

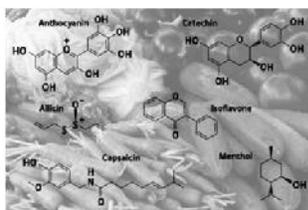
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## Lecture 14: SECONDARY METABOLITES



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Chapter 24. Buchanan *et al.* (eds. 2015)

The world is a healthier, more colorful, tasty, and fragrant place because of the **phenolics** that plants produce.

## LEARNING OUTCOMES

Students, after mastering materials of the present lecture, should be able

1. to explain secondary metabolites in plants.
2. to explain more detail terpenoids including biosynthesis.
3. to explain more detail cyanogenic glucosides including biosynthesis.
4. to explain more detail alkaloids including biosynthesis

## LECTURE OUTLINE

### I. INTRODUCTION

1. Definition
2. Classification

### II. TERPENOIDS

1. Definition
2. Classification
3. Functions
4. Biosynthesis

### III. ALKALOIDS

1. Definition
2. Functions
3. Biosynthesis

### IV. PHENOLICS

1. Definition
2. Functions
4. Biosynthesis

### V. CYANOGENIC GLUCOSIDES

1. Definition
2. Classification
3. Functions
4. Biosynthesis

Notes. Due to time limitation, discussion will be focused on Terpenoids, Alkaloids & Phenolics, but cyanoglucoside materials are presented in the appendix

## I. INTRODUCTION

### 1. Definition

- Plant secondary metabolites, also referred to as natural products or specialized metabolites, constitute an enormously rich reservoir of chemical biodiversity.
- The secondary metabolites have been the subject of research since 1850s for their practical utility as dyes, polymers, fibers, glues, oils, waxes, flavors, fragrances, drugs, insecticides, and herbicides.
- Today it is recognized that natural products have important ecological roles in plants, and their study has transitioned into the realm of modern biology.
- In the absence of a valid distinction between primary and secondary metabolites based upon structure or biochemistry, a functional definition is used herein.

- Secondary products are defined as substances that influence communication between the plant and its environment, and primary products as substances that participate in nutrition and essential metabolic processes in the plant.
  - In comparison with primary metabolites, which are essential to plant growth and development, secondary metabolites have internal roles in plants and also are integral to the communication of a plant with its environment.
- The interaction between a plant and its environment takes many forms.
  1. It can be an accumulation of pigments in flower petals, or a release of volatile chemicals by flowers to attract pollinators.
  2. It can be the release of volatiles by a leaf damaged by a grazing caterpillar to attract predatory wasps in a tritrophic interaction, or the production of bitter or toxic chemicals that serve as antifeedants.

3. It can also be the release by roots of secondary metabolites into the rhizosphere to attract beneficial soil microorganisms.

## 2. Classification

- More than 200,000 diverse chemical structures have been identified.
- However, primary and secondary metabolites cannot be readily distinguished by their precursor molecules, chemical structures, or biosynthetic origins.
  - For example, the diterpenes kaurenoic acid and abietic acid are formed by a similar sequence of related enzymatic reactions (Fig. 24.1).
  - Kaurenoic acid is an essential intermediate in the synthesis of gibberellins
  - Abietic acid is a resin component (a secondary metabolite) largely restricted to members of the Fabaceae and Pinaceae.

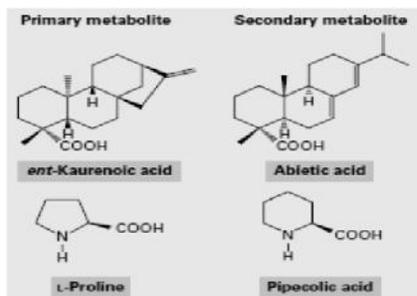


FIGURE 24.1 Kaurenoic acid and proline are primary metabolites, whereas the closely related compounds abietic acid and pipecolic acid are considered secondary metabolites.

- The essential amino acid proline is a primary metabolite, whereas the C6 analog pipecolic acid (Fig. 24.1) is considered an alkaloid and, thus, a secondary metabolite.
- Even lignin, the essential structural polymer of wood and second only to cellulose as the most abundant organic substance in plants, has been considered a natural product rather than a primary metabolite.

- Plant natural products can be divided into several major groups based on their chemical structures, with the best studied being the terpenoids, cyanogenic glucosides and glucosinolates, alkaloids, and phenolics.
- There is no fixed, commonly agreed upon system for classifying secondary metabolites. Based on their biosynthetic origins, plant secondary metabolites can be divided into three major groups:
  - Flavonoids and allied phenolic and polyphenolic compounds,
  - Terpenoids and
  - Nitrogen-containing alkaloids and sulphur-containing compounds.

## II. TERPENOIDS

### 1. Definition

#### *What are terpenoids*

- Terpenoids, also referred to as **isoprenoids**, are organic chemicals derived from five-carbon units, sometimes called isoprene ( $C_5H_8$ ) units, assembled and modified in thousands of ways.
- The term of isoprene units is based on the fact some terpenoids decompose to give off the gas isoprene at elevated temperatures (Fig. 24.2).

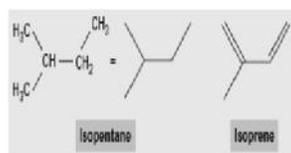


Fig. 24.2 The structure of the basic five-carbon ( $C_5$ ) units of terpenoids. Isopentane (left) is a branched  $C_5$  hydrocarbon, and isoprene (right) is a gas formed when certain terpenoids decompose.

- Terpenoids (isoprenoids) represent the largest and most diverse class of chemicals among the myriad compounds produced by plants (Tholl, 2015).
- The terms “terpenoid” and “terpene” originate from the word turpentine (“terpentin” in Germany) because some of the first terpenes described were isolated from turpentine (a fluid from the resin of live trees).
- **Terpenoids** can be thought of as modified terpenes, wherein methyl groups have been moved or removed, or oxygen atoms added. Terpenes [ $(C_5H_8)_n$ ] are hydrocarbons resulting from the condensation of several 5-carbon isoprene [ $(C_5H_8)_n$  or  $CH_2=C(CH_3)CH=CH_2$ ] units.
- Terpenoids contribute to
  - the scent of eucalyptus ( $\alpha$ -pinene)

- the flavors of cinnamon (cinnamaldehyde and *trans*-cinnamaldehyde), cloves, (Caryophyllene, -caryophyllene) and ginger (*Zingiberene*, a monocyclic sesquiterpene),
- the yellow color in sunflowers, ( $\beta$ -carotene, tetraterpenoids) and the red color in tomatoes (lycopene, bright red carotene).
- Well-known terpenoids include
  - citral, present in the oils of several plants,
  - menthol, obtained from several plants (corn mint, peppermint and others),
  - camphor, derived from the wood of the *camphor* tree (*Cinnamomum camphora*),
  - salvinorin A, found in the plant *Salvia divinorum*,
  - cannabinoids found in cannabis,
  - ginkgolide and bilobalide found in *Ginkgo biloba*, and
  - curcuminoids found in turmeric and mustard seed.

## 2. Classification

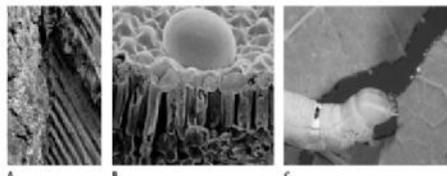
- Although terpenoids are found in all living organisms, they reach their greatest structural and functional diversity in plants.
- Many terpenoids have a well-characterized function in basic plant growth and development and so can be classified as primary, rather than secondary metabolites.
- Terpenoids—with over 30,000 members described to date—take the honors for being the largest class of small molecule natural products in plants.
- The classification of terpenoids has a long history, and the 10-carbon terpenoids were once thought to be the smallest naturally occurring representatives of this class.

- Hence, these were called monoterpenes, and the name persists.
- The designation of the 10-carbon terpenoids as monoterpenes (one terpene) leads to the name of
  - five-carbon terpenoids as hemiterpenes (*half terpenes*),
  - 15-carbon terpenoids as sesquiterpenes (one and one-half terpenes),
  - 20-carbon terpenoids as diterpenes (two terpenes),
  - 30-carbon terpenoids as triterpenes (three terpenes), and so on.

### 3. Functions

- **Ecological Roles.** Most of the thousands of terpenoids produced by plants have no discernible roles in growth and development and are, therefore, secondary metabolites.
- Many of these are volatile compounds or constituents of essential oils, resin, latex, and waxes. These terpenoids, once thought of as metabolic waste products, actually serve a suite of ecological roles, and
  - can defend against herbivores and pathogens, inhibit germination and growth of competing plants, or attract animals that disperse pollen and seeds.
- Many terpenes form sticky, oily, smelly, or irritating mixtures (Fig. 24.3), so it is easy to appreciate their defensive properties.

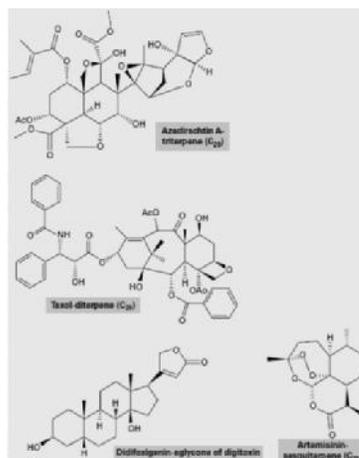
Fig.E 24.3 Terpenoids can be used for plant defense. These compounds often form oily, sticky, or irritating mixtures that deter herbivore feeding and pathogen invasion.



(A) The resin of conifers comprises mainly monoterpenes (C<sub>10</sub>) and diterpenes (C<sub>20</sub>). When the tree is damaged and resin ducts are severed, the smelly monoterpenes quickly evaporate from the extruded resin, leaving behind the sticky diterpenes, which become polymerized. (B) The monoterpene-rich oil of peppermint (*Mentha* sp.) is stored in glandular hairs on the surface of leaves and other organs. Shown in this cutaway view of a young leaf is a single glandular hair, about 0.5 mm in diameter, on the leaf surface. (C) Plant latex is a milky fluid that is made up of an emulsion of proteins, natural products, and other cellular constituents that often contains diterpenes, triterpenes, or higher order terpenes, including rubber. Stored in ducts known as laticifers, it is exuded after injuries, such as that caused by herbivory. Source: (A) Reiderer, University of Würzburg, Germany; (B, C) Wittstock & Gershenzon (2002). *Curr. Opin. Plant Biol.* 5:300–307.

- For example, the triterpene azadirachtin (Fig. 24.4) from the seed oil of the Asian neem tree (*Azadirachta indica*) is a powerful insect feeding deterrent and exerts a variety of toxic effects on insects as well.

Fig. 24.4 Structures of some economically important terpenes. Azadirachtin is a triterpene (C<sub>30</sub>) derivative from the seed oil of the Asian neem tree (*Azadirachta indica*) used in insect pest control. Taxol, a diterpene (C<sub>20</sub>) derivative, is from the yew tree (*Taxus brevifolia*) and used in cancer treatment. Digitoxigenin is an aglycone of digitoxin, a steroid glycoside used to treat heart disease. Artemisinin is a sesquiterpene from *Artemisia annua* used against malaria.

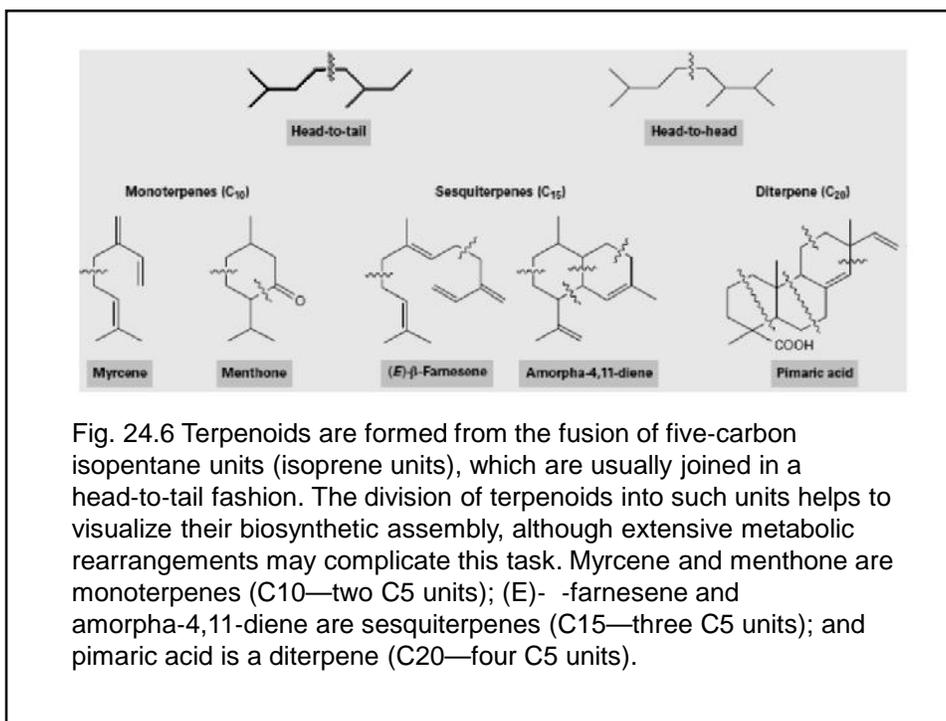


- **Utility For Humans.** Terpenoids play important roles in human society (used as flavors and fragrances of foods, beverages, soaps, perfumes, toothpaste, and other products).
- Some find use as industrial materials (resins and rubber) or pigments (carotenoids), and yet others are insecticides that are of value because of their low toxicity to humans and lack of persistence in the environment (azadirachtin and pyrethrins).
- Many terpenoids are also of nutritional or pharmaceutical significance, including vitamins A, D, E, and K as well as some well-known drugs (Fig. 24.4):
  1. Taxol is a diterpene from yew (*Taxus brevifolia*) that has become a blockbuster drug for the treatment of ovarian and breast cancer,

2. Artemisinin is a sesquiterpene from *Artemisia annua* used against malaria, and
3. Cardenolides (triterpenes, such as digitoxigenin) extracted from foxglove (*Digitalis lanata*) are prescribed to millions of patients for the treatment of heart disease.
4. Carotenoids are also becoming more popular as “neutraceuticals” (foods with health benefits) believed to help prevent cancer, heart disease, and macular degeneration.

### 3. Biosynthesis

- The five-carbon isopentane or isoprene units that make up terpenoids are usually joined in a “head-to-tail” fashion (Fig. 24.6).
- This pattern was first recognized in the late 1800s and updated in the 1930s, but other types of reactions could occur in terpenoid formation because of the chemical mechanisms involved.



- However, all terpenoids were proposed to be formed from a “biological” isoprene unit. These units can be joined in head-to-tail, head-to-head, and by various head-to-middle fusions, and substantial structural rearrangement can occur during biosynthesis.
- In such modified terpenoids, it may be difficult to discern the original organization of the isoprene units (Fig. 24.6).
- The biosynthesis of terpenoids can be conveniently divided into four stages :
  - (i) the synthesis of the biological five-carbon isoprene unit,
  - (ii) repetitive condensations of the five-carbon unit to form a series of larger and larger prenyl diphosphates,
  - (iii) conversion of prenyl diphosphates to the basic terpenoid skeletons, and

- (iv) further modifications to the basic skeletons, including oxidation, reduction, isomerization, conjugation, and other transformations.
- The biosynthesis of basic 5-carbon unit of terpenoids is represented by isopentenyl diphosphate and dimethylallyl diphosphate.
    - These intermediates are synthesized in plants by two completely different routes that are spatially separated but exchange intermediates: the mevalonate pathway and the methylerythritol 4-phosphate (MEP) pathway.
  - The mevalonate pathway, demonstrated initially in yeast and mammals and well-characterized sequence, begins with the condensation of three molecules of acetyl-CoA in two steps to form the six-carbon compound, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) (Fig. 24.7).

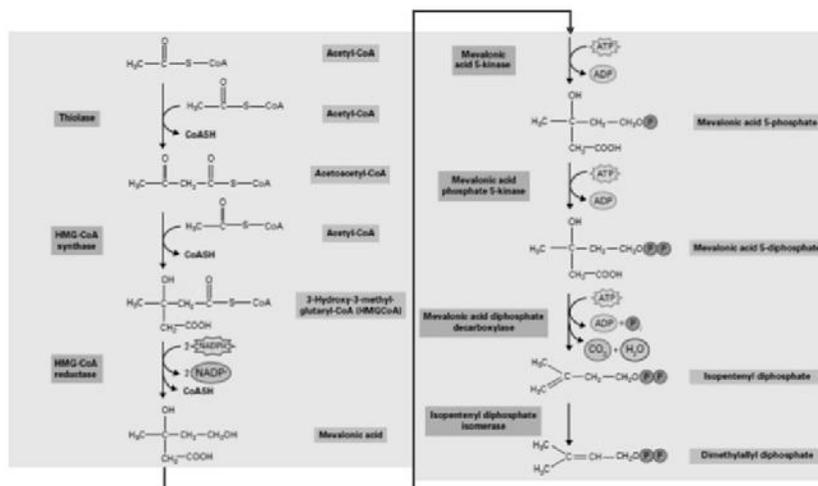


Fig. 24.7 The mevalonate pathway for the formation of isopentenyl diphosphate, the basic five-carbon unit of terpenoid biosynthesis. Synthesis of each isopentenyl diphosphate unit requires three molecules of acetyl-CoA. The mevalonate pathway occurs in the cytosol of plant cells.

- The discovery of a second route for producing the basic five-carbon building blocks of terpenoid biosynthesis, a route completely distinct from the mevalonate pathway, is one of the most exciting advances in plant biochemistry in recent years was (Fig. 24.8).
- This route begins with pyruvate and glyceraldehyde 3-phosphate and is usually named for its second intermediate, 2C-methyl-d-erythritol 4-phosphate (MEP).
- The existence of a second, nonmevalonate pathway to isopentenyl diphosphate in plants had been suspected for many years based on the poor incorporation of mevalonate into certain types of terpenoids.

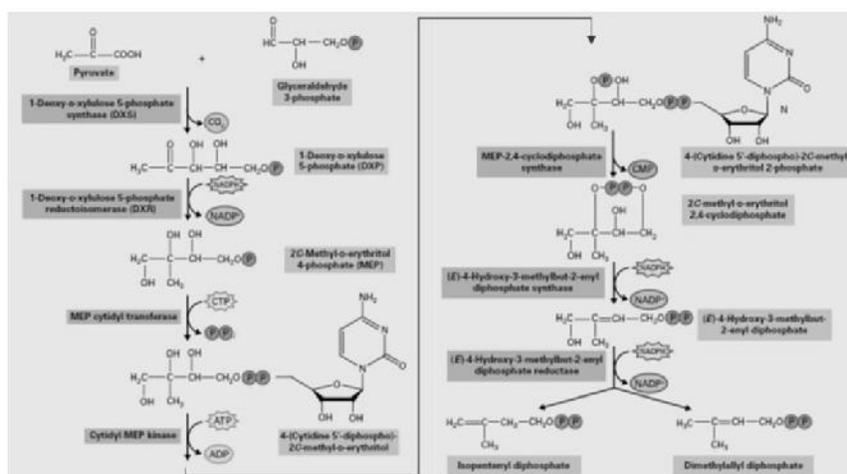
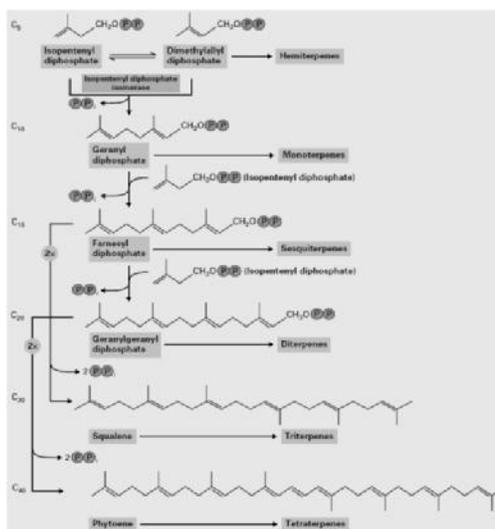


Fig. 24.8 The MEP pathway, a second route for the formation of isopentenyl diphosphate in plants, occurs in plastids.

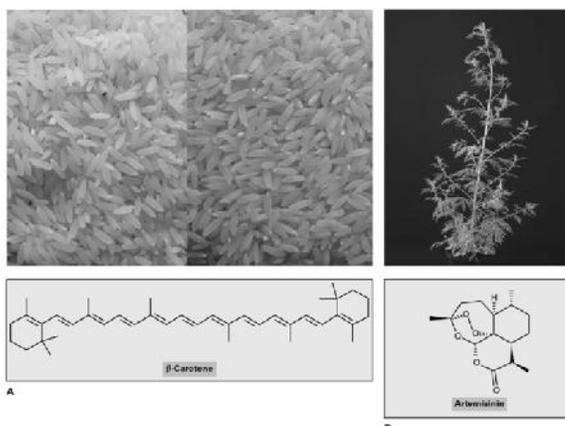
- The second stage of terpenoid biosynthesis involves fusion of the basic C5 building blocks, isopentenyl diphosphate and dimethylallyl diphosphate, into larger prenyl diphosphates and other metabolic intermediates (Fig. 24.9).
  - Dimethylallyl diphosphate, as the smallest prenyl diphosphate with an allylic double bond, is a primer to which varying numbers of isopentenyl diphosphate units can be added in sequential chain elongation steps. Thus, isopentenyl diphosphate and dimethylallyl diphosphate condense in head-to-tail fashion to form the allylic C10 compound, **geranyl diphosphate**.
  - Another molecule of isopentenyl diphosphate may then condense head-to-tail with geranyl diphosphate to generate the C15 allylic diphosphate, **farnesyl diphosphate**. Addition of a further isopentenyl diphosphate gives the C20 **geranylgeranyl diphosphate**.

Fig. 24.9 The major subclasses of terpenoids are biosynthesized from the basic C5 building blocks, isopentenyl diphosphate and its isomer, dimethylallyl diphosphate, which is formed from isopentenyl diphosphate via isopentenyl diphosphate isomerase. Reactions catalyzed by prenyltransferases condense varying numbers of isopentenyl diphosphate and dimethylallyl diphosphate units to geranyl diphosphate, the precursor of monoterpenes (C10),



farnesyl diphosphate, the precursor of sesquiterpenes (C15), and geranylgeranyl diphosphate, the precursor of diterpenes (C20). To make triterpenes (C30), two farnesyl (C15) units are combined, while to make tetraterpenes (C40), two geranylgeranyl (C20) units are joined.

Fig. 24.16 (A)  
Metabolic engineering of plant terpene production has yielded a variety of rice ("golden rice", here compared to ordinary rice on the left) with high levels of a vitamin A precursor,  $\beta$ -carotene, to help reduce vitamin A deficiency in many rice-eating countries.



(B) The antimalarial drug artemisinin was originally isolated from *Artemisia annua*. Much effort has been devoted to breeding *A. annua* with higher artemisinin levels. In addition, much of the artemisinin pathway has been engineered into microbes to increase production. Source: (A) Golden Rice Humanitarian Board, [www.goldenrice.org](http://www.goldenrice.org); (B) HarroBouwmeester, Wageningen University, The Netherlands.

### III. ALKALOIDS

#### 1. Definition

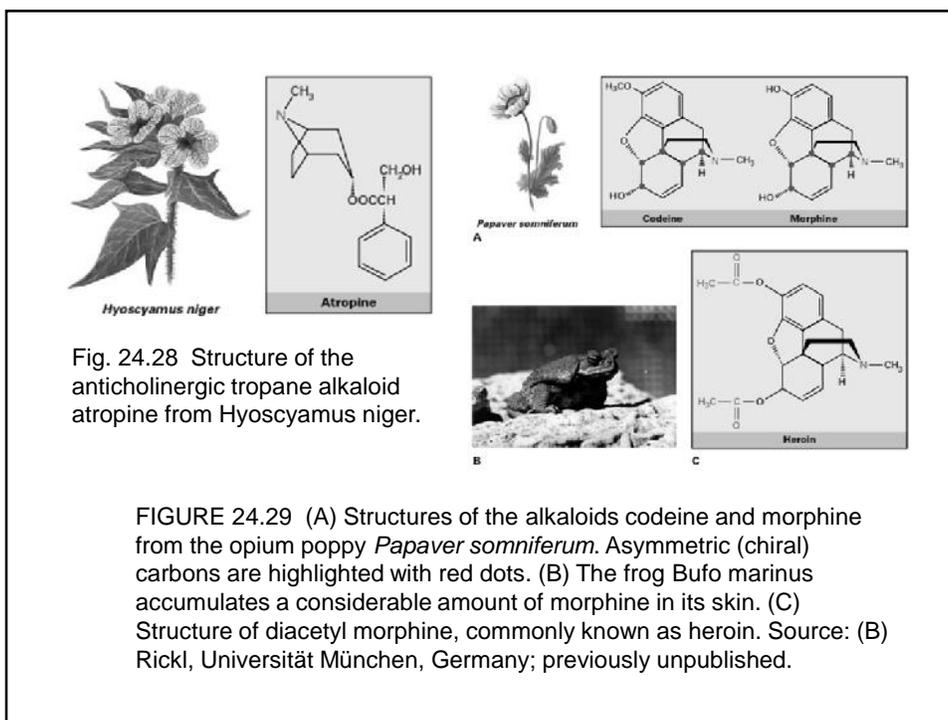
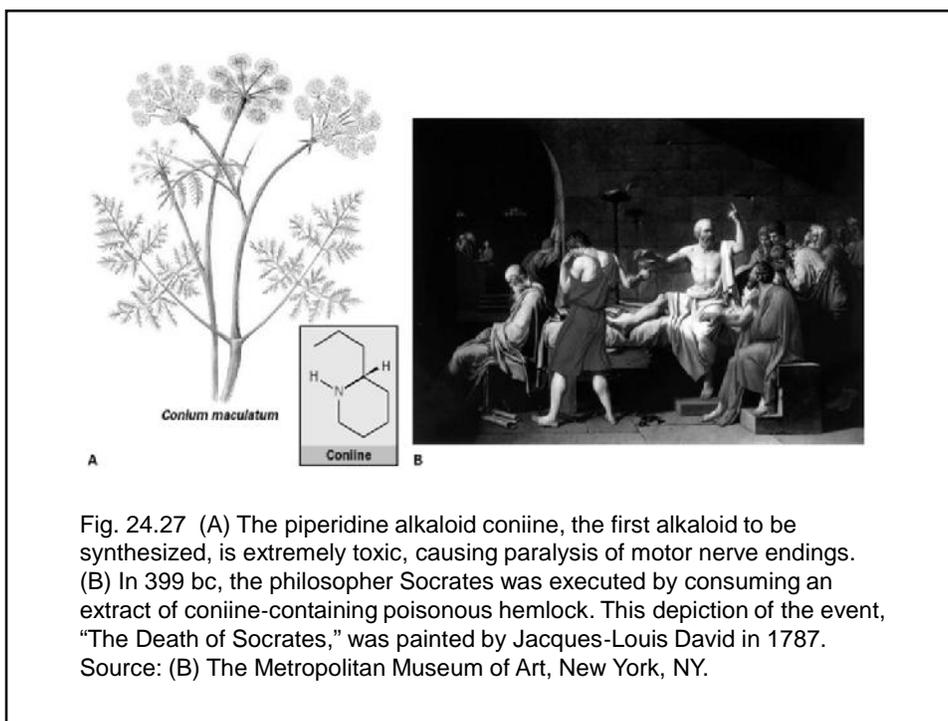
- The term alkaloid, coined in 1819 in Halle (Saale) Germany, finds its origin in the Arabic name *al-qali*, the plant from which soda was first isolated.
- Alkaloids were originally defined as pharmacologically active, nitrogen-containing basic compounds of plant origin.
  - After 200 years of alkaloid research, this definition no longer encompasses the entire alkaloid field, but in many cases it is still appropriate. Well-known alkaloids include morphine, strychnine, quinine, ephedrine, and nicotine.
  - Alkaloids are not unique to plants, and have also been isolated from numerous animal sources. The alkaloid morphine, for example, has been detected in mammals and is synthesized *de novo* in mouse.

- Many of the alkaloids that have been discovered are not pharmacologically active in mammals, and some are neutral rather than basic in character, despite the presence of a nitrogen atom in the molecule.

## 2. Uses of Alkaloid

- For much of human history, alkaloid-containing plant extracts have been used as ingredients in potions and poisons.
- In the eastern Mediterranean, use of the latex of the opium poppy (*Papaver somniferum*) can be traced back at least to 1400–1200 bc.
- The Sarpagandha root (*Rauwolfia serpentina*) has been used in India since approximately 1000 bc.

- Ancient people used medicinal plant extracts as purgatives, antitussives, sedatives, and treatments for a wide range of ailments, including snakebite, fever, and insanity.
  - During his execution in 399 bc, the philosopher Socrates drank an extract of coniine-containing hemlock (*Conium maculatum*; Fig. 24.27).
  - In the last century bc, Queen Cleopatra used extracts of henbane (*Hyoscyamus*), which contains atropine (Fig. 24.28), to dilate her pupils and appear more alluring to her male political rivals.
- Alkaloid-containing plants were mankind's original "materia medica," and many are still in use today as prescription drugs (Table 24.1).
- One of the best-known prescription alkaloids is the antitussive and analgesic codeine from the opium poppy, *Papaver somniferum* (Fig. 24.29).



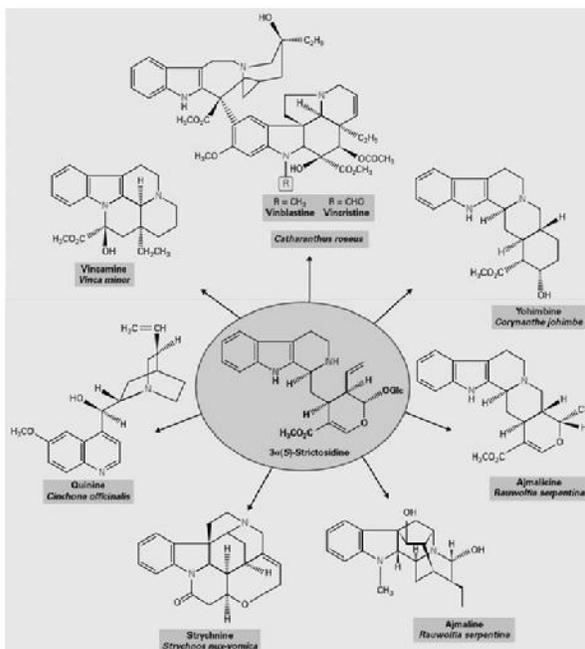
### 3. Biosynthesis

- Until the mid-20th century, our view of plant alkaloid biosynthesis was based on biogenic hypotheses.
- In the 1950s, alkaloid biosynthesis became an experimental science, as radioactively labeled organic molecules became available for testing hypotheses.
- These early precursor-feeding experiments established that alkaloids are, in most cases, formed from L-amino acids (e.g., tryptophan, tyrosine, phenylalanine, lysine, and arginine), either alone or in combination with a steroidal, secoiridoid (e.g., secologanin) or other terpenoid-type moiety.
- One or two transformations can convert these ubiquitous amino acids from primary metabolites to substrates for species-specific alkaloid metabolism.

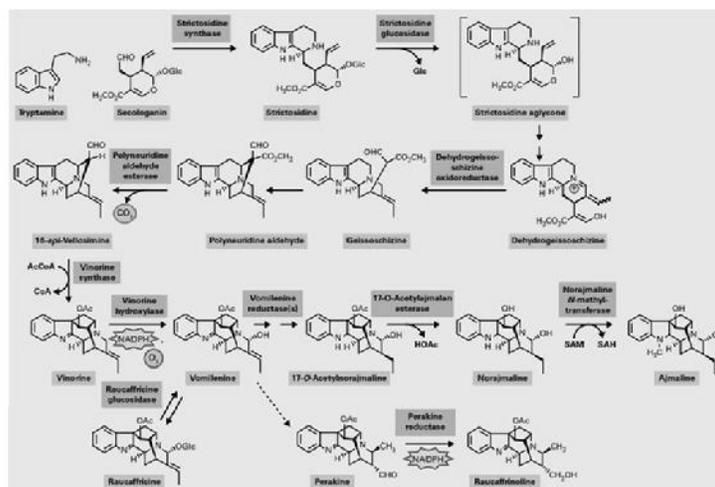
- Although we do not thoroughly understand how most alkaloids are made by plants, several systems can serve as examples of the types of building blocks and enzymatic transformations that have evolved in alkaloid biosynthesis.
- Ajmalicine (Fig. 24.39), an L-tryptophan-derived monoterpenoid indole alkaloid, was the first alkaloid for which biosynthesis was clarified at the enzyme level.
- In plants, the biosynthesis of ajmalicine and more than 1800 other monoterpenoid indole alkaloids begins with the decarboxylation of the L-amino acid tryptophan by tryptophan decarboxylase to form tryptamine.

**Fig. 24.39**

Strictosidine, the product of tryptamine and secologanin, is the precursor for many species-specific alkaloids.



- Then tryptamine, by action of strictosidine synthase, is stereospecifically condensed with the secoiridoid secologanin (derived in multiple enzymatic steps from geraniol) to form 3 (S)-strictosidine. Strictosidine can then be enzymatically permuted in a species-specific manner to form a multitude of diverse structures (Fig. 24.39).
- The elucidation of the enzymatic formation of ajmalicine laid the groundwork for analysis of more complex biosynthetic pathways, such as those leading to two other l-tryptophan-derived monoterpenoid indole alkaloids, ajmaline (Fig. 24.40) and vindoline.



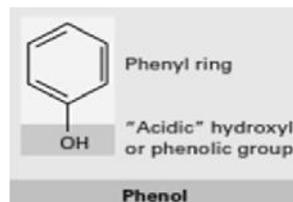
**Fig. 24.40** The biosynthesis of the antiarrhythmic monoterpene indole alkaloid ajmaline in *Rauwolfia serpentina* from tryptamine and secologanin is one of the best-understood alkaloid biosynthetic pathways. Several of the enzymes have been crystallized, and their atomic structures have been determined (Section 24.13.2).

## IV. PHENOLICS

### 1. Definition

- The transition of early vascular plants to a terrestrial habitat was successful in large part because of the development and elaboration of a diverse group of compounds known generally as “phenolics.”
- Although the majority of phenolics are structural components of cell walls, a vast array are the toxins and antifeedants of plant defense, coloring agents of flowers and fruits, aroma complement of plant organs (such as flower scents and fruit flavors), and antioxidants of wood, bark, and seeds.
- Phenolics (phenols) are a class of chemical compounds consisting of a hydroxyl group ( $\text{—OH}$ ) bonded directly to an aromatic hydrocarbon group.

- Plant phenolics vary greatly in size and complexity, but all generally possess (or are derived from compounds that once possessed) an aromatic arene (phenyl) ring with at least one hydroxyl group attached (Fig. 24.49).



- The phenolic hydroxyl group is acidic compared to other hydroxyl groups because it resides on an arene ring, which can readily stabilize a deprotonated oxygen substituent.
- As a result, plant phenolics are reactive and well suited to being the building blocks of large polymers, such as lignins or suberins, and in the generation of a large number of compounds that play important roles in many aspects of plant biology.

- Phenolic compounds can be classified in various ways, for example according to the functional groups attached to the phenol, or based on the number of phenol units in the molecule.
- Major subclasses of phenolic compounds include the flavonoids, anthocyanidins, isoflavones, chalcones, stilbenes, coumarins and furanocoumarins, monolignols and lignans, naphtha- and anthraquinones, and diarylheptanoids.

## 2. Uses of Phenolics

- Human needs. Human societies would not exist in their present form without the properties imparted by phenolic compounds (Table 24.3).

- Leather, which throughout early human history enabled more rapid transportation and thereby better trade (and war), has been produced for millennia by treating raw animal hides with “tannins,” either gallate esters or condensed tannins.
- The wheel was perfected because of the properties of wood, the strength and durability of which can be attributed to the lignin polymers and lignans, flavonoids, and hydrolyzable tannins.
- Much of the world relies on wood for building as well as a fuel to provide warmth.
- Source of energy. We are now turning to wood products as a source of lignocellulosic materials for biofuel production.
- As alternatives to dwindling natural resources are sought, plants, based in part on the phenolics that they contain, are among the best choices for renewable industrial feedstocks and materials.

- Medicines. Human health is also intimately tied to this class of compounds, as many medicinal compounds are derived or inspired by plant phenolics.
  - Examples include the lignan podophyllotoxin from May apple (*Podophyllum peltatum*), which is derivatized to form teniposide, etoposide, and etophos, used to treat a number of cancers.
  - The diarylheptanoid curcumin from turmeric (the curry spice), which has potent anti-inflammatory properties and is used worldwide to treat arthritis and other inflammatory diseases; and the stilbene resveratrol from red grapes and wine, which has been demonstrated to improve heart health and deter cancer development.
- The world is a healthier, more colorful, tasty, and fragrant place because of the phenolics that plants produce.

## QUESTIONS

1. What is secondary metabolites based on functional definition?
2. How does a plant interact with its environment? is
3. What are the main constituents of conifer resin?
4. What is taxol?
5. What are the biosynthetic pathways of basic 5-carbon unit of terpenoids?
6. What is atropine?
7. What is codeine?
8. What are the early precursors of alkaloids?
9. What is strictosidine?
10. What is
11. What is
  
12. What is

### 3. Biosynthesis

- Phenolic compounds account for approximately 40% of organic carbon in plants and are derived primarily from **phenylpropanoid** and **phenylpropanoid-acetate** backbones (Fig. 24.50), although related biochemical pathways, such as those leading to “hydrolyzable” tannins, also contribute.
- Most phenolics originate from the **phenylpropanoid** and the **phenylpropanoid-acetate pathways**. Both pathways share the first three biochemical steps, the core phenylpropanoid pathway (Fig. 24.52).
- These steps begin with an L-phenylalanine precursor and end with the formation of 4-coumaroyl CoA, a reactive compound that can participate in further reactions that lead to the wealth of compounds that are the plant phenolics.
  - The phenylpropanoid and phenylpropanoid-acetate pathways produce products that ameliorate the challenges that faced early land plants.

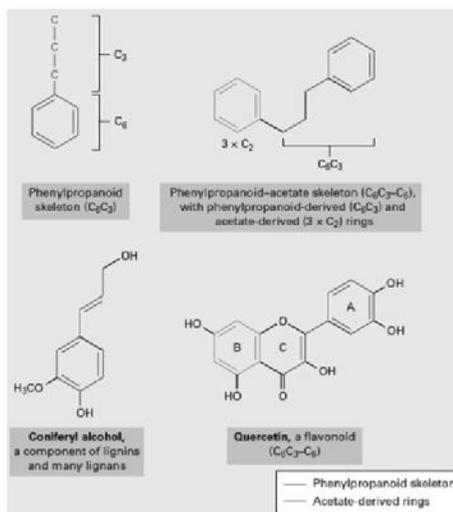
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  - The phenylpropanoid and phenylpropanoid-acetate pathways produce products that ameliorate the challenges that faced early land plants.
  - These challenges persist and provide selection pressure to maintain the phenylpropanoid pathway in plants (Table 24.2).
- Evolution of the phenylpropanoid-acetate pathway helped overcome challenges such as damaging UV irradiation which was faced by plants even before they left the water.

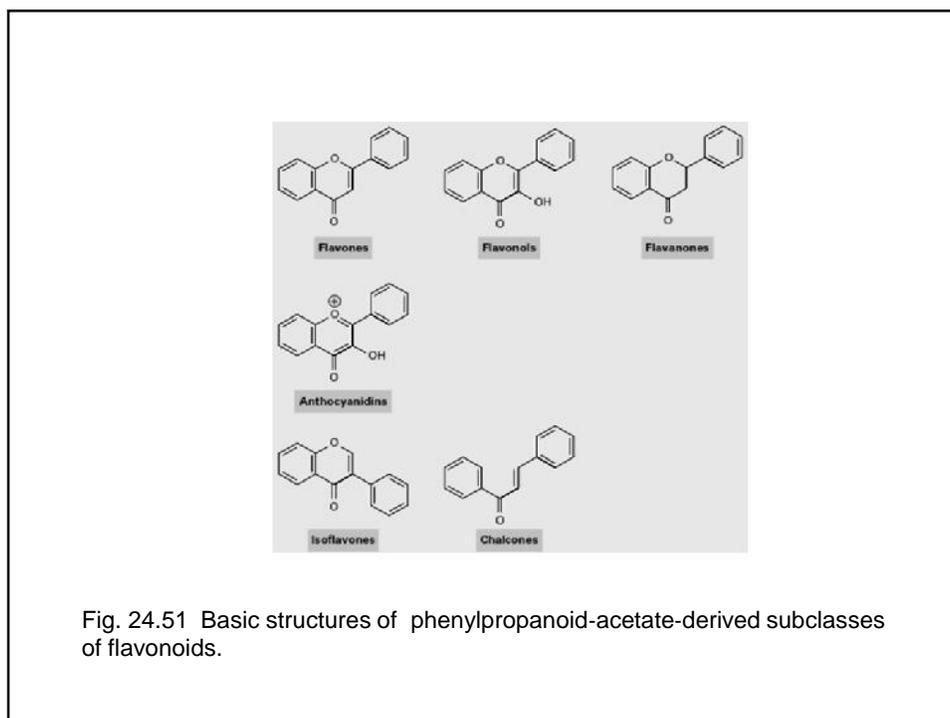
- Most phenolics originate from the **phenylpropanoid** and the **phenylpropanoid-acetate pathways**. Both pathways share the first three biochemical steps, the core phenylpropanoid pathway (Fig. 24.52). These steps begin with an L-phenylalanine precursor and end with the formation of 4-coumaroyl CoA, a reactive compound that can participate in further reactions that lead to the wealth of compounds that are the plant phenolics.

- This pathway leads to production of a large and diverse class of compounds called **flavonoids**, which has more than 5,000 members.
- Flavonoids, such as quercetin (Fig. 24.50), consist of a basic three-ring core structure that is modified to produce subclasses (Fig. 24.51), such as the anthocyanins (pigments), proanthocyanidins or condensed tannins (feeding deterrents and wood protectants), isoflavonoids (active in plant defensive and signaling), and flavones and flavonols (anti-inflammatory agents in animals).
- The most basic flavonoids—the flavones, flavonols, and flavanones—are widespread in the plant kingdom and typically absorb damaging UV rays.

**Fig. 24.50** Phenylpropanoid and phenylpropanoid-acetate and skeletons and representative plant compounds based on those structures. Flavonoids, such as quercetin, typically have three interconnected rings at their core, the A, B, and C rings.



Modifications to the C ring are responsible for creation of new classes of compounds, whereas modifications to the A and B rings lead to diversification within the compound class.

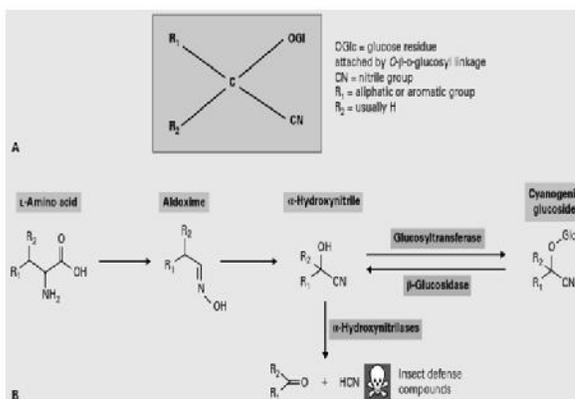


## V. CYANOGENIC GLYCOSIDES

### 1. Definition

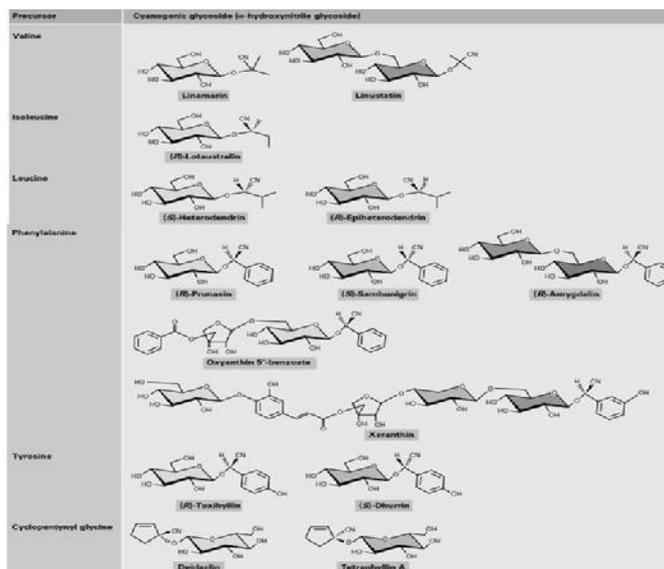
- **Cyanogenic glycosides** (Fig. 24.17) are  $\alpha$ -glycosides of  $\alpha$ -hydroxynitriles (cyanohydrins), and characterized by their ability to liberate hydrogen cyanide (HCN) when hydrolyzed by  $\alpha$ -glycosidases.
- This process (**cyanogenesis**) typically occurs when plant tissue containing cyanogenic glycosides is disrupted, for example, when bitten, chewed, or ingested by animals or insects.
- Cyanogenic glycosides are important components of plant defense against generalist herbivores due to their bitter taste and release of toxic HCN upon tissue disruption.

Fig. 24.17 (A) General structure of cyanogenic glycosides. The sugar residue is always a d-glucose that is joined by an O-  $\alpha$ -d-glucosyl linkage (referred to more specifically, then, as cyanogenic glucosides), but additional sugars present may be different.



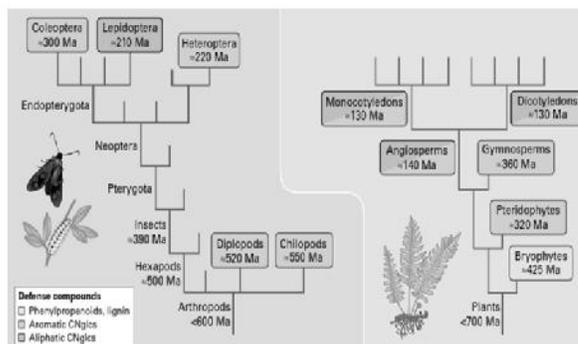
(B) Cyanogenesis. Cyanogenic glycosides are formed from a limited number of l-amino acids and converted to cyanogenic glycosides with  $\alpha$ -oximes and  $\alpha$ -hydroxynitriles as key intermediates. Upon hydrolysis of the cyanogenic glycoside by the action of  $\alpha$ -glycosidases and  $\alpha$ -hydroxynitrilases, toxic hydrogen cyanide (HCN) and ketones or aldehydes are produced.

- Cyanogenic glycosides are derived from five protein amino acids (Val, Ile, Leu, Phe, and Tyr) and the nonproteinogenic amino acid cyclopentenyl glycine (Fig. 24.18).
- Cyanogenic glycosides are widely distributed among more than 2,600 different species of pteridophytes, gymnosperms, and angiosperms.
- Whereas pteridophytes and gymnosperms contain cyanogenic glycosides derived from aromatic amino acids, angiosperms may contain cyanogenic glycosides derived from either aliphatic or aromatic amino acids (Figs. 24.18 and 24.19).
- Many crops, including **sorghum** (*Sorghum bicolor*), **cassava** (*Manihot esculentum*), and **barley** (*Hordeum vulgare*), are cyanogenic;



**Fig. 24.18** Structures of selected cyanogenic glycosides (α-hydroxynitrile glycosides).

Fig. 24.19 Evolutionary trees depicting the evolution of arthropods and plants and the presence of different classes of defense compounds, including cyanogenic glycosides.



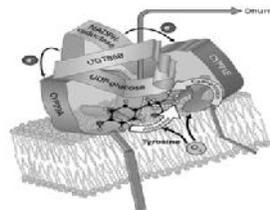
Plants and insects have coevolved for the last 400 million years, and both groups of organisms produce toxic secondary metabolites like cyanogenic glucosides to defend themselves. A few arthropod families also accumulate cyanogenic glucosides, for example, *Zygaena* larvae that has evolved the ability to either sequester cyanogenic glucosides from *Lotus* plants or, if reared on acyanogenic *Lotus*, to synthesize cyanogenic glucosides de novo.

## 2. Functions

- Cyanogenic glycosides are widely distributed among more than 2,600 different species of pteridophytes, gymnosperms, and angiosperms.
- Cyanogenic glycosides acting as plant defense compounds is one of the most notable functions of cyanogenic glycosides in plants.
- The defense process depends on the activation of cyanogenic glycosides by  $\beta$ -glycosidases to release toxic volatile HCN, as well as a ketone or aldehyde, to fend off herbivores and pathogens (Fig. 24.17).
- In addition to serving as defense compounds, cyanogenic glycosides serve many other functions that afford an advantage at certain developmental stages or following specific environmental challenges.



Fig. 24.22 Metabolon formation in cyanogenic glycoside synthesis. The two cytochrome P450 enzymes (CYP79A1 and CYP71E1) and UDP-glucosyltransferase (UGT85B1) interact to channel intermediates in the biosynthetic pathway directly into formation of dhurrin.



- Subsequent studies in other cyanogenic species involved metabolomics, proteomics, and transcriptomics, genome sequencing, heterologous expression of candidate genes, and natural variation and mutants.
- They have shown the pathway for cyanogenic glycoside biosynthesis in these species also utilizes cytochrome P450 enzymes and UDP- glycosyltransferases and follows the same sequence of transformation of intermediates as identified in sorghum.

- Sequence comparisons, however, indicate that the genes encoding the biosynthetic enzymes in different cyanogenic plant species are not necessarily orthologous (*genes in different species that evolved from a common ancestral gene by speciation*).
- When the genes encoding the pathway for cyanogenic glycoside formation were identified in *L. japonicus*, *S. bicolor*, and cassava (*M. esculentum*), it became apparent that the genes were clustered within all three species (Fig. 24.21).
- This indicates a strong evolutionary mechanism promoting this type of genomic organization. However, the clusters differ substantially in size, gene density, and with respect to the additional genes present.

