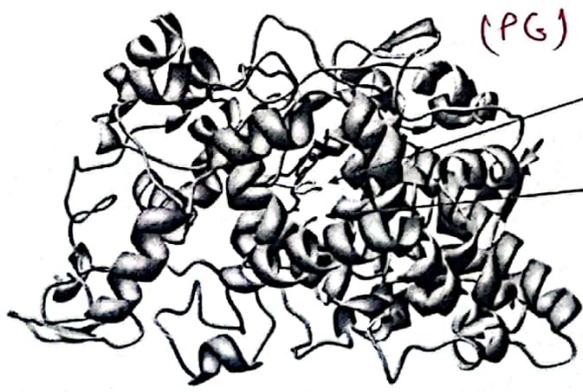
like: aspirin, Ibuprofen  
NSAID

non selective  
Cox 1/Cox 2  
ex: acetyl salicylic acid  
selective

Cox 2  
only  
ex: celecoxib

inhibition  
Cox 1  
Cox 2

cell membrane



2, 3, 4  
Pain, redness, fever, swelling

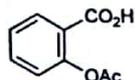
*In GI*  
 generate PG which involved in protection of GI mucus  
 mediate inflammation and pain in sites throughout the body

COX-1 is a constitutive enzyme that is expressed in virtually all mammalian cells

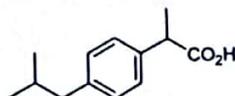
COX-2 is an inducible enzyme that is expressed as a result of a biochemical response; expressed in phagocytes (macrophages) as part of an inflammation response.

NSAIDs: non-steroidal anti-inflammatory drugs

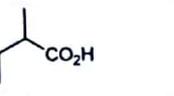
Aspirin, ibuprofen, and naproxen are non-selective inhibitors of COX



(celecoxib)

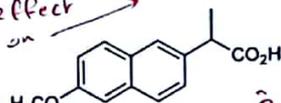


(rofecoxib)



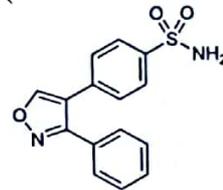
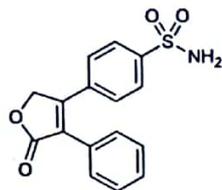
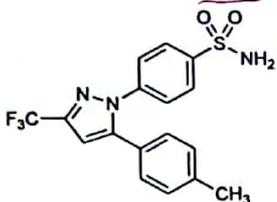
(valdecoxib)

side effect on GI effect → *GI effect*



Celebrex, vioxx, and brextra are selective inhibitors of COX-2 (coxibs)

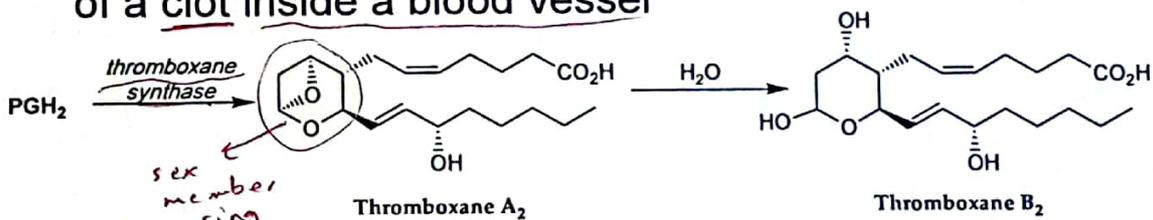
✓ Cardiovascular effect



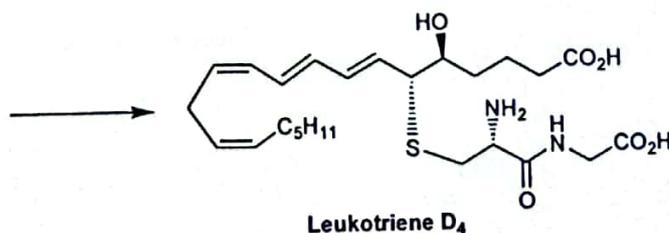
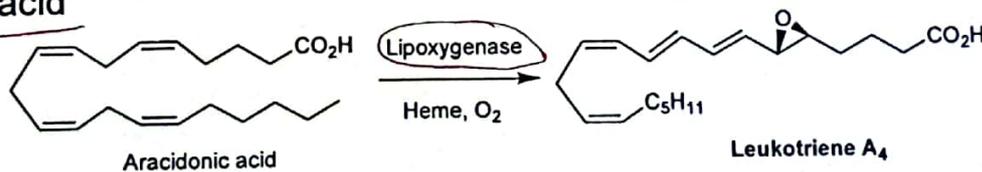
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*sex member ring*

Thromboxanes: named for their role in thrombosis, the formation of a clot inside a blood vessel



Leukotrienes: a family of eicosanoid inflammatory mediators produced in leukocytes by the oxidation of the essential fatty acids arachidonic acid



## Antibiotics derived from the acetate metabolism

### 1- Antibiotics with fused ring system:

- Griseofulvin

- Tetracyclines

- Anthracyclines

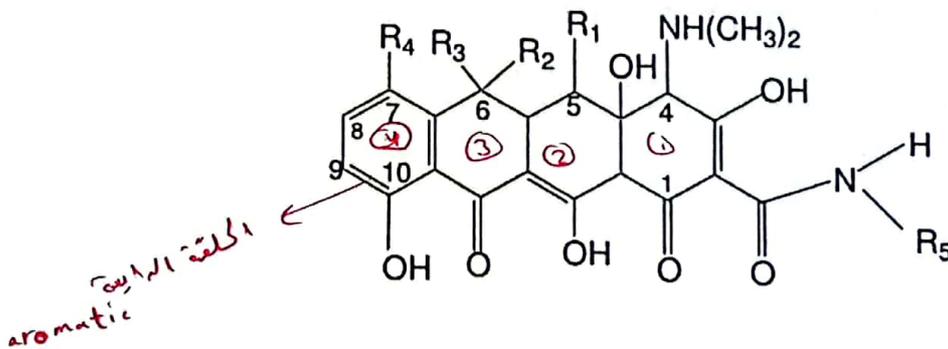
### 2- Macrolide antibiotics

### 3- Polyene antibiotics

## Tetracyclines

حفظ

4 → cyclic structure



# Tetracyclines

- Biosynthesized from 1 MalonamylCoA + 8 MalonylCoA من كل درجة
  - (1NH<sub>2</sub>-CO-CH<sub>2</sub>-CO-SCoA + 8 HOOC-CH<sub>2</sub>-CO-SCoA) → C-19 Polyketide → → cyclisation → C-6 methylation → OH at C-4 → dearomatization → 4-keto derivative → Cl<sup>-</sup> at C-7 → amination and stepwise methylation at C-4 → hydroxylation C-6 → reduction of double bond in ring B
- Biosynthesized in *Streptomyces* spp. (*S. aureofaciens*, *S. rimosus*,...)
- Broad spectrum activity يعني قادر المركب يستعمل على other pathogenic bacteria
- Protein synthesis inhibitor
- Side effects!

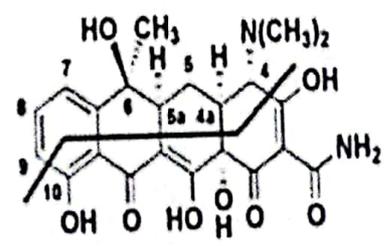
X

X

↓  
من اصفر  
يعمل  
discoloration of teeth + chelating agent  
يعني انه يرتبط مع الحديد  
specific for calcium

## Tetracyclines

Positions amenable to modification



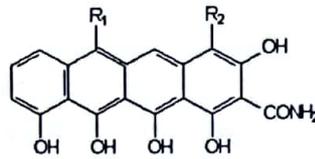
Positions believed to be key to ribosomal binding

↓  
يعني قادر على منع ال protein synthesis في البكتيريا

# Biosynthesis

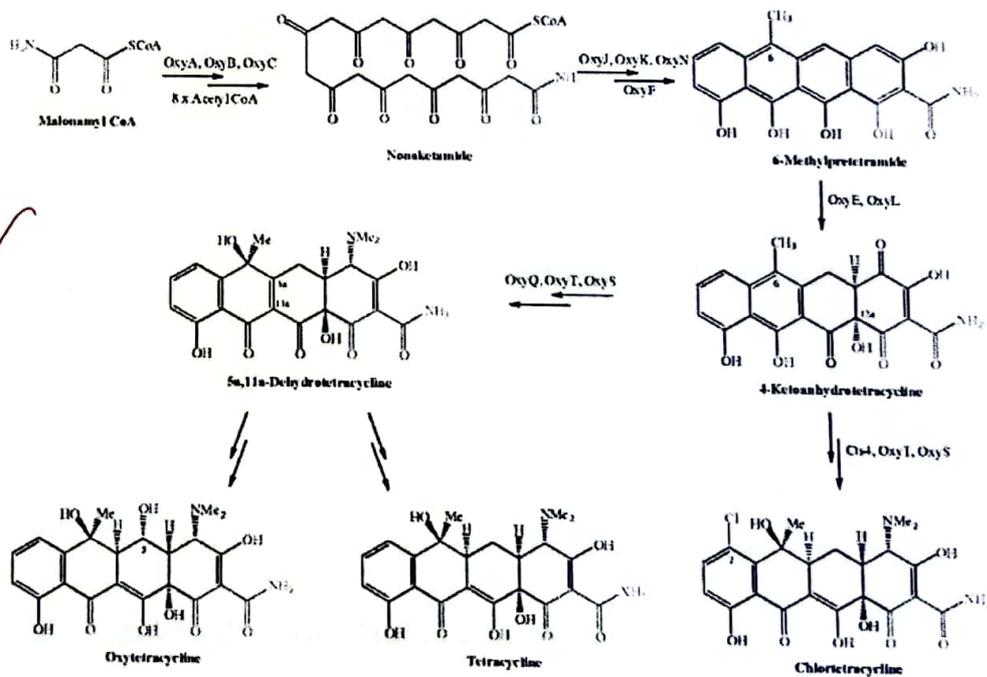
غير مطلوب

- A biosynthesis of tetracycline, particularly in its latter stages, has been studied with the use of mutant cultures. It has been established that the so-called **pretetronids**:



- are intermediates, convertible by non-mutated *Streptomyces aureofaciens* into tetracyclines. Cosynthesis, by use of blocked mutants, has demonstrated that 4-hydroxy-6-methylpretetranid ( $R_1 = \text{Me}$ ,  $R_2 = \text{OH}$ ) is a transformable intermediate and the precursor of the 6-methyltetracyclines. The complete biosynthesis is as follows :

غير مطلوب



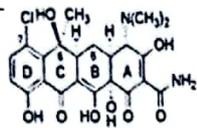
directly synthesizing in the bacteria without any change modification.

Naturally occurring: Tetracycline, Chlorotetracycline, Oxytetracycline, Demeclocycline

Semi-synthetic: Doxycycline, Meclocycline, Methacycline, Minocycline, Tigecycline,...

chemical modification structure

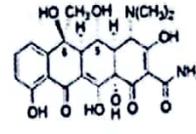
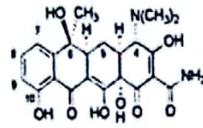
Natural Tetracyclines:



US FDA Approval:

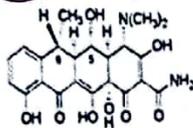
1950 Chlorotetracycline

1953 (-)-Tetracycline

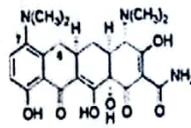


1964 Oxytetracycline

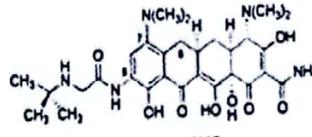
Semi-Synthetic Tetracyclines:



1967 (-)-Doxycycline



1971 (-)-Minocycline



2005 (-)-Tigecycline

من المطلوب نظرهم

السنوات من المطلوب كان

**Antineoplastic anthracycline derivatives**

Produced by cultures of *Streptomyces* spp.; inhibit DNA dependent RNA synthesis

SE: nausea, bone marrow depression, hair loss, local tissue necrosis;

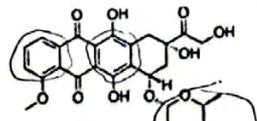
Biosynthesis: 1 PropionylCoA + 9 MalonylCoA

anticancer + antibacterial effect

مما يؤدي الى قتل cancer cell

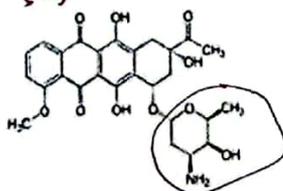
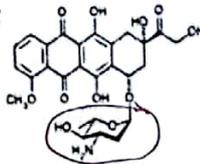
مطلوب تعرف زيج هيك 4 cyclic structure اثنى من اروماتيك اminated sugar من المطلوب هيك

**Doxorubicin**

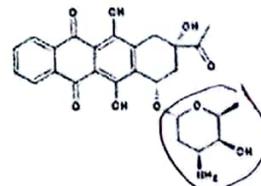


aminated sugar

**Epirubicin**



**Daunorubicin**



**Idarubicin**

### Griseofulvin:

Produced by *Penicillium* spp (*P. griseofulvum*, ...)

1 AcetylS-CoA + 6 MalonylS-CoA → Polyketide →  
Griseophenone C → B → A → Dehydrogriseofulvin →  
Griseofulvin

هذا المطلوب بس

structure 11 عبارة  
two aromatic ring  
esteric ring



esteric lactone ring

penicilline

↑

13:15

### Macrolide antibiotics

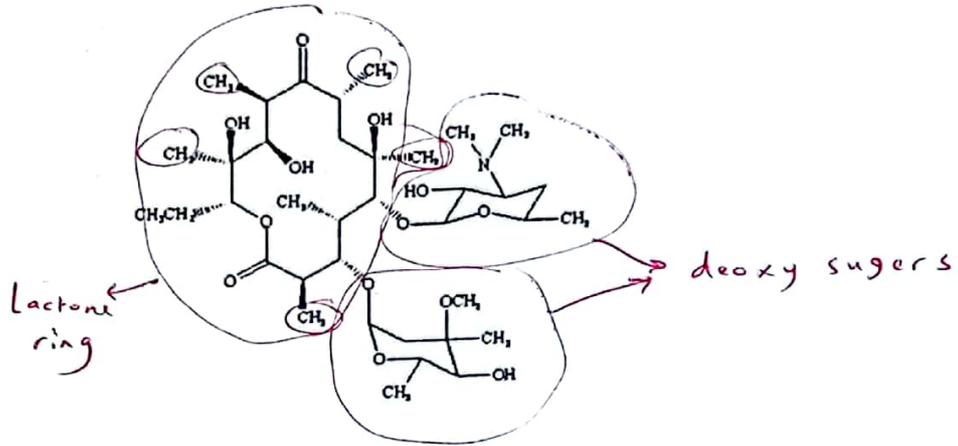
important

upper respiratory tract infection

- ❖ Synthesized from acetate units
- ❖ Produced by *Streptomyces* spp. <sup>ملا بلا</sup>
- ❖ Large lactone ring (12, 14, 16 or 17 atoms)
- ❖ Numerous CH<sub>3</sub> substituents in lactone ring
- ❖ 1-3 deoxy-sugar/sugar moieties attached to the ring
- ❖ Erythromycin A, B as examples
- ❖ Mainly active against Gram-positive bacteria and *Mycoplasma* spp.; useful in pat. with penicilline allergy
- ❖ Protein synthesis inhibitors
- ❖ SE: few, mainly GI symptoms

مربط

**Erythromycin A:** 1 [PropionylCoA] + 6 [2-MethylmalonylCoA] → Poly-keto-acid → condensation → Erythronolide ring (14 atoms) → glycosidation → Erythromycine (Azithromycine is its semi-synthetic analog)  
 [ 1 CH<sub>3</sub>-CH<sub>2</sub>-CO-SCoA + 6 HOOC-CH-(CH<sub>3</sub>)-CO-SCoA ]



## سلسلة Polyenes double Bond

- The group of antibiotics known collectively as polyenes is characterized by a large lactone ring (20–44 membered) containing a series of conjugated double bonds.
- The macrolide ring is often linked via a hydroxyl group to an aminosugar unit
- The macrolide ring is probably derived from acetate and propionate. *acetate malonate pathway*
- They are often mixtures of closely related compounds.
- Streptomyces are the usual producing organisms, and to date over 200 polyenes have been claimed
- Candida albicans is susceptible to the polyenes
- Cutaneous, intestinal and vaginal infections of Candida

Hydroxyl group  
مربط  
sugar

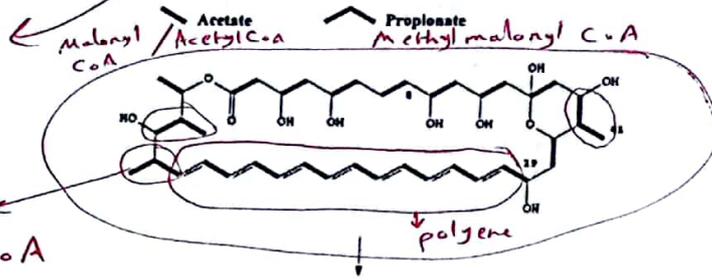
# Example of polyene

**Amphotericin B:** formed of 16 acetate units (1 AcetylCoA + 15 MalonylCoA) + 3 MethylmalonylCoA; macrolactone ring followed by glycosidation with D-mycosamine via OH at C-19

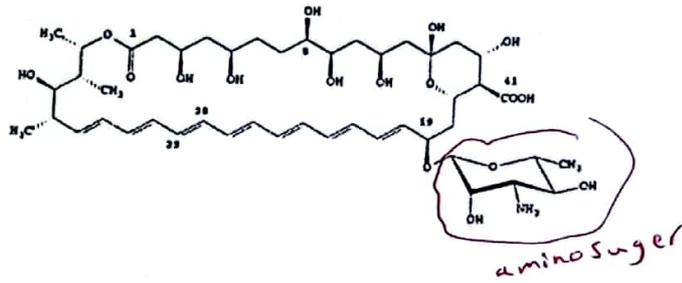
$32 = 16 \times 2$   
carbon

$9 = 3 \times 3$   
carbon

methyl malonyl CoA

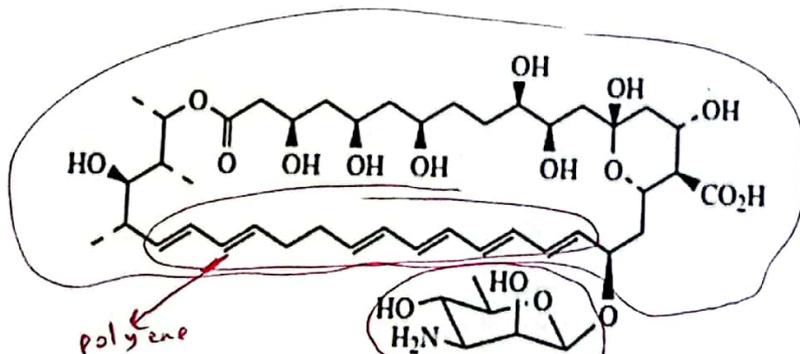


22-44 atom



## Nystatin A<sub>1</sub>

Anti fungal



Large lactone ring

polyene

nystatin A<sub>1</sub>

D-mycosamine

amino acid ~~sugar~~ sugar