# Terpenoids

- The widest biosynthetic group of secondary metabolites
  - (> 22 000 of structures)
  - From 70ies 2× more of described compounds
- Function in plant
  - Hormons
  - Pigments
  - Electron transporters
  - Intermediates in sugar metabolism
  - Building material
  - Communication
  - Attractants
  - Repelers
  - Defensive compounds
- Relatively high levels in
  - Essential oils
  - Waxes
  - Resins
- Many times volatiles – possibility of inhalation
- On the surface – possibility of contact

- Esters
  - Hydrolysis to alcohols and carboxylic acids
  - Mostly in liver
- Products detoxified
  - Primary by conjugation with glucuronic acid – excretion in urine
  - Unsaturated alcohols 4-oxidysed at allyl
    - polar metabolites – diols
    - conjugation - excretion
    - or excreted freely
    - Primary alcohols could be further oxidized
  - Metabolites of acyclic alcohols – oxidation to $CO_2$.

**Figure 1. Metabolism of linalool in mammals**

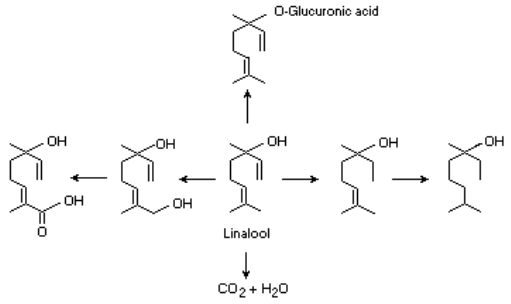
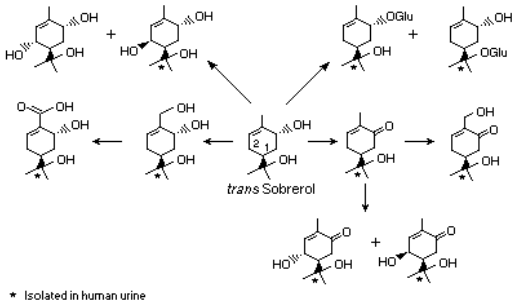


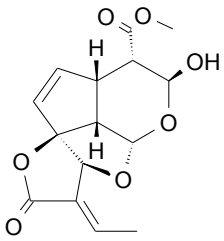

**Figure 3. Metabolism of trans-sobrerol in rats, dogs, and humans**



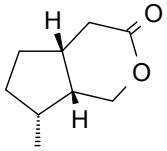

* Isolated in human urine

- Monoterpenes
  - Volatile part of essential oils
  - *Lamiaceae, Cupressaceae, Asteraceae, Apiaceae*
  - Sub-groups
    - Iridoids
    - Cyclic monoterpenes
    - Acyclic monoterpenes

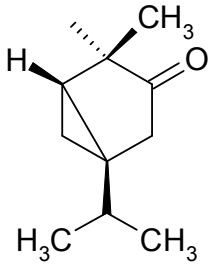
- Toxic iridoids
  - Alamandin
    - *Allamanda cathartica* Apocynaceae
    - South America
    - *Golden Trumpet*
    - Irritating after contact
    - Per os only high amounts
      - Vomiting and diarrhea


  - Boschnialacton
    - *Boschniakia rossica* Orobanchaceae
    - Parasitic plant
    - Toxic for *Felidae* (cats)
      - excitation



- Thujone
  - Natural mixture of isomers α,β (33% α, 67% β)
  - *Artemisia absinthium, A. vulgaris, Salvia officinalis*, *S. sclarea*
  - *Tanacetum vulgare*
  - *Thuja occidentalis*
  - Folk medicine:
    - Abortive, emenagogue, digestive, carminative, antiphlogistic, anthelmintic
  - Analgesic, analeptic, antidepressive

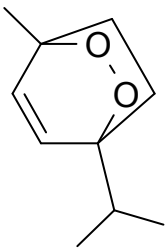



  - Toxicity:
    - CNS effect
      - Tonic-clonic convulsions, cumulative effect
      - Absinthism
        - » hyperexcitability, hallucination
    - Nephrotoxicity (degenerative changes)
    - Hepatotoxicity
      - Dependence on dosage and sensitivity
  - Mechanism of effect:
    - Blockator of $GABA_A$ chloride channel (similarly to picrotoxine)
    - α-thujone 2.3× more effective than β-thujone
    - Low affinity to cannabinoid receptors
    - Metabolism:
      - Reduction of ketone to hydroxyl, excretion in urine
      - 7-OH-thujon, dehydrothujon – also active
  - Absinthism
  - Oscar Wilde:
    - "The first stage is like ordinary drinking, the second when you begin to see monstrous and cruel things, but if you can persevere you will enter in upon the third stage where your see things that you want to see (what is the most horrible thing)."

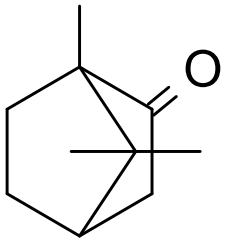
*Tanacetum vulgare*

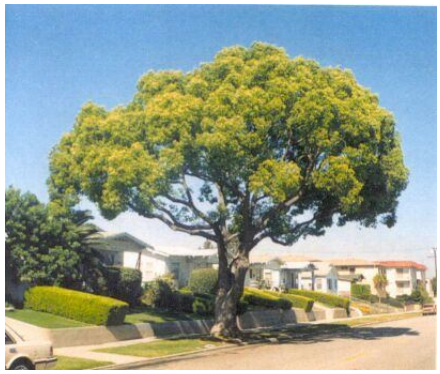

*Thuja occidentalis*

- Toxic cyclic monoterpenes
  - Ascaridol
    - *Chenopodium ambrosioides* var. *anthelmintikum* Chenopodiaceae
    - *Peumus boldus* Monimiaceae
    - Vomiting, vertigo, gastritis, muscular weakness
    - Affection of cardiac activity and blood pressure, CNS depression, convulsions
    - Cancerogene

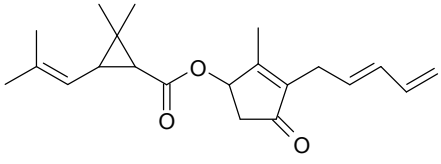



- **Toxic cyclic monoterpenes**
  - **Camphora**
  - *Cinamomum camphora* (+)-form
  - *Tanacetum parhenium, Arthemisia, Lavandula* (-)-form
  - Hydroxylation at many positions
    - glucuronisation
  - Nauzea, vomiting, headache, blue-red vision
  - Excitation of CNS
    - Unassines, derangement, hallucination, tremor
    - Convulsions, respiratory depression, coma
  - Hyperaemic skin
  - Cardiotoxicity
    - Similarly to caffeine
  - High toxicity for foetus



- Toxic cyclic monoterpenes
  - **Pyrethrins**
    - Pyrethryns I and II
    - Cynerins I and II
    - Jasmolins I and II
    - *Pyrethrum parthenium*, syn. *Chrysanthemum parthenium, Tanacetum parthenium* (řimbaba) Asteraceae
    - Metabolism:
      - unchanged
      - Metabolized to chrysanthemumic acid and further
        - » Less toxic metabolites
        - » In liver, into bile
    - Acute toxicity:
      - Inhalation – asthmatic attack
      - Neurotoxic poison – $Na^+$ a $Ca^{2+}$ a $Cl^-$ channels
        - » lethargy, vomiting, tremor, convulsions, irritability
        - » Hypersensitivity to stimules
        - » Paralysis, respiratory distress
    - Chronic toxicity low



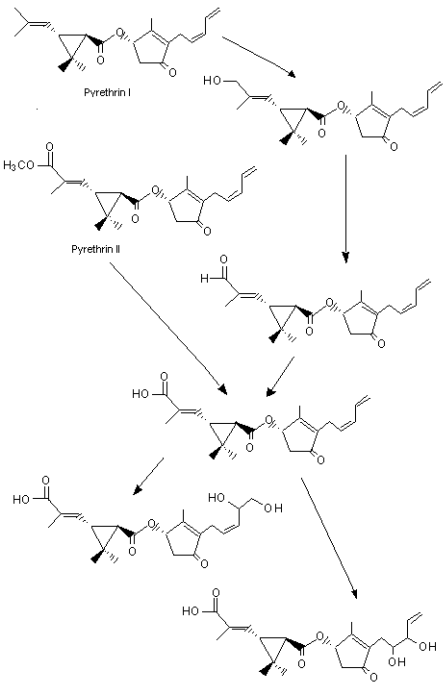
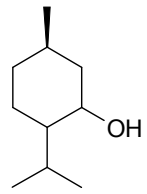
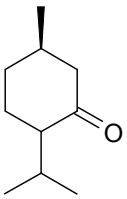


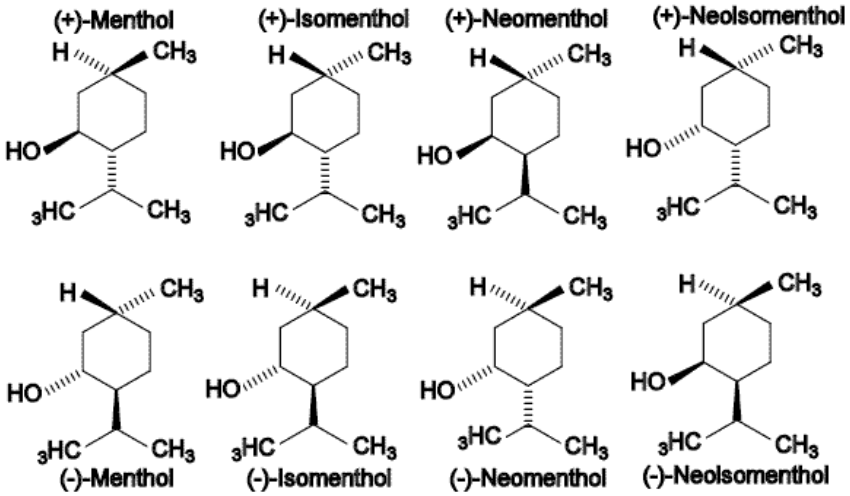

**Figure 1. Pathways for the formation of metabolites in the urine of rats treated orally with pyrethrins I and pyrethrins II** From Casida & Quistad (1995)

1. Pyrethrin I:
   - •Oxidation
2. Pyrethrin II:
   - •Oxidation after hydrolysis
3. Both via carboxylic chrysanthemumic acid
4. Diol

- Menthol
  - *Mentha spp*. Lamiaceae
  - Toxic in high doses
    - Stomach pain, vomiting
    - Vertigo, coma
    - Children:
    - asphyxiation via spasm of glottis
- Pulegone
  - *Mentha spp*. Lamiaceae
  - Toxic in high doses
    - Stomach pain, vomiting
    - Hepatotoxicity
    - Kidney insufficiency
    - Metabolite - menthofuran



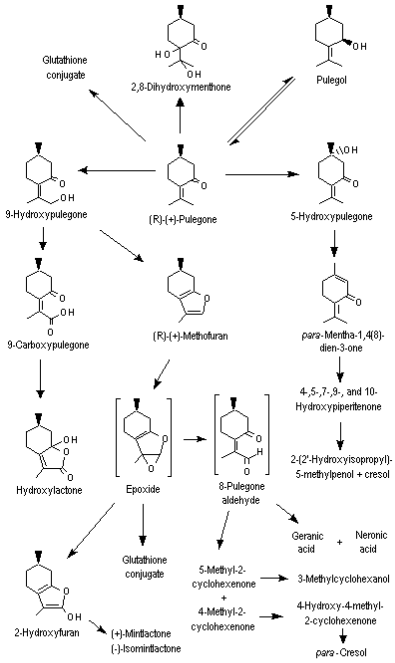
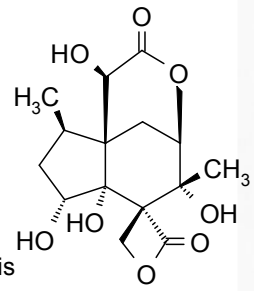




**Figure 2. Metabolism of pulegone, para-mentha-1,4(8)-dien-3-one, and menthofuran**

- **Sesquiterpenes**
  - Mostly lactones
    - Division:
      - Guajanolides
      - Eremophilanolides
      - Pseudoguajanolides
      - Xantholides
      - Germacranolides
  - Fragrant and bitter substances
  - Toxicity
    - Convulsants
    - Irritation of GIT
    - Alergenes
      - Exocyclic methylene group
        - » Binding to amino acids
      - Crossed reactivity
      - Dependent on concentration, individual sensitivity
    - Often observed cytotoxicity
  - Family Asteraceae

- Toxic sesquiterpenic lactones
  - Absinthin
    - *Arthemisia absinthum* Asteraceae
    - Neurotoxicity dubious
  - Alantolactone
    - *Inula spp*. Asteraceae
    - Alergic contact dermatitidis
  - Anisatine
    - *Illicium anisatum* Illiciaceae
    - Neoanisatine, pseudoanisatine
    - Picrotoxine type of toxin
      - Non-competitive GABA inhibitor
      - Binding at picrotoxine site
    - Neurologic and gastrointestinal toxicity
      - Nausea, vomiting
      - Tremor, myoclony, convulsions



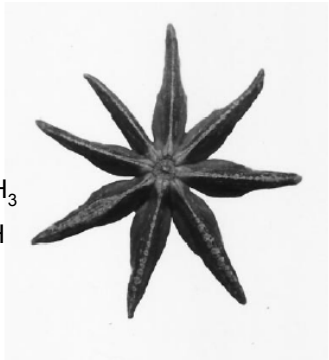
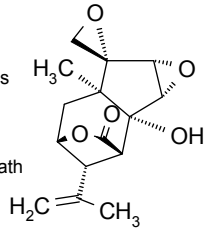



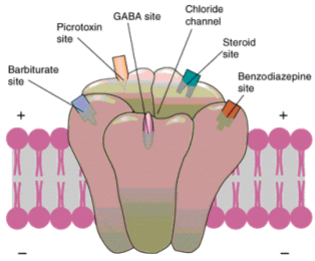
Fig 1. Morphology of Chinese anise star fruit.

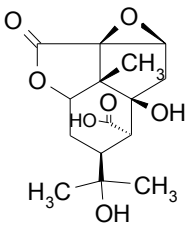
– **Coriamyrtine**
  - *Coriaria* spp. Coriariaceae
  - Picrotoxine type
  - Toxicity for mammals
  - GABA inhibition
    - Epileptiphormous convulsions
    - Excitation of CNS
    - Myosis, asthma
    - Apnoe, coma
    - Cardio-pulmonary failure, death

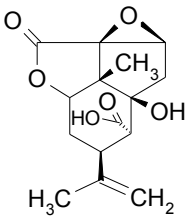


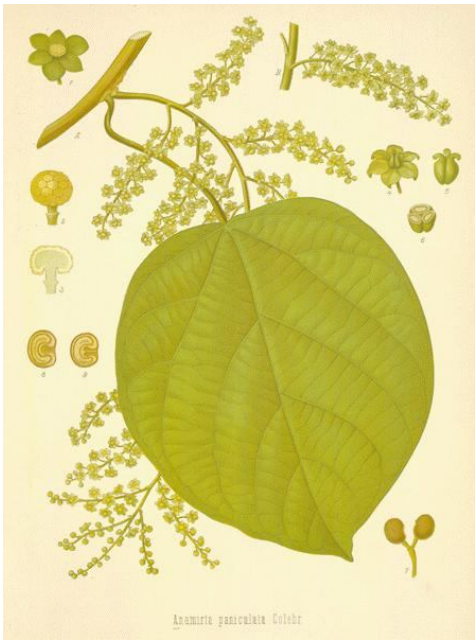

– **Picrotoxine**
  - Picrotine and picrotoxinine 1:1
  - *Anamirta paniculata* Fishberry Menispermaceae
  - Ichtyotoxine
    - Paralysis of air bladder
    - Intoxicated meat
  - Inhibition of $GABA_A$ receptor
  - Excitation of CNS
    - Mainly *medulla oblongata*
  - Myoclony, uncoordinated movements, stupor, delirium, epileptiformous convulsions
  - Coma, insensitivity
  - Cardio-pulmonary failure, death
  - Stimulation of glandular secretion
    - GIT problems
  - Slowering of cardiac function - arrest

► **Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites**

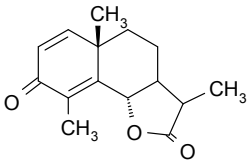


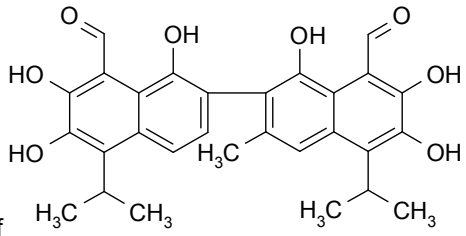
– **Helenaline**
  - *Helenium* (sneezeweed), Arnica and further Asteraceae
  - Toxicity
    – Aborts
    – Vomiting, tachycardia
    – Facial hyperemia
    – Respiratory distress
    – Death *via* circulatory collapse




– **α-santonin**
  - *Artemisia cina* Asteraceae
  - Anthelmintic
  - Mainly for children
  - Headache, apathy, disorders of hearing
  - Cardiovascular and respiratory collapse
  - Irritation of CNS
    – Convulsions, hallucination

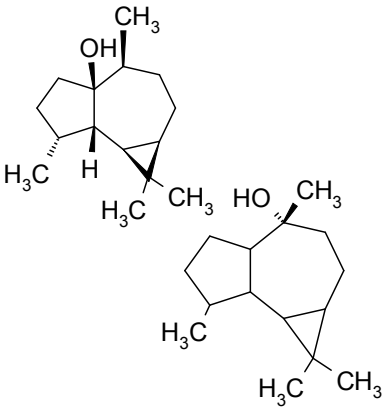
- Other toxic sesquiterpenes

  – **Gossypol**
    - *Gossipium* spp., *Montezuma* spp. Bombacaceae
    - Pigment of *bis*sesquiterpene type
    - Reproductional toxicity:
      – Oligospermy, abnormality of spermatozioides
      – Destruction of seminiferous tubules
    - Neurosis of GIT, changed libido, hypokalemia
    - Important hepatotoxicity
    - Acute toxicity:
      – Loss of weight, diarrhea, bleeding, dysrythmia

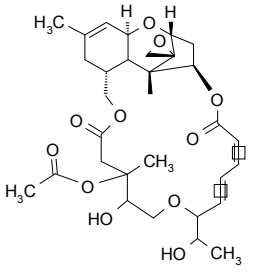



## Ledol a palustrol

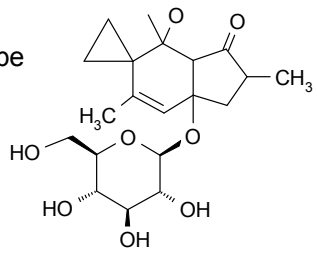
- *Ledum palustre* Ericaceae
- Tricyclic sesquiterpene
- Toxicity
  - Central stimulation
  - Psychomotoric excitation
  - Convulsions to paralysis




- Miotoxin C, roridin A
  - *Baccharis cordifolia* Asteraceae
  - Sesquiterpene of trichothecene type
  - Probably metabolite of symbiotic fungus (*Fusarium*)
  - Toxic for sheep and cattle
    - GIT disorders
    - Neural disorders
  - Antileukemic properties



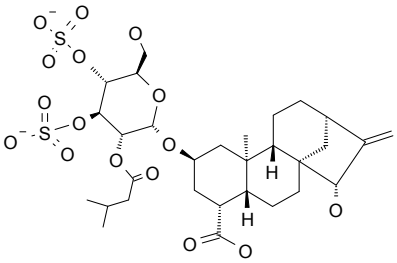
– **Ptachiloside**
  - Norsesquiterpenic glucoside of iludane type
  - Different types of ferns
    – *Pteridium, Pteris, Chelanthes* Dennstaedtiaceae
  - Potent cancerogene
    – Urinary bladder
    – Guts
    – Esophagus
  - Hepatotoxicity
  - Cattle pasturing these ferns
    – Transfer to milk



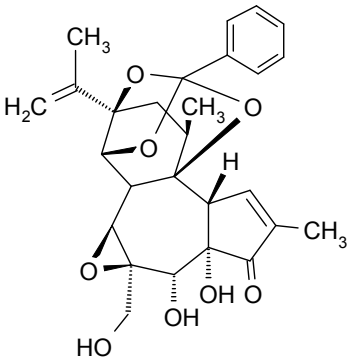

- **Diterpenes**
  – Compounds containing 20 carbon atoms (4 × 5)
  – Toxikologically important families:
    - Ericaceae (grayanotoxins)
    - Euphorbiaceae (Euphorbia factors)
    - Asteraceae
    - Rubiaceae

$K^{+(l)}$

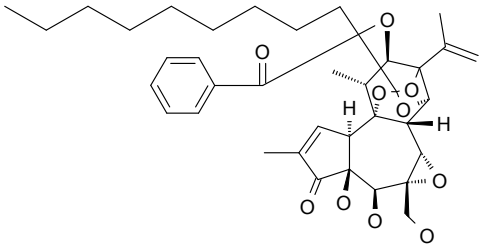
- Toxic diterpenes
  - **Atractylosides A-I**
    - *Xanthium* (cocklebur), *Atractylis*, *Wedelia* Asteraceae
    - Derivative carboxyatractylosid, in *Wedelia* wedeloside
    - Glycosides
      - Carboxyl derivative 10x effective
      - Aglycone low effectiveness only
    - Strychnine-like effect
    - Inhibitors ADP/ATP transportation through membrane of mitochondria
      - Binding to carrier – block at outer side of membrane – block of transfer to matrix – block of oxidative phosphorylation
    - Nephrotoxicity – necrosis of proximal tubulus
    - Hepatotoxicity – centrilobular necrosis

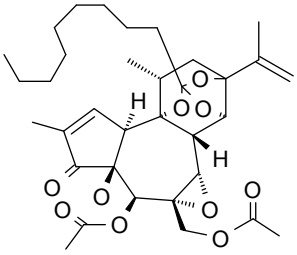


- Toxic diterpenes
  - Daphnetoxin, mezerein
    - *Daphne mezereum* and other Thymelaceae species
    - Poisonous fruits and leaves
    - Mainly children – to 30% mortality
    - Contact – irritation
    - GIT – ulceration, damage of mucose
      - Convulsions, vomiting, diarrhea
    - Hepatotoxicity
      - Interaction with mitochondrial phosphorylation
      - Increases the transition of membranes for ions
    - Neurologic symptoms
      - Convulsions
      - Headache, vertigo
    - Arrhythmias

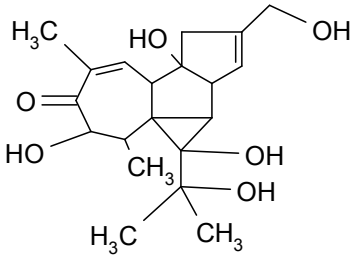


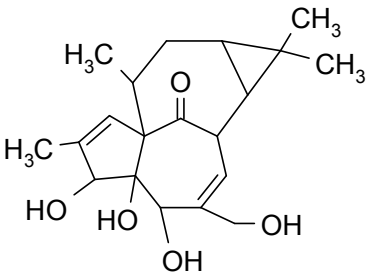

– Gnidilatine and its derivatives
  - Gnidia factors
    – simplexine
  - *Gnidia* spp. Thymelaceae
  - Skin irritants
  - Convulsants
  - Carcinogens
  - Cattle disease
    – St. Georg desease – cardio-pulmonal syndrom





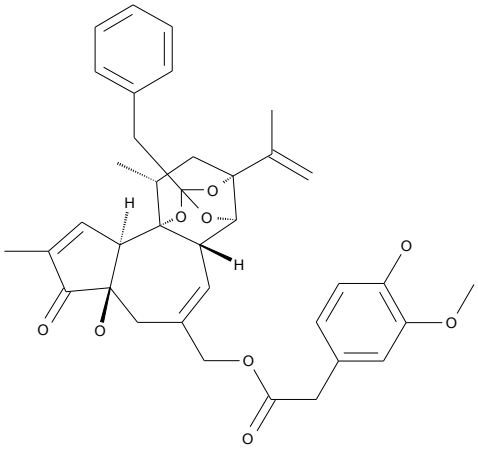
- Toxic diterpenes
  - **Phorbol and its esters**
    - *Croton, Sapium, Euphorbia* Euphorbiaceae
    - Tetracyclic diterpen
    - In plant latex
    - Skin and mucosal irritation
    - Conjunctivitis
    - Irreversible damage of lysosomal and mytochondrial membranes
    - Acute toxicity
      - burning, edema, mucoses turning red
      - Vomiting, paralysis of veins in GIT
      - Mydriasis, vertigo, collapse
    - Potent inductor of carcinogenesis
  - **Ingenol esters**
    - Rod *Euphorbia* Euphorbiaceae
    - Latex
    - Inflammation of skin and mucosa
    - Monoesters more aggressive



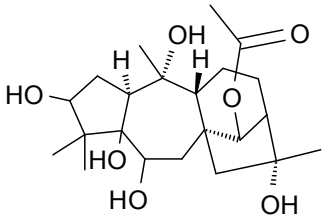





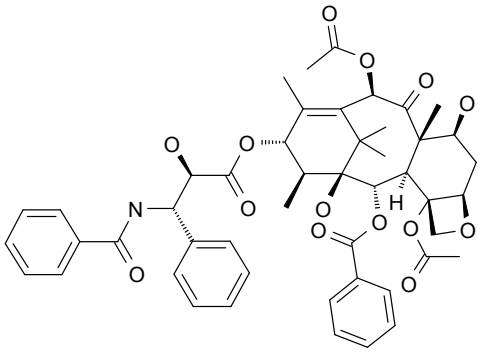
– Resiniferatoxine
  - So called Euphorbia factors
    – One of most active irritants
    – Carcinogen
    – Lowers body temperature
    – Analogue of capsaicin 1000 × stronger
    – Neurotoxicity
      » Terminal hypoalgesia
      » Inhibition of potassium channels

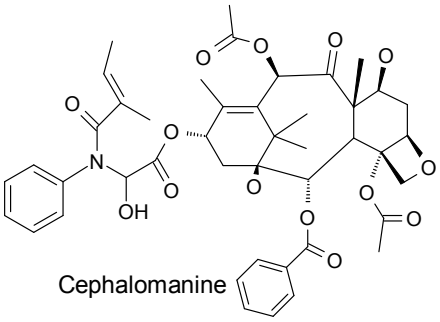


– Grayanotoxine, Asebotoxine II
  - Hepatotoxicity (mainly sheep)
  - *Andromeda*, *Rhododendron* spp. Ericaceae
  - *Pieris japonica* Ericaceae
  - Similar to aconitine intoxication
    – Progressive paralysis from numbs to diaphragm
  - Ionotropic effect
    – Increase of Na+ transition through membrane of cardiocytes
  - Stimulation – paralysis of *nervus vagus*
  - Salivation, nausea, vomiting, diarrhea, GIT disorders, bradycardia

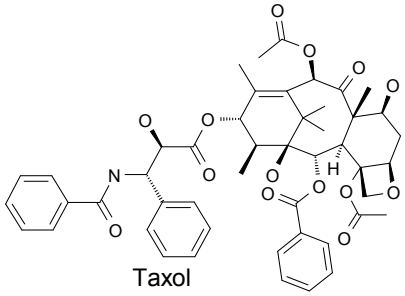



– Taxol 0.01-0.03%
  – Pacific - *Taxus brevifolia*
  – Europe - *Taxus baccata*
  – Japon - *Taxus cuspidata*
  – Himalaya - *Taxus wallichiani*
  - Taxaceae
  - Cephalomanine
    – *Taxus baccata*
  - Mitotic poison
    – Suport of microtubule formation
    – Inhibition of depolimerisation
  - Neutropenia
  - Neurotoxicity
    – Peripheral neuropathy
  - Myalgia, alopecia
  - Ulceration of GIT

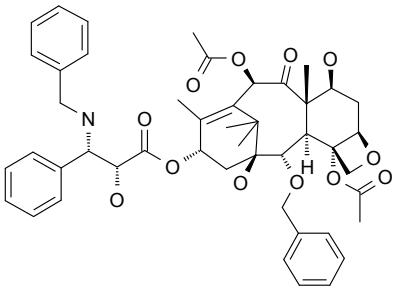




Cephalomanine

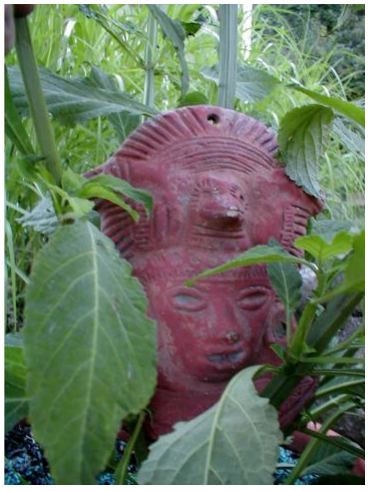


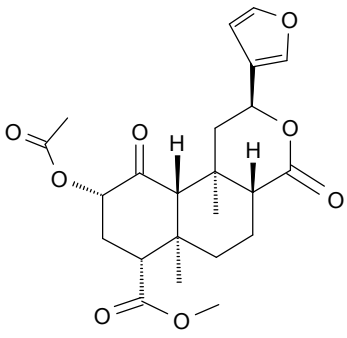
Taxol



Paclitaxel

– Salvinorin A
  - Diterpene of clerodadiene type
  - *Salvia divinorum* Lamiaceae
  - Hallucinogenic
  - Shamanic plant



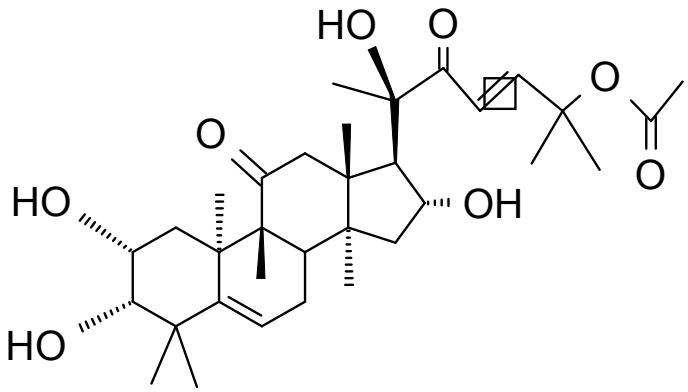


- Triterpenes
  - Different structural forms
  - Different biologic activity
  - Cucurbitaceae, Verbenaceae

- Toxic triterpenes
  - **Cucurbitacines A-V, Q1**
    - Tetracyklic triterpenes
      - Several keto groups
      - Free or glycosides
    - Cucurbitaceae
      - *Citrullus*
      - *Cucumis*
      - *Luffa*
      - And further
    - Toxicity
      - Neurotoxicity (up to 24 hours)
      - Drastic laxative (up to 3 days)
    - **Cucurbitacine D**
      - Relative long latention (including high dosages)
      - Diarrhea, exhaustion, tachypnoe
      - Persisting bloody diarrhea, necrosis of gut
      - Circulatory collapse, coma, death
      - Nephrotoxicity, hepatotoxicity
        - » Histological changes of liver, pancreas, guts, kidneys, lungs
      - Conjunctivitidis, cataract, blindness
      - Icterus

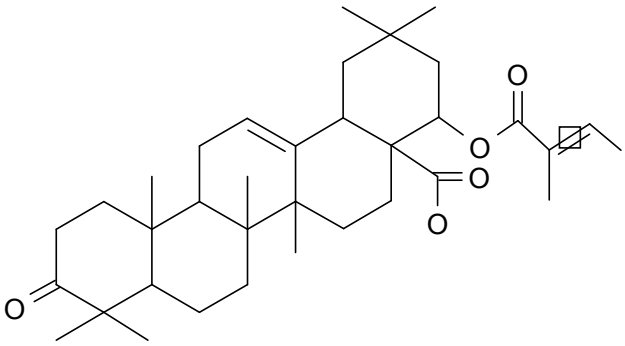
*Cucumis myriocarpus*


*Luffa aegyptiaca*




Cucurbitacine

- Lantadenes
  - Triterpenes of oleanane type
  - *Lantana camara, Lippia rehmanii* Verbenaceae
  - Acute toxicity
    - Hepatotoxic
    - Gastroenteritides
      - » Bloody and watery diarrheas
  - Chronic toxicity
    - Photosenzibilization



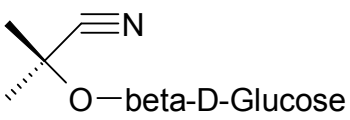

Lantadene A

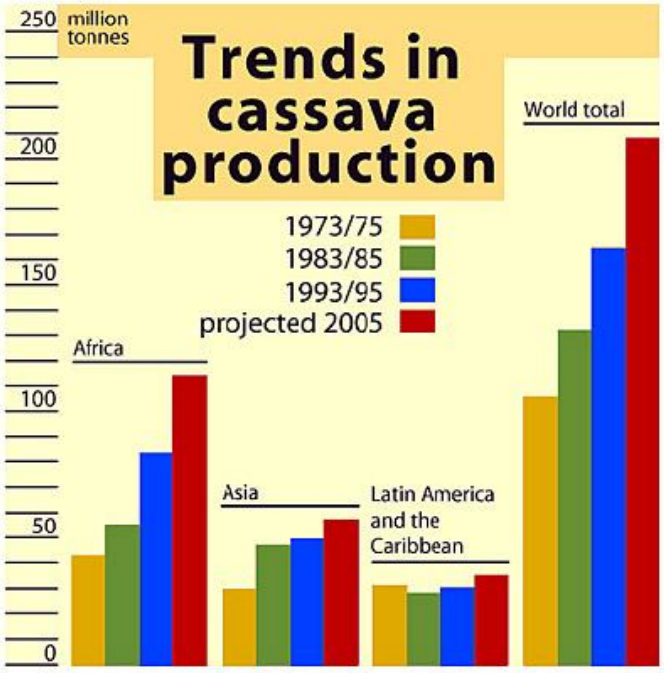
- Glycosides
  - Various structures
    - Sugar part
      - D-β-sugar
      - L-α-sugar
    - Ester, ether, thioether, amide, C-C bond
  - Hydrolysis
    - Activation
      - Nitrotoxines, cyanogennic glycosides
    - Deactivation
      - Polycyclic aglycons

- Cyanogennic glycosides
  - 2-hydroxynitriles + β-D-glucose
  - Hydrolysis produces:
    - HCN
    - Sugar
    - Residue (acetone, benzaldehyde)
  - Widely distributed
    - Rosaceae
    - Fabaceae
    - Euphorbiaceae
    - Passifloraceae
  - Toxic concentration of HCN 0.5-3.5 mg/kg
    - Massive consumation
    - Hydrolysis in GIT
  - Rapid detoxication in organism
    - Production thiocyanate
  - Toxicity
    - Cytotoxic anoxia
      - Bonds at cytochrome c
      - Disabling of $O_2$ utilization

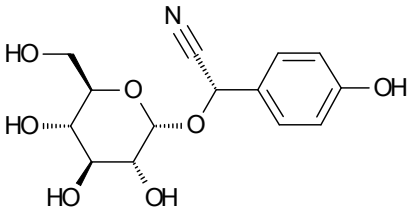
- Three phases of intoxication:
  1. Dispnoe and irritation
  2. Convulsions
  3. Terminal adynamy
- Mild intoxication
  - Headache
  - Anxiety and respiratory distress
  - Vomiting, palpitation
  - Tachycardia, dyspnoe
- Higher doses
  - Peripheral anesthesia
  - Insane mind
  - Cyanosis, stupor, tonic-clonic convulsions
  - Respiratory arrest, death
- Alimentary intoxications
  - Manioc
  - Sorghum
  - Bitter almonds
  - Several Asian and American species of beans

- Manioc
  - *Manihot esculenta* Euphorbiaceae
  - Linamarine, lotaustraline
  - Inhibition of Na+/K+ ATPase
    - Loss of potassium, ion disbalance
  - Damage of kidneys and liver
  - Acute intoxication
    - Stomach pain, diarrhea
    - Coma, cardiopulmonary failure
  - Chronic intoxication
    - Tropical neuropathic ataxia
      - Damage of skin and mucosa
      - Damage of optic and auditory nerve
      - Depletion of sulphur-containing AMA

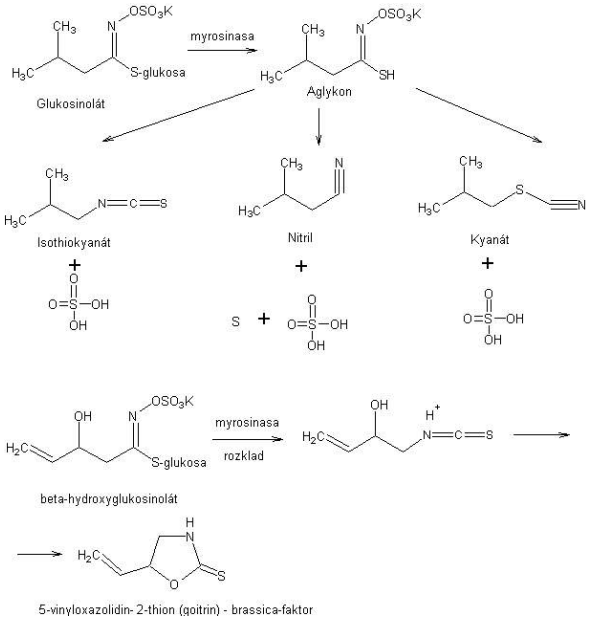



250
million tonnes
Trends in cassava production
1973/75
1983/85
1993/95
projected 2005
200
150
100
50
0
Africa
Asia
Latin America and the Caribbean
World total

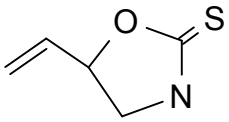
- Sorghum
  - *Sorghum* spp. Poaceae
  - Dhurrin
    - *p*-hydroxymandelonitril-*β*-glucoside
  - High content in young shoots
  - Hydrolysis releases HCN




- Toxic glucosinolates (thioglycosides)
  - *Brassicaceae*
  - *Capparaceae*
  - *Tropelolaceae*
  - *Resedaceae*
  - Strumigens
  - Glucose residue
  - Sulphate group
  - Aglycone
    - Aliphatic
    - Aromatic
    - Heteroaromatic
  - Enzymatic hydrolysis
    - Myrozinase
      - Isothiocyanates or nitriles
      - Glucose + sulphate



- Cyclic products of decomposition
  - –Oxazolidinthiones
  - –The most toxic
    - Goitrine and its precursors – progoitrines
    - Inhibition of incorporation of inorganic iodine into thyroxin precursors
      - – Insufficient production of thyroidal hormones
      - – Histomorphologic changes
        - » Goiter - hyperplasia
        - - hypertrophy
      - – Retardation of growth
      - – Liver damage
      - – Toxic amount 2-5 mg/1g of food




- Toxic anthraquinone glycosides
  - – Many families
    - *Aloe* Liliaceae
    - *Cassie, Gleditchia* Caesalpiniaceae
    - *Andira* Fabaceae
    - *Polygonum, Rheum, Rumex* Polygonaceae
    - *Frangula, Rhamnus* Rhamnaceae
  - – Aglycon
    - Derivatives of 9,10-anthraquinone
    - Reduction
      - – Rise of anthrones, anthranoles and dimers
    - Substitution of aromatic carbons
      - – OH, -OCH3, -CH2OH, -COOH
  - – Intoxication
    - Usually overdose of laxative
    - Disturbance of balance of water absorption
      - – Active transport of sodium
    - Disturbance of water secretion
      - – Hydrostatic pressure
      - – Prostaglandins released chloride secretion
    - Anthrones are produced via reduction mediated by gut microflora
      - – 100× cytotoxic than precursors
      - – Cytotoxic for gut mucosa

- Metabolism
  - **Aglycons**
    - Rapid absorption
    - Detoxification in liver
      - Excretion as glucuronides and sulphates
  - **Glycosides**
    - Do not absorbed
    - Transport to colon
      - Colon microflora metabolism
  - **Chronic intoxication**
    - Laxative abuse syndrome
      - Loss of electrolytes
      - Changes of gut mucosa
      - *Melanosis coli*
      - Degenerative changes of inervation of colon
  - **Acute intoxications**
    - Loss of water and electrolytes
      - Hypocalemia
      - Tubular nephropathy
      - Lowering of muscular activity
      - Arrhythmia, bradycardia
  - **Mutagenicity**
    - Chrysophanol, emodine…
  - **Hypericismus**
    - Photosenzibilisation
    - Formation of singlet oxygen