Biosynthesis of coumarins

\[
\text{cinnamic acid} \xrightarrow{(a)} \text{o-coumaric acid} \xrightarrow{(b)} \text{o-coumaric acid-\(\beta\)-D-Glucoside} \xrightarrow{(c)} \text{coumarin}
\]
Khellin

- It is a furanochromone, an organic compound which is a derivative of chromone (1,4-benzopyrrone) and furan.
- It has lipophilic properties and causes vasodilation (widening of blood vessels).
- It is found in the plant *Ammi visnaga* (Family: Apiaceae) which has been used in Egyptian folk medicine.
- It has activity as a spasmolytic and vasodilator.
In Egypt, the plant "Khella" was used for **renal colic**. The incidence of **renal colic** was due mostly to **schistosomiasis** (bilharzia, snail fever) infections and stone formation.

The plant mixture **had diuretic properties** that were seen to relieve renal colic in Egyptian folk medicine.

After the chemical compound **khellin** was identified, people began to study its properties. It was found to **relax the ureter** and **coronary arteries**.

**It is not used as a systemic medication because:**

1. It is difficult to absorb.
2. It causes a range of undesirable side effects such as dizziness, headache, gastrointestinal disorders and nausea.

However, it has been used successfully to **treat vitiligo by topical application**.
In the early 20th century, researchers searched for khellin analogs with lower toxicity and better efficacy.

A number of drugs were discovered through this research and amiodarone and cromolyn sodium are khellin analogs used in current medical practice.
Bergapten (5-methoxypsoralen)

- Is a furomcoumarin found in:
  - Bergamot essential oil (Citrus bergamia, the bergamot orange is a fragrant fruit having the size of an orange, with a yellow color similar to a lemon)
  - Other citrus essential oils.
  - In grapefruit juice.
- These compounds may be produced by the plant as a protection mechanism **against high doses of sunlight** and some coumarins are **formulated into sunscreens** and cosmetics for this purpose.
- Bergapten-free bergamot essential oil or synthetics are now used in **perfumery**.

![Chemical structure of bergapten](image-url)
Aesculin is a coumarin glucoside that naturally occurs in the horse chestnut, *Aesculus hippocastanum* and family *Hippocastanaceae*).

- **Medicinal Uses**: As medication, aesculin is sometimes used as a vasoprotective agent.
- **Laboratory use**: Aesculin is also used in a microbiology laboratory to aid in the identification of bacterial species.
- Aesculin is incorporated into agar with ferric citrate and bile salts (bile aesculin agar). **Hydrolysis of the aesculin** forms **aesculetin** (6,7-dihydroxycoumarin) and glucose. The **aesculetin forms dark brown or black complexes with ferric citrate**, allowing the test to be read.
- **Aesculin will fluoresce** under long wave ultraviolet light (360 nm): hydrolysis of aesculin results in loss of this fluorescence.
- A positive test can occur with *Enterococcus, Aerococcus* and *Leuconostoc*. 
Picrotoxin (also known as cocculin)

- Is a poisonous crystalline plant compound, first isolated by Pierre Boullay in 1812.
- The name "picrotoxin" is a combination of the Greek words "picros" (bitter) and "toxicon" (poison).
- Found primarily in the fruit of the climbing plant *Anamirta cocculus*.
- It has a strong physiological action.
- It acts as a noncompetitive antagonist for the GABA$_A$ receptor chloride channels.
- It is therefore a channel blocker rather than a receptor antagonist.
- As GABA itself is an inhibitory neurotransmitter, infusion of picrotoxin has stimulant and convulsant effects.
- As such, picrotoxin can be used to counter barbiturate poisoning that can occur during general anesthesia or during a large intake outside of the hospital.
Terpenes and Terpenoids

• **Terpenes** - *Class of >20,000 natural organic compounds containing carbon atoms in multiples of five (5)*

• **Terpenoids** - *Oxygen-containing terpenes* *(alcohols, ketones, aldehydes)*

• The name ‘terpene’ is derived from the Greek word ‘terebinth’. Terebinth is a type of pine tree from which terpene-containing resins are obtained.

• Terpenes and terpenoids are the primary constituents of the *essential oils* of many types of plants and flowers.

![Molecular structures](image.png)

- menthol
  - peppermint oil
- geraniol
  - geranium oil
  - (rose oil)
- zingiberene
  - oil of ginger
  - (zencefil)
- $\beta$-selinene
  - oil of celery
  - (kereviz)
• The basic molecular formulae of terpenes are multiples of \((C_5H_8)_n\) where \(n\) is the number of linked isoprene (2-methyl-1,3-butadiene) units. This is called the isoprene rule or the \(C5\) rule.

• All terpenes are built up from units of isoprene- isoprene units linked in a “head-to-tail” fashion
  
  • “Head” - branched end of isoprene
  
  • “Tail” - unbranched end of isoprene

One isoprene unit contains five carbon atoms
Building of terpenes from isoprene

Isoprene units can be linked:

- head to tail to form **linear terpenes**
- in rings to form **cyclic terpenes**.

**Myrcene – a linear terpene**
Myrcene is a component of plants, including bay, ylang-ylang and thyme.

![Myrcene structure]

112
Menthol – a cyclic terpenoid

Limonene – a cyclic terpenoid

Limonene (skin of citrus fruits)
(a strong smell of oranges)

This terpene has been oxidised to a terpenoid

Menthol (peppermint)
\(\beta\text{-carotene} \text{ (Tetraterpene)}\)  

8 isoprene units (40 carbon atoms)  

\(\beta\text{-carotene} \) is the compound that causes carrots and apricots to be orange
Monoterpenes consist of two isoprene \((10C)\) units and have the molecular formula \(C_{10}H_{16}\). Examples: geraniol, limonene and terpineol.

Sesquiterpenes consist of three isoprene \((15C)\) units and have the molecular formula \(C_{15}H_{24}\). Examples: humulene, farnesenes, farnesol.

Hemiterpenes consist of a single isoprene unit. Isoprene itself is considered the only hemiterpene.

But oxygen-containing derivatives are hemiterpenoids such as prenol (found in citrus fruits, cranberry, grapes, raspberry, blackberry, tomato) and isovaleric acid (found in essential oils).

<table>
<thead>
<tr>
<th>Carbon atoms</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>monoterpenes</td>
</tr>
<tr>
<td>15</td>
<td>sesquiterpenes</td>
</tr>
<tr>
<td>20</td>
<td>diterpenes</td>
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<tr>
<td>25</td>
<td>sesterterpenes</td>
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<tr>
<td>30</td>
<td>triterpenes</td>
</tr>
<tr>
<td>40</td>
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• **Diterpenes** are composed of *four isoprene units (20C)* and have the molecular formula **C$_{20}$H$_{32}$**.

• Diterpenes also form the basis for biologically important compounds such as **retinol**, **retinal**, and **phytol**. They are known to be antimicrobial and antiinflammatory.

![Chemical structure of squalene](image)

**Retinol** is one of the forms of **vitamin A**

• **Sesterterpenes**, consist of *five isoprene units (25 carbons)*, Example: geranylfarnesol.

• **Triterpenes** consist of *six isoprene units* with molecular formula **C$_{30}$H$_{48}$**. The linear triterpene **squalene**, the major constituent of **shark liver oil**.

• **Squalene** has a natural and vital part in the synthesis of all plant and animal sterols, including cholesterol, steroid hormones, and vitamin D in the human body.
• (Tetraterpene) contain *eight isoprene units (40 carbons)* and have the molecular formula \( \text{C}_{40}\text{H}_{64} \). Biologically important tetraterpenes include the **acyclic** lycopene, the **monocyclic** gamma-carotene, and the **bicyclic** alpha- and beta-carotenes.

![lycopene](image)

• **Lycopene's** eleven conjugated double bonds give it its **deep red color** and are responsible for its **antioxidant activity**.

• **Lycopene is responsible for the red color in tomatoes and watermelon.**

• **Polyterpenes** consist of long chains of *many isoprene* units. Natural **rubber** consists of polyisoprene in which the double bonds are **cis**.
Biosynthesis of monoterpenes

1. Isopentenyl diphosphate
2. Dimethylallyl diphosphate
3. Geranyl diphosphate
4. trans-Isopiperitenol
5. trans-Carveol

(-)-Limonene

(-)-Menthol

(-)-Carvone
Acyclic monoterpenes

Linalool

- Found in aromatic plants like *Rosmarinus officinalis*.

- **Used in:**
  1. Perfume industry.
  2. Cosmetics.
  3. As preservative.

**Medicinal uses:**

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

2. Anti-spasmodic.

3. Sedative activity to counteract the convulsant activity (Rats experiment).

4. Local anesthetic.
Linalool
Cyclopropane Monoterpenes

Pyrethric acid and Chrysanthemic acid

- They are transformed into **pyrethrin** which is a compound used as an **insecticide** for certain types of insects like spiders, lice, as well as potentially disease-carrying mosquitoes.
- Found in the **flowers** of *Chrysanthemum cinerariaefolium*.

![Pyrethric acid and Pyrethrhin](image)
Cyclopropane Monoterpenes

• *Chrysanthemum cinerariaefolium*
Menthanes Monoterpenes

Menthoglycol or *para*-menthane-3,8-diol, PMD

- It 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**.
Menthol

- It is found in *Mentha piperita* leaves which contain volatile 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.

**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.
Thymus species

- *Thymus vulgaris*
  - 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**.
Thujone monoterpenes

Thujone

- It is found in *Artemisia absinthium* as α-thujone and β-thujone.
- It is a poisonous monoterpenic ketone.
- They induce genotoxicity, neurotoxicity, reproductive toxicity and carcinogenicity.
- They are convulsant due to blockage of the GABA, (γ – aminobutyric acid) receptors.
Sesquiterpenes

Plants containing sesquiterpenes

- **Matricaria recutita**: (German chamomile) 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](image)

Bisabolol
Feverfew
أقحوان زهرة الذهب

*Tanacetum parthenium*

- This plant has a strong aromatic odor.
- It contains *parthenolide* which is a prophylactic remedy for migraine.

![Parthenolide](image)
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.
Diterpenes
ستيفيا ريبواديانا

**Stevia rebaudiana**

- 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.
TANNINS
Tannins

- A tannin (or tannoid) is an astringent, polyphenolic biomolecule that binds to and precipitates proteins and various other organic compounds including amino acids and alkaloids.

- The term tannin (from tanna, an Old High German word for oak or fir tree) refers to the use of wood tannins from oak in tanning animal hides into leather; hence the words "tan" and "tanning" for the treatment of leather.

- The consequence of tanning is the formation of bonds between the collagen fibers in the hide, which imparts resistance to water, heat, and abrasion.

- This capability of tannins to combine with macromolecules explains why they precipitate cellulose, pectins, and proteins.
Tannins

- The tannin compounds are widely distributed in many species of plants, where they play a role as
  - Source of acids in fruits.
  - Source of energy by oxidation in plant growth regulation.
  - Antiseptic and astringent.
  - Prevent damage by insects.
  - Binds quickly to precipitate proteins and other organic compounds.
  - Finally destroyed or deposited.

**Tannins general characters**

- Not crystallisable.
- Precipitate solutions of proteins.
- Antidote for alkaloids poisoning.
- Astringent (tend to contract body tissues)
- Antimicrobial, Anti-inflammatory.
- Antiulcer, Antioxidant.
- Anti-viral.
Types of Tannins

- The tannin compounds are divided into two (2) classes
  A. Hydrolysable tannins
  B. Condensed tannins

A. Hydrolysable tannins:

- These are ester of sugars and phenolic acid molecules like gallic acid (Gallotannins) or ellagic acid (Ellagittannins).
- HTs are of low M.W (500-3000)
- HTs are soluble in water and their solution produces blue color with ferric chloride.

![Diagram showing the structure of hydrolysable tannins](image-url)
Types of Tannins

B. Condensed tannins:

- These are Proanthocyanidins
- Condensed tannins are formed through the polymerization of flavan-3-ol (catechin) and flavan–3,4-diols (leucoanthocyanidins).
- The polymers may include 2 to 50 monomer units.

- On treatment with acids or enzymes condensed tannins are converted into red insoluble compounds known as phlobaphenes.
- Phlobaphenes give the characteristic red colour to many drugs such as red cinnamon bark.
- On dry distillation, they yield catechol derivatives.
- Condensed tannins are also soluble in water and produces green colour with ferric chloride.
Condensed Tannins

Flavan-3,4-diol structure

A dimeric structure

Non-hydrolysable tannin (flavonoid trimer)
Hydrolysable Tannins

Nutmeg:
➢ Galls are *vegetable growths* formed on the young twigs (branches) of the *dyer’s oak = Aleppo Oak* (*Quercus infectoria*) as a result of the deposition of the eggs by small insect (*Adleria gallaeinctoriae*).

Uses:
• Astringent.
• For aphthous ulcer.
• Putrid sore throat
• Anti-heommorrhagic.
• Burns.
Nutgall Constituent: Tannic acid (C$_{76}$H$_{52}$O$_{46}$)

Acorn cups from *Quercus* spp., Fagaceae

*Quercus infectoria*
Witch Hazel

- Leaves of *Hamamelis virginiana*
- Family: *Hamamelidaceae*
- It contains *hamamelitannin*, vegetable oil, gallic acid.

Hamamelitannin
Witch Hazel USES

- The leaves and bark may be used to produce an astringent.
- Hamamelitannin reported to exert a protective action against colon cancer [Ref: *J. Nat. Prod.*, 2012, 75 (1), pp 26–33.; DOI: 10.1021/np200426k].
- It is mainly used externally on sores, bruises, and swelling.
- Witch hazel hydrosol is used in skin care. It is a strong antioxidant and astringent.
- It is often used as a natural remedy for psoriasis, eczema, aftershave applications, ingrown nails, cracked or blistered skin, for treating insect bites.
- The extracts are also used as a treatment for varicose veins and hemorrhoids.
Chestnut leaves

- Leaves of *Castanea dentata*
- Family: *Fagaceae*
- Constituent: Tannic acid
- **Uses:** astringent
Green Tea leaves

- *Thea sinensis*, (Family: Theaceae)
- Main Constituents: Catechins

**Effects:**
1. Limits the growth of **colorectal cancer**.
2. Reduces **mortality** due to different causes and cardiac diseases.
3. Reduces **cognitive impairment**.
4. Reduces **obesity**.
Green tea contains:

- (+)-gallocatechin (GC), (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechingallate (ECG), (-)-epigallocatechingallate (EGCG) which shows numerous biological activities including antibacterial, anti-oxidant, anti-tumor and cancer preventive activities.
Green tea Uses:

• (+) Catechin prevents cancer (liver, lung, breast and colon cancer) in at least one of three ways:
  - First, they can prevent the formation of carcinogens,
  - Second, they tone up the body's natural detoxification defences,
  - Finally, they suppress cancer promotion.

• (+) Catechin has other promising qualities: antiviral agent, regulating cholesterol and blood pressure, and reducing blood clotting tendencies that may cause heart attacks or strokes.

• Catechins may stimulate the secretion of Bile salts and the faecal excretion of cholesterol.

• Catechins also have anti-hyperglycemic action and normalizing insulin release
Identification tests of tannins

With FeCl$_3$: 

• Hydrolysable tannins: **BLUE** color.

• Condensed tannins: **GREEN** color.
Thank You