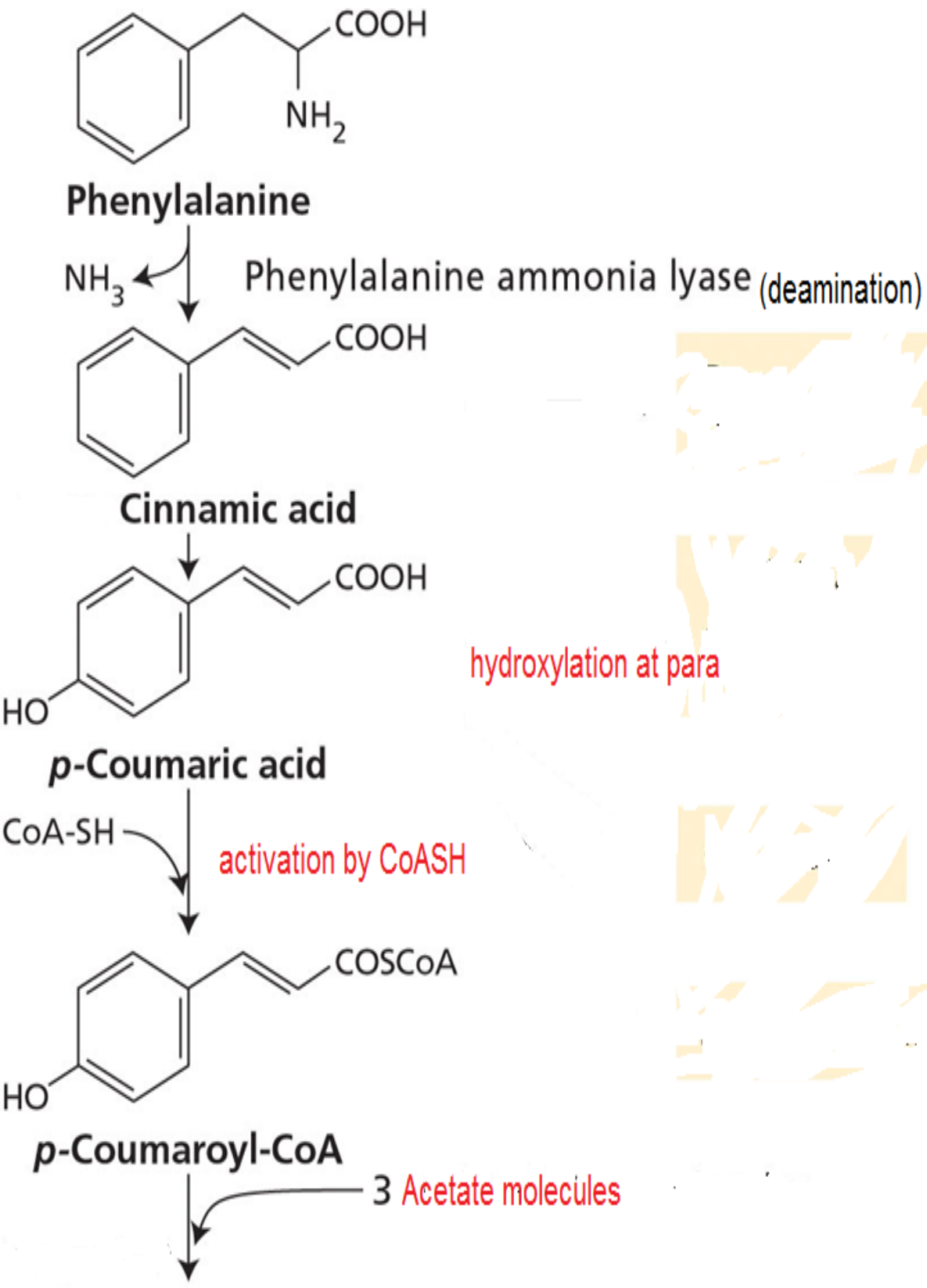
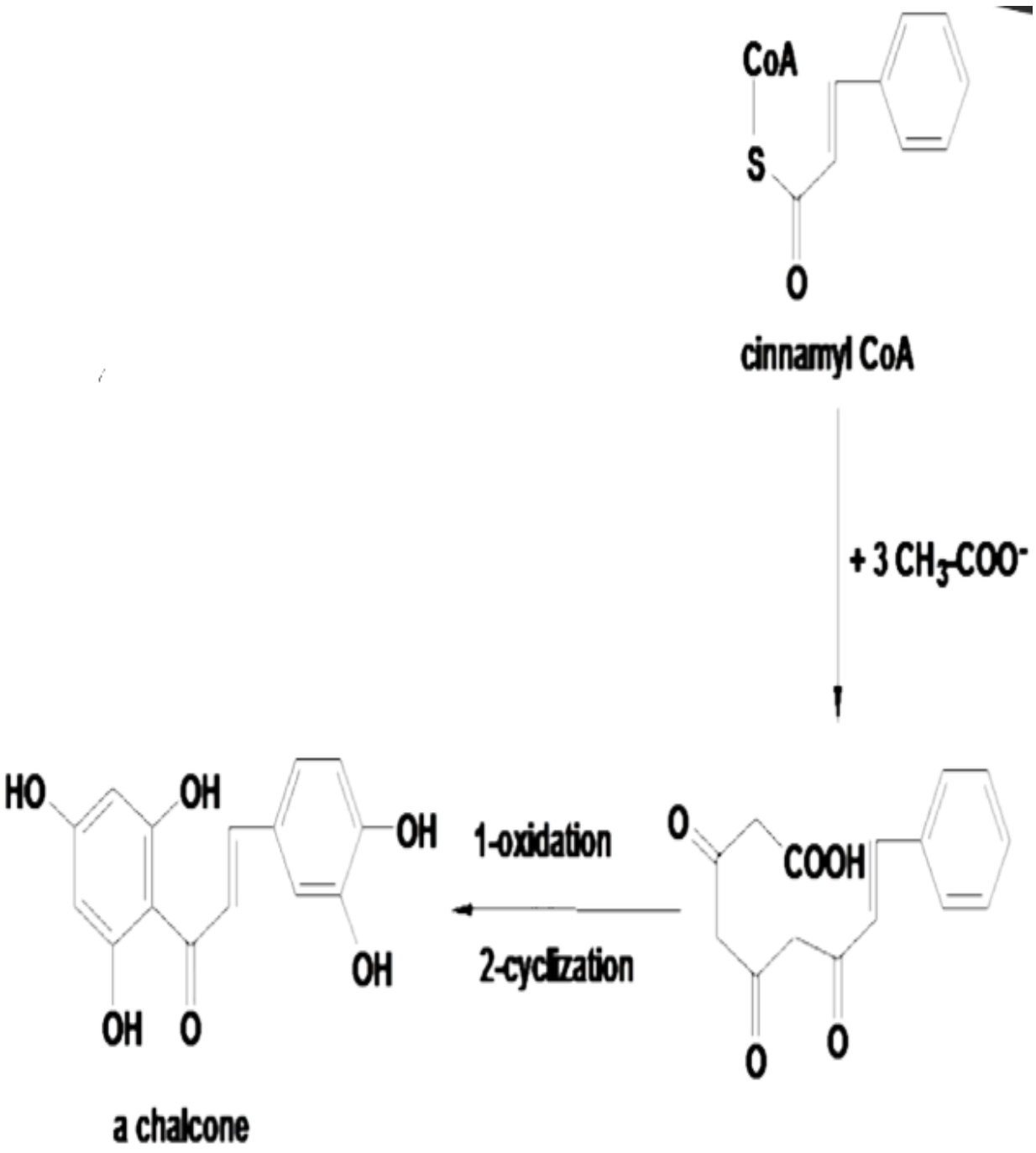
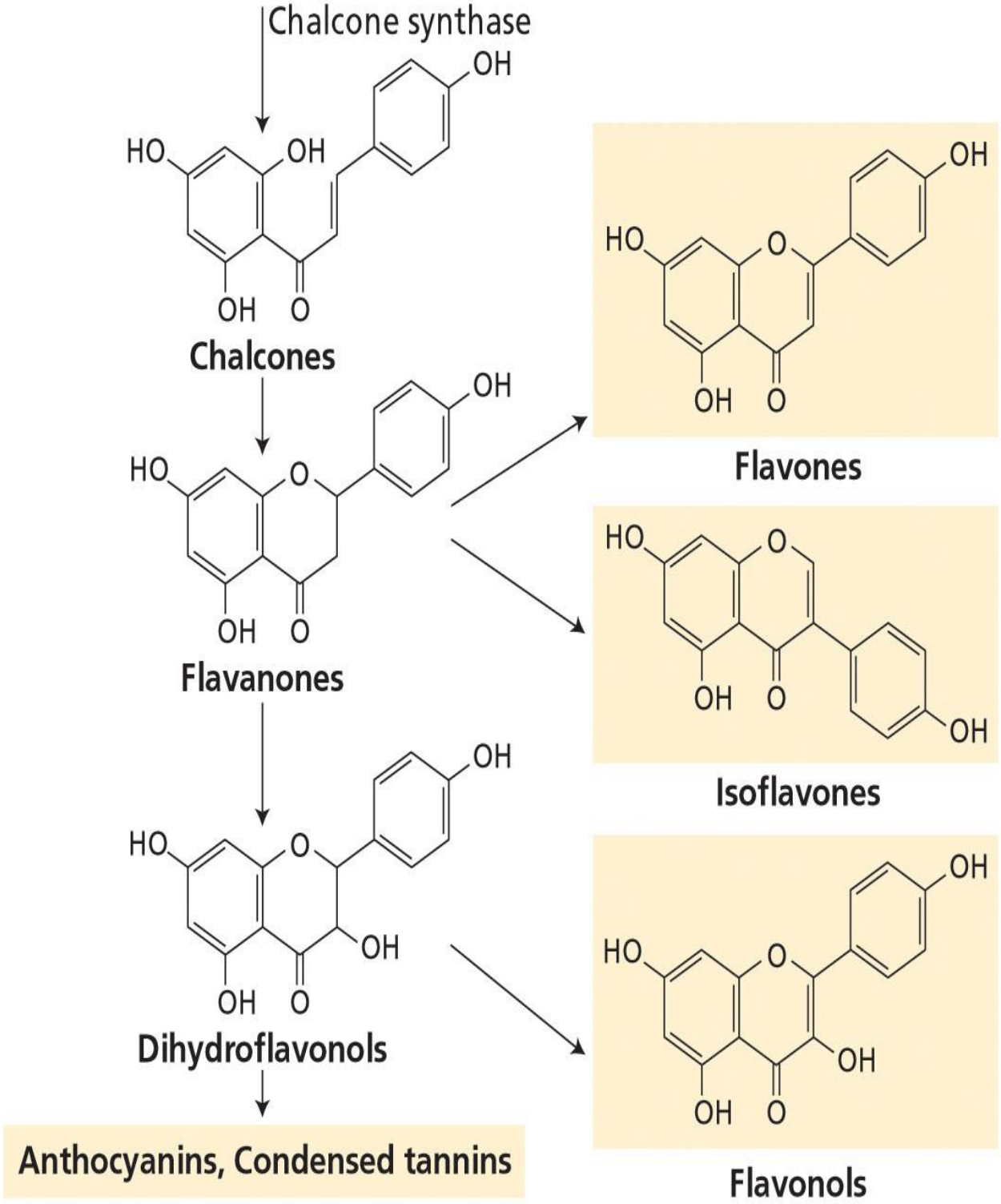
Flavonoids glycosides

Biosynthesis of Flavonoids: -

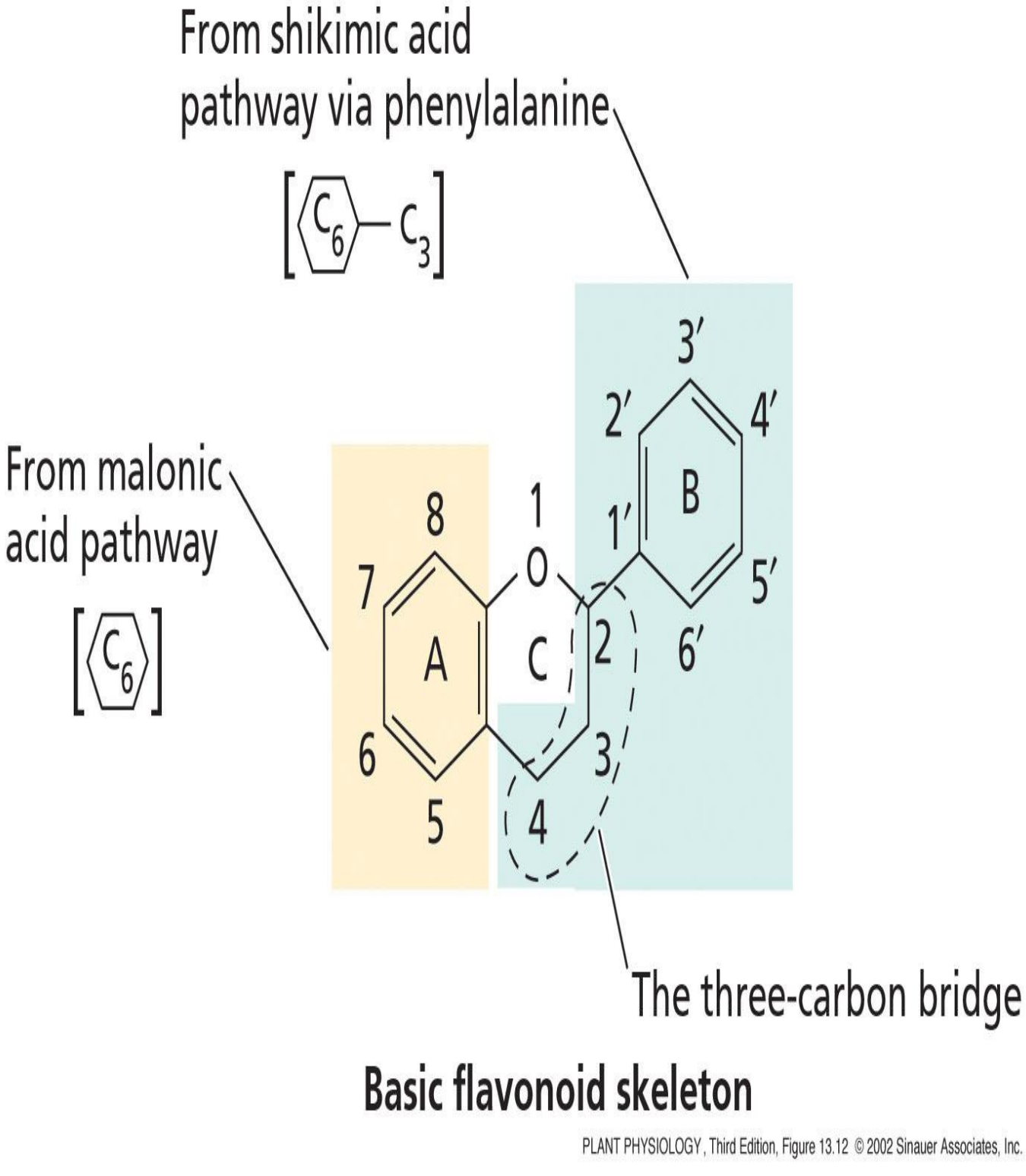
Flavonoids are synthesized by the phenyl-propanoid metabolic pathway (shikimic acid pathway) in which the amino acid phenylalanine first undergo deamination to give cinnamic acid or called coumaric acid which is then hydroxylated at the (para) position to produce (4-hydroxycoumaryl or cinnamyl-CoA) or called *p*-hydroxy coumaryl or cinnamyl CoA which is then combined with three acetate molecules to yield the true backbone of flavonoids, a group of compounds called chalcone, which contain two phenyl rings. Conjugate ring-closure of chalcone results in the familiar form of flavonoids.


COOH
NH2
Phenylalanine
NH3
Phenylalanine ammonia lyase (deamination)
COOH
Cinnamic acid
COOH
HO
hydroxylation at para
p-Coumaric acid
CoA-SH
activation by CoASH
COSCoA
HO
p-Coumaroyl-CoA
3 Acetate molecules


CoA
S
O
cinnamyl CoA
+ 3 CH3-COO-
HO
OH
OH
OH
OH
O
a chalcone
1-oxidation
2-cyclization
O
COOH
O
O



PLANT PHYSIOLOGY, Third Edition, Figure 13.10 (Part 2) © 2002 Sinauer Associates, Inc.



Basic flavonoid skeleton

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(FLAVONOIDS) Pharmacological action: -

A)) Direct radical scavenging: -

Body cells and tissues are continuously threatened by the damage caused by free radicals and reactive oxygen species, which are produced during normal oxygen metabolism or are induced by exogenous damage, Flavonoids can prevent injury caused by free radicals in various ways. One way is the direct scavenging of free radicals. Flavonoids are oxidized by radicals, resulting in a more stable, less-reactive radical. In other words, flavonoids stabilize the reactive oxygen species by reacting with the reactive compound of the radical. Because of the high reactivity of the hydroxyl group of the flavonoids, radicals are made inactive, according to the following equation: -

Flavonoid(OH) + R• > flavonoid(O•) + RH

where **R•** is a free radical and **O•** is an oxygen free radical

(Indirect action): flavonoids also interfere with inducible nitric-oxide synthase activity. Nitric oxide is produced by several different types of cells, including endothelial cells and macrophages. the much higher concentrations of nitric oxide produced by inducible nitric-oxide synthase in macrophages can result in oxidative damage. Nitric oxide reacts with free radicals, thereby producing the highly damaging peroxynitrite. When flavonoids are used as antioxidants, free radicals are scavenged and therefore can no longer react with nitric oxide, resulting in less damage also nitric itself can directly scavenged by flavonoids.

When reactive oxygen species are in the presence of iron, lipid peroxidation results. Specific flavonoids are known to chelate iron (28), thereby removing a causal factor for the development of free radicals. Quercetin in particular is known for its iron-chelating and iron-stabilizing properties so provide direct inhibition of lipid peroxidation flavonoids may have preventive action against atherosclerosis.

Characteristics of flavonoid structure for most effective radical-scavenging activity:-

1. The catechol (O-dihydroxy) group in the ring confers great scavenging ability.

2. A pyrogallol (trihydroxy) group in ring B of a catechol, as in myricetin, produces even higher activity.

3. The C2-C3 double bond of the C ring appears to increase scavenger activity because it confers stability to the phenoxy radical produced.

4. The 4-oxo (keto double bond at position 4 of the C ring), especially in association with the C2-C3 double bond, increases scavenger activity by delocalizing electrons from Bring.

5.The 3-OH group on the C ring generates an extremely active scavenger; in fact, the combination of C2-C3 double bond and 4-oxo group appears to be the best combination on the top of the catechol group

6.The 5-OH and 7-OH groups may also add scavenging potential in certain cases.

B)) Anti-inflammatory effects: -

Cyclooxygenase and lipoxygenase play an important role as inflammatory mediators. They are involved in the release of arachidonic acid, which is a starting point for a general inflammatory response. Selected phenolic compounds were shown to inhibit both the cyclooxygenase and 5-lipoxygenase pathways. This inhibition reduces the release of arachidonic acide thus diminishing the formation of these inflammatory metabolites.

Another anti-inflammatory feature is the ability of flavonoids to inhibit eicosanoid biosynthesis Eicosanoids, such as prostaglandins, are involved in various immunologic responses and are the end products of the cyclooxygenase and lipoxygenase pathways. Another anti-inflammatory property of flavonoids is their suggested ability to inhibit neutrophil degranulation. This is a direct way to diminish the release of arachidonic acid by neutrophils and other immune cells.

C)) Antitumor effects: -

The antitumor activity of flavonoids is still a point of discussion. Antioxidant systems are frequently inadequate, and damage from reactive oxygen species is proposed to be involved in carcinogenesis. Reactive oxygen species can damage DNA, and division of cells with unrepaired or mis-repaired damage leads to mutations. If these changes appear in critical genes, such as oncogenes or tumor suppressor genes, initiation or progression may result. Reactive oxygen species can interfere directly with cell signaling and growth. The cellular damage caused by reactive oxygen species can induce mitosis, increasing the risk that damaged DNA. Flavonoids, as

antioxidants, can inhibit carcinogenesis by inhibiting cell proliferation (potent growth inhibitory effects on several malignant tumor cell) by inhibiting several biochemical events associated with cellular growth example: Quercetin impeded aerobic glycolysis in tumor cell, Kaempferol inhibit DNA, RNA and protein synthesis in the tumor cell. Other flavonoids may inhibit both cytosolic & membranal Tyrosine Kinase ez which play very important role in the signal transduction pathway that regulates cell proliferation.

D)) Hepatoprotective effect: -

Silymarin, Quercetin & Rutin possess a powerful antioxidant activity which help to prevent free radical oxidative damage to cells also help in the treatment & prevention of alcohol and chemical-induced hepatotoxicity by increase Glutathione in the liver, Glutathione responsible for detoxifying a wide range of drugs & chemicals which cause liver damage also increased protein synthesis in the liver this action has important therapeutic implications in the repair of damaged hepatocytes and restoration of normal functions of liver.

E)) Effect on blood vessels

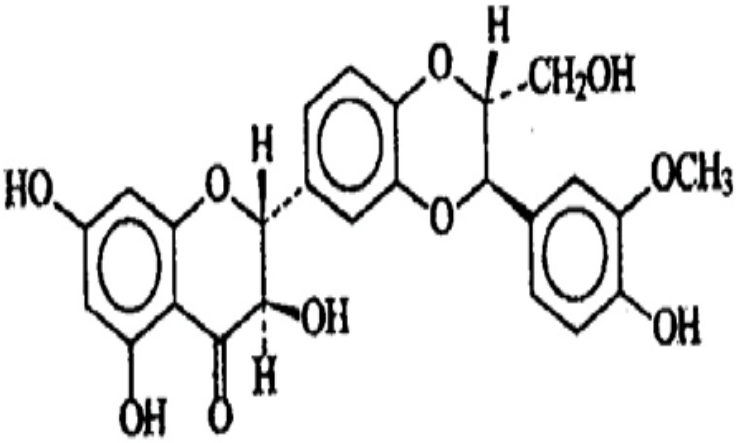
Rutin and Hesperidin have been called Vitamin P or Permeability factors they have been used in the treatment of various conditions characterized by capillary bleeding & increased capillary fragility.

Drugs: -

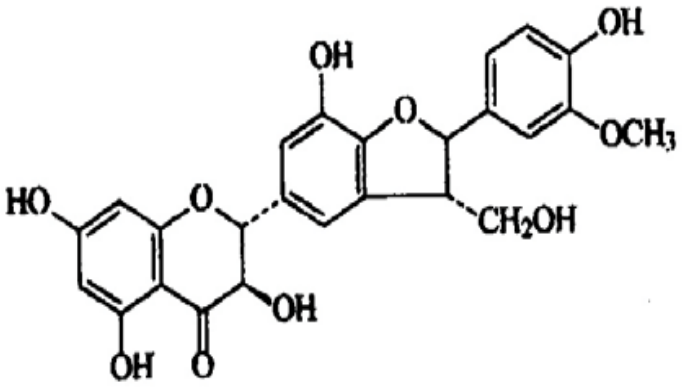
Silymarin

is a flavonol-lignan mixture of silybin, silychristin and silydianin, which is obtained from seeds of Milk thistle ***Silybum marianumn*** *(L). Family Asteraceae* chemical formula: (C25H22O10) شوك الحليب

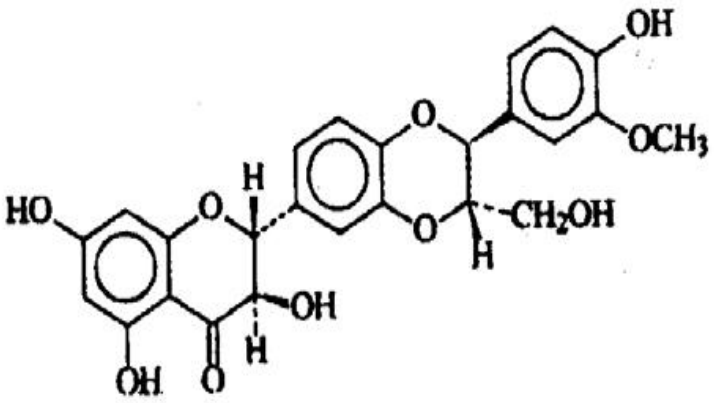
Silybin



Silychristin



Silydianin



Research suggests that silymarin prevent and repair damage to the liver from toxin. The efficacy of silymarin in preventing drug-induced liver damage in patients taking psychotropic drugs long-term has been investigated and silymarin was found to reduce damage to the liver caused by lipid peroxidation in patients taking these drugs.

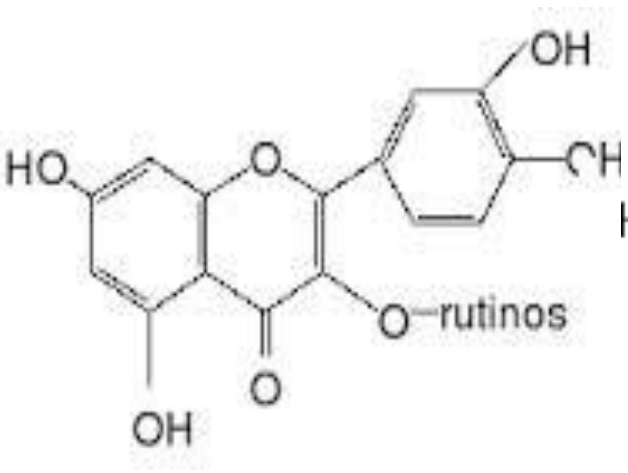
Silymarin on evaluation exhibited significant anti-inflammatory and antiarthritic activities in the papaya latex induced model of inflammation and mycobacterial adjuvant induced arthritis in rats. Results of the study indicate its action through inhibition of 5-lipoxygenase for anti-inflammatory and ant arthritic activities.

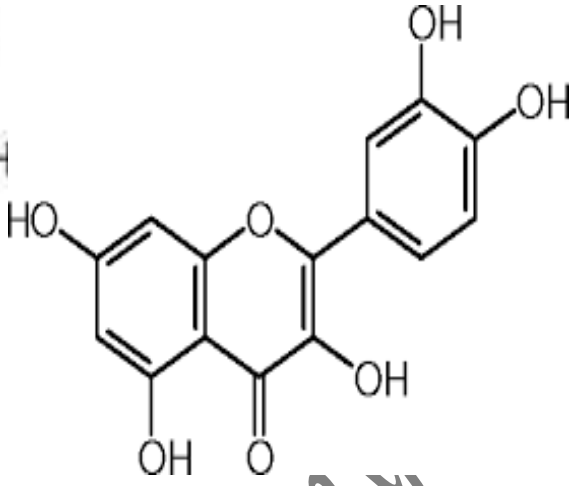
Other uses

- Lowering cholesterol levels
- Reduces cell damage caused by radiation and chemotherapy treatments
- Reducing insulin resistance in people with type 2 diabetes who also have cirrhosis,
- Reducing the growth of cancer cells in breast, cervical, and prostate cancers
- Alzheimer's disease prevention or treatment.

Quercetin, a tetraoxyflavonol, is a plant-derived flavonoid. It can be found in nature not only alone, but also as an aglycone, the non-sugar compound remaining after replacement of the glycosil group from a glycoside by a hydrogen atom. Quercitrin and rutin are two examples of glycosides containing quercetin as an aglycone.

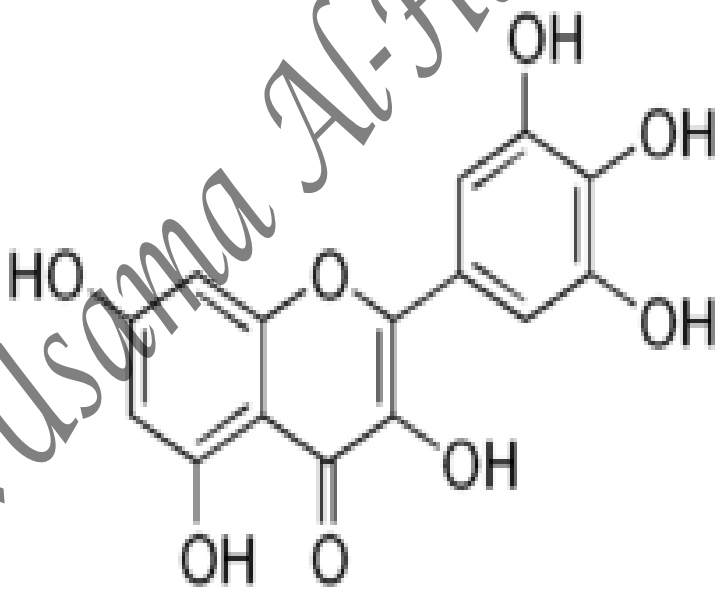
Quercetin has powerful antioxidant role in the cell. This function helps to reactivate tocopherol (i.e. vitamin E), work off superoxide ions, which are reactive oxygen species (ROS). ROS can be accumulated in the skin when it is exposed in an excessive manner, in terms of time or intensity, to sunrays. Also, quercetin blocks the production of nitric oxide (NO) (Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 during inflammation.





Rutin **Quercetin**

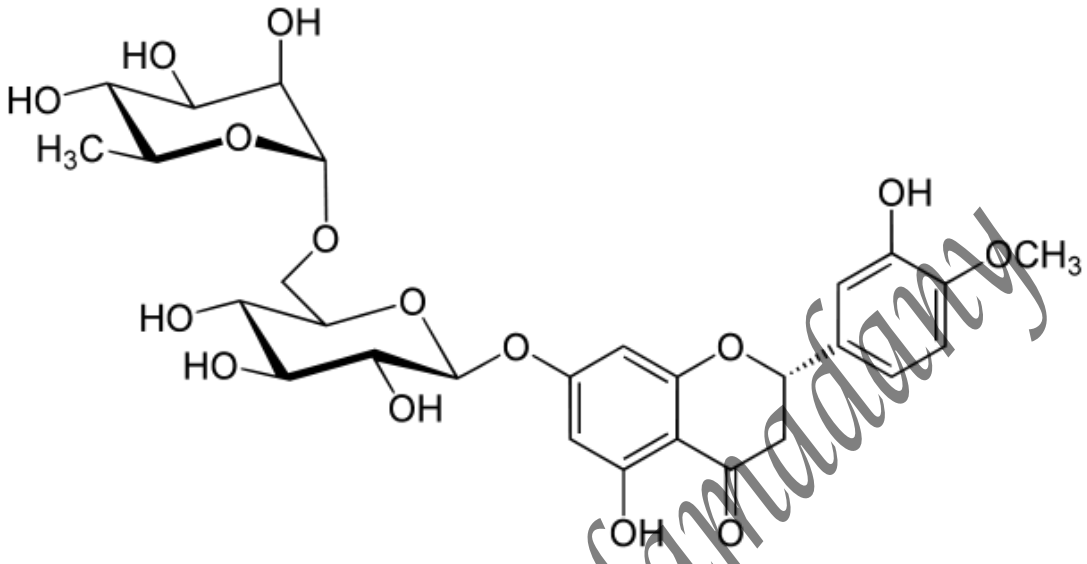
Myricetin is a flavonoid, which means it is a natural polyphenolic compound with antioxidant properties. It is commonly derived from vegetables, fruits, nuts, berries, tea.



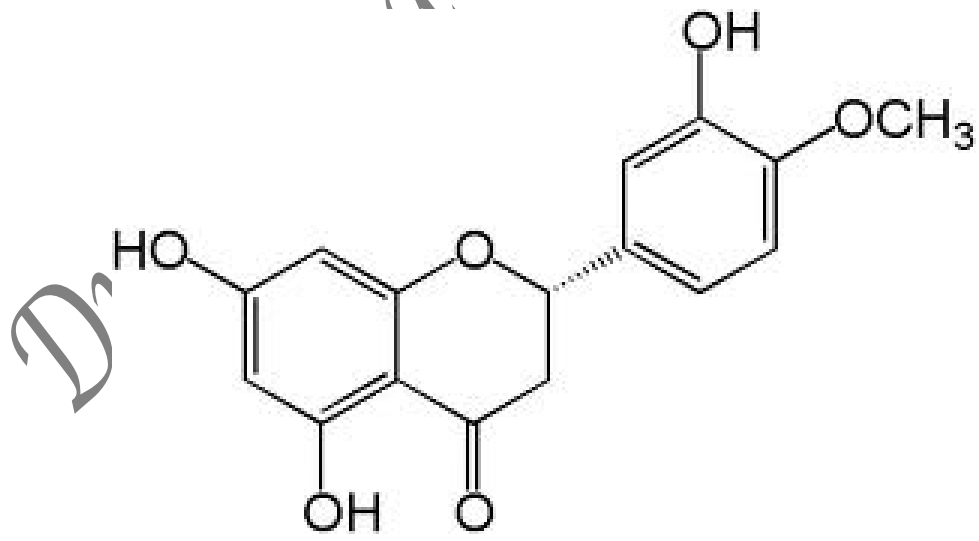
Myricetin is very effective in protecting cells from carcinogenic mutation. Myricetin provided protection against most type of tumors by different mechanisms like free radical scavenger action.

Hesperidin (glycoside) & Its aglycone (hesperetin)

Found in high concentration in fruit of citrus trees.



Hesperidin



Hesperetin