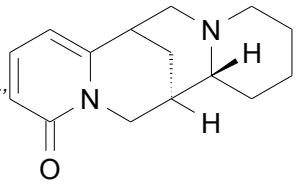
Toxicology of alkaloids
I.

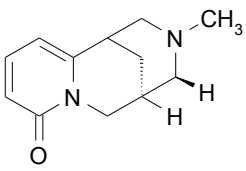
- **Alkaloids**
  - Nitrogenous compounds
  - Metabolic transformation of aminoacids or /and other precursors (pseudoalkaloids)
  - One or more atoms of nitrogen
    - built into cycle (heterocyclic alkaloids)
    - aliphatic (protoalkaloids)
  - Heterocyclic alkaloids:
    - Quinolizidine, piperidine, pyridine, pyrrolizidine,
    - Isoquinoline, indol, quinoline, imidazol, terpenic, steroid
  - Important pharmacological and toxikological activity

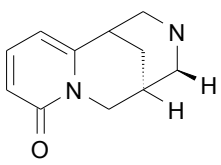
– **Quinolizidine alkaloids**
  - Activity similar to quinidine
  - Activity on ion channals (Na, K), nicotinic and muscarinic receptors, affection of proteosynthesis

– **Anagyrine**
  - *Anagyris foetida, Cytisus spp., Genista spp., Lupinus spp., Sophora spp*. Fabaceae
  - Vasoconstriction
    – Central
    – Increased release of adrenalin
  - Teratogenic
    – Skeletal contractive deformation
    – Cleft palate
    – Mainly described for calfs
    – Inhibition of foetus movement in uterus
    – U lidí
      » Erythrocytary aplazia
      » Vascular anomalies
      » Skeletal dysplazia

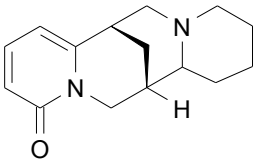


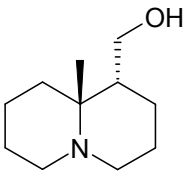
•**Cytisine, *N*-methylcytisine**
  –*Laburnum anagyroides, Cytisus spp., Genista spp., Sophora spp*. Fabaceae
  – Common intoxications
  – Similar to nicotine intoxications
    • Mydriazis, salivation, sweting
    • Burning in mouth
    • Central irritation causing vomiting
  – Large amount
    • Delirium, excitation
    • Tonic-clonic convulsions
    • Respiratory distress



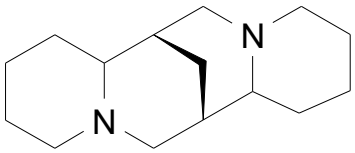


- Lupanine, lupinine, isolupinine
  - *Lupinus* spp., *Genista* spp., *Cytisus* spp. Fabaceae
  - Mostly pasturing animals
  - Lupinosis
    - Anxiety, convulsions
    - Icterus





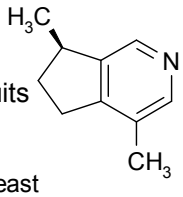
- Sparteine
  - *Sarothomnus scoparius, Genista tinctoria* Fabaceae
  - Effect most similar to quinidine
    - Delay and slowering of excitement transfer
      - Ventricular arrhythmia to arrest
    - Minimal effect on CNS
    - Peripherial:
      - Paralyse terminations of motoric nerves
      - Curare-phormous affection of sympathic ganglia
    - Image of intoxication:
      - Nausea, diarrhea, vomiting
      - Vertigo
      - Tachycardia?
      - Circulatory collapse
      - Decrease of glycaemia
        - » Increased release of insulin

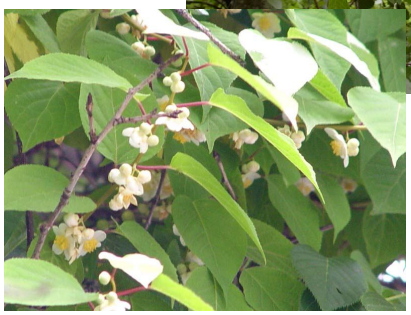


- Metabolism of sparteine
  - Genetic polymorphism CYP2D6
  - 5-10% of population slow metabolisers
  - 2,3-dehydrosparteine
  - Hydroxylation, conjugation
  - Excretion *via* kidneys

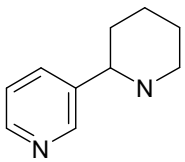
- Piperidine and pyridine alkaloids
  - Toxicologic importance
  - Coniine, nicotine, tropane alkaloids

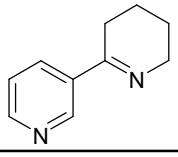
- Actinidine
  - *Actinidia polygama* Actinidiaceae silver vine
  - Similar to kiwi, edible fruits
  - Poisonous leaves
    - Sedative effect
    - Excitation of Felidae beast
  - Toxic substance of defensive secret of some insects
- *N*-(p-OH-phenylethyl)-actinidine
  - Inhibitor of cholinesterase
  - *Valeriana officinalis* Valerianaceae



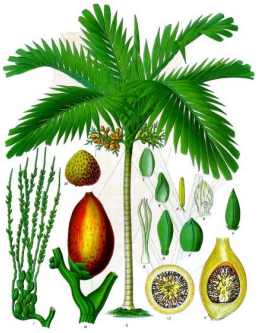


- Anabasine
  - *Nicotiana* spp. Solanaceae
  - *Anabasis* aphylla Chenopodiaceae
  - Similar to nicotine
  - Highly toxic
  - Often intoxications
  - Teratogen
    - Poultry, cattle, pigs
    - tzv. arthrogryposes
- Anabaseine
  - *Aphaenogaster rudis*





- Arecoline
  - *Areca catechu* betel Arecaceae
  - Muscarinic effect
  - Higher dosage affects also nicotinic receptors
  - Salivation, perspiration, miosis



Areca catechu L.
Image processed by Thomas Schoepke
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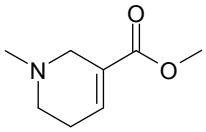
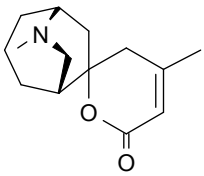
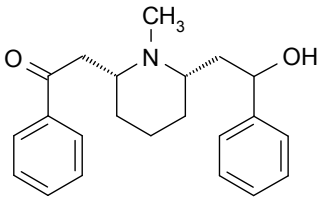


- Dioscorine
  - yam
  - *Dioscorea* spp. Dioscoreaceae
  - Anticholinergic
  - Convulsions

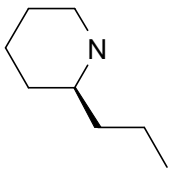


– Lobeline
  - *Lobelia* spp. Lobeliaceae
  - *Campanula medium* Campanulaceae
  - Nausea
  - Stimulation of CNS and GIT

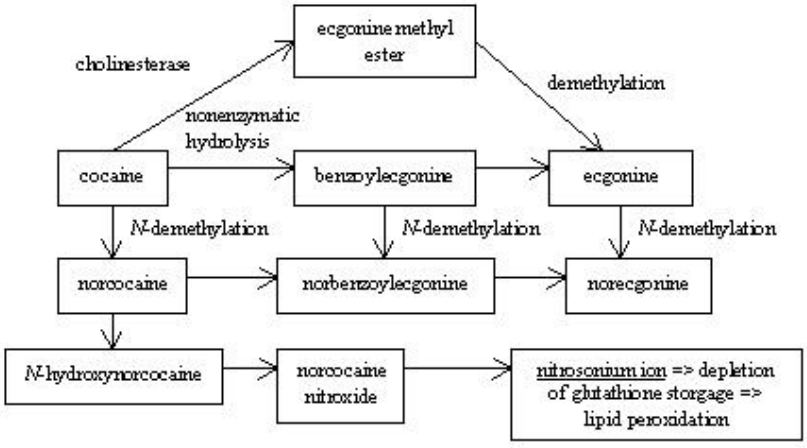
– 4´-*O*-methylpiridoxine
  - B6-antivitamin
  - Hypersensitivity, convulsions, death
  - Mainly cattle
    – Pasture of *Albizia* spp.
  - *Gingko biloba*



- Coniine, *N*-methylconiine
- γ-coniceine (*Aloe globuligemma*)
  – *Conium maculatum* Apiaceae
  – Local irritation
  – Paralysis of snesoric and motoric nerves
  – Typical ascending paralysis of skeletal muscles
  – Terminal stage
    - Respiratory arrest in full consciousness nad heart action
  – Symtoms
    - Nausea, salivation, vomitus
    - Stomach pain with diarrea
    - Landry´s ascending polyneuritis
  – Chronic intoxication
    - teratogenic



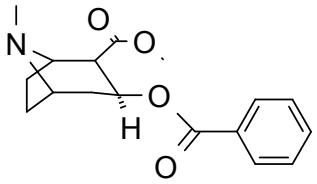
- Cocaine
- *Erythroxylon cocca*, Erythroxylaceae
  - History
    - Indians of Chibcha tribe
    - Incas
    - Spanish
    - Coca-cola till 1904
    - 1860 Albert Niemann – pure cocaine
    - Sigmund Freund, Carl Coller



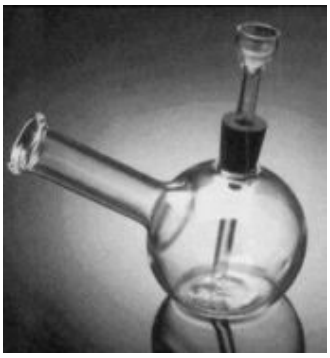
–Metabolism

–Formation of ethylderivative during intoxication by ethanol

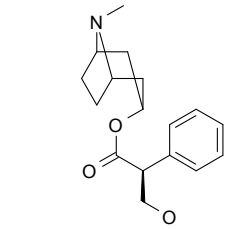
- Mechanism of rffect
  - Indirect sympathomimetic (inhibitor of noradrenaline reuptake)
  - Block of ion channels of neurons (disorder of excitement transmission)
  - Adrenergic stimulation
- Peripheral effects
  - Vasoconstriction, hypertermia, mydriazis
  - Low dosage - ↓ of heart rate
  - High dosage - ↑ of heart rate, cardial arrest
- Central stimulation
  - Euphoria, depletion of neutransmiters (NA), short depressive effect
  - Rise of psychic dependence
    - Does not induces physical dependence
  - Intelectual stimulation, hyperactivity, hyperlucidity
  - Self-deceit, paranoid psychosis



- Cocaine
  - Complications during usage
    - Cardiovascular failure
  - Way of use
    - As salt (chloride) or base
    - Chloride
      - Snuffing, i.v.
    - Base
      - Smoking (crack), inhalation
    - Mixture with heroine
      - snowball
    - Mixture with alcohol
      - Cardiotoxic
      - Highly euphoric



- Tropane alkaloids
  - Azabicyklo[3,2,1]octane
  - Apoatropine, atropine, hyoscyamine, scopolamine
  - Solanaceae
  - Parasympatholytic
    - Competitive antagonists of acetylcholinergic receptors
      - Muscarine type
  - Intoxication
    - Facial redness, dry mucose, thirst
    - Tachycardia, mydriasis
    - Hypertermia, central excitation, halucination
    - Coma, respiratory distress



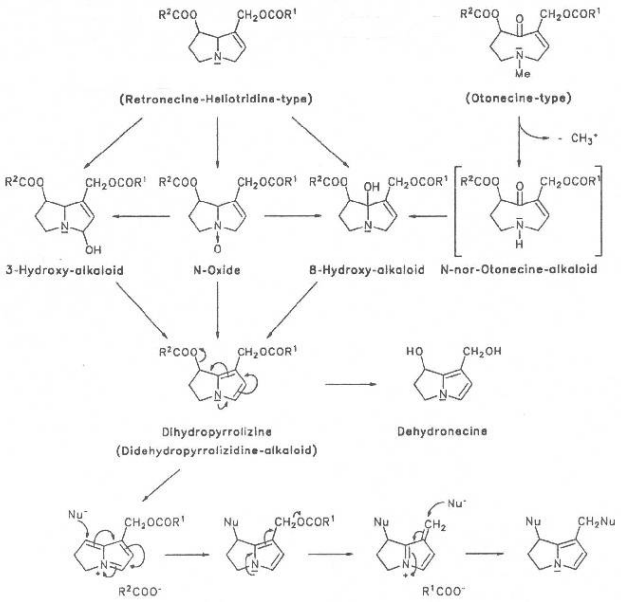
- Pyrrolizidine alkaloids
  - Asteracea, Fabaceae, Boraginaceae
  - Ester bonded alkaloids
    - Necine part (base, bicyclic pyrrolizidine, sometimes 1,2 dehydroform)
    - Necic acid or fragment
  - Dehydroform more toxic
  - 360 compounds
    - Makrocyclic diesters
    - Open diesters
    - Monoesters
  - Metabolism in plant:
    - Synthesis in roots via *N*-oxides
    - Transport through phloem
    - Storage in vacuoles, in water as *N*-oxides
    - Loss of water – tertiary bases

***Senecio* spp.**

***Heliotropium* spp.**

Symphytum officinalis

–Metabolism in vertebrae
- *N*-oxides polar and non-toxic
  - –Do not cross membranes
  - –Unstable
  - –Reduction in gut to tertiary amines
  - –Crossing membranes thanks to lipophilicity
    - »Non-protonated
- Partially cleaved to base and acid
  - –Non-specific blood esterase
  - –Non-toxic (no metabolites)
  - –Conjugation and urine excretion
  - –Steric protection – not cleaved
- In liver
  - –Oxidation to pyrrol, hydrolysis
  - –Derivatives with exocyclic methylene



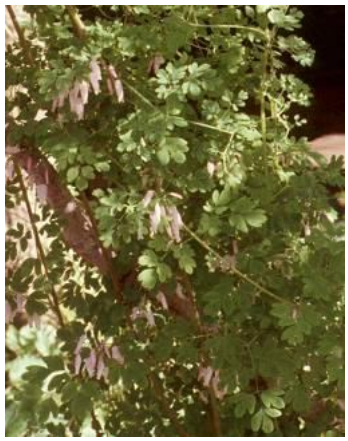
E. Röder. *Pharmazie* 50 (1995), 83-98.

- Toxicity
  - *N*-oxides similarly toxic to tertiary alkaloids
  - Polar – therefore rapid excretion
  - Acute toxicity
    - Hepatotoxicity
      - Megalocytosis of hepatocytes (upto 30 times bigger)
      - Enlargement of hepatocytes nuclei
      - Disorder of hepatocyte metabolism
      - Disorder of mitosis
      - Cellular destruction
      - Fat degeneration
    - Intake of 10-20 mg of alkaloids
    - Larger scale of cells destruction – liver failure, death.
  - Chronic toxicity
    - Proliferation of bile ducti epitel
    - Inflammatory changes
    - Centrilobular necrosis
    - Cirrhosis, ascites
    - Venooclusive disease
      - seneciosis
  - Clinical symptoms
    - Pain in underbelly
    - Vomiting, diarrhea
    - Ascites
    - Swelling of liver
    - Vasomotoric collapse
    - Blood regurgitation, blood diarrhea
    - After liver damage
      - Pulmonary damage, stimulation of pulmonary arterial epithelium
      - Cor pulmonale

- Intake of sub-toxic doses for long time (about 1 mg)
  - Megalocytosis
  - VOD
  - Fat degeneration of liver
  - Adenomas or carcinomas
    - Middle and South Africa
      - Usage of several medicinal plants
      - *Crotalaria*, *Cynoglossum*, *Heliotropium* and *Senecio*
- Mutagenicity
  - senkirkine > monocrotaline > seneciphylline > senecionine > 7-acetyl-intermedine > heliotrine > retrorsine > 7-acetyllycopsamine > symphytine > jacoline > symlandine > intermedine > indicine > lycopsamine > indicin *N*-oxide > supinine
  - Hydroxylation of structure decrease mutagenicity
- Teratogenity
  - 50 to 200 mg alkaloid/kg of body weight
    - Damage and changes
  - Death of fetus
    - More than 200 mg/kg

- Isoquinoline alkaloids
  - Different structures
  - Different biogenetic pathways
  - Wide occurrence
  - Isoquinoline nucleus
  - Derived from tyrosine
    - Tetrahydroisoquinoline
    - Benzyltetrahydroisoquinoline
    - Bis(Benzyltetrahydroisoquinoline)
    - Amaryllidaceae
    - Monoterpenoid

- Adlumine
  - Phtalidoisoquinoline alkaloid
  - *Adlumia fungosa*, *Fumaria* a *Coryldalis* spp. Fumariaceae
  - Convulsions, cardial depression
  - Gut stimulation
  - Uterotonic
- Bicuculine
  - Phtalidisoquinoline alkaloid
  - *Corydalis, Fumaria, Adluminia* Fumariaceae
  - Antagonist of $GABA_A$
  - For experimental purposes

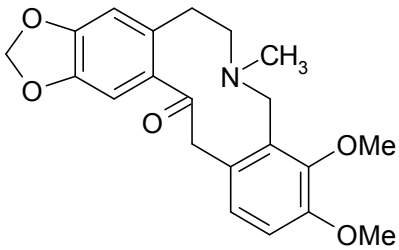


Adlumia fungosa

Fumaria officinalis

Corydalis lutea

- Allocryptopine
  - Benzylisoquinoline alkaloid of protoberberine type
  - *Bocconia* spp., *Chelidonium* spp., *Glaucium* spp. Papaveraceae
  - *Corydalis* spp. Fumariaceae
  - *Zanthoxylum* spp., *Fagara* spp. Rutaceae
  - *Thalictrum* spp. Ranunculaceae
  - Increases bond of GABA to receptors (benzodiazepine activity)
  - Inhibition of phosphodiesterases
  - Bond to adrenergic α-receptors
  - Toxicity
    - Non-specified cardial toxicity

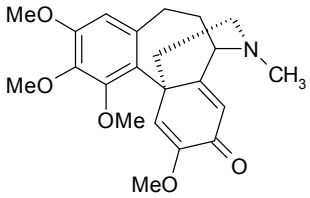


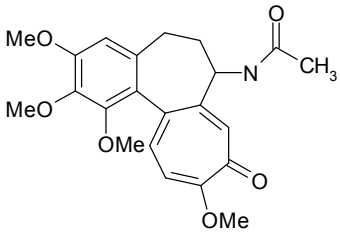
Escholzia californica

Bocconia spp.

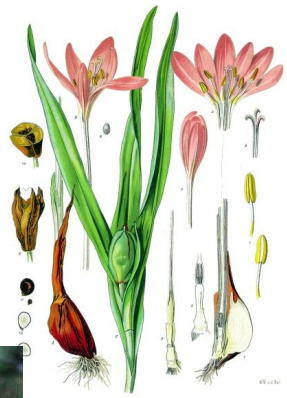
Chelidonium majus

- Androcymbine
  - *Androcymbium melanthoides* Liliaceae
  - Homomorphinan alkaloid
- Colchicine
  - *Colchicum* spp., *Gloriosa superba*, *Merendera* spp. Liliaceae
  - Exocyclic amine derived from tyrosine
  - Toxicity
    - Toxin of cell division
      - Inhibition
        - » Transport of proteins and saccharides in neural cells
        - » Transport of vesicules to memebranes
        - » Transport of chromosomes from equatorial position to poles
      - GIT, heart, neural tissue, haemopoiesis
    - After consumation rapid absorption, strong linkage to plasmatic proteins, later biliar elimination
      - Gut reabsorpce (lonf termed toxicity, cumulation of low dosage)





Androcymbium spp.



Colchicum autumnale L.
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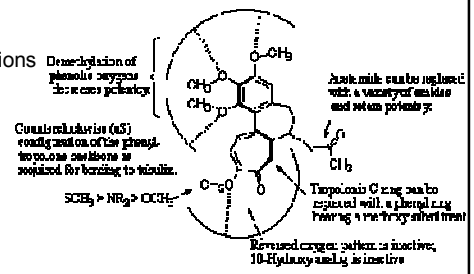
Merendera spp.

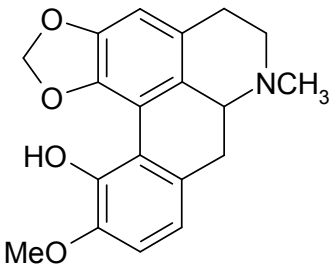
Gloriosa superba

- **Symptoms**
  - Similar to arsenic intoxication
    - Burning of oral and throat mucosa
    - Nausea, vomitus
    - Stomach pain, colics, convulsive urination
    - Watery and bloody bowel movement, hemorrhage to GIT
    - Loss of liquids, plasma, electrolytes
    - Circulatory disorders, hypotension, tachycardia, shock

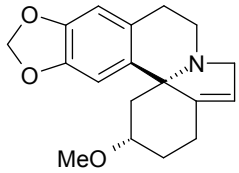
- **Toxicity**
  - Damage of liver tissue
  - Damage of nerves
    - Mental confusion, tonic-clonic convulsions
    - Loss of tendinous reflexes
  - Alopecia
  - Lethal dosage variable
    - 7 mg to 50 mg, 20-30 mg in average
  - Acts slowly
    - First symptoms in several hours
    - Death comes first in 12 hours

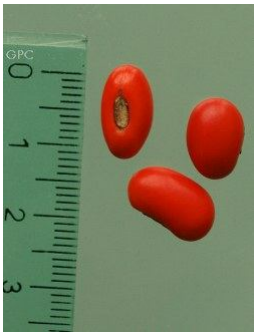


- Bulbocapnine
  - Aporphine type of alkaloid
  - *Corydalis* spp., *Fumaria* spp.
  - *Glaucium* spp. Papaveraceae
  - Toxicity
    - So called bulbocapnine numbness
      - Catatonia
      - Slowering of cognitive function
      - Bizarre movements of extremities
      - High dosage
        - » Tremor, convulsions
        - » Circulatory disorders, respiratory paralysis
    - Inhibition of peristaltic
    - Stimulation to paralysis of uterus
    - Hyperglycemia

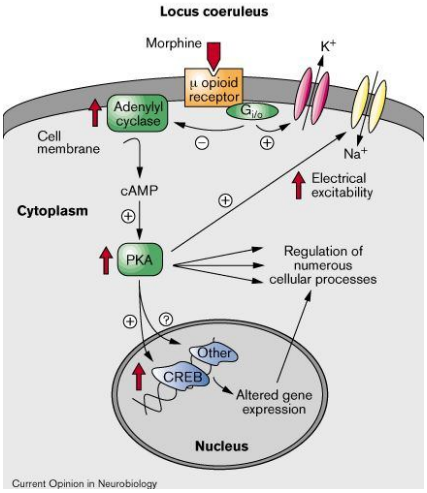


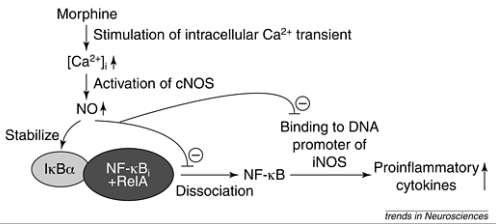
- Erythrina alkaloids
  - β-erythroidine, erysonine, erythratidine
  - *Erythrina* spp. Fabaceae
    - Mostly *Erythrina americana*
  - Highest concentration in seeds
  - Boiling lowers toxicity
  - Toxicity
    - Used as halucinogenic (Mexico)
    - Vomiting and diarrhea
    - Peroral administration of pure substances
      - Neuromuscular blockator
        - » Curare-forming effect
        - » Sedative effect on CNS
        - » Depression of respiratory centre



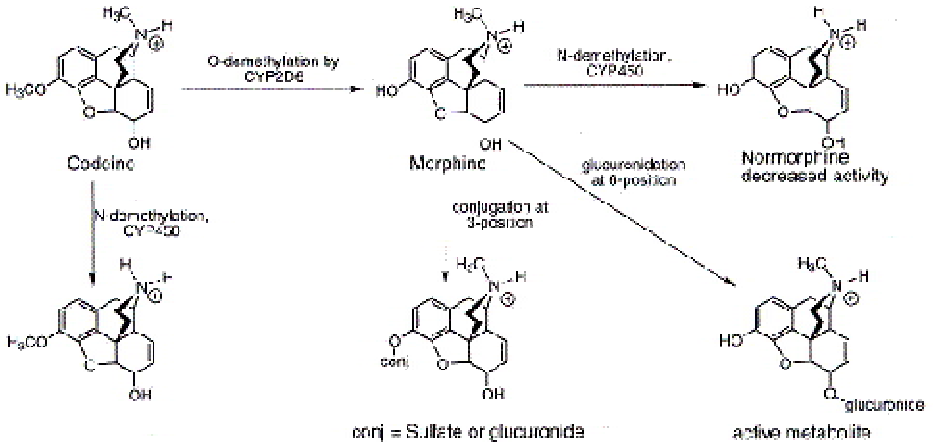


- **Morphine, codeine, heroine**
  - –Morphinan alkaloids
  - –Effective levorotary form
  - –Morphinan type of alkaloids
    - Typical for *Papaver* spp. Papaveraceae
    - Morphine
      - –*P. somniferum, P. setigerum* Papaveraceae
  - –Stereospecific, reversibile linkage to opioid receptors
    - At diiferent levels of CNS
  - –Agonist at presynaptic receptors of myelinized fibers of small diameter
    - Nociception, inhibition of substance P release
    - Uprise of physical dependance
      - –Inhibition of enkephaline production and simultaneous occupation of receptors
      - –Insufficiency of natural ligands and morphinans
        - » Withdrawal syndrome
  - –Effect on respiration
    - Depression of respiratory centre
      - –Decrease of sensitivity to hypoxia and pCO_2
      - –Dependent on dose
      - –Tempo of onset dependent on way of administration
  - –Miosis of central origin
  - –Depression of centre for cough
  - –Complex effect on centre for vomiting
    - Nausea and vomiting
  - –Influence on hypophysis
    - ↓secretion of FSH, LH, ACTH
  - –Influence on hypothalamus
    - ↑secretion of ADH
  - –Influence on fibers of smooth muscles
    - Constipation and urinary retention

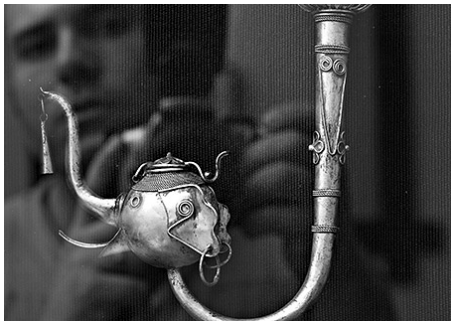




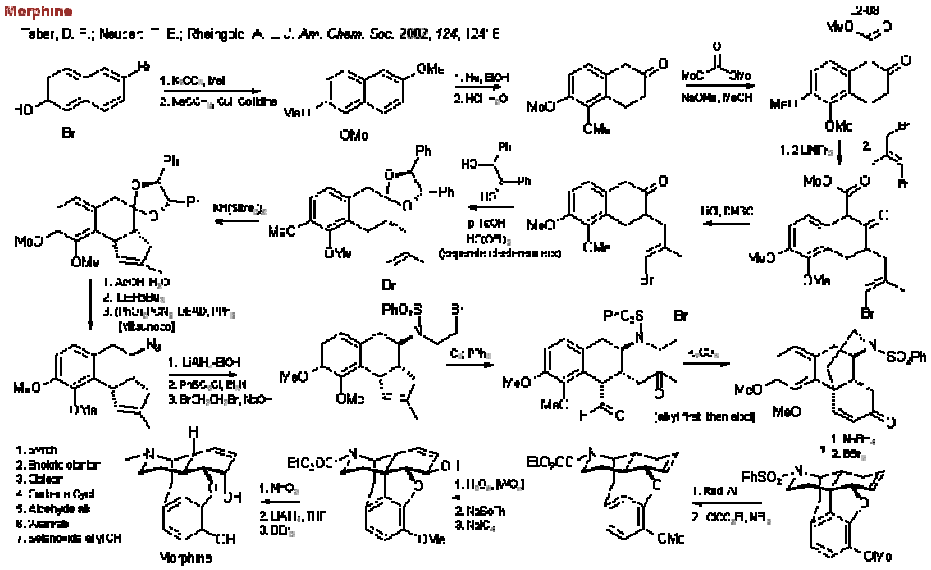
- Morphine metabolism

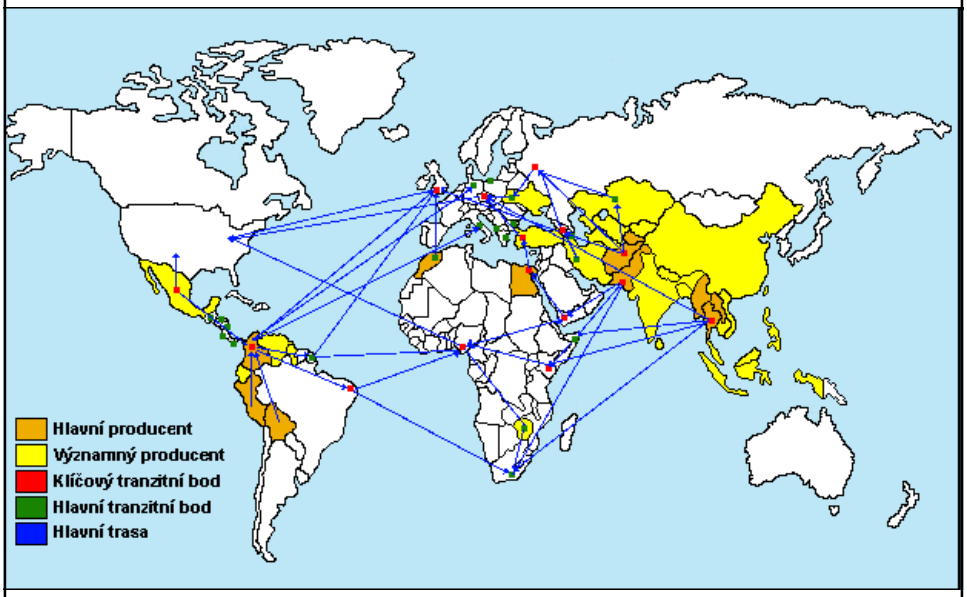


- Symptoms of withdrawal
  - Chronic users
    - Nasal bleeding, perspiration, lachrymation, anxiety
    - Mydriasis, myalgia and pain of joints
    - Insomnia, tachycardia, arrhythmias, polypnoe, dispnoe
    - Nausea, diarrhea
- Acute intoxication
  - Usually overdose from different reasons
  - High dosage
    - Immediate depression of CNS
  - Lower dosage
    - Initial short stimulation
    - Successive malaise, fatigue, somnolence
    - Heart rate decreases and tends to fade
    - Respiration slow and shallow
    - Loss of consciousness
    - Relaxation of muscles, extinction of reflexes
    - Cold, pale, wet skin
  - If the dose high enough
    - Coma, relaxation of muscles
    - Circulatory failure, cyanosis
    - Death caused by CNS depression
      - Respiratory arrest

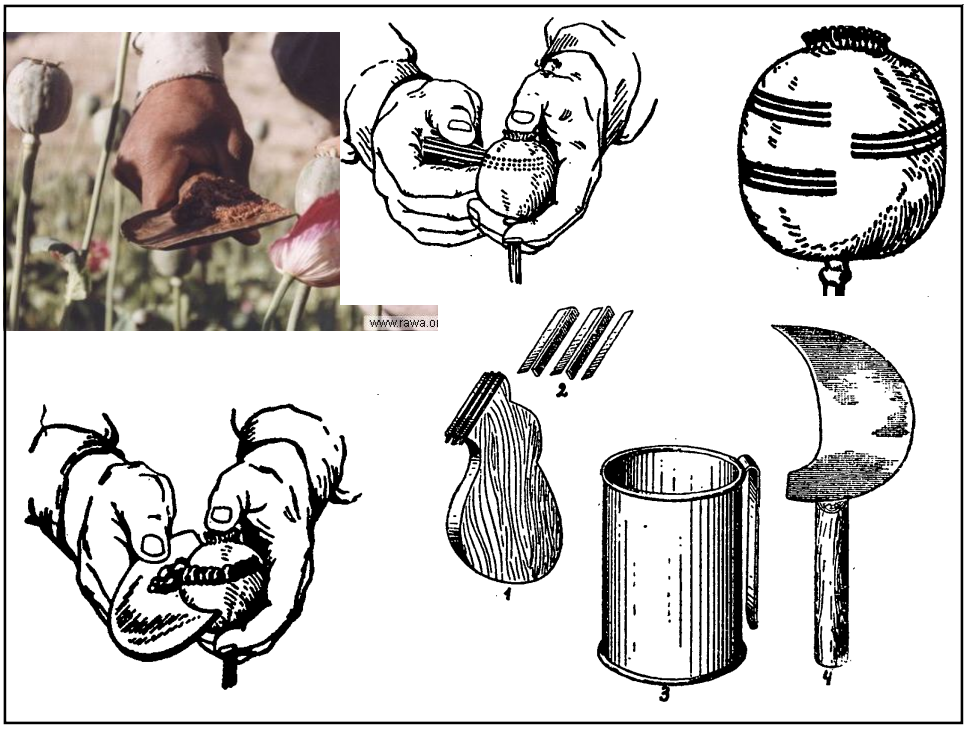


- Chronic intoxication
  - Morphinism
    - Short time of uprise
      - Strong analgetic
      - Experiments with drug
    - Tolerance to dosage
    - Combination of health problems
      - Social excomunication
        - » Psychical and physical dilapidation
      - Criminality
      - Prognosis adverse
        - » Accompanying diseases
        - » Suicidal tendences

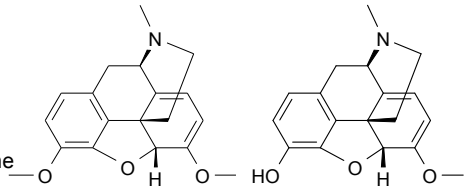


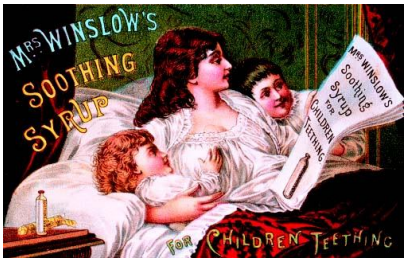


http://www.mujweb.cz/www/jpdepot/danger/Drugs.htm

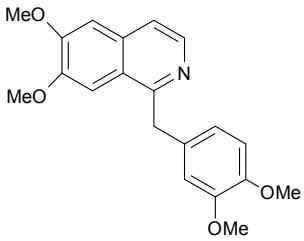


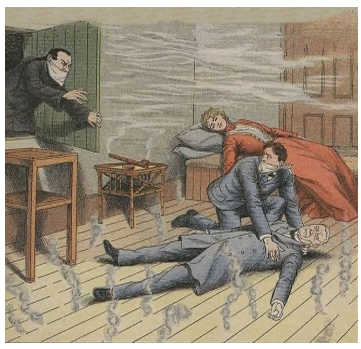
- Thebaine
  - Morphinane type of alkaloid
  - *Papaver somniferum, Papaver bracteatum* Papaveraceae
  - Metabolism
    - oripavine, nororipavine and codeine
  - Symptoms similar to strychnine
    - Higher doses convulsion
  - Inhibitor of cholinesterase
  - Stimulation of CNS
  - ↑ deliberation of histamine
  - More toxic than morphine, lower risk of triggering dependence



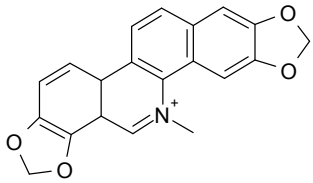


- Papaverine
  - Benzylisoquinolin alkaloid
  - *Papaver somniferum*
    - In opium cca 1 %
  - No effect on CNS
  - Relaxation of smooth muscles
    - Vessels, lungs, GIT
  - Quinidine effect on heart
    - Risc hypotension and arrhythmias
  - Symptoms of intoxication
    - Cardiovascular system
    - Headache
    - Constipation, vomiting
    - Sweating

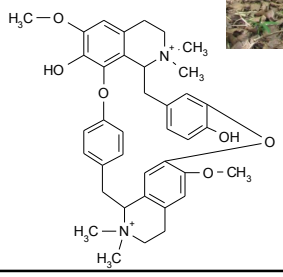




- Sanguinarine
  - Benzophenanthridine alkaloid
  - *Sanguinaria canadensis*, *Papaver somniferum*, *Chelidonium majus* Papaveraceae
  - *Fumaria officinalis* Fumariaceae
  - Peroraly only low toxicity
  - Parenteral administration
    - Much higher toxicity
    - Depressor of heart function
    - Effect on CNS
  - Symptoms
    - Vomiting, gastritis, stomach pain
    - More difficult respiration
    - Miosis, syncope
    - Cardiac arrest
  - Epidemiologic studies
    - Higher incidence of glaucoma



- **Tubocurarine**
  - *Chondrodendron* spp., mostly *Ch. tomentosum* Menispermaceae
  - Part of curare
    - Active after parenteral administration only
  - Competition with acetylcholine
    - On the nicotine receptor of neuromuscular disc
    - Prevent formation of excitement
    - No influence of other type of excitement formation
    - Do not prevent muscle contraction triggered by direct stimulation
  - Effect of curare
    - Lowering of muscle tonus
    - Advancing atonia
    - Muscular paralysis
      - Firstly face and eye lid
      - Neck and numbs
      - Abdominal and respiratory muscles
      - Diaphragm
    - Peripheral myorelaxant
    - Effect not persisting
  - Teratogenic



- **Alkaloids of Amaryllidaceae**
  - *Galanthus, Leucojum, Narcissus, Lycoris, Amaryllis, Hippeastrum*
  - More than 100 of toxic alkaloids
  - Several sub-groups
    - Most important lycorine, galanthamine, narciclasine

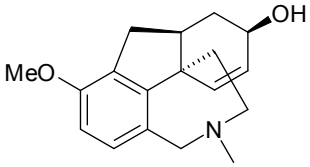
Lycoris radiata

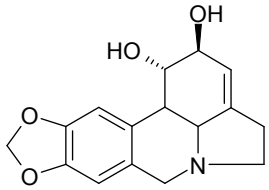
Amaryllis spp.

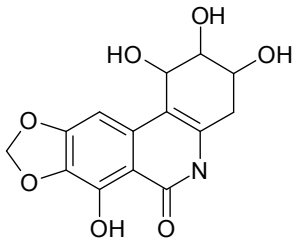
Hippeastrum equestre

Haemanthus spp.

- **Galanthamine**
  - Reverse inhibitor of acetylcholinesterase
    - Mostly in CNS
    - Less on peripheria
  - Disorders of atrioventricular transmission
  - Bradycardia
  - Nausea, vomiting, hypotension, analgesia
- **Lycorine**
  - Respiratory depression, death caused by respiratory arrest
  - Strong emetic
  - Symptoms
    - Vomiting, diarrhea, congestion of GIT musosa
    - Congestion of pleura and endocardium
  - It is cytotoxic
- **Narciclasine**
  - Antimitotic activity
    - Inhibition of protein synthesis by blocking the bigger ribosome subunit







- Monoterpenic isoquinoline alkaloids
  - Emetine
    - *Cephaelis* spp. Rubiaceae
    - *Hedera* spp. Araliaceae
  - Intoxication
    - Usually overdose of drug
    - Muscular weakness, tachycardia, abnormalities on ECG
    - Changes in ALT, AST levels
    - GIT malaise
      - vomiting, diarrhea, pyloric inflammation
    - Lethal dose cca 1 gram