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College of Science
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Plant Toxins
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General Mechanisms of Plant Defense and Plant Toxins

Lec.1 &Lec.2

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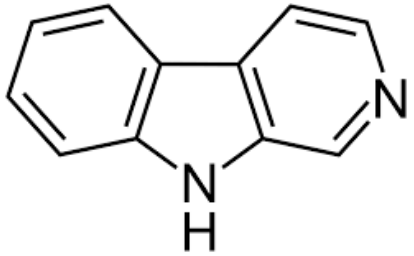
Classification of Plant Toxins

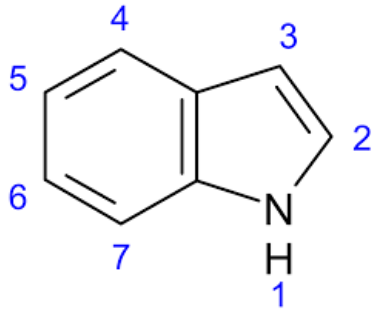
a) Alkaloids •

These are organic compounds containing nitrogen in heterocyclic ring, basic in nature and derived from amino acid, most of which exhibit strong physiological activity.For example, colchicines, nicotine, atropine, taxine,cocaine and many others.

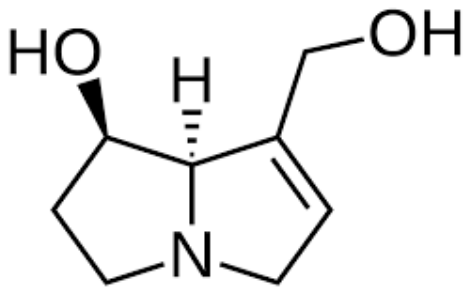
Some common toxins from this class include:

1– Indole alkaloids: beta-carbolines like harmine active on the central nervous system.

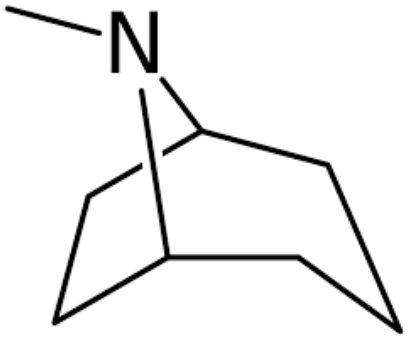




2– Pyrrolizidine: are hepatotoxic, that is, damaging to the liver. have two fused five-member carbon rings with a nitrogen atom at one bridgehead



3–Tropanes: is a nitrogenous bicyclic organic compound. such as: atropine, scopolamine, hyoscyamine, active on the autonomous nerve system.



4– Glycoalkaloid: The greatest worry for glycoalkaloid toxicity is its acute toxicity. There have been many reported cases of human poisonings (sometimes fatal) due to the ingestion of damaged or sprouted potatoes as a consequence of high levels of glycoalkaloid i.e. solanine

b) Glycosides

is a molecule in which a sugar is bound to another functional group via a glycosidic bond. Glycosides play numerous important roles in living organisms. Many plants store chemicals in the form of inactive glycosides. These can be activated by enzyme hydrolysis which causes the sugar part to be broken off, making the chemical available for use.

1- Cyanogenic glycosides Plants that make cyanogenic glycosides store them in the vacuole, but, if the plant is attacked, they are released and become activated by enzymes in the cytoplasm. These remove the sugar part of the molecule, allowing the cyanohydrin structure to collapse and release toxic hydrogen cyanide. Storing them in inactive forms in the vacuole prevents them from damaging the plant under normal conditions.

2- Cardiac glycosides such as digitoxin from *Digitalis purpurea* (Common foxglove). Digoxin inhibits the enzyme Na-K-ATPase.

c) Tannins

- Tannins (or tannoids) are a class of astringent, polyphenolic biomolecules that bind to and precipitate proteins and various other organic compounds including amino acids and alkaloids.
- the term tannin is widely applied to any large polyphenolic compound containing sufficient hydroxyls and other suitable groups (such as carboxyls) to form strong complexes with various macromolecules.

d) Proteins

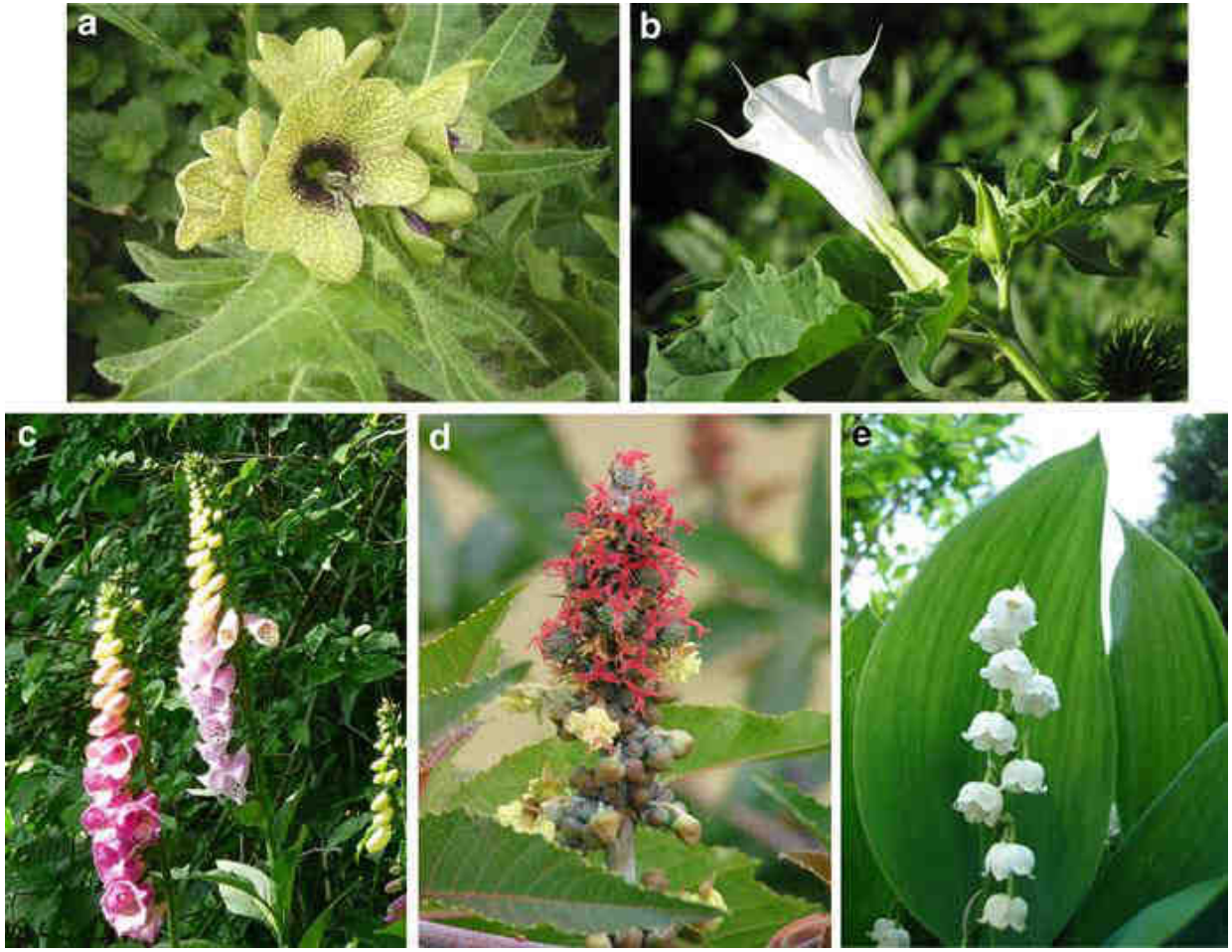
A number of protein toxins produced by plants enter eukaryotic cells and inhibit protein synthesis enzymatically. Examples of poisonous proteins include ricin (castor plant), abrin *Abrus precatorius* (rosary pea). Abrin is a ribosome inhibiting protein like ricin.

e) Anti-vitamins

Some substances work against the vitamins, e.g. thiaminases in horsetails and bracken (breakdown of thiamine) and anti-vitamin K such as coumarins.

f)Volatile oils

Volatile oils are liquid substances formed in special oil cells, glands, hairs, or channels. They are all soluble in alcohol. At certain concentrations, Volatile oils are mixture of hydrocarbon terpenes, sesquiterpenes and polyterpenes.



Selected toxic plant species. (a) Hyoscyamus niger (Black henbane; hyoscyamine, alkaloid); (b) Datura stramonium (Jimson weed; atropine, alkaloid); (c) Digitalis purpurea (Purple foxglove;digitoxin, steroid) (d) Ricinus communis (Castor oil plant; ricin, lectin); (e) Convallaria majalis (Lily of the valley; convallatoxin, steroid)

Plant-Attacking Organisms

Plant attacking organisms are of different nature. In general, they are called **biotrophs**, or more specifically **phytotrophs**. Among the various plant feeders and pathogens, viruses, bacteria, fungi, and insect herbivores are the **phytotrophs** causing the most economical damages to crop plants.

Viruses

Viruses: The first known hosts for viruses were plants, and the study of plant viruses have been a focus of research for more than 100 years.

- There are thousands of virus species and those affecting plants.
- Plant viruses utilize specific plant feeding insects as their primary vector(s). Insects are the most common vectors for plant viruses in the aerial parts, while below-ground transmission occurs through nematodes, and others.

Virus movement

virus movement depends on the presence of virus-encoded movement proteins (MPs) that target plasmodesmata of plant.

Virus movement

Movement proteins modify the plasmodesmata by one of two well-understood molecular mechanisms.

The first mechanism: The movement proteins of many plant viruses form a transport tubule within the pore of the plasmodesmata that allows the transport of mature virus particles. Examples of viruses that use this mechanism are cowpea mosaic virus (CPMV) and tomato spotted wilt virus (TSWV).

The second mechanism by which movement proteins work is by associating with and coating the genome of the virus, causing the ribonucleoprotein complexes to be transported through plasmodesmata into neighbouring cells.

Bacteria

Plants are an attractive source of nutrients and represent a life environment for many bacteria. Bacteria enter their host through natural openings or wounds.

Once they have entered the plant, bacteria may colonize different tissues and environments such as phyllosphere, rhizosphere, apoplast, xylem, phloem, and cell organelles.

examples of bacterial infection in plants.

The pathogenic ***Agrobacteria*** use genetic transformation of the host cell as an infection strategy, via stable integration into the host genome of a DNA fragment called T-DNA. This genetic transformation results in oncogenic reprogramming of the host to the benefit of the pathogen.

Gram-negative bacterial pathogens such as ***pseudomonads*** and ***xanthomonads*** use toxins and effector proteins to cause serious crop diseases such as the bacterial spot and speck of tomato, black rot of crucifers, and bacterial blight on rice. They act directly in host cells by inhibiting plant immune and facilitating bacterial colonization.

- The protection of plants against pathogens is determined by a multilayered immune system which includes specific and nonspecific innate immunity.
- However, the plant immune system not only acts to limit current pathogen invaders, but can also prime the plant and its progeny for heightened resistance against subsequent attack. Localized effector-triggered immunity leads to subsequent transmission of mobile signals to distal plant tissue, priming defense responses resulting in systemic resistance against future attack.

Fungi

Fungi: Fungal plant pathogens are of huge economic importance because of their potential to threaten the production of crops and cause postharvest diseases. Estimates suggest that approximately 10% of agricultural production in more than 10,000 different crops is lost annually owing to fungal infection.

- Fungi have diverse lifestyles in which they deploy distinct strategies to interact with their host plants.
- Pathogenic fungi reduce the photosynthetic potential of their host plants, divert and metabolize photosynthates in their own biomass, thus reducing the plant carbon sequestration. For instance, rust infections may reduce dry matter yield in excess of 40%

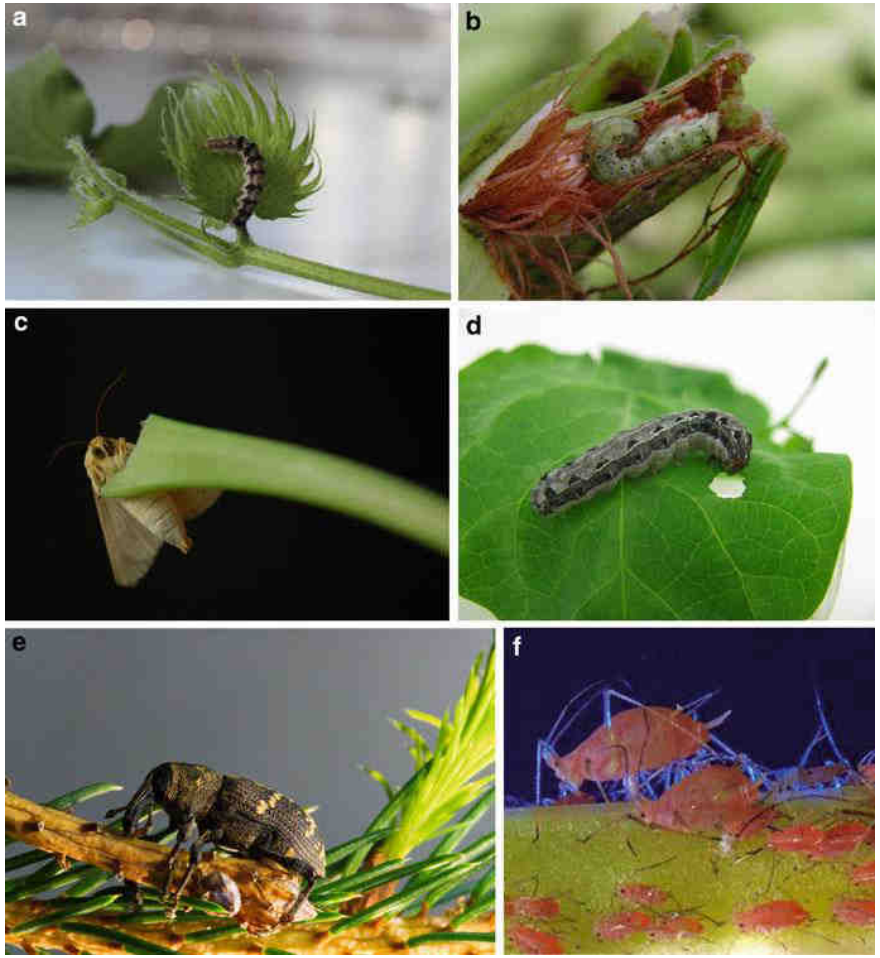
- Plants can detect infecting fungi through the perception of microbe-associated molecular pattern (MAMPs), e.g., chitin oligosaccharides; however, fungal pathogens have developed counterstrategies to escape from the chitin-mediated detection by using effectors and/or changing their cell walls.

- Plant-fungal interactions are not limited to the pathogenic effect of fungal invasion. Plants can develop mutualistic relationships with beneficial arbuscular mycorrhizal fungi (AMF) or endophytic beneficial fungi. These symbiotic interactions can provide resistance that may exert systemic protection against a wide range of attackers by sharing defense mechanisms with systemic acquired resistance (SAR) after pathogen infection and induced systemic resistance (ISR) following root colonization by nonpathogenic rhizobacteria.

Herbivores

Among all the biotic invaders, insects have been recognized to be the most significant herbivores considering the fact that almost half of the total Herbivorous insects have evolved a variety of feeding mechanisms to acquire nutrients from their host plants. **Chewing herbivores**, like *Spodoptera littoralis*, consume leaves by continuously clipping off and ingesting small pieces of tissue reducing both photosynthetic capacity and biomass of fed plants.6 million insect species are herbivorous

Spider mites (*Tetranychus* spp.) are leaf parenchyma cell feeders and during feeding they suck the full content of a plant cell, largely composed of chloroplasts containing chlorophyll. As microbial biotrophs, insects are able to attack plants both above and belowground. Root herbivory causes tissue damage that eventually leads to water limitation in the whole shoot, while leaf herbivory limits the photosynthetic capacity of the plant. As plants are sessile organisms and cannot escape their predators, they have evolved diverse mechanisms to react specifically to each attacking biotroph.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Strategies of Defense

Constitutive vs. **inducible** defense: Plant defense mechanisms can be classified in two main categories, constitutive and induced. Constitutive defense is always present, independent on the presence or absence of an attack. Many physical defenses are constitutive as well as toxic compounds that are synthesized and stored in certain plant tissues. In contrast, induced defenses are activated only when necessary, i.e., upon attack by an herbivore. Almost all induced reactions belong to chemical-based defenses.

- A substantial redirection of the metabolism from growth toward defense – as is characteristic of induced defenses – is costly for the plants; on the other hand, the constitutive
- Synthesis and storage of toxic compounds is costly as well, but paid continuously.
- The defense costs are paid mainly in the form of energy, carbon, and nitrogen. The different costs reflect the compounds synthesized; for example, phenolics are suggested to be cheaper than alkaloids because of the additional effort that is required to make inorganic nitrogen bioavailable.

Direct vs. indirect defense

Both constitutive and inducible defense mechanisms can be further classified into direct and indirect defense modes and vice versa.

A direct defense: is aimed at affecting the survival or performance of the attacking organism.

Indirect defenses: protect the plant through help provided by other organisms. These might be predators or parasitoids of an attacking herbivore.

Thus, indirect defenses employ a third trophic level by attracting natural enemies of the plant's attacker.

- A well-studied mechanism of indirect defense is provided by many ant species living on “ant-plants,” so-called **myrmecophytes.** Here the plants offer food and accommodation to the ants. Accommodation is provided for living and growing the offspring in so-called **domatia**. Food sources are provided by extrafloral and floral nectar or specific food bodies.
- To keep these privileges, the ants defend their host plant against any other organism.

Domatia (singular Domatium) are structures produced by plants for arthropods(insects) to use. Commonly domatia are small chambers inside the plant or made by hairs on leaves that offer shelter to arthropods. The domatia are intended to be used by organisms that have a symbiotic relationship with the plant.

For example, ***Pseudomyrmex*** ants live in domatia within the thorns of some Acacia trees. The tree benefits from the ants as the ants eat animals feeding on the Acacia. In return, the ant colony is protected within the domatia.

Domatia

Volatile organic compounds

- In response to herbivory, plants release volatile organic compounds (VOC) to the environment which are attractive for many enemies of the feeding insect.
- VOC carry different types of information: information for the herbivores to localize their host, information for indirect defense by attracting natural enemies of the plants attackers, and information for distant parts of the same plant as well as neighboring plants to adjust their defensive status.

Physical defense

- This type of defense is almost exclusively constitutive and includes morphological and structural features on both the macroscopic and microscopic level. Constitutive physical barriers are represented by spines or prickles that can directly deter larger herbivores from feeding. Thick cuticles or cell walls, the accumulation of resin, or high levels of lignification can only deter smaller herbivores.

- Chemical defense: Plants, like animals, use chemicals for purposes that include communication and reproduction but also aggression and defense. Plant defense based on chemistry is the most important type of defense. Plants are masters of biosynthesis and plenty of defense strategies are based on the immense diversity within plant biochemistry.
- plants are able to synthesize at least more than 200,000 low molecular weight compounds

- These compounds belong to various chemical classes: isoprene-derived terpenoids including steroids and saponins; N-containing alkaloids; (poly)phenolic compounds including flavonoids, tannins; glucosinolates; cyanogenic glucosides; and amino acid derivatives such as γ-amino butyric acid (GABA). But also peptides/ proteins (proteinase inhibitors, lectins, sporamin); latex; and inorganic compounds (oxalate, selenium) are efficient defensive substances

- The presence of all these compounds can reduce herbivore attack; some can kill insects directly upon incorporation, some can delay/disturb herbivore development, they can reduce the digestive efficiency thus lowering resistance to disease and limiting fecundity, they can repel herbivores, or they can attract organisms of another trophic level. In order to cope with herbivores, all of these strategies contribute to successfully defend a plant against an aggressor.

- It is not necessary that the herbivore is killed directly; if the herbivore simply stops feeding or leaves the plant, the chance for the plant to survive increases drastically. Often a combination of several defense mechanisms, each of which alone is not able to hinder the herbivore, is much more helpful than a single highly effective. In principle, plants with high variability in defensive chemicals exhibit a better defense compared with those with moderate variability

Mechanisms of Plants' Self-Protection Against Their Own Toxins

Lec. 3& 4

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- The presence of toxic compounds in plant tissues requires appropriate mechanism and strategies in order to avoid self-intoxication. The easiest strategy to reach this goal is to generate only compounds that show specific toxicity against certain pathogenic but not against targets present in plants

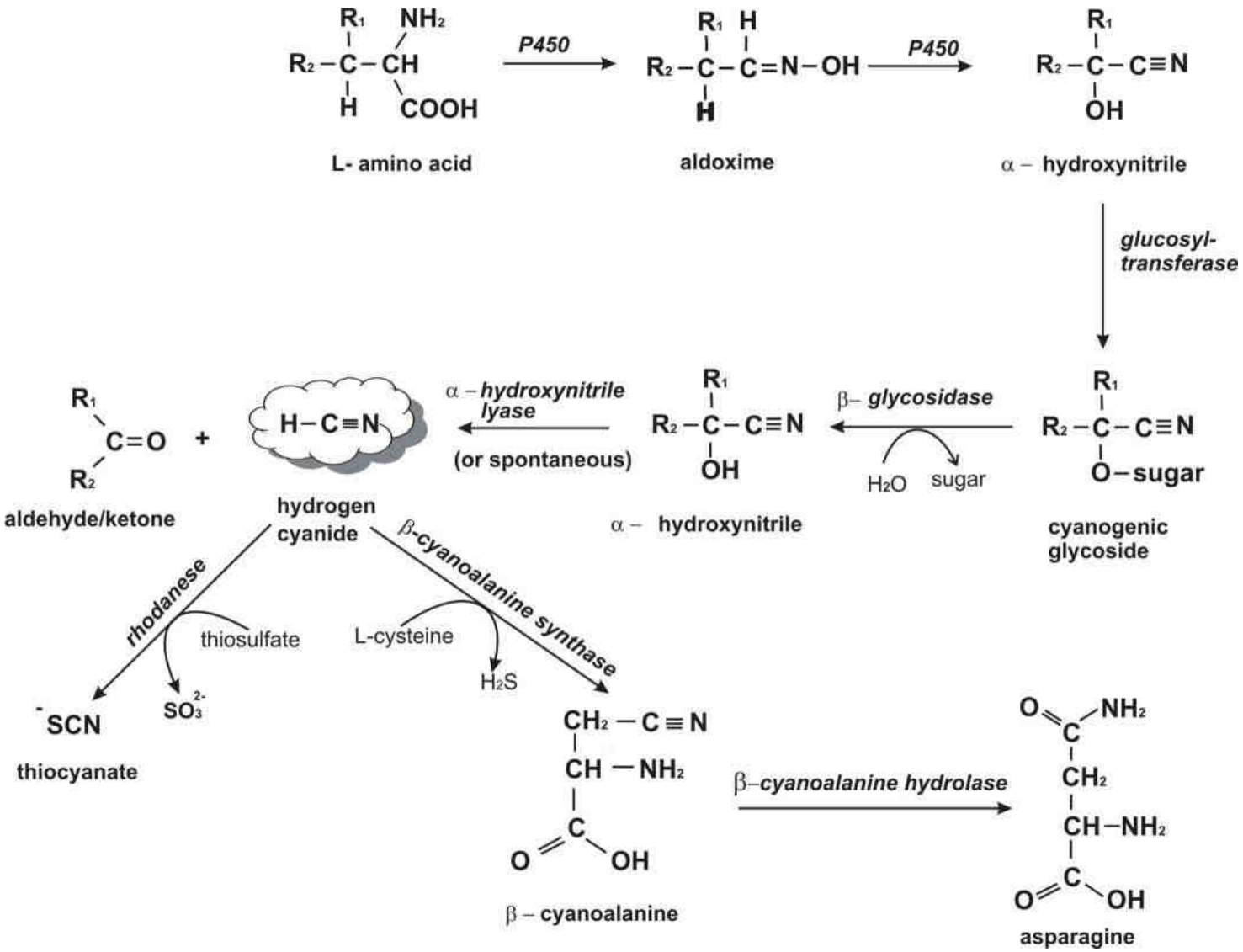
very often plants follow a strategy where they form a pretoxic compound which becomes toxic only after enzymatic cleavage. Therefore, putative toxic compounds are stored in the plant as nontoxic derivatives such as glycosides. Those glycosides are physically separated from related hydrolyzing enzymes, which release the toxic moiety immediately upon contact.

- Such a compartmentalization of pretoxic glycosides and their hydrolyzing enzymes prevents a suicidal hydrolysis in intact plant tissue. Examples are cyanogenic glucosides or glucosinolates.
- Compartmentation of enzymes and substrates is realized at the subcellular or at tissue level.

Cyanogenic glucosides

- In case of cyanogenic glucosides, compartmentation is present within the same cell.
- Only the glucosides are stored in the vacuole, the β-glucosidases and α-hydroxynitrile lyases that can hydrolyze the cyanogenic glucosides thereby causing the release of HCN.
- Thus, hydrogen cyanide detoxification is necessary in plants as well and is mainly provided by a reaction between HCN and the amino acid cysteine catalyzed by cyanoalanine synthase and generating β-cyanoalanine; this is followed by the subsequent conversion of β-cyanoalanine into aspartic acid or into asparagine. The cyanoalanine synthase activity in plants is found primarily in mitochondria, the organelle being most sensitive to HCN because of the respiratory chain.

Biosynthesis and catabolism of cyanogenic glycosides. Enzymes involved are shown in italic.

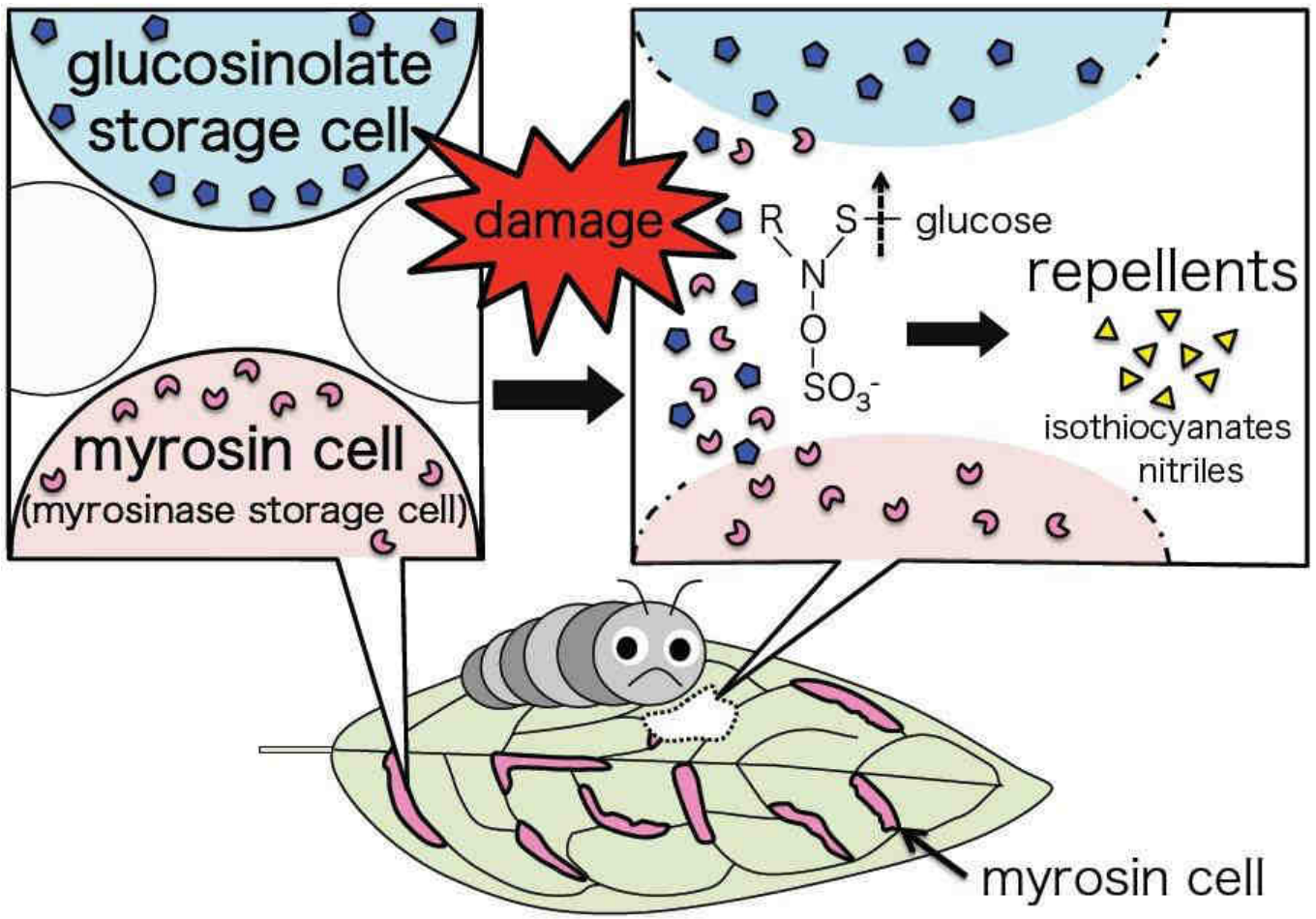


Rhodanese, also known as rhodanase, is a mitochondrial enzyme that detoxifies cyanide (CN−) by converting it to thiocyanate (SCN−).

The HCN inhibits the activity of cytochrome oxidases by binding to Fe^{+++} and Fe^{++} ions leading to inhibition of ATP production due to inhibition of oxidation phosphorylation.

glucosinolates

Compartmentation of enzymes and substrates is realized at the subcellular or at tissue level. In the case of glucosinolates as pretoxic defensive compounds, the glucosinolate-hydrolyzing myrosinase system, which is responsible for isothiocyanate generation, shows tissue compartmentation. Myrosinases are stored separately from their substrates. For example, in *Arabidopsis thaliana* leaves, glucosinolates are not uniformly distributed. Their levels are highest in the outer lamina and the midvein area. Within the veins, glucosinolates are primarily stored in S-cells (sulfur-rich cells) that are localized close to the phloem. In addition, myrosinases are stored separately in idioblasts, also known as myrosin cells, as well as in guard cells.


glucosinolate
storage cell
damage
myrosin cell
(myrosinase storage cell)
R
S
glucose
N
O
SO_3^-
repellents
isothiocyanates
nitriles
myrosin cell

Toxicity of Selected Compounds and Their Effects on Target Organisms

- Over the past decade, interest in drugs derived from higher plants, especially the phytotherapeutic ones, has increased expressively. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants.
- However, not all plants are suitable for phytotherapy and many metabolites cannot be considered safe for consumption just because they are produced naturally.
- Therefore, the effect of plants on humans and animals can be curative, nutritive, or fatal. Many natural compounds found in several commonly consumed plants are potential carcinogens or tumor promoters and should be avoided.

Phenolic compounds

- **Phenolic compounds:** Flavonoids are a class of low molecular weight phenolic compounds widely distributed in the plant kingdom.
- They are constituents of fruits, vegetables, nuts, plant-derived beverages such as tea and wine and traditional Eastern medicines such as *Ginkgo biloba*
- Several flavonoids exert toxic effects on mitochondria by opening the mitochondrial permeability transition pore (PTP) and/or affecting the mitochondrial membrane permeabilization (MMP). For instance, **curcumin** opens the PTP and induces mitochondrial swelling, calcium release, causes respiration impairment, and depolarizes the mitochondrial membrane potential.

- Curcumin is a bright yellow chemical produced by some plants. It is the principal curcuminoid of turmeric (*Curcuma longa*), a member of the ginger family, Zingiberaceae.
- Chemically, curcumin belonging to the group of curcuminoids, which are natural phenols responsible for turmeric's yellow color.

Terpenoids

Monoterpenes show a broad range of biological activities against bacteria, fungi, and various arthropods, and some of these terpenes can be toxic to both animals and humans. Monoterpenes, along with sesquiterpenes (see below), are natural constituents of essential oils. Many essential oil components are toxic compounds. The acaricidal activity of camphor, a bioactive monoterpene derived from ***Rosmarinus officinalis*** oil, was effective against *Tyrophagus putrescentiae.*

Sesquiterpene lactones are one of the largest biogenetically homogeneous groups of low molecular weight molecules, found mainly in the Asteraceae (Compositae) family. One of the most promising new developments in the field of malaria chemotherapy is the sesquiterpene artemisinin, a natural product of ***Artemisia annua.*** This compound exerts also strong cytotoxicity against tumor cells

Zerumbone, a sesquiterpene has attracted considerable interest in the realm of cancer research because of its pleiotropic anticancer and chemopreventive activity.

- Extracts of ***Melia azedarach*** have proven insecticidal properties. Melianone is a triterpene and the major constituent of *M. azedarach* extracts with antifeedant activity against *Pieris rapae* and *Spodoptera frugiperda* larvae.

Alkaloids

- Alkaloids: Alkaloids are nitrogenous plant constituents with basic properties and consistent physiological effects in microbes, animals, and humans. The Veratrum alkaloids, which are chemically similar to steroids, include veratrine (poisonous substance consisting of a mixture of alkaloids that occurs in the seeds of *sabadilla* and related plants, used, especially, to relieve neuralgia and rheumatism.)

- One of the most toxic members of the plant kingdom is the plant species ***Conium maculatum*** (hemlock, poisonous hemlock) that contains piperidine alkaloids: coniine, N-methyl-coniine, conhydrine, and γ-coniceine. Hemlock is more poisonous to cows than to sheep, goats, rabbits, poultry, and insects. Extract of the plant was used often to execute criminals or political prisoners in ancient Greece, This poison disrupts the central nervous system—a small dose **can cause** respiratory collapse. **Death can** result from blockage of the neuromuscular junction **caused** by coniine.

Besides secondary metabolites, plants produce a variety of other compounds, including toxic proteins like lectins, ribosome-inactivating protein, protease inhibitors, α-amylase inhibitors, ureases, antimicrobial peptides.

- *Catharanthus roseus* is another source of interesting alkaloids with potent bioactivity. **Vinblastine** is one of the most widely recognized alkaloids in *C. roseus* that have become an important part of modern cancer chemotherapy.
- Many other alkaloids exert biological effects on animals and humans. Among these are the highly successful pharmaceuticals such as taxol, with anticancer activity, serpentine that shows antihypertensive properties,

Future Directions

- The interactions and coevolution between plants and their natural enemies have resulted in the accumulation of an impressive array of chemical defenses, toxins, in the plant kingdom.
- This wide repertoire of bioactive compounds continues to offer great chances for human health, as many therapeutically relevant compounds are of plant origin and originally evolved for plant defense.
- The ongoing arms-race between plants and their attackers will drive the generation and production of new compounds besides all of the substances that have not been identified up to now.
- In addition, endophytic beneficial fungi and bacteria interact with plants and it is estimated that there are over one million endophytic fungi existing in nature. There is currently a lot of attention to the potential of exploitation of these microorganisms for the production of novel antibiotics with antibacterial substances that can both respond to current antimicrobial resistance and anticipate evolving resistance and might act positively in human medicine.
- Moreover, knowing the relevant defensive compounds and defensive mechanisms can provide important tools for agriculture. Traditional breeding or bioengineering may generate plants that produce repellents, toxins, and other protecting compounds, thereby strengthening the particular crop to successfully withstand herbivore and pathogen attacks.

Toxic Chemicals from Invasive Alien Plants

Lec. 5& 6

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Toxic Chemicals from Invasive Alien Plants

- Allelopathy is a phenomenon by which a plant produces natural chemicals that influence the growth, survival, and reproduction of other organisms.
- These natural defense or cooperative chemicals in plants are known as allelochemicals. Allelopathy has either inhibitory or stimulatory effects on other organisms.
- The term allelopathy was coined from the Greek word allelo and pathy, meaning mutual and feeling, by Hans Molisch in 1937. He used the term to describe interactions – both inhibitory and stimulatory effects, but many people did not read his original book and had misunderstandings that allelopathy phenomena were only inhibitory effects.

Weed management

- In weed management, allelopathy has three different approaches: One is allelopathy of weeds as one of the detrimental effects of these on crops;
- another approach is the reciprocal effect –allelopathy of crops which can inhibit the growth of weeds. Utilization of allelopathic cover crop to inhibit the growth of weeds is now being disseminated as an alternative way of weed control.
- The third approach is to make new herbicides from allelochemicals.

Plants-Related Allelochemicals and Biological Properties

1. **Black Walnuts (Juglans nigra)**

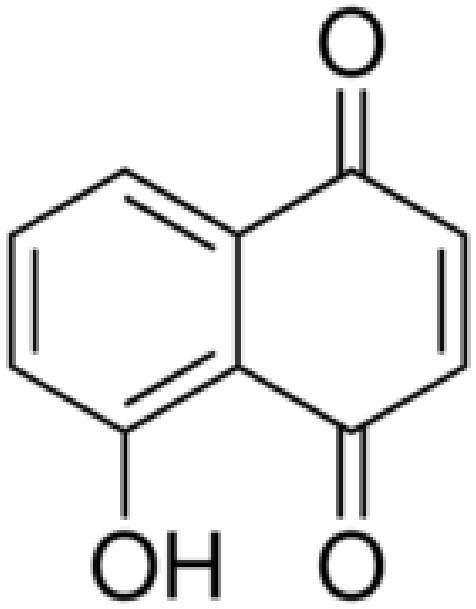
The Walnut tree produce a compound called 'Juglone'() from its buds, leaves, nut shells and roots. The substance affects growth of adjoining plants such as tomatoes, peppers, potato. found that *Juglans nigra* and Juglans cinerea were damaging apple trees in Virginia. The trees that were within an average of 11.9 meters from the walnut trees were found dead.

2. **Eucalyptus**

The Eucalyptus tree too affects the seed germination, growth of seedlings and root length of cotton and wheat growing in its vicinity. The foliage and leaves of the tree have compounds that are found to be having inhibitory effect on other plants.

Juglone

is a hydroxy-1,4-naphthoquinone that is 1,4-naphthoquinone in which the hydrogen at position 5 has been replaced by a hydroxy group.



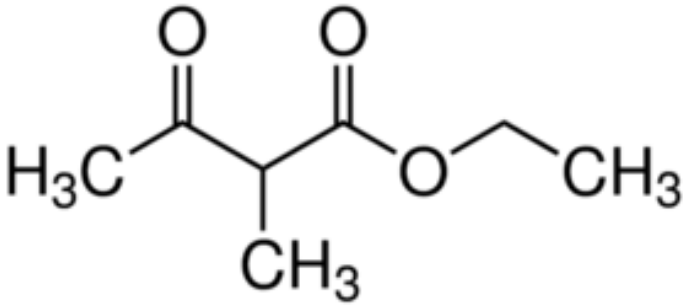
Ethyl 2-Methylacetoacetate (EMA)from *Phragmites australis*

- The novel allelochemical, **ethyl 2-methylacetoacetate** isolated from the reed (*Phragmitis australis*) inhibited the growth of three common species of algae.
- Ethyl 2-methylacetoacetate significantly inhibited the growth of the toxic cyanobacterium *Microcystis aeruginosa* in a concentration dependent way. The cellular structure and metabolic activity of *M. aeruginosa* were also influenced by EMA and the oxidative damage induced by this compound may be an important factor responsible for the growth inhibition of *M. aeruginosa.*

Phragmites australis

Ethyl 2-Methylacetoacetate

belongs to the class of Fatty Acid Esters. These are carboxylic ester derivatives of a fatty acid.



Atropine and Scopolamine from Datura spp.

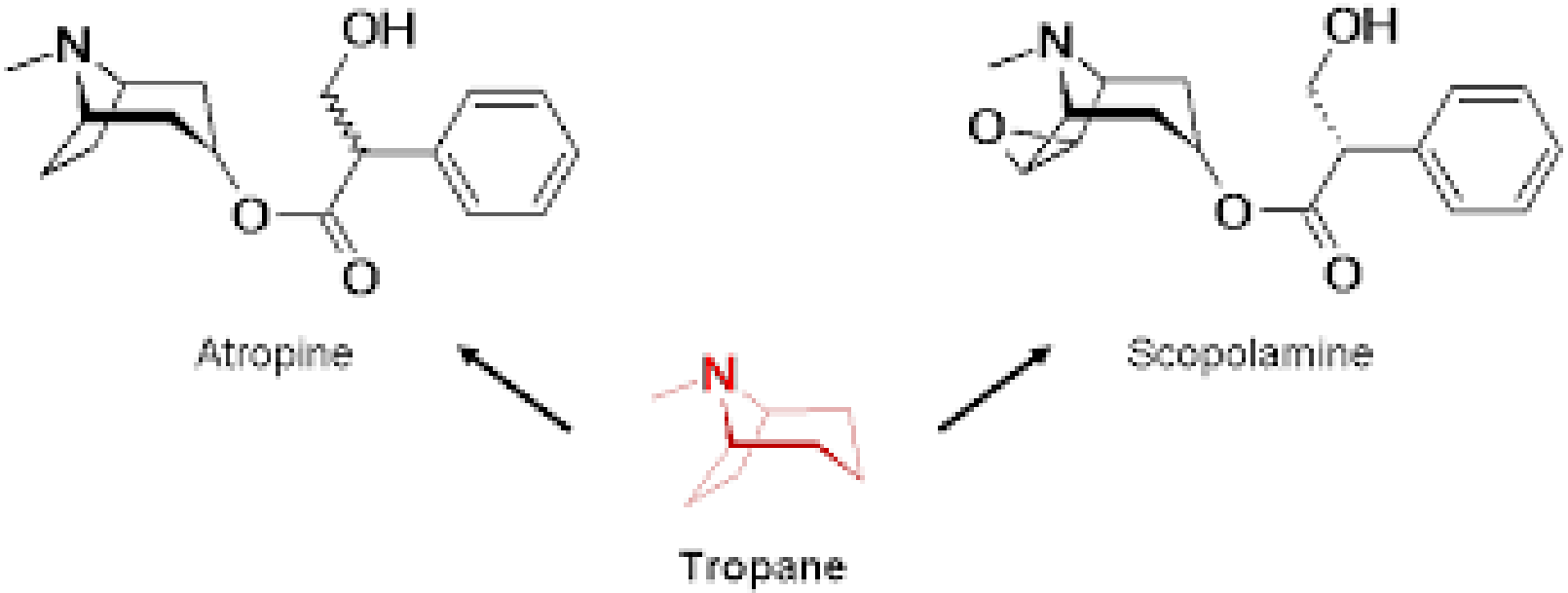
- *Datura* spp. are tropical weeds belonging to the family of Solanaceae. The family produces the nerve toxins (tropane alkoloids) one of these is atropine. The same toxic alkaloids are contained in *Hyoscyamus niger, the genus Mandragora* (mandrake), and *Atropa belladonna*. As for sensitivity, pigs are the most sensitive animal species followed by cows, horses, and chickens, in that order. For pigs, more than 1.5 mg/kg is toxic, whereas for chicken, the toxic dose is above 75 mg/kg.
- Allelopathic potential of aqueous leaf extracts of *Datura stramonium* L. was assessed on seed germination, seedling growth, root tip morphology, anatomy, and cell division of soybean. The extracts inhibited the seed germination and the degree of inhibition was concentration dependent. The extracts inhibited the primary root elongation and lateral root development and the degree of inhibition increased with increasing extract concentration.

Datura stramonium

Atropa belladonna.

Hyoscyamus niger

Atropine and Scopolamine



Plant Toxins as Sources of Drugs

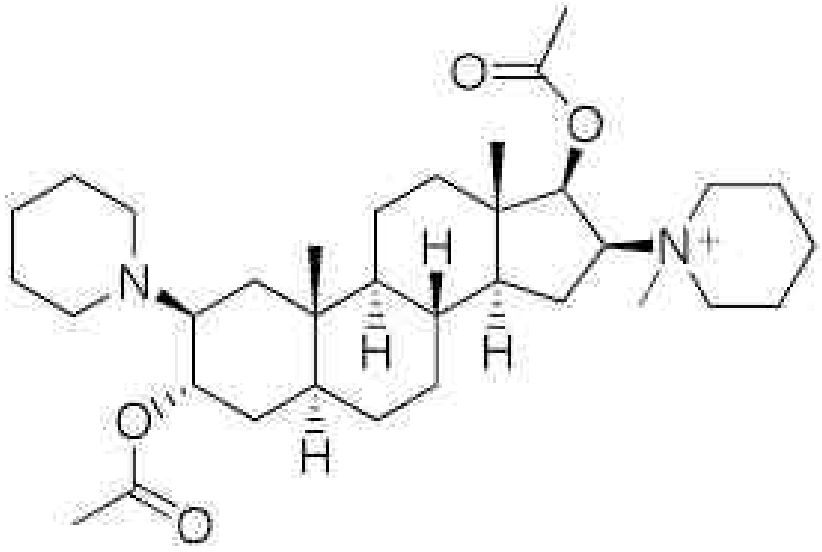
- the main constituents of most animal toxins are peptides and proteins.
- plant toxins are representative of a large group of structurally diverse small molecules that result from plant secondary metabolism.
- Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of plants. These compounds are also referred to as plant allelochemicals, and they can be synthesized by plants themselves and by nonpathogenic endophytic microorganisms living within plants. The secondary metabolites help plants to survive environmental stresses, protect plants from microbial infections and environmental pollutants, provide them with a defense against insects and herbivorous organisms, and attract natural predators of such organisms, as well as luring pollinators and other symbionts of these plants.

Curare

- Curare is the common name of various plant extract alkaloid toxins originating from Central and South America. At first, it was known as “arrow poison” because the indigenes used it for hunting; it was produced by boiling diverse plants (e.g., *Chondrodendron tomentosum, or Strychnos*) according to traditional recipes. The resulting paste was applied to arrowheads and used to kill many humans and animals over the centuries.
- it was only a matter of time until the underlying molecular mechanism piqued the interest of European scientists and physicians.

Curare structure

Curare: A muscle relaxant used in anesthesia (and, in the past, in arrow poisons by South American Indians). **Curare** competes with acetylcholine, a chemical that carries information between nerve and muscle cells, and blocks transmission of the information



- most discovery studies have focused on synthetic compounds with curarimimetic actions: **the toxin provided the template for drug design.** With the ongoing rapid development of medical science, new derivatives, such as **atracurium, succinylcholine, gallamine, pancuronium, rocuronium, and mivacurium,** could be synthesized with better pharmaceutical characteristics, and thus the original curare from Amazonia lost its relevance to modern medicine.
- Atracurium was introduced in 1983, followed by cisatracurium in 1995. Still, much research was necessary to develop the modern drugs in current use, but there is no doubt that curare and its derivatives are the oldest muscle relaxants in use.

Chondrodendron tomentosum

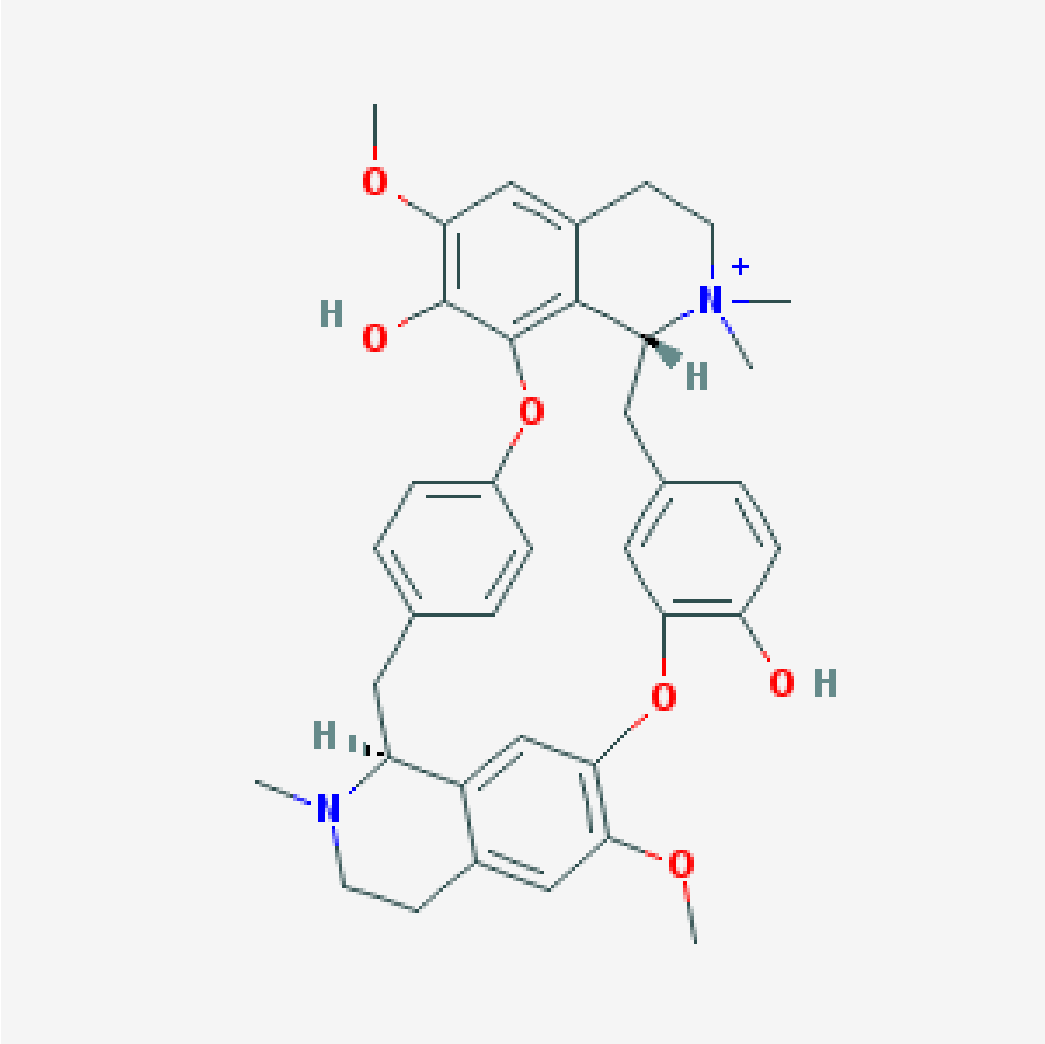
Strychnos

- Curare was taken to the Old World by Spanish conquistadors. In 1846, Claude Bernard demonstrated that curare injected into a limb prevented muscle contraction in response to nerve stimulation.
- In the 1860s, the scientists Thomas Richard Fraser and Alexander Crum Brown, working on the relationship between chemical structure and biological activity, discovered that when alkaloids such as atropine, brucine, codeine, morphine, and nicotine **had their nitrogen atoms changed from the tertiary to the quaternary form, they acquired curare-like activity.**

Mechanism of curare

- Like most alkaloids, tubocurarine consists of a cyclic system with a nitrogen atom in an amine group.
- Because of this structure, tubocurarine can bind readily to the receptors for acetylcholine (ACh) at the neuromuscular junction, which blocks nerve impulses from being sent to the skeletal muscles, effectively paralyzing the muscles of the body.
- Since tubocurarine binds reversibly to the ACh receptors, treatment for curare poisoning involves adding an acetylcholinesterase (AChE) inhibitor, which will stop the destruction of acetylcholine so that it can compete with curare.

tubocurarine



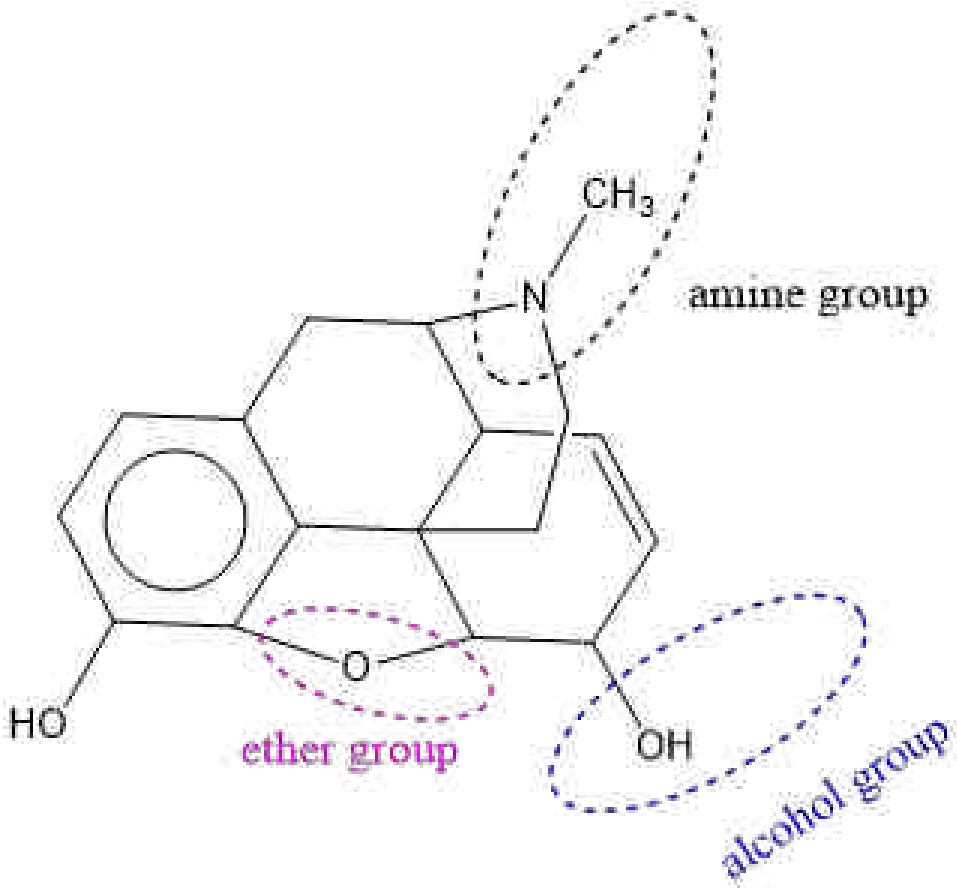
Drugs Acting on the Central Nervous System

Morphine

- Morphine's history begins with the use of opium poppy plants (*Papaver somniferum*), which are native to Eurasia and have been cultivated for more than 5,000 years.
- Opium ingestion was used for pain relief and sedation, and its poisonous effects are characterized by lethal respiratory depression at high doses.
- The molecule was discovered in 1805 by Friedrich Wilhelm Adam (1783–1841), a pharmacy pupil in Germany who was working on active opium compound isolation.

- Morphine C17H19NO3 is a highly-potent **opiate** (Opiate is a term classically used in pharmacology to mean a drug derived from opium).
- **An opioid (both natural and synthetic)** is any agent that binds to opioid receptors, found principally in the central nervous system and gastrointestinal tract.
- There are four broad classes of opioids: endogenous opioid peptides, produced in the body; opium alkaloids, such as morphine (the prototypical opioid) and codeine; semi-synthetic opioids such as heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids.
- Like other opiates, e.g., diacetylmorphine (heroin), morphine acts directly on the central nervous system (CNS) to relieve pain, and at synapses.
- Studies done on the efficacy of various opioids have indicated that, in the management of severe pain, no other analgesic is more effective or superior to morphine The word "morphine" is derived from Morpheus, the Greek god of dreams.

Structure



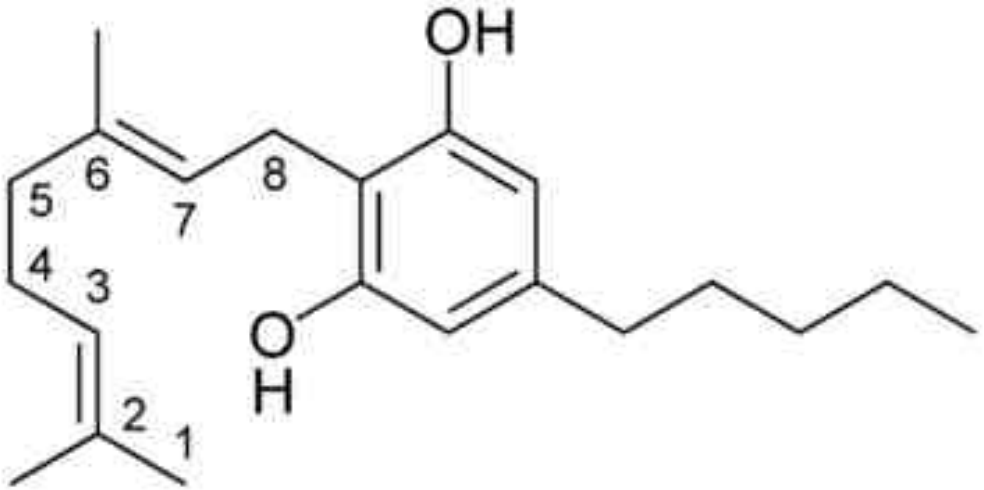
Morphine

Cannabinoids

- Cannabinoids belong to terpenophenolic class and are the main active compounds isolated from ***Cannabis sativa* (marijuana)**. Although the plant is the most commonly used illicit drug in Europe, it is generally regarded as causing low acute toxicity.
- Acute psychoactive effects of cannabinoids are impairment of memory, reductions in psychomotor, and cognitive performance, while extremely high consumption might impair cognitive and memory performance, especially in children and adolescents. The current data at least assures that Cannabis consumption by adolescents doubles their risk of developing schizophrenia in the future.
- The first information on the therapeutic use of Cannabis spp. dates back to the third millennium B.C., aiming to treat gout, rheumatism, malaria, constipation, and absent-mindedness.

- However, recent pharmacology studies have shown that *sativa* can actually cause sleep disorders and heighten neurological and psychiatric illness.
- Among the active compounds in Cannabis extracts tetrahydrocannabinol (THC) is the strongest psychotropically active component, followed by cannabidiol (CBD), cannabigerol, and cannabichromene.

Cannabinoid



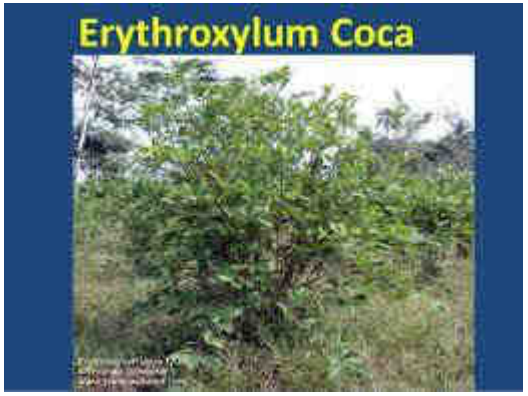
Cannabinoid receptors

- Before the 1980s, it was often speculated that cannabinoids produced their physiological and behavioral effects via nonspecific interaction with cell membranes, instead of interacting with specific membrane-bound receptors.
- The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fish, and reptiles. At present, there are two known types of cannabinoid receptors, termed CB1 and CB2

Cocaine

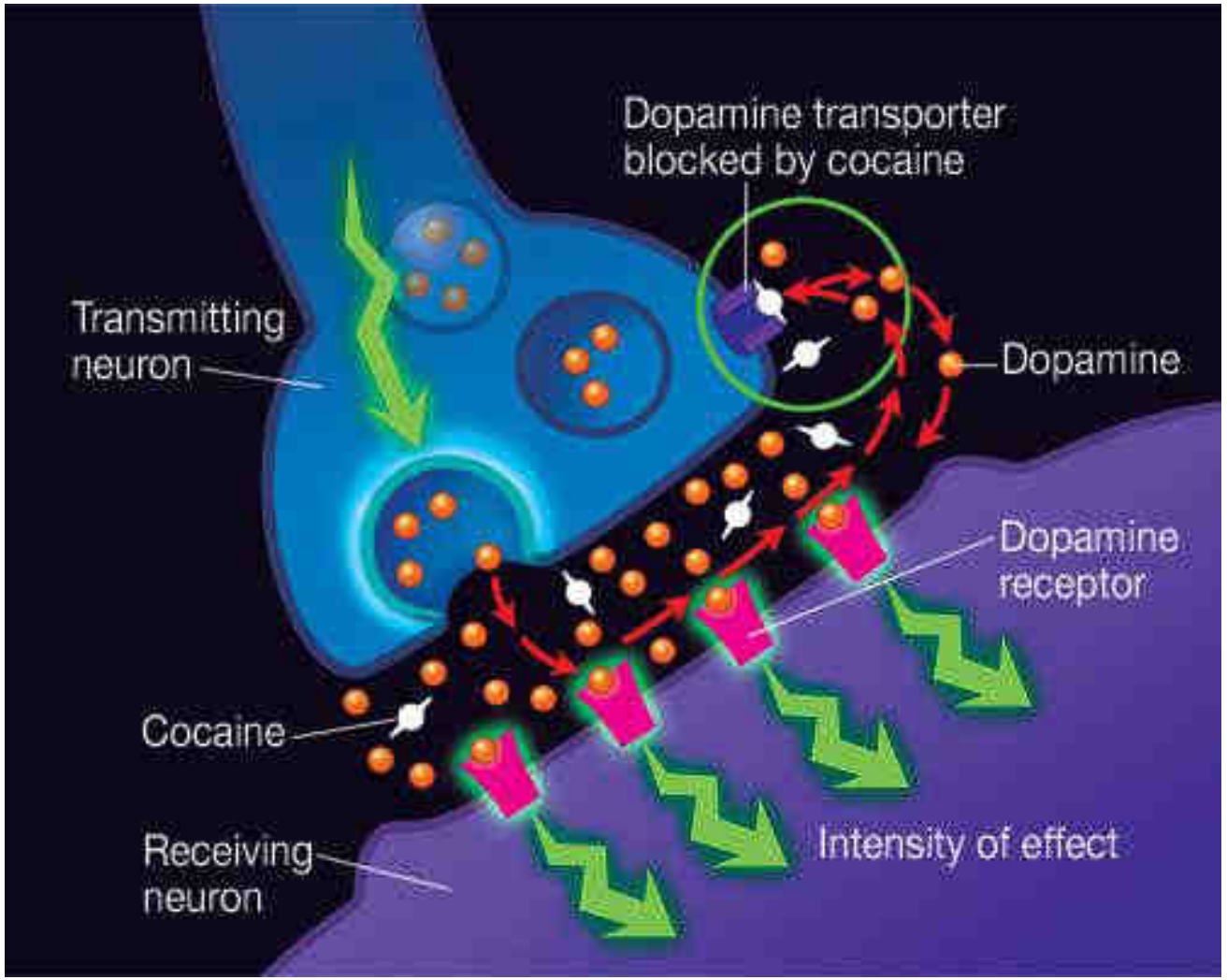
- Cocaine is the white euphoria powder, cocaine (benzoylmethylecgonine), is a tropane alkaloid obtained from the leaves of the South American shrub ***Erythroxylum coca***. This molecule is considered to be one of the most frequently used illegal recreational drugs worldwide, obviously imposing several health problems and even life threatening cardiotoxicity.
- Cocaine is the second most frequently used illegal drug globally, after cannabis

Erythroxylum coca

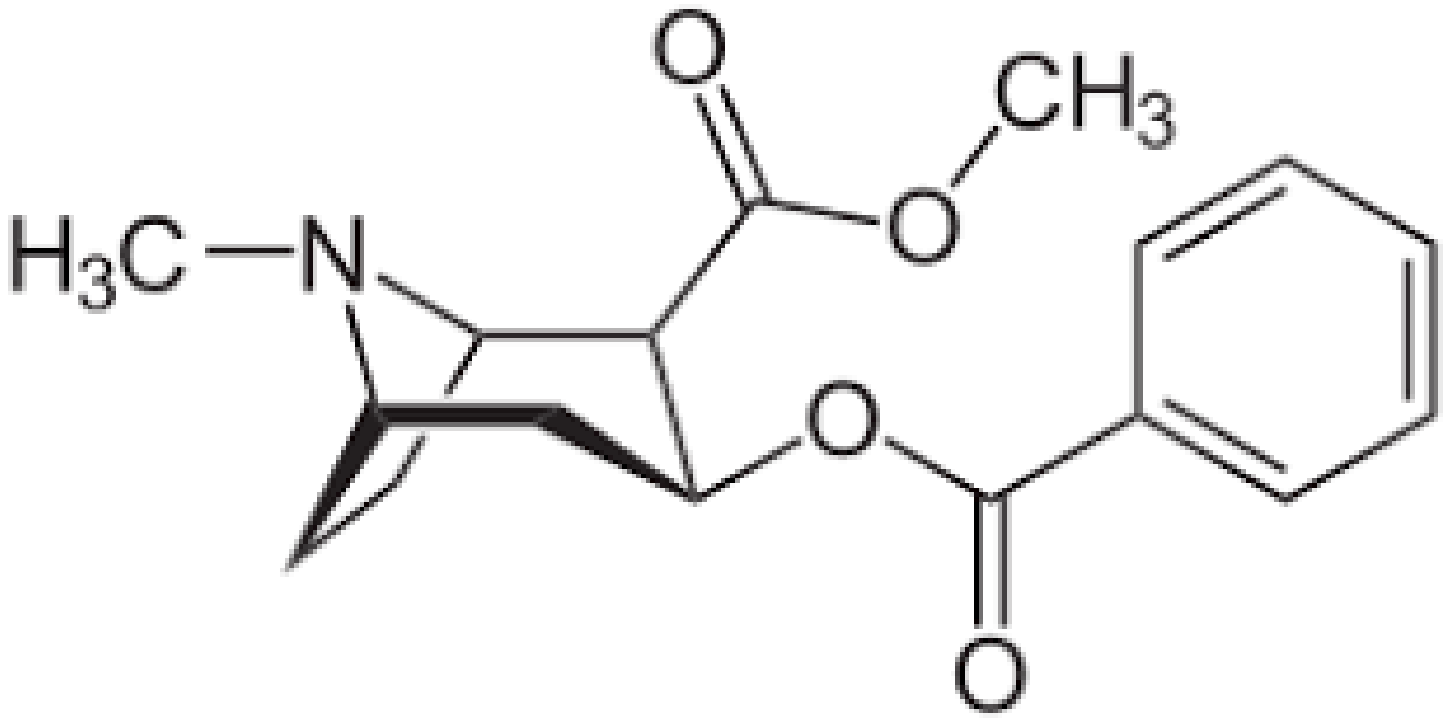


- The therapeutic use of cocaine dates back to 1884, when Karl Koller used it in an ophthalmic surgery and attempted to determine the molecule's properties with his colleague Sigmund Freud, who used the substance as a stimulant.
- In fact, **cocaine is the only local anesthetic with vasoconstrictor properties**. The local anesthetic effect then occurs by blocking the action of axonal membrane sodium channels.
- It acts mainly by increasing dopamine levels by binding to the dopamine transporter and blocking the reuptake of dopamine into the presynaptic cell.
- Cocaine acts by inhibiting the reuptake of serotonin, norepinephrine, and dopamine. This results in greater concentrations of these three neurotransmitters in the brain. It can easily cross the blood–brain barrier and may lead to the breakdown of the barrier.

mechanism of cocaine



Structure of Cocaine



The identification of the **benzoyl moiety** of cocaine enabled the synthesis of different molecules, such as benzocaine, which is the cocaine benzoic acid ester (in 1890 by Ritsert); procaine, which is the cocaine para-aminobenzoic acid (more soluble and less toxic than benzocaine) (in 1905 by Einhorn and Braun); and, finally, lidocaine (in 1943 by Löfgren), the diethyl-aminoacetic acid derivative of cocaine that started the amide-type local anesthetic age.

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Lec. 7

Antitumor Agents

Podophyllotoxin:

also known as **podofilox**, is a medical cream that is used to treat genital warts.

- Podophyllotoxin is t is a non-alkaloid toxin lignan extracted from the roots and rhizomes of Podophyllum species. a resin produced by species belonging to the *Podophyllum* genus(*Podophyllum* is an herbaceous perennial plant in the family Berberidaceae, described as a genus by Linnaeus in 1753.), such as *P. emodi* and *P. peltatum* (Berberidaceae).

Podophyllum genus

P. emodi

P. peltatum

- Podophyllotoxin possesses a large number of medical applications, as it is able to stop replication of both cellular and viral DNA by binding necessary enzymes.
- It can additionally destabilize microtubules and prevent cell division. Because of these interactions it is considered an antimitotic drug.
- Podophyllotoxin and its derivatives are used as, antiviral agent, antihelminthic, and antitumor agents.
- Podophyllotoxin derived antitumor agents include etoposide and teniposide. These drugs have been successfully used in therapy against numerous cancers including, breast, pancreatic, lung, stomach, and ovarian cancers.

- The first clinical trial of etoposide was reported in 1971, and it was approved by the Food and Drug Administration (FDA) in 1983.
- Etoposide's toxicity is lower than podophyllotoxin's toxicity because of the introduction of a glucose unit in the structure of podophyllotoxin and the subsequent acetylation of the hydroxyl at positions 4 and 6. It acts by inhibiting deoxyribonucleic acid (DNA) topoisomerase II, which causes double strand breaks in DNA and prevents DNA synthesis at the premitotic stage. Etoposide is used in combination with other chemotherapeutic agents for the treatment of refractory testicular tumors, small-cell lung cancer, lymphoma, nonlymphocytic leukemia.

Structural characteristic

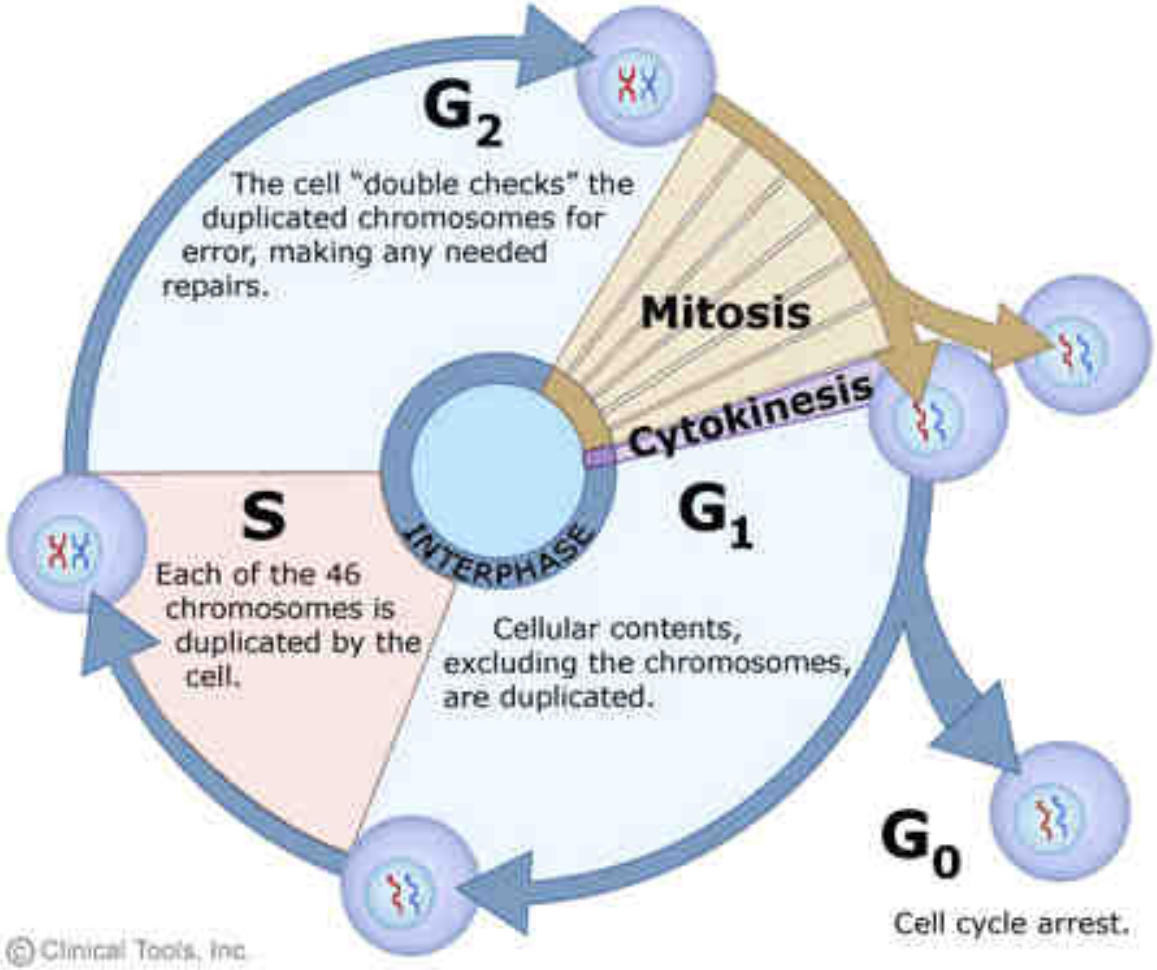
The structure of podophyllotoxin was first elucidated in the 1930s. Podophyllotoxin bears four consecutive chiral centers, labelled C-1 through C-4 in the following image. The molecule also contains four almost planar fused rings. The podophyllotoxin molecule includes a number of oxygen containing functional groups: **an alcohol**, **a lactone**, **three methoxy groups**, and **an acetal.**

Podophyllotoxins

Mechanism of Action

- Blocks cells in the late S-G_2 phase of the cell cycle through inhibition of *topoisomerase II*
- Resulting in DNA damage through strand breakage induced by the formation of a ternary complex of drug, DNA, and enzyme

Life cycle of cell



Taxanes

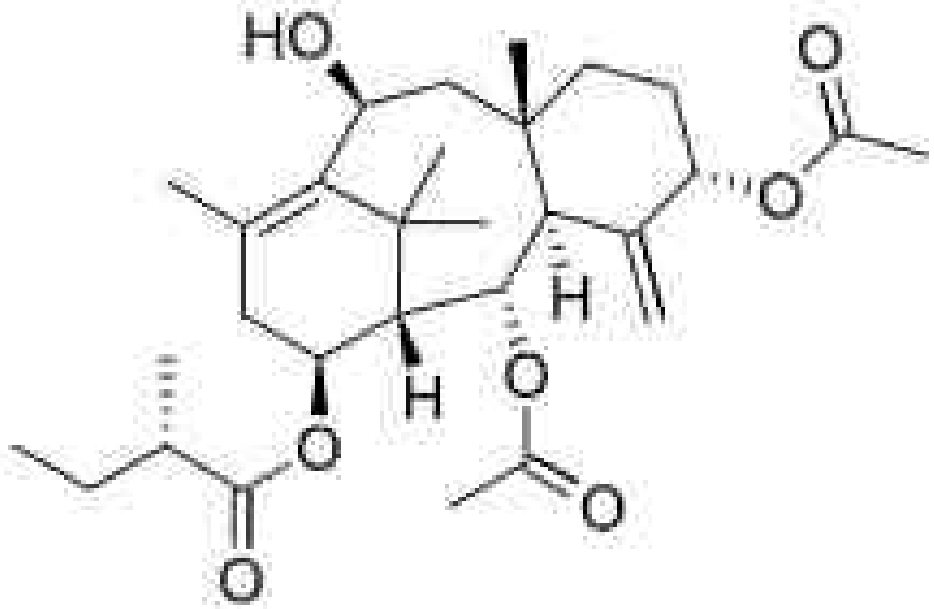
- Taxanes gained popularity in the 1980s and 1990s as an innovation against cancer. Considered at the time as the most promising new chemotherapeutic agents developed for cancer treatment, Paclitaxel (Taxol) and docetaxel (Taxotere) dominated the scene. To date, several taxanes have been isolated and their structural analogues described.
- Taxanes are modified diterpenes (also classified as non-heterocyclic pseudoalkaloids) produced by the yew tree, belonging to *Taxus* spp. The poisonous nature of yew has been cited since the second century B.C., when yew "juice" used to be handled for poisoning and extracts were consumed in ritual suicides.

Taxus (yews)

Taxus (yews)

Taxus is a small genus of coniferous trees or shrubs known as yews in the family Taxaceae. They are relatively slow-growing and can be very long-lived, and reach heights of 2.5–20 metres (8.2–65.6 ft), with trunk girth averaging 5 metres (16 ft). They have reddish bark.

Taxanes



Mechanism of action

- The principal mechanism of action of the taxes is the disruption of microtubule function. Microtubules are essential to cell division, and taxanes stabilize GDP-bound tubulin in the microtubule, thereby inhibiting the process of cell division as depolymerization is prevented. Thus, in essence, taxanes are mitotic inhibitors. In contrast to the taxanes, the vinca alkaloids prevent mitotic spindle formation through inhibition of tubulin polymerization. Both taxanes and vinca alkaloids are, therefore, named spindle poisons or mitosis poisons, but they act in different ways.
- Guanosine diphosphate, abbreviated GDP, is a nucleoside diphosphate. It is an ester of pyrophosphoric acid with the nucleoside guanosine.

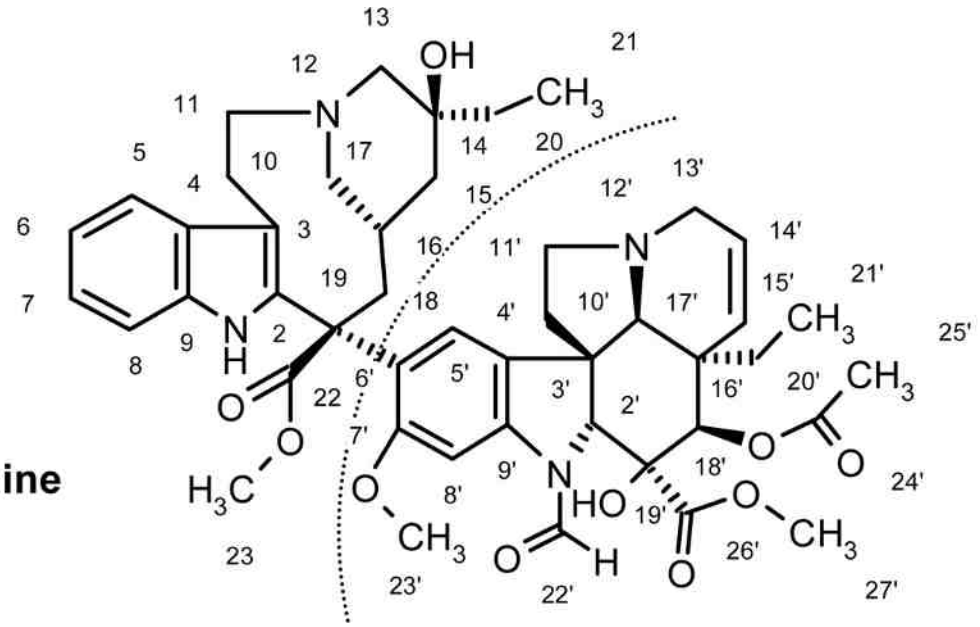
Vincristine and Vinblastine

- The vinca alkaloids are indole alkaloid molecules primarily encountered in the pink periwinkle plant *Catharanthus roseus*, known as the vinca plant that is native and endemic to Madagascar and also encountered in Europe, Northwest Africa, Southwest Asia, and Southern USA.
- They have dimeric chemical structures containing an indole (catharanthine) and a dihydroindole nucleus (vindoline) joined together with other complexes. The earlier therapeutic use of vinca is related to diabetes treatment in the population of Madagascar. Further evaluation of the hypoglycemic activity of its extracts evidenced a granulocytopenia produced as a result of bone marrow suppression in animals, directing studies to model leukemia and lymphoma treatment. Confirmation of such activity led to the isolation of vinblastine and vincristine alkaloids, which are currently used in the treatment of Hodgkin's lymphoma, Kaposi's sarcoma, ovarian cancer, and testicular and infant acute lymphoblastic leukemia.

Catharanthus roseus

Dihydro-hydroxycatharanthine

(DHC)



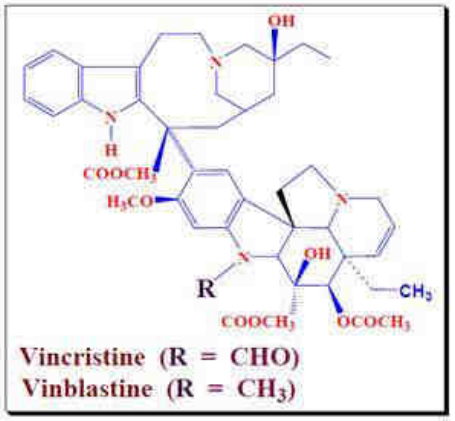
***N*-Formylvindoline**

(NFV)

Difference:Vincristine and Vinblastine

Structure

- Vincristine and Vinblastine differ only in the substitution on the N-atom of the dihydroindole nucleus.
- **Vinblastine** (Vincaleukoblastine) is produced by coupling of Catharanthine and Vindoline.
- **Vincristine** (leurocristine) has CHO instead of CH_3 in the vindoline part of Vinblastine.



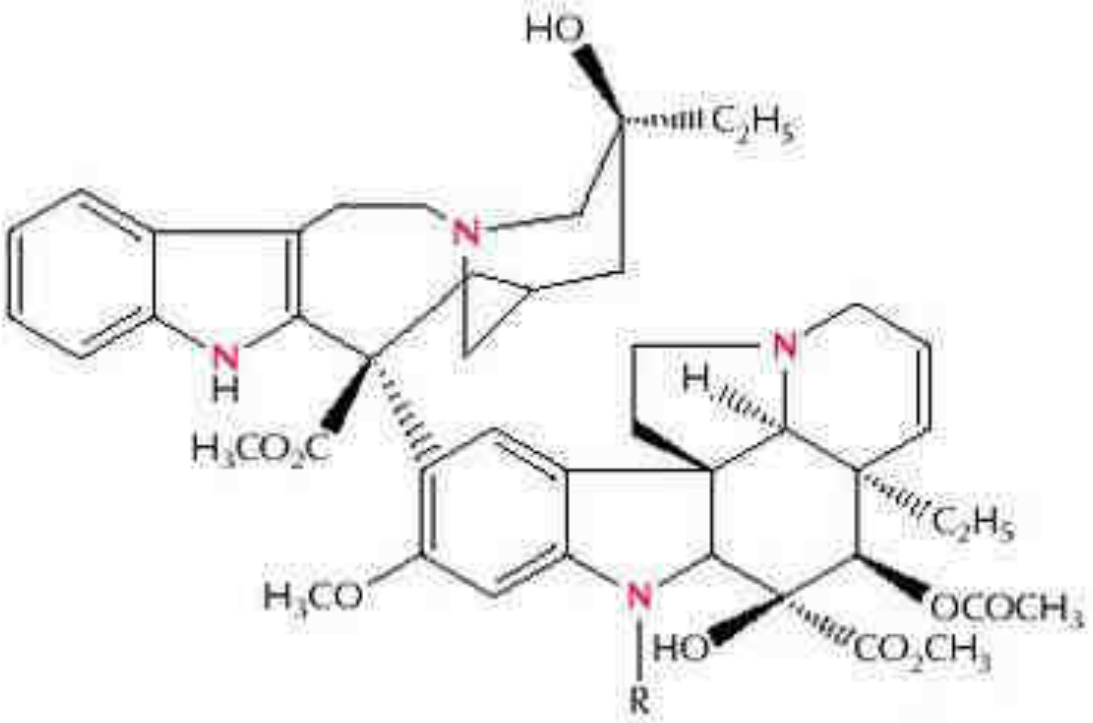
Vincristine (R = CHO)
Vinblastine (R = CH_3)

Uses:

- Vincristine used in treatment of Leukemia in children, small cell lung cancer, cervical and vaginal cancers.
- Vinblastine is used for treatment of Hodgkin's disease.

Mechanism of action:

- They are antimitotics.
- They bind to tubuline and prevent the formation of the microtubules and so block the mitosis in meta phase.



R = CH_3	R = CHO
Vinblastine	**Vincristine**

Medicinal plants: Future source of new drugs

Lec. 8

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A medicinal plant is:

(1) any plant used in order to relieve, prevent or cure a disease or to alter physiological and pathological process, or (2) any plant employed as a source of drugs or their precursors. A phytopharmaceutical preparation or herbal medicine is any manufactured medicine obtained exclusively from plants (aerial and non-aerial parts, juices, resins and oil), either in the crude state or as a pharmaceutical formulation. A medicine is a product prepared according to legal and technical procedures that is used for the diagnosis, prevention and treatment of disease and has been scientifically characterised in terms of its efficacy,safety and quality. A drug is a pharmacologically active compound, which is a component of a medicine, irrespective of its natural, biotechnological or synthetic origin.

- The use of natural products with therapeutic properties is as ancient as human civilisation and, for a long time, mineral, plant and animal products were the main sources of drugs (see historical review by De Pasquale, 1984).
- The Industrial Revolution and the development of organic chemistry resulted in a preference for synthetic products for pharmacological treatment. The reasons for this were that pure compounds were easily obtained, structural modifications to produce potentially more active and safer drugs could be easily performed and the economic power of the pharmaceutical companies was increasing.

- About 25% of the drugs prescribed worldwide come from plants, 121 such active compounds being in current use. Of the 252 drugs considered as basic and essential by the World Health Organisation (WHO), 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors.
- Examples of important drugs obtained from plants are **digoxin** from Digitalis spp., quinine and quinidine from *Cinchona* spp., **vincristrine** and **vinblastine** from *Catharanthus roseus*, **atropine** from *Atropa belladona* and **morphine** and **codeine** from *Papaver somniferum*. It is estimated that 60% of anti-tumour and anti-infectious drugs already on the market or under clinical trial are of natural origin The vast majority of these cannot yet be synthesised economically and are still obtained from wild or cultivated plants.

In recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants. This interest in drugs of plant origin is due to several reasons, namely, conventional medicine can be inefficient (e.g. side effects and ineffective therapy), abusive and/or incorrect use of synthetic drugs results in side effects and other problems.

- The NCI (National Cancer Institute, USA) has tested more than 50,000 plant samples for anti-HIV activity and 33,000 samples for anti-tumour activity.
- In 1993, the International Program of Co-operation for Biodiversity (IPCB) was launched in order to promote natural products in Latin America and Africa, linking universities, industries and governments in a multidisciplinary programme for the sustained development and preservation of the environment.
- Large pharmaceutical companies, such as Merck, CIBA, Glaxo, Boehringer and Syntex, now have specific departments dedicated to the study of new drugs from natural sources.
- However, the potential use of higher plants as a source of new drugs is still poorly explored. Of the estimated 250,000–500,000 plant species, only a small percentage has been investigated phytochemically and even a smaller percentage has been properly studied in terms of their pharmacological properties; in most cases, only pharmacological screening or preliminary studies have been carried out. It is estimated that 5000 species have been studied for medical use (Payne et al., 1991).
- Between the years 1957 and 1981, the NCI screened around 20,000 plant species from Latin America and Asia for anti-tumour activity, but even these were not screened for other pharmacological activities.

Selecting a plant

- The approach for drug development from plant resources depends on the aim. Different strategies will result in a herbal medicine or in an isolated active compound. However, apart from this consideration, the selection of a suitable plant for a pharmacological study is a very important and decisive step. There are several ways in which this can be done, including traditional use, chemical content, toxicity, randomised selection or a combination of several criteria.

- The most common strategy is careful observation of the use of natural resources in folk medicine in different cultures; this is known as ethnobotany or ethnopharmacology. Information on how the plant is used by an ethnic group is extremely important. The preparation procedure may give an indication of the best extraction method. The formulation used will provide information about pharmacological activity, oral versus non-oral intake and the doses to be tested. However, certain considerations must be taken into account when the ethnopharmacological approach of plant selection is chosen.

For instance, each ethnic group has its own concepts of health or illness, as well as different healthcare systems. The signs and symptoms should be translated, interpreted and related to western biomedical concepts, thus allowing a focused study of a particular therapeutic property.

- Selection based on chemical composition uses phylogenetic or chemotaxonomic information in the search, mainly in certain genera and families, for compounds from a defined chemical class with known pharmacological activity.
- The search for highly specific potent drugs for therapeutic use and, more precisely, as a investigation tool in biological research has been quite productive in toxic plants. A number of important compounds now used in research came from toxic plants and several examples have been mentioned earlier.

Plant Secondary Metabolites as Drug Precursors

Some natural products obtained from plants can be used as small-molecule drug precursors, which can be converted into the compound of interest by chemicalmodification or fermentation methods. The semisynthetic approach is usually used to resolve the shortage of supply due to the low yield of compounds from plants and/or the high cost of total synthesis. For compounds with complex structures and many chiral centers, protracted methods may be needed for their synthesis, and thus these methods would not be feasible economically. The following examples indicate that some secondary metabolites from plants are useful drug precursors, although they are not necessarily pharmacologically active in their original naturally occurring forms.

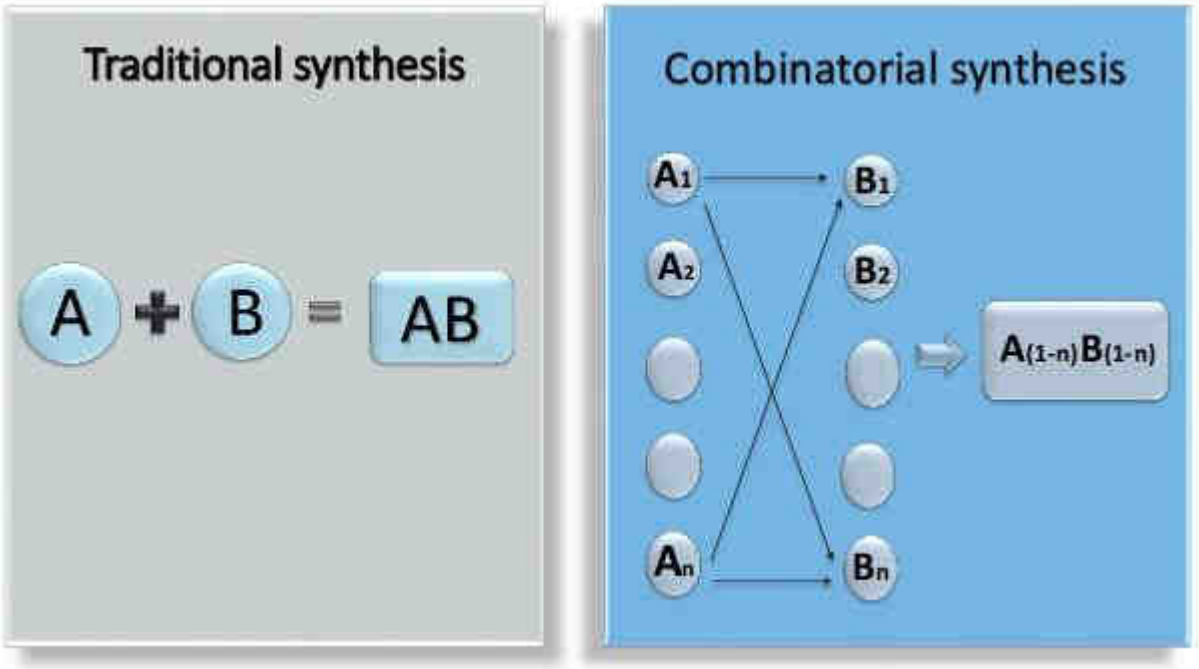
Cropping of the bark of the slow-growing Pacific yew tree, Taxus brevifolia Nutt., is not a feasible method to provide sufficient amounts of the antitumor drug paclitaxel (1, Taxol) to meet the market demand (paclitaxel was originally isolated in only 0.014 % w/w yield from the bark of Taxus brevifolia) [23]. Even though this compound can be produced by total synthesis, this has proven to be inefficient in affording large quantities of paclitaxel [24, 25]. Fortunately, 10-deacetylbaccatin III (2) can be isolated in relatively large amounts from the needles of other related yew species, such as Taxus baccata L. (a renewable resource), and can be converted chemically in several steps into paclitaxel [26, 27]. During the period 1993–2002, the main pharmaceutical manufacturer, Bristol- Myers Squibb, adopted the semisynthetic method developed by the Holton research group to produce paclitaxel from 10-deacetylbaccatin III [27, 28]. Since 2002, Bristol-Myers Squibb has produced paclitaxel using a plant cell culture method, which will be mentioned in section 1.4 of this chapter [29]. Diosgenina steroidal sapogenin obtained from the tubers of various Dioscorea species that grow in Mexico and Central America, can be converted chemically in several steps into progesterone (4), a hormone that can be used as a female oral contraceptive [30]. Originally, progesterone was isolated from sow ovaries with a very low yield (20 mg from 625 kg of ovaries), and later was synthesized from cholesterol with very low efficiency [31]. Progesterone is also a key intermediate for the production of cortisone (5), an important anti-inflammatory drug. Progesterone can be converted into 11α-hydroxyprogesterone (6)
by microbial hydroxylation at C-11, followed by chemical reactions, to produce

Plant Secondary Metabolites as Drug Prototypes

Sneader has defined a drug prototype as “the first compound discovered in a series of chemically related therapeutic agents”. As of 1996, from a total of 244 drug prototypes identified in one analysis from minerals, plants, animals, microbes, and chemical sources, plant secondary metabolites contributed 56 of these (23 %) [5]. With advances in organic chemistry, medicinal chemists started preparing analogs from these drug prototypes to provide safer and more potent drugs. Sometimes, new compounds with novel pharmacological properties havebeen developed in the process of developing such derivatives. In the following examples, podophyllotoxin, camptothecin, and guanidine have been selected as drug prototypes with analogs having the same pharmacological action as the parent compound, while atropine is a drug prototype that has furnished many analogs that have additional pharmacological properties.

Development of Herbal drug and its challenges

The development of plant drug started when development of chemistry, isolation, purification, characterization of plant active compounds. Herbal medicine is effective, lesser side effect, and affordable than the medicines bought from an allopathic medicine. Herbal medicines include herbs, herbal materials, herbal preparations, and herbal products that contain different parts of plants or other plant materials as active ingredients. It has been well documented that herbal plants and their derivatives play critical roles in modern drug development. Medicinal plants are the natural resources in developing of new drugs [19, 20, 21]. Fig. 1.2 showed the following steps for the development of new herbal drug from plants.


Traditional synthesis
A
B
AB
Combinatorial synthesis
A1
A2
An
B1
B2
Bn
A(1-n)B(1-n)

Suicidal Plant Poisoning

Lec. 9&10

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- Plant poisoning is normally related to accidental exposure to toxic compounds via ingestion. However, the suicidal plant poisoning is common in some parts of the world.
- As the public is aware of toxicity of native plants and they are easily accessible, plants are used for suicidal purposes. Considering the high prevalence of suicide as a worldwide cause of death, knowledge on the varied forms employed to kill oneself is useful in death prevention. Toxicity of plants depends on many factors, ranging from plant characteristics to patient age, size, and weight. In this lecture, plant groups with major toxicity concerns are presented, along with emergency treatment options in cases of intoxication (suicidal or otherwise). This lecture is by no means intended to serve as a manual or reference for suicide, rather as an emergency guide for treating possible suicidal patients.

- It is estimated that over 800,000 people die due to suicide every year, and it is the second leading cause of death in age range of 15–29 years. It is believed that for each adult who died of suicide, there may have been more than 20 others attempting suicide. Exact number of plant poisoning in the world is not known.
- An effective strategy for preventing suicides is to restrict access to the most common means, which include pesticides, household chemicals, firearms, medications, and plants. Unlike others methods, it is difficult to restrict access to plants as they occur in the nature or urban habitats. It is dangerous to consume plants that are not clearly identified.
- Toxicity of plants depends on several factors. These include which parts of the plant are consumed; how fresh are the leaves, flowers, berries, or seeds; and the age and weight of the person.

This lecture discusses plants that are used for suicidal purposes all over the world.

Hemlock (*Conium maculatum*)

- *Conium maculatum* (hemlock or poison hemlock) is a highly poisonous perennial herbaceous flowering plant in the family Apiaceae, native to Europe and North Africa.
- Widely known for its uses in ancient Greece as a means of execution, hemlock's most famous victim was the philosopher Socrates, who suffered the effects of the plant's most potent toxin, coniine.
- There are four species belonging to the genus, and all of them are extremely poisonous. The plants contain a compound called **cicutoxin**, a chemical that is most concentrated in the plant's root system. These roots, when pulled freshly out of the ground, are often mistaken for edible plants like parsnip.

- Ingestion of even small amounts of coniine (6–8 leaves, or an even smaller dose of the seeds or roots) causes death by disrupting the body's neuromuscular junctions, resulting in "ascending muscular paralysis." The paralysis typically begins in a person's legs and ascends up the body until it reaches the respiratory muscles, resulting in death.
- Plants containing nicotine and nicotine-like alkaloids that have been reported to be poisonous to humans include *Conium maculatum, Nicotiana glauca* and *Nicotiana tabacum,* They contain the toxic alkaloids nicotine, anabasine and cytisine. These alkaloids act agonistically at nicotinic-type acetylcholine (cholinergic) receptors (nAChRs).

Conium maculatum

- Nicotine and nicotine-like alkaloids are absorbed readily across all routes of exposure and are rapidly and widely distributed, readily traversing the blood–brain barrier and the placenta, and are freely distributed in breast milk. The treatment modalities include hemodialysis, hemoperfusion, forced diuresis, and artificial ventilation. The cicutoxin molecule size is found to be dialyzable.

Yellow Oleander (*Thevetia peruviana*)

The yellow oleander (*Thevetia peruviana*). (YO) is an ornamental tree of the Apocynaceae family that is common throughout the tropics. It contains cardiac glycosides including thevetin A and B and neriifolin and possibly other as yet unidentified substances that are toxic to cardiac myocytes and autonomic nervous system.

Yellow Oleander

Ingestion of its seeds results in poisoning similar to digoxin toxicity. Severely affected patients may manifest as resistant ventricular fibrillation.

Poisoning due to deliberate self-harm with seeds of yellow oleander results in significant morbidity and mortality each year in South Asia including Sri Lanka.

- Patients should be treated with gastric lavage and activated charcoal or multiple-dose activated charcoal.
- Features of severe toxicity such as persistent vomiting, severe abdominal pain, neurological signs, and persistent hyperkalemia are associated with a high risk of mortality and morbidity.

- Careful observation of cardiac rhythm should continue for a minimum of 24 h. Patients with brady arrhythmias can be treated with intravenous boluses of atropine.
- Anti-digoxin fab fragments can be used in cardiotoxicity induced by ingestion YO.

Glory Lily (*Gloriosa superba*)

Gloriosa superba, well known as the glory lily or superb lily, is a tropical climbing plant that features an exotic red flower. *G. superba* is a plant of the family Colchicaceae. Common names of this plant include flame lily, climbing lily, creeping lily, glory lily, gloriosa lily, tiger claw, and fire lily. The plant is poisonous because of high concentrations of colchicine in all parts of the plant. It is commercially grown for use in Ayurveda medicine and as a cash crop for extracting colchicine in India and Africa. It is a wild plant in Sri Lanka, where commercial cultivation is rare.

- *G. superba* is used in traditional medicine practiced in tropical Africa and Asia.
- The extracts from seeds are effective in the treatment of acute gout, intestinal worms, infertility, and wounds. **The tuber is poisonous and not to be consumed**. It is widely cultivated in India and also in Sri Lanka and Australia. In Africa, it is cultivated in Nigeria and Zimbabwe.
- It is the national flower of Zimbabwe. Accidental and suicidal poisonings with *Gloriosa* tubers are well known and reported.
- There are several alkaloids in tubers of this plant, with highlights to colchicine and gloriosine. Poisoning with *G. superba* is indistinguishable from colchicine overdose. Colchicine inhibits microtubule polymerization by binding to tubulin, and therefore colchicine effectively functions as a “mitotic poison” or spindle poison. This effect is greatest on cells.

Management includes gastric lavage, activated charcoal, and fluid replacement. Ventilation and intensive care treatment may be required.

Castor Oil Plants (*Ricinus communis*)

Castor oil plants (*Ricinus communis*) can be found in houses and gardens all over the world, despite the fact that their seeds are actually very dangerous. It is considered the world's most poisonous plant. The seeds have a toxic protein called ricin or ricinine, and a lethal dose is considered to be in the range of 4–8 seeds. Ricin, similar to abrin, is an enzyme which inhibits ribosomal function, halting protein synthesis and leading to cellular death. Ingestion of the seeds can lead to burning sensations in the mouth and throat, intense abdominal pain, and bloody diarrhea within 36 h and can lead to dehydration, shock, respiratory failure, and death within 3–5 days if leftuntreated.

Conclusion and Future Directions

- Plant poisoning is not very common as a way of suicide, but it is certainly not to be ignored by clinicians.
- Plant intoxication is far more common when happening by accident, either by confusion of lethal plants with edible ones or by ingestion by unsupervised children. Being familiar with these plants is of the highest importance when suspecting of a clinical intoxication scenario. As more information is gathered about plant physiology and their biosynthesis pathways, it is expected that more dangerous compounds may be discovered. Native populations in diverse regions of the world have used various plants as ways of hunting and fishing. Frequently, medicinal plants can also be toxic, and even lethal, depending on the dose, how the plant material is prepared, and ways of administration. Most of this ethnobotanic knowledge is yet to be studied. Even if no one is willing to take their own lives with such plants, to know that they are under risk is at least salutary.

Selecting a plant as medicinal plant

- The approach for drug development from plant resources depends on the aim. Different strategies will result in a herbal medicine or in an isolated active compound. However, apart from this consideration, the selection of a suitable plant for a pharmacological study is a very important.
- There are several ways in which this can be done, including traditional use, chemical content, toxicity, randomised selection or a combination of several criteria.

- The most common strategy is careful observation of the use of natural resources in folk medicine in different cultures; this is known as ethnobotany or ethnopharmacology.
- Information on how the plant is used by an ethnic group is extremely important. The preparation procedure may give an indication of the best extraction method.
- The formulation used will provide information about pharmacological activity, oral versus non-oral intake and the doses to be tested. However, certain considerations must be taken into account when the ethnopharmacological approach of plant selection is chosen.

For instance, each ethnic group has its own concepts of health or illness, as well as different healthcare systems. The signs and symptoms should be translated, interpreted and related to western biomedical concepts, thus allowing a focused study of a particular therapeutic property.

- Selection based on chemical composition uses phylogenetic or chemotaxonomic information in the search, mainly in certain genera and families, for compounds from a defined chemical class with known pharmacological activity.
- The search for highly specific potent drugs for therapeutic use and, more precisely, as a investigation tool in biological research has been quite productive in toxic plants. A number of important compounds now used in research came from toxic plants and several examples have been mentioned earlier.