Secondary metabolites derived from Shikimic acid (Phenyl propanoids and Lignans)

![Shikimic acid structure](image)

Shikimic acid
Learning Objectives

• Recognize the role of shikimic acid, chorismic acid and prephenic acid in biosynthesis.

• Recognize that cinnamic acid derivatives are precursors to other natural products like lignans and coumarines.
The Shikimic Acid Pathway

This pathway (unique to plants) leads to the formation of the aromatic amino acids phenylalanine and tyrosine and to the formation of many other phenyl-C$_3$ compounds (phenylpropanoids).

Phenylpropanoids
Cleavage of the C3 side chain leads to many phenyl-C1 compounds.

\[ \text{β-Oxidation} \quad \rightarrow \quad \text{Phenyl-C1} \]
Biosynthesis of Shikimic Acid

The shikimate pathway begins with the condensation of PhosphoEnolPyruvate (PEP) and D-erythrose 4-phosphate giving 3-Deoxy-D-Arabino-Heptulosonate-7-Phosphate (DAHP) in a reaction catalysed by the enzyme phospho-2-dehydro-3-deoxyheptonate aldolase (DAHP synthase).
Chorismate is a key intermediate in the synthesis of tryptophan, phenylalanine, and tyrosine.

Aromatic rings are not readily available in the environment, even though the benzene ring is very stable. The branched pathway to tryptophan, phenylalanine, and tyrosine, occurring in bacteria, fungi, and plants, is the main biological route of aromatic ring formation.
Phenylalanine Ammonia Lyase (PAL)

Phenylalanine $\xrightarrow{\text{PAL}}$ Cinnamic acid

Tyrosine Ammonia Lyase (TAL)

Tyrosine $\xrightarrow{TAL}$ $p$-Hydroxycinnamic acid
Coumarins are secondary metabolites with the general formula:

\[
\text{C}_{6}\text{-C}_{3}
\]

Coumarins have a \( \text{C}_{6}\text{-C}_{3} \) skeleton, with an oxygen heterocycle as part of the \( \text{C}_{3} \)-unit.

It has a sweet scent, readily recognized as the scent of newly-mown hay.

Coumarins owe their class name to ‘Coumarou’, the vernacular name of the tonka bean (\textit{Dipteryx odorata Willd.}, Fabaceae), from which coumarin itself was isolated in 1820.
Examples of Coumarins

- Umbeliferone
- Aesculetin
- Herniarin
- Psoralen
- Imperatorin
Biosynthesis of Coumarins

Cinnamic acid

\[ \text{Cinnamic acid} \xrightarrow{\text{NADPH, } \text{O}_2} \text{o-Coumaric acid} \]

\[ \xrightarrow{2 \text{ NADPH, } \text{O}_2} \text{Coumarin} \]

\[ \xrightarrow{\text{Lactone formation}} \text{Umbelliferone} \]
Lignans are a large group of natural products characterized by the coupling of two $\text{C}_6\text{C}_3$ units.

Lignans are a class of naturally occurring plant phenols that are derived biosynthetically from dimerization of cinnamic acid.
Biosynthesis of Lignans

Cinnamic acid

\[ \text{NADPH} \rightarrow \text{O}_2 \rightarrow \text{SAM} \]

Conniferyl alcohol
Radical pairing $A + D; B + D; D + D$, etc yield different types of lignans.
Dimerization
Secondary metabolites derived from mixed biosynthetic origin (The flavonoids).
The flavonoids comprise a large group of secondary metabolites which are derived from sub-units supplied by the acetate and shikimate pathways.

They occur almost exclusively in higher plants and are responsible for much of the flavor of food and drink of plant origin and for the colors of flowers.
In plants, flavonoids are involved in such diverse processes such as UV protection, pigmentation, stimulation of nitrogen-fixing nodules and disease resistance.

The term “flavonoid” is generally used to describe a broad collection of natural products that has a $\text{C}_6\text{-C}_3\text{-C}_6$ (two benzene rings joined by three carbons) carbon framework.
From Polykeide pathway

From shikimic acid pathway
Chalcones

- Chalcone
- Dihydrochalcone
- Retro-Chalcone

Flavonoids

- Flavan
- Flavanone
- Flavone
Isoflavonoids

Isoflavan

Isoflav-3-ene

Isoflavanone

Isoflavone

Pterocarpan

Rotenoid
Naming of flavonoids

IUPAC NAME
(S)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one

SEMISYSTEMATIC NAME
4’,5,7-Trihydroxyflavanone
IUPAC Name
7-Hydroxy-3-(4-hydroxyphenyl)-6-methoxy-4H-chromen-4-one

Semisystematic Name
4',7-Dihydroxy-6-methoxyisoflavone
IUPAC Name

9-Methoxy-8-(3-methylbut-2-enyl)-6a,11a-dihydro-6H-benzofuro[3,2-c][1,3]dioxolo[4,5-g]chromene

Semisystematic Name

9-Methoxy-2,3-methylenedioxy-8-prenylpterocarpan
Flavonoids are synthesized by extension of \textit{p}-hydroxycoumaroyl CoA with three molecules of malonyl CoA in linear manner in order to form a tetraketide intermediate.

This step is catalyzed by the enzyme CHalcone Synthase (CHS).
$p$-Hydroxycoumaroyl CoA

\[ \text{3-SCoA} \]

Tetraketide intermediate
The intermediate then folds and condenses further to give a chalcone. This reaction is the first committed step in flavonoid biosynthesis and is also catalyzed by chalcone synthase (CHS).
Leguminosae + other plant families.

Narigenin-chalcone

Chalcone

Isoliquiritigenin

Leguminosae

NADPH, -H₂O

CHS

SCoA
CHalcone Isomerase (CHI) is the second enzyme involved in the biosynthesis of flavonoids and it catalyzes the stereospecific intramolecular cyclization of the chalcones isoliquiritigenin and naringeninichalcone into the flavanones (2S)-liquiritigenin and (2S)-narigenin, respectively.
Flavanone

Narigeninchalcone → Isoliquiritigenin

(2S)-Naringenin → (2S)-Liquiritigenin
These flavanones are the precursors for the construction of 5-deoxyflavonoid and 5-hydroxyflavonoid skeletons.

\[
\text{NADPH, O}_2 \quad \text{-H}_2\text{O} \quad \text{Flavone synthase (FNS)}
\]

(2S) -Naringenin

(2S) -Liquiritigenin

Flavone
1,2-aryl migration

Isoflavone

Naringenin

H₂O

Genistein

O₂

NADPH
Pterocarpan
Biosynthesis of Rotenoids

Demethylmunduserone

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Anthocyanin
Flower Pigments
Anthocyanin Leaf Pigments

Autumn Leaves

In Spring and Summer chlorophyll (green) masks the anthocyanin colors.
Anthocyanidins and Anthocyanins

Naringenin (R=H)

Anthocyanins are red, violet or blue Pigments, have sugar at C-3.

pelargonidin (R=H)
cyanidin (R=OH)
cyanidin is blue pelargonidin is pink

Anthocyanidins plant flower and leaf pigments

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Sun flower (Compositae)
Anthocyanin
Knifofia

ANTHRAQUINONES
Biosynthesis of Alkaloids

What are Alkaloids?

‘any non-peptidic & non-nucleotide nitrogenous secondary metabolite’
Alkaloids have one or more nitrogen, typically as primary, secondary, or tertiary amines, and this usually confers basicity to the alkaloid, facilitating their isolation and purification since water-soluble salts can be formed in the presence of mineral acids. There also alkaloids which are neutral.

The name alkaloid is in fact derived from alkali.
The nitrogen atoms in alkaloids originate from an amino acid, and, in general, the carbon skeleton of the particular amino acid precursor is largely retained intact in the alkaloid structure, though the carboxylic acid carbon is often lost through decarboxylation.
The most common amino acids from which alkaloids are derived from are:

I) Ornithine

\[
\text{ornithine} \quad \text{H}_2\text{N} - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CH}_2\text{NH}_2
\]

II) Lysine

\[
\text{lysine} \quad \text{H}_2\text{N} - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CH}_2\text{NH}_2
\]

III) Tryptophan

\[
\text{tryptophan} \quad \text{N} - \text{CH} = \text{CH} - \text{CH} = \text{CH} - \text{CH}_2\text{NH}_2
\]
IV) Tyrosine

H₂N
\[
\text{tyrosine}
\]

V) Phenylalanine

\[
\text{phenylalanine}
\]

VI) Nicotinic acid

\[
\text{nicotinic acid}
\]
Decarboxylation

\[
\text{Decarboxylases} \rightarrow \text{Pyridoxal phosphate (PLP)} \rightarrow \text{Pyridoxal phosphate}
\]

\[
\text{NH}_2 \quad \text{O} \quad \text{H} \quad \text{O} \\
\text{R} \quad \text{R} \\
\alpha\text{-amino acid} \quad \text{NH}_2 + \text{O} = \text{C} = \text{O}
\]
Ornithine contains both δ- and α- amino groups, and it is the nitrogen from the former group which is incorporated into alkaloid structures along with the carbon chain, except for the carboxyl group.
Tropinone

\[
\text{NADPH} \rightarrow \text{CoAS} \rightarrow \text{OH}
\]

\[
\text{N} \quad \text{O} \quad \text{N} \quad \text{O}
\]

\[
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\]
ALKALOIDS DERIVED FROM TRYPTOPHAN

Tryptophan

\[ \text{PLP} \rightarrow \text{Tryptamine} \]

\[ 2 \text{SAM} \rightarrow \text{Psilocin} \]
Tryptamine $\rightarrow$ Secoganin $\rightarrow$ Strictosidine
ALKALOIDS DERIVED FROM TYROSINE

L-tyrosine

Transamination

Decarboxylation

Decarboxylation

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Reticuline (HO NMe MeO)

Bulbocapnine

Boldine (MeO NMe 'H)

Reticuline (MeO NMe 'H)

Salutaridine (O Me)

Oxidative coupling

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ALKALOIDS DERIVED FROM PHENYLALANALINE

phenylalanine
phenylalanine

- NH₃

HSCoA

β-Oxidation

Pyruvate

Khat = MIRAA

(-)-ephedrine

SAM

NADPH

(-)-cathinone

NADPH

(-)-norpseudoephedrine

(+)-pseudoephedrine

(+)-pseudoephedrine

Methamphetamine
Khat (Catha edulis, family Celastraceae; Arabic: قات; Somali: Jaad; pronounced [ˈkæt]; Ge'ez ምት čāt; miraa in Kiswahili), is a flowering plant native to tropical East Africa and the Arabian Peninsula.

Khat contains the alkaloid called cathinone, an amphetamine-like stimulant which causes excitement, loss of appetite, and euphoria. In 1980 the World Health Organization classified khat as a drug of abuse that can produce mild to moderate psychological dependence.
ALKALOIDS DERIVED FROM NICOTINIC ACID

nicotinic acid
Nicotinic acid

\[ \text{NADPH} \quad \text{Nicotinic acid} \quad \rightarrow \quad \text{Dihydronicotinic acid} \]

\[ \text{Me} \quad \text{From L-orinthine} \]

\[ \text{Nicotine} \]

From L-orinthine

\[ \text{NADP}^+ \]
Nicotinic acid → From L-lysine

Anabasine

NADP^+
Nicotinic acid $\rightarrow$ 1,2-Dihydropyridine $\xrightarrow{\text{Enamine-Imine tautomerization}}$ 1,4-Dihydropyridine

Nicotinic acid $\rightarrow$ Anatabine