The sequence of enzymatic steps in the synthesis of a specific end product in a living organism is called **Biosynthesis**, whereas production or generation of living organisms from other living organisms is called **Biogenesis**. Organisms vary widely in their capacity to synthesize and transform chemicals.

The pathways for general modifying and synthesizing carbohydrates, proteins, fats, and nucleic acids are found to be **essentially the same** in all organisms, apart from minor variations. These processes are collectively described as **primary metabolism**, with the compounds involved in the pathways being termed primary metabolites.

**Primary metabolites** are compounds that are commonly produced by all plants and that are directly used in plant growth and development. The main primary metabolites are carbohydrates, proteins, nucleic acids, and lipids.
Secondary Metabolism

- The products of **secondary metabolism** are substances often present only in a few specialized/differentiated cell types, and are not necessary for the cells themselves, but they are useful to the body as a whole.

The secondary metabolites are grouped into classes based on similar structures, biosynthetic pathways, or types of plants that produce them. The largest such classes are the **terpenoids**, **phenolics**, and **alkaloids**. Secondary compounds often occur in combination with one or more sugars. These combination molecules are known as glycosides. Usually the sugar is glucose, galactose or rhamnose.
Plant Secondary Metabolites

- Plants make a variety of less widely distributed compounds such as morphine, caffeine, nicotine, menthol, and rubber. These compounds are the products of secondary metabolism, which is the metabolism of chemicals that occurs irregularly or rarely among plants, and that have no known general metabolic role.
- Secondary metabolites or secondary compounds are compounds that are not required for normal growth and development, and are not made through metabolic pathways common to all plants.
- Most plants have not been examined for secondary compounds and new compounds are discovered almost daily.
Functions of Secondary Compounds in Plants

• The most common roles for secondary compounds in plants are ecological roles that govern interactions between plants and other organisms.
• Many secondary compounds are brightly colored pigments like anthocyanin that color flowers red and blue. These attract pollinators and fruit and seed dispersers.
• Nicotine and other toxic compounds may protect the plant from herbivores and microbes.
• Other secondary compounds like rubber and tetrahydrocannabinil (THC) from cannabis plants have no well known function in plants.

![Nicotine molecule](image)

![THC molecule](image)
Micotoxin from Mold and Fungi

- **Aflatoxin** is a naturally occurring mycotoxin produced by two types of mold: *Aspergillus flavus* and *A. parasiticus*, plus related species, *A. nomius* and *A. niger*. *A. flavus* is common and widespread in nature and is most often found when certain grains are grown under stressful conditions such as drought. At least 13 different types of aflatoxins are produced in nature with aflatoxin B1 considered as the most liver toxic. *(cause cancer in animals!)*

- Aflatoxins mainly occur in contaminated crops like corn, peanuts, and other seed. Occasionally can be found in milk, cheese and milk products through contaminated animal feed. Other nuts, figs and spices can be contamated.
Functions of Secondary Metabolites in Plants

DEFENSE
- Herbivores
- Fungi
- Bacteria
- Virus
- Plants

ATTRACTION AND STIMULATION
- Pollination
- Dissemination
- Deposition
- Food-Plant Storage
- Pharmacology
- Symbiosis
- N\textsubscript{2} fixation
- Mycorrhizae

PROTECTION FROM PHYSICAL EFFECTS
- Light UV
- Evaporation
- Cold
Interest in Secondary Metabolites

- Aroma substances
- Dyes
- Pharmacological and nutraceutical substances

**BIODIVERSITY**

More than 275,000 known species of angiosperms

> 100,000 known compounds.

UN Conference on Environment in Rio de Janeiro, 1992

Convention on Biological Diversity

**Sustainable use** of components of biological diversity in ways and at times that do not lead to the depletion of biodiversity
PROTECTION

• **Plant strategies:**
  - Induction of defense molecules in response to attack by herbivores or pathogens (*phytoalexins*)
  - *Pro-toxins harmless* activated by an enzyme triggered as a result of an attack
  - Buildup of constitutive defense products
  - Production of *food substances deterents* (tannins; toxic subst.)
  - production of *substances that mimic animal hormones* (plant sterols produced by mimicking the hormone of the set)
  - production of *compounds that attract predators* of the herbivores
Examples of Defense Metabolites

Saponins

Produced in rots of oat (defense from fungi).

Glucosinolates

Preformed glucosinolates

Myrosinase

Wounding increases myrosinase activity

Unstable aglycone intermediate

Various bioactive toxic compounds released
Examples of Defense Metabolites: Cyanogenic Glycosides

Amigdaline

Prunasine

Mandelonitrile

1. Gluc-Gluc
2. Gluc
3. HO
4. CHO
5. HCN

Cyanide group

two glucose molecules

Amigdaline
ALLELOPATHY
mutual influence between plants through the secretion of specific substances.

Tomato plants evidence diseases and die if grown up near a walnut tree (*Juglans nigra*). The toxicity area is defined by the tree canopy size.

*a* glycosylated molecule that, when hydrolyzed and oxidized, in soil becomes a potent toxin.

![Chemical structure of juglone](image)
Secondary Metabolites - Three Main Groups:

- Terpenes
- Phenolic Compounds
- Alkaloids

They are synthesized from primary metabolites.
Main Pathways to Secondary Metabolites

chlorophyll + CO₂ + H₂O + light

Respiration

Photosynthesis

polysaccharides

monosaccharides

O₂

O₂

mevalonic acid

acetate acid (acetil CoA)

pyruvic acid

acetic acid

malonic acid

polyketides

3,3-dimethylallyl pyrophosphate

terpenoids

shikimic acid

prephenic acid

peptides

aliphatic amino acids

aromatic amino acids

phenolics

cinnamic acids

coumarins

aliphatic amino acids

aromatic amino acids

peptides

alkaloids

fatty acids, fats

polyketides
Main Metabolic Pathways to Secondary Metabolites

chlorophyll + CO₂ + H₂O + light

- carbohydrates
- pentose’s cycle
- phosphoenolpyruvic acid

shikimic acid

- aromatic amino acids
- cinnamic acids

alkaloids

- Acetyl Coenzyme A
- Malonyl Coenzyme A
- Mevalonic acid

phenylpropanoids

- flavonoids
- phenolic compounds
terpénoids
- carotenoids
- steroids
General View of Plant Metabolism

**PRIMARY CARBON METABOLISM**

- CO₂ Photosynthesis
- Erythrose-4-phosphate
- Phosphoenolpyruvate
- Pyruvate
- Acetyl CoA
- Tricarboxylic acid cycle

**SECONDARY CARBON METABOLISM**

- Phosphoenolpyruvate (3-PGA)
- Aliphatic amino acids
- Shikimic acid pathway
- Malonic acid pathway
- Mevalonic acid pathway
- MEP pathway
- Aromatic amino acids
- Nitrogen-containing secondary products
- Phenolic compounds
- Terpenes
TERPENES

- 30,000 known compounds

Wallach (1910) **Isoprene rule**

Terpenes can be hypothetically build from repetitive 5-units of isoprene molecules

Firstly isolated from turpentine
Recognition of the isoprene unit as a component of the structure of terpenes has been a great aid in elucidating their structures.

Many terpenes also have isoprene units linked in rings, and others (terpenoids) contain oxygen.
Over 40,000 compounds derived from isopentenyl pyrophosphate (IPP) have been characterized.*

In mammals, these include: cholesterol, bile acids, steroid hormones, dolichol, coenzyme Q, and prenylated proteins. In plants, the isoprenoid pathway generates a wide variety of compounds including rubber, isoprene gas, carotenoids and some vitamins.

---

*Sacchettini, James C.; Poulter, C. Dale 1997 Creating Isoprenoid Diversity. Science 277(5333) 1788-1789
Mevalonic Acid as Source of IPP

The biological precursor of all terpenes is the isopentenyl diphosphate (IPP) synthesized or from MEVALONIC ACID (cytosol ER) or from glyceraldehyde phosphate / pyruvate (plastids)

3,5-dihydroxy-3-methylpentanoic acid

3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGR)

HMG-CoA REDUCTASE

IN ANIMALS RULES THE CHOLESTEROL BIOSYNTHESIS

IN PLANTS IS INDUCIBLE BY PATHOGENS
Pyruvic Acid as Source of IPP

1. Acetyl-CoA + H₂O → Acetoacetyl-CoA + ATP
2. Thiolase: HMG-CoA synthase
3. HMG-CoA reductase
4. MVAP chinase
5. MVAPP decarboxylase
6. Isopentenyl diphosphate (IPP)
**Biosynthetic Pathways to Terpenes**

**Mevalonate Pathways**
- **ER cyt**
  - 3×Acetyl-CoA → Glyceraldehyde 3-phosphate → Mevalonic acid → Mevalonate pathways
  - Isopentenyl diphosphate → Dimethylallyl diphosphate → Isoprene

**Plastids**
- Pyruvate → Methylerythritol phosphate pathways
  - Produce geranyl pyrophosphate (GPP; C10), farnesyl pyrophosphate (FPP; C15), geranylgeranyl pyrophosphate (GGPP; C20)

**Prenyl Transferase**
- Determine the chain extension: produce geranyl pyrophosphate (GPP; C10), farnesyl pyrophosphate (FPP; C15), geranylgeranyl pyrophosphate (GGPP; C20)

**Terpene Synthases**
- Modify the products of prenyl transferase (cyclizations) producing a great variety of terpenes. (monoterpene synthase, sesquiterpene synthase, diterpene synthase)

**Terpenes**
- Monoterpens → Sesquiterpenes → Triiterpenes
- Diterpenes → Tetraterpenes
- Polyterpenoids
TERPENES SYNTHESIS FROM IPP BASIC UNIT

C<sub>5</sub> \[ \text{Isopentenyl diphosphate} \] \[ \text{IPP Isomerase} \] \[ \text{Dimethylallyl diphosphate} \] \[ \rightarrow \text{Hemiterpenes} \]

C<sub>10</sub> \[ \text{Geranyl diphosphate} \] \( \rightarrow \text{Monoterpines} \)

C<sub>15</sub> \[ \text{Farnesyl diphosphate} \] \( \rightarrow \text{Sesquiterpenes} \)

C<sub>20</sub> \[ \text{Geranylgeranyl diphosphate} \] \( \rightarrow \text{Diterpenes} \)

C<sub>30</sub> \[ \text{Squalene} \] \( \rightarrow \text{Triterpenes} \)

C<sub>40</sub> \[ \text{Phytoene} \] \( \rightarrow \text{Tetraterpenes} \)
Sites of Production of Terpenes

Monoterpenes $C_{10}$
Diterpenes $C_{20}$
Tetraterpenes $C_{40}$

Sesquiterpenes $C_{15}$
Triterpenes $C_{30}$

Glandular trichomes

present on the leaf surface, they accumulate and secrete terpenes
(mint, thyme, lemon)
Monoterpenes

- Myrcene
- Limonene
- Nerol
- Geraniol
- Citral
- Citronellal
- \(\alpha\)-Pinene
- Menthol
- Canphor
- (R)-Carvone; Spearmint aroma

Volatile substances
- Pollinator attraction
- Insect repellent

DMAPP + IPP → GPP

- Deterrent food for herbivores - allelopathy
• LIMONENE SYNTHASE

Catalyzes the simplest of cyclization reactions of terpenoids and serves as model for this type of reactions

\[
\text{Geranyl pyrophosphate} \rightarrow \text{(-)-Limonene}
\]

\[
\text{(3S)-Linalyl pyrophosphate (trans)} \rightarrow \alpha\text{-Terpinyl cation}
\]

\[
\text{(3S)-Linalyl pyrophosphate (cis)} \rightarrow \alpha\text{-Terpinyl cation}
\]
Pinenes are among the most common monoterpenes and are the main components of turpentine produced from pine and fir trees: they are toxic to fungi and insects.

- **Limonene**
  - ![Limonene structure](image)
  - Formula: $\text{CH}_3\text{CH}=	ext{CHCH}_2\text{H}_3\text{C}$

- **Menthol**
  - ![Menthol structure](image)
  - Formula: $\text{CH}_3\text{C}=\text{O}\text{H}$

*Image of beetles attacking a pine stem*
Monoterpene

**Insecticides:** pinenes, piretrins

**Attraction of pollinators:** Linalool, cineole

**Leaves deterrents:** camphor, cineole
Attilio Citterio

SESQUITERPENES C15

GPP + IPP → FPP
Farnesyl-PP

Farnesyl-pyrophosphate

Sesquiterpenes

- Farnesol
- Bisabolene
- Cadinene
- Selinene
- Vetivone
- Patchoulool (Partum)
- Abscisic acid (Phytohormon)

sesquiterpene lactones (chicory, artichoke, endive, etc.) deterrents food (bitter taste) used to flavor bitters.

→ Helenalin from ARNICA

used as anti-inflammatory
Sesquiterpene Synthases Produce Several Phytoalexins

Capsidiol phytoalexin

Tobacco phytoalexin

epi-Aristolochene synthase

δ-Cadinene synthase

Vetispiradiene synthase

δ-Cadinene

Vetispiradiene

Gossypol (sesquiterpene dimer)

Lubimine

Potato phytoalexin
DITERPENES C20

\[
\text{FPP + IPP} \rightarrow \text{GGPP} \\
\text{Geranylgeranyl-PP}
\]

Diterpenes

- Casbene (Phytoalexin)
- Giberellic acid (Phytoalexin)
- Abietic acid (amber)

- Taxol (anti-cancer)
Diterpene Synthases

- 2 different cyclization mechanisms

![Diagram of diterpene synthases]

Abietic Acid: conifer resin

Labdadienyl (copalyl) diphosphate

Abietadiene synthase

Phytoalexin of castor oil

Abietadiene synthase

Casbene synthase

Taxadiene synthase

Phytoalexin of castor oil

Taxol precursor

Abdetaiene
TRITERPENES C30

**FPP + FPP → SQUALENE**

Head to head linkage

squalene

sitosterol

Saponins
glycosylated toxic substances produced by the roots and stems of many species
All arise from squalene, generate growth regulators (brassinosteroids) and compounds of surface waxes.

SQUALENE

Oxidosqualene

Cycloartenol

Brassinolide

β-Amyrin

Oleanolic acid

Found in fruit waxes
Limonoids: Triterpenes responsible of bitter taste in lemons; deterents for herbivores;

**azadiractina** powerful deterrent to insects, low toxicity for mammals: insecticide sold in Africa and Asia.

isolated from ferns: plant steroids hormone-like suit of insects when ingested by insects interfere with the molting process.
Products formed by condensation head to head of two GGP molecules to form the phytoene

Phytoene synthase: mechanism similar to the one of squalene synthase

**PHYTOENE:**
- Desaturations
- Cyclizations

CAROTENOIDS
The carotenes are tetraterpenes. They can be thought of as two diterpenes linked in tail-to-tail fashion. The carotenes all can be converted to vitamin A by enzymes in the liver.
Subsequent Modifications

- Modifications of the base skeletons, as oxidation, reduction, isomerization, conjugation, produce thousands of different terpenoids with a variety of biological activities in plants and animals.

Example:
- Components of mint essential oil derived from modifications of limonene

Pennyroyal

Peppermint
Reactions similar to those responsible for the production of essential oils generate thousands of compounds of biological and pharmaceutical interest.
The isoprene units of natural rubber are all linked in a head-to-tail fashion and all of the bonds are \textit{cis}.

Pure rubber is soft and tacky, so it must be vulcanized by heating with sulphur. A reaction takes place that produces cross-links between the cis-polyisoprene chains and makes the rubber much harder.
Steroids are important “biological regulators” that nearly always show dramatic physiological effects when they are administered to living organisms.

**STRUCTURE AND SYSTEMATIC NOMENCLATURE**

- Steroids are derivatives of the perhydrocyclopentanophenanthenrene ring system
In most steroids the B, C and C, D ring junctions are *trans*. The A, B ring junction may be either *cis* or *trans*.

Angular methyl groups: The methyl groups that are attached at points of ring junction

β substituents: other groups that lie on the same general side of the molecule as the angular methyl groups.

α substituents: groups that lie on the bottom.
When $\alpha$ and $\beta$ designation are applied to the hydrogen atom at position 5, the ring system in which the A, B ring junction is *trans* become the $5\alpha$ series; if the junction is *cis* becomes the $5\beta$ series. In systematic nomenclature, the R group at position 17 determines the base name of an individual steroid.
Cholesterol can be isolated by extraction of nearly all animal tissues. Part of the difficulty in assigning an absolute structure to cholesterol is that cholesterol contains eight tetrahedral. For example:

Cholesterol is known to serve as an intermediate in the biosynthesis of all of the steroids of the body.
The sex hormones can be classified into three major groups:

1. The female sex hormones, or estrogens.
2. The male sex hormones, or androgens.
3. The pregnancy hormones, or progestins.

- The first sex hormone to be isolated was an estrogen, estrone.

\[\text{Estradiol} \quad \text{Estrone}\]
Examples of the Second Sex Hormones

Testosterone and estradiol are the chemical compounds from which “maleness” and “femaleness” are derived. They differ slightly in their structure. Progesterone and norethindrone are important progestins.
At least 28 different hormones have isolated from the adrenal cortex. Included in this group are the following two steroids:

Most of adrenocortical steroids have an oxygen at position 11. Cortisol is the major hormone synthesized by the human adrenal cortex.
Vitamin D2 can be produced by photochemical reaction in which the dienoid ring B of ergosterol opens to produce a conjugated triene.
Other Structures

- Digitoxigenin is a cardiac aglycone that can be isolated by hydrolysis of digitalis.
- Cholic acid is the most abundant acid obtained from the hydrolysis of human or ox-bile.
Vegetable Steroids

Stigmasterol is a widely occurring plant steroid that is obtained commercially from soybean oil.

Diosgenin is obtained from a Mexican vine, *cabeza de negro*, Genus *Dioscorea*. It is used as the starting material for a commercial synthesis of cortisone and sex hormones.
The stereochemistry of steroid reactions is often quite complex. It is strongly influenced by the steric hindrance presented at the β face of the molecular methyl groups. So, when the epoxide ring of 5α,6α-Epoxycholestan-3β-ol is opened, attack by chloride ion must occur from the β face, but it takes place at the more open 6 position.

\[
\begin{align*}
\text{5α,6α -Epoxycholestan-3β -ol} & \xrightarrow{\text{HCl}} \text{5α,6α -Epoxycholestan-3β -ol} + \text{Cl}^- \\
\end{align*}
\]

The relative openness of equatorial groups also influences the stereochemical course of steroid reactions.
But many reagents react preferentially relatively at the α face.

\[
\begin{align*}
\text{Cholesterol} & \quad \xrightarrow{\text{H}_2, \text{Pt}} \quad \text{5}_\alpha\text{-Cholestan-3}_\beta\text{-ol (85-95%)} \\
\text{5}_\alpha,6_\alpha\text{-Epoxycholestan-3}_\beta\text{-ol (only product)} & \quad \xrightarrow{\text{C}_6\text{H}_5\text{COOOH}} \\
\text{5}_\alpha\text{-Cholestane-3}_\beta,6_\alpha\text{-diol (78%)} & \quad \xrightarrow{1) \text{THF}:\text{BF}_3, 2) \text{H}_2\text{O}_2, \text{OH}^-}
\end{align*}
\]
Prostaglandins are C20-carboxylic acids that contain a five-membered ring, at least one double bond, and several oxygen-containing functional groups. Two of the active prostaglandins are prostaglandin E2 and prostaglandin F1α.

The biosynthesis of prostaglandins of the 2 series begins with a C20 polyenoic acid, arachidonic acid.
• Plant colonization of terrestrial environments: the need for mechanical support and waterproofing

Structural and adaptive role
Functions of Phenolic Compounds

- defense against herbivores and pathogens
- mechanical support (lignin)
- pollinator attraction
- absorption of harmful UV radiation
- allelopathic substances
MOST OF PHENOLIC COMPOUNDS RESULT FROM 2 PATHWAYS:

1) FROM PHENYLPROPANOID \( \text{C}_6\text{C}_3 \)

OR

2. FROM PHENYLPROPANOID – ACETATE \( \text{C}_6\text{C}_3\text{-C}_3 \)

(derivatives of benzoic acids \( \text{C}_6\text{C}_1 \) are also phenolic compounds)
Structural Units of Phenolic Compounds

Phenylpropanoid Skeleton ($C_6C_3$)

Phenylpropanoid-acetate skeleton ($C_6C_3-C_6$), with phenylpropanoid-derived ($C_6C_3$) and acetate-derived ($3 \times C_2$) rings

Caniferyl alcohol, a component of lignin and many lignans

Quercetin, a flavonoid ($C_6C_3-C_6$)

Phenylpropanoid skeleton

Acetate-derived rings
Metabolism of Phenolic Compounds

Erythrose 4-P (from pentose phosphates pathway)

Phosphoenolpyruvate (from glycolysis)

Shikimic Acid

Phenylalanine

Cinnamic Acid

Gallic Acid

Simple phenolic compounds

Hydrolysable Tannins

Acetyl-CoA

Malonyl-CoA

Lignin

Condensed Tannins
**Structural Units of Lignin**

**Phenylalanine ammonia lyase (pal)**

**LIGNIN** is formed from 3 different phenylpropanoid alcohols: coniferyl, coumaryl and sinapyl. These are formed from phenylalanine via different derivatives.

![Chemical diagrams and reactions](diagram.png)

- Coniferyl alcohol
- Sinapyl alcohol
Enzymatic Catalysis in the Biosynthesis of Phenolic Compounds

The biochemical pathways that lead to the biosynthesis of various classes of phenolic compounds have many characteristics in common.

**PAL enzyme:**
Phenylalanine ammonia lyase is the key enzyme in the synthesis of phenolic compounds.

[Chemical diagram of the biosynthesis pathway of phenolic compounds]
Antocyanins and Flavonoids

Chalcone synthase

Chalcones

Flavanones

Dihydroflavonols

Anthocyanins, Condensed tannins

Flavones

Isoflavones

Flavonols
Typical Isoflavones

Daidzein

Genistein

Glycitein
Benzoic Acid Derivatives $\text{C6C1}$

(C)

Vanillin

Salicylic acid

Benzoic acid derivatives $[\text{C}_6\text{C}_1]$
Simple Phenolic Compounds C6C3

(A) Simple phenylpropanoids

Caffeic acid

Ferulic acid

(B) Coumarins

Umbelliferone, a simple coumarin

Psoralen, a furanocoumarin
Flavonoids  C6C3-C6

From shikimic acid pathway via phenylalanine

\[
\begin{array}{c}
\text{C}_6 - \text{C}_3 \\
\end{array}
\]

From malonic acid pathway

\[
\begin{array}{c}
\text{C}_6 \\
\end{array}
\]

The three-carbon bridge

Basic flavonoid skeleton
The Complex Tree of Flavonoids
Hydrolysable tannins
(leather water proofing)

Condensed tannins

Flavonoids

Mimosa

Pines

+ formaldehyde = adhesives
High Levels of Polyphenols and Antioxidants Include Fruits and Vegetables

- Green tea: catechin
- Wine: resveratrol
- Apple & onion: quercetin
- Bean: isoflavon
- Fruits: flavonoids
- Black tea: polyphenols
Tannins

- Not carbohydrate – do not contain sugar

- Polyphenolic compounds of different nature
  1. Hydrolysable tannins
     Residues of gallic acid that are linked to glucose via glycosidic bonds
  2. Condensed tannins (non hydrolyzable)
     Biphenyl condensates of phenols

- Anti-nutrient effects
  - Combine with proteins, cellulose, hemicellulose, pectin and minerals
  - Can inhibit microorganisms and enzymes

- In plants
  - Most domesticated plants have been selectively bred for low concentrations of tannins – bird resistant milo exception
  - Many warm season legumes and browse contain tannins
  - Colored seed coats indicative of tannins - Acorns
Biomass as Alternative Source of Phenols

- Phenols are present in nature in plants and in ferns whereas they are nearly absent in animals.

- Phenols are characteristic and specific to each type of biomass.

- $3 - 8\%$ by weight of biomass
Alkaloids generally include alkaline substances that have nitrogen as part of the structure and originate from amino acids. More than 20,000 alkaloids are known and are the largest and differentiated class of secondary compounds. They are very common in certain plant families, especially:

- *Fabaceae* – peas and beans
- *Asteraceae* - sunflowers
- *Papaveraceae* - poppies
- *Solanaceae* – nightshade, tomato
- *Apocynaceae* - dogbanes
- *Asclepiadaceae* - milkweeds
- *Rutaceae* – citrus

Non-peptidic, non-nucleosidic nitrogen containing compounds, basis of 25% of drugs on the market.
ALKALOIDS: Overview

- Most commonly isolated from plants but known in most other orders of organisms from fungi to mammals
- Selected alkaloids have been used as
  - Poisons (hunting, murder, euthanasia)
  - Euphoriants, psychedelics, and stimulants (morphine, cocaine)
  - Medicines (ephedrine)
- Many of our modern drugs contain alkaloids or synthetic analogs
- Originally defined as nitrogenous compounds from plants of complex molecular structure and significant pharmacological activity.
- More recently defined as cyclic, nitrogen containing compounds which are true secondary metabolites
- Most compounds in this class derive part of their structure from amino acids or their derivatives.
- Being basic, they form salts in acidic medium.
Biological Properties of Alkaloids

- Alkaloids can act as poisons
  - Coniine
  - Hemlock

- Alkaloids can act as stimulants
  - Caffeine
  - Coffee and tea

- Alkaloids can act as hallucinogens
  - Mescaline
  - Peyote cactus

- Alkaloids can act as medicines
  - Quinine
  - Anti-malaria
Basicity of Alkaloids

- As the name implies alkaloids are basic in nature \((pK_a > 7)\)*
- Medicinally important alkaloids are usually administered as the ammonium salts

\[
\begin{align*}
\text{Cocaine} & \quad \text{smokable} \\
\text{Cocaine hydrochloride} & \quad \text{not smokable but water soluble (i.e. snortable)}
\end{align*}
\]

- The hydrochloride salt is what is sold as “Coke”
- Basification of the hydrochloride leads to the “Free Base” which is known as “Crack”

*Warhurst et al. Malaria Journal 2003 2, 26.*
Functions of Alkaloids in Plants

- They may act as **protective** against insects and herbivores due to their bitterness and toxicity.
- They are, in certain cases, the final **products of detoxification** (waste products).
- **Source of nitrogen** in case of nitrogen deficiency.
- They, sometimes, act as **growth regulators** in certain metabolic systems.
- They may be utilized as a **source of energy** in case of deficiency in carbon dioxide assimilation.
Classification of Alkaloids

Hagnauer system of classification:

- **True alkaloids** (nitrogen in a heterocyclic ring. e.g. Atropine).
- **Proto alkaloids** (amphetamine, aconitine, ..., no heterocyclic ring)
- **Pseudo alkaloids** (caffeine, theobromine, ... not from amino acids)

- **Other classifications:**
  - **Biogenetic.**
    - Based on the biogenetic pathway that form the alkaloids.
  - **Botanical Source.**
    - According to the plant source of alkaloids.
  - **Type of Amines.**
    - Primary, Secondary, Tertiary alkaloids.
  - **Basic Chemical Skeleton**
Classification by Basic Chemical Skeleton

- Main structural motif in true alkaloids:
  - Tropane alkaloids
  - Quinoline alkaloids
  - Pyridine, piperidine alkaloids
  - Imidazole alkaloids
  - Indole alkaloids
  - Isoquinoline alkaloids

Starting amino acid
- ornithine
- tryptophan
- [pyridine]
- lysine
- tyrosine
Classification of Alkaloids. Alkaloids from Ornithine and Lysine

- Classified according to amino acid from which they were formed

- Biosynthesis through symmetrical diamines

- Alkaloids: generally aliphatic in nature
Examples of Alkaloids from Ornithine and Lysine

- Two examples of these alkaloids are:

Nicotine
ex ornithine

Tobacco alkaloids

Piperidine alkaloids

N-Methylpelletierine
ex lysine
Alkaloids from Phenylalanine and Tyrosine

- All these alkaloids possess Ar-C-C-N moiety
- Intermediates in biosynthesis:

Esempi:

Morphine ex tyrosine
Papaver somniferum L.

Mescaline

Dopamine
Alkaloids from Tryptophan

- Alkaloids derived from Tryptophan have tryptamine as intermediate:

- Two examples of these alkaloids are:
Psychoactive Alkaloids

• Lysergic acid (precursor of *ergot alkaloids*) is an indole alkaloid isolated from a growth on rye called *Claviceps Purpurea*.

• Cocaine is an alkaloid of tropane structure found in leaves of the South American shrub *Erythroxylon coca*.
Other Examples of Alkaloids

- The nerve toxin physostigmine (indole alkaloid) is isolated from the “bean of Calabar” *Physostigma venenosum*

![Phyostigmine](image)

- Cincona alkaloids (quinoline derivatives) are isolated from dried barks of *Cinchona succirubra* (Rubeaceae).

![Cincha alkaloids](image)
Biosynthesis of Alkaloids: The “Reagents”

- Aldehydes and Amines are the common intermediates from amino acids

![Chemical structures of various amino acids and their derivatives]
Other Biosynthetic Building Blocks

- Precise biosynthetic pathways: frequently not known
- Most use a small number of building blocks
- Amino acids (see previous) and:

Biosynthetic Transformations

Major enzyme catalysed reactions:

1) Decarboxylations
2) Transaminations
3) Methylations
4) Oxidations/Reductions
5) Carbon-carbon bond formation

Many, many other enzyme catalysed these reactions.
Pharmacological Activity

1. Analgesics and narcotics: morphine and codeine.
2. CNS stimulants: caffeine and strychnine.
3. Anticancer: vincristine, vinblastine and taxol.
5. Anti-asthmatics: ephedrine.
6. Anti-tissue: codeine.
10. Skeletal muscle relaxants: δ-tubocurarine.