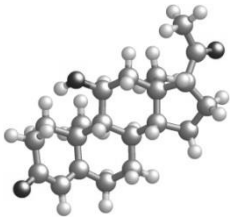

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Murder, Magic and Medicine

Professor John Mann, Queen's University, Belfast, Northern Ireland

First published in *Chemistry in Britain*, May, 1989

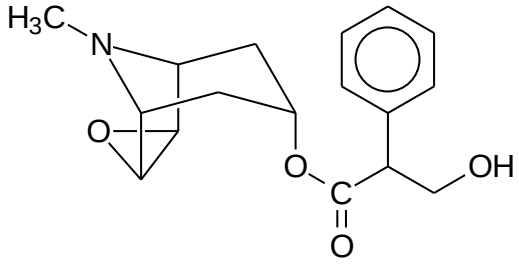
Then on the still night air,
The bark of a dog is heard,
A shriek! A groan!
A human cry! A trumpet sound!
The mandrake root lies captive on the ground.

This anonymous poem from the Middle Ages provides a graphic description of the collection of a mandrake. After a liberal sprinkling of female urine and menstrual blood, the plant was uprooted by a dog while the collector blocked his ears with wax, fearing the "shrieks like mandrake torn out of the earth, that living mortals hearing them run mad" (*Romeo and Juliet*). This superstitious nonsense was probably invented to deter the fainthearted and to ensure that the root did not fall into the wrong hands.

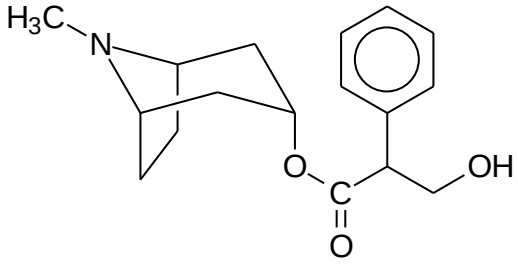
Mandrake, *Mandragora officinarum*, is indigenous to countries bordering on the Mediterranean Sea and has a long association with murder, magic and medicine. Its value as an anaesthetic and sedative was recognised by Hippocrates who wrote (*ca* 400 BC): "a small dose in wine, less than would occasion delirium, will relieve the deepest depression and anxiety"; and the *De viribus herbarium* (a 5th century manuscript) states: "If anyone is to have a member amputated, cauterised or sawed, let him drink an ounce and a half [of mandrake bark] in wine. He will sleep until the member is taken off". Its use as a poison was an obvious extension of its medicinal uses and in Elizabethan times, Arab traders were a prime source of toxic Satan's apples, genies' apples and devil's testicles, as mandrake berries were aptly known. Alternatively, the root was fermented until it became a green, evil smelling pulp, and then administered to the victim concealed in food or drink. Death was preceded by faintness, trembling, stomach pains and epileptic fits. The Arabs also supplied supposed antidotes based

upon complex mixtures of butter, honey, oatmeal, radish, dill, mint, fennel, celery, nutmeg, ginger *etc*.

Both the toxic and anaesthetic properties of the mandrake resulted primarily from the tropane alkaloid scopolamine [**1**]. This exhibits similar, but more potent, activity to atropine [**2**] from *Atropa belladonna*, which was a major ingredient in witches' salves.



[**1**] Scopolamine



[**2**] Atropine

These salves were applied under the arms an "in other hairy places", before "flying" to the sabbat.* This feeling of light headedness and mild euphoria will be familiar to anyone who has received a premedication treatment of scopolamine before surgery. Scopolamine is also a major constituent of henbane, *Hyoscyamus niger*, and this plant also has a long association with witchcraft, magic and necromancy. The priestesses of the Delphic oracle supposedly inhaled the smoke from burning henbane seeds and then became prophetic; while witches became intoxicated with "magic drinks" containing henbane as part of their preparations for the sabbat rituals.

These drugs exert their biological effects via the selective blocking of certain activities of the neurotransmitter acetylcholine (see **Figure 1** and **Figure 2**). The interconnections between nerve cells, and between nerve cells and the points of activation for muscles (so-called motor endplates), occur at the ends of dendrites and are called synapses and neuroeffector junctions respectively. The nerve impulse causes release of a transmitter substance – acetylcholine – from the synaptic vesicles, and this travels across the synaptic cleft to reach a receptor on the post-synaptic membrane of another neurone, or on the motor endplate of a muscle. A new nerve impulse, or the activation of muscular activity, is then initiated, and the acetylcholine – having accomplished its task – is degraded by the enzyme acetylcholine esterase.

* The sabbat, or witches Sabbath, is an occult midnight meeting at which the Devil presides.

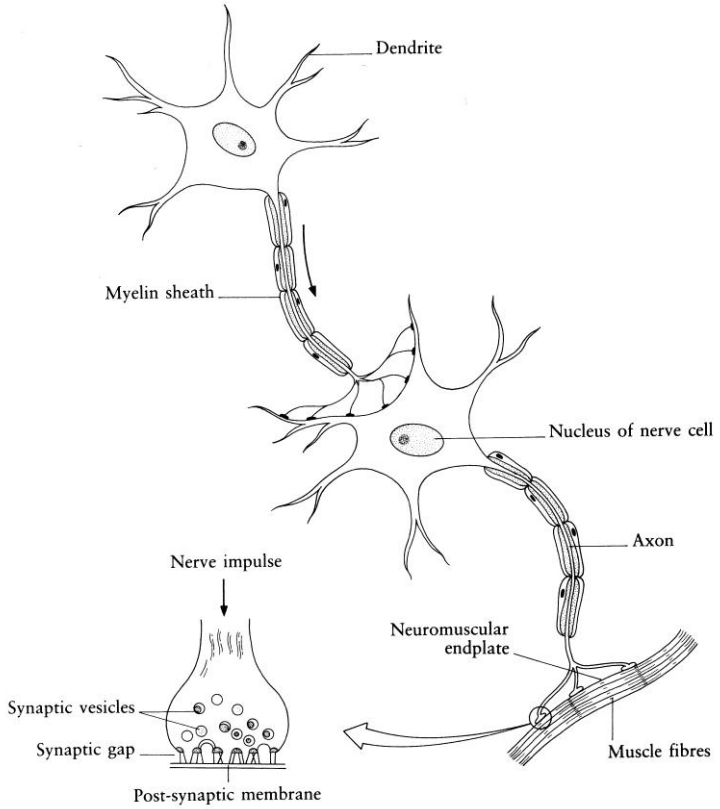


Figure 1.

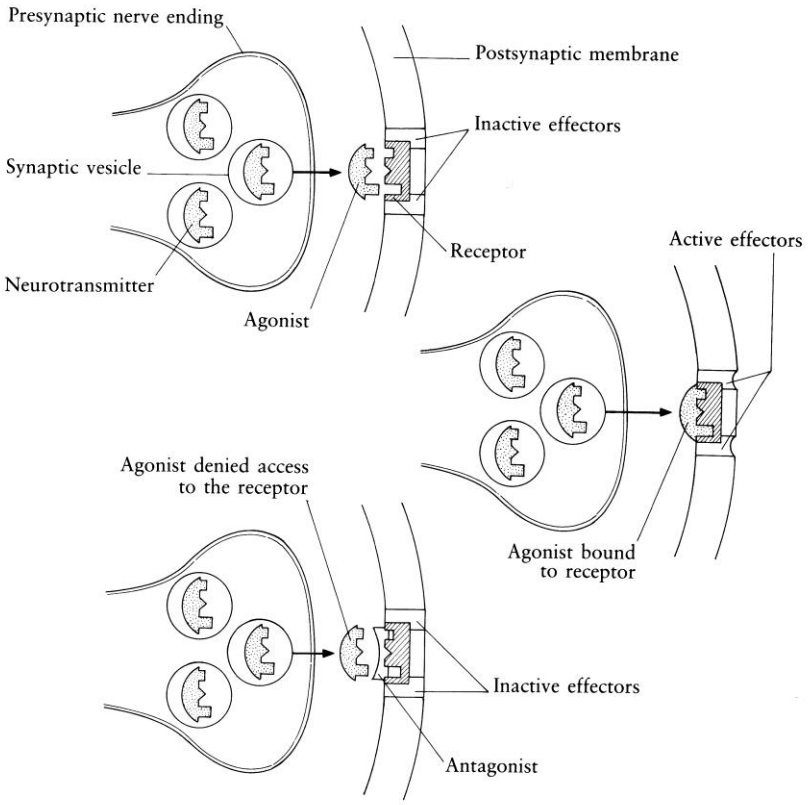


Figure 2.

Arrow Poisons

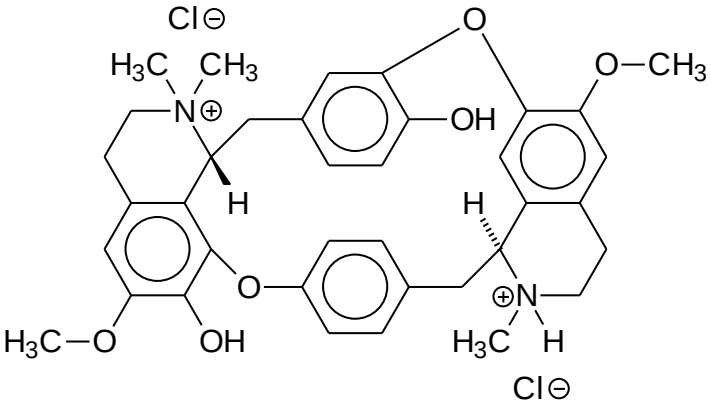
Not all plant extracts have such a plethora of uses, but most have their origins in man's quest for "agents of death" – required for hunting, euthanasia and execution; for inducing a state of euphoria and for folk medicine. Food was the most basic requirement of primitive man, and arrow poisons were widely used for hunting. Many of the most potent poisons originated from South America, and in the 16th century the early explorers of this continent reported that the Indians of Brazil, Peru, Ecuador and Colombia were using arrows tipped with *curari* or *woorali*. These were local names for what we now term "curare", which is a crude, dried extract of the plant *Chondodendrum tomentosum* and various *Strychnos* species.

Vivid accounts of the efficiency of these arrow poisons were related by (amongst others) the Spanish explorer Francisco de Orellano: "the Indians killed another companion of ours… and in truth, the arrow did not penetrate half a finger, but, as it had poison on it, he gave up his soul to our Lord"; and Sir Walter Raleigh: "the party shot indureth the most sufferable torment.. and abideth a most ugly and lamentable death". But generally, fantastic and largely misleading tales reached Europe. In particular, myths arose about the modes of preparation, and the efficiency was believed to be somehow related to the type of storage vessel used – *i.e.* "tube", "pot" or "gourd" curares. More accurately, the preparations were classified as "one tree curare" if a wounded monkey could only make one leap before expiring, while "three tree curare" could be used to capture animals alive.

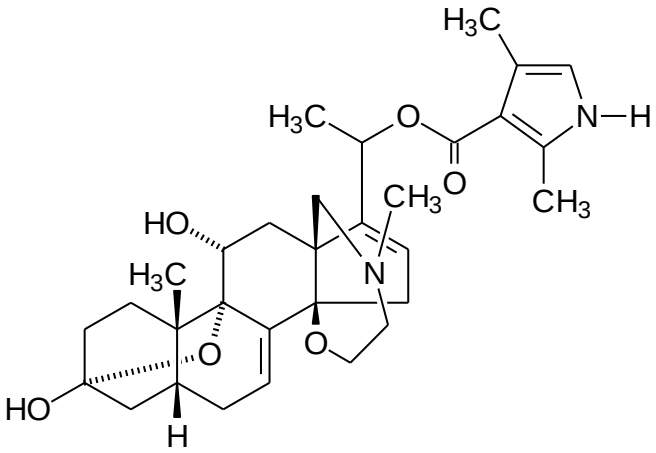
There was total ignorance concerning the mode of action of the toxin until Charles Waterton began his experiments with animals in the 1820s. His crucial experiment involved a female ass, which appeared to expire 10 minutes after he administered curare, but was then revived by artificial ventilation of its lungs with a bellows. The animal went on to make a full recovery, and the obvious implication was that curare caused death by asphyxiation. In 1844, the French physiologist Claude Bernard, using nerve-muscle preparations from frogs, confirmed that curare blocked the transmission of nerve impulses to the muscles. Injection of the arrow poison into the blood stream thus caused death by respiratory failure, because the chest and abdominal muscles were paralysed.

The most potent constituent of curare, tubocurarine [**3**], was first isolated in 1935 by Harold King from a dried museum sample of curare! Later on, greater quantities of tubocurarine became available through work at the companies Squibb and Wellcome, allowing clinical evaluation to begin. Then, as today, the early clinical trials were done by using company employees as guinea pigs; and Frederick Prescott, Wellcome's director of clinical research, was

one of the first to have himself injected with the new drug. The sensational press reports – "Doctor died for seven minutes" – helped to ensure a speedy entry of the drug into the clinic.



[**3**] Tubocurarine



[**4**] Batrachotoxin

It is now known that tubocurarine binds to muscle motor endplate receptors (see **Figure 1** and **Figure 2**) and thus denies access to acetylcholine, with a resultant paralysis of muscles. For surgery, it reduces the amount of general anaesthetic required to achieve complete muscle relaxation, though the resultant paralysis of the respiratory muscles means that artificial ventilation of the patient is necessary. Interestingly, tubocurarine is poorly absorbed via the gastrointestinal tract, so it is not dangerous to eat prey killed with curare.

Batrachotoxin

Plants were not the only source of arrow poisons. Colombian frogs of the genuses *Phyllobates* and *Dendrobates* were also found to contain particularly potent and useful neurotoxins. The frogs secrete these toxins when under stress and the local Indians would force the amphibians to release them by passing a pointed stick down their throat and out of one of their legs. A yellow oil accumulated on the stick and was used to prepare as many as 50 arrows. The structures of many of these toxins were investigated in the 1960s by Witcop and Daly and some 200 structures have now been identified. Of these, batrachotoxin [**4**], from the frog *Phyllobates aurotaenia*, is particularly potent; *ca* 2 μg of this toxin is sufficient to kill a mouse, which makes it one of the most toxic non-proteinaceous substances known.

Many toxins work by interfering with the mechanism of impulse propagation. Normally, nervous impulses are transmitted by a series of large (though transient) changes in permeability of the axonal membrane to sodium and potassium ions. Before excitation there is a potential

difference of –60 mV across the membrane, with an excess of potassium ions on the inside over sodium ions on the outside (see **Figure 3**).

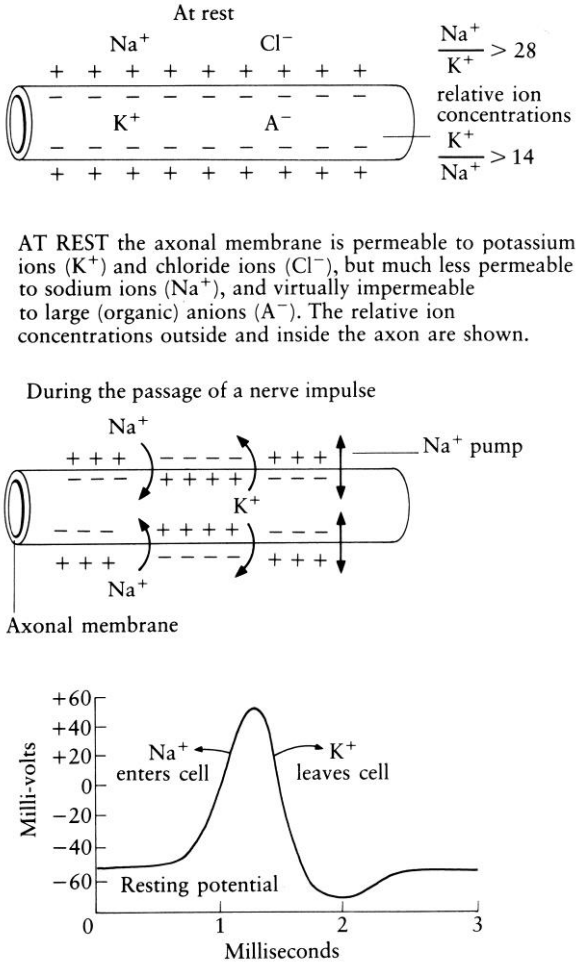
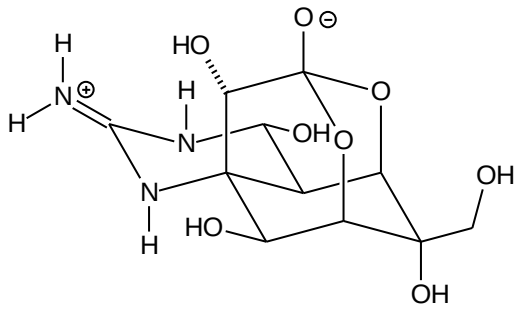


Figure 3.

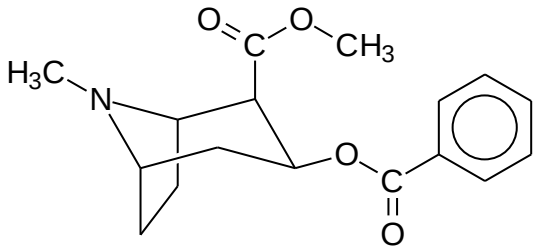
At rest the axonal membrane is permeable to potassium ions (K^+) and chloride ions ($Cl^–$), but much less permeable to sodium ions (Na^+) and virtually impermeable to large organic anions ($A^–$). Upon excitation, there is a selective inrush of sodium ions via special sodium ion channels, leading to a depolarisation and then to a rise of potential difference to +30 mV all within a millisecond. At this point the sodium ion channels close and separate potassium ion channels open to allow an outflow of potassium ions and the restoration of the original potential difference. The nerve impulse is thus propagated as a series of depolarisations and repolarisations.

The frog batrachotoxin [**4**] acts by increasing the permeability of nerve calls to sodium ions, resulting in an irreversible electrical depolarisation of the cell. In the heart, this causes dysrhythmia, fibrillation and ultimately heart failure. Interestingly, its effects are antagonised by

another potent toxin – tetrodotoxin [**5**] from the puffer fish – and the two neurotoxins are thus of great interest in neurochemical research.



Tetrodotoxin [**5**]



Cocaine [**6**]

All of these poisons were also used in warfare, executions and euthanasia; but certain plant toxins were used in a more subtle way for trials by ordeal. The report in 1956 by the anthropologist Donald Simmons of one such trial – involving the Calabar bean from *Physostigma venenosum* – is exemplary:

> The *Efik* (people) believe that the *esere* (extract of the bean) possesses the power to reveal witchcraft. A suspected person is given eight of the beans ground and added to water as a drink. If he is guilty, his mouth shakes and mucous comes from his nose. His innocence is proved if he lifts his right hand and then regurgitates. If the poison continues to affect the suspect after he has established his innocence, he is given a concoction of excrement mixed in water which has been used to wash the external genitalia of a female.

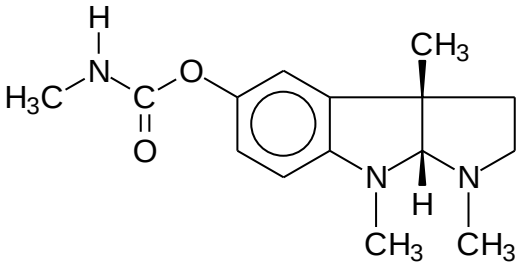
The outcome of these trials was probably predetermined by the judges, and the correct toxic or emetic dose administered.

Toxicology

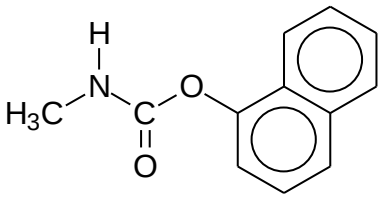
Stories of this kind had reached Scotland via the missionary service as early as 1846 and toxicology studies were begun at Edinburgh University in the 1850s by Sir Robert Christison. Not satisfied with his animal experiments, he consumed a small piece of Calabar bean (*ca* 0.5 g). He rapidly became very giddy, and becoming alarmed he “took immediate means for getting quit of it [the poison], by swallowing the shaving water I had just been using”. He subsequently noted his feeble heart beat, and spent several hours in bed before recovering. This experience did not deter him from other studies. At the age of 78 he experimented with

cocaine [**6**], walking long distances and clambering around mountains to demonstrate the fatigue and hunger reliving properties of the drug.

The major constituent of *Physostigma venenosum* – physostigmine [**7**] – was isolated isolated in pure form in 1864, though its structure was not elucidated until 1925. More recently it has been shown to act as an inhibitor of the enzyme acetylcholine esterase, which catalyses the hydrolysis of the neurotransmitter. This biological activity was first exploited 50 years ago in the treatment of myasthenia gravis, a chronic disease that is manifested by progressive muscle weakness. The cause of this disease is still unknown, but the underlying neurochemical problem involves the reduced availability of acetylcholine. Physostigmine thus spares the limited supplies of the neurotransmitter from the effects of acetylcholine esterase. The so-called carbamate insecticides like carbaryl [**8**] are also acetylcholine esterase inhibitors, though physostigmine itself does not possess useful insecticidal properties.



Physostigmine [**7**]



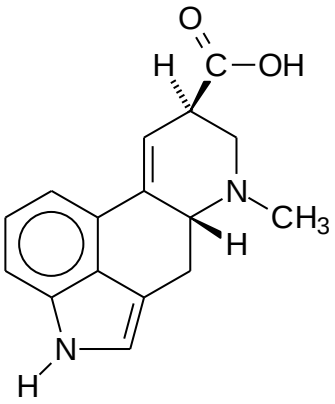
Carbaryl [**8**]

Lysergic Acid Amides

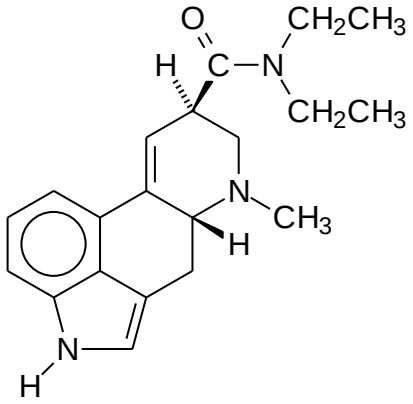
As for stimulants, euphoriants and psychedelic drugs, these range from various native brews containing caffeine (cola, cocoa, tea, coffee and maté), to the hallucinogenic snuffs and mushrooms and, most potent of all, plant extracts containing lysergic acid amides. Seeds from the vine *Rivea corymbosa* provided the Aztecs with their magic potion *ololiuqui*; the morning glory *Ipomea violaceae* yielded *tlililtzin*; and the Mazatecs used leaves of the plant *Salvia divinorum* as the basis of an infusion known as *poyomatli* or *pipilzintzintli*. A Spanish missionary of the 16th century provided one of the first accounts of the effects of these hallucinogenic plants: "*Ololiuqui* deprives all who use it of their reason… and they are deceived by various hallucinations which they attribute to the deity they say resides in the seeds". The Aztecs are also claimed to have used a body rub comprising *ololiuqui*, tobacco and crushed insects, during sacrificial ceremonies.

Most of these plants contain lysergic acid amides, and work at Sandoz provided Albert Hofmann with samples of lysergic acid [**9a**]. He subsequently synthesised the diethylamide,

LSD [**9b**], in 1938, but not until 1943 did he discover the potency of this psychedelic drug. He described his sensations after accidentally ingesting traces of the compound: “I was seized by a peculiar sensation of vertigo and restlessness. Objects as well as the shapes of my associates… appeared to undergo optical changes… with my eyes closed, fantastic pictures of extraordinary plasticity and intensive colour seemed to surge towards me.”

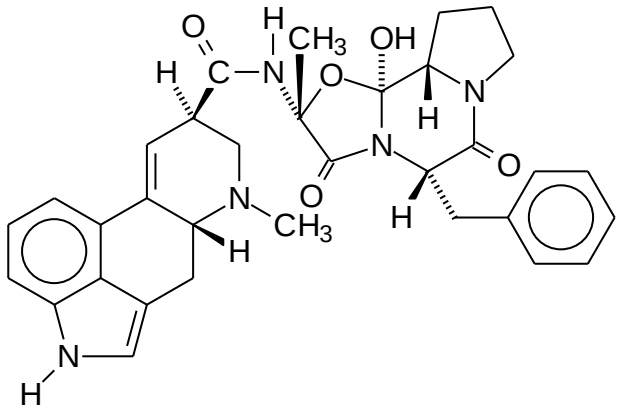


Lysergic Acid [**9a**]

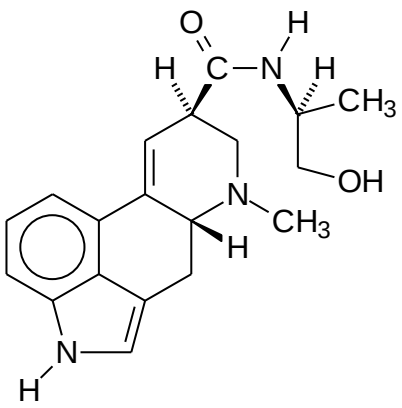


Lysergic Acid Diethylamide [**9b**]

LSD has since achieved notoriety as part of the hippy culture of the 1960s and has some value in the treatment of mental illness, but it is the lysergic acid derivatives produced by the fungus *Claviceps purpurea* that are of more historical and clinical importance. The so-called ergot alkaloids, like ergotamine [**10**], produced by the fungus, were common contaminants of rye bread in the Middle Ages and were responsible for the outbreaks of ergotism that ravaged Europe. These “plagues” were second only to bubonic plague in their genocidal effects, and entire communities were eradicated. With some strains of the fungus, death resulted from epileptic seizures and other neurological problems, while with other strains the vasoconstrictive (blood vessel narrowing) effects of ergotamine led to generalised gangrene.



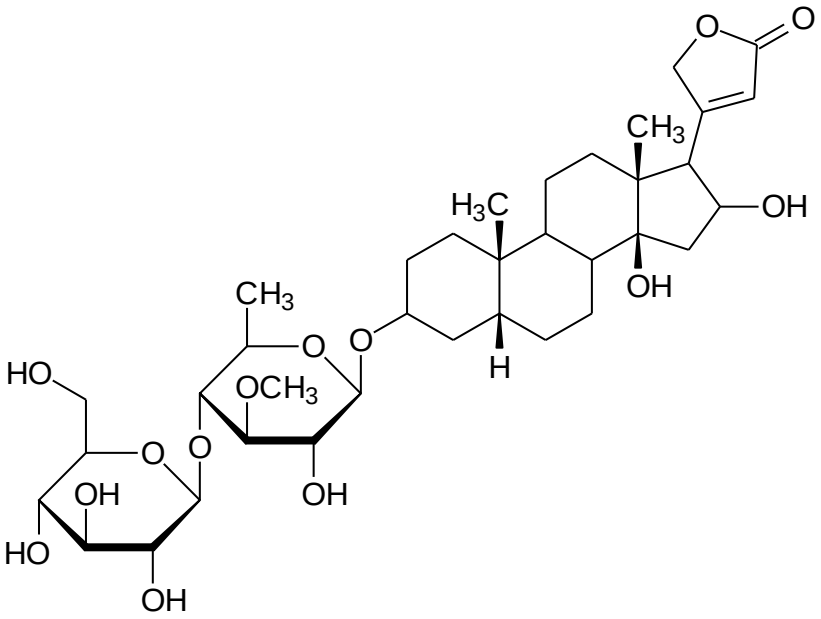
Ergotamine [**10**]



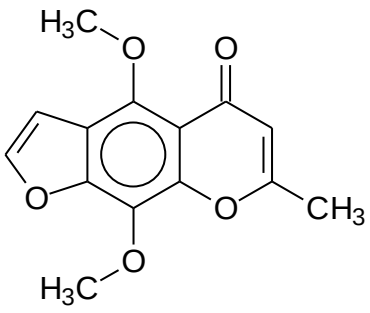
Ergometrine [**11**]

Medical Uses

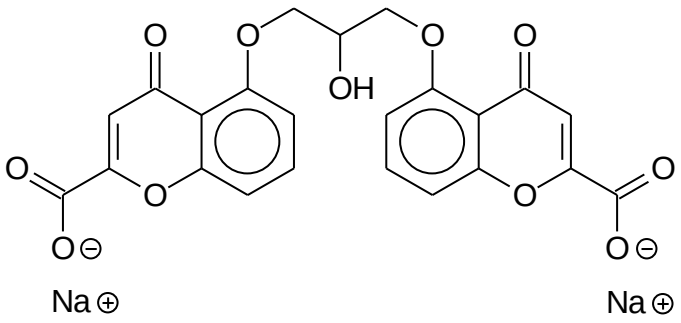
The use of plants in folk medicine and modern medicine has been common – the foxglove and digitalin [**12**] for the treatment of coronaries; and khellin [**13**] from the plant *Ammi visnaga* which provided the basis for the development of the antiasthmatic drug sodium chromoglycate – intal [**14**]. It has been estimated that around 50 per cent of our drugs are derived from natural products or are synthetic analogues with structures chosen for optimised biological potency. Two stories of drug discovery exemplify the value of folklore.



Digitalin [**12**]



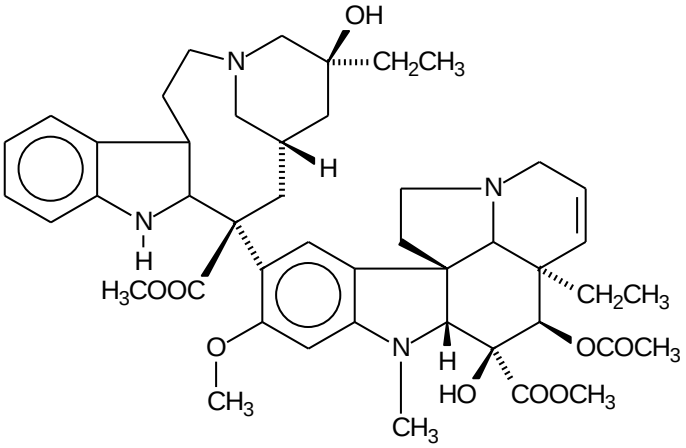
Khellin [**13**]



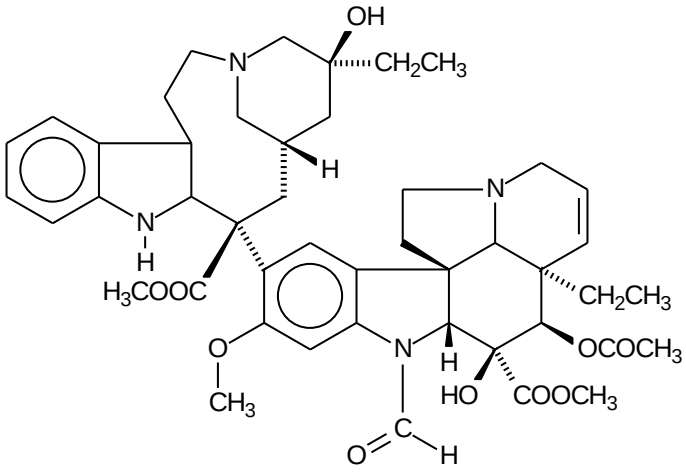
Intal [**14**]

The first involves the use of the Madagascar periwinkle, *Catharanthus roseus*, as a native treatment for diabetes. Investigation of this claim in the late 1950s led to the isolation of vinblastine [**15a**] and vincristine [**15b**], and although the folklore claims proved to be unfounded, the compounds did function as potent inhibitors of cell mitosis (cell division). Their subsequent development by Eli Lilly for cancer chemotherapy provided one of the major success stories in

this area. Three cancers – Hodgkin's lymphoma, childhood leukaemia, and testicular teratoma – are now usually curable through the use of these drugs (in combination with others) and many other tumours also respond.



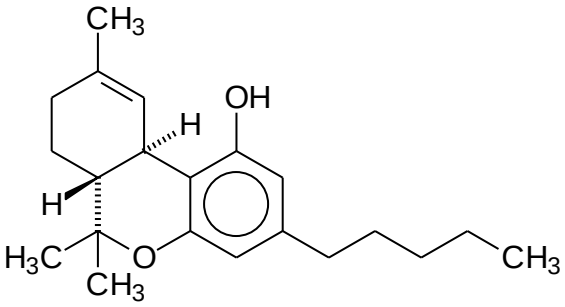
Vinblastine [**15a**]



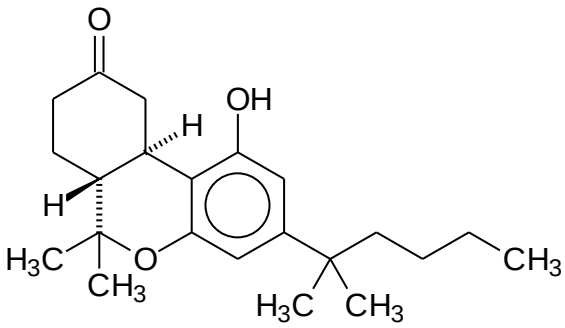
Vincristine [**15b**]

The second example involves modern folklore and concerns the plant *Cannabis sativa*. In biblical times the plant was valued for its seeds as a source of protein and oil for lamps, and the fibrous plant stalk was used to make hemp ropes. Its use as a euphoriant can be traced back at least 2500 years – in 500 BC Herodotus described how the Scythians inhaled vapours from the plant: "…a dish is placed upon the ground into which they put a number of red hot stones and then add Hemp seed… immediately it smokes… and the Scyths, delighted, shout for joy…". Its popularity, then and now, can be judged by the number of names used to describe extracts of the plant – hashish, marijuanha, charas, bhang, ganja, daga, pot *etc* – and it has been estimated that 200 – 300 million people use the drug on a regular basis.

In the late 1960s stories began to circulate which suggested that the consumption of cannabis helped to prevent the sickness induced by overindulgence in alcohol. Studies of the antiemetic properties of Δ^9–tetrahydrocannabinol [**16**], the major psychoactive constituent of cannabis, established the validity of this "hippy folklore" and subsequent synthetic and pharmacological endeavours by the Eli Lilly company have yielded the analogue nabilone [**17**] as a highly potent antiemetic agent. Its main use is in the control of the severe sickness caused by many anticancer agents, but a future rôle as a proprietary drug for the treatment of travel sickness or morning sickness is not impossible.



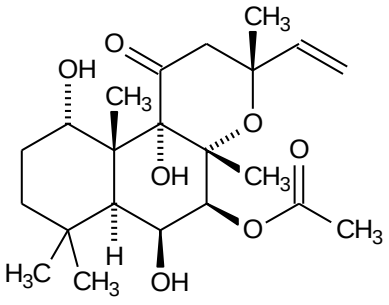
Δ^9–tetrahydrocannabinol [**16**]



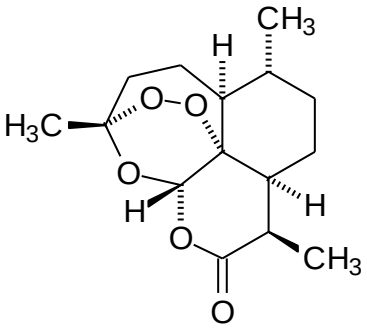
Nabilone [**17**]

Numerous other folk medicines are currently under investigation and forskolin [**18**] from *Coleus barbatus* and qinghaosu [**19**] from *Artemesia annua*, are two constituents of particular contemporary interest. The former shows promise as a drug for the treatment of hypertension, glaucoma, asthma and certain tumours, while the latter has potent antimalarial activity.

Plants are superlative “chemists”, and there is no doubt that other native poisons, magical potions and medicines await discovery and exploitation. But with the rainforests disappearing at the rate of 100 acres a minute and the rapid destruction of other natural habitats and cultures, time is not on our side.



Forskolin [**18**]



Qinghaosu [**19**]