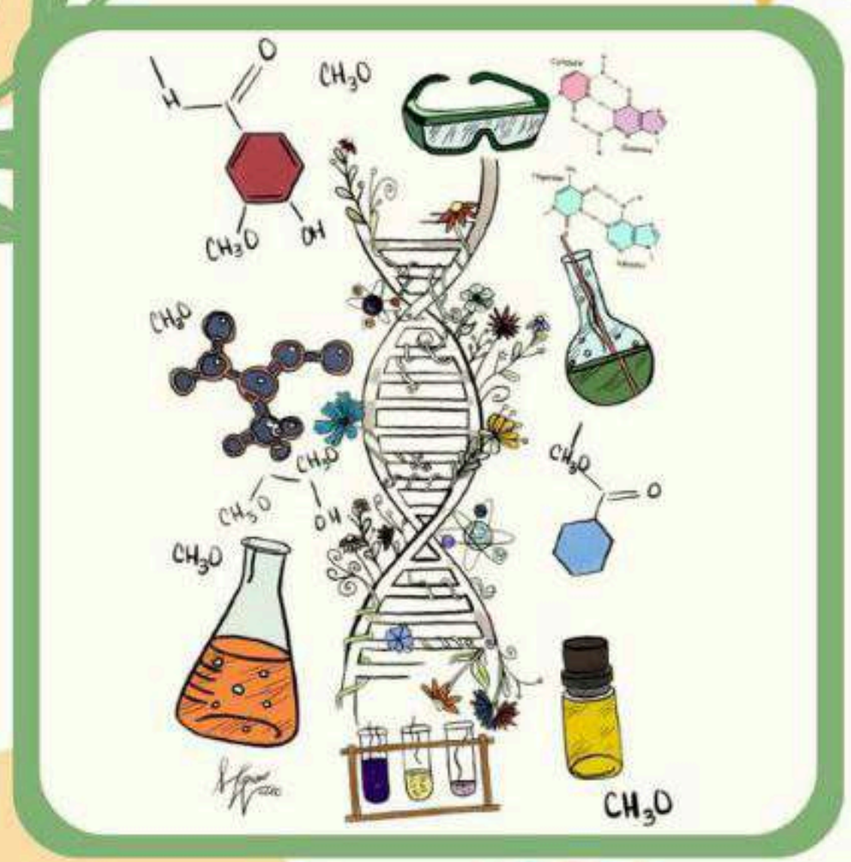
تفريغ عقاقير



اسم الموضوع: Shikimates acid pathway

إعداد الصيدلاني/ـة: *Alaa Otoum*

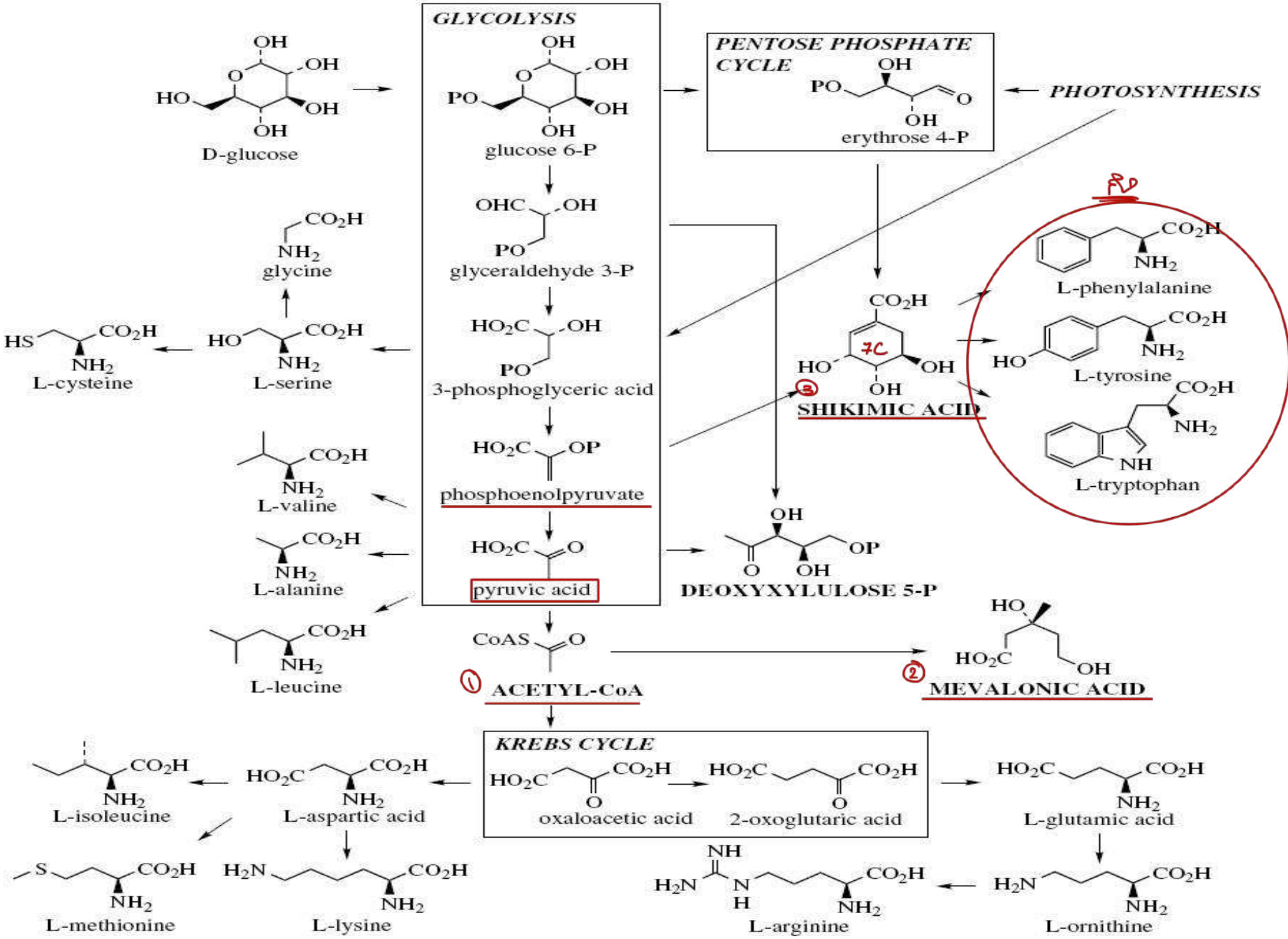
Seul Academy

لجان الدفعات

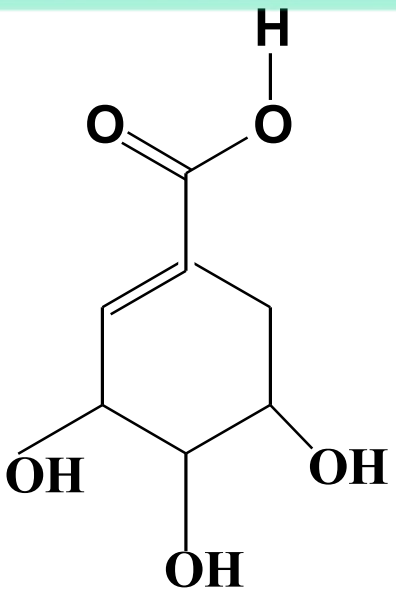
Shikimic acid pathway

Dr Dana Atoum

THE BUILDING BLOCKS



Shikimic Acid Pathway



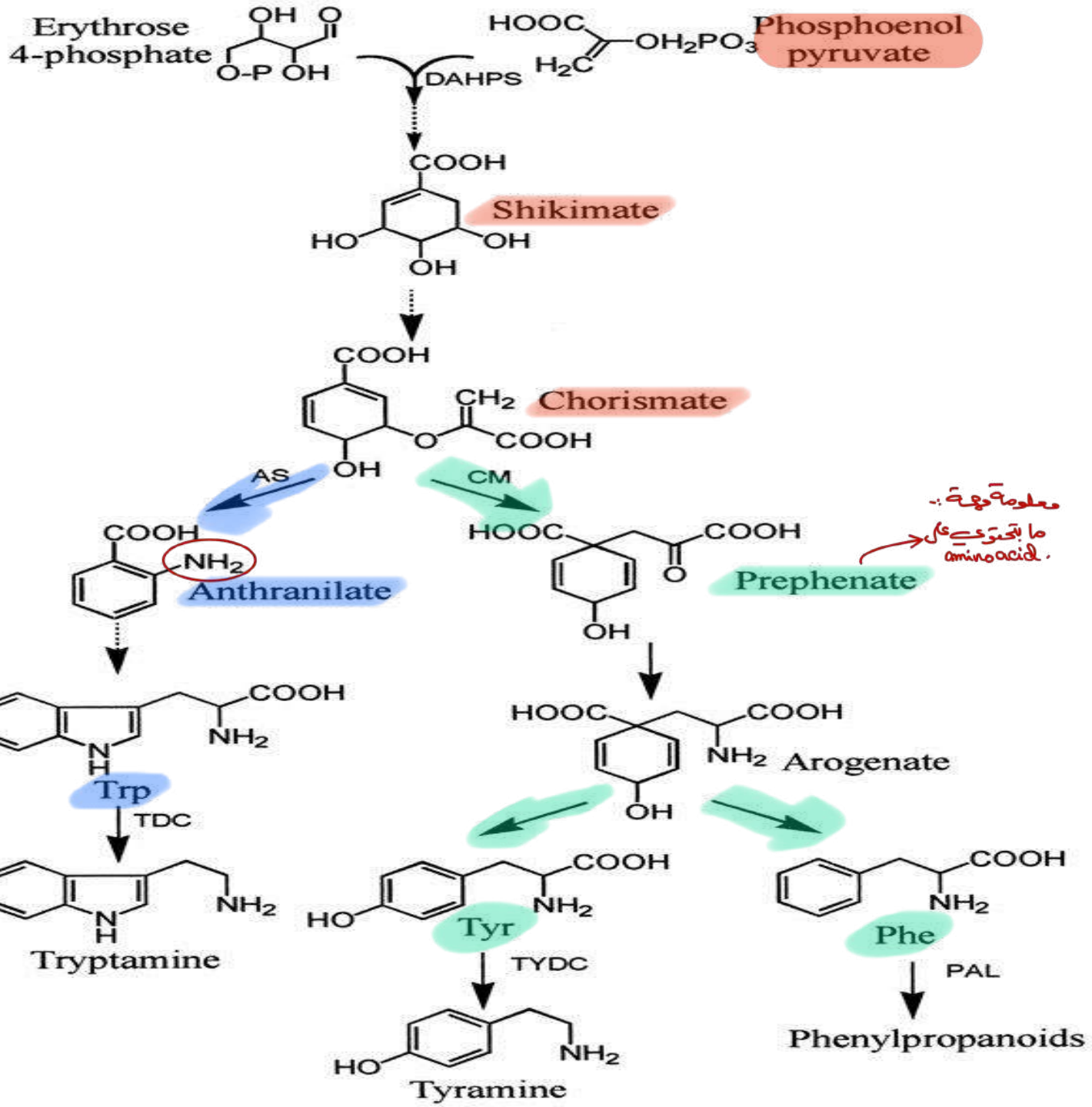
Shikimic Acid

Illicium anisatum **L. Illicinaceae {Shikimino-ki in Japanese} (1885)**

E. coli **mutant strains pathway intermediate**

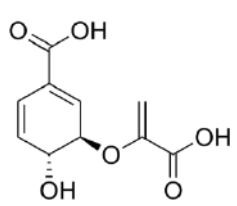
Shikimic Acid Pathway

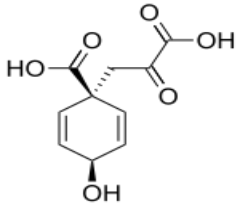
- Important for aromatic compounds
- Precursor of aromatic amino acids (Phe, Tyr, Try) biosynthesis in bacteria, fungi & higher plants. ANIMALS! HUMAN!
- Building block for other compounds: certain alkaloids, coumarins, phenyl propanes, vol. oils,..
- Starting point for tannins in all plants
- Provide protection of plants against micro-organisms

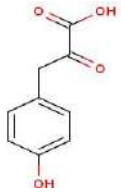

Erythrose 4-phosphate
DAHPS
Phosphoenol pyruvate
Shikimate
Chorismate
AS
CM
Anthranilate
Prephenate
معلومة قيمة :
ما يحتوي على amino acid .
Trp
TDC
Tryptamine
Arogenate
Tyr
TYDC
Tyramine
Phe
PAL
Phenylpropanoids

Scheme of the conversion of shikimic acid to cinnamic acid

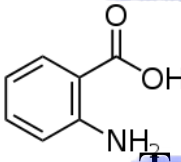
Shikimic acid → Chorismic acid → Prephenic acid → p-OH-phenylpyruvate

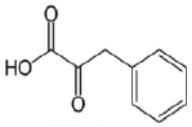


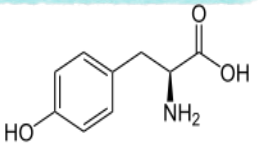




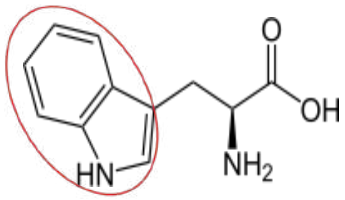
Anthranilic acid — Phenylpyruvate — Tyrosine→alkaloids

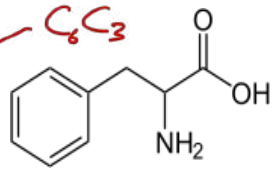


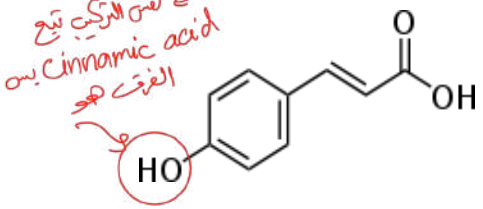




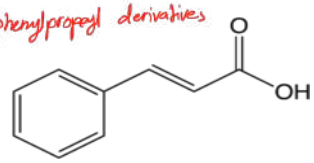
Tryptophan (1) — Phenylalanine (2) — p-coumaric acid







Cinnamic acid



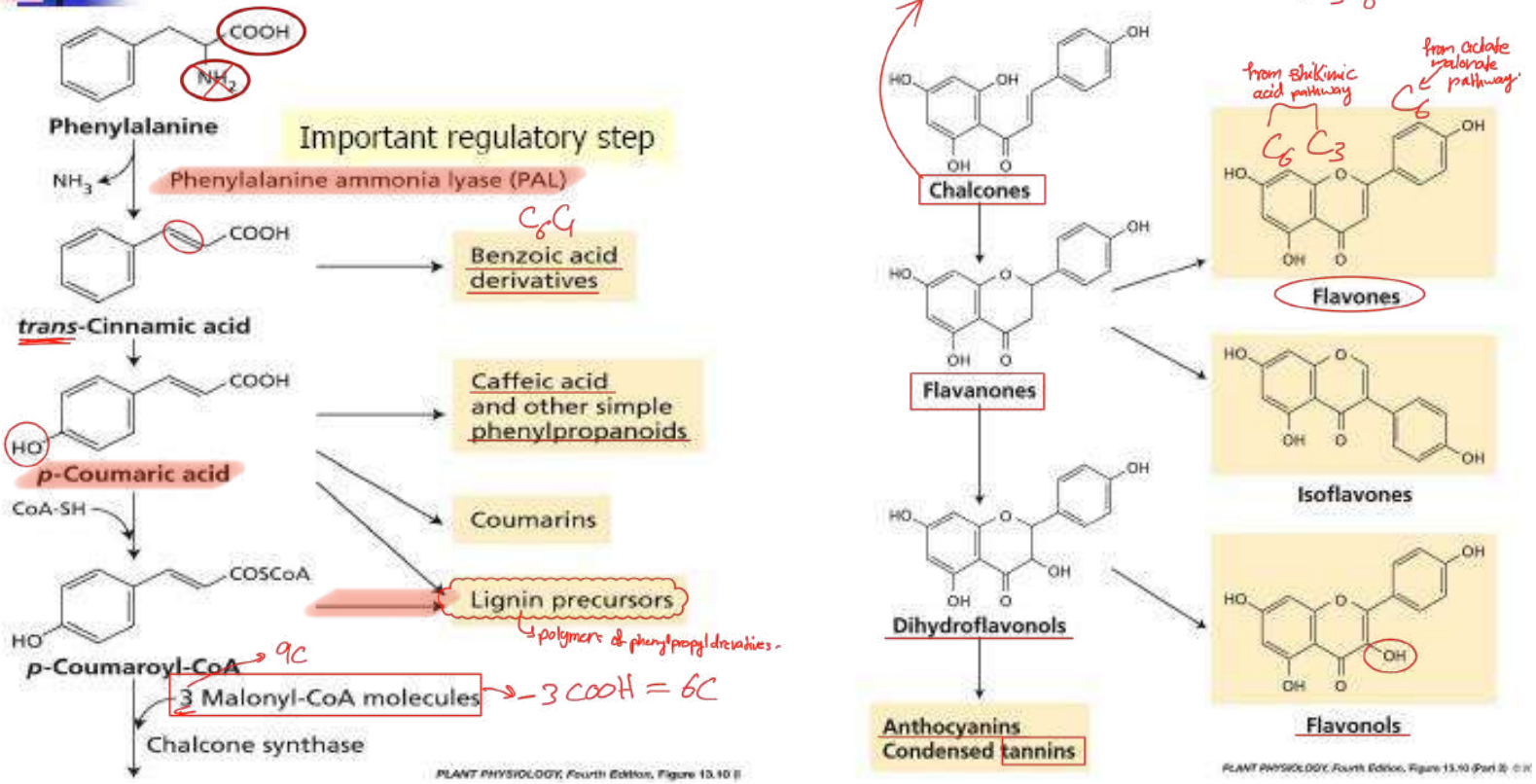
p hytohormones (indol-3-ace tic acid

Alkaloids

alkaloids

Phenolic biosynthesis from phenylalanine

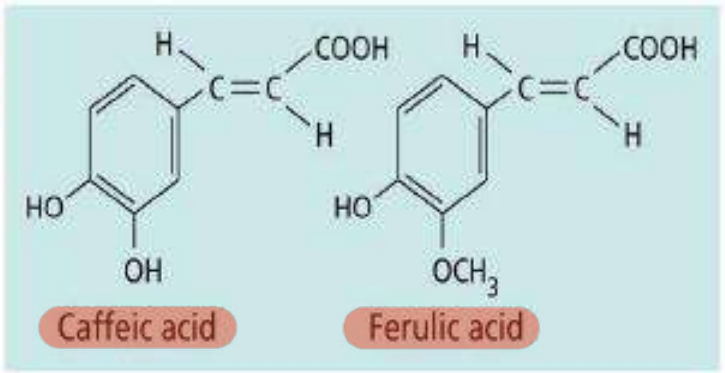
-most abundant sources of plant phenolic compounds



Simple phenolic compounds play a great diversity of roles in plants

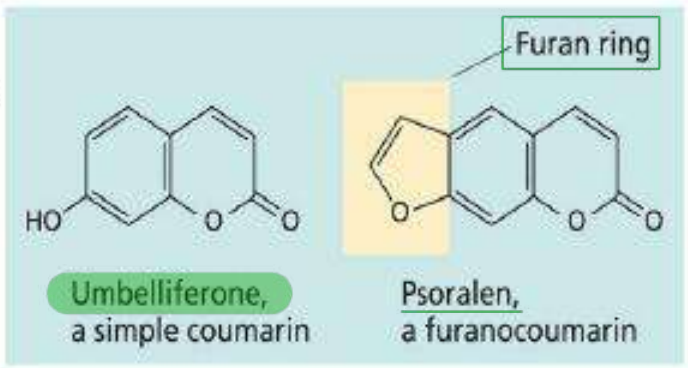
phenylpropyl derivatives -

(A)



Simple phenylpropanoids $[C_6-C_3]$

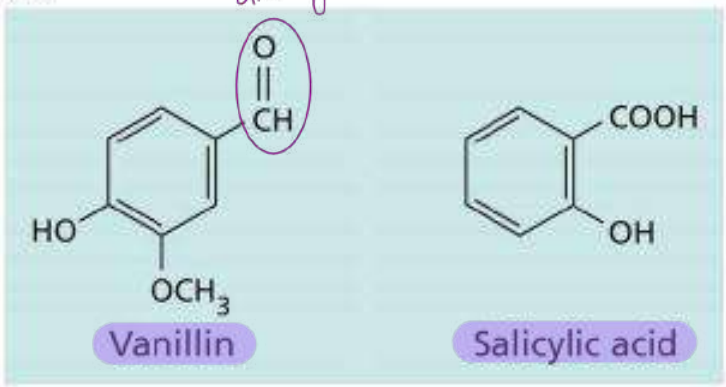
(B)



Coumarins $[C_6-C_3]$

(C)

aldehyde



Benzoic acid derivatives $[C_6-C_1]$

secondary metabolite -

(A) Caffeic acid and ferulic acid may be released into the soil and inhibit the growth of neighboring plants----allelopathy.

(B) Psoralen exhibits phototoxicity to insect herbivores after activation by UV-A.

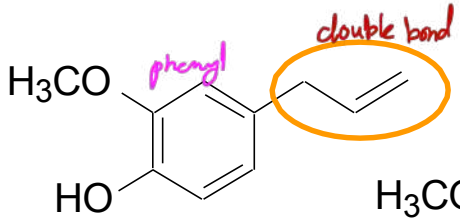
(C) Salicylic acid is a plant growth regulator involved in systemic resistance to plant pathogens.

Phenylpropanoids (Cinnamates):

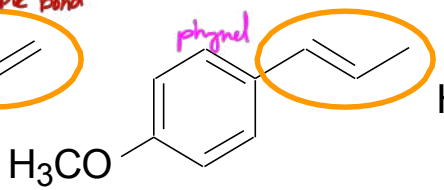
- Definition: Phenylpropanoids represent a large group of natural products containing a phenyl ring attached to a three-carbon propane side chain(C_6-C_3) in their structure.
- Biosynthesis: Derived from the aromatic amino acids phenylalanine and tyrosine or the intermediates of the shikimic acid biosynthetic pathway. The basic simplest nucleus of phenyl propanoids is **Cinnamic acid**.
- Categories: Simple Phenylpropanoids (phenylpropenes, phenylpropyl alcohols, phenylpropionaldehydes, phenylpropionic acids)

Simple phenylpropanoids

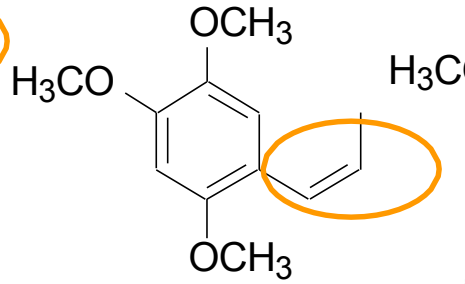
Phenylpropenes



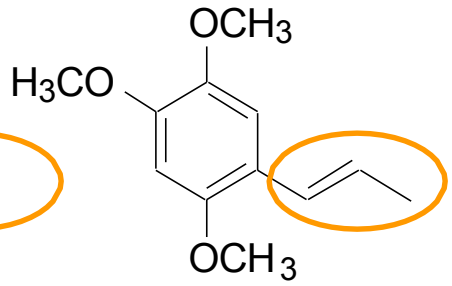
1 eugenol



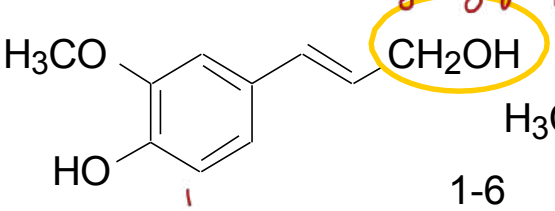
2 anethole



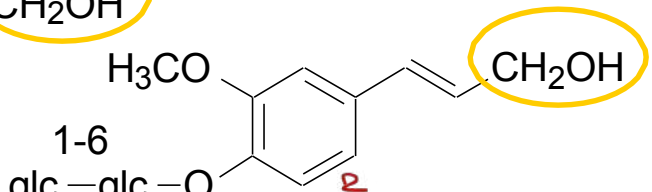
3 beta-asarone



4 alpha-asarone

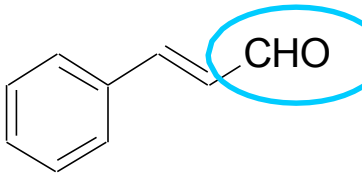


coniferol



syringinoside

phenylpropyl alcohols



cinnamaldehyde

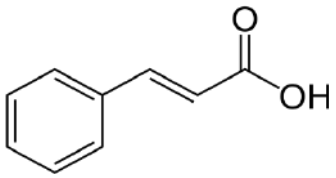
Phenylpropionaldehydes

Possibilities of derivatives of cinnamic acid

1 Substitution in aromatic ring

2 State of the oxidation of the side chain

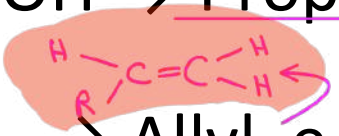
- -CH=CH-COOH → Propenic acid, cinnamic acids

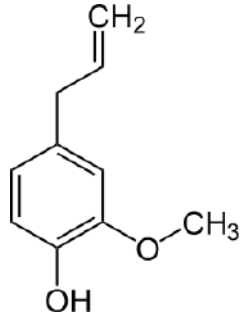


- -CH=CH-CH_2OH → Propenol, coniferylalcohols

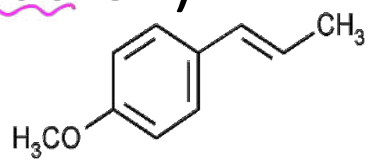
double bond

alcohol

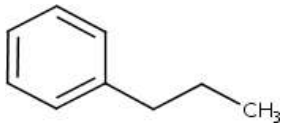




- -CH_2-CH=CH_2 → Allyl, e.g. Eugenol (in Clove Oil)
- -CH=CH-CH3 → Propenyl, e.g. Anethole (in Anise Oil)



- -CH_2-CH_2-CH_3 → n-propyl



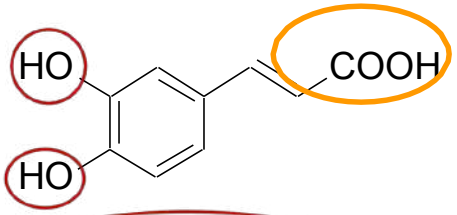
3- Shortening of the side chain

Formation of phenol carboxylic acids and simple phenols

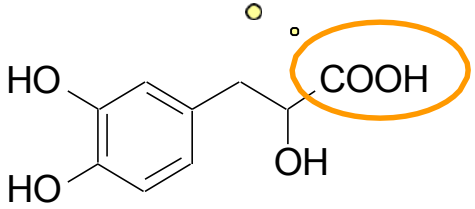
Simple phenylpropanoids

Phenylpropionic acids

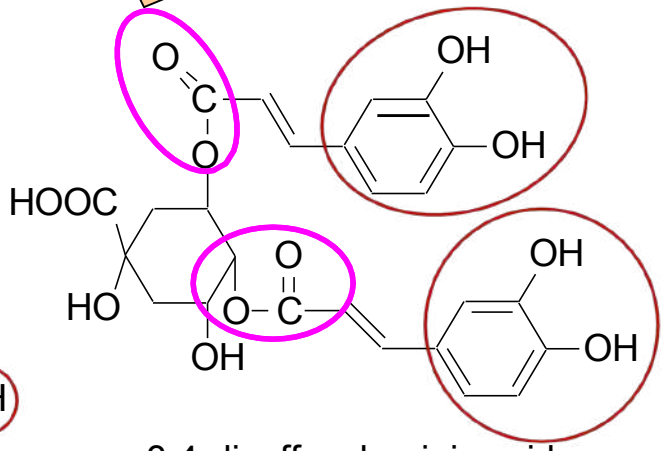
Phenylpropenate Ester



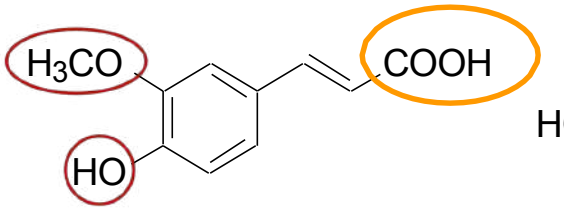
caffeic acid



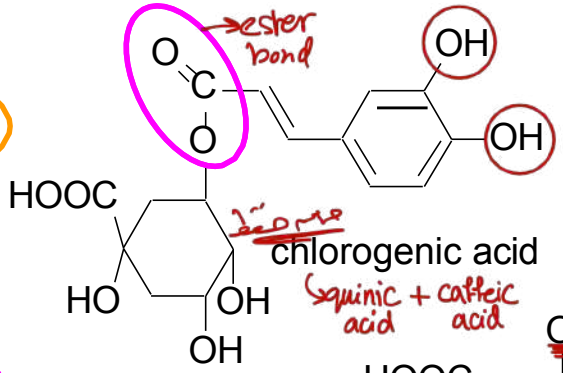
danshensu



3,4-dicaffeoyl quinic acid

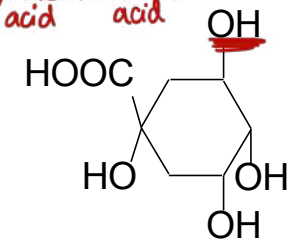


ferulic acid



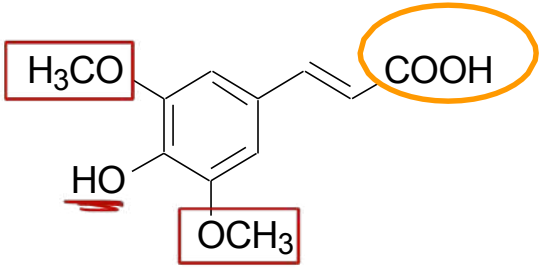
chlorogenic acid

quinic + caffeic acid

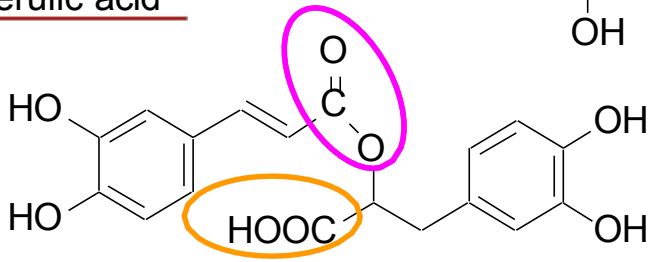


quinic acid

sugar acid



sinapic acid

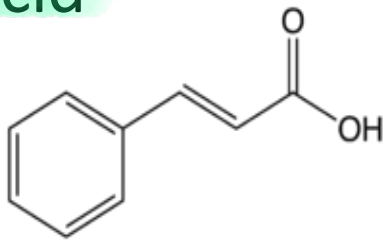


rosmarinic acid

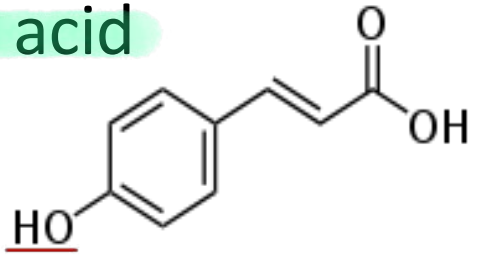
2 caffeic acid

Cinnamic acids (Phenylpropionic acids)

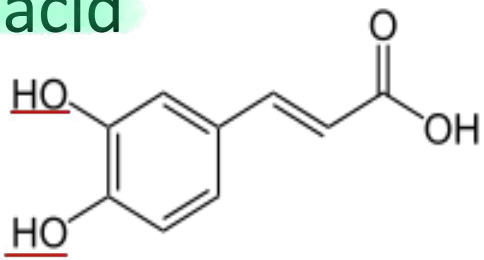
Cinnamic acid



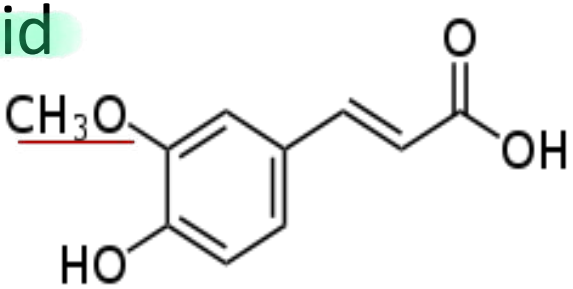
p-coumaric acid



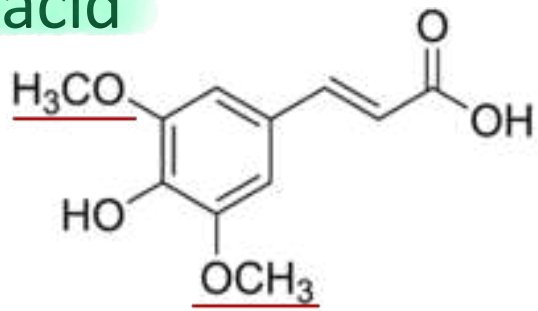
Caffeic acid



Ferulic acid



Sinapic acid



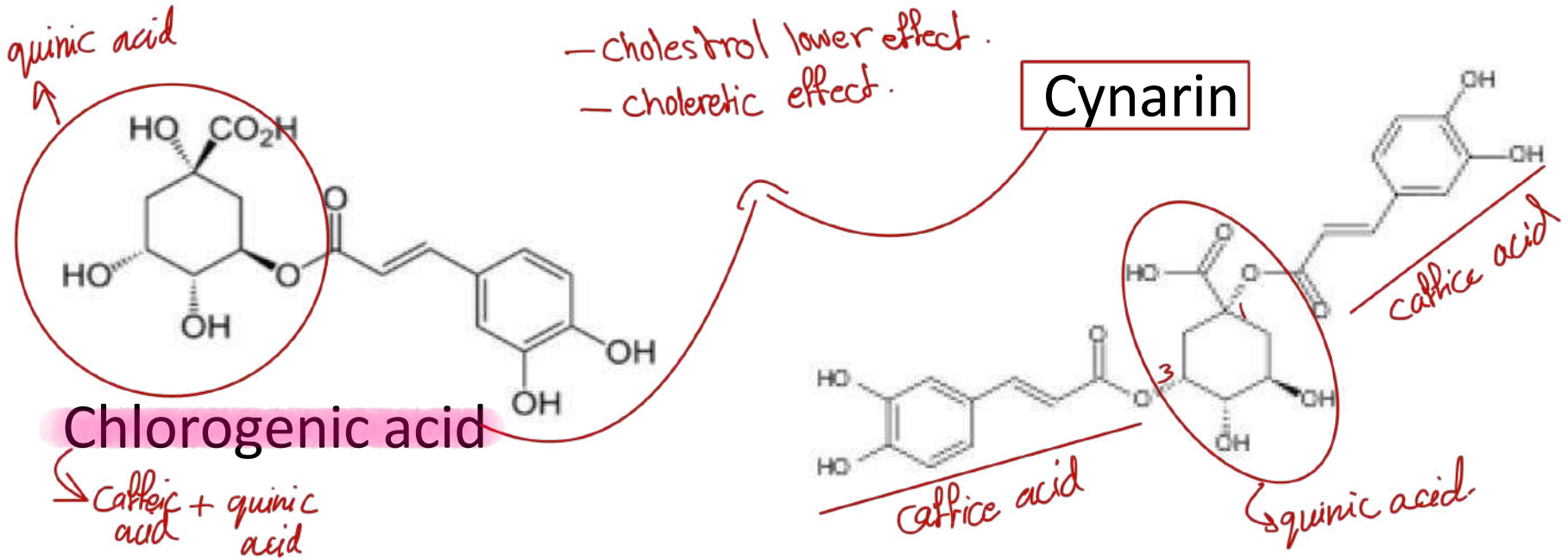
5-OH-ferulic acid

Tri-OH-cinnamic acid

Caffeic acid containing phenolics

Chlorogenic acid (3-caffeoylester of quinic acid) and cynarin (1,3,4 dicaffeoylester of quinic acid)

- C6-C3 acids may occur in the plants in free forms, as glycosides or as esters



Caffeic acid containing phenolics

Cynara scolymus
(artichokeخرشوف)

Part used: Leaves

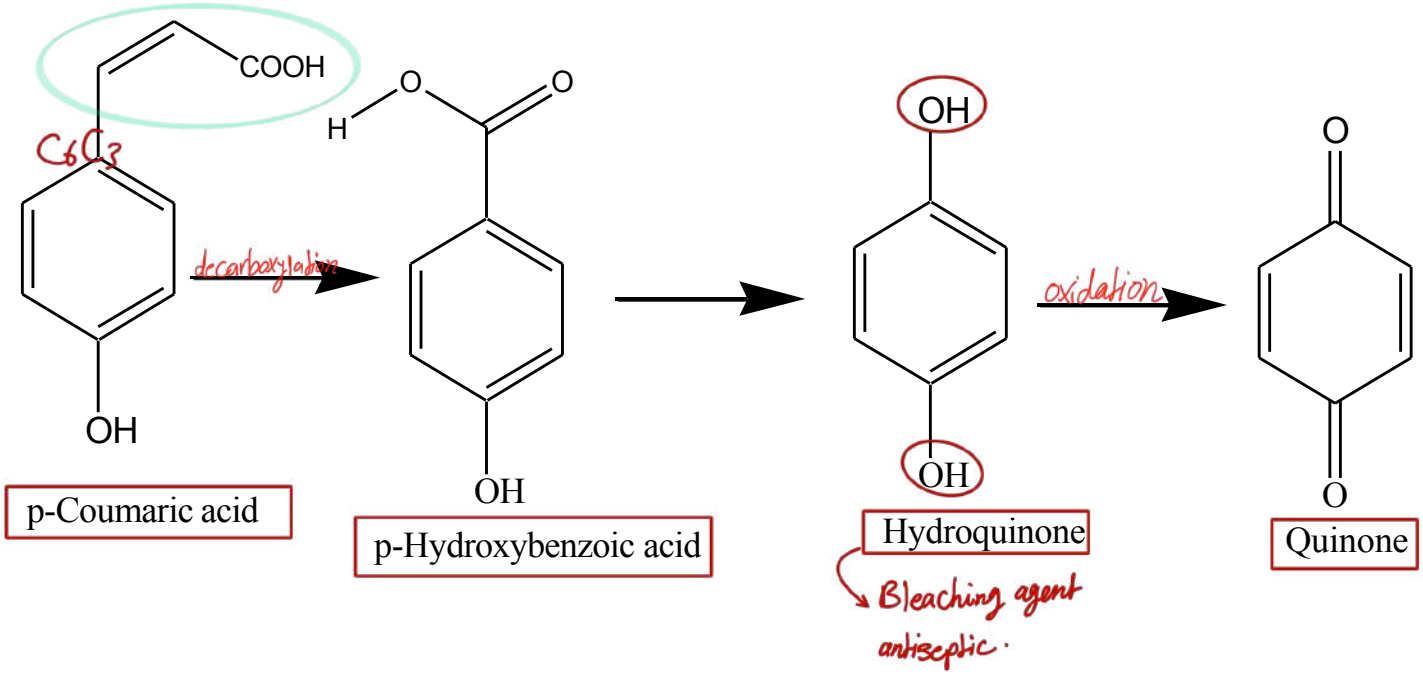
Coffea arabica **(Coffee plant)**

Part used: Beans

Both plants are source of Chlorogenic acid and Cynarin best known for their choleretic and lipid lowering effects (decrease cholesterol and triglycerides) and helpful in weight reduction regimens.

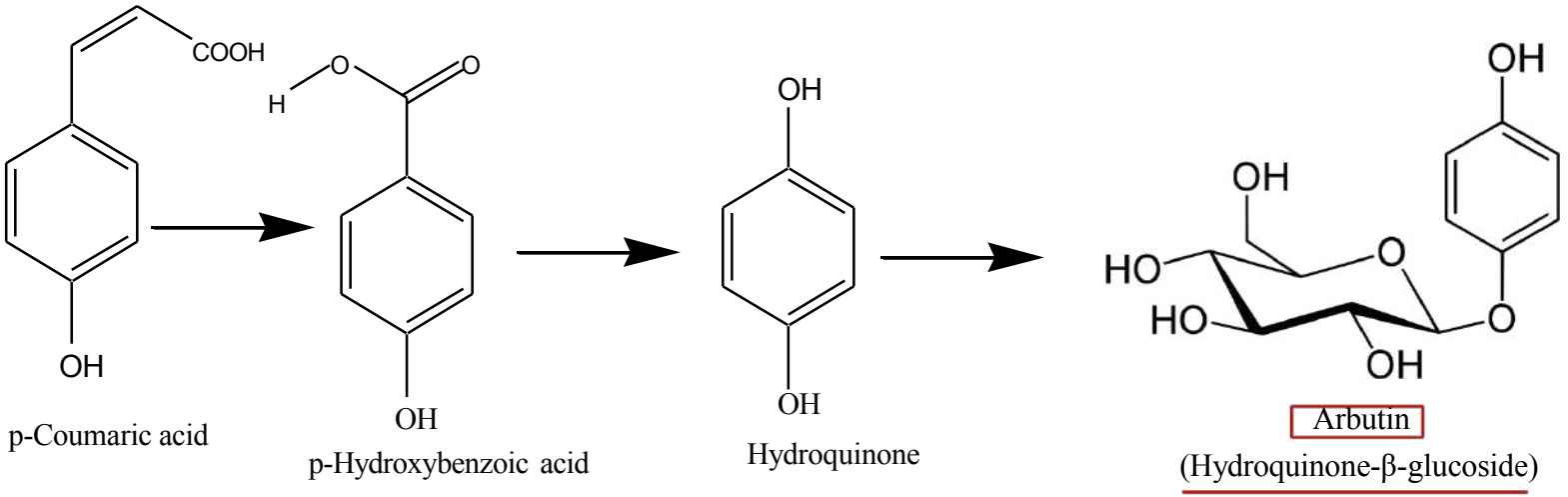
Formation of Phenylpropane Derivatives with Shorter Side Chain:

Shortening of side chain by β-oxidation and subsequent decarboxylation (simple phenols) which might be linked to oxidation→hydroquinone → quinone



Simple phenolics from SAP
C6 Phenols (hydroquinones)

- Seldom occur naturally, but from benzoic acid decarboxylation (oxidative or not)
- Examples include Arbutin (in bearberry leaves): bioformed from 4-hydroxy benzoic acid:



Simple phenolics from SAP

Bearberry (بدلا بنع) عنب الدب

- SN: *Arctostaphylos uva-ursi* L.
- Part used: Leaves
- Chemical composition: 6-10% phenolic glycosides: mainly arbutin and methyl-arbutin
- Pharmacology and uses:
  - Under alkaline urine, arbutin forms hydrquinone which is antiseptic.
  - Bearberry leaf extract is antiseptic and diuretic: traditionally used for Rx of benign UTIs and to enhance renal secretion.
  - Hydroquinone (and its methyl derivative: mequinol) is a topical skin bleaching agent (inhibits melanin synthesis): used for topical treatments of burn scars, chloasma (الكلف), and freckles (النمش).

Arctostaphylos uva-ursi
Bearberry

Benzoic acids (C6-C1) related to cinnamic acids

Cinnamic acid .....Benzoic acid

p-coumaric acid.....*p*-OH-benzoic acid

Caffeic acid.....Protocatechuic acid

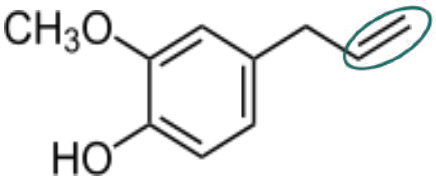
Ferulic acid.....Vanillic acid

Sinapic acid..... Syringic acid

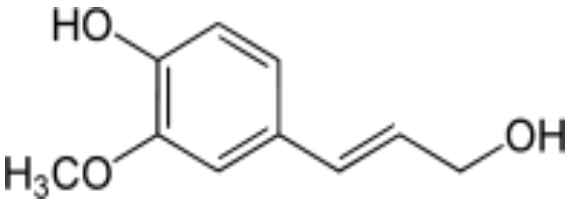
Tri-OH-cinnamic acid.....Gallic acid

Vanilla planifolia (Orchidaceae)

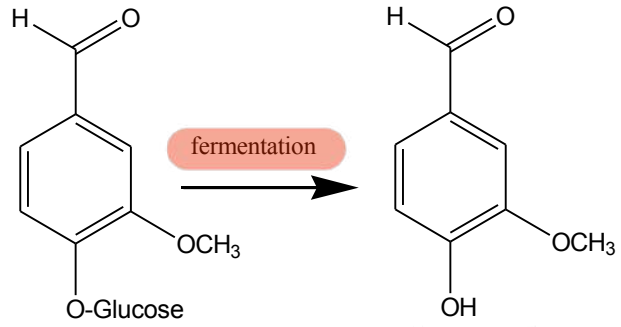
- Vanillin produced from eugenol (in plants) or lignin is a degradation by-product of paper from wood (large scale preparation of vanillin)
- Fermentation under blankets in the sun



Eugenol



Coniferylalcohol (lignin monomer)

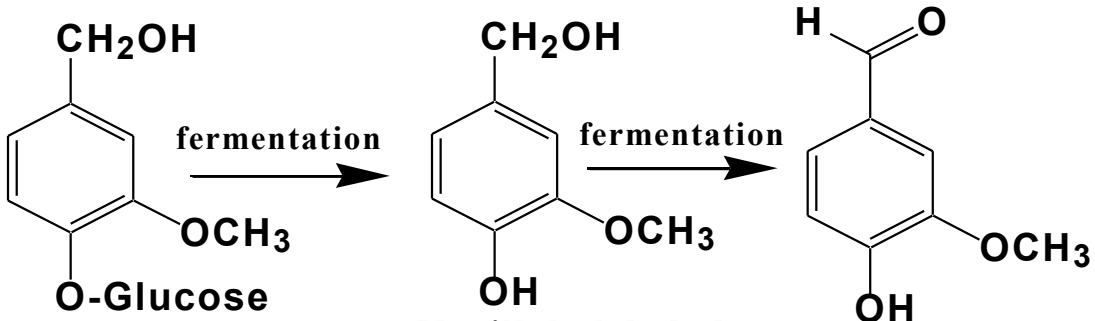


Vanilloside

Vanillin glucoside

Vanillin

Vanilloside (odourless) is liberated during fermentation & oxidized to vanillin



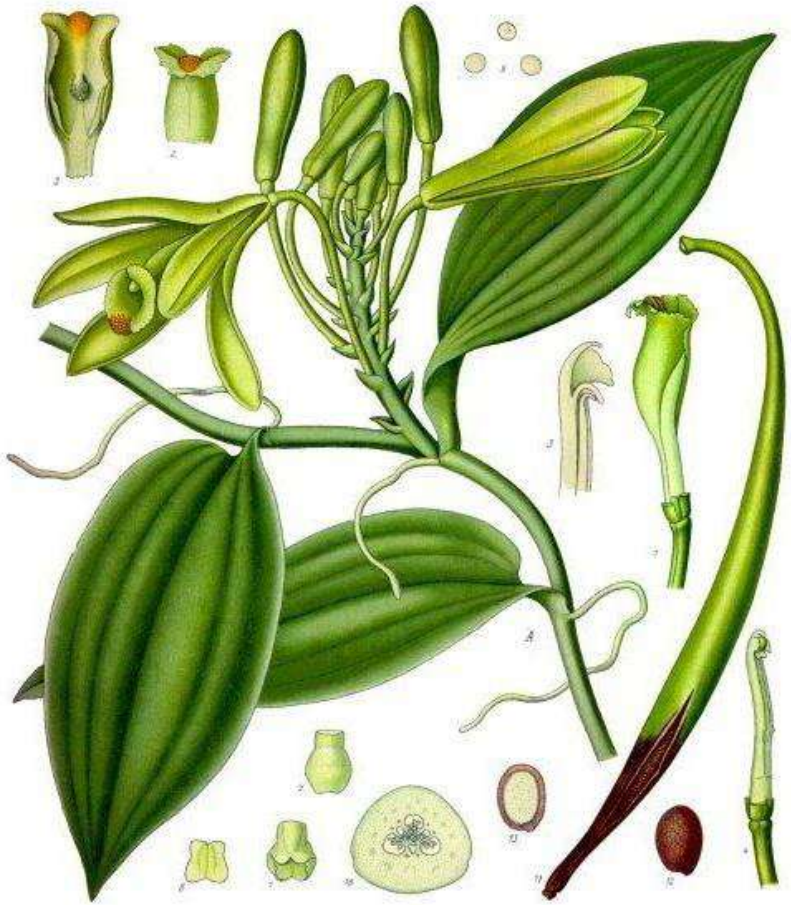
Vanilloloside
Vanillic alcohol glucoside

Vanillyl alchohol

Vanillin

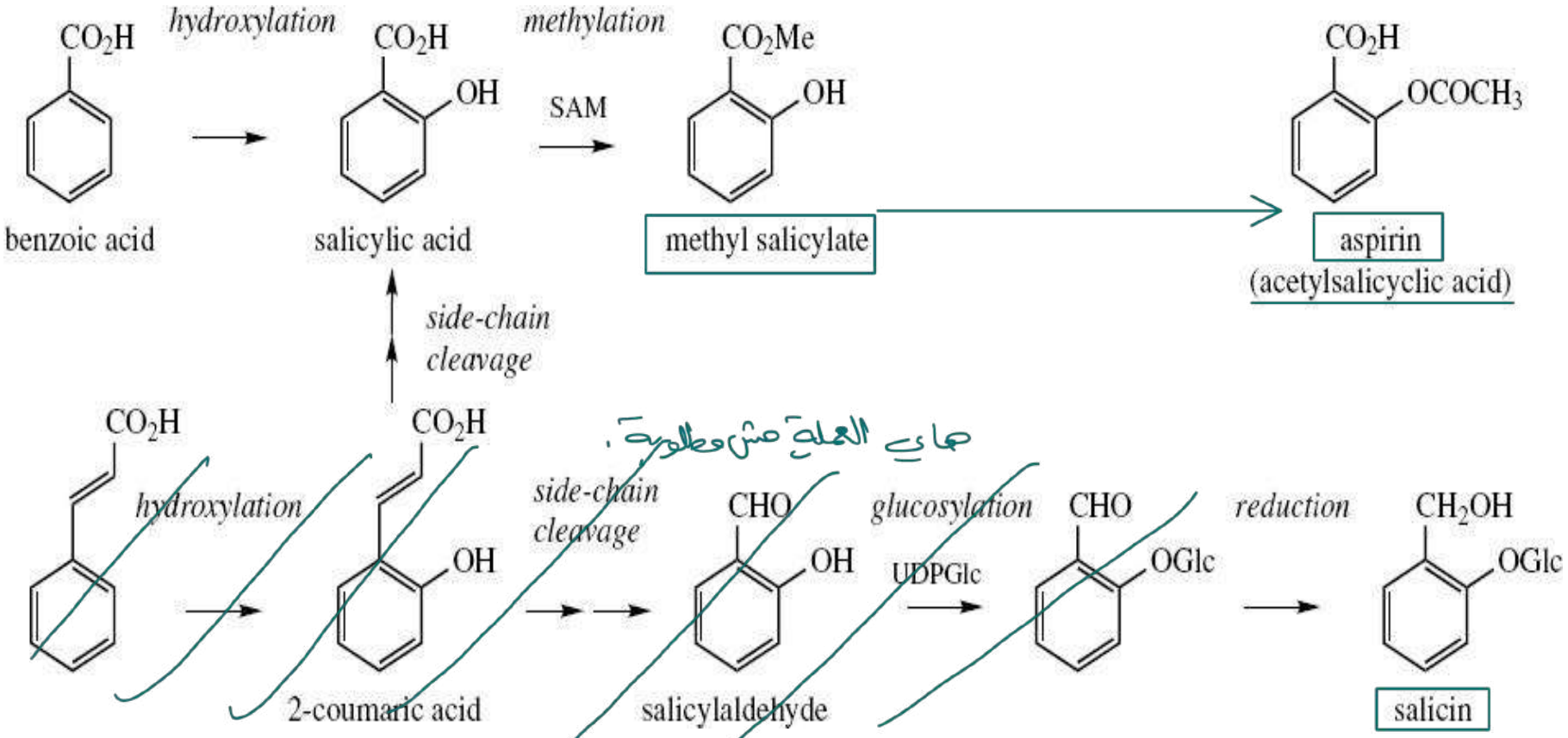
- Fine aroma and taste is due to other compounds better than pure vanillin

Vanilla planifolia

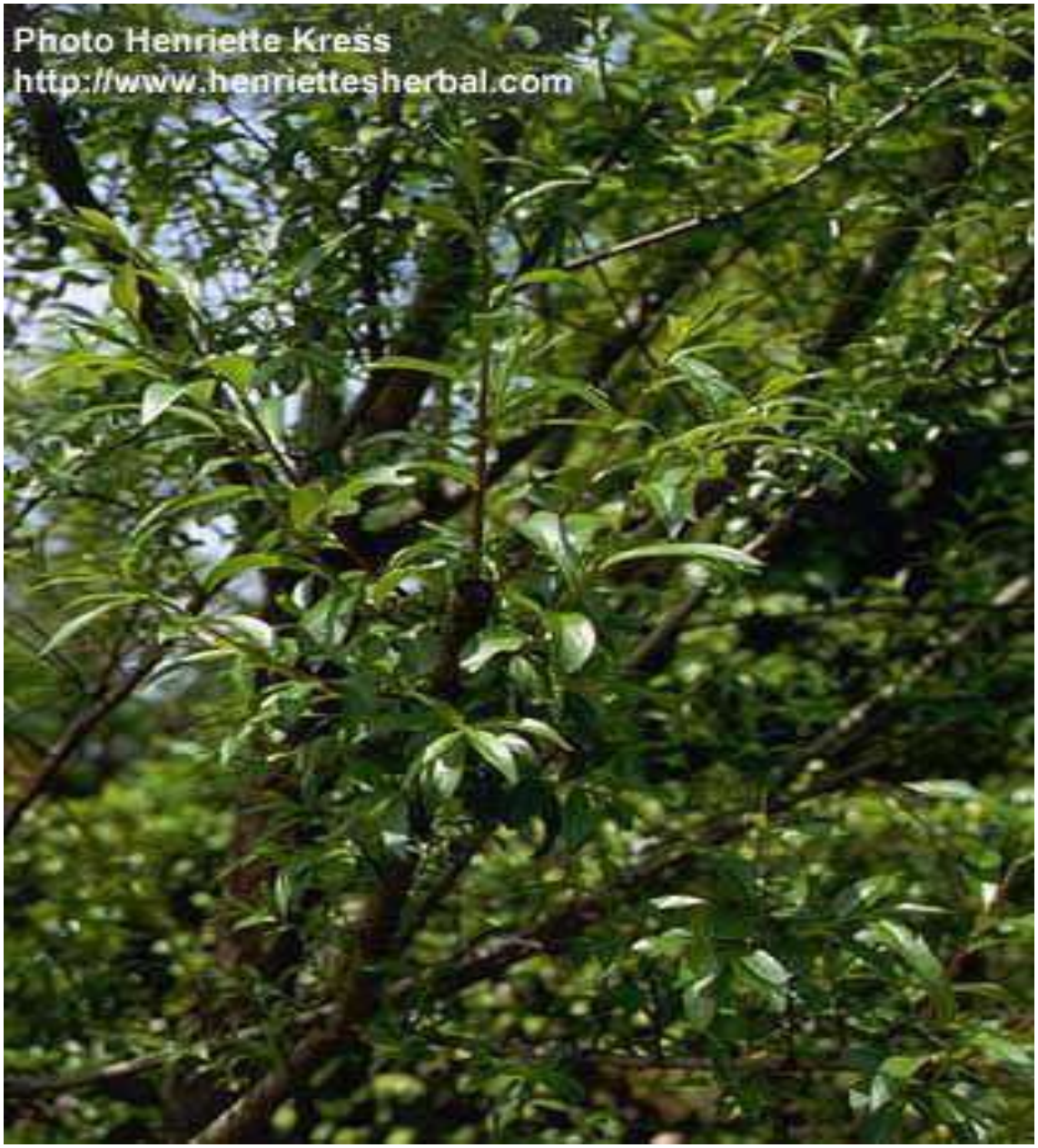


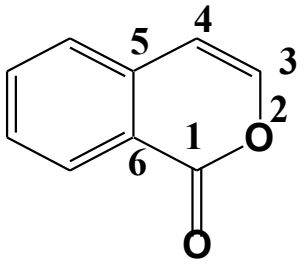
Vanilla pods (***Vanilla planifolia)***

Salicylates



- *Salix alba* (Willow)

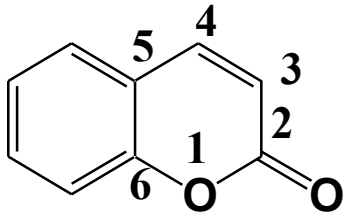




5,6-Benzopyran-1-one
isocoumarin

Coumarins

C_6C_3



5,6-Benzopyran-2-one
coumarin

Chromophore ← بمتصوال "UV" يستخدم في حالات tanning . light .

❖Name derived from **Coumarouna** (local Guyana name) for the seeds of *Dipteryx odorata* (Fabaceae), common named for Tonka bean

❖Seeds as spirits spice (not used now, hepatotoxic & carcinogenic)

❖Characteristic **new mown hay smell** رائحة التبن

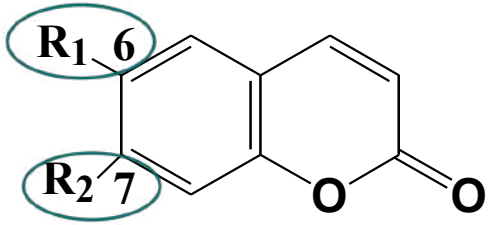
❖Commonly used as sun **UV protector**

❖**Absorb** short wave UV **230-315** nm & **transmit** long-wave UV **315 - 400** nm resulting in brown sun tan

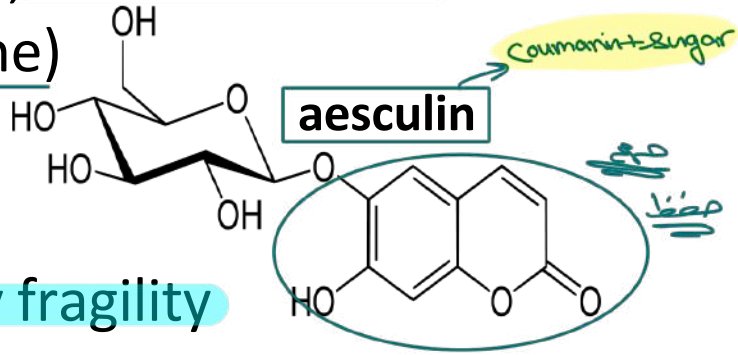
Dipteryx odorata (Tonka beans)

Characters of Coumarins

- Free coumarins are **organic solvents-soluble**
- Derivatives of α-chromone, differ in benzene ring substitutions (OH, OCH_3, CH_3)
- Common in **Apiaceae**, **Asteraceae**, **Fabaceae**, **Lamiaceae**, **Poaceae**, **Moraceae**, **Rutaceaea** & **Solanaceae**
- Characteristic UV (blue, yellow & purple) enhanced by ammonia
- **Umbelliferone** R_1=H, R_2=OH
- **Aesculetin** R_1=R_2= OH
- **Scopoletin** R_1=OCH_2, R_2= OH



- *Aesculus hippocastanum* (horse-chestnut) (Hippocastanaceae) leaves & bark rich in aesculin (6β-D-glucosyloxyl-7-OH-coumarin, or 6β-D-glucosyl-Aesculetin); used in sun tan preparations (both glycoside & aglycone)



- Symptomatic Rx of cutaneous capillary fragility

- Leaves & bark of Horse chest nuts

نصحلا عنك

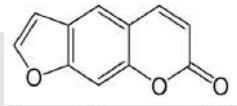
Dicoumarol and Warfarin

The cause of fatal haemorrhages in animals fed spoiled sweet clover (*Melilotus officinalis*; Leguminosae/Fabaceae) was traced to dicoumarol (bishydroxycoumarin) (Figure 4.31). This agent interferes with the effects of vitamin K in blood coagulation (see page 163), the blood loses its ability to clot, and thus minor injuries can lead to severe internal bleeding. Synthetic dicoumarol has been used as an oral blood anticoagulant in the treatment of thrombosis, where the risk of blood clots becomes life threatening. It has been superseded by salts of **warfarin** and **acenocoumarol (nicoumalone)** (Figure 4.32), which are synthetic developments from the natural product. An overdose of warfarin may be countered by injection of vitamin K_1.

Warfarin was initially developed as a rodenticide, and has been widely employed for many years as the first choice agent, particularly for destruction of rats. After consumption of warfarin-treated bait, rats die from internal haemorrhage. Other coumarin derivatives employed as rodenticides include **coumachlor** and **coumatetralyl** (Figure 4.32). In an increasing number of cases, rodents are becoming resistant to warfarin, an ability which has been traced to elevated production of vitamin K by their intestinal microflora. Modified structures **defenacoum** and **brodifenacoum** have been found to be more potent than warfarin, and are also effective against rodents that have become resistant to warfarin.

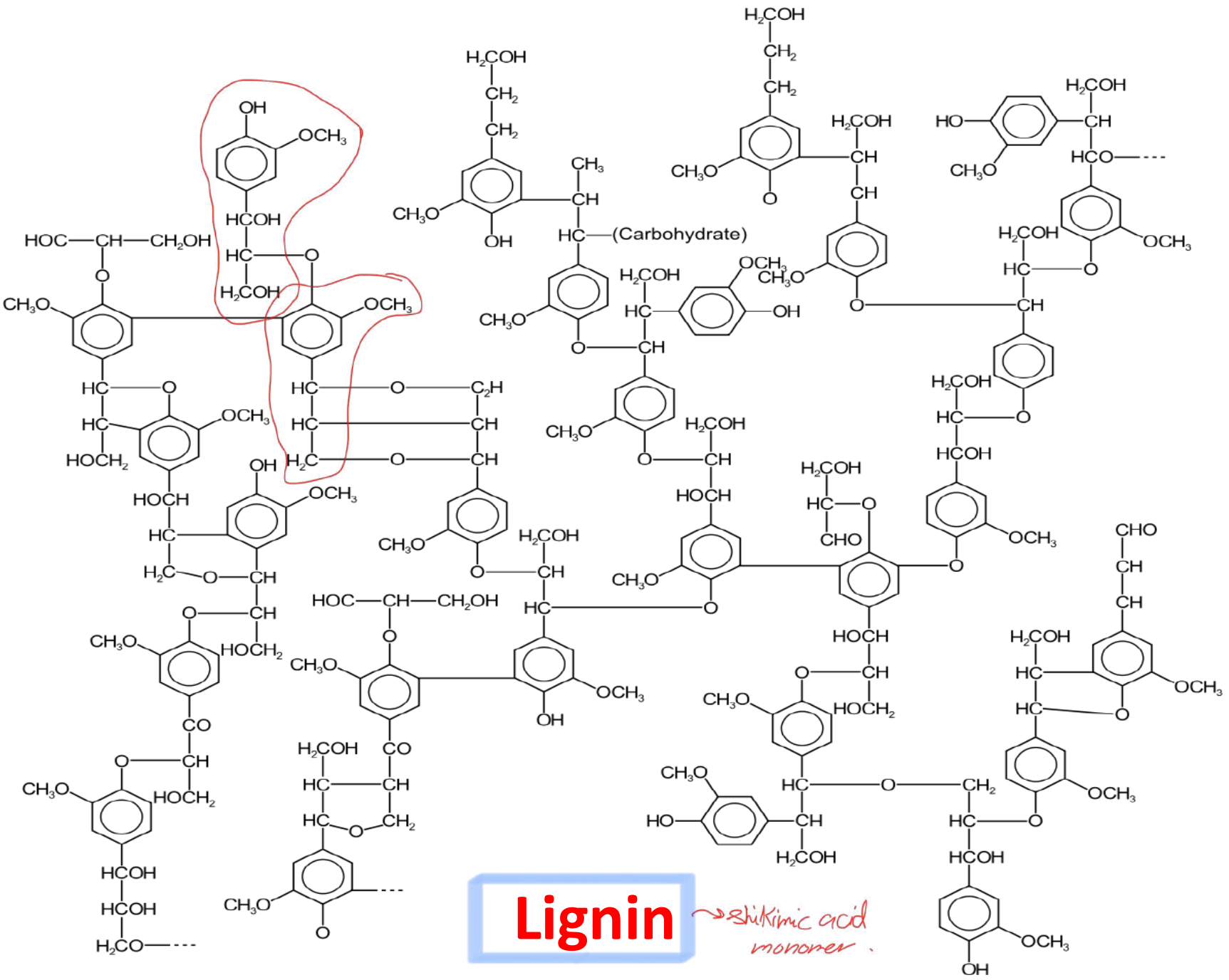
Melilotus officinalis البرسيم الحلو

Psoralens



Psoralens are linear furocoumarins which are widely distributed in plants, but are particularly abundant in the Umbelliferae/Apiaceae and Rutaceae. The most common examples are psoralen, bergapten, xanthotoxin, and isopimpinellin (Figure 4.33). Plants containing psoralens have been used internally and externally to promote skin pigmentation and sun-tanning. Bergamot oil obtained from the peel of *Citrus aurantium* ssp. *bergamia* (Rutaceae) (see page 179) can contain up to 5% bergapten, and is frequently used in external suntan preparations. The psoralen, because of its extended chromophore, absorbs in the near UV and allows this radiation to stimulate formation of melanin pigments (see page 129).

Methoxsalen (xanthotoxin; 8-methoxypsoralen) (Figure 4.36), a constituent of the fruits of *Ammi majus* (Umbelliferae/Apiaceae), is used medically to facilitate skin repigmentation where severe blemishes exist (vitiligo). An oral dose of methoxsalen is followed by long wave UV irradiation, though such treatments must be very carefully regulated to minimize the risk of burning, cataract formation, and the possibility of causing skin cancer. The treatment is often referred to as PUVA (psoralen + UV-A). PUVA is also of value in the treatment of psoriasis, a widespread condition characterized by proliferation of skin cells. Similarly, methoxsalen is taken orally, prior to UV treatment. Reaction with psoralens inhibits DNA replication and reduces the rate of cell division. Because of their planar nature, psoralens intercalate into DNA, and this enables a UV-initiated cycloaddition reaction between pyrimidine bases (primarily thymine) in DNA and the furan ring of psoralens (Figure 4.36). In some cases, di-adducts can form involving further cycloaddition via the pyrone ring, thus cross-linking the nucleic acid.

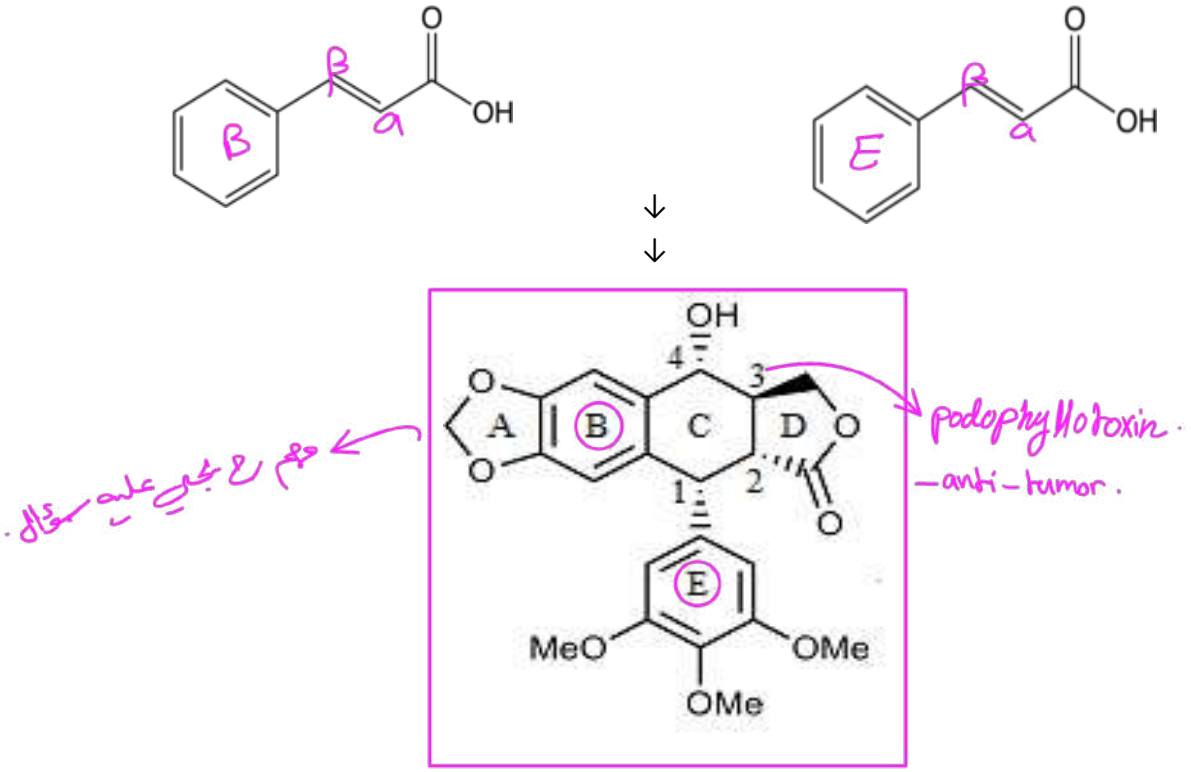

Lignin
shikimic acid
monomer

Lignin & Lignans

- Lignin is plant polymer acting as strengthening material for plant cell wall & matrix for cellulose micro-fibrils
- Represent a large no. of aromatic material based on C_6C_3 building unit
- Lignins formed by oxidative coupling of hyroxycinnamyl alcohol monomers by peroxidase enzymes [p-coumaryl-, coniferyl- and sinapyl-alcohol]
- Lignans are dimeric phenylpropanes (C-18) coupled at the central carbon of the side chain [via their ß-carbon of the side chain]

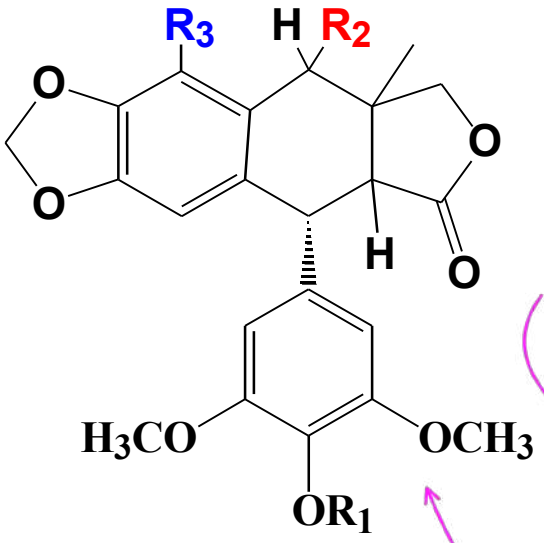
Formation of the lignans

Dimers of cinnamic acid linked via their ß-carbons and further modifications; i.e. Podophyllotoxin



Podophyllotoxin & Peltatins

- Lignans formed by oxidative coupling of 2 cinnamic acid residues (dimeric phenylpropane derivatives) known as **LIGNANS**

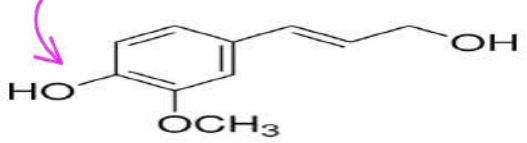


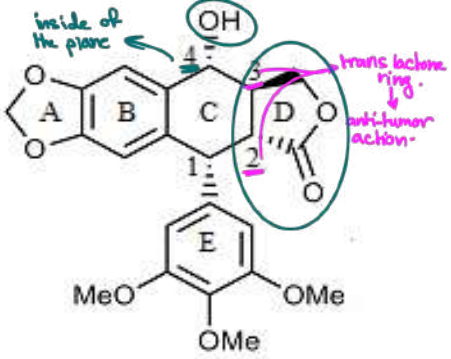
Podophyllotoxin	$R_1 = CH_3$	$R_2 = OH$	$R_3 = H$
Alpha-Pelatin	$R_1 = H$	$R_2 = H$	$R_3 = OH$
Beta- Pelatin	$R_1 = CH_3$	$R_2 = H$	$R_3 = OH$

مش مطلوب أمين بينهم لكن مطلوب أعرف شكل الـ Structure

Podophyllotoxin: 2 C_6C_3 [Coniferylalcohol]

via several intermediates





- Dried root & rhizhome of *Podophyllum peltatum* [May apple, mandrake] (Berberidaceae) USA & Canada
- Structure elucidated in 1930's; planar structure with 4 chiral centers
- **C_2H_5OH extract = Podophyllin** (20% podophyllotoxin, 10% β-peltatin, 5% α-peltatin)
- **Traditionally as cathartic, purgative, antiviral, warts remedy** الثواليل
- Trans lactone ring is essential for anti-tumor action; aromatization of ring C↓activity. Too toxic to be used clinically!
- [OH^-] converts into **inactive isomer** (e.g. ***epi***-podophyllatoxin) inactive غير
- Classified as microtubule inhibitor [inhibits polymerization of tubulin and stop cell division at the beginning of metaphase]

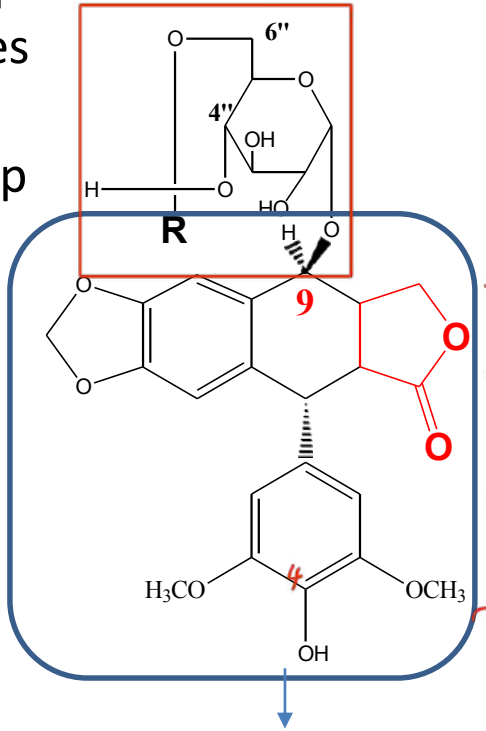
R_1 = H, R_2 = OH podophyllotoxin (**1**)

R_1 = OH, R_2 = H *epi*-podophyllotoxin (**2**)

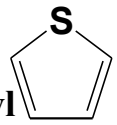
Root & Rhizhome of *Podophyllum peltatum*

Podophyllotoxin Derivatives
Mitotic Spindle Poisons

- *epi*-podophyllotoxin glycoside is used to prepare 2 clinically useful compounds for malignant diseases
- **Mechanism of action:** inhibit polymerization of tubulin and stop cell division at the beginning of metaphase
- **Tiniposide:** Rx bladder cancer
- **Etoposide:** Rx small cell lung cancer, leukemia & Hodgkin's disease



Teniposide : R= Thienyl



Etoposide : R = CH_3

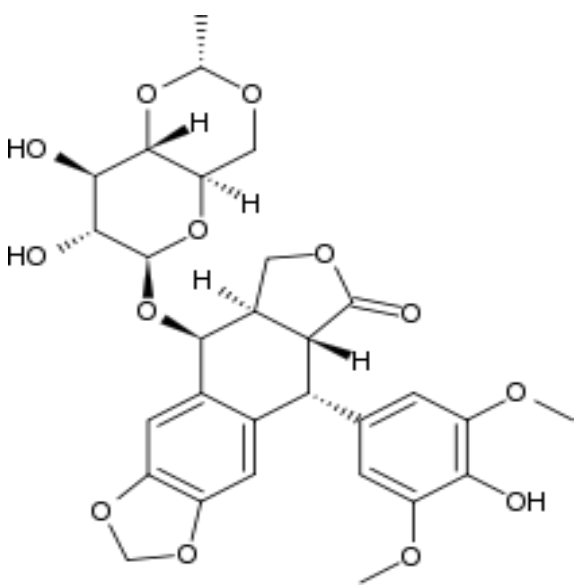
Semisynthetic anti cancer.

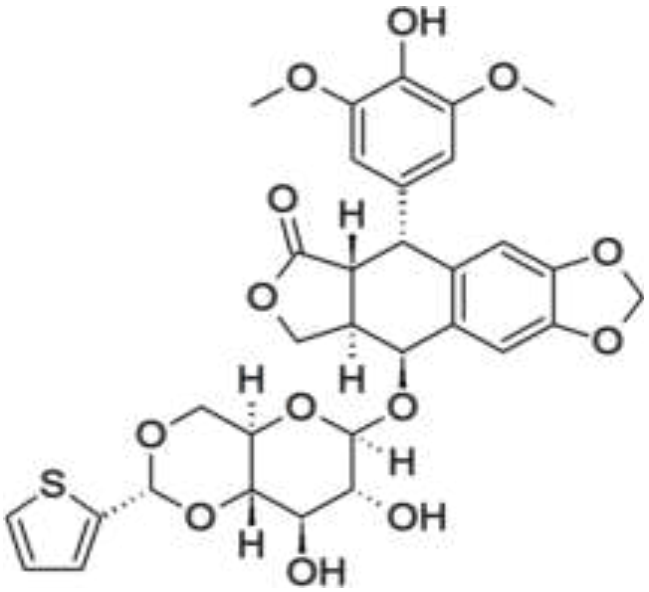
Topo II inhibitors.

4' demethylepipodophyllotoxin

Etoposide and teniposide

- As semisynthetic anticancer agents developed from 4'-demethylepipodophyllotoxin
- They act as Topo II inhibitors (prevention of DNA synthesis and replication)
- **Etoposide** : small cell lung cancer, breast cancer, leukemia & Hodgkin's disease,… **Teniposide** : brain and bladder cancer,…
- **Glycosides < active than genins < side effects**





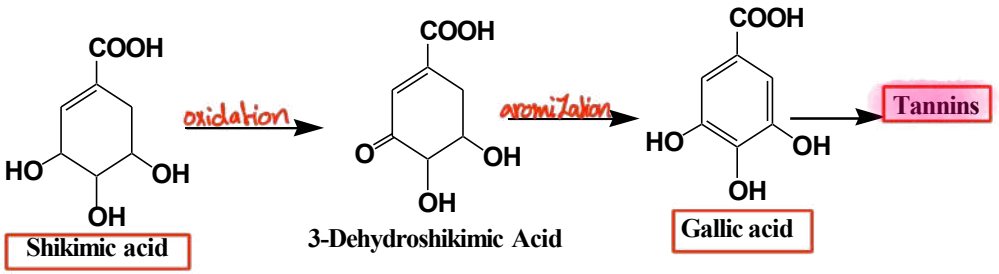
4′-demethylpodophyllotoxin glucoside. Attempted synthesis of the glucoside inverted the stereochemistry at the sugar–aglycone linkage, and these agents are thus derivatives of 4′-demethylepipodophyllotoxin (Figure 4.21). **Etoposide** is a very effective anticancer agent, and is used in the treatment of small cell lung cancer, testicular cancer and lymphomas, usually in combination therapies with other anticancer drugs. It may be given orally or intravenously. The water-soluble pro-drug **etopophos** (etoposide 4′-phosphate) is also available. **Teniposide** has similar anticancer properties, and, though not as widely used as etoposide, has value in paediatric neuroblastoma.

Remarkably, the 4′-demethylepipodophyllotoxin series of lignans do not act via a tubulin-binding mechanism as does podophyllotoxin. Instead, these drugs inhibit the enzyme topoisomerase II, thus preventing DNA synthesis and replication. Topoisomerases are responsible for cleavage and resealing of the DNA strands during the replication process, and are classified as type I or II according to their ability to cleave one or both strands. Camptothecin (see page 365) is an inhibitor of topoisomerase I. Etoposide is believed to inhibit strand-rejoining ability by stabilizing the topoisomerase II–DNA complex in a cleavage state, leading to double-strand breaks and cell death. Development of other topoisomerase inhibitors based on podophyllotoxin-related lignans is an active area of research. Biological activity in this series of compounds is very dependent on the presence of the *trans*-fused five-membered lactone ring, this type of fusion producing a highly-strained system. Ring strain is markedly reduced in the corresponding *cis*-fused system, and the natural compounds are easily and rapidly converted into these *cis*-fused lactones by treatment with very mild bases, via enol tautomers or enolate anions (Figure 4.22). Picropodophyllin is almost devoid of cytotoxic properties.

Podophyllotoxin is also found in significant amounts in the roots of other *Podophyllum* species, and in closely related genera such as *Diphylleia* (Berberidaceae).

Tannins & Gallic acid

- Gallic acid is the building block of many tannins



Properties of Tannins:

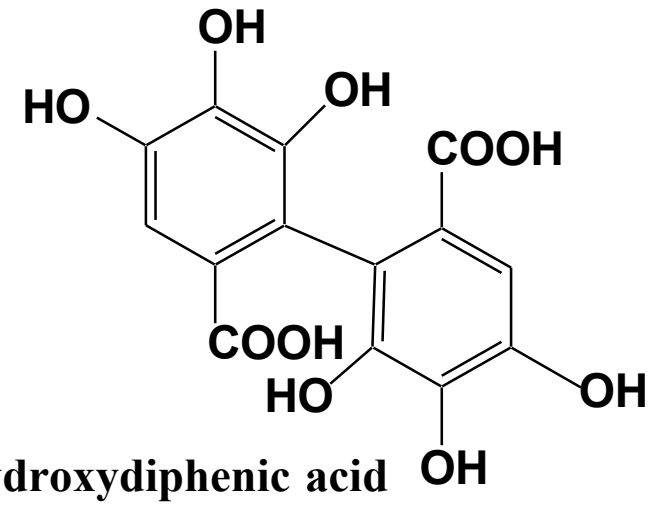
- H_2O solubility !! (colloidal aq. Solution in A` PH) high solubility.
- Binds proteins to form indigestible complex (leather tanning)
- Amorphous
- Astringent taste (unripe fruits, in all organs or organ-specific) الفواكة غير الناضجة
- Fe^{+2} salts binding producing dark blue or greenish black sol. Complexes (ink)
- Ppt with metals e.g. Cu, Pb (acetate salts to separate tannins from extracts); ppt gelatin and alkaloids;
- Large MW (1000-5000)
- Pseudotannins (MW~500)

Hydrolysable tannins

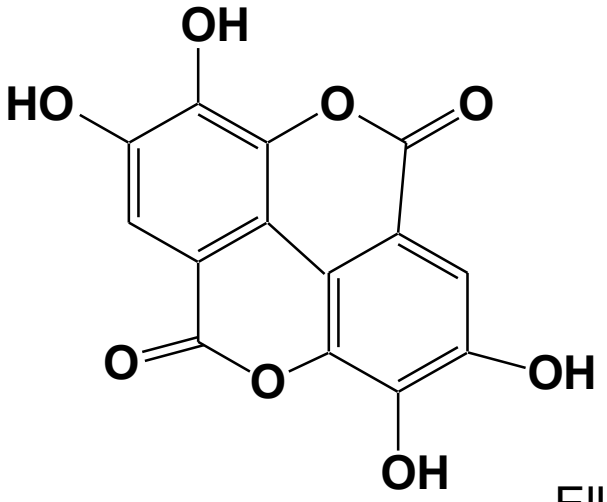
they must have a sugar.

~ a dimer or trimer of gallic acid + sugar.

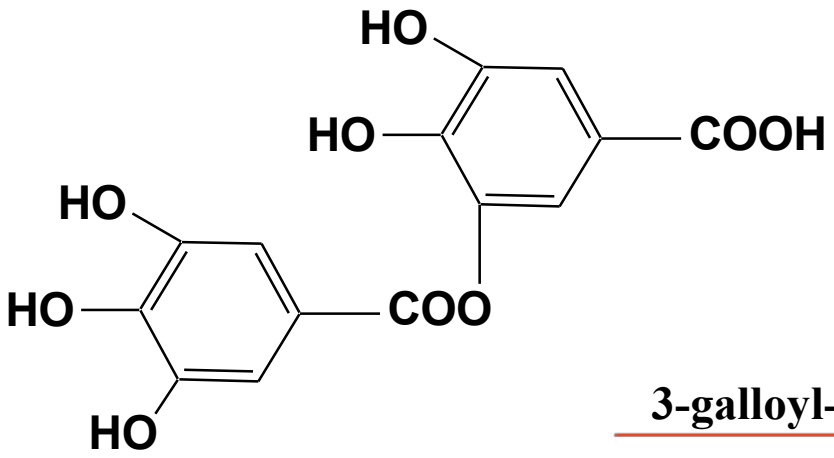
- Possibilities of condensation of the gallic acid



Hexahydroxydiphenic acid



Ellagic Acid



3-galloyl-gallic acid

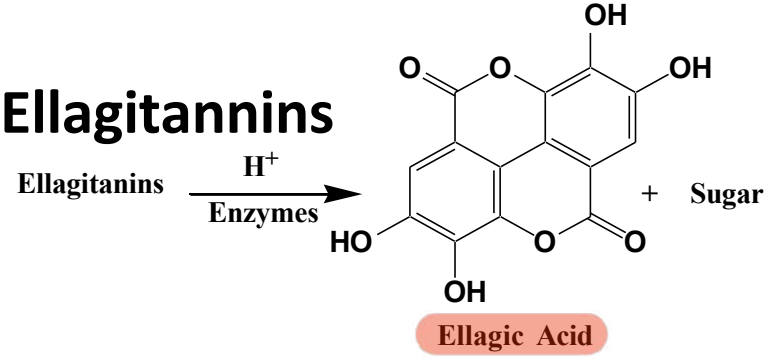
Classification of Tannins

1 Hydrolysable

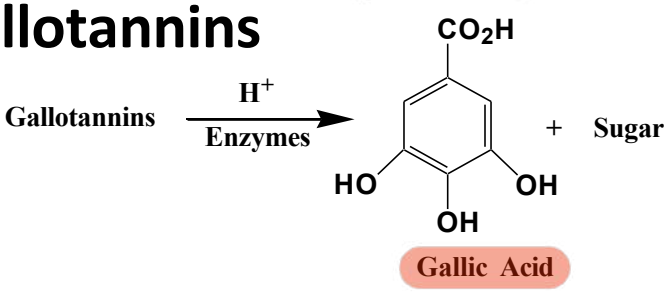
H^+ or enzymes Rx produce simple molecules

Simple, hydrolysable, Galloyl esters of sugars, phenolic moiety is shikimate-derived

A) **Ellagitannins**



B) **Gallotannins**

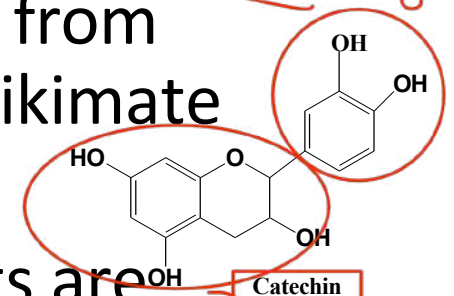


2 Condensed

don't contain a sugar.

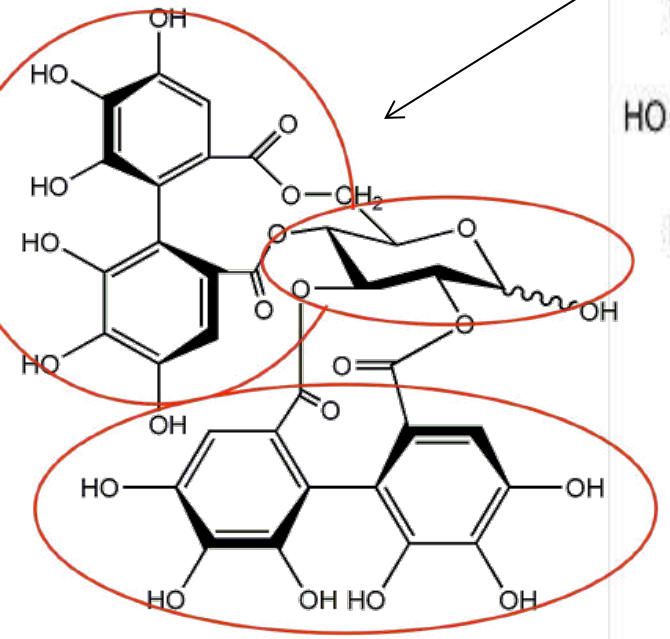
- H^+ or Enzymes Rx produce complex insoluble compounds
- Complex polymers
- Biosynthesis from acetate & shikimate pathway
- Building units are catechins which are a type flavonoids

acetate melanate pathway.



C_6C_3

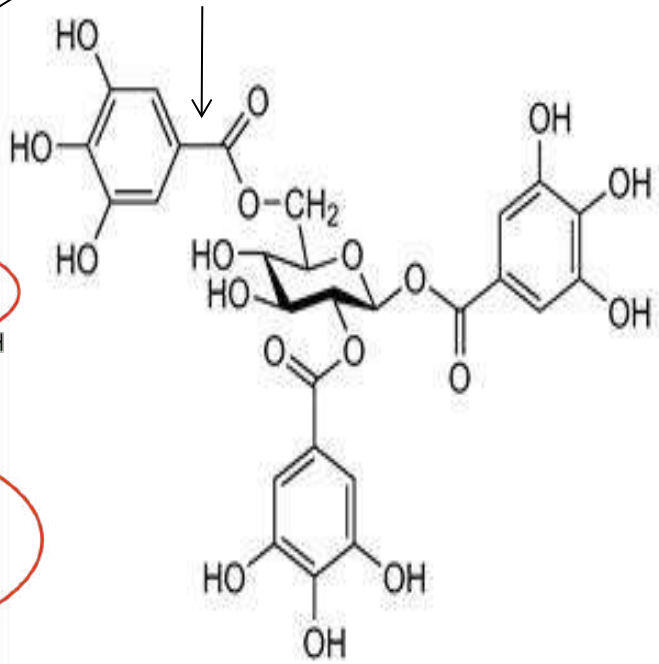
shikimic acid pathway



Pedunculagin

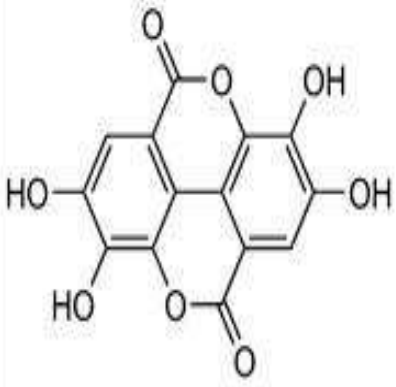
(Ellagitannin)

Hydrolysable tannins



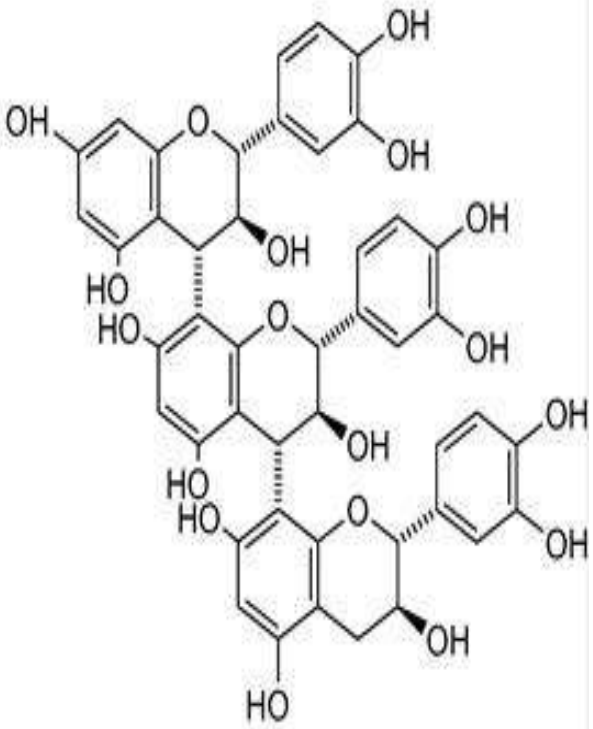
1,2,6-Trigalloyl glucose (Gallotannin)

H⁺ enzyme → gallic acid + sugar.



Ellagic acid

Non-hydrolysable tannins



Trimer of epicatechin

→ condensation of Flavanoid.

Medicinal Value of Tannins

Limited Application:

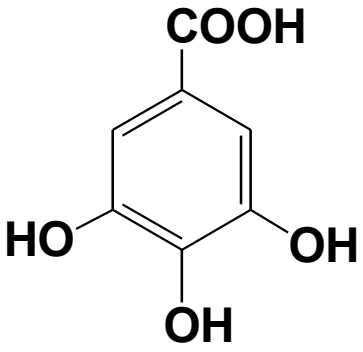
Based on ability to bind proteins to form indigestible complex

1. Diarrhea
2. Bleeding gums
3. Skin injuries preparations

Hamamelis (witch-hazel)

البندق

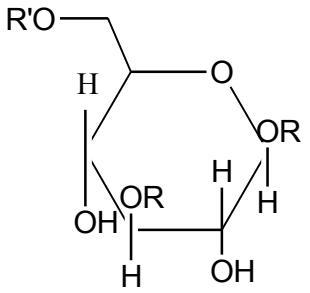
- Dried leaves of *Hamamelis virginiana* L. (Hamamelidaceae)
- Sources: North America & Canada
- Rich in gallotannins → hydrolyizable tannin.



Gallic acid

Uses:

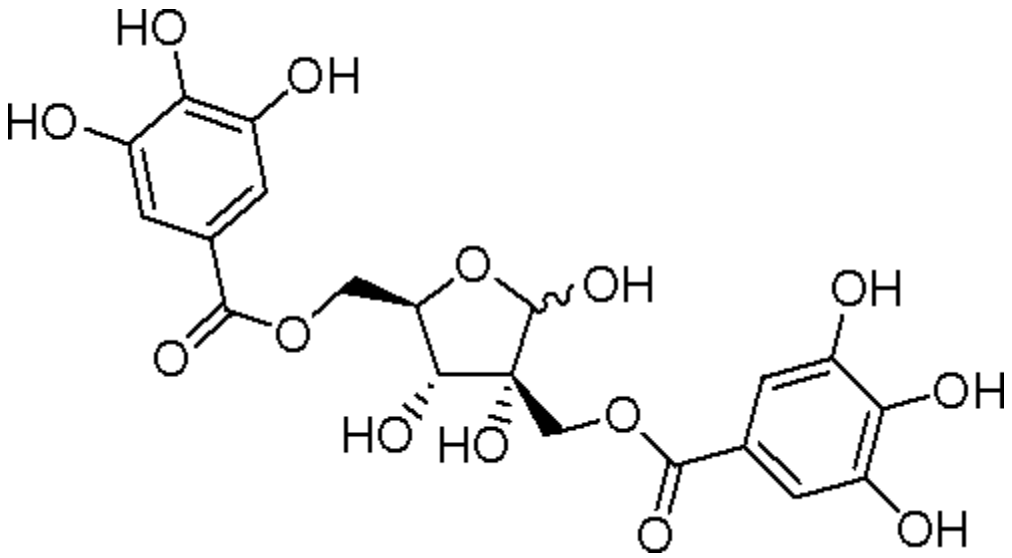
1. Infusions & extracts in hemorrhoids (topical pharmaceuticals)
2. Topically skin inflammation
3. Face lotions as astringent



R= GALLIC ACID

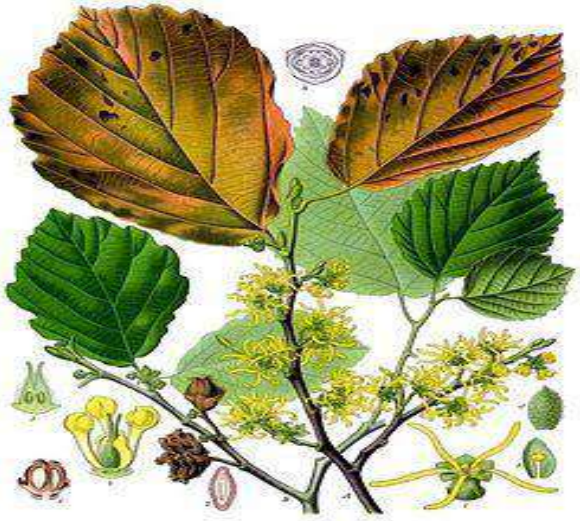
R' = TRIGALLIC ACID

Hamamelis virginiana (Witch Hazel) Tannins



Hamamelitannin

2-C-(hydroxymethyl)-D-ribofuranose 2’,5-digallate

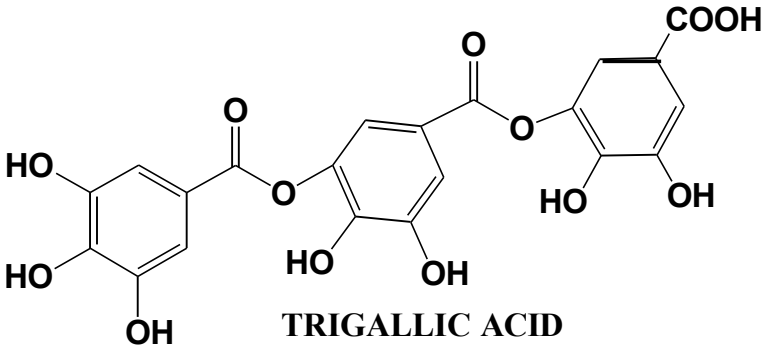


Hamamelis virginiana

(witch-hazel)

Galls (Nutgalls)

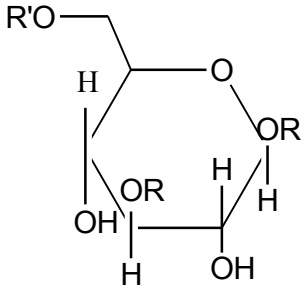
- Vegetable growths as a result of insect infections of the leaves & twigs of *Quercus infetoria* (Fagaceae), Oak (طولبلا)
- Contains 70-80% tannins (Sources: Turkey, Syria, Greece & Iran)



TRIGALLIC ACID

Uses:

1. Rx of catarrh & infection
2. Stop bleeding locally
3. Alkaloid poisoning remedy (insoluble comlex)
4. Ink preparation
5. Textiles dyeing esp. leather



R= GALLIC ACID

R' = TRIGALLIC ACID

Galls (Nutgalls) of *Quercus infectoria* (Oak)

- Caused by insects

Nutgalls