PHARMACOGNOSY-II

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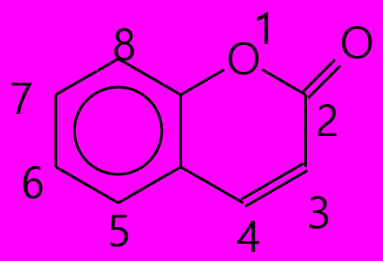
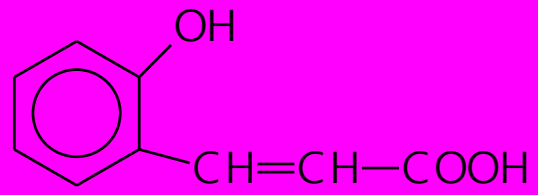
COUMARIN GLYCOSIDES

- Glycosides when hydolized release sugar and aglycon in coumarin structure
- Coumarin → o-hydroxy cinnamic acid lacton = benzo α-pyrone



COUMARIN Benzo-alpha-pyrone



COUMARIN GLYCOSIDES

- Coumarin was firstly isolated from “Tonka bean” at 1820, by Vogel. Later it was proved that the compound isolated from the melilot was the same compound.
- The etymology of the name coumarin is COUMAROUN (TONKA).
- Plant name: *Coumarouna odorata;* contain 1-3% coumarin.
- This plant has been used as commercial coumarin source for many years.

COUMARIN GLYCOSIDES

- A researcher named Perkin was first synthesized coumarin at 1868.
- Generally they can found in whole parts of plants.
- Since 1950, approximately 1500 coumarins isolated up to now
- They are distributed in about 30 different families' 150 species.

COUMARIN GLYCOSIDES

- -OH containing coumarins give blue, blue-green or violet colours under UV at 366 nm
- Odourous compounds

Identification and Quantification

- Chromatographic techniques are used regarding their fluorescence property
- Quantification on the basis of phenolic -OH content.

COUMARIN GLYCOSIDES

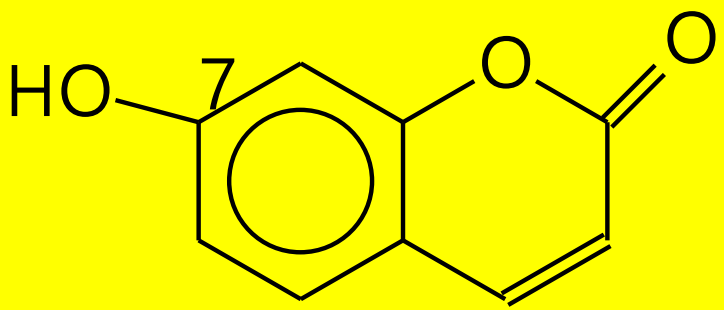
Classification

1) Basic Coumarins: Benzo α-pyrone skeleton; there are –OH, alcohol or other substituents on the main skeleton.

- In nature → In free state or in glycosidic form

COUMARIN GLYCOSIDES

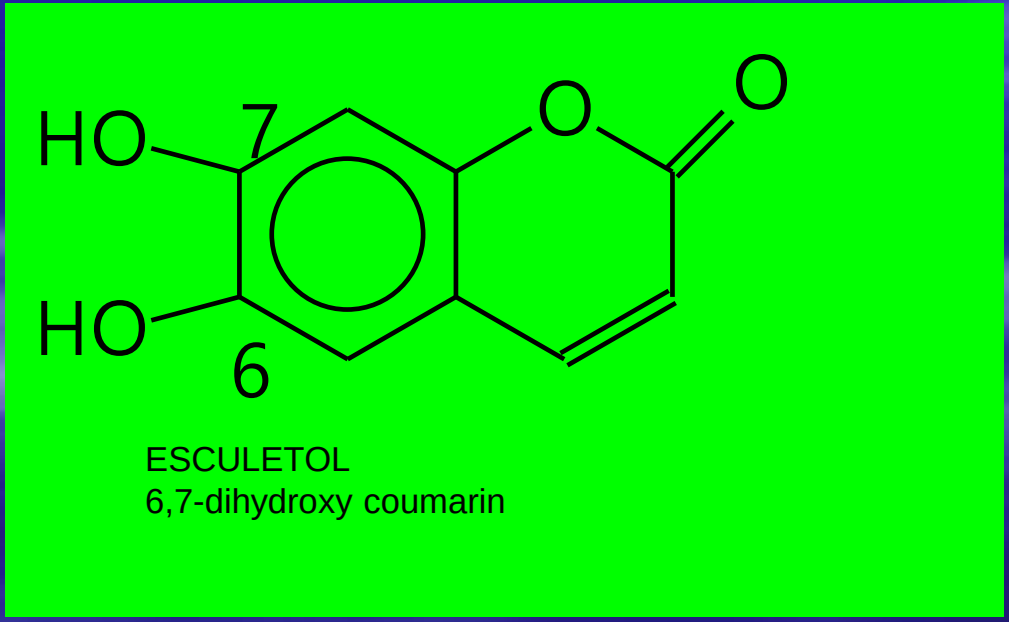
- Apiaceae (Umbelliferae)
- UMBELLIFERONE is found in plants both free and in glycosidic form.



UMBELLIFERONE
7-hydroxycoumarin

COUMARIN GLYCOSIDES

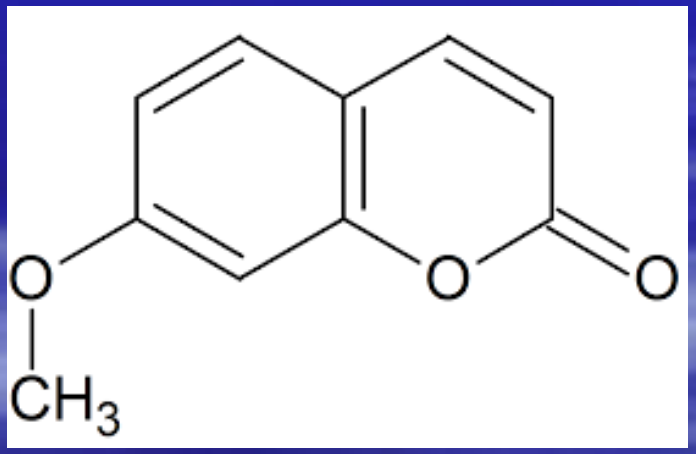
- ESCULETIN → *Aesculus* ve *Fraxinus* sp. Free/glycoside



ESCULETOL
6,7-dihydroxy coumarin

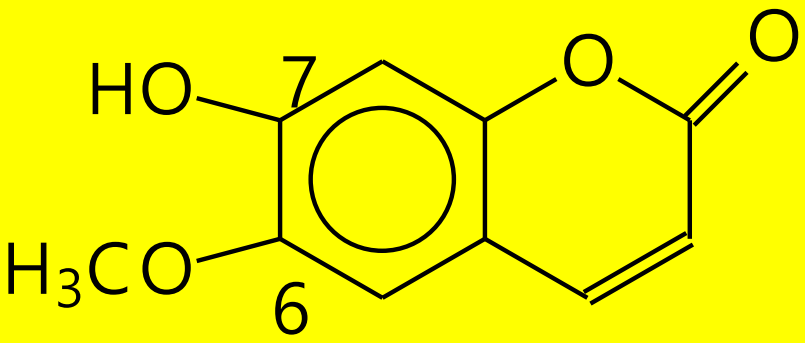
COUMARIN GLYCOSIDES

- HERNIARIN → *Lavandula spica* and some other Asteraceae

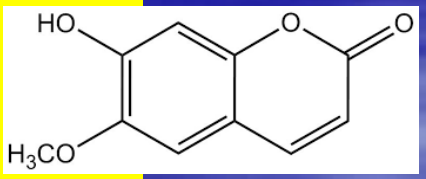


COUMARIN GLYCOSIDES

- SCOPOLETIN → Solanaceae family (F. Bellanonnae)

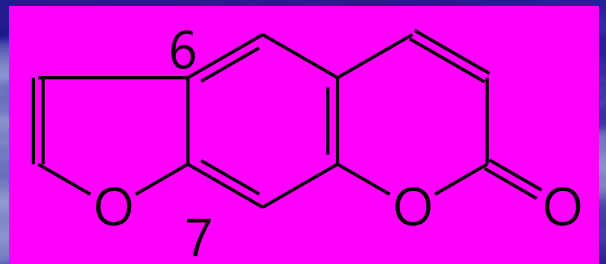


SCOPOLETIN
6-methoxy, 7-hydroxycoumarin

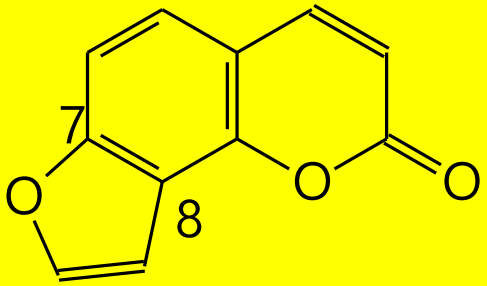


COUMARIN GLYCOSIDES

2-FURANOCOUMARINS: A furan ring is attached to benzene ring. The attachment whether can be from 6-7. (linear) or 7-8. (angular) positions.



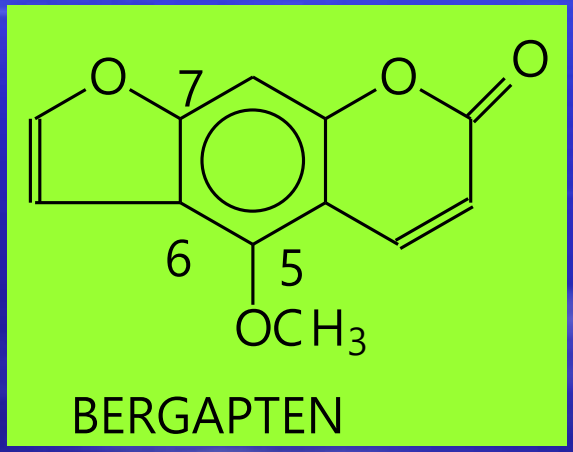
PSORALEN
(linear)



ANGELISIN
(angular)

COUMARIN GLYCOSIDES

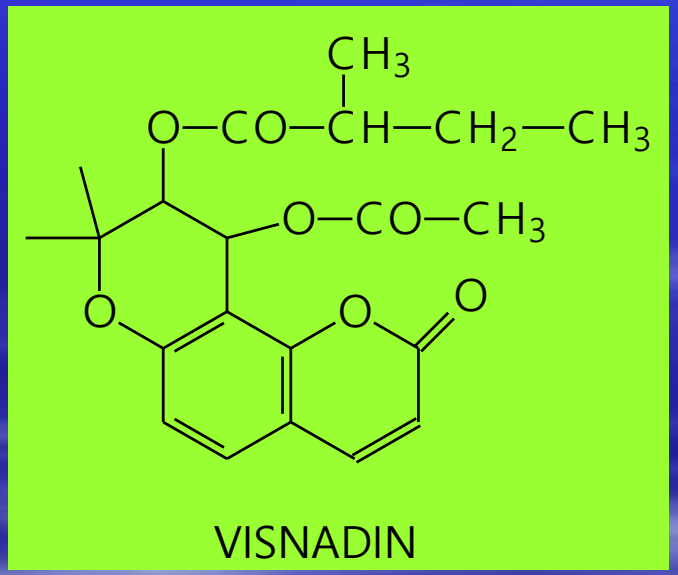
- They are known to found in Rutaceae and Apiaceae families in free state.



BERGAPTEN

COUMARIN GLYCOSIDES

3-PYRANOCOUMARINS: There is a pyran ring attached to the structure from benzene ring. The attachment whether can be from 6-7. (linear) or 7-8. (angular) positions. They are found in Apiaceae (Umbelliferae) plants.

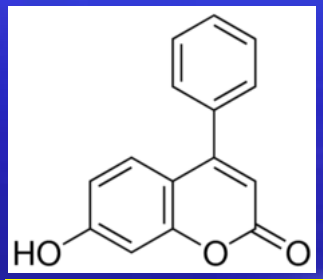


VISNADIN

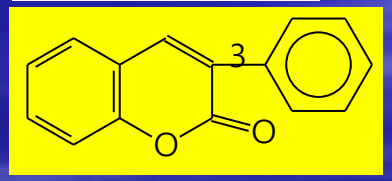
COUMARIN GLYCOSIDES

4- COUMARINS Substitued from Pyron Ring:

- ✓ a) 4-phenyl coumarins:



- ✓ b) 3-phenyl coumarins:

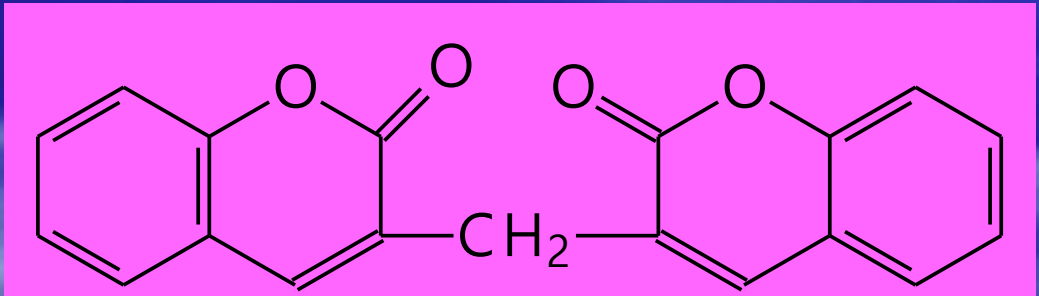


- ✓ c) 3,4-benzocoumarins:

COUMARIN GLYCOSIDES

- **5- <u>Biscoumarins:</u>**

  Formed by condensation of 2 coumarins



DICOUMAROL

COUMARIN GLYCOSIDES

- General extraction methods can be applied for the isolation of coumarins.
- Extraction can be started with a polar solvent or extraction can start with solvents from low polarity to increasing polarity, gradually.
- Ether or hexane is used to remove the lipids in the plant. However, there are also coumarins that can be dissolved in the ether. So the extract should be checked.

COUMARIN GLYCOSIDES

- The amount of coumarins varies according to the season or the peak periods of the physiological activities of the plant.

COUMARIN GLYCOSIDES

- Specific techniques are used for the coumarin isolation depending on the structure of the coumarin:

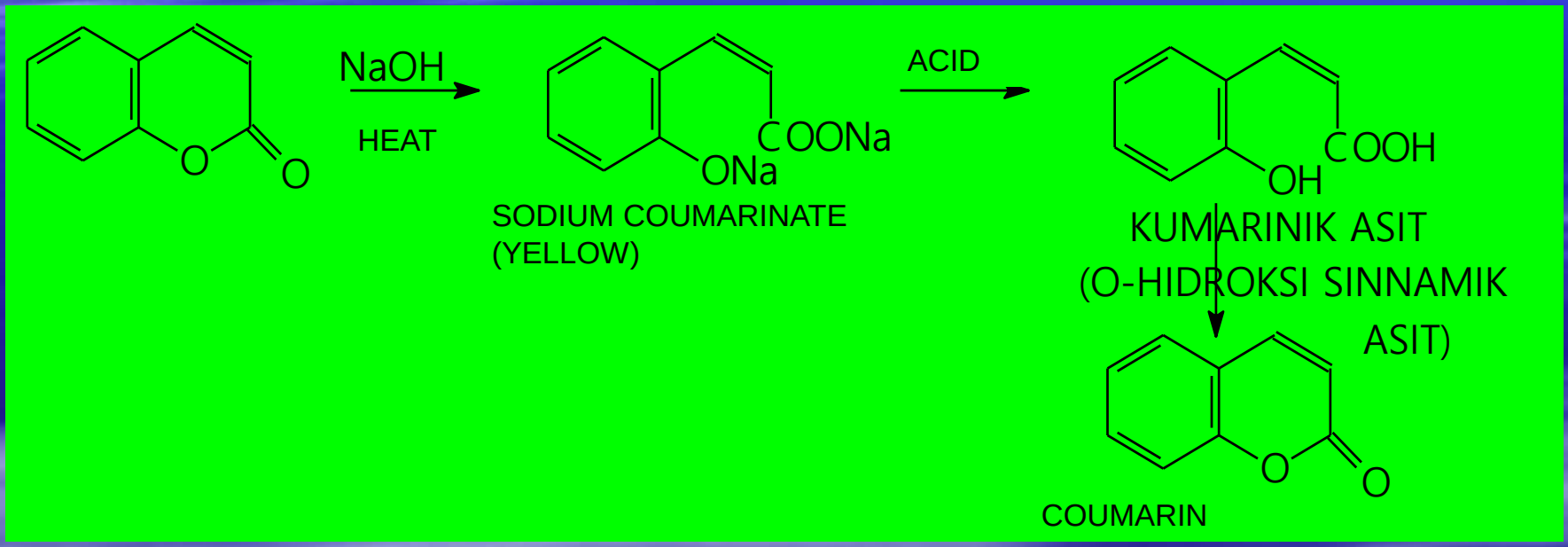
1. Standard Method: A total extract is prepared by using a polar solvents such as MeOH; then isolation process can continue with chloroform : ethylacetate : butanol
2. Lactone Seperation: This is a cleaning method and aqueous sodium carbonate solution is used to remove the plant acids from the coumarin.

COUMARIN GLYCOSIDES

- Separation of the coumarins from other substances is benefited from their being in lactone structure. For this, diluted hydroxides (NaOH / KOH) are added over the coumarin containing ethanol extract
- These hydroxides, open up the lactone ring of the coumarins and yellow coloured coumarinates occur.

COUMARIN GLYCOSIDES

- This solution is mixed with an organic solvent which is not soluble in water (e.g. ether) and compounds found in the medium drawn into the organic solvent, leaving only water-soluble sodium coumarinates in the aqueous phase. By acid addition to the aqueous phase, the ring is closed. Thus, the coumarins are regained, purely.


NaOH
HEAT
COONa
ONa
SODIUM COUMARINATE
(YELLOW)
ACID
COOH
OH
KUMARINIK ASIT
(O-HIDROKSI SINNAMIK
ASIT)
O
O
COUMARIN

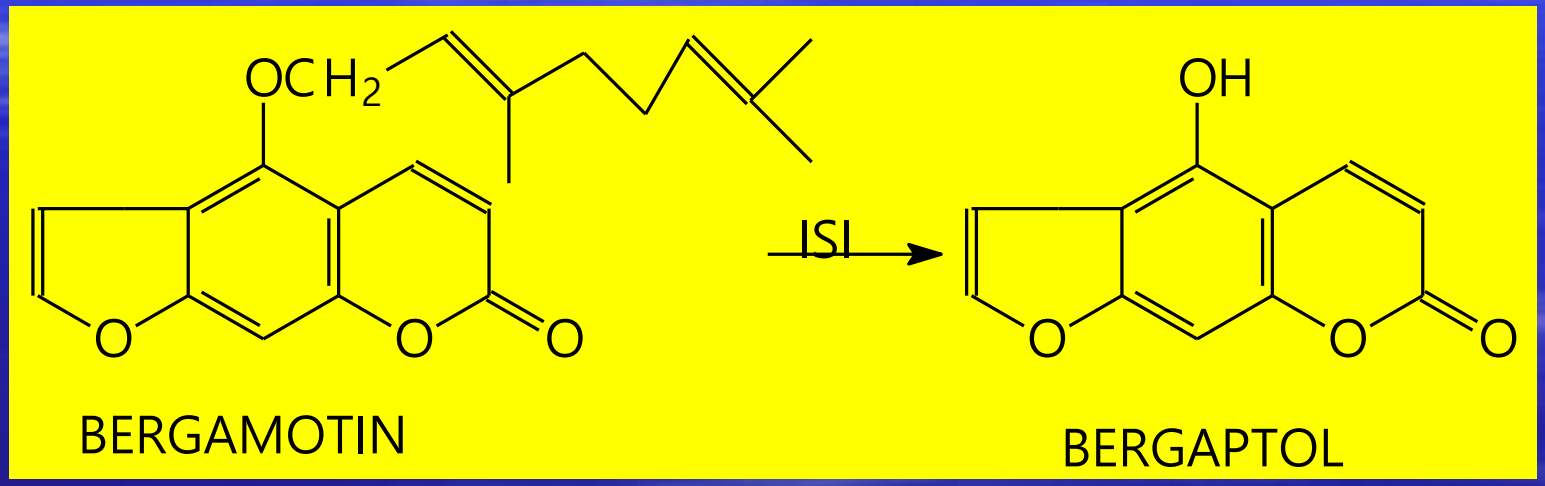
COUMARIN GLYCOSIDES

3. Fractionated Crystallization: Since, coumarins are difficult soluble in petroleum ether, this property is utilized in plants carrying high amount of coumarins → To this end, the petroleum ether is slowly added to the hot ether solution to precipitate the coumarins.

COUMARIN GLYCOSIDES

4. Vacuum Distillation and Sublimation:

- This method can be applied to heat-resistant coumarins. Thus both seperation and isolation can be done.
- While working with coumarins, it is not usually possible to exceed 60^0C, so that primary compounds are obtained.
- Sometimes, by heat effect the isoprene side chain separate from the main ring; this is a degradation product; for example BERGAPTOL.


OCH2
O
O
O
BERGAMOTIN
ISI
OH
O
O
O
BERGAPTOL

COUMARIN GLYCOSIDES

5. Column Chromatography: One of the most used technique for the isolation of coumarins. Alkaline and asidic Al_2O_3 and silica gel is used as stationary phase
6. Others: Preparative TLC, Gas Chromatography, HPLC, DCCC can also be applied for separation and isolation.

COUMARIN GLYCOSIDES

- Since coumarins give fluorescence at UV 366 nm, is is easy to identify the type of the coumarin:
- Basic coumarins---BLUE or BLUE-GREEN
- Furanocoumarins---YELLOW, BROWN or BLUE-GREEN fluorescence
- If alcoholic potas reagent is sprayed to the region of furanokumarins, the intensity of the fluorescence will increase.

COUMARIN GLYCOSIDES

- If the spots kept in ammonia vapor, the colour will not change but the intensity of the spots increase; this indicates presence of a phenolic –OH.
- Coumarins carrying phenolic –OH, give green tonnes and precipitate with 1% $FeCl_3$ reagent. These compounds can also be identified using diazosulfonic acid and diazo-p-nitroaniline reagents.

COUMARIN GLYCOSIDES

- EMERSON reagent (alcoholic potas+ aminopyridine+ potassium ferricyanide) Used in linear and angular furanocoumarin identification. Angular furanocoumarins give RED-PURPLE colour.

COUMARIN GLYCOSIDES

Effect- Usage

1) Aromatizer and taste improver

2) Dicoumarol--- Anticoagulant

Decreases the form of protrombin --- prevents blood clotting--- protective or therapeutic against thrombosis

Dicoumarol---Mouse poison

3) Respiratory analeptic

4) Vasodilator

5) Antispasmodic

6) Esculetol----P vit. effect.

COUMARIN GLYCOSIDES

7) Scopoletol ve Umbelliferone → increase bile secretion.

8) Furanocoumarins--- photosensitizer; make the skin sensitive to light.

Psoriasis

Used against Vitiligo

9) Some of them are toxic----Aflatoxin---cause food poisoning

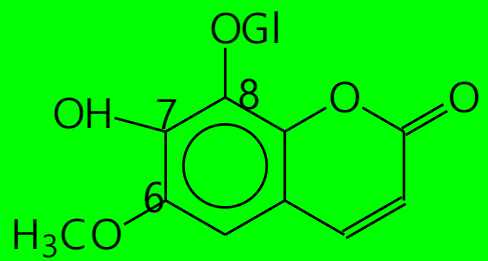
10) Antibiotic effect---Novobiosin

FOLIA FRAXINI

- *Fraxinus excelsior* (Oleaceae) (European ash - Dişbudak)
- Growing in Europe, North Asia, North Anatolia; plants with compound leaves
- 20-30 m length, with 9-15 foliols
- Leaflets are lanceolate, deticulated
- Leaves are collected on the begining of summer, spread in thin layers to dry in shadow.
- Leaves which are not dried properly turn to brown

FOLIA FRAXINI

- Leaves;
- Coumarin glycosides---Fraxoside---hydr.---Fraxetol+gl



FRAXOSIDE
(6,7,8-trihydroxycoumarin-6-methyl ether -8glycoside)

- Tannin---10%
- Flavonoid----Rutoside

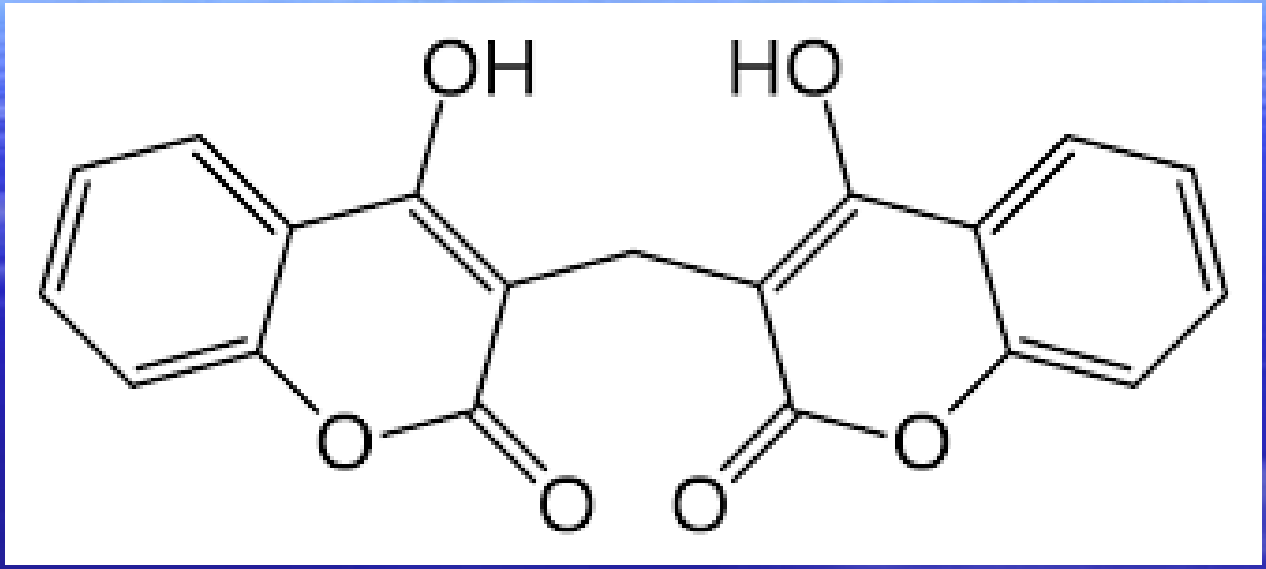
FOLIA FRAXINI

- Bark; contains coumarin glycosides
- Leaves diuretic
- Used against rheumatism and arthritis
- Used in preparation of refreshing drinks.
- Common species in Turkey:
- *Fraxinus ornus*---West and South Anatolia
- *Fraxinus angustifolia*---Medium and East Anatolia

HERBA MELILOTI

- ***Melilotus officinalis*** **(Leguminosae), common melilot, kokulu yonca**
- **Growing in Eurupe and Turkey.**
- **Coumarin glycosides----MELILOTOSIDE---hydr.—coumarinic acid----after hydrolysis immediately converting to coumarin**

HERBA MELILOTI



If not dried in suitable conditions then DICOUMAROL may occur.

HERBA MELILOTI

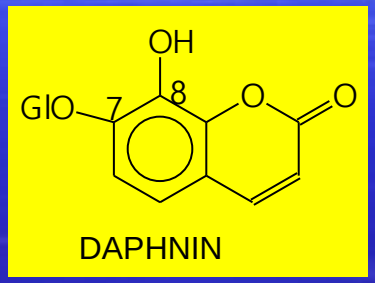
- Drug should be dried in suitable conditions.
- Emollient
- Diuretic
- Used against pains in rheumatism
- Antiiflammatory --- used as eye lotions

CORTEX GNIDII

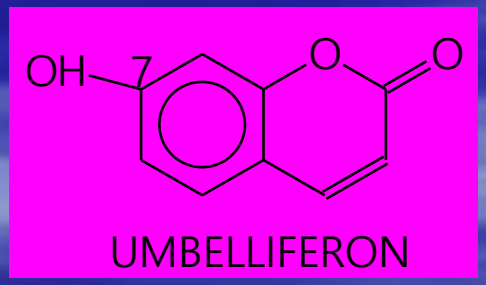
- *Daphne gnidium* (Thymelaeaceae) Flax-leaved daphne
- Mediterranean plant, 120 cm height,
- Leaves and stem barks are used;
- Resin ---- vesicant effect

CORTEX GNIDII

- Coumarin Derivatives:
- DAPHNIN----hydr.---daphnetin+glu



- UMBELLIFERON----7-hydroxy coumarin



- DAPHNORETIN----dimeric structure

CORTEX GNIDII

- *Daphne pontica*---daphnin, umbelliferone and daphnoretin
- *D. gnidoides*
- *D. sericea*
- *D. oleoides*
- *D. mezereum*; these species are growing in Turkey.

FRUCTUS AMMI VISNAGAE, Toothpick-plant - Dişotu Meyvesi

- *Ammi visnaga* (Apiaceae)
- Toothpick-plant, bisnaga, diş otu, kürdan otu, hıltan
- Common in Middle East countries and Turkey

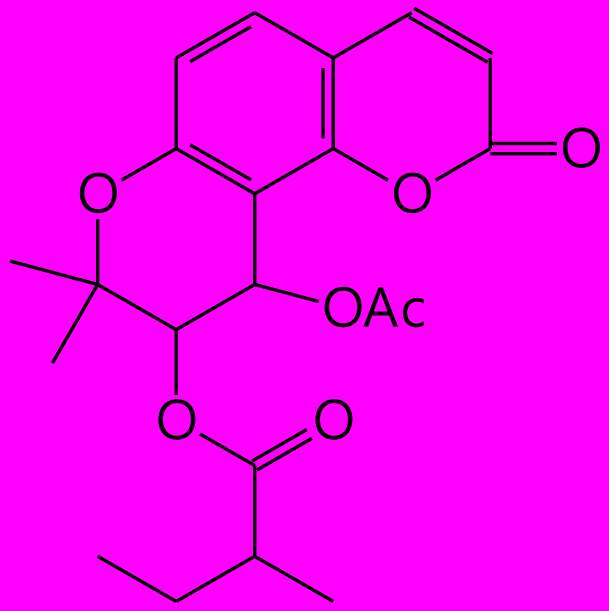
❖ Pyranocoumarin type compounds

❖ VISNADIN

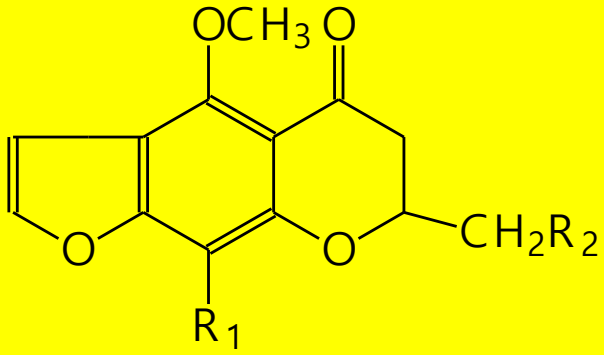
❖ SAMIDIN

FRUCTUS AMMI VISNAGAE, Toothpick-plant - Dişotu Meyvesi

- Compounds in furanocromon structure;
- KHELLIN--- has preparations in injectable and tablet form
- VISNADIN----%0.1
- KHELLOL GLY----%0.3
- Essential oil----%0.03
- Fixed oil----%20



VISNADIN



R1 ----OCH3 R2---H----KELLIN

R1--H R2----H------VISNAGIN

R1--H R2--O-GL------ KHELLOL GLY.

FRUCTUS AMMI VISNAGAE, Toothpick-plant - Dişotu Meyvesi

1) Visnadin (Pyranocoumarin)---antispazmodic, 3 times stronger than papaverin

- Kidney colitis
- Spastic urinary system diseases
- To pass kidney stones

2) Coronary vasodilator----Angino pectoris

3) Bronchial asthma

- Its usage is limited due to excessive side effects