COMPOUNDS AFFECTING CENTRAL NERVOUS SYSTEM

Activity of CNS is a result of two-way exciting or inhibiting affection of its single parts.

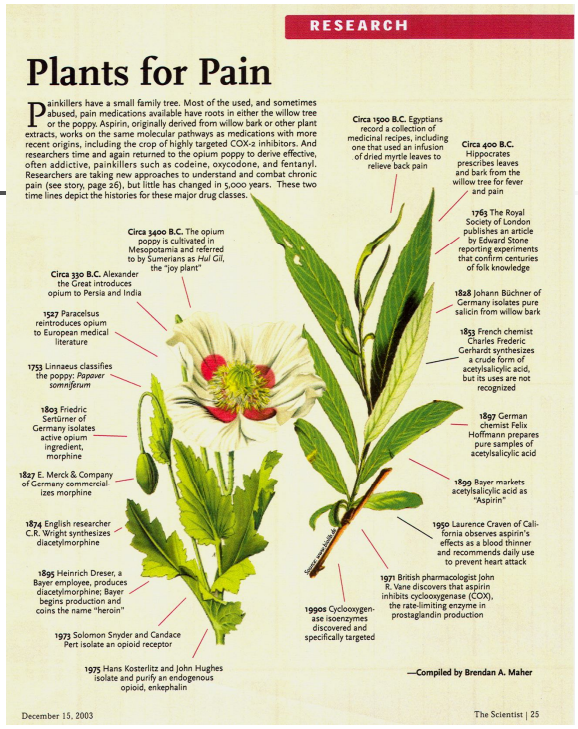
Compounds affecting CNS are known from prehistoric times – today ones of the most utilized therapeutics
(misuse to increase the feeling of wellness – euphoria, ecstasy).

Therapeutics affecting mostly on specific receptors, which modulate synaptic transmission.

COMPOUNDS AFFECTING CENTRAL NERVOUS SYSTEM

ANALGETICS
- Analgesics – anodynes
- Analgesics - antipyretics

- SEDATIVES
- PSYCHOPHARMACS
  - Neuroleptics
  - Psychostimulants
  - Psychodysleptics
- ANTIPARKINSONICS
- CENTRAL ANALEPTICS



RESEARCH

Plants for Pain

Painkillers have a small family tree. Most of the used, and sometimes abused, pain medications available have roots in either the willow tree or the poppy. Aspirin, originally derived from willow bark or other plant extracts, works on the same molecular pathways as medications with more recent origins, including the crop of highly targeted COX-2 inhibitors. And researchers time and again returned to the opium poppy to derive effective, often addictive, painkillers such as codeine, oxycodone, and fentanyl. Researchers are taking new approaches to understand and combat chronic pain (see story, page 26), but little has changed in 5,000 years. These two time lines depict the histories for these major drug classes.

Circa 3400 B.C. The opium poppy is cultivated in Mesopotamia and referred to by Sumerians as *Hul Gil*, the "joy plant"

Circa 330 B.C. Alexander the Great introduces opium to Persia and India

1527 Paracelsus reintroduces opium to European medical literature

1753 Linnaeus classifies the poppy: *Papaver somniferum*

1803 Friedric Sertürner of Germany isolates active opium ingredient, morphine

1827 E. Merck & Company of Germany commercial izes morphine

1874 English researcher C.R. Wright synthesizes diacetylmorphine

1895 Heinrich Dreser, a Bayer employee, produces diacetylmorphine; Bayer begins production and coins the name "heroin"

1973 Solomon Snyder and Candace Pert isolate an opioid receptor

1975 Hans Kosterlitz and John Hughes isolate and purify an endogenous opioid, enkephalin

Circa 1500 B.C. Egyptians record a collection of medicinal recipes, including one that used an infusion of dried myrtle leaves to relieve back pain

Circa 400 B.C. Hippocrates prescribes leaves and bark from the willow tree for fever and pain

1763 The Royal Society of London publishes an article by Edward Stone reporting experiments that confirm centuries of folk knowledge

1828 Johann Büchner of Germany isolates pure salicin from willow bark

1853 French chemist Charles Frederic Gerhardt synthesizes a crude form of acetylsalicylic acid, but its uses are not recognized

1897 German chemist Felix Hoffmann prepares pure samples of acetylsalicylic acid

1899 Bayer markets acetylsalicylic acid as "Aspirin"

1950 Laurence Craven of California observes aspirin's effects as a blood thinner and recommends daily use to prevent heart attack

1971 British pharmacologist John R. Vane discovers that aspirin inhibits cyclooxygenase (COX), the rate-limiting enzyme in prostaglandin production

1990s Cyclooxygenase isoenzymes discovered and specifically targeted

—Compiled by Brendan A. Maher

December 15, 2003

The Scientist | 25

ANALGESIGS – ANODYNES (NARCOTIC ANALGESICS)

Opiate alkaloids, especially morphine and its semisynthetic derivatives

- Huge analgesic effect
- Risk of euphoria and addiction
- Narcotic effect of higher doses
- Suppression of respiratory center and center for cough (antitussic)

Analgesic effect show also polypeptides of animal origin

- Encephalins
- Endorphins

§§ OPIUM

§§ OPIUM CRUDUM (ČL 2002) – RAW OPIUM

Contains at least 10,0 % of morphine — counted for drug
and at least 2,0 % of codeine — dried at 100-105 ^{0}C

Raw opium is used only as material for galenic preparation. It is not used independently!

Year overall production cca 8.000 tons
For medicinal purposes used approx. 400 tons/year.

§§ OPIUM

§§ OPII PULVIS NORMATUS (ČL 2009) – OPIUM POWDERED STANDARDIZED

It is raw powdered opium dried at temperature no more than 70 ^{0}C
Yellow-green to dark brown colored powder

Containing:

- morphine ($C_{17}H_{19}NO_3$): 9,8 % to 10,2 % — drug dried 4 h
- codeine ($C_{18}H_{21}NO_3$): at least 1,0 % — at 100 to 105 ^{0}C

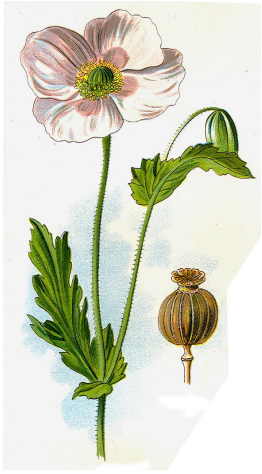
If necessary, the contain is modified by addition of suitable additive at raw powdered opium.

Material for preparation of galenic preparations.

§§ OPIUM

Source: *Papaver somniferum* L., poppy (Papaveraceae)

- Annual cultivated plant
- Whole plant (especially fruit) is rich in lactiferous ducts
- Lots of variants – differ in color of flowers, seeds, shape and size of fruits, in content of alkaloids and in their spectrum
- UN – permission for opium production: India, Turkey (formerly also Yugoslavia, Greece, Bulgaria, some parts of USSR)



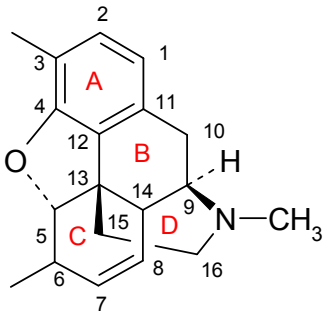
§§ OPIUM

OPIUM – air dried milky latex, rapidly getting brown, distributed in pieces of dark-brown color with characteristic odor

- Obtained by cutting of un-ripen fruits 1-2 weeks after falling of corolla leaves
- From one capsule can be obtained 20-30 mg of opium

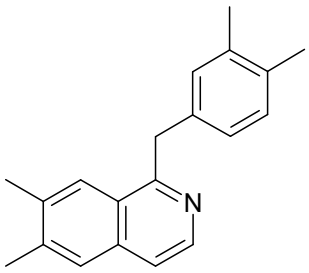
Dried opium is hard, fragile, on the section grainy. At 37 ^{0}C becomes plastic and sticky

MORPHINANE TYPE OF OPIUM ALKALOIDS



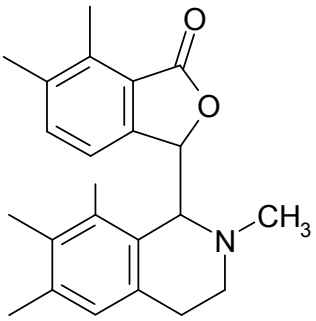
- morphine
- codeine
- thebaine
- 10-hydroxycodeine
- 6-methylcodeine
- neopine
- pseudomorphine
- salutaridine

BENZYLISOQUINOLINE TYPE OF OPIUM ALKALOIDS



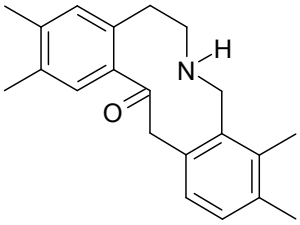
- papaverine
- laudanine
- codamine
- laudanosine
- reticuline
- somnipherine

PHTALIDE-TETRAHYDROIQUINOLINE TYPE OF OPIUM ALKALOIDS



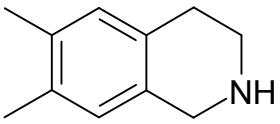
- noscapine (= narcotine)
- narcotoline
- narceine

PROTOPINE TYPE OF OPIUM ALKALOIDS



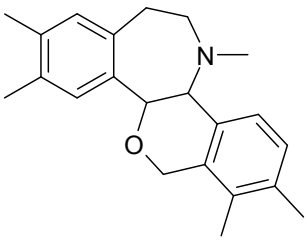
- protopine
- cryptopine
- α-allocryptopine

TETRAHYDROISOQUINOLINE TYPE OF OPIUM ALKALOIDS



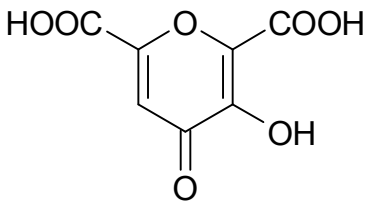
- hydrocotarnine

RHOEADINE TYPE OF OPIUM ALKALOIDS



- rhoeadine
- papaverrubine

SPECIFIC MECONIC ACID

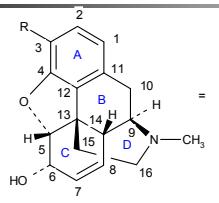


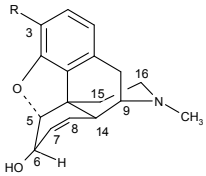
OPIUM

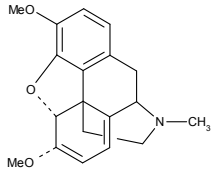
CONTAIN COMPOUNDS

- more than 40 alkaloids, total content oscillates from 15 to 25 %
- alkaloids in form of meconates, fumarates, lactates and sulphates
- meconic acid 3 to 8 %
- mucilages, pectins, sugars
- resins, proteins
- cautchuc
- mineral compounds

IMPORTANT OPIUM ALKALOIDS

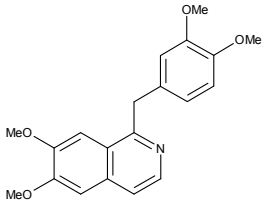




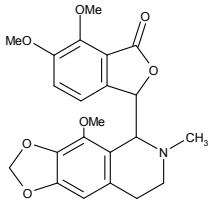


morphine R=OH
codeine R=OCH_3

thebaine



papaverine



noscapine

PERCENTUAL CONTENT OF IMPORTANT ALKALOIDS IN OPIUM %

MORPHINE	3	to	23	in average 13
CODEINE	0,2		3	1,3
THEBAINE	0,2		1,3	0,5
PAPAVERINE	0,5		1,3	1
NOSCAPINE	2		10	5

OTHER SOURCES OF OPIUM ALKALOIDS

Matured dried fruits without seeds (empty poppy heads)

1823 – pharmacist Tiloy from Dijon – poppy is a source of morphine
1934 – Hungarian pharmacist János Kabay applied a patent of industrial procedure

Drug is formed from matured dried capsules of *Papaver somniferum* de-seeded (*Papaveris fructus maturi sine semine*), or more often poppy hay (*Papaveris stramentum*), formed from capsules without seeds and maximal 10 cm long residue of stem.

Capsules contain alkaloids, with spectrum similar to opium, prevalent is morphine. Its contain fluctuates between 0,1 to 1 %. Present time: isolation from poppy hay represents approx. ¼ of world morphine consumption.

PAPAVERIS FRUCTUS MATURI SINE SEMINE

OPIUM ALKALOIDS - UTILIZATION

Morphine was the first described alkaloid, discovered by pharmacist Sertürner in 1806. Absolute structure resolved after 164 years.

It is prepared via isolation from opium or poppy hay only.

It is used as strong analgesic – anodyne / high risk of addiction

- to suppress pain of malignant tumors, post-surgery, after serious injury, heart attack and pulmonary embolism
- sometimes surgery pre-medication.
- In combination with atropine (spasmolytics) is used for suppression of pain in kidney and gallbladder colics.

Morphine is approx. from 90 % used for preparation of semi synthetic derivatives

- methylmorphine (CODEINE), ethylmorphine (DIOLAN), morpholinoethylmorphine = folcodine (NEOCODIN)
- antagonists of morphine, for example NALORFINE.

Heroine – diacetylmorphine – strong analgesic, rapidly penetrates into CNS, where is hydrolyzed to morphine. In therapy it is not used, triggers strong addiction. It is misused as narcotic substance.

OPIUM ALKALOIDS - UTILIZATION

Codeine – central affecting antitusic, lowers bronchial secretion. A part of analgesic mixtures. Natural occurrence in opium does not cover the requirement, therefore it is prepared from morphine via semisynthetic route (less from thebaine). In organism is from 10-15 % demethylated to morphine and can trigger the addiction when used repeatedly.

Thebaine is starting reagent for preparation of CODEINE, hydrocodon (VICODIN), non-addictive analgesic butorphanol, addictive oxycodon (DINARKON, OXYCONTIN), which is in mixture with scopolamine and ephedrine part of BENARCOS injections – premedication before anesthesia. From thebaine is derived allyloxycodon = NALOXON, antagonist of morphine

Papaverine belongs to spasmolytics, lowers tonus of smooth muscles by direct action on cells. Opium isolations do not cover utilization, therefore it is prepared via synthesis. Spasmolytic effect of papaverine is predominantly demonstrated on gastrointestinal tract, it lowers tonus of smooth muscles of cardiovascular system and respiratory and urinary tract.

Noscapine (formerly narcotine) – long time waste product of opium processing. Nowadays central antitusic with parallel papaverine relaxation effect. It does not trigger addiction and therefore is used instead of codeine in antitusics and analgesics.

OPIUM ALKALOIDS IN PHARMACOPEA

§§ OPIUM CRUDUM
§§ OPII PULVIS NORMATUS

§§ MORPHINI HYDROCHLORIDUM TRIHYDRICUM
§§ MORPHINI SULFAS PENTAHYDRICUS

§§† CODEINI PHOSPHAS HEMIHYDRICUS
§§† CODEINI PHOSPHAS SESQUIHYDRICUS
§§† CODEINUM MONOHYDRICUM

† PAPAVERINI HYDROCHLORIDUM

NOSCAPINUM
NOSCAPINI HYDROCHLORIDUM MONOHYDRICUM

Law n. 167/1998 Sb., about addictive compounds and about changes of some other corresponding laws

Narcotics and psychotropic substances are according to this law compounds listed in supplement n. 1 to 7 of this law

Law 167/1998 Sb. Changes also the handling with precursors (supplement n. 9) and adjuvants (supplement 10 or 11)

Table I: Narcotic and psychotropic substances

Supplement n. 1 – narcotics listed in pharmacopeia 1 (selection) „§§"

- Cocaini hydrochloridum
- Morphini hydrochloridum trihydricum
- Morphini sulfas pentahydricus
- Opium crudum

Supplement n. 2 - narcotics listed in pharmacopeia 2 (selection) „§§†"

- Codeinum in all forms (phosphas, hydrochloridum, monohydricum)
- Ethylmorphini hydrochloridum dihydricum

Law n. 167/1998 Sb., about addictive compounds and about changes of some other corresponding laws

Supplement n. 9 – Precursors from pharmacopeia listed in table I (selection) „(§)†“ or „(§)††“

- Ephedrini hydrochloridum and other forms
- Ergometrini maleas
- Ergotamini tartras
- Pseudoephedrini hydrochloridum

Table II: Venena (poisons)

Contains therapeutics strongly active (especially danger poisons), assigned in pharmacopeia with „††“ (selection)

Atropini sulfas monohydricus

Digitoxinum

Table III: Separanda

Contains strongly active substances and corrosives assigned in pharmacopeia with „†“ (selection)

Belladonnae folium

Papaverini hydrochloridum

ANALGESICS OF PEPTIDE CHARACTER ENDOGENOUS OPIATES / OPIOID PEPTIDS

1973 – S. Snyder and C. Pert – isolation of opioid receptor

1975 – H. Kosterlitz aj. Hughes – isolation of first encephalin

Propiomelanocortine – β-lipotropic hormon – fragmentation –

High-molecular endorphins, low-molecular encephalins

β-endorphine (aminoacids 61-91); 48× more effective than morphine

α-endorphin (61-76)

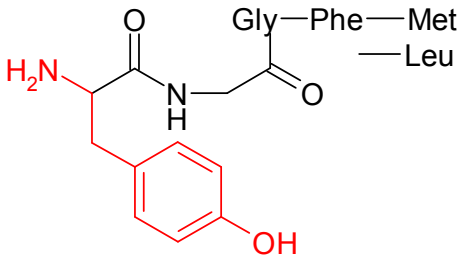
γ-endorphin (61-77)

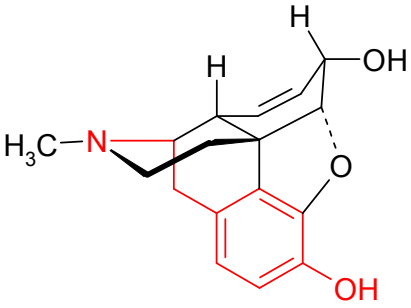
Met-encephalin Tyr-Gly-Gly-Phe-Met (61-65)

Leu-encephalin Tyr-Gly-Gly-Phe-Leu

ANALGESICS OF PEPTIDE CHARACTER
ENDOGENOUS OPIATES / OPIOID PEPTIDES

Rtg structural analysis





morphine

ANALGESICS OF PEPTIDE CHARACTER
ENDOGENOUS OPIATES / OPIOID PEPTIDES

KYOTORPHIN – Tyr-Arg – acting indirectly, increases secretion of opioid peptides

CASOMORPHINS (EXORPHINS) – tetra-, penta-, hexa- and heptapeptides from milk; fragments of β-kaseine and α-lactalbumine

ENDORPHINS

- in brain, hypophysis, circulate in blood, excreted in urine
- trigger morphine effects – analgesia, euphoria, respiratory suppression, spasms of smooth muscles
- strong short-termed effect, strongly triggering euphoria
- produce psychic and somatic addiction
- Similarity of effect to neuroleptics – γ-endorphin „specific antischizophrenic neuroleptic

ANALGESICS – ANTIPYRETICS

CHARACTERISTICS:

- effect mild analgesic
- effect antipyretic
- effect antiphlogistic

Derivatives of salicylic acid
Quinine
Preparation from *Aconitum napellus*
Snake products

Potentiating of effect – caffeine in dosage up to 50 mg

DERIVATIVES OF SALICYLIC ACID – HISTORY

- 400 BC Hippokrates prescribed leaves and bark of willow to combat fever and pain
- 1763 Journal of Royal Society in London – E. Stone – experiments confirmed hundred years of folk observation
- 1828 Johann Büchner (Germany) isolated salicin from willow bark
- 1853 Ch.F. Gerhardt (France) synthesized raw acetylsalicylic acid (ASA), effects were not studied
- 1897 Felix Hoffmann (Germany) prepared pure ASA
- 1899 Bayer trades ASA as ASPIRIN
- 1950 L. Craven (USA) – ASA „dilutes blood", recommends preventively against heart attack
- 1971 Joh R. Vane (GB) – ASA inhibits COX (enzyme limiting production of prostaglandins – mechanism of antiphlogistic effect

SALICIS CORTEX – WILLOW BARK (ČL 2009)

Source: Salix species - willow (Salicaceae); *S. purpurea*, *S. fragilis*, *S. daphnoides*

Dioecious shrubs or trees, in mild and subarctic areas

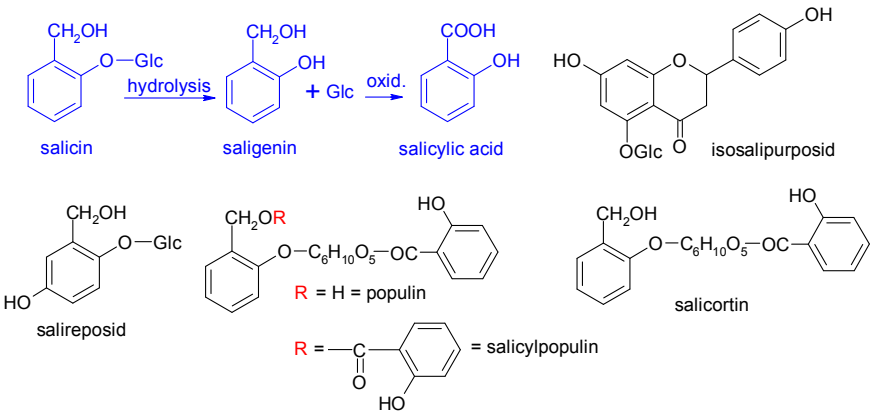
Drug is formed by dried bark of young branches or its fragments, harvested in the spring. It possesses strong bitter taste.

SALICIS CORTEX – WILLOW BARK

CONTENT COMPOUNDS

- At least 1,5 % of salicylic acid derivatives, counted as salicin
- Catechine tannins
- Hydroxyderivatives of cinnamic acid
- Flavonoids (isosalipurposide, isoquercitrine, naringenine)

SALICIS CORTEX – CONTENT COMPOUNDS



SALICIS CORTEX – WILLOW BARK

INTERNAL USAGE

Maceration (1,5 g/200 ml of water)

- diseases from cold
- Inflammatory diseases
- Rheumatic disorders

Problems of GIT triggered by tannins

EXTERNALLY (9 g/200 ml of water)

- astringent

Individual intoleration on salicylates (urtica, spasms of bronchi)

SPIRAEAE FLOS – FLOWER OF MEADOWSWEET

Filipendula ulmaria L., *Spiraea ulmaria L.* – meadowsweet (Rosaceae)

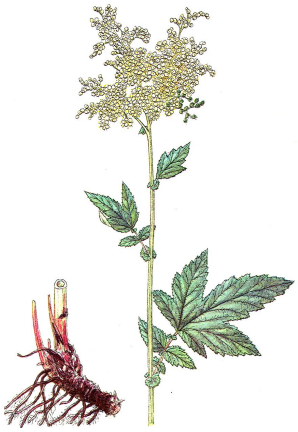
- perennial plant of moist places
- harvest in VI – VII

Drug – dried white-yellow flowers

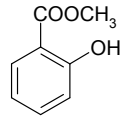
- Smells like oranges
- Bitter acrid taste

Usage

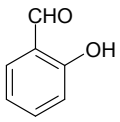
- antiphlogistic, diuretic, folk medicine



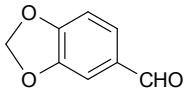
SPIRAEAE FLOS – FLOWER OF MEADOWSWEET



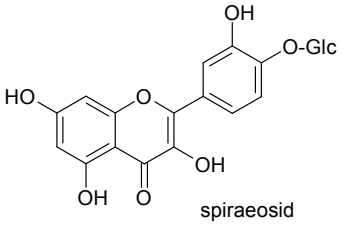
methylester of salicylic acid



salicylaldehyde



piperonal (= heliotropin)



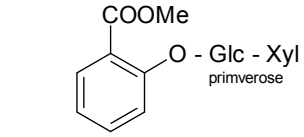
spiraeosid
quercetin - 4'-O-glucosid

DERIVATIVES OF SALICYLIC ACID

Gaultheria procumbens – wintergreen

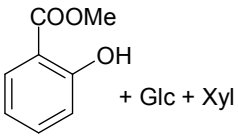
Monotropa hypopitis – Dutchmen's pipe

Betula lenta – sweet birch



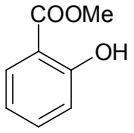
monotropitosid
= gaultherin

H^+



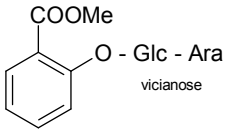
methylester of salicylic acid

DERIVATIVES OF SALICYLIC ACID



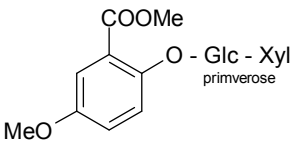
methylester of salicylic acid

Senegae radix

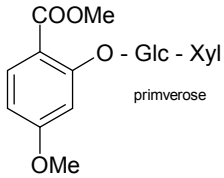


violutosid

Violae tricoloris herba



primulaverosid



primverosid

Primulae radix

QUININE

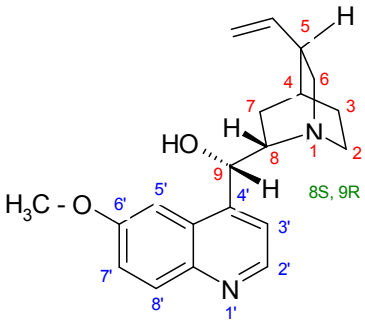
Sources: species of Cinchona;
C. Succirubra
C. calissaya (Rubiaceae)

Drug: Chinae cortex – cinchona tree bark, contains at least 6,5 % of alkaloids quinine type (quinine, quinidine)

QUININI HYDROCHLORIDUM DIHYDRICUM (ČL 2005)
QUININI SULFAS DIHYDRICUS (ČL 2005)
Prepared only by isolation from cinchona tree bark

Effect analgesic

- Effect antipyretic
- Effect antiinflammatory
- Prolongs and stimulates effect of other antipyretics
- In combination (Harburn, Harbureta) for acute diseases of upper respiratory trackt of viral etiology with fever
- Antimalaric



ACONITINE

Source: *Aconitum napellus* L. –
Aconite Ranunculaceae
Perennial plant, turnip-shaped tubers.

Drug: tuber of dark-brown color,
for pharm. Purposes is cultivated, harvest in autumn, when is content of aconitine the highest.

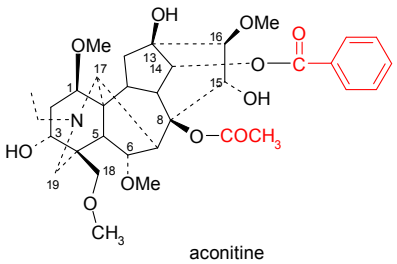
Content compounds: 0,6 – 2 % diterpene ester alkaloids (aconitine, napeline), starch, tannins

ACONITINE

Usage: Narrow therapeutic width,
The most potent alkaloid poison, LD 2-5 mg!!
Externally
- Inflammation of n. trigeminus
- Chronic joint inflammations
- arthritis uratica

Internally
- anestetic dolorosum (obsolete)

Products of hydrolysis less active benzoylaconine 1/400, aconine 1/4000



aconitine

SNAKE POISONS

Mixtures of compounds with different composition. Common characteristic – presence of hyaluronidase (fast penetration and absorption of poison into tissues)

Naja tripudians – cobra (COBRATOXIN)

Sterile lyophilized poison – ophiotoxin. Partially hydrolyses lecithine to lysocithine, which suppresses pain without disruption of neural transmission.

Strictly subcutaneous injection (for tumores).

Vipera ammodytes – horned viper (VIPERALGIN)

Sterile lyophilized toxin, injections, component of external remedy with camphora and essential oils – analgesic, hyperemic for symptomatic treatment of rheumatism and neuralgias.

ANTIMIGRAINICS

Migraine – seizures of reversible pain mostly often one half of head (hemicrania), accompanied by vertigo, vision disorders, nausea

Caused – increased release of neuromediator serotonin

Antimigrainics – compounds inhibiting serotonin

Ergotamini tartras (ČL 2005) (*Secale cornutum*)

In combination with caffeine

In prodromal state benefiting effect of caffeine vasodilatation