

PHILADELPHIA UNIVERSITY
FACULTY OF PHARMACY

Coumarins, Lactones and Chromones

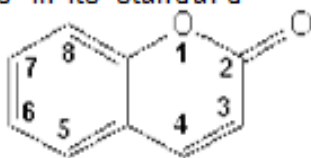
Phytotherapy

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Brief description of some drugs belonging to coumarins, lactones and chromones.

COUMARINS: Bitter principles

- { Coumarin is a **fragrant** (having **sweet odor**; **vanilla odor**) organic chemical compound in the **benzopyrone** chemical class, which is a colorless crystalline substance in its standard state.
- It is a natural substance found in many plants.
- The name comes from a French term for the tonka bean, *coumarou*, one of the sources from which coumarin was first isolated as a natural product in 1820.
- It has a sweet odor, readily recognised as the scent of new-mown (cut) hay, and has been used in perfumes since 1882. }
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- Although coumarin is widely distributed in plants, glycosides containing coumarin as such are **rare**.
- Several glycosides of hydroxylated coumarin derivatives, however, occur in plant materials, and **none of the hydroxylated coumarin glycosides is of particular medicinal importance**.
- Examples of these coumarin glycosides: **skimmin** in **Japanese star-anise** and **aesculin** (**saponin**) in **horse chestnut** tree.
- Some use has been made of natural coumarin but **not in glycosidic linkage** like **scopletin** which has antispasmodic activity and found in *Viburnum prunifolium* **الزعفرور الأسود** and *Viburnum opulus* (Fam.: **Caprifoliaceae** **المعزية الورقية**).
- Other lacton-containing natural products include: **cantharidin** and **methoxsalen** which are used for **dermatologic purposes**, and **santonin** which is obtained from **Artemisia** species (Fam. **Compositae = Asteraceae**).

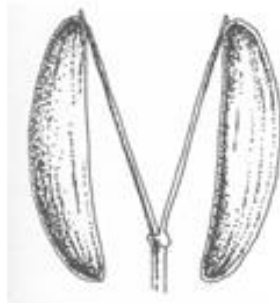
1. **Scopoletin**: is a glycoside found in the Quassia wood {**Quassia** is a collective term for 2 plants: *Picrasma excelsa* and *Quassia amara* L. Family: **Simaroubaceae**}, stem wood of *Picrasma excelsa* (*Picconia excelsa* or *Aeshrion excelsa*) (**Simaroubaceae**).



Use: this glycoside is used as **antispasmodic** for its uterine sedative activity.

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2. **Psoralens**: these are photosensitizing furocoumarins that occur in a number of plant families like **Umbelliferae = Apiaceae** الفصية الخيمية, where they are a common cause of **phototoxicity**.
- **Methoxsalen = 8-methoxy psoralen (oxsoralen[®])** or **xanthotoxin**, a constituent of cremocarps (a description of the fruit of fennel etc.) of *Ammi majus* Linné الخلة الشيطانية (F. Umbelliferae) is used to **1. facilitate repigmentation in idiopathic vitiligo البهاق (leukoderma)** and **2. for symptomatic control of severe disabling psoriasis.**



Cremocarp



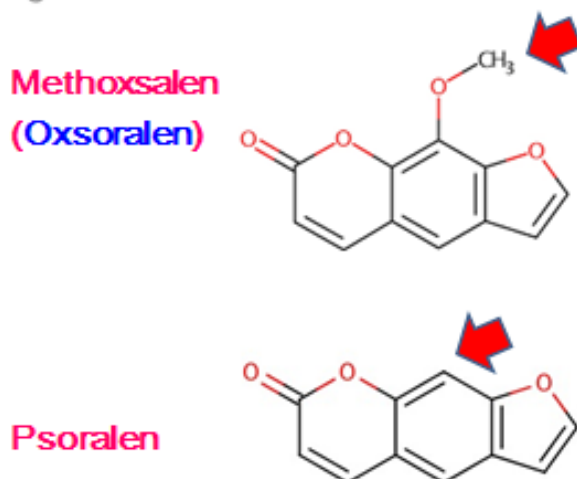
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Psoralens: uses



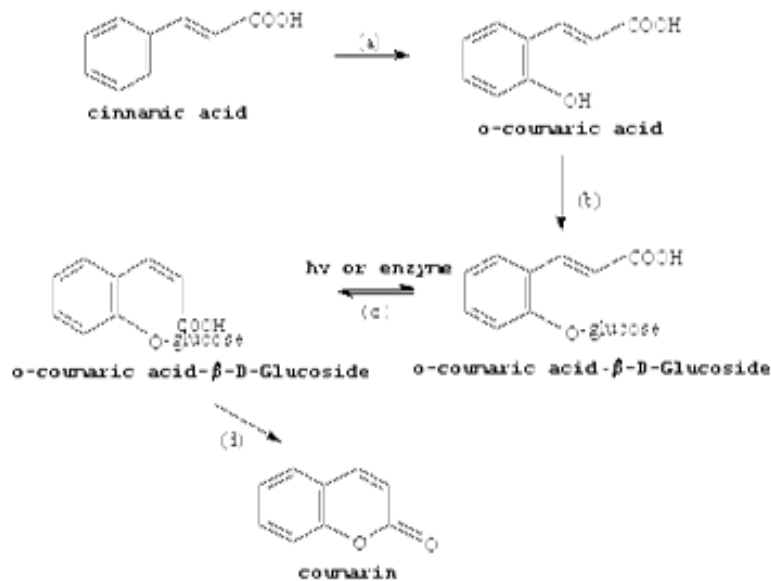
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- Methoxsalen may be applied topically or taken internally, and with exposure to U.V. light.
- Risks are inherent in therapy with methoxsalen including **carcinogenesis**.



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• **Biosynthesis of coumarins:**



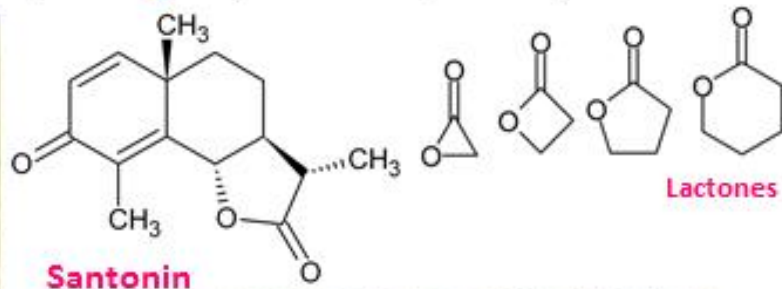
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❖ **Lactones:**

Santonin: this lactone is obtained from the unexpanded flower heads of *Artemisia cina* Berg, *Artemisia maritima* Linné and other *Artemisia* species الشبج (Fam. **Compositae**).



Artemisia cina



Artemisia maritima



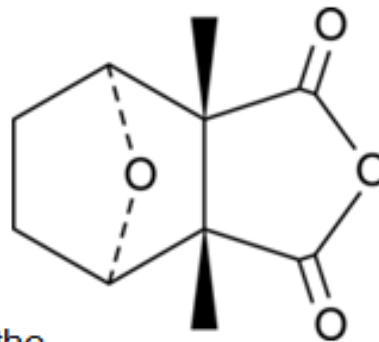
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- **Use:** It was used formerly as an **anthelmintic**, but its use has been discontinued in the USA because of its potential toxicity.
- ❖ **Cantharidin:** is the chief component of cantharides, or the Spanish flies or Russian flies or blistering flies which is the **dried insect** of:
 - ***Cantharis vesicatoria*** (Fam. Meloidae ; Blister Beetles)
 - Cantharis is Greek and means beetle, and vesicatoria from Latin vesica, meaning a bladder and refers to the blistering qualities.
 - This insect is found on certain shrubs of Caprifoliaceae and Oleaceae **الفصيلة الزيتونية** which grow in Southern and Central Europe.
 - The mature insects are collected in June or July in the early morning, killed by plunging them into dilute vinegar, by exposure to the fumes of hot vinegar, or chloroform, ether, dried at 40 C and the drug stored in light containers.



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- Cantharidin is a blistering agent secreted by the beetles as a defensive mechanism.



Cantharidin

Uses:

- Cantharidin is an irritant, rubefacient, if taken internally it is excreted by kidney, and it irritates the urinary tract and this accounts for its reputation as **aphrodisiac (stimulates sexual desire)**.
- Internal administration of the drug is dangerous and deaths have been reported.
- Topical application of the solution of cantharidin is effective in **removal of certain types of warts**, in a preparation of **0.7%** concentration of cantharidin.

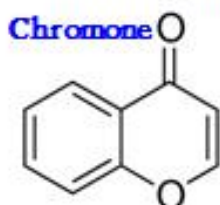
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5. Khellin:

- Is a furanochromone, an organic compound which is a derivative of chromone (1,4-benzopyrone) and furan.
- It has lipophilic properties and **causes vasodilation** (widening of blood vessels).
- It is found in the plant *Ammi visnaga* which has been used in Egyptian folk medicine.

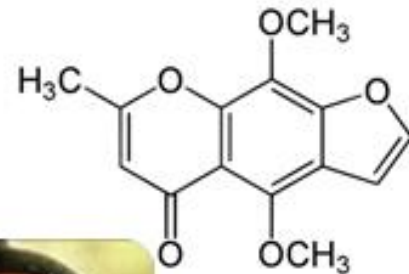


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- In Egypt, the plant "Khella" was used for renal colic. The incidence of **renal colic** was due mostly to schistosomiasis (**bilharzia, snail fever**) infections and stone formation.
- The plant mixture **had diuretic properties** that were seen 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**.

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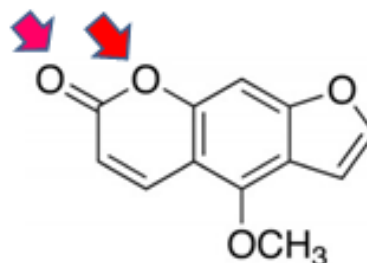
- In the early 20th century, researchers searched for khellin analogs with **lower toxicity** and **better efficacy**.
- A number of drugs were discovered through this research and **amiodarone** and **cromolyn sodium** are khellin analogs used in current medical practice.



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6. Bergapten (5-methoxypsoralen):

- Is a psoralen (also known as furocoumarins) **found in:**
 1. **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}
 2. **Other citrus essential oils.**
 3. **In grapefruit juice.**
- It is the chemical in bergamot oil that causes **phototoxicity**.
- Bergapten-**free** bergamot essential oil or synthetics are now used in **perfumery**.



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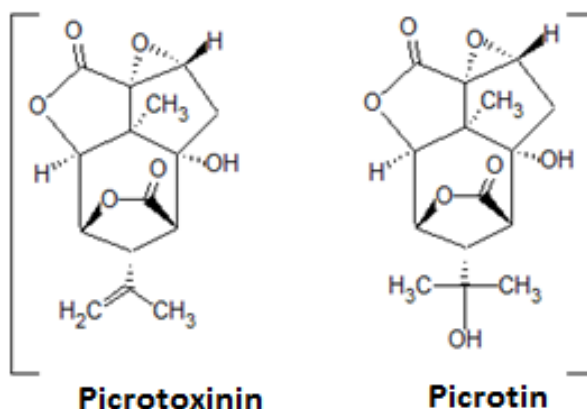
7. Picrotoxin (also known as cocculin):

- 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 "*toxicos*" (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**.

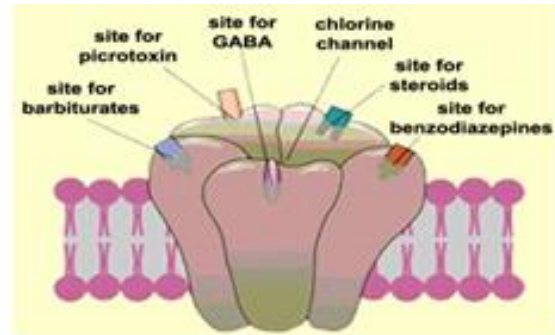
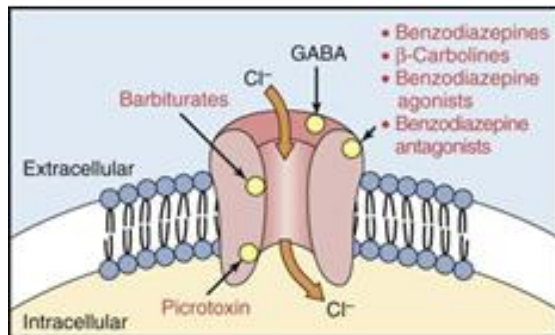


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- It is therefore a channel blocker rather than a receptor antagonist.
- As GABA itself is an inhibitory neurotransmitter, infusion of picrotoxin has stimulant and convulsant effects.
- **As such, picrotoxin** can be **used** to counter barbiturate poisoning that can occur during general anesthesia or during a large intake outside of the hospital.



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GABA-BZD receptor

- ◆ Receptor antagonists (e.g., picrotoxin)
 - impedes Cl^- entrance into the cell preventing hyperpolarization
 - thus neuron is not inhibited from firing

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8. Quassin:

- Is a white bitter, crystalline substance extracted from the quassia tree.
- It is one of the **most bitter substances** found in nature with a bitter threshold of 0.08 ppm and it is 50 times more bitter than quinine.



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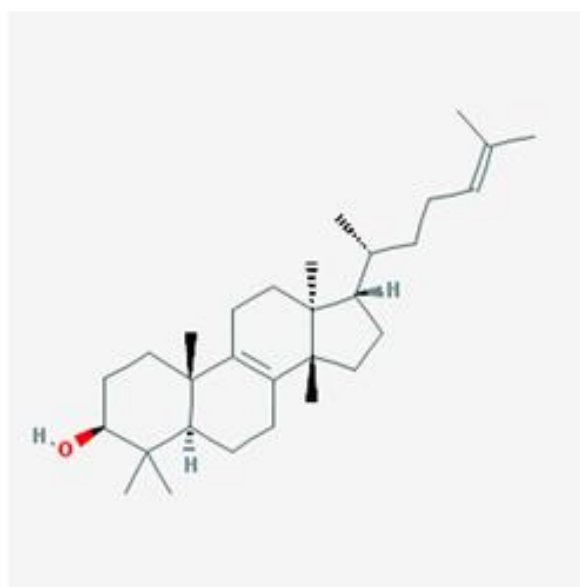
- ❖ Quassin is used as a medicine in traditional Chinese medicine.
- ❖ **Uses:** as a **1. bitter tonic** and **2. anthelmintic**.
- ❖ Extracts of the Bitter tree (or bitter wood) (*Quassia amara* L. or *Picrasma excelsa*) are also used as **3. additives in soft drinks**.
- ❖ Although its skeleton possesses 20 carbon atoms, quassin is not a diterpene, but rather a triterpene lactone (30 carbons), which is derived from by loss of 10 carbons.

Quassia Wood الخشب المر

- **Botanical Origin**

Quassia is the dried wood of the trunk and branches of *Picrasma excels* (Sw.) Planch. (Jamaica *Quassia*) or of *Quassia amara* L. (Surnam *Quassia*), Family Simaroubaceae.

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Euphol

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