Phytotherapy

Terpenes

Faculty of Pharmacy

Dr. Yousef Abusamra

Terpene compounds

They comprise a large group of compounds in plant kingdom

1- Monoterpenes (cyclic, acyclic)
2- Sesquiterpenes
3- Diterpenes
4- Sesterterpenes
5- Triterpenes
6- Sesquarterpenes
7- Tetraterpenes
8- Polyterpenes

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Terpenoids compounds

{{{The **terpenoids**, sometimes called **isoprenoids**, are a large and diverse class of naturally occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways.

- Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products. About 60% of known natural products are terpenoid.
- Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies. Terpenoids contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, the yellow color in sunflowers, and the red color in tomatoes.}}}

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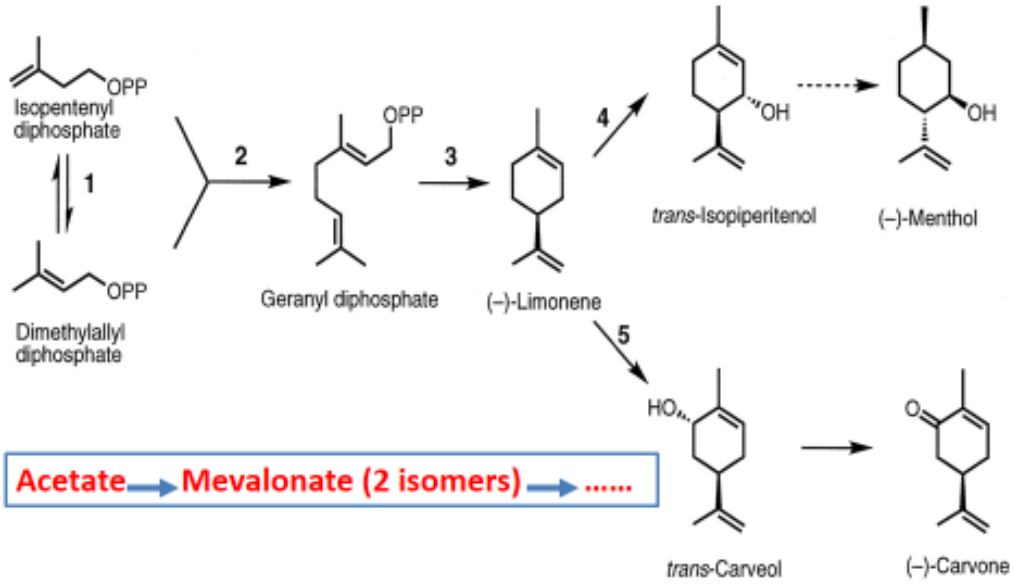
Biosynthesis of monoterpenes



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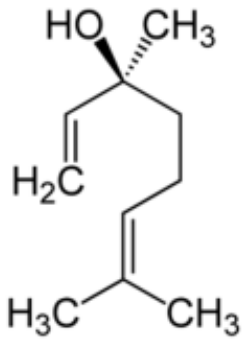
Acyclic monoterpenes

❖Linalool:



- Found in aromatic plants like *Rosmarinus officinalis*.
- Used in:

1. Perfume industry.
2. Cosmotics .
3. As preservative.

Medicinal uses:

1. A potent antimicrobial for G-negative and G-positive bacteria as well against yeast.

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Linalool

2. Anti-spasmodic.
3. Sedative activity to counteract the convulsant activity (Rats experiment)
4. Local anesthetic.

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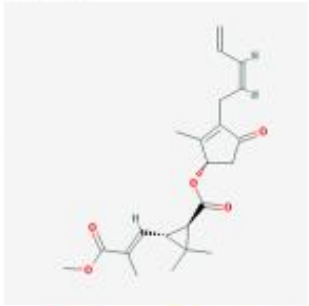
Cyclopropane monoterpenes

❖ Pyrethric acid and chrysanthemic acid:

- They arevtransformed into pyrethrin which is a compound used as insecticide for certain types of insects like spiders, lice, as well as potentially disease-carrying mosquitoes.

Pyrethric acid



Pyrethrin

- In the flowers of *Chrysanthemum cinerariaefolium*.
- Efficient contact insecticide but harmless to human.

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Cyclopropane monoterpenes

- *Chrysanthemum cinerariaefolium* أقحوان رمادي الورق

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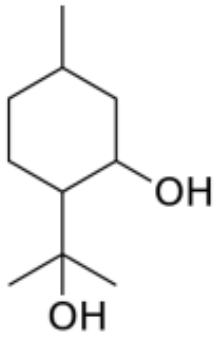
Menthanes monoterpenes

- {{*p*-Menthane-3,8-diol, also known as *para*-menthane-3,8-diol, PMD, or **menthoglycol**, is an active ingredient used in insect repellents. It smells similar to menthol and has a cooling feel.



- There are eight possible isomers of PMD, and the exact composition is rarely specified and is commonly assumed to be a complex mixture.}}

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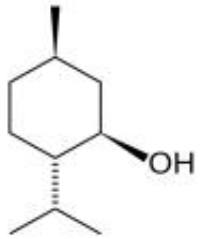
Menthane monoterpenes

- Menthol: found in *Mentha piperita* leaves which contain v.oil as the chief constituents.
- The oil is distilled from **young** plants containing large quantities of menthofuran with a **lower** grade than the one from **old** plant.



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Menthol uses

- Antibacterial.
- Antipruritic.
- Chilling sensation when applied on skin, thus can be used as a remedy for **itching**.
- The volatile oil is largely consumed for making tooth pastes, chocolate and sweets.

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Citrus essential oil

- **Citrus fruits** contain v. oils in the peels in the schizolysigenous pockets located in the outer layer of the mesocarp.
- **Bergamot oil:** from ***Citrus aurantium*** (Bitter orange) which contains **limonene**, **β-pinene**, **ϒ- terpinene** and **bergapten** which causes photosensitivity {{(5-methoxypsoralen) is a psoralen (also known as furocoumarins) found in bergamot essential oil, in other citrus essential oils, and in grapefruit juice}}

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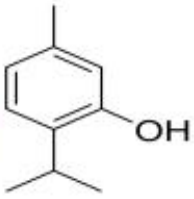
Thymus species

- *Thymus vulgaris* الزعتر has different chemotypes .
- The **bactericidal** activity is strongest for thymol and carvacrol-containing types.
- Traditionally, thyme is used as antispasmodic and for cough.
- Locally, it is used to treat minor wounds, analgesic for oral cavity.
- Used for common cold.



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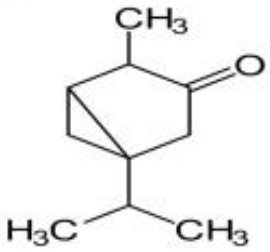
Thujone monoterpene

- Thujone: found in Artemisia species as α-thujone and β-thujone.
- It is a poisonous monoterpene ketone.
- They induce genotoxicity, neurotoxicity, reproductive toxicity and carcinogenicity.
- They are convulsant due to blockage of the GABA, (ϒ – aminobutyric acid) receptors.



Artemisia absinthium

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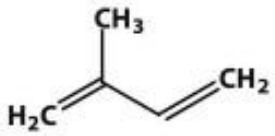
Sesquiterpenes

{{**Sesquiterpenes** are a class of terpenes that consist of three isoprene units and have the empirical formula $C_{15}H_{24}$.



Isoprene

- Like monoterpenes, sesquiterpenes may be **acyclic** or contain **rings**, including many unique combinations.
- Biochemical modifications such as oxidation or rearrangement produce the related **sesquiterpenoids**.}}

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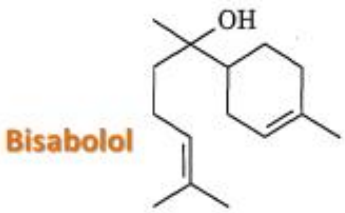
Sesquiterpenes

Plants containing sesquiterpenes:

- *Matricaria recutita*: (German chamomile) البابونج الألماني consists of the flower heads.
- Main constituent: volatile oil which contains **bisabolol** up to 50%.
- Bisabolol has an anti-ulcer activity.
- Also it contains **chamazulene** which has a blue color.



Bisabolol

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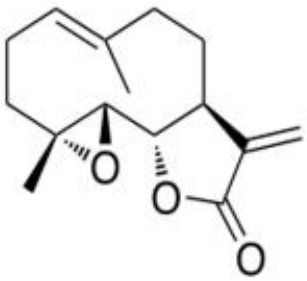
Feverfew

أقحوان زهرة الذهب

- *Tanacetum parthenium*:

➢ This plant has a strong aromatic odor .

➢ It contains parthenolide which is a prophylactic remedy for migraine.



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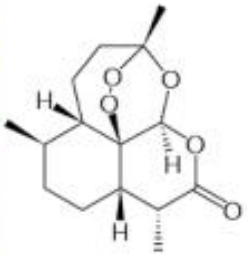
Artemisia annua

شيح حولي

- Is cultivated in China and other East Asian countries.
- Artimisinine is found in the leaves or flower tops.
- It is toxic to malaria parasites at nano-molar concentrations.



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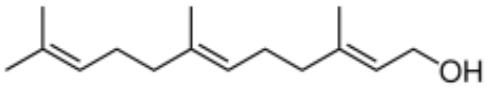
Sesquiterpenes

Farnesol:

- is a natural acyclic 15-carbon organic compound which is an acyclic sesquiterpene alcohol.
- It is hydrophobic, thus insoluble in water, but miscible with oils.



- It is doubled to yield squalene (30 carbons), which is the precursor to steroids in plants, animals and fungi.
- It is found in rose essential oil.
- Examples of botanical source: star anise, cassia قرفة صينية, citronella حشيشة الليمون أو الإذخر الليموني and rose.

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Sesquiterpenes

Uses:

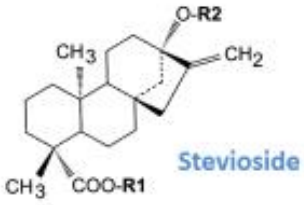
- Skin care products:
  - Smoothening effect on wrinkles and enhances skin vitality and elasticity.
  - Regulation of sebum production.
  - Activates collagen and elastin production.
- Moisturizing effect.
- Bactericidal effect.
- Antiinflammatory and anti-allergic effect.
- Is used in the manufacture of perfumes.

Citronella 37

Diterpenes

***Stevia rebaudiana*: ستيفيا ريباوديانا**

- It is **native** to Brazil and cultivated in many parts of the world.
- The leaves contain glycosides such as stevioside which is a natural sweetener.
- It is 200 time more potent than sucrose and devoid of toxicity



Stevioside

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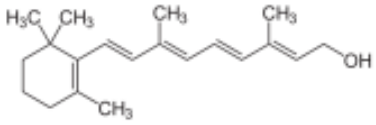
Diterpenes

Retinol:

- **Retinol**, also known as **Vitamin A_1**, is a vitamin found in food and used as a dietary supplement.
- Is abundant as such only in the animal kingdom, particularly in fish-liver oil



[a nutritional supplement derived from liver of cod fish].

- Occurs in 3 forms, **retinol**, **retinal** and **dehydroretinal** (vit. A_2- has a second unsaturated double bond in the ring system).
- Carotenes (40 C's) found in the plant kingdom and are converted to vitamin A in the small intestine and other organs (each molecule of a carotene gives only one molecule of vitamin A).
- Vitamin A is essential for the normal functioning of the body

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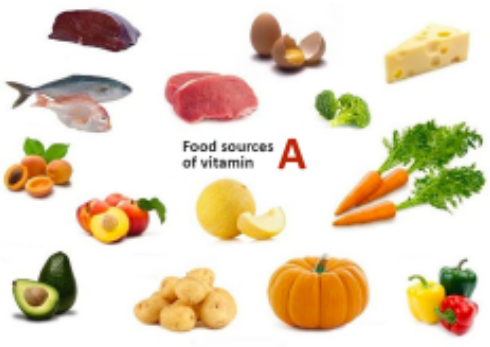
Diterpenes

… epithelia and retina.

- Deficiency is indicated in night blindness and by a drying and crusting تقشر of the mucous membranes.

- Excess preformed vitamin A during early pregnancy has also been associated with a significant increase in birth defects.



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Diterpenes –retinol (vitamin A1)

Vitamin A - toxicity

- Toxic dose:
  - single dose of more than 200 mg
  - more than 40 mg per day
- Acute symptoms - headache, vomiting, impaired consciousness.
- Chronic intoxication – weight loss, vomiting, pain in joints, muscles, blurred vision, hair loss, excessive bone growth.
- Both vit. A excess and deficiency in pregnancy are teratogenic – retinoic acid is gene regulator during early fetal development
- Carotenoids are non toxic - accumulation in tissues rich in lipids (the skin of babies overdosed with carrot juice may be orange).

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Sesterterpenes

- A recently recognized family of 25-carbon compounds.
- Formed by the addition of a C5 isopentenyl unit to gerenyl gerenyl diphosphate (gerenyl contains 10 carbons).
- Examples are mainly confined to fungi, some marine organisms (e.g. sponges) and insect waxes.

❖ **Manolide** is the parent compound of a series of marine sponge metabolites belonging to the sesterterpene class.

❖ Manolide displayed antibacterial activity against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) but was inactive against *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*.

❖ Manoalide was further investigated and found to be a potent inhibitor of phospholipase A_2 (anti-inflammatory effect.)

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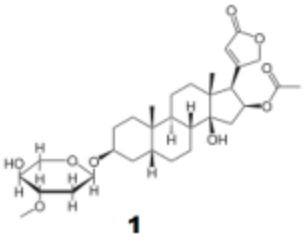
Triterpenes and triterpenoids

- These C30 are abundant in nature, particularly in resins, and may occur as glycosides or esters.
- They may be aliphatic (e.g. squalene, compound **3**, found in animals), tetracyclic or and pentacyclic.
- Tetracyclic such as the cardiac glycosides (compound **1**).
- Triterpenoid saponins, most of which are pentacyclic (compound **2**). (studied earlier).



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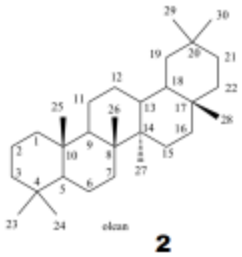

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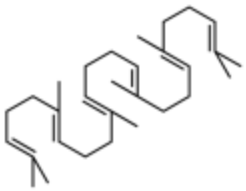

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Sesquarterpenes

- Sesquarterpenes are composed of *seven isoprene* units and have the molecular formula $C_{35}H_{56}$.
- Sesquarterpenes are typically microbial in their origin.

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Tetraterpenes – carotenoids

- Contain *eight isoprene* units and have the molecular formula $C_{40}H_{64}$.
- Important among these compounds are the yellow or orange-red carotenoid pigments of which about 500 have been reported.
- They are formed by the tail to tail union of two molecules of the C_{20} geranylgeranyl diphosphate to give an acylic intermediate with a *cis*-configuration of the central double bond.

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Tetraterpenes – carotenoids

tail to tail

- By a change of configuration of the latter to *trans* and further desaturation of the isoprenoid chain, **lycopene**, the all-*trans* pigment of the ripe tomato fruit is formed.
- The various **carotenes** and derivatives can be formed by cyclization of one or both **ends** of the lycopene molecule.

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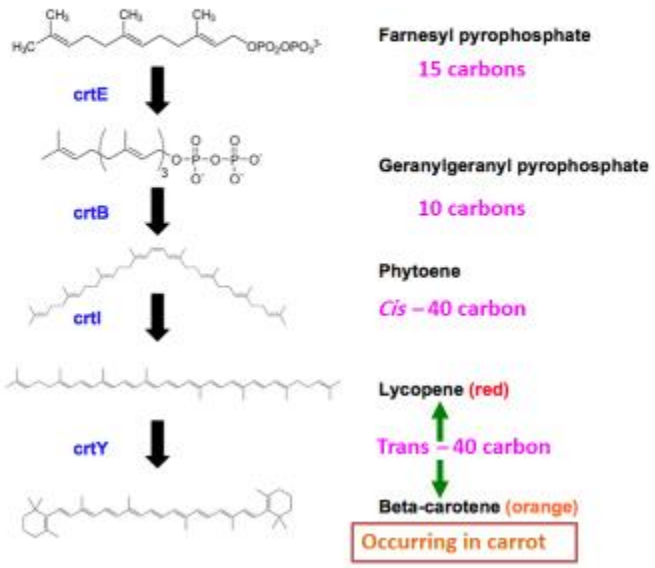
Tetraterpenes – carotenoids



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Tetraterpenes – carotenoids

- There are many derivatives of the carotene molecule.

Carotenoid	Formula	Occurrence
Bixin	$C_{25}H_{30}O_4$	Annatto بكسة أورلانية
Capsanthin	$C_{40}H_{56}O_3$	*Capsicum* spp.
Capsorubin	$C_{40}H_{60}O_4$	*Capsicum* spp.
Crocetin	$C_{20}H_{24}O_4$	Saffron
Crocin	$C_{44}H_{64}O_{24}$	Saffron
Fucoxanthin	$C_{40}H_{60}O_6$	Brown algae
Lutein	$C_{40}H_{56}O_2$	*Tagetes erecta* مخملية قائمة (Mexican marigold)

Annatto

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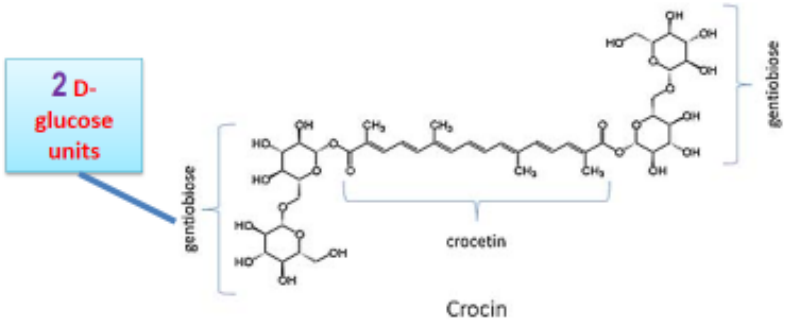
Tetraterpenes – carotenoids



Crocin

Benefits of carotenoids:

As antioxidants, carotenoids are helpful for protecting vision and combating cellular damage. Recent studies have also identified carotenoids as paramount supporters for the cardiovascular system and male reproductive health. Lycopene, a carotenoid found in tomatoes (among other fruits and vegetables), has even been linked to keeping the liver, prostate, breast, colon, and lungs healthy.

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Tetraterpenes – carotenoids

Five benefits of carotenoids can be summarized as follows:

1. Support eye health: carrots are an excellent source of carotenoids, including retinol and pro-vitamin A, both of which have therapeutic value for degenerative diseases of the retina.
2. Cardiovascular health: population-based studies have demonstrated that carotenoids are effective for supporting cardiovascular health.
3. Possible anti-tumor properties: owing to their chemical structures, they can combat tumor formation. They also reinforce the immune system and have effects against harmful organism, two effects are thought to have some relations with tumor formation.
4. Male fertility: the antioxidant activity of carotenoids have been demonstrated to increase chances of pregnancy occurrence owing to their antioxidant effect which is highly beneficial for sperm health.61

Tetraterpenes – carotenoids

5. Skin health: studies have reported that the carotenoids such as beta-carotene protect skin, tissue, and cells from environmental toxins and disease. Carotenoid-rich nutrients can be accessed easily with a diet rich in fresh fruits, vegetables, nuts, and seeds.

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Polyterpenes

- Consist of long chains of *many isoprene* units.
- Natural **rubber** consists of polyisoprene in which the double bonds are *cis*.
- Some plants produce a polyisoprene with *trans* double bonds.

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