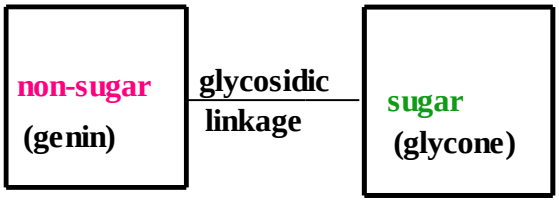
UNIT II

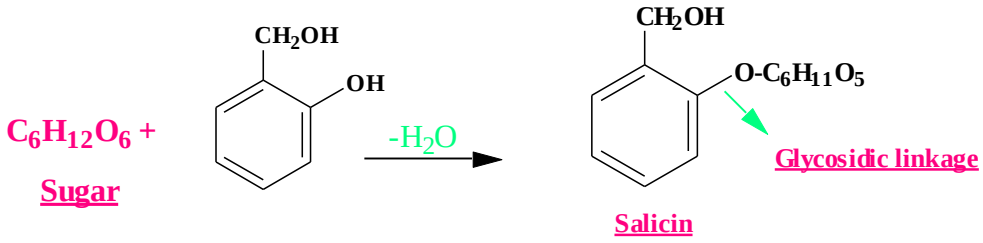
Glycosides

Definition:

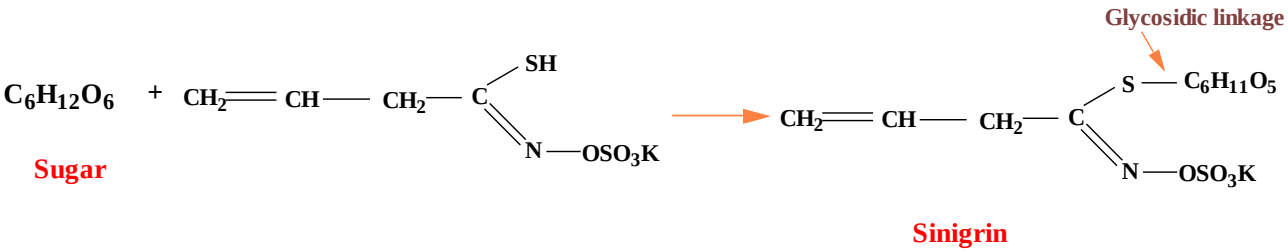
Glycosides are (usually) non-reducing compounds, on hydrolysis by reagents or enzymes yield one or more reducing sugars among the products of hydrolysis.



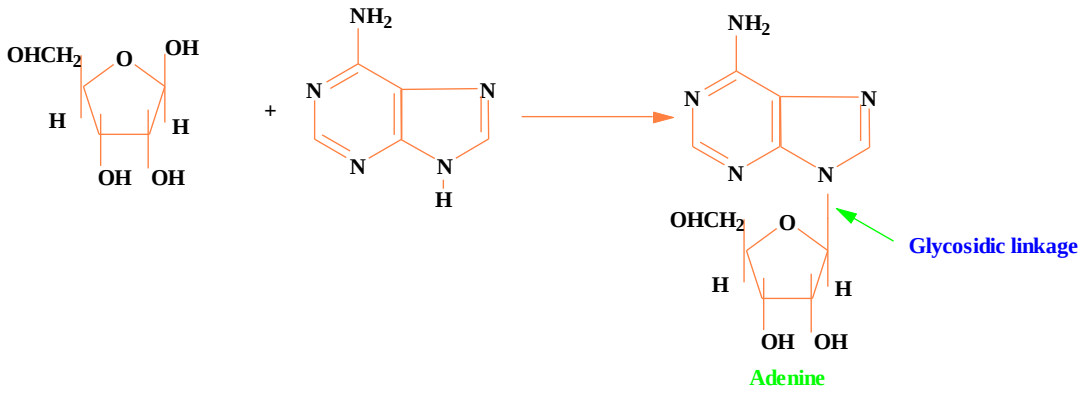
1- Alcoholic or phenolic (aglycone): e.g., O-Glycoside



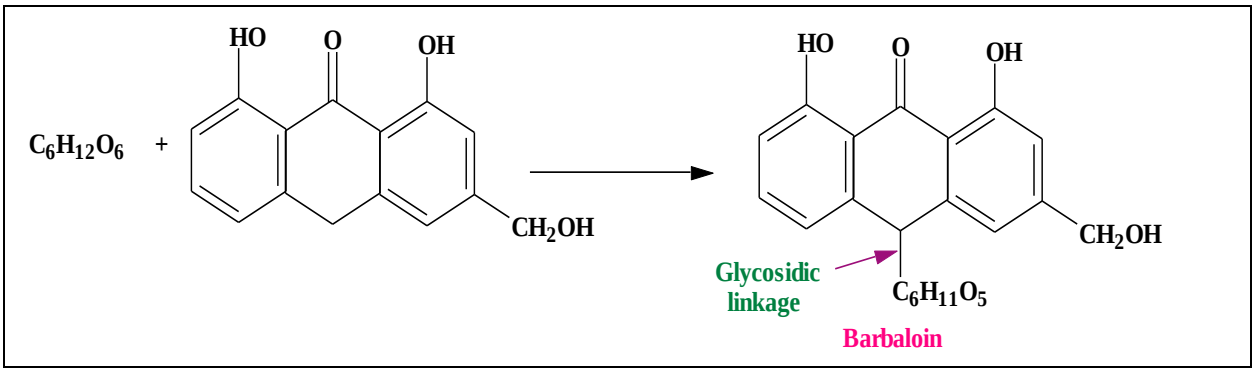
2- Sulphur containing compounds: e.g., S-Glycoside



3- Nitrogen containing compounds: e.g., N-Glycoside



4- C-Glycoside



CLASSIFICATION

.**According to chemical nature of aglycone moiety:**

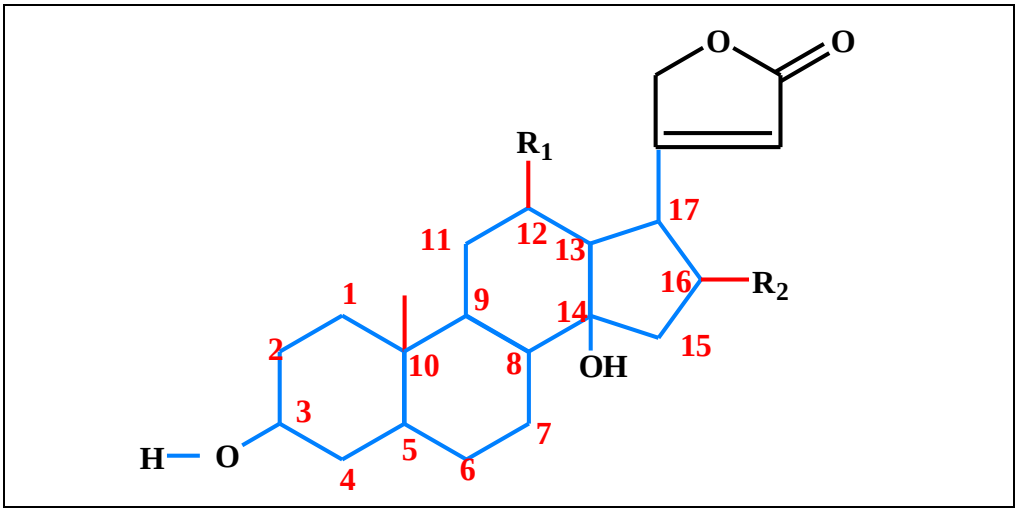
A).Anthraquinone glycosides : Senna.Aloe,Rhubarb,Cascara,Cochineal. **B**). **Sterol or cardiac glycosides** : Digitalis, Thevetia ,Squill, Strophanthus, Quabain**. C). Saponin Glycosides:** Dioscorea, Licorice, Shatavari ,Bramhi ,Ginseng, Gokhru. **D). Cyanogenetic or cyanophoric glycoside**: Bitter almond, wild cherry bark. **E).Isothiocyanate glycosides**: black mustard. **F).Flavonolglycosides**: citrus fruits, gingko. **G).Coumarin&furanocoumaringlycosides** :Ammi ,Mylabris, Tonkabean. **H).Aldehyde glycosides:** vanilla pods. **I). phenol glycosides**:bearberry. **J).Steroidal glyco-alkaloids:** solanum. **K).Glycosidal bitters &miscellaneous:**gentian, Chirata,Quassia(Bitter Wood),Kalmeg, Gymnema,Henna

CARDIAC GLYCOSIDES

DIGTILIS

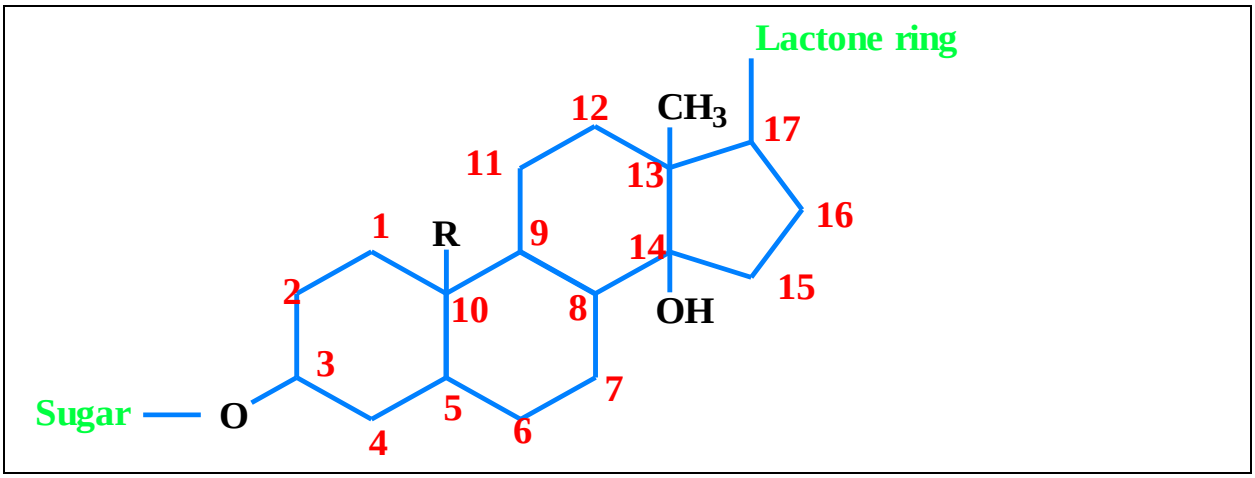
Origins. purpurea, D. lanata, D. lutea and D. thapsi

The structures of the common aglycones of the digitalis group are indicated below:



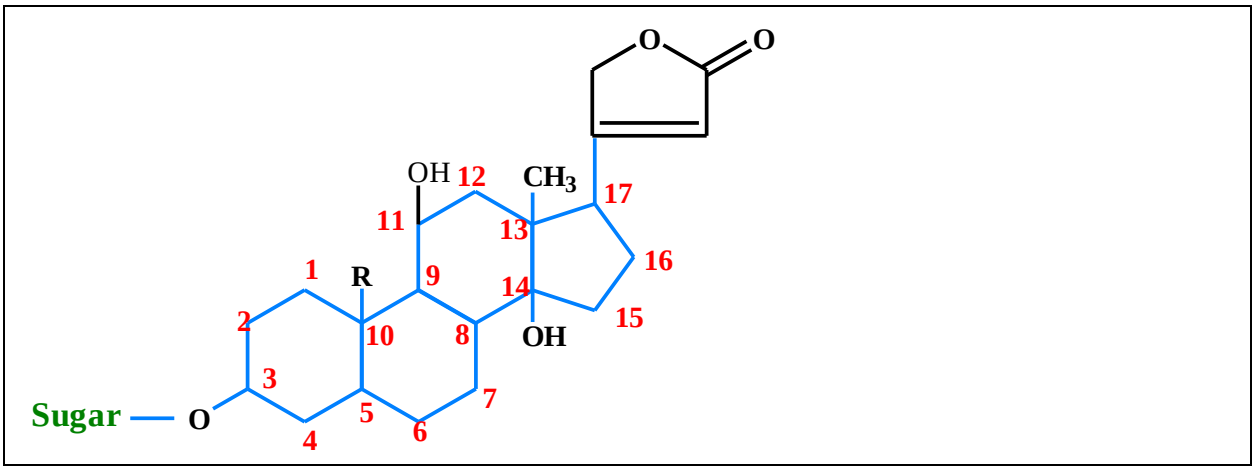
Compounds	R1	R2
Digitoxigenin	H	H
Gitoxigenin	H	OH
Digoxigenin	OH	H

- -The genins of all cardiac glycosides are steroidal in nature that acts as cardio tonic agents.
- -They are characterized by their highly specific action cardiac muscle, increasing tone, excitability and contractility of this muscle, thus allowing the weakened heart to function more efficiently.



STRUCTURE ELUCIDATION FOR DIGOXIN

1. its molecular formula is C41H64O14
2. The presence of *β*-OH at position C-3, which is always involved in a glycosidic linkage to a mono, di, tri, OR tetra saccharide.
3. The presence of another *β*-OH group at C-14.
4. The presence of unsaturated 5 or 6- membered lactone ring at position C-17, also in the *β* configuration.
5. The A/B ring junction is usually (cis), while the B/C ring junction is always (Trans) and the C/D ring junction is in all cases (cis).
6. Additional OH groups may be present at C-5, C-11 and C-16.
7. Cardiac glycosides that α-β unsaturated5-membered lactosering in position C-17 are known as cardenolides. These are represented by the digitalis and straphanthus group.
8. Digitalis glycosides contain angular methyl group at C-10, while strophanthus glycoside are characterized by presence of either an aldehydic (CHO) or primary alcoholic (C`H_2OH) group at C-10.

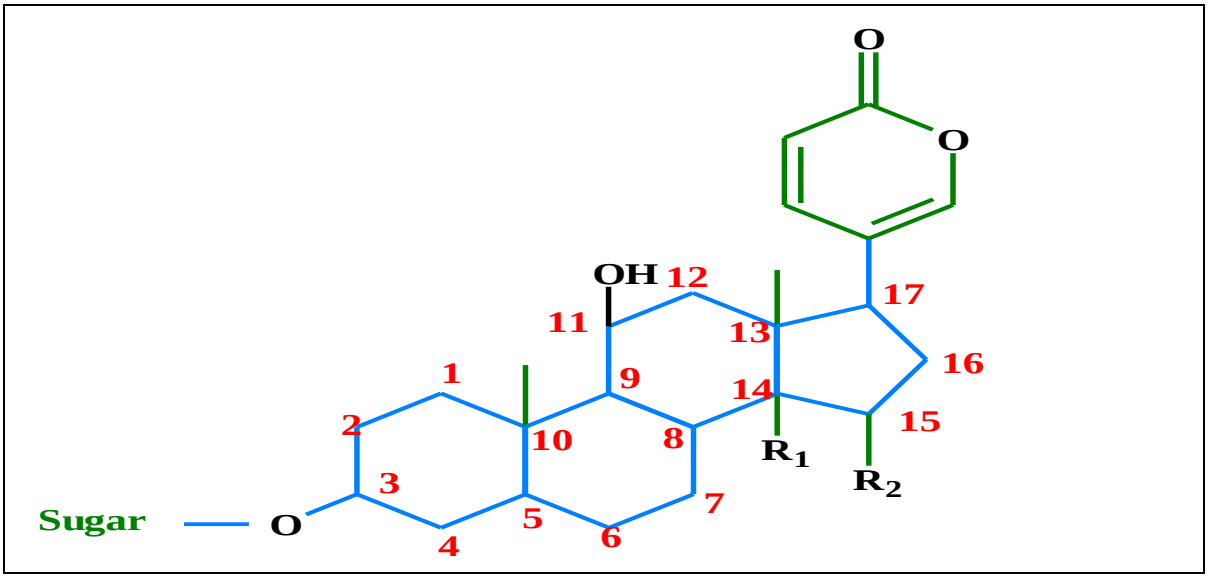


Cardenolides

Digitalis glycosides R=CH_3

Strophanthus glycosides R=CHO OR CH_2OH

9. Cardiac agents that have doubly unsaturated 6-membered lactone ring in position C-17 are referred to as Bufadienolides.
10. This group includes the squill glycosides and the toad venom, Bufotoxin



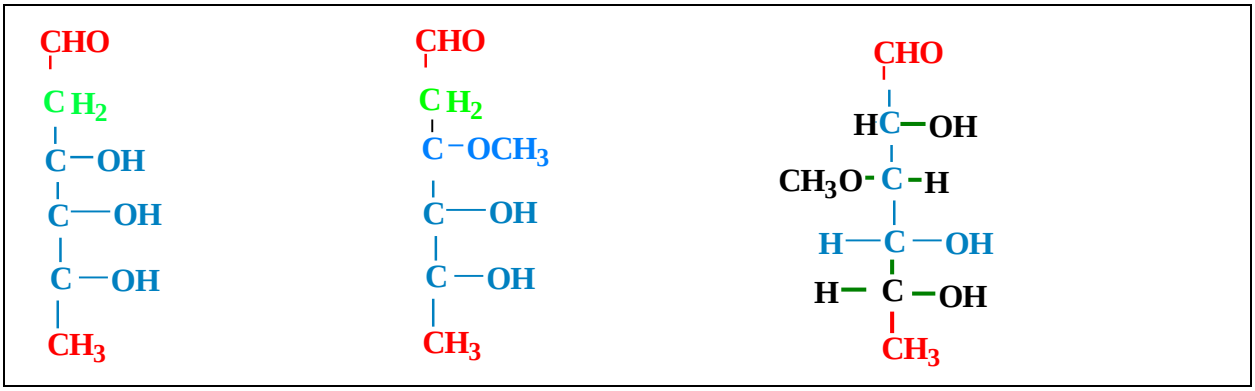
Bufadienolides

Squill glycosides R_1=OH, R_2=H

Bufotoxin R_1 & R_2 = ester group

11-The glycone portion at position C-3 of cardiac glycosides may contain four monosaccharide molecules linked in series. Thus, from a single genin one may have a monoside, a bioside, a trioside or a tetroside.

12- With the exception of D-glucose and L-rhamnose, all the other sugars that are found in cardiac glycosides are uncommon deoxy-sugars e.g., Digitoxose, Cymarose, Thevetose.



Digitoxose Cyamarose Thevetose

PHYSICAL AND CHEMICAL PROPERTIES OF CARDIAC GLYCOSIDE

SOLUBILITY

The different cardiac glycosides show different solubility's in aqueous and organic solvents. They are usually soluble in water or aqueous alcohol and insoluble in the fat solvents with exception of chloroform and ethyl acetate. The higher number of sugar units in the molecule, the greater solubility in water but lowers soluble in chloroform. Alcohols are good solvents for both the glycosides and the aglycones. Therefore, they are considered as the solvents of choice for the extraction of all CG from drugs. Pet. Ether and ether are used for defatting process of drug, they do not dissolve CG

CHEMICAL IDENTIFICATION OF CARDIAC GLYCOSIDE

1- CGs is steroidal in nature, give +Ve with Liebermann's and Salkoviski's test.
2- CG that contains deoxy-sugars is distinguished by Keller Kiliani's test, e.g., digitoxose and cymarose.
3- Cardenolides are distinguished from the scillarins by agroup of color reagents, that are all alkaline solutions of aromatic nitro compounds, namely,

4-Kedde's reagent, (3,5 dinitrobenzoic acid) = violet colour

5-Raymond's reagent, metadinitrobenzene,

6-Baljet's reagent, picric acid,

7-Legal's test, alkaline solution of sodium nitroprusside.

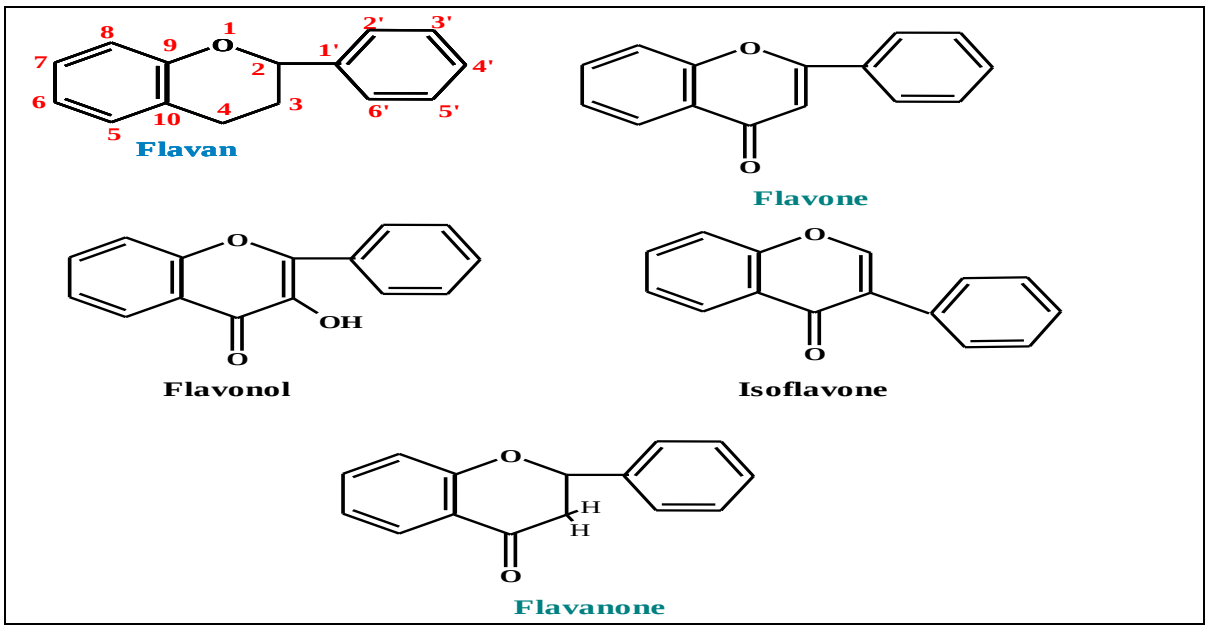
ISOLATION OF CARDIAC GLYCOSIDES. The drug is **pul**verized and extracted with ethanol at low temperature , followed by addition of lead acetate solution to remove the impurities , the ppt are removed by centrifugation , the cardiac glycosides present in the supernatant are extracted with chloroform , the chloroform extract is evaporated under vacuum and the residue (cardiac glycoside) left behind is further purified by chromatography

FLAVONOIDS (QUERCETIN)

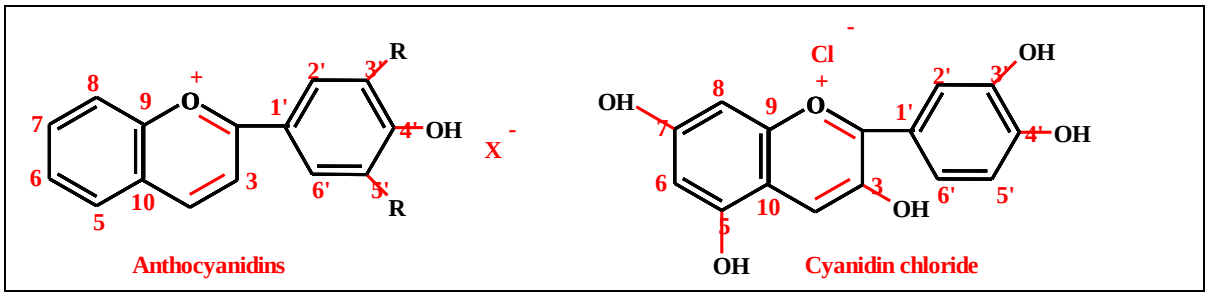
These are mostly yellow pigmet in plant. They are phenolic in nature. They are derivative of 2-phenyl-benzopyran. Many flavonoidal compounds present as a glycosidic or as a free forms.

All derived from the same parent nucleus, 2-phenyl-benzopyran (flavan), thus they have a basic C-15 skeleton.

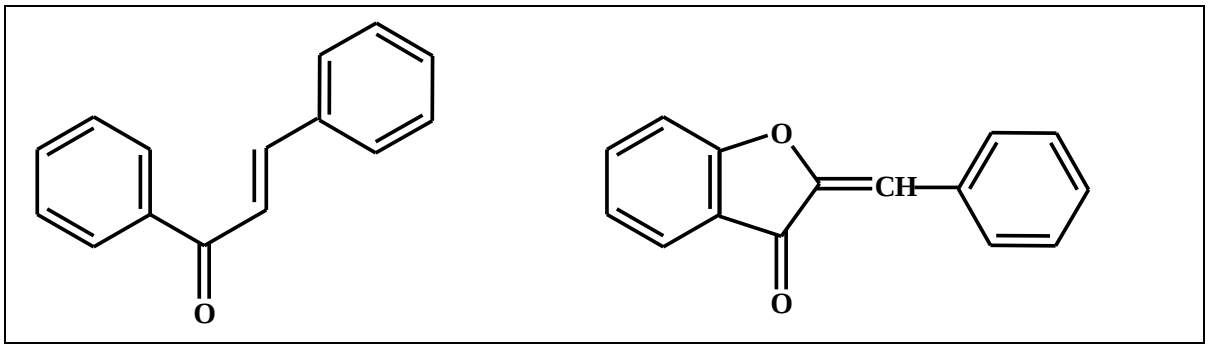
Flavonoidal compounds are classified according to the oxidation level of central pyran ring they are classified into flavones, isoflavones, flavonols, flavanones, (true flavanoids) anthocyanidins, chalcones and aurones. True flavones, are 2-phenyl chromones (2-phenyl benzopyrone), while isoflavones are 3-phenyl chromones der. Flavonols are 3-hydroxyflavones, while flavanones are 2,3-dihydro der. of flavones (2,3-double bond is lacking).



Anthocyanidines, chalcones and aurones are lack the typical flavone structure. Anthocyanidins and its glycosides (anthecyanins) are ionic oxonium salts. This is responsible for the permanent blue, purple, violet, mauve, and red color of flower, fruits and leaves of higher plants. Anthocyanidins and anthecyanins are soluble in polar solvents. Cyanidin chloride is an example of anthocyanidines .



Chalcones, have no<u>central pyrone ring</u>, so they are not true flavonoidal compounds. The parent compound chalcone, is chemically phenyl-styryl ketone, or benzylidene acetophenone. Aurones are oxidized forms that are obtained by enzymatic oxidation. Instead of the central pyrone ring of the normal flavonoidal structure, aurones have five membered ring.



Chalcone Aurone

PROPERTIES OF FLAVONOIDS:

These are crystalline compound, soluble in water, dilute mineral acid. They are ppted by lead acetate. They give red brown colour with ferric chloride. Flavonoids dissolve in alkalis give intense yellow color solution, on the addition of acid become colorless. Flavonoids exhibit strong fluorescence under UV light.Flavonoidal glycosides are soluble in water and alcohol. Ethylacetate is the solvent of choice for the extraction of flavonoids from aqueous solution. Rutin and quercetrin

are examples of flavonol glycosides .Rutin occurs in the leaves of buckwheat. It is the 3-rhamnoglucoside (called rutinose) of the genin quercitin. It gives on hydrolysis the aglycone (quercitin) beside one molecule of glucose, and one molecule of rhamnose.

(QUERCETIN)

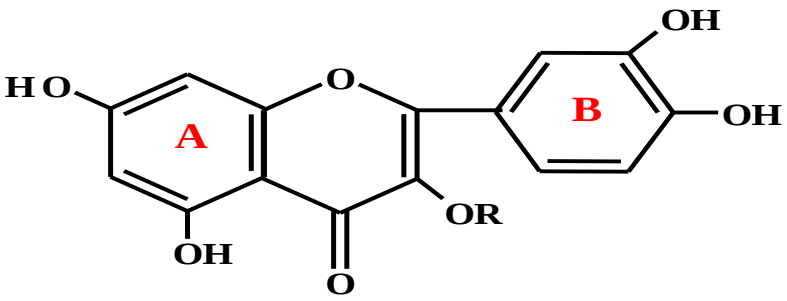
Source-It obtained from the bark of Quercus tinctoria. Quercitrin is quercitin 3-O-rhamnoside. Quercitrin yield upon acid hydrolysis rhamnose and quercetin.The aglycone quercetin occurs in bearberry leaves (Uva Ursi) and has a diuretic action of the leaves.

EXTRACTION AND ISOLATION.

Plant parts are dried. Finely ground plant material extract with methanol. The extract is concentrated to dryness in vacuum at 40 0c to remove methanol. The extract is treated with a mixture of hexane, DCM, ETOAc, BuOH. The Combined organic layer of each partition is evaporated to dryness in vacuum at 40 0c using rotatory evaporator. The extract flavonoids can be isolated by column chromatography.

PROPERTIES OF QUERCETIN. It is yellowish powder. It has M.P. 316. Soluble in ethanol. Acetone. Acetic acid. Insoluble in water.

STRUCTURE ELUCIDATION.



Quercetin: R=H
Quercetrin: R= rhamnosyl
Rutin: R=rutinosyl

1- Molecular formula is $C_{15}H_{10}O_7$.
2- It contains 5 hydroxyl groups.
3- Quercetin is fused with KOH to produced phloroglucinol and protocatechuic acid.

4- Quercetin is methylated and produces pentamethylquercetin, boiled with alkali ethanol gives 6-hydroxy, 2, 4, trimethoxyacetaphenone and vatic acid. Indicate that quecrectin is 3, 3,4,5,7 pentahydroxy flavones.

USES OF FLAVONOIDS:

1- Increase capillary resistance and decrease vitamins C & P deficiency.
2- They are recommended in the treatment of thrombopenia (blood coagulation).
3- They are reported of value in the treatment of influenza, when given with ascorbic acid

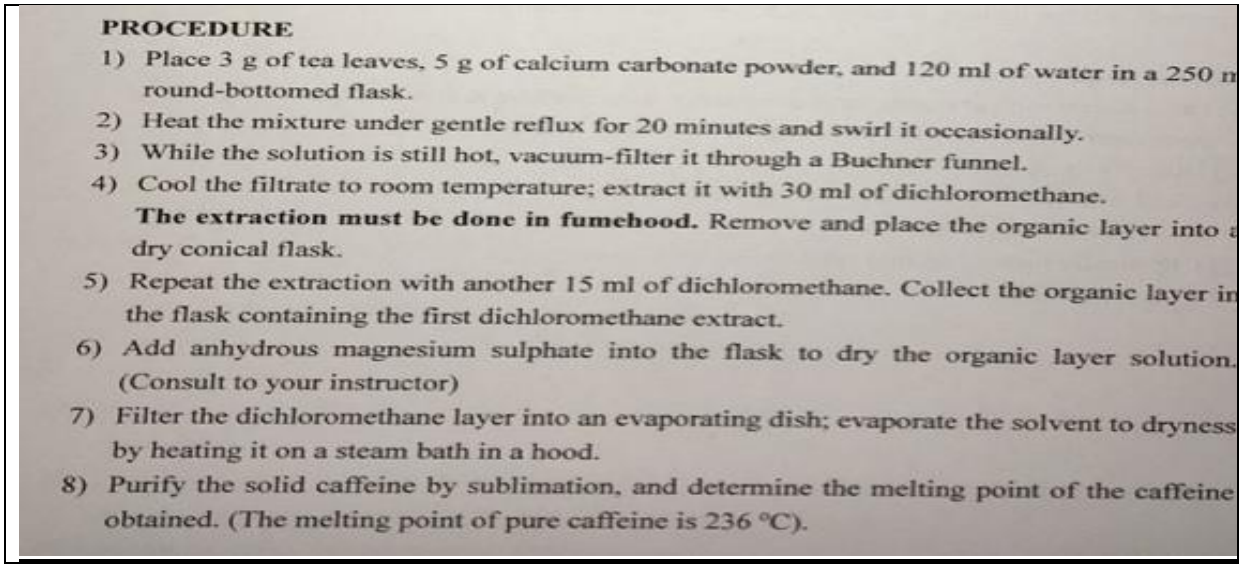
PURINE (CAFFEINE)

A **purine** is a heterocyclic aromatic organic compound that consists of a pyrimidine ring fused to an imidazole ring. A moderate amount of purine is also contained in beef, pork, poultry, fish and seafood, asparagus, cauliflower, spinach, mushrooms, lentils, beans, oatmeal, wheat bran, wheat germ, and haws.

CAFFEINE

Caffeine, 1, 3, 7 - trimethylxanthine, belongs to a wide class of compounds known as alkaloids. These are plant derived compounds with complex structure containing nitrogen, and usually have roles in physiological activity. The melting point of Caffeine is 238°C.
Caffeine is a bitter, white crystalline purine, a methylxanthine alkaloid, and is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is found in the seeds, nuts, or leaves of a number of plants native to South America and East Asia and helps to protect them against predator insects and to prevent germination of nearby seeds. The most well known source of caffeine is the coffee bean, Beverages containing caffeine are ingested to relieve or prevent drowsiness and to improve performance. To make these drinks, caffeine is extracted by steeping the plant product in water, a process called infusion.

Extaction and isolation ;



PROCEDURE

1) Place 3 g of tea leaves, 5 g of calcium carbonate powder, and 120 ml of water in a 250 m round-bottomed flask.
2) Heat the mixture under gentle reflux for 20 minutes and swirl it occasionally.
3) While the solution is still hot, vacuum-filter it through a Buchner funnel.
4) Cool the filtrate to room temperature; extract it with 30 ml of dichloromethane. **The extraction must be done in fumehood.** Remove and place the organic layer into a dry conical flask.
5) Repeat the extraction with another 15 ml of dichloromethane. Collect the organic layer in the flask containing the first dichloromethane extract.
6) Add anhydrous magnesium sulphate into the flask to dry the organic layer solution. (Consult to your instructor)
7) Filter the dichloromethane layer into an evaporating dish; evaporate the solvent to dryness by heating it on a steam bath in a hood.
8) Purify the solid caffeine by sublimation, and determine the melting point of the caffeine obtained. (The melting point of pure caffeine is 236 °C).

Structure elucidation of caffine

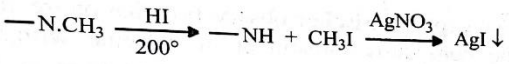
...absorbed caffeine is then

3.4.2.2. Structure Elucidation

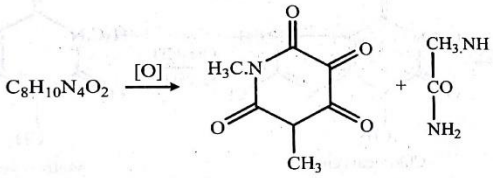
The structural elucidation of caffeine is described below:

1) Its molecular composition is $C_8H_{10}N_4O_2$.

2) On heating with hydriodic acid at about 200°, caffeine gives three moles of methyl iodide [Herzig method] suggesting the presence of three N—CH_3 groups.

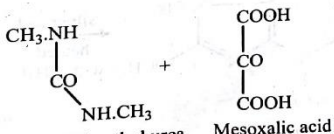


3) Caffeine on oxidation with potassium chlorate in hydrochloric acid solution gives 1, 3-dimethylalloxan and monomethyl urea. 1, 3-Dimethylalloxan is identified as mesoxalyl-*sym*-dimethyl urea since on hydrolysis, it gives *sym*-dimethyl urea and mesoxalic acid.



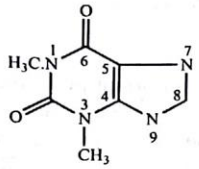
Caffeine — 1,3-Dimethylalloxan — Monomethyl urea

Hydrolysis

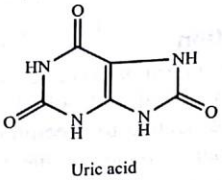


sym-Dimethyl urea — Mesoxalic acid

The oxidation of caffeine to 1, 3-dimethylalloxan and monomethyl urea suggests beyond doubt that the caffeine has uric acid skeleton which on oxidation gives alloxan and urea. Moreover, the formation of 1, 3-dimethylalloxan also establishes the position of two of the three methyl groups. Hence the part structure of caffeine may be written as below:

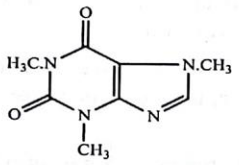


Part structure of caffeine



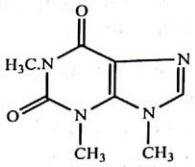
Uric acid

4) Now the only problem is to assign the position of the third N-methyl group. From the above part structure of caffeine, it is obvious that the third N-methyl group may either attach to N_7 or N_9 and theoretically the following two structures are possible for caffeine.



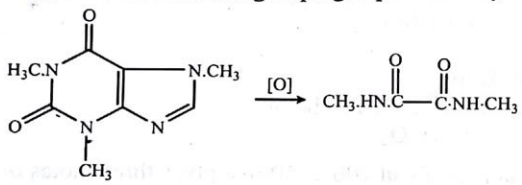
I

Or



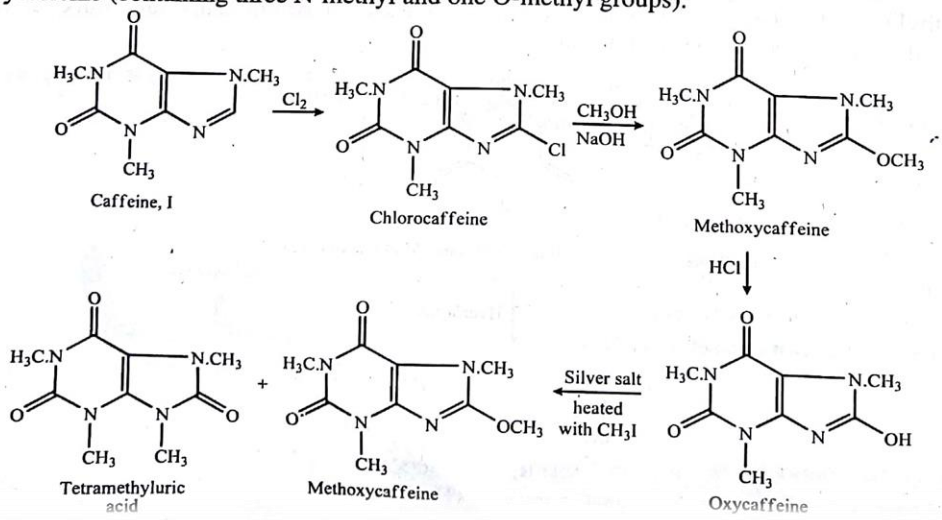
II

5) On vigorous oxidation, caffeine gives *sym*-dimethyloxamide ($CH_3NH.CO.CO.NHCH_3$) as one of the products which indicates the presence of the grouping $CH_3.N—C—C—N{\cdot}CH_3$. From the observation of the above two structures of caffeine, it is clear that this grouping is present only in structure I.



Caffeine, I

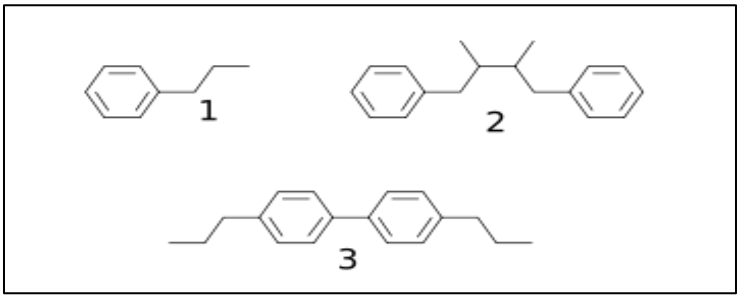
6) The structure I for caffeine also explains **Fischer** observation that on treatment with CH_3I, the silver salt of oxycaffeine, obtained by the consecutive treatment of caffeine with chlorine, methanolic-alkali and hydrogen chloride, gives a mixture of tetramethyl uric acid (containing four N-methyl groups) and methoxycaffeine (containing three N-methyl and one O-methyl groups).



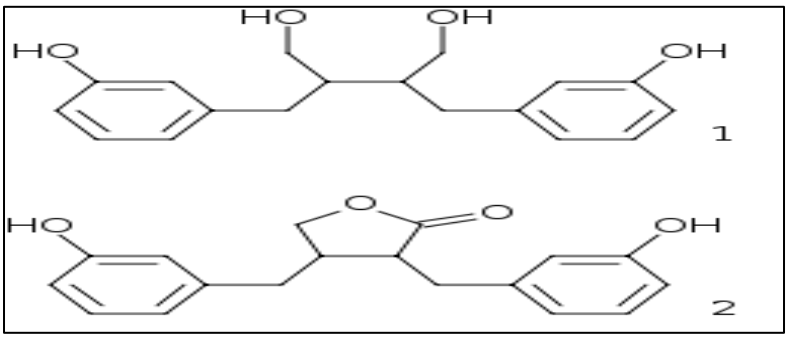
Caffeine, I — Chlorocaffeine — Methoxycaffeine — Oxycaffeine — Methoxycaffeine — Tetramethyluric acid

LIGNAN

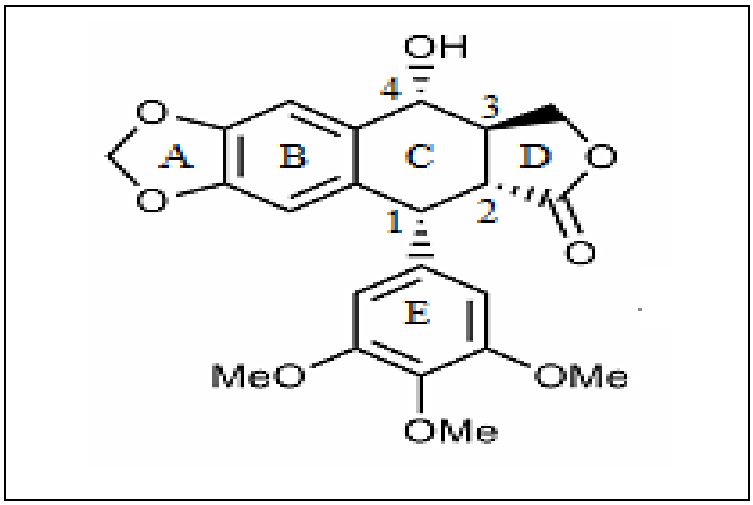
The **lignans** are High molecular wt phenylpropanoids.lignan are most abundant natural aromatic organic polymer foun in all vascular plants.lignan are a group of chemical compound found in plant particularly in flax seed. plant lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols known as monolignols, to a dibenzylbutane skeleton this reaction is catalysed by oxidative enzymes and is often controlled by dirigent proteins.



Many natural products, known as phenylpropanoids, are built up of C-6 toC-3 units (a propyl benzene skeleton **1**) derived from cinnamyl units just as terpene chemistry builds on isoprene units. Structure **3** is a neolignan, a structure formed by joining the two propyl benzene residues at other than the β-carbon atom of the propyl side chain.Some examples of lignans are pinoresinol, podophyllotoxin, and steganacin.When a part of the human diet, some plant lignans are metabolized by intestinal bacteria to mammalian lignans **enterodiol** (**1**) and **enterolactone (2).** Lignans that can be metabolized to mammalian lignans are pinoresinol, lariciresinol, secoisolariciresinol, matairesinol, hydroxymatairesinol syringaresin ol and sesamin. Lignans are one of the major classes of phytoestrogens, which are estrogen-like chemicals and antioxidants. The other classes of phytoestrogens are isoflavones and coumestans.



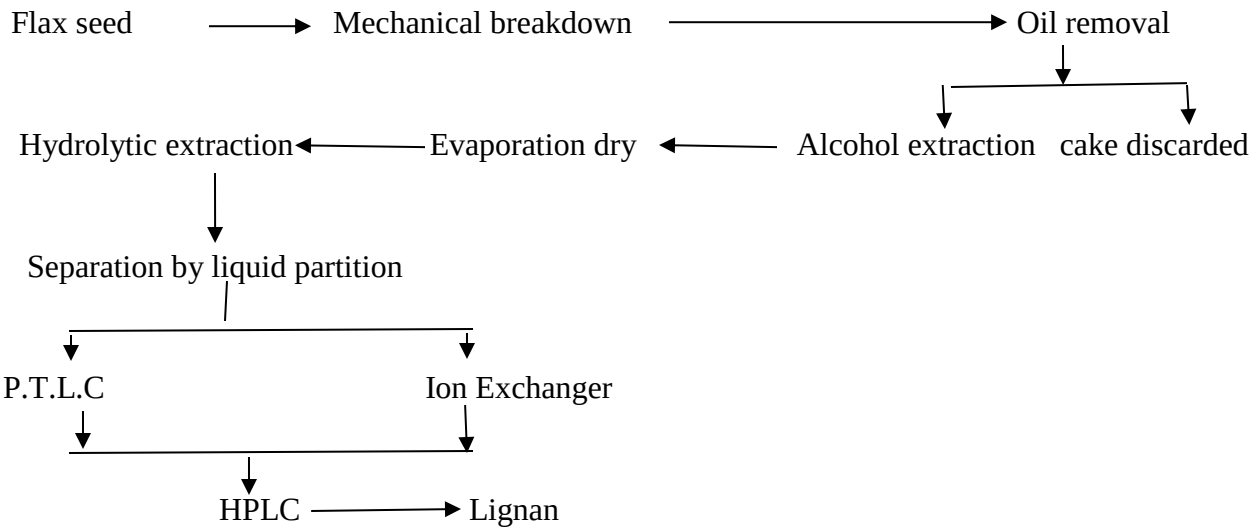
PODOPHYLOTOXIN



It is a non-alkaloid toxin lignan extracted from the roots and rhizomes of Podophyllum species.A less refined form known as podophyllum resinis also available, but has greater side effects.it is anatural product isolated from podophyllum peltatum and podophyllum emodi. Etoposide, a podophyllotoxin used in the treatment of cancer.

The structure of podophyllotoxin was first elucidated in the 1930. Podophyllotoxin bears four consecutive chiral centers. The molecule also contains four almost planar fused rings. The podophyllotoxin molecule includes a number of oxygen containing functional groups: an alcohol, a lactone, three methoxy groups, and an acetal.

EXTRACTION AND ISOLATION



Plant lignans are co-passengers of dietary fiber, and therefore fiber-rich food items are often good sources of lignans. Flax seed and sesame seed contain higher levels of lignans than most other foods. The principal lignan precursor found in flaxseed is secoisolariciresinol glucoside. Other sources of lignans include cereals (rye, wheat, oat and barley - rye being the richest source), soybeans, cruciferous vegetables such as broccoli and cabbage, and some fruit, particularly apricots and strawberries.

Secoisolariciresinol and matairesinol were the first plant lignans identified in foods. Pinoresinol and lariciresinol are more recently identified plant lignans that contribute substantially to the total dietary lignan intakes.