Chapter 18

Utilization of Alkaloids in Modern Medicine

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1. INTRODUCTION

As outlined in Part III, alkaloids have evolved as a chemical defense against herbivores, microorganisms, and viruses or against other plants (Chapters 11, 14, 15, and 16). Assuming an evolutionary molecular modeling, the structures of many alkaloids have been shaped through natural selection so that they can interfere with a wide variety of molecular or physiological targets of animals and microorganisms (Chapter 12).

Homo sapiens encountered these active molecules, first in their vegetal food items and later as a means to hunt, kill or murder other animals or his contemporaries (see examples given in Chapters 2 and 3). In addition we have to assume that early humans used alkaloidal and other plants as painkillers, stimulants, or hallucinogens. The treatment of disease or illness with medicinal plants has been rather well documented for the last 3000 to 5000 years (see Chapter 2).

Finding useful properties in plants certainly proceeded by trial and error but does not seem to be restricted to humans: It has been documented by E. Rodrigues (1985, 1993) that chimpanzees in the wild selectively pick plants rich in antimicrobial thiophenes when suffering from severe diarrhea. Many birds of prey decorate their nests with oak leaves rich in tannins. Because the birds defecate into their nests, the antimicrobial tannins might help to control the development of bacteria and fungi.

The medicinal use of alkaloids and other natural products could be regarded as an exploitation of properties that originally had been selected and developed in an ecological or evolutionary context (Wink, 1993). The right plants and concentrations became excellent means for the therapeutic treatment of illness and disease. In this chapter we describe those alkaloids that are used in modern medicine (relevant handbooks include Reynolds, 1993; Budavari, 1989; Roth et al., 1994; Teuscher and Lindequist, 1994; Gilman, 1991;...
Harborne and Baxter, 1993). Alkaloids are discussed in alphabetical order with a short summary of their occurrence in plants and their therapeutic and traditional use in medicine (including important trade names). The biochemical/molecular mechanisms of action are given wherever known. Some of these have been discussed in more detail in Chapters 2 and 12.

2. ALKALOIDS USED IN MODERN MEDICINE

2.1. Aconitine

![Aconitine molecule]

Source: *Aconitum napellus* (Ranunculaceae); tubers contain about 0.3–3% and the leaves 0.1–1% alkaloids of which aconitine is the major component.

*Pharmaceuticals (examples):* Aconitysat™, Bronpax™, Etermol™, Pectovox™, Pulmo-Xeedol™, Sirop Famel™, Vocadys™.

*Therapeutic use:* Liniments have been used in the treatment of rheumatism, neuralgia, and sciatica.

*Mechanism of action:* Aconitine increases the permeability of excitable membranes for Na⁺ ions and prolongs the Na⁺ influx during the action potential. As a consequence, sensile nerve endings and motor endplates are first activated but later blocked.

2.2. Ajmaline

![Ajmaline molecule]

Source: Industrially, ajmaline is isolated from *R. vomitoria* or *Catharanthus roseus.*

*Pharmaceuticals (examples):* Aritmina™, Gilurytma™, Rauwopur™, Ritmos™.
Therapeutic use: Ajmaline is a class Ia antiarrhythmic agent and used in the treatment of supraventricular and ventricular arrhythmias. It might also be useful for patients with myasthenia gravis.

Mechanism: Ajmaline prolongs the refractory phase of the heart through a blockade of Na⁺ channels. In addition, the action potential is prolonged and an increase of the depolarization threshold occurs. It has negative inotropic properties accompanied by a small decrease of the heart rate.

2.3. Atropine

![Atropine structure]

Source: Mainly Atropa belladonna (Solanaceae); its roots contain about 0.45–0.85% alkaloids. Alkaloid content of the leaves varies between 0.2 and 1.5%. The major component is L-hyoscymine, which racemizes to DL-hyoscymine (= atropine) during storage or alkaline isolation. Industrially atropine is prepared from leaves of Australian Duboisia species (e.g., D. myoporoides and D. leichhardtii; Solanaceae) or from seeds of Hyoscyamus muticus and H. niger.

Pharmaceuticals (examples): The following preparations contain mostly atropine sulfate: Abdominol™, Atropinol™, Atropisol™, Dilaudid-Atropin™, Espasmo™, Protecor™, Rutuss™, Spasmosol™, Spersatropine™, Tonaton™.

Therapeutic use: (1) As an antispasmodic in the treatment of gastrointestinal, urinary, and biliary colics; (2) in preparation of general anesthesia, to reduce bronchial and salivary secretion and to avoid bronchospasms; (3) in combination with morphine, to suppress its effect on the vomiting center and the gastrointestinal; (4) against parkinsonism (displaced by benhexol); (5) as an antidote against phosphoric acid ester and mushroom poisoning; (6) against myasthenia gravis; (7) in the management of arrhythmias; (8) in the local treatment of muscular rheumatism, sciatica, and neuralgia; (9) in ophthalmology as a mydriatic and cycloplegic drug.

Use in traditional medicine: The extracts from A. belladonna were used as cosmetics, because of their dilatatory effect on the pupils. In the treatment of bronchial asthma, the dried leaves of Datura stramonium (Solanaceae) were burned and the smoke inhaled (see also Chapter 2).

Mechanism: Atropine blocks muscarinic cholinergic receptors competitively, and therefore acts as a parasympatholytic at parasympathetically innervated organs. Atropine also has central effects, because as a tertiary amine it is able to cross the blood–brain barrier.
2.4. Berberine

![Berberine structure]

Source: *Berberis vulgaris* (Berberidaceae); the bark contains up to 8% alkaloids, with berberine as the major component (about 5%). Berberine also occurs in several *Hydrastis* species (Papaveraceae) and *Chelidonium majus* (Papaveraceae).

**Pharmaceuticals (examples):** Kollyr™, Murine™, Pastilles JesSEL™, Sedacollyre™.

**Therapeutic use:** In the treatment of infected eyes and other eye irritations; it might also be useful in the treatment of AIDS, because of its inhibitory properties on HIV-1 reverse transcriptase. It also has a favorable effect on toxic hepatitis induced by intoxication.

**Use in traditional medicine:** The extract of the root has been used as an antiamoebic in the treatment of cholelithiasis and liver disorders. It is also used as a bitter in alcoholic drinks and as flavor in food.

**Mechanism:** Berberine exhibits antimicrobial activity, which might be related to its effects on several molecular targets: DNA intercalation, inhibition of esterases, inhibition of DNA and RNA polymerases, inhibition of cellular respiration. Some affected organisms are: *Shigella dysenteriae*, *Neisseria gonorrhoeae*, *Phymatotrichum omnivorum*, *Candida albicans*, several species of *Escherichia* and *Aerobacter*, *Bacillus subtilis*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Berberine also increases biliary secretion.

2.5. Boldine

![Boldine structure]

Source: *Peumus boldo* (Monimiaceae); leaves contain 0.4–0.5% alkaloids. Boldine is the major component (20–25%) of the alkaloidal fraction.

**Pharmaceuticals (examples):** Boldina Houde™, Boldoflorine™, Boldosal™, Digedryl™, Ibsesal™, Menabil Complex™, Oxyboldine™, and Sambil™.
Therapeutic use: Treatment of cholelithiasis, stomachic disorders, vomiting, constipation, and dyspepsia.

Use in traditional medicine: In Chile boldine is used as an anthelmintic drug; it has diuretic properties and stimulates liver metabolism.

Mechanism: Boldine exhibits morphinelike antinociceptive properties. Besides opioid receptors, alpha receptors might also be involved in this action (Zetler, 1988).

2.6. Caffeine

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{CH}_3 & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{CH}_3 & \\
\end{align*}
\]

caffeine

Source: Coffea arabica (Rubiaceae), Paullinia cupana (Sapindaceae), Cola nitida and C. acuminata (Sterculiaceae). The caffeine content of the above-mentioned plants varies between 0.6 and 5.0%. Caffeine is also synthetically available.

Pharmaceuticals (examples): (A small selection of more than 300 preparations) Agevis™, Analgen™, Antigrippal™, Coffein-Enervit™, Doppel-Spalt N™, Kontragripp™, Panax™, Percoffedrinol™, Thomapyrine™, Vomex A™.

Therapeutic use: Caffeine is added to analgesics to increase their activity. It is also used in the treatment of neonatal apnea and atopic dermatitis.

Use in traditional medicine: As a stimulant and in the treatment of headache.

Mechanism: Caffeine inhibits phosphodiesterase and thus influences calcium-mediated signaling through an increase of cAMP levels. In addition, caffeine exhibits competitive antagonistic effects on central adenosine receptors. Its diuretic action is based on its vasodilatory activity on renal blood vessels. The use against headache is related to a constriction of brain vessels and decrease of liquor pressure.

2.7. Cathine

\[
\begin{align*}
\text{OH} & \quad \text{CH}_3 \\
\text{NH}_2 & \quad \text{C} \\
\end{align*}
\]

cathine

Source: Catha edulis (Celastraceae); the leaves contain 1% alkaloids. Cathine [(+)-norpseudoephedrine] is the major component. It is also a minor component of several Ephedra species.
Pharmaceuticals (examples): Amorphan™, Antidiapositum X 112™, Appetrol™, Eetless™, Recatol™, Vitamin-Schlanktropfen™.

Therapeutic use: As an anorectic drug.

Use in traditional medicine: In Africa and the Middle East the drug is chewed for its stimulant effects.

Mechanism: Cathine is central stimulant, acting as an indirect sympathomimetic. It increases the release of serotonin, noradrenaline, and dopamine and decreases their reuptake. An inhibitory activity on monoamine oxidase (MAO) has also been discussed.

2.8. Cocaine

\[
\begin{align*}
&\text{H}_3\text{C}^\text{N} \quad \text{COOCH}_3 \\
&\quad \text{H} \quad \text{O} \\
&\quad \text{H} \quad \text{O} \\
&\text{cocaine}
\end{align*}
\]

Source: Erythroxylon coca (Erythroxylaceae); leaves contain 0.7–2.5% alkaloids. In general, cocaine is the major component.

Pharmaceuticals (examples): There are none readily available. They are prepared as described in several pharmacopoeias (e.g., USP, BPC).

Therapeutic use: As a local surface anesthetic, in ophthalmology for corneal anesthesia, and for treatment of epistaxis.

Use in traditional medicine: Cocaine is abused for its stimulant effects on the central nervous system. It causes euphoria and mood elevation. For this purpose, either leaves are chewed or pure cocaine is sniffed or injected.

Mechanism: Cocaine blocks the uptake of catecholamines (especially of dopamine) at adrenergic nerve endings and potentiates the action of catecholamines.

2.9. Codeine

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\begin{align*}
&\text{H}_3\text{C}^\text{N} \quad \text{OCH}_3 \\
&\quad \text{H} \quad \text{O} \\
&\quad \text{OH} \\
&\text{codeine}
\end{align*}
\]

Source: Codeine is a component of opium, which is obtained from the dried or partly dried latex by incision of the unripe capsules of Papaver somniferum (Papaveraceae). Opium contains 0.2–3.0% codeine. Because of its low content in the plant, codeine is
obtained through methylation of morphine. It is also preparable from thebaine, which is the major component of roots, aerial parts (1%) and the capsules (3.5%) of \textit{Papaver bracteatum} (Papaveraceae).

\textbf{Pharmaceuticals (examples):} (A small selection of more than 200 preparations: Antituss™, Bisolvon-Gribletten™, Bronchicium Tropfen mit Codein™, Codicaps™, Codipront™, Contrapect™, Contrapect Infant N™, Dolodens™, Dolorol Forte™, Spasmo-Cibalgin comp.™, Tussipax™).

\textbf{Therapeutic use:} As antitussive in the treatment of cough, and as an analgesic and mild sedative.

\textbf{Mechanism:} Codeine binds to opiate receptors, diminishes bronchial secretion, and acts as a suppressant on the cough center of the medulla oblongata.

2.10. Colchicine

\begin{center}
\includegraphics[width=0.5\textwidth]{colchicine.png}
\end{center}

\textit{colchicine}

\textit{Source:} \textit{Colchicum autumnale} (Liliaceae); seeds contain 0.2–1.2% and the tubers 0.1–0.6% colchicine.

\textbf{Pharmaceuticals (examples):} ColBenemid™, Colchimax™, Colgout™, Verban™.

\textbf{Therapeutic use:} Colchicine is used in the treatment of acute gout and the prophylaxis of recurrent gout. It can also be used for the treatment of amyloidosis.

\textbf{Mechanism:} Colchicine inhibits the polymerization of tubulin and thus arrests mitosis in the metaphase (Capraro and Brossi, 1984). But colchicine has too many side effects to be employed for the treatment of cancer. In acute gout colchicine decreases the mobility of phagocytes through inhibition of microtubule formation, important for cell movements. Phagocytes are attracted to sites of inflammation and normally get ruptured after phagocytosis of urate crystals, which causes in turn a decrease of pH followed by further precipitation of urate. This will lead to a stronger inflammation and will attract even more leukocytes. This vicious circle can be disrupted by colchicine.

2.11. Emetine

\textit{Source:} \textit{Cephaelis acuminata} (Rubiaceae); roots contain 1.8–3.5% alkaloids. Emetine content varies between 35 and 80%. It is also prepared from cephaeline through methylation.

\textbf{Pharmaceuticals (examples):} Cophylac™, Ipecac™, Rectopyrine™.

\textbf{Therapeutic use:} As a second choice in the treatment of severe intestinal amoebiasis and
hepatic amoebiasis when nitroimidazoles are not effective or contraindicated. It is also used in low doses as an expectorant drug with secretolytic and secretomotoric properties. *Use in traditional medicine:* As an emetic drug. *Mechanism:* Emetine acts indirectly on the bronchia through activation of nervus vagus. Because emetine is a strong inhibitor of protein biosynthesis, it has a strong toxic potential (Fujii and Ohba, 1983).

### 2.12. Ephedrine

**Source:** *Ephedra sinica* and *E. shunnungiania* (Ephedraceae) contain about 0.2-2.0% alkaloids with L-ephedrine as the major component. *Pharmaceuticals (examples):* Amidoyna™, Bronchicum™, Bronchisan™, Coughcod™, Dorex™, Endrine™, Epehepect™, Grippon™, Nasenöl-ratiopharm™, Peripherin™, Rectinol™, Solamin™, Vicks Medinite™. *Therapeutic use:* As a nasal decongestant for the relief of cold symptoms. Ephedrine may also be employed in the treatment of edema in insulin-dependent diabetics. As a bronchodilator it is used in the treatment of bronchial asthma. *Use in traditional medicine:* The herb for the treatment of asthma. *Mechanism:* Ephedrine has alpha- and beta-adrenergic activity. In therapeutic doses it increases blood pressure by raising cardiac output and by causing peripheral vasoconstriction. Its central actions include stimulant activity on the respiratory center. It reduces motility and intestinal tone and uterus tone, causes bronchodilation, relaxes the bladder wall and the detrusor muscle while contracting the sphincter muscle.
2.13. Ergometrine

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\text{ergometrine}
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*Source:* Ergometrine is prepared semisynthetically from amides of *Claviceps paspali* (Clavicipitaceae). The ascomycete can be cultivated on nutritive solutions for alkaloid production.

*Pharmaceuticals (examples):* Ergometron™, Ergotrate Maleat™, Syntometrine™.

*Therapeutic use:* Ergometrine is used in the prevention and treatment of postpartum or postabortal hemorrhage.

*Use in traditional medicine:* Ergometrine and other ergot alkaloids are smoked for their hallucinogenic properties (see Chapter 2).

*Mechanism:* Ergometrine acts directly on the uterus muscle, causing rhythmic contraction, because of its high affinity to uterine alpha₂ receptors.

2.14. Ergotamine

\[
\text{ergotamine}
\]

*Source:* *Claviceps purpurea* (Clavicipitaceae), the alkaloid content in cultivated species is about 1%.


*Therapeutic use:* Ergotamine is used in the treatment of migraine.

*Use in traditional medicine:* See ergometrine.

*Mechanism:* Ergotamine is a strong vasoconstrictor through blockade of alpha receptors.
It exhibits a complex effect on the cardiovascular system, which consists of a combination of central inhibitory activity on the vasomotoric center, a peripheral vasoconstriction through partial agonism at serotoninergic, alpha-adrenergic, and tryptaminergic receptors and an antagonism at alpha receptors.

2.15. Eserine (= Physostigmine)

![Eserine](image)

Source: *Physostigma venenosum* (Leguminosae); seeds contain 0.3–0.5% alkaloids with eserine as the major component (about 0.15%).

*Pharmaceuticals (examples):* Anticholium™, Antilirium™, Isopto Pilomin™, Miopos-POS stark™, Miosica Doble™, Pilo-Eserin™, Pilo/Eserin in der Ophthiole™, Piloserin™.

*Therapeutic use:* Eserine is used in ophthalmology to reduce intraocular pressure in the treatment of glaucoma and as a miotic. It is also given as an antidote in acute poisoning with antimuscarinic agents such as atropine.

*Use in traditional medicine:* In some African tribes the beans are used for ordeals.

*Mechanism:* Eserine acts through blockade of acetylcholine esterase.

2.16. Galanthamine

![Galanthamine](image)

Source: *Galanthus woronowii* and *G. nivalis* (Amaryllidaceae). Alkaloid contents of bulbs are about 0.1%.

*Pharmaceuticals (examples):* Nivalina™.

*Therapeutic use:* It is used to curtail the muscle relaxant activity of nondepolarizing drugs
such as gallamine and tubocurarine. Recently, its use in the treatment of Alzheimer's disease has been proposed.

**Mechanism:** Galanthamine blocks acetylcholine esterase activity.

### 2.17. Hydrastine

![Hydrastine structure](image)

**Source:** Dried rhizome and roots of cultivated *Hydrastis canadensis* (Berberidaceae), indigenous to Canada and the eastern United States, containing 1.5–4.0% hydrastine.

**Pharmaceuticals (examples):** Gine Sedans™, Kollyr™

**Therapeutic use:** Treatment of gastrointestinal disorders.

**Mechanism:** Hydrastine acts as a sympatholytic and thus causes a slowdown of heart action. It is paralyzing to the CNS and causes limp paralysis of all muscles.

### 2.18. Hyoscine (= Scopolamine)

![Hyoscine structure](image)

**Source:** *Duboisia myoporoides* and *D. leichhardtii* (Solanaceae), but also *Datura* and *Hyoscyamus.*

**Pharmaceuticals (examples):** Buscopan™, Hyospasmol™, Lotanal™, Oportunin™, Scop™, Scopoderm T™, Spasmofen™, Transcop™, Transderm™

**Therapeutic use:** Hyoscine is used in transdermal plasters in the prophylactic treatment of acute motion sickness. As a premedicant, hyoscine is injected subcutaneously or intramuscularly, usually in combination with papaveretum, up to one hour before induction of general anesthesia.

**Mechanism:** Hyoscine blocks muscarinic cholinergic receptors competitively. It is more powerful than atropine. The central effects differ from those of atropine. In the brain hyoscine depresses the motor areas of cerebral cortex.
2.19. Hyoscyamine

Source: See atropine.

Pharmaceuticals (examples): bella sanol™, Bellatard™, Cystospaz™, Donnatab™, Neurovegetalin™, Solamin™, Tropax™, Urised™, Wigraine™.

Therapeutic use and mechanism: See atropine.

2.20. Lobeline

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\text{lobeline}
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Source: Lobelia inflata (Lobeliaceae); aerial parts contain 0.2–0.6% alkaloids.

Pharmaceuticals (examples): Cig-Ridettes™, Citotal™, Lobatox™, Refrane™, Smokeless™, Stopsmoke™.

Therapeutic use: Lobeline is used to discourage smoking. It also has been used in preparations against bronchial asthma, chronic bronchitis, emphysema, cough, nervous and vascular disorders, and insomnia. An injection of lobeline hydrochloride is used to resuscitate newborns.

Use in traditional medicine: Indians smoked it, like tobacco, as cigarettes.

Mechanism: It has similar central and peripheral activities as nicotine, because it affects nicotinic acetylcholine receptors. In therapeutic doses it activates respiration through an increase of excitability of chemoreceptors to the oxygen pressure of the blood.

2.21. Morphine

\[
\text{morphine}
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Source: Papaver somniferum (Papaveraceae); morphine is a component of opium, which is obtained from the dried or partly dried latex after incision of the unripe capsules. The incision is done 8–10 days after the corolla leaves have fallen.

Pharmaceuticals (examples): Collis Brown’s™, Diastat™, Diocalm™, Duromorph™, Enterosan™, Morphalgin™, Nepenthe™, Oramorph™, Roxanol™, Spasmofen™.
Therapeutic use: Morphine is used in the control of moderate and severe pain, e.g., in cancer patients. It is also used in the treatment of diarrhea.

Use in traditional medicine: Morphine has been used for its euphorizing properties. For this purpose it is smoked in cigarettes and water pipes. It is also a long-known analgesic.

Mechanism: It has agonistic activity at µ-opiate receptors and also, to a lesser extent, at κ-receptors. Morphine also acts directly on smooth muscles as, for example, in the intestine.

2.22. Narceine

![Narceine Structure](image)

Source: *Papaver somniferum* (Papaveraceae). It is a minor component of opium (0.1–0.7%). For preparation of opium see morphine.

Pharmaceuticals (examples): Paneraj™.

Therapeutic use: Treatment of cough.

Mechanism: As in codeine (see above).

2.23. Nicotine

![Nicotine Structure](image)

Source: *Nicotiana tabacum* and *N. rustica* (Solanaceae); leaves contain 0.5–9% nicotine, depending on species, developmental stages, and environmental conditions.

Pharmaceuticals (examples): Nicabate™, Nicoderm™, Nicorette™, Nicotinell™, Nicotrol™, nikofrenon™, ProStep™, Résolution™, Stubit™.

Therapeutic use: It is used in gums and transdermal plasters as aids to giving up smoking.

Traditional use: Tobacco is smoked for its stimulatory effects. Nicotine has also been used as a natural insecticide.

Mechanism: Nicotine exhibits agonistic activity at nicotinic acetylcholine receptors. In low doses it stimulates ganglia through depolarization of the postsynaptic membranes of vegetative ganglia; in higher doses it blocks them through permanent depolarization.
2.24. Noscapine (= Narcotine)

Source: *Papaver somniferum* (Papaveraceae): opium (see morphine) contains about 2–10% noscapine.

Pharmaceuticals (examples): Bequitusin™, Capval™, Degoran™, Difmetus™, Finipect™, Lyobex retard™, Nipaxon™, Nitepax™, Noscalin™, Rea Tos™, Rectolmin Bronquial™, Ribelfan™, Tossamine™, Tussisedal™, Tussoretard™.

Therapeutic use: It is used as a central cough suppressant.

Mechanism: Noscapine affects the cough center directly, increases respiration, and acts as a weak bronchodilator.

2.25. Papaverine

Source: *Papaver somniferum* (Papaveraceae). Papaverine is a component of opium (about 1%) and also of *Chelidonium majus* (Papaveraceae); the aerial parts contain about 0.1–1.0% alkaloids.

Pharmaceuticals (examples): Acticarbine™, Opdensit™, Optenyl™, Pameion™, Panergon™, Pavabid™, Pavaline™, Paveron™, Riddobron™, Vasocalm™.

Therapeutic use: It is used as a vasodilator, because of its smooth muscle relaxant properties. Papaverine is also used in the treatment of impotence by intracavernosal injection. It has been given to patients with cerebral, peripheral, and vascular disorders. In the treatment of gastrointestinal disorders it is employed as an antispasmodic.

Mechanism: Papaverine is a direct relaxant on all smooth muscles. It inhibits the activity of phosphodiesterase and thus causes an increase in cAMP level. In turn, Ca²⁺ concentrations are reduced, which are an important trigger in muscle contraction.
2.26. Physostigmine (see Eserine)

2.27. Pilocarpine

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\text{pilocarpine}
\]

Source: Pilocarpus jaborandi, P. pennatifolius, P. racemosus, and P. microphyllus (Rutaceae). P. microphyllus has the highest alkaloid content (0.7–0.8% alkaloids). Pilocarpine is the major component.


Therapeutic use: It is used as a miotic in the treatment of open-angle glaucoma. The miotic action is also exploited to antagonize the effects of mydriatics (e.g., phenylephrine) on the eye, but it is ineffective against mydriasis from antimuscarinic agents, such as atropine. In the treatment of leprosy it is used to induce sweat secretion. For this purpose the nitrate salt is injected into the skin of patients with leprotic skin lesions.

Mechanism: Pilocarpine has the antimuscarinic actions of acetylcholine. This leads to contraction of the musculus sphincter pupillae and the ciliary muscle and thus to a pupil contraction. In addition, the drain of chamber water is enhanced, resulting in a decrease of intraocular pressure.

2.28. Quinidine

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\text{quinidine}
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Source: Cinchona succirubra (Rubiaceae); bark should not contain less than 6.5% alkaloids. 30–60% of the alkaloidal fraction are quinine-type alkaloids.

Pharmaceuticals (examples): Biquin Duriles™, Cardioquin™, Duraquin™, Quinalan™, Quinidex™, Rhythmochin I™.
**Therapeutic use:** Quinidine is a class Ia antiarrhythmic, which is used in the treatment of ventricular and supraventricular arrhythmias, malaria (as an alternative to quinine), and in the prevention of nocturnal cramps.

**Use in traditional medicine:** As an antimalarial bark extract.

**Mechanism:** Antimuscarinic and alpha-adrenergic blocking reagent. The schizonticide action is based on the inhibition of nucleic acid synthesis through DNA intercalation and of carbohydrate metabolism. Quinidine binds to sarcoplasmic reticulum vesicles and diminishes binding and uptake of Ca²⁺. It also binds to Na⁺/K⁺-ATPase and inhibits it partially (Besch and Watanabe, 1977).

### 2.29. Quinine

![Quinine structure]

**Source:** Cinchona succirubra (Rubiaceae); bark contains not less than 6.5% alkaloids. 30–60% of the alkaloidal fraction are quinine-type alkaloids.

**Pharmaceuticals (examples):** Adaquin™, Biquinate™, Quinoctal™, Witte Kruis™, Zynedo-B™.

**Therapeutic use:** Treatment of Resochine-resistant malaria, babesiosis, and myotonic disorders.

**Traditional use:** Quinine is used for treatment of night cramps, fever, and as a bitter in tonic water.

**Mechanism:** Schizonticide (for exact mechanism see quinidine) against *Plasmodium falciparum, P. ovale, P. vivax, and P. malariae*. Quinine also blocks alpha-adrenergic receptors to the same degree as quinidine.

### 2.30. Raubasine (= Ajmalicine)

**Source:** Rauwolfia serpentina (Apocynaceae); roots contain about 0.8–2% alkaloids. Raubasine is also isolated from *R. vomitoria*.

**Pharmaceuticals (examples):** Card-Lamuran™, Circolene™, Cristanyl™, Duxil™, Duxor™, Hydrosarp®n™, Iskedyl™, Isosarpan™, Isquebral™, Lamuran™, Melanex™, Salutcin Co™, Salvation™, Sarpan™.
**Therapeutic use:** Treatment of peripheral and cerebral vascular disorders.

**Mechanism:** Raubasine acts as a selective alpha₁ sympatholytic drug. It depletes peripheral noradrenaline stores, resulting in a decrease of peripheral resistance and blood pressure. It also causes depletion of catecholamine and serotonin stores in the brain, heart, and many other organs.

### 2.31. Rescinnamine

![Rescinnamine](image)

**Source:** *Rauwolfia serpentina* (Apocynaceae); roots contain about 0.8–2% alkaloids with rescinnamine as a major component (0.15%).

**Pharmaceuticals (examples):** Detensiral™, Diuraupur™, Diu Rauwiplus™, Modenol™, Moderil™, Rauwopur™, Regulaserp™, Saltucin Co™.

**Therapeutic use:** Treatment of hypertension: properties and applications are similar to those of reserpine (see below).

**Mechanism:** See reserpine.

### 2.32. Reserpine

**Source:** *Rauwolfia serpentina* (Apocynaceae); roots contain about 0.15% alkaloids of the reserpine group.

**Pharmaceuticals (examples):** Abicol™, Adelphan-Esidrix™, Briserin™, Diutensen-R™, Pressimed™, Sandril™, Serpasil™, Serpasol™, Terbolan™.
Therapeutic use: Reserpine is applied in cases of mild to moderate hypertension and has also been used in the treatment of chronic psychoses.

Use in traditional medicine: In the Indian literature whole roots are employed in the treatment of psychoses and hypertension.

Mechanism: Reserpine acts as an alpha sympatholytic. It depletes peripheral noradrenaline stores, thus decreasing peripheral resistance and blood pressure. This action is explained through inhibition of a Mg\(^{2+}\)-dependent ATPase at the vesicle membrane, which pumps protons into the storage vesicles. Thus, the concentration of H\(^+\) decreases and basic substances as noradrenaline and dopamine cannot be protonated intravesicularly. The remaining noradrenaline follows the concentration gradient and diffuses into the cytoplasm where it is destroyed by intraneuronal monoamine oxidase, so that little or no neurotransmitter remains. It also causes depletion of catecholamine and serotonin stores in the brain, heart, and many other organs, in a similar way.

2.33. Sanguinarine

Source: Sanguinaria canadensis (Papaveraceae); rhizomes contain 4–7\% roots about 1.8\% alkaloids.

Pharmaceuticals (examples): Sanguinarine is used in toothpastes and mouthwashes.

Therapeutic use: As an antiplaque agent and also as an expectorant.

Mechanism: Sanguinarine modulates a number of molecular targets such as: intercalation to DNA, complexation of SH groups in enzymes, inhibition of esterases. Na\(^+\)/K\(^+\) ATPase, alanine aminotransferase, human sputum elastase and others. Some of the affected
organisms are: several *Escherichia* and *Aerobacter* species, *Bacillus anthracis*, *Trichomonas vaginalis*, *Trypanosoma lewisi*, several *Vibrio* species. It is also active against several oral microbial isolates, such as several *Actinomyces*, *Bacteroides*, *Eubacterium*, *Streptococcus*, and *Propionibacterium* species, *Leptotrichia buccalis*, *Campylobacter concisus*, and others (Simeon et al., 1989). Furthermore it has adrenolytic, sympatholytic, anti-inflammatory, cytotoxic, antifungal, and local anesthetic effects. Antibacterial and antiviral activities appear plausible.

### 2.34. Scopolamine (see Hyoscine)

### 2.35. Sparteine

![Sparteine structure](image)

**Sparteine**

**Source:** *Cytisus scoparius* (Leguminosae); aerial parts contain about 0.8–2% alkaloids, with sparteine as the major component.

**Pharmaceuticals (examples):** Anxoral™, Ariven™, Cardiopax™, cordi sanol forte™, Depasan™, Diffucord™, Digi-Pulsnorma™, Gelsadon™, Hypolind™, Hypotonin™, Jatamanisin™, Kanovenol™, Morfi™, Normotin™, Palpipax™, Perivar™, Pulsnorma™, RR-plus™, Sedol™, Tachynerg™.

**Therapeutic use:** In the treatment of cardiac arrhythmias and to induce uterine contractions. Because approximately 10% of the patients cannot metabolize sparteine, the latter application has become obsolete.

**Use in traditional medicine:** The herb is used as a diuretic. This action might be related to the positive inotropic action of sparteine, but also to the diuretic flavonoids present.

**Mechanism:** Sparteine inhibits Na⁺ channels and thus Na⁺ transport through the membranes. Sparteine activates muscarinergic acetylcholine receptors (Schmeller et al., 1994). As a result, conductivity of the cardiac muscle is modulated. Small doses stimulate and large doses paralyze the autonomic ganglia.

### 2.36. Strychnine

**Source:** *Strychnos nux-vomica* (Loganiaceae); seeds contain 1.5–5% alkaloids.

**Pharmaceuticals (examples):** Dysurgal™, Neuroftal™, Pastilles Jessel™, Pasuma™, Retinovix™, Rubistenol™, Senirakt™, Sulfa-Dysurgal™.

**Therapeutic use:** Strychnine is used in patients with eye disorders and optic nerve atrophy. It has been tried in the treatment of nonketotic hyperglycemia.

**Traditional use:** As a poison against several animals, such as moles and mice.
Mechanism: Strychnine binds to glycine receptors and competes with glycine, which is an inhibitory neurotransmitter to motoneurons and interneurons in the spinal cord. In therapeutic doses strychnine increases the muscle tonus and stimulates respiration and circulation, which leads to an increase of activity in physically weakened patients.

2.37. Taxol

Source: *Taxus brevifolia* (Taxaceae); bark contains several diterpene alkaloids, including taxol.

Pharmaceuticals (examples): Taxol™.

Therapeutic use: Taxol was recently introduced into medicine for the treatment of mamma and ovary carcinoma and several other malignancies.

Mechanism: Taxol inhibits the disassembly of microtubules into tubulins and promotes the assembly of microtubules. Thus, it disrupts normal cell division in the G₂ and the M phase of the cell cycle.

2.38. Theobromine

Source: *Theobroma cacao* (Sterculiaceae); testae contain about 1.5% theobromine.

Pharmaceuticals (examples): Atrofed™, Circovegetalin™, Dynamol™, Eupond™, Menstraleve™, Nephronorm™, Opticardon™, Seominal™, Spasdilt™, Urodonal™.
Theobromine

*Therapeutic use:* Treatment of asthma and in combination with other drugs for several purposes. Theobromine was used as a diuretic and in the treatment of angina pectoris.

*Traditional use:* Important ingredient of chocolate and cacao drinks.

*Mechanism:* Similar to caffeine as an inhibitor of phosphodiesterase and as a ligand for the adenosine receptor. Theobromine relaxes various smooth muscles, notably the bronchial muscle, stimulates cardiac muscle, stimulates the CNS, and increases blood flow in the kidney. Because it displays only low activities, it has almost been displaced by other drugs.

2.39. Theophylline

*Source:* Because the yield from natural sources is very low, theophylline is prepared synthetically.


*Therapeutic use:* It is used for relief of bronchospasms in asthma, bronchitis, and emphysema. In acute asthma theophylline is administered intravenously. It is also used to prevent chronic bronchospasms.

*Traditional use:* Minor component of green and black tea (*Camellia sinensis*).-

*Mechanism:* See caffeine and theobromine. The smooth muscle relaxant activity is the highest among the purines.

2.40. Tubocurarine

*Source:* *Chondodendron tomentosum* (Menispermaceae); the drug contains 2–7% of (+)-tubocurarine.

*Pharmaceuticals (examples):* Jexin™, Tubarine™.
**(+)-tubocurarine chloride**

*Therapeutic use:* In surgical procedures to produce muscle relaxation. Tubocurarine is also used intravenously or intramuscularly to control muscle spasms and convulsions of tetanus.

*Traditional use:* As an arrow poison (see Chapter 3).

*Mechanism:* Tubocurarine is a competitive inhibitor at nicotinic acetylcholine receptors on the motor endplate. Thus, it blocks the transmission of the nerve impulse to the muscle fiber.

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**2.41. Vinblastine**

![Vinblastine Structure]

vinblastine, \( R = \text{CH}_3 \)

vincristine, \( R = \text{CHO} \)

*Source:* *Catharanthus roseus* (Apocynaceae). In aerial parts with low content of about 0.001 – 0.005%.

*Pharmaceuticals (examples):* Periblastine™, Velban™, Velbe™, Velsar™.

*Therapeutic use:* Treatment of Hodgkin’s disease and other lymphoma, testicular cancer, and a variety of solid neoplasms. It is also used in patients with neuroblastoma, choriocarcinoma, and Kaposi’s sarcoma. Vinblastine has been used in several autoimmune blood disorders.

*Mechanism:* Vinblastine binds to microtubules of the spindle apparatus, thus arresting mitosis in the metaphase. It also affects amino acid metabolism and DNA synthesis, and has some immunosuppressant properties.
2.42. Vincamine

![Vincamine structure]

Source: Vinca minor (Apocynaceae); aerial parts contain 0.2–0.7% alkaloids with vincamine as a major component. Vincamine is also prepared synthetically.

Pharmaceuticals (examples): (Selection of about 50 preparations) Aethroma™, Angiopac™, Arteriovinca™, Cerebramina™, Dilarterial™, Pervin™, Vasonett™, Vincible™, Vincimax™.

Therapeutic use: As a vasodilator in the therapy of cerebral disorders.

Mechanism: Vincamine increases cerebral circulation and utilization of oxygen and glucose.

2.43. Vincristine

Source: See vinblastine.

Pharmaceuticals (examples): Norcristine™, Oncovin™, Pericristine™, Vincasar PSF™, Vincrisul™.

Therapeutic use: See vinblastine. It is also used in the treatment of Burkitt's lymphoma, Wilms' tumor, myeloma, rhabdomyosarcoma, and in patients with tumors of the brain and lung.

Mechanism: See vinblastine.

2.44. Yohimbine

![Yohimbine structure]

Source: Rauwolfia vomitoria (Apocynaceae).

Pharmaceuticals (examples): Aphrodyne™, Dayto Himbin™, Ichtho-Himbin™, Passeuma™, Pluriviron™, Prowess™, Yocon™, Yohimex™.
**Therapeutic use:** For impotent male patients and as an aphrodisiac. It is also used in the treatment of urinary incontinence.

**Use in traditional medicine:** As in therapy.

**Mechanism:** Yohimbine blocks presynaptic alpha₂ adrenoceptors, and thus it increases the noradrenaline release at sympathetic nerve endings. It therefore increases heart rate and blood pressure and produces orthostatic hypotension. The antiuretic effect can be explained through an increase of vasopressin release from the neurohypophysis.

### 3. CONCLUSIONS

As shown in this chapter, many alkaloids are used in modern medicine and the exploitation of alkaloids and alkaloidal plants is economically interesting and important. It has been estimated that approximately 20% of all plants produce alkaloids. As only 10 to 15% of all plants have been studied phytochemically and even less pharmacologically, it is safe to assume that we probably know and utilize only a small proportion of naturally occurring alkaloids and their properties. From a medical and economic standpoint it would be interesting to systematically evaluate the composition of natural products in plants (and also in some animals; see Chapters 15 and 16), not only those from temperate climates but also those from tropical rain forests (which still hold many unknown species). It seems to be important that new alkaloids be screened using modern pharmacological assays to fully understand their targets and their potential action and application. Furthermore, as the underlying biology and biochemistry are usually very interesting and challenging, these new discoveries will open a wide range of basic research, including biotechnological approaches that might be useful for producing the alkaloids in question on an industrial scale.

### REFERENCES

**Major Reviews**


**Key References**


