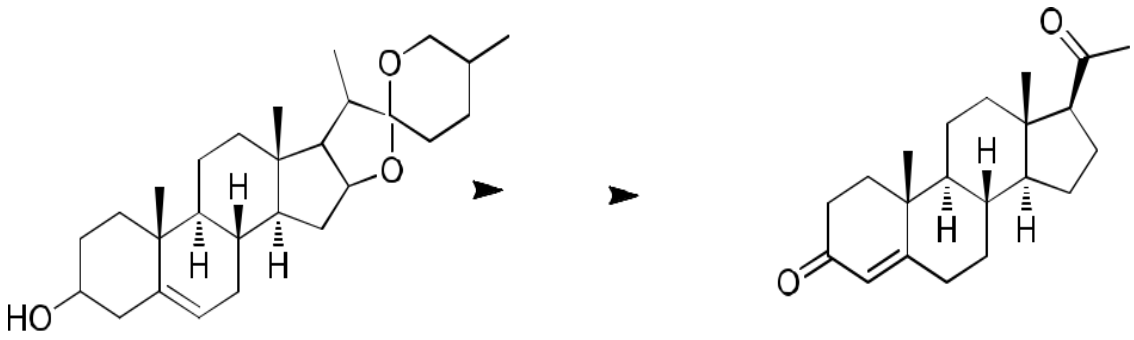
PharmacognosyII

Lec. 4 **3rd stage 1st semester** **Year 23-24**

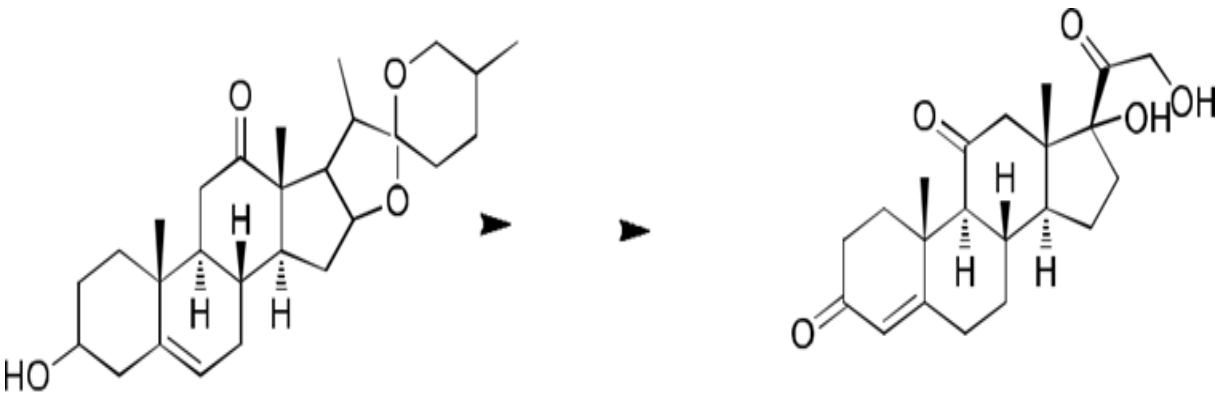
Lecturer: Dr. Jamel Fani

The two major types of steroidal sapogenin are diosgenin and hecogenin. Sapogenin are used in the commercial production of sex hormones for clinical use, for example, progesterone is derived from diosgenin (from the plant Dioscorea in Mexico).



Diosgenin progesterone

Other steroidal hormone like cortisone can be prepared from hecogenin which can be isolated from Sisal leaves found extensively in East Africa.



Hecogenin Cortisone

In triterpenoid saponins, the aglycone is a triterpene which is found in many plants, for example, liquorice contains glycyrrhetic acid that is used as an expectorant, and ginseng that is used as a tonic.

Ginseng roots (Panax roots)

Panax quinquefolius (panax ginseng) contains saponin glycoside (ginsenoside/ panaxoside) which is class of triterpenoid and steroidal nucleus.

Ginseng root uses: 1- Stimulant. 2- Tonic. 3- Anti-stress. 4- Adaptogenic agent.

Drugs:

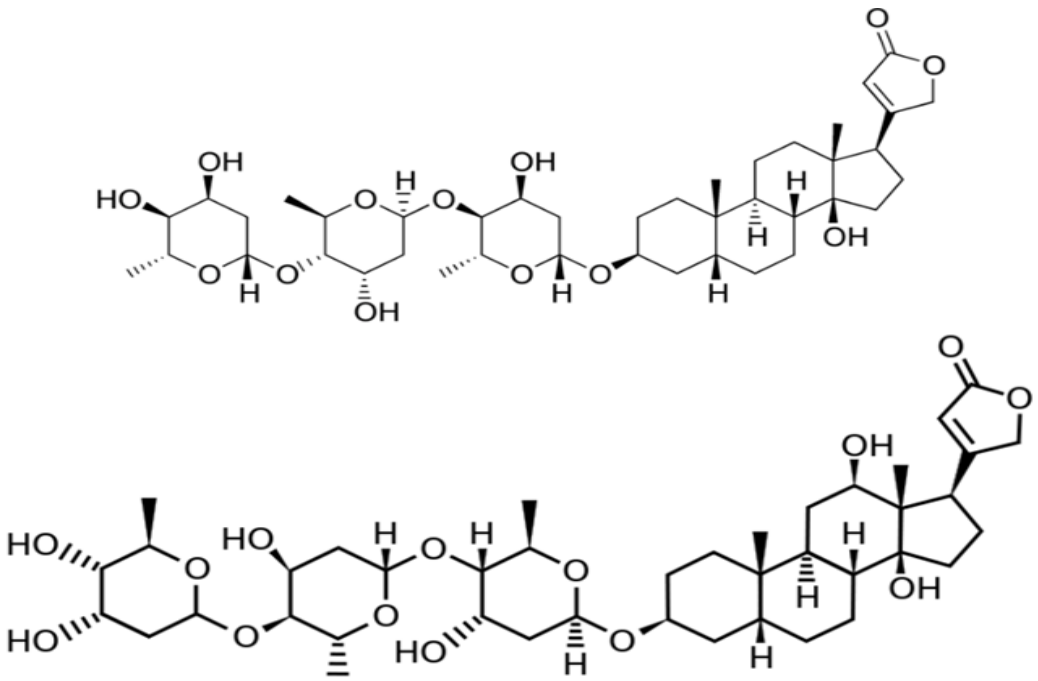
1- Geriatric pharmaton

2-Gerimax

3-Polyvit

Cardiac glycosides

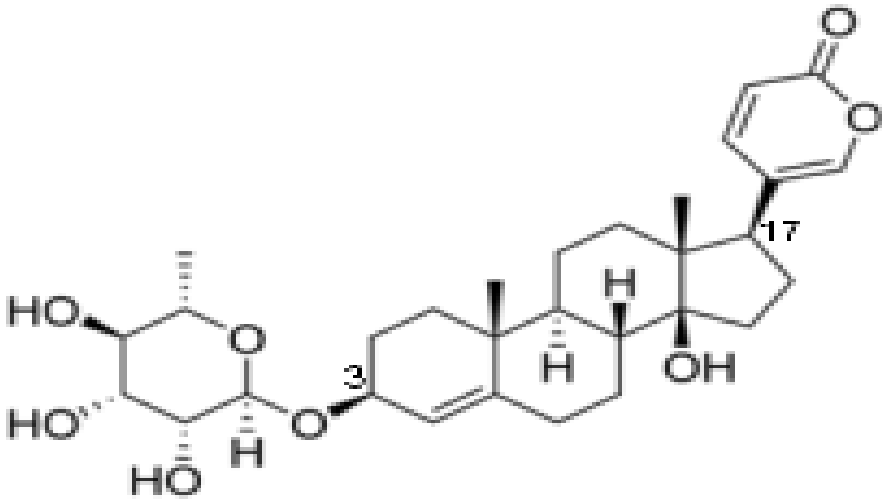
Glycosides that exert a prominent effect on heart muscle and heart rhythm are called cardiac glycosides example digitoxin from Digitalis purpurea. Their effect is specifically on myocardial contraction. They are commonly found in the genera *Convallaria*, *Nerium* and *Digitalis*. The aglycone portion is steroidal in nature and it is sometimes referred to as a **cardenolide** being **card**ioactive and possessing an alkene and **olide** (cyclic ester).



Digitoxin and digoxin

The most widely studied plant that contains these compounds is the foxglove (*Digitalis purpurea*) of the family Scrophulariaceae which is used from 18 century for the treatment of heart disease. The plant contains the medicinal agent's digoxin (which is more widely used) and digitoxin. Digoxin is also found in *Digitalis lanata*. Digitoxin yields one molecule of digitoxigenin and three of digitoxose. Digitoxin is insoluble in water and slightly soluble in Related glycosides which because they are very fast acting compounds are used in emergencies via IV routs are lanatoside C and diacetyl-lanatoside C.

Bufanolides (derived their name from the generic name of toad that produce bufalin) in which the lactone (cyclic ester) contains 6 member ring is less abundant in nature, for example proscillardin A, found in the plant squill (*Scilla maritime*). This glycoside is used as rodenticide due to sever toxicity.



Both sugar and aglycone parts are responsible for activity. The sugar probably enhances the binding to heart muscle and the aglycone moiety has the desired effect on heart muscle. α- β unsaturated latone ring that is attached on the 17 position of the steroid nucleus is responsible for activity. Reduction of the double bond in the lactone ring results in inactive compound. For activity that is more prominent 3-OH should be on β- position. Oxygen substitution on the steroid nucleus influences the distribution and metabolism of the glycosides. In general, the more hydroxyl groups in, the molecule the more rapid the onset of action.

Drug interaction

Digoxin interacts with cation levels. Potassium depletion increase the susceptibility to cardiac glycoside toxicity, therefore patient on thiazide diuretics which cause potassium depletion should decrease the dose of digoxine or receive a potassium therapy. Conversely high calcium level enhances the activity of digoxin; therefore, ingestion of high amount of milk or calcium gluconate should be avoided in patient on digoxin therapy.

Mechanism of action

Cardiac glycoside inhibits the Na^+, K^+ -ATPase in cardiac and other tissue, causing intracellular retention of Na.

The mechanism of action of the cardiac glycosides is still not completely known; however, observation has implicated Na^+, K^+ -ATPase as the receptor enzyme. This enzyme catalysis the active transport of Na^+ out of the cell and subsequent transport of K^+ into the cell. In myocardium, the ion exchange is rapid because it is required after each heart beat; therefore, an inhibition of ATPase has a great effect on heart tissues.

Biosynthesis of cardiac glycosides

The steroid nucleus is biosynthesized via acetate mevalonate pathway (polyketide). If we look to the side chain of cortisone, we may suggest that the hydroxyl may oxidize to acid then lactonization occurs.

Physical and chemical properties

The glycosides are fairly soluble in water and slightly soluble in ethanol and chloroform: digitoxin is far more soluble in chloroform than digoxin, which is fairly soluble in dilute ethanol and in ethanol-chloroform mixtures. Both are sparingly soluble in ethyl acetate. Cardiac glycosides containing 3 or 4 monosaccharides are soluble in water. Aglycones of cardiac glycosides are soluble in organic solvents and practically insoluble in water. Cardiac glycosides easily hydrolyze. Upon hydrolysis, they yield sugars and aglycone. Primary glycosides such as lanatoside C are water-soluble, soluble in dioxane, sparingly soluble in chloroform (1 g in 2 L), and virtually insoluble in methanol. The presence of the lactone renders the molecule labile, and likely to open in an alkaline medium.

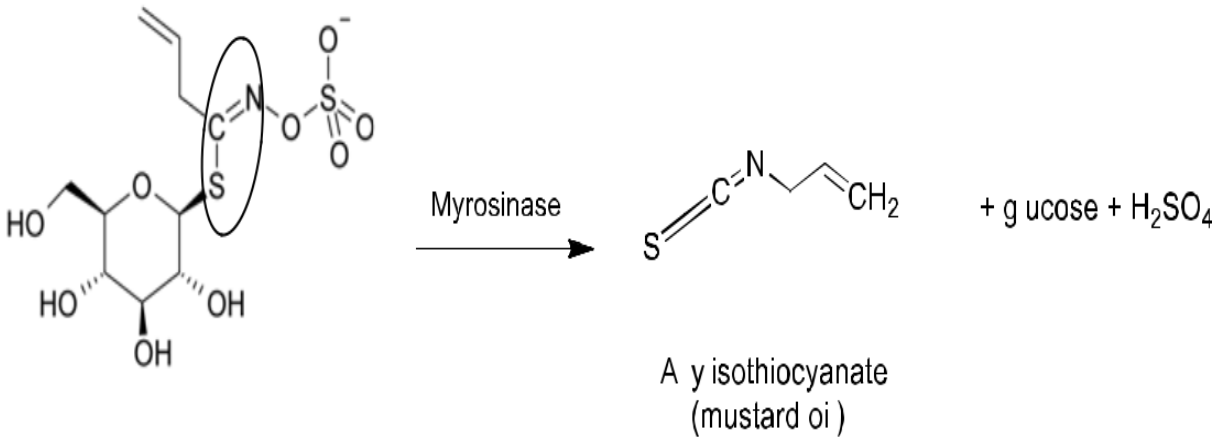
Other cardioactive drugs

Oleander: The leaves of *Nerium oleander*, Fam: Apocyanaceae have been used to treat cardiac diseases. Oleandrin is a derivative of digoxin.

Strophanthus: The dried ripe seeds of *Strophanthus kombe*, Fam: Apocyanaceae. K strophanthoside, also known as stroposide is the principle glycoside in the plant that has been used in Africa as arrow poisoning.

Isothiocyanate glycosides (glucosinolates)

A group of glycosides which upon hydrolysis by the enzyme myrosinase yield a glucose and aglycon which undergo spontaneous rearrangement with the loss of sulphate to give an isothiocyanate as the major product. In this type of glycoside, the sulfur atom is bonded to sugar (S-glycoside) and the second sulfur present in sulfonated oxime group (C=NOH).

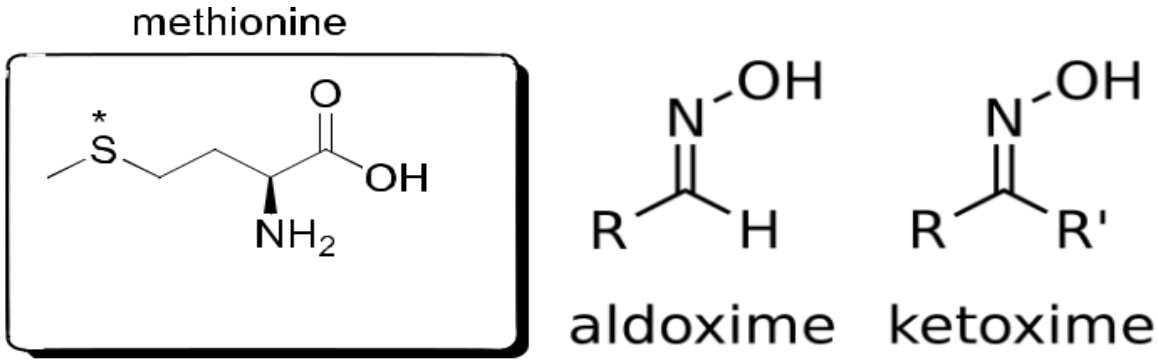


Hydro ysis of sinigrin

Glucosinolates have a limited distribution in the plant families and are characteristic constituent of the mustard family (Brassicaceae), including rape seed, mustard, turnip, broccoli and cabbage. Mustard family vegetables have been found to have anticarcinogenic properties. For example, indole-3 carbinol derived from indomethyl-glucosinolate which is widely distributed in the mustard family has been shown to reduce the risk of estradiol linked cancer. Broccoli was found to contain enzymes that have a protection against cancer (prevention).

Biosynthesis of glucosinolates

Biosynthetic pathway involves N-hydroxylation and oxidative decarboxylation to yield an aldoxime intermediate. The aglycones may be aliphatic (in black mustard) or aromatic (in white mustard) derived from amino acids.



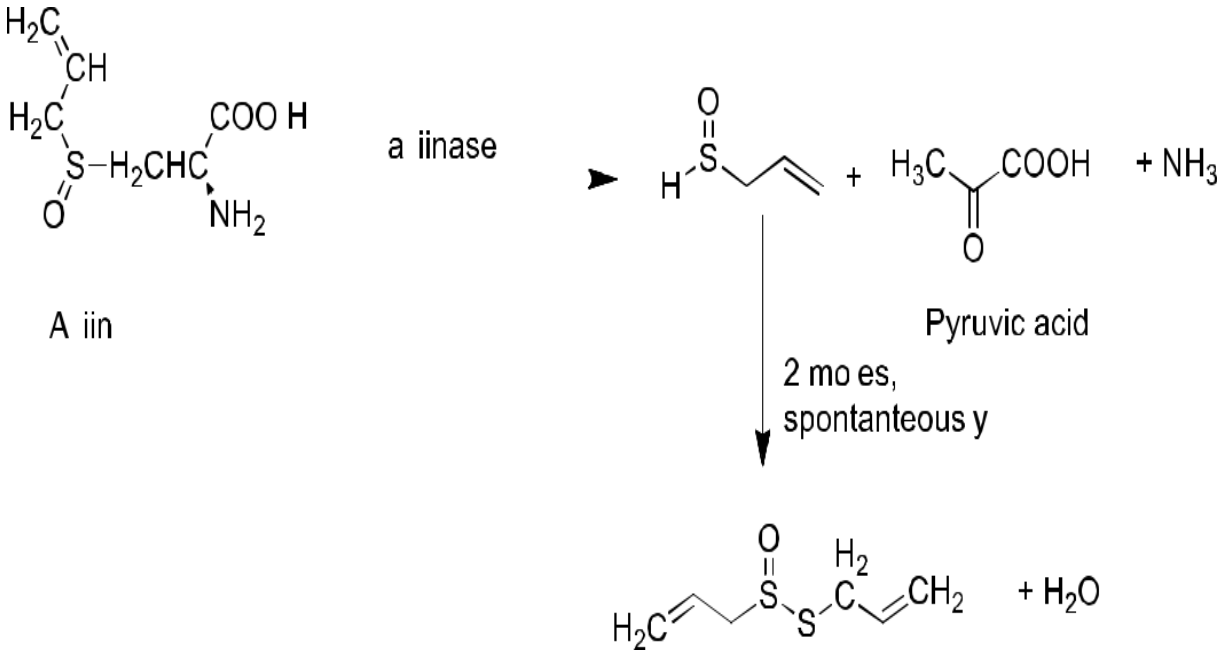
Uses

Black mustard is a local irritant and an emetic. Externally the drug is rubefacient. Commercially it is used as a condiment.

Other organosulfur drugs

Garlic

Consist of the bulb of *Allium sativum* Fam: Lilicaeae. The plant was used as food and medicine from the time of Pharaohs. The intact cells of garlic contain the odorless sulfur containing amino acid derivative (+)-S-allyl-L-cysteine sulfoxide (alliin). When the cell is crushed, it comes into contact with the enzyme alliinase which converts it to allicin (bad smell, diallyl thiosulfinate). Allicin has a powerful antibacterial activity. Garlic also possesses antihyperlipedemic and inhibit platelets aggregation.



Measurement of the total activity of garlic is determined by the amount of bioactive allicin produced; therefore, commercial garlic preparations have a great variation in their ability to produce allicin because the mode of preparation greatly influences the stability of alliin and alliinase. Enteric coated tablets or capsules have enhanced activity because stomach acid inactivates allinase.

Alcohol glycosides

Salicin

Is a glycoside obtained from *Salix purpurea* and *Salix fragilis*. Emulsin is the enzyme responsible for the hydrolysis of salicin to salicyl alcohol and glucose. Its action is similar to salicylic acid; probably it oxidized in the body to this acid. The glycoside populin (benzoylsalicin) is also found in with salicin in the barks of Salicaceae.

Phenolic glycosides

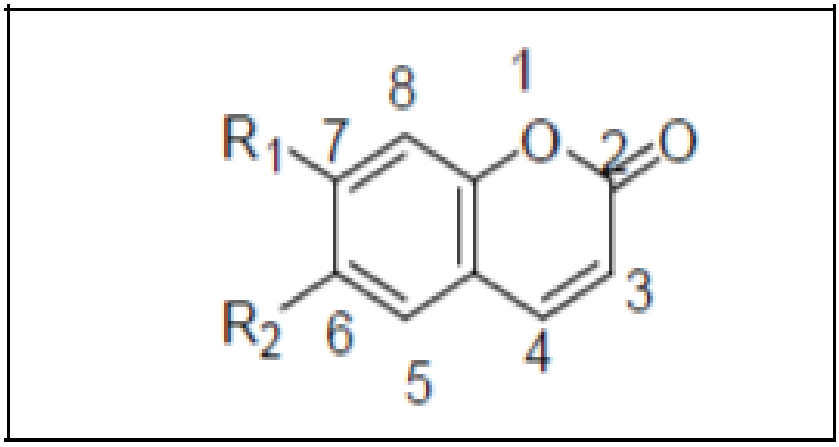
Phenolic compounds are C-6-C3 metabolites derived from shikimic acid.

Coumarin glycosides

R1 = OH, R2= O-glucose

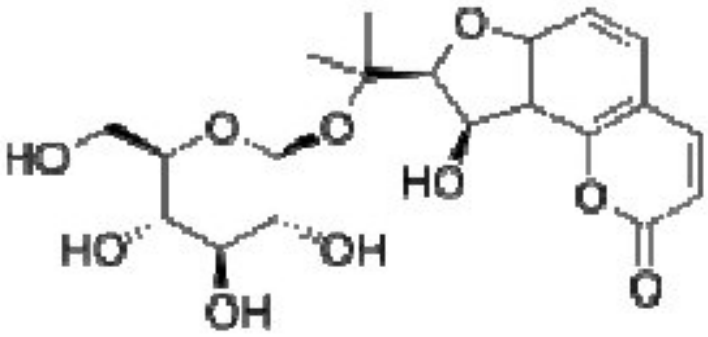
Acsulin used as Antidiarrhoea

Fraxin opposite used as tonic



Apterin

Is a furanocoumarin glucoside reported to dilate coronary arteries as well as block calcium channels. It can be found in plants of the Apiaceae family. It has been isolated from the root of plants in the genus *Angelica*.



Flavonoid glycosides

Here the aglycone is a flavonoid. Examples of this large group of glycosides include:

• Hesperidin (aglycone: Hesperetin, glycone: Rutinose)

• Naringin (aglycone: Naringenin, glycone: Rutinose)

• Rutin (aglycone: Quercetin, glycone: Rutinose)

• Quercitrin (aglycone: Quercetin, glycone: Rhamnose)

Among the important effects of flavonoids are their antioxidant effect.

They are also known to decrease capillary fragility.

Flavonoid glycosides are a group of chemical compounds that occur in small but significant amounts in fruits and vegetables.

More than 4,000 different flavonoids have been identified, some of which have been researched in detail and are believed to have beneficial effects on human health.

Some of the health related benefits associated with this group of compounds include strengthening of the immune system, protection against cancer, and a reduction in capillary fragility.

A variety of different foods contain these compounds. Fruits, vegetables, seeds, legumes and soy products are known to contain flavonoid glycosides.

Onions, apples, green tea, and red wine are known to be rich in these nutrients, however. Known to have antioxidant properties, flavonoid glycosides are believed to help protect individuals from diseases, such as cancer.

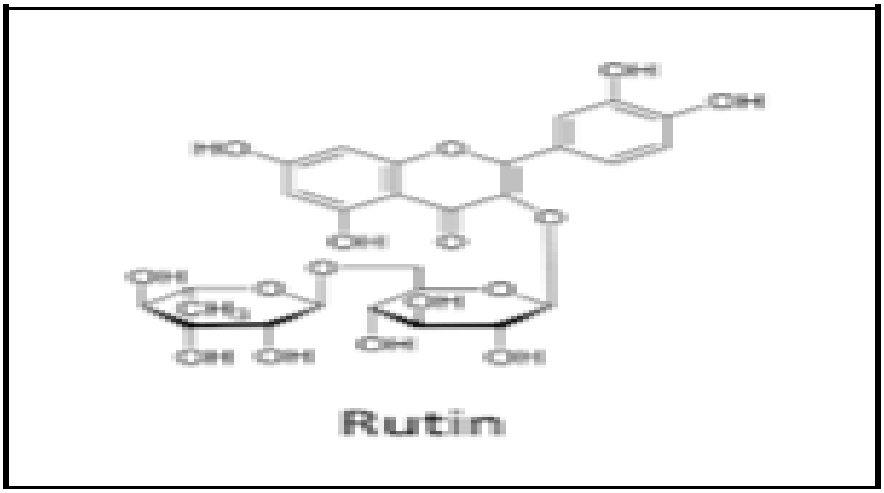
Antioxidants are known to stabilize unstable molecules, known as free radicals, which can potentially damage genetic materials and cells. Thus, this group of compounds can strengthen a person immune system.

Although many types of flavonoid glycosides have been identified, few have been studied in any depth. The flavonoids that have been researched in detail include rutin, hesperedin, anthocyanaosides, and genistein.

Each of these has been found have specific benefits for human health.

Rutin

is found in buckwheat and research has demonstrated that this particular flavonoid glycoside may have several implications for human health. Capillary fragility, or the weakening of delicate blood vessels, is common in the elderly or those who suffer from a vitamin C deficiency. Consumption of rutin is believed to strengthen weakened blood vessels and also reduce the risk of heart disease. Hemorrhoids are also often treated with rutin.



Hesperetin:

Is found in citrus fruits and is also a known antioxidant.

Studies have indicated that it can reduce blood pressure and lower cholesterol.

In addition, hesperetin has anti-inflammatory effects and, as such, is thought to reduce pain in the joints and muscles, particularly among those who suffer from arthritic conditions.

Anthrocyanosides:

Are found in bilberries and known to have several positive health implications. Anthocyanoside flavonoid glycosides are believed to help maintain healthy skin, teeth, eyes, and hair. In addition, anthocyanosides are thought to improve cardiovascular health and help to protect against conditions such as diabetes.

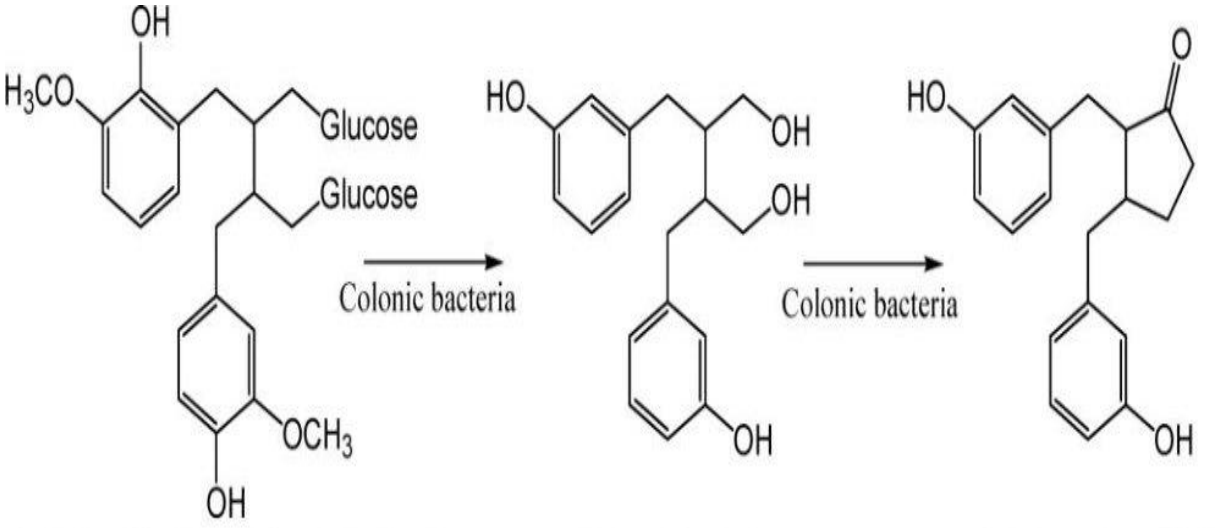
Since they are rich in antioxidants, flavonoid glycosides are believed to help boost a person's immune system. With such bolstered immune function, it is thought people can protect themselves from serious illnesses.

For this reason, a diet rich in foods that contain flavonoid glycosides may benefit many people. Those considering a major dietary change or taking supplements, however, should check with a physician or nutritionist to be sure of dosage and safety.

Lignan glycosides

Flaxseed (FS) is the richest source of the phytoestrogen secoisolariciresinol diglycoside (SDG), a plant lignan that can be metabolized by bacteria in the animal or human colon to the mammalian lignans enterodiol and enterolactone.

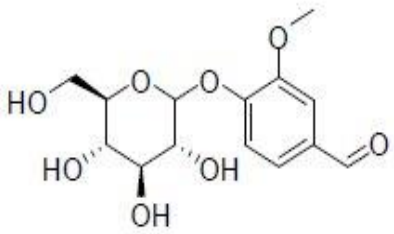
It is also a very rich source of α-linolenic acid because these compounds have been suggested to have anticancer effects, FS is a food that has a very high potential to reduce cancer risk.



Secoisolariciresinol diglucoside (SDG) **Enterodiol (ED)** **Enterolactone (EL)**

Aldehyde glycosides:

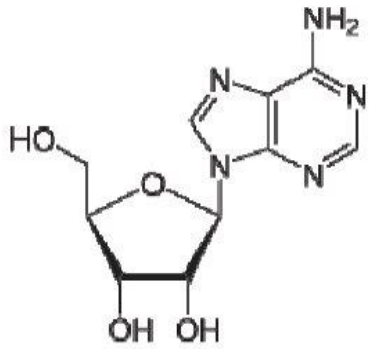
Vanilla pod the green seed has no flavour of vanilla. After being harvested, their flavor is developed by a months-long curing process.



vanillin glucoside

β-D-glucoside of vanillin

N- Glycosides:



Adenosine, a component of RNA, results from the sugar ribose and adenine via the formation of an N-glycosidic bond (shown as the vertical line between the N and the sugar cycle

Hydroquinol glycosides

Example on phenolic glycoside is arbutin.

Arbutin is a glycoside; glycosylated hydroquinone extracted from the bearberry plant in the genus Arctostaphylos.

Inhibits tyrosinase and thus prevents the formation of melanin. Arbutin is therefore used as a skin-lightening agent.