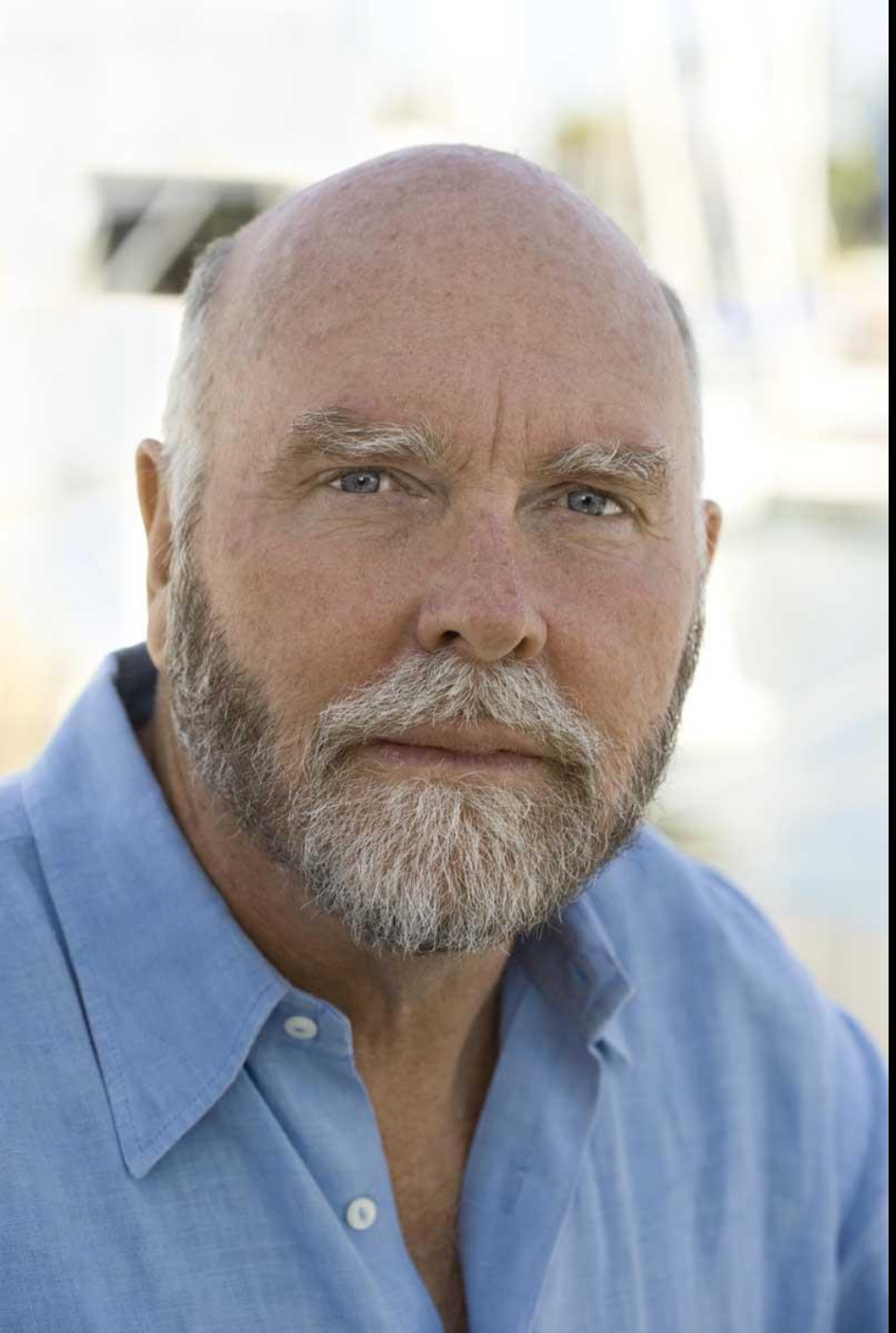
An Introduction to Medicinal Chemistry

Murder
Magic
Medicine



"A doctor can save a few hundred lives in a lifetime. A researcher can save the whole world."

Dr. Craig Venter

What is a drug?

Drugs are normally low molecular weight chemicals that interact with macromolecular targets within the body to produce a pharmacological effect. The effect may be beneficial or harmful depending upon the drug used and the dose administered.

What kind of molecules do drugs react with in the body?

* Enzymes.

Enzymes are proteins that catalyse the body's chemical reactions.

* Receptors.

Most receptors are proteins that traverse the cell membrane with a binding site on the extracellular region.

* Carrier proteins.

Carrier proteins transport important polar molecules across the cell membrane.

* Structural proteins.

An example of a structural protein is *tubulin* that polymerises to form microtubules that serve a variety of cellular functions.

What kind of molecules do drugs react with in the body?

* Nucleic acids.

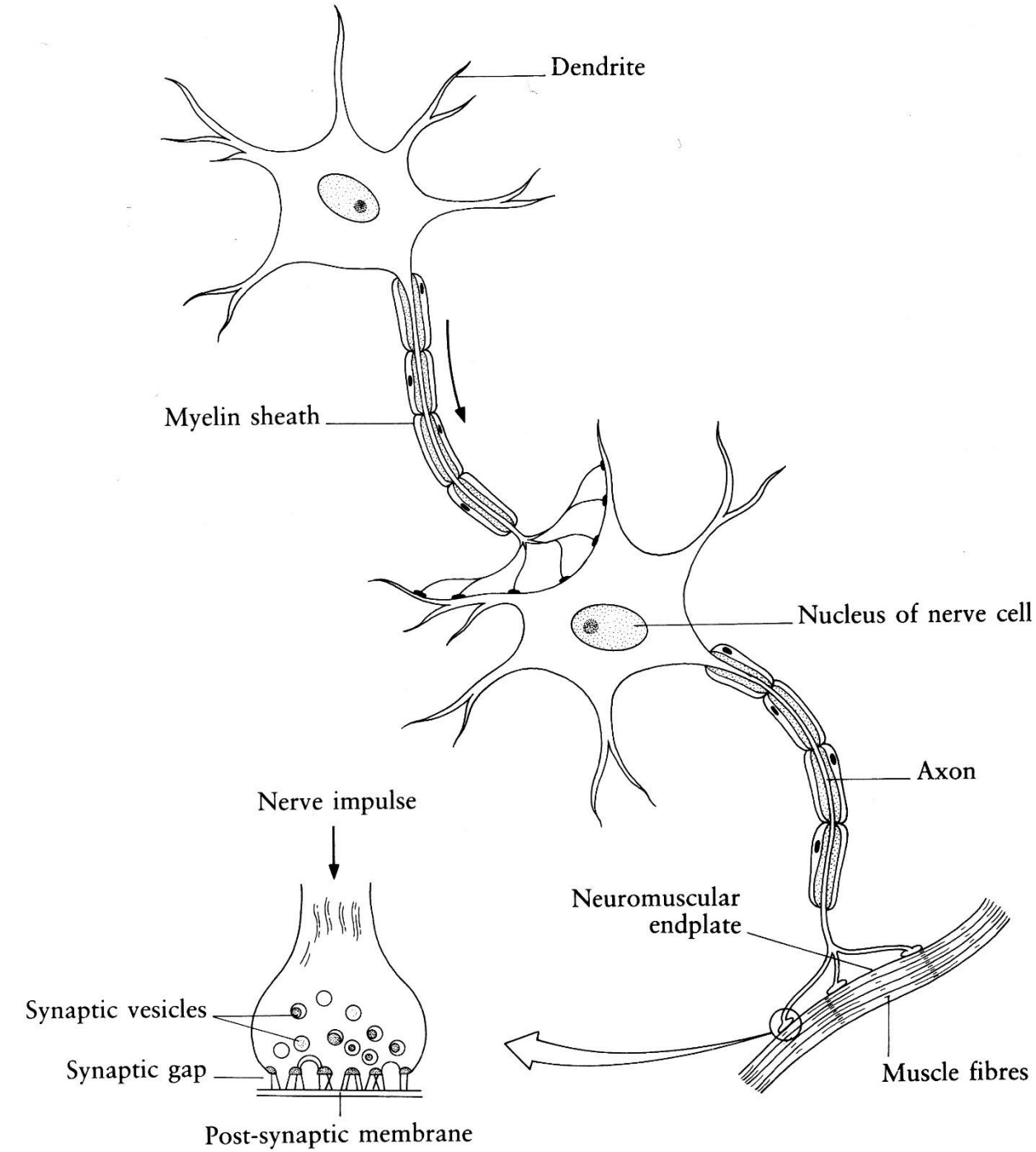
There are two types of nucleic acid – DNA and RNA.

* Lipids.

Cell membranes are composed of a lipid bilayer. The cell membrane acts as a hydrophobic barrier to the flow of ions, water and polar molecules.

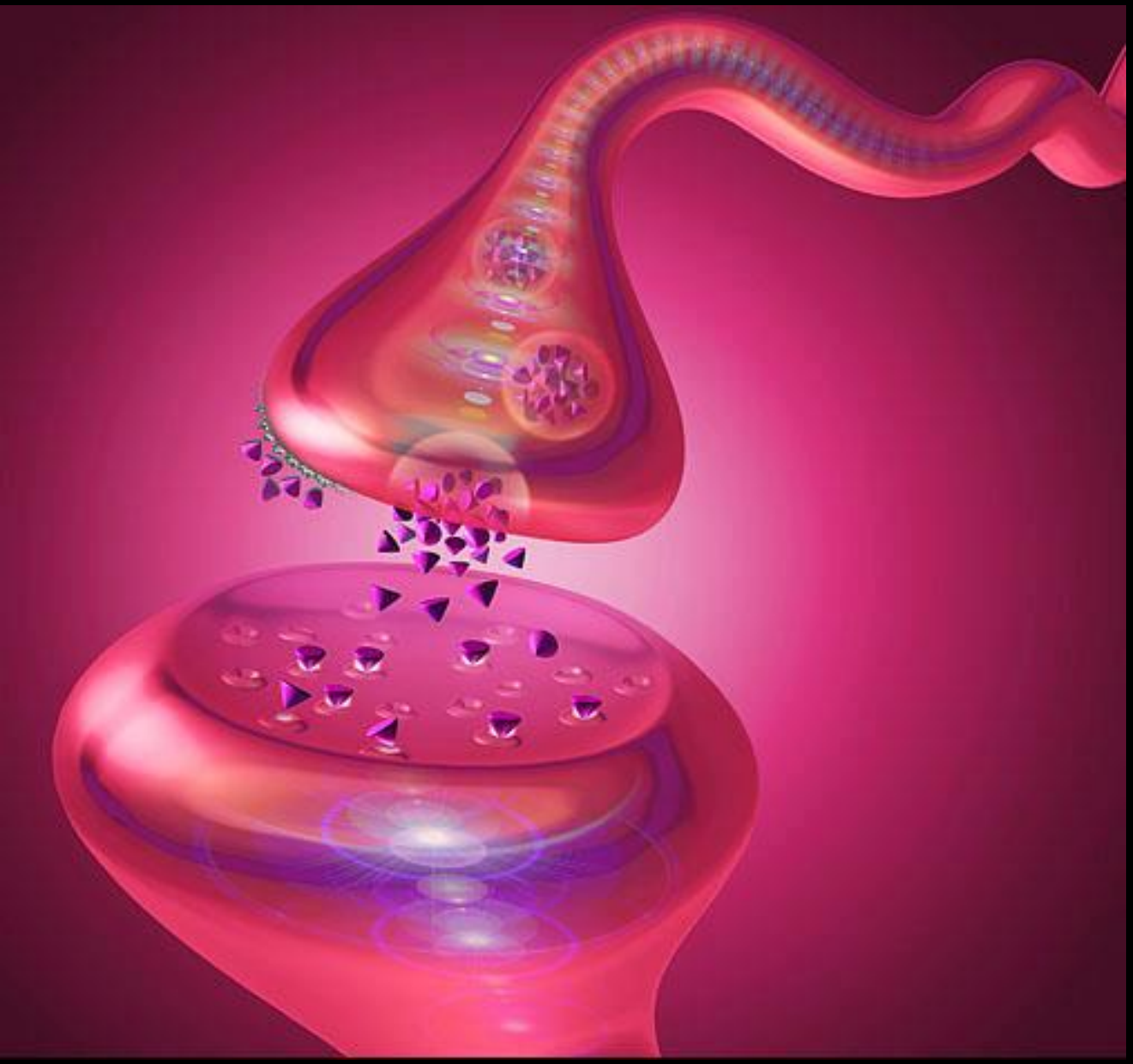
* Carbohydrates.

Cell surface carbohydrates are promising drug targets for the future.



Physiology and Biochemistry

Nerve axon, synapse and neuromuscular endplate.



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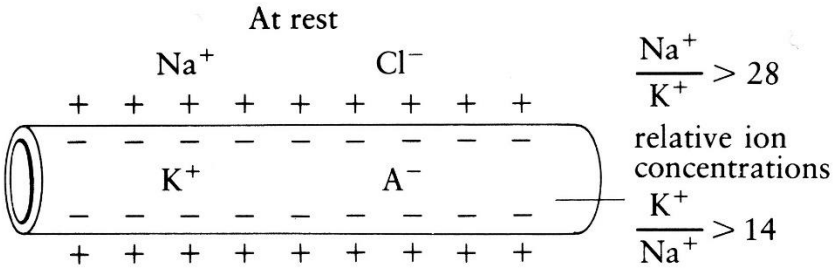
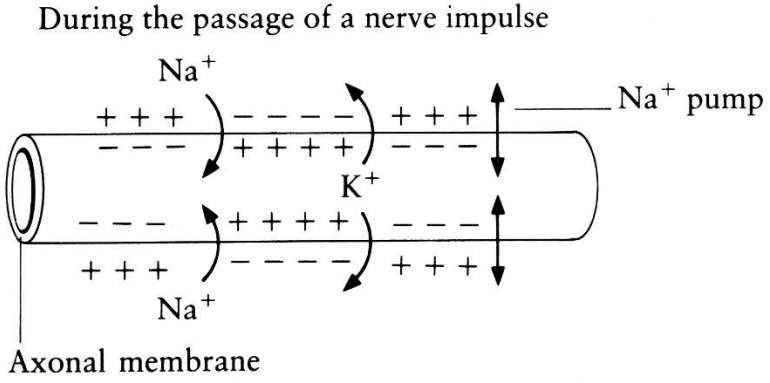
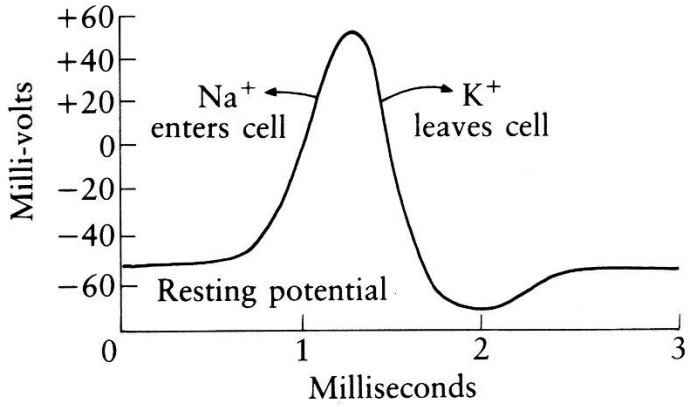


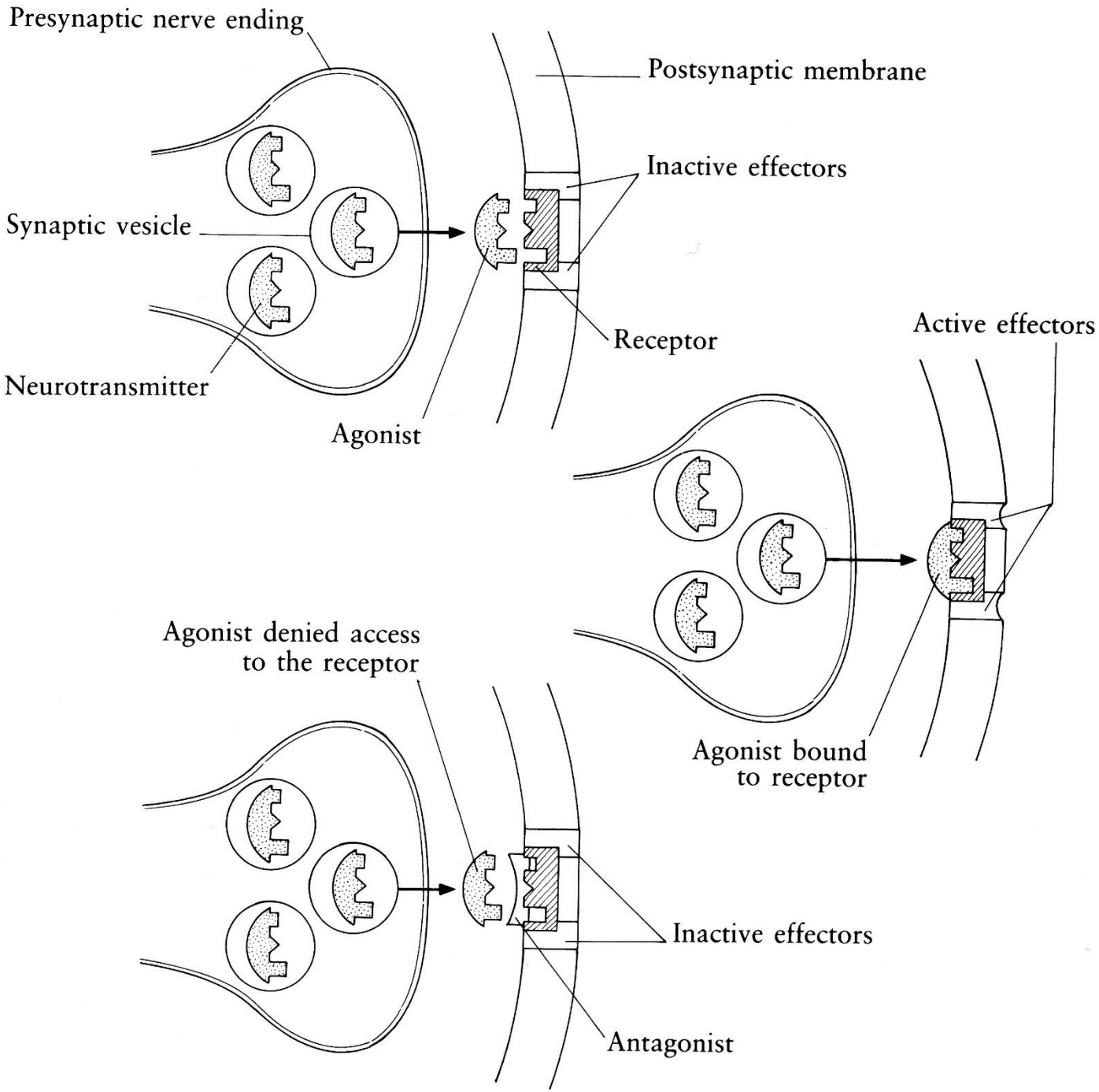
AT REST the axonal membrane is permeable to potassium ions (K^+) and chloride ions (Cl^-), but much less permeable to sodium ions (Na^+), and virtually impermeable to large (organic) anions (A^-). The relative ion concentrations outside and inside the axon are shown.





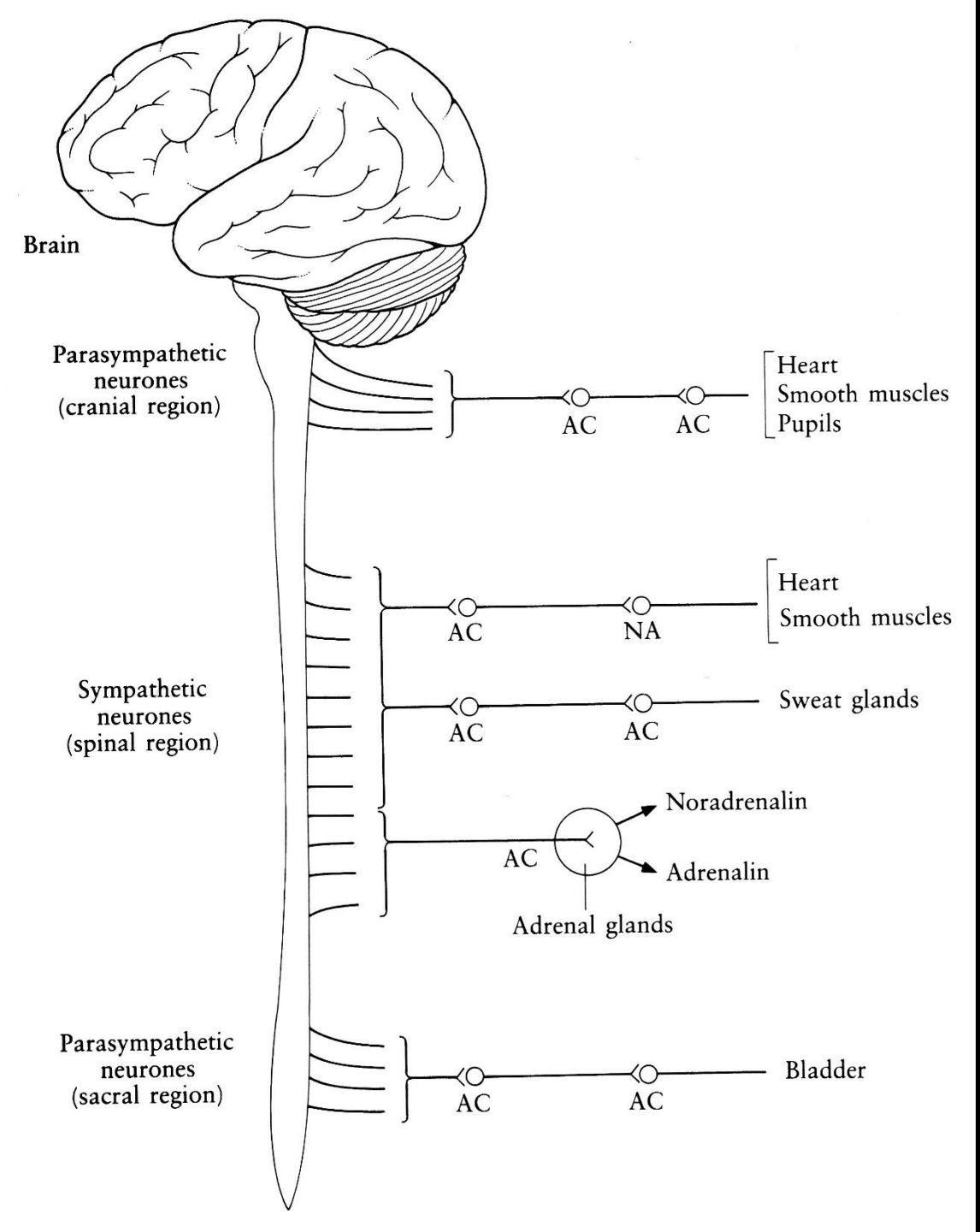
Physiology and Biochemistry

Biochemistry of the nerve impulse.



Physiology and Biochemistry

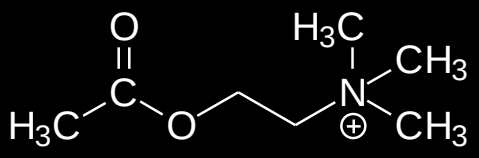
The synapse: agonists and antagonists.



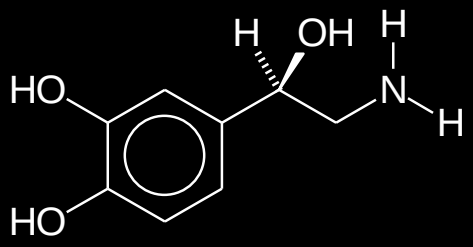
Physiology and Biochemistry

Organisation of the nerves. AC and NA denote neuronal junctions at which acetylcholine or noradrenalin are employed.

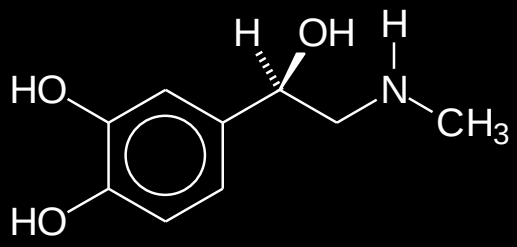
Physiology and Biochemistry: Neurotransmitters



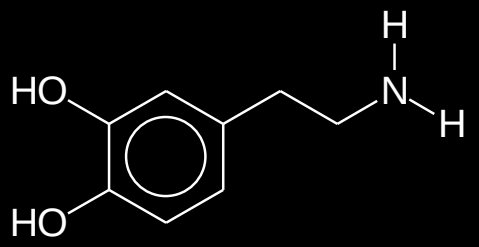
Acetylcholine



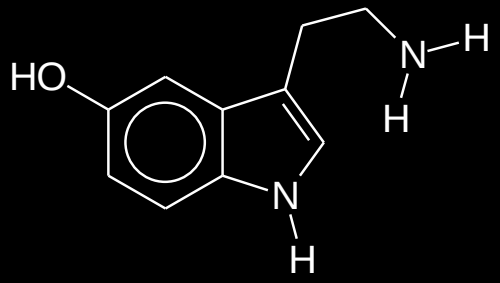
Noradrenaline



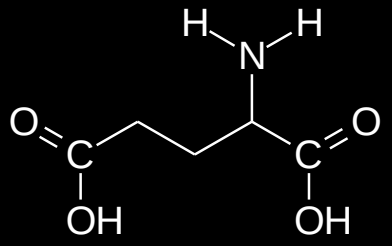
Adrenaline



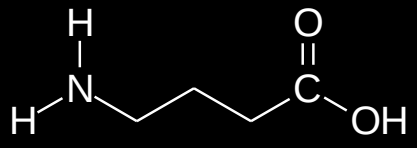
Dopamine



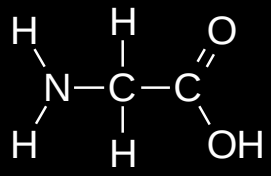
Serotonin



Glutamic Acid



γ-Aminobutanoic Acid (GABA)



Glycine

Murder

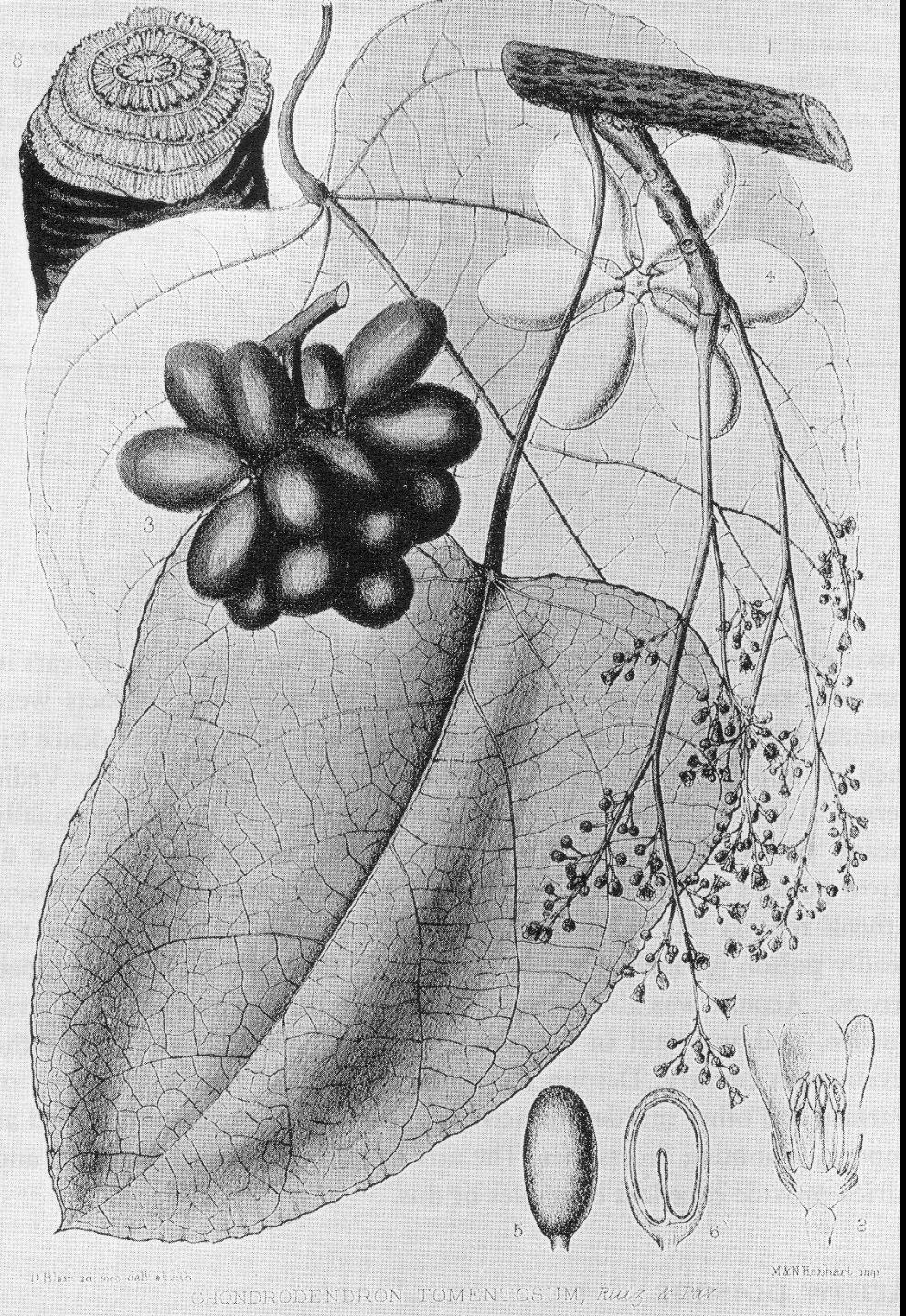
Ophelia (1852)
John Everett Millais

Murder

Toxic plant and animal products have been used for thousands of years in hunting, execution and warfare.

The Maku Indian hunters of Columbia smear a poisonous plant extract called *curare* over the tips of their arrows.

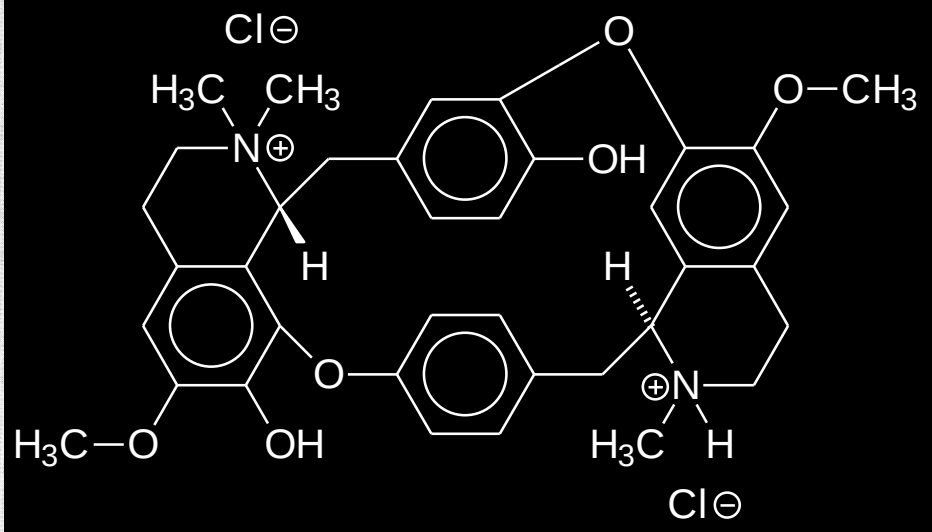
In the sixteenth century, explorers reported that the Indians of Brazil, Peru, Ecuador and Colombia were using arrows tipped with curare. The Spanish explorer Francisco de Orellano wrote, "*The Indians killed another companion of ours, and in truth, the arrow did not penetrate half a finger, but, as it had poison on it, he gave up his soul to our Lord*."



Murder

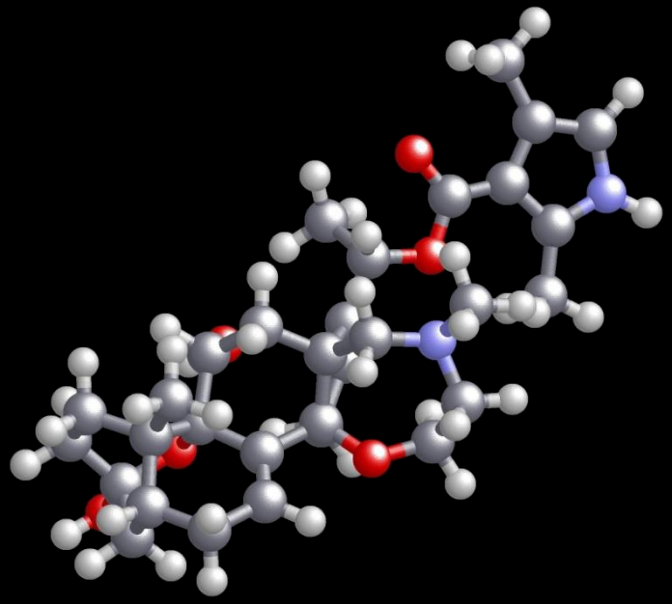
The main component of curare is *tubocurarine* which is extracted from the plant *Chrondrodendron tomentosum*.

Tubocurarine binds to the motor end-plate receptors and thus denies access to the neurotransmitter acetylcholine, with resultant paralysis of the muscles.



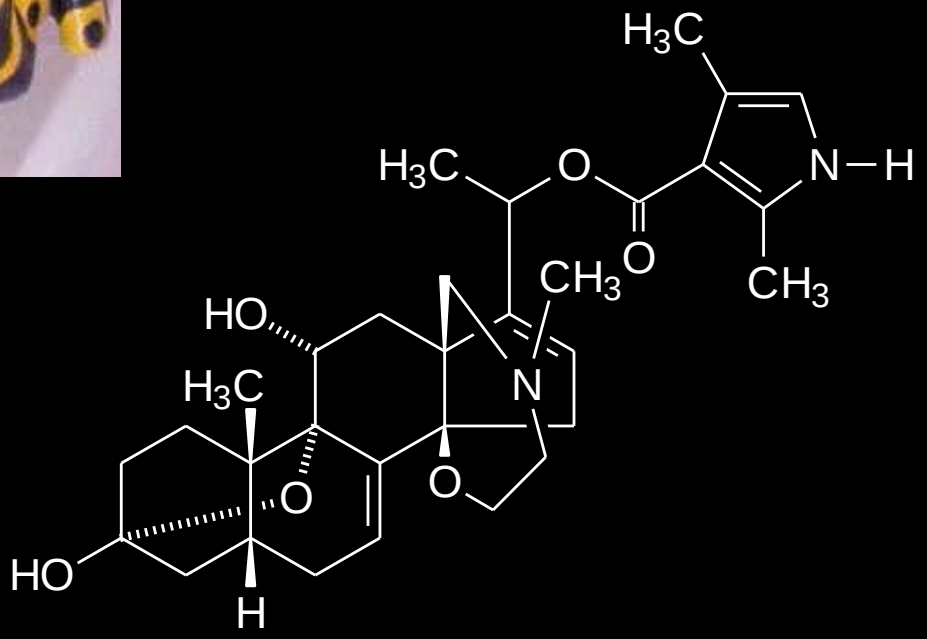
Murder

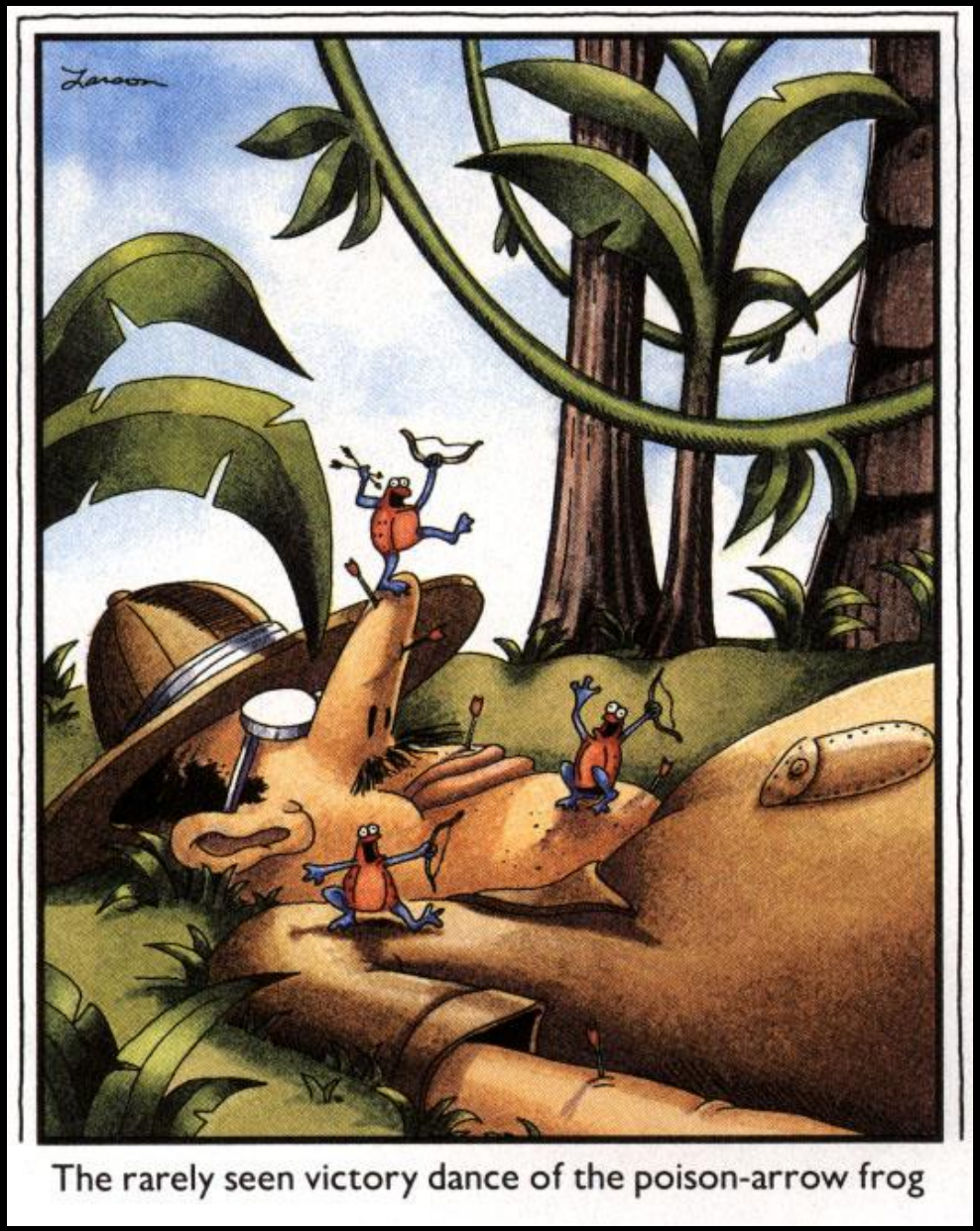
Plants are not the only source of arrow poisons. Colombian frogs of the genuses *Phyllobates* and *Dendrobates* secrete a potent neurotoxin called *batrachotoxin* when placed under stress. The yellow oil secreted by one frog may be used to prepare as many as 50 arrows.



Murder

The frog batrachotoxin acts by increasing the permeability of nerve cells to sodium ions, resulting in an irreversible electrical depolarisation of the cell. In the heart, this causes dysrhythmia, fibrillation and ultimately, heart failure.





The rarely seen victory dance of the poison-arrow frog

PLATE XIX.—*Physostigma venenosum.* Physostigmine (Eserine) is prepared from the bean (seed). It is called Calabar bean. Calabar is a coast district in West Africa. The seed was called *esere* by the natives; hence, the name eserine. (From Jackson: *Experimental Pharmacology and Materia Medica.*)

Murder

In primitive societies, when a person was accused of a crime they were often subject to a *trial by ordeal* involving the admission of a toxic plant extract.

The anthropologist Donald Simmons wrote in 1956 of his encounters with the Efik people, "*The Efik people believe that the esere 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 mucus comes from his nose*."

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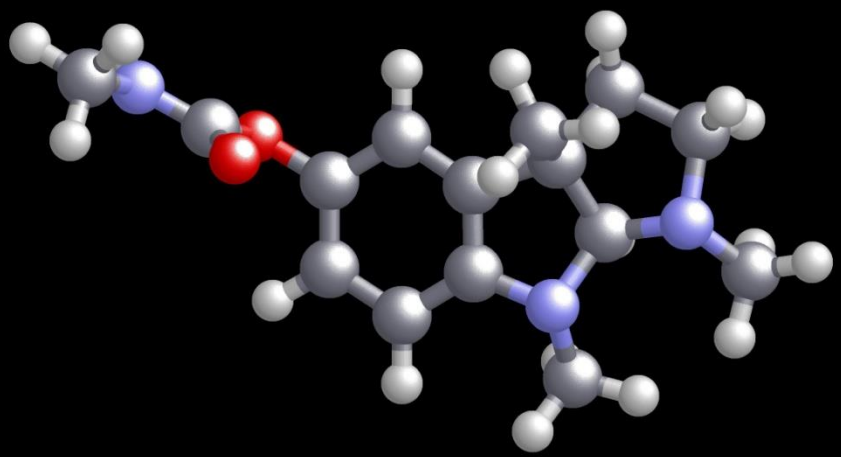
The beans that Simmons describes are those of the plant *Physostigma venenosum* which contain the chemical *physostigmine*. This chemical acts by inhibiting the enzyme *acetylcholine esterase* which is responsible for the hydrolysis of acetylcholine in the synaptic cleft.



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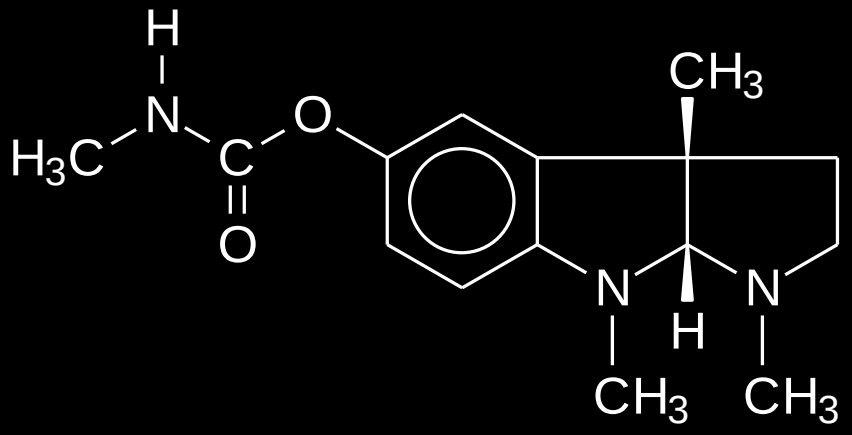


Murder

Mandrake, *Mandragora officinarum*, is indigenous to countries bordering the Mediterranean Sea and has long been associated with murder, magic and medicine. Its value as an anaesthetic and sedative was recognised by *Hippocrates* (ca. 400 B.C.) who wrote, "*A small dose in wine, less than would occasion delerium, will relieve the deepest depression and anxiety*."

A 5th century manuscript titled *De Viribus Herbarium* also contains references to mandrake, "*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*."

Murder

As the mandrake root became more highly prized in medieval Europe, so the herbalists invented fanciful legends to deter other people from obtaining the plant.

Typical of these was the one that warned of the terrible shriek that issued from the mandrake as it was pulled from the ground. This sound was so awful that the collector, upon hearing it, would die. To avoid this fate, a dog was used (with a rope tied around its neck and attached to the plant) to uproot the mandrake while the collector blocked his ears with wax.

Romeo and Juliet (1884)
Frank Dicksee

Murder

William Shakespeare makes reference to mandrake in his plays.

In *Romeo and Juliet*, Juliet feared the, "*Shrieks like mandrakes, torn out of the Earth. That living mortals, hearing them, run mad*." (IV, iii).

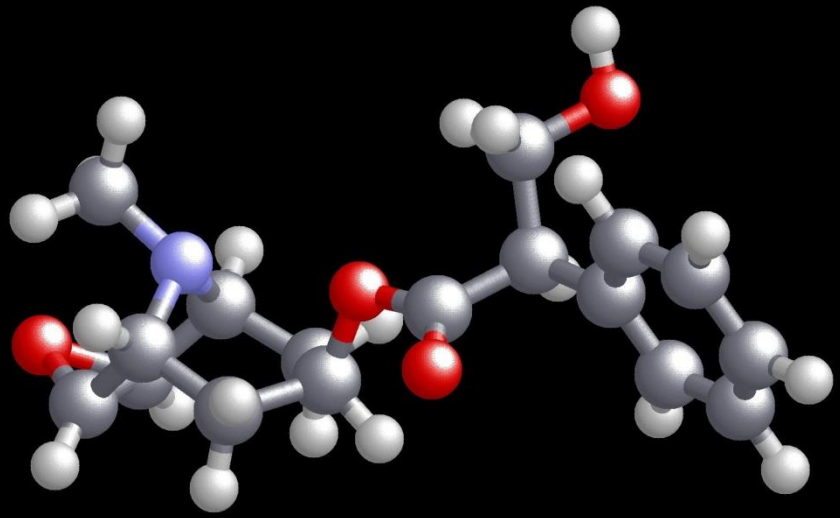
From *Henry IV (Part II)*, the Duke of Suffolk yearns to revenge the murder of the Duke of Gloucester, "*Would curses kill, as doth the mandrake's groan*." (III, ii).

And finally from *Macbeth*, "*Or have we eaten on the insane root that takes the reason prisoner?*" (I, iii).

J. K. Rowling also makes reference to mandrake in *Harry Potter and the Chamber of Secrets*.
https://youtu.be/HTRsduxSouY

Murder

Both the toxic and anaesthetic properties of mandrake result from the compound *scopolamine*. This drug exerts its biological effect by selectively blocking the biochemistry of the neurotransmitter *acetylcholine*.



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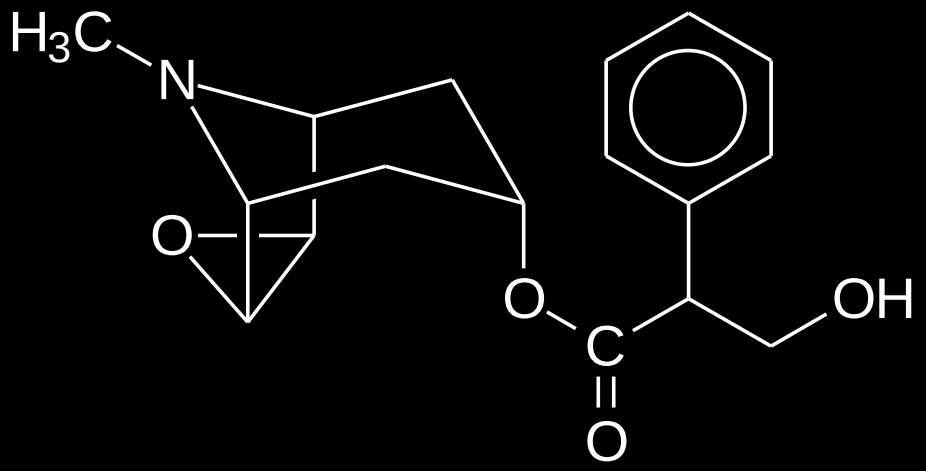

Magic

The Magic Circle (1886)
John William Waterhouse

Magic

Double, double toil and trouble;
Fire burn and cauldron bubble.
Fillet of a fenny snake,
In the cauldron boil and bake;
Eye of newt and toe of frog,
Wool of bat and tongue of dog,
Adder's fork and blind worm's sting,
Lizard's leg and howlet's wing,
For a charm of powerful trouble,
Like a hell-broth boil and bubble.

Macbeth, Scene IV, Act i.

Magic

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Magic

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Scale of dragon, tooth of wolf,
Witches' mummy, maw and gulf
Of the ravin'd salt-sea shark,
Root of hemlock digg'd i' the dark,
Liver of blaspheming Jew,
Gall of goat and slips of yew
Silvered in the moon's eclipse,
Nose of Turk and Tartar's lips…

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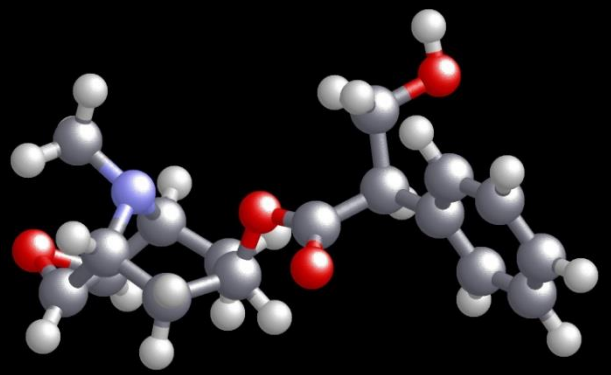
Magic

In addition to being found in mandrake, scopolamine is also a major component of *henbane*, *Hyoscyamus Niger*.

This plant, like mandrake, also has a long association with witchcraft, magic and necromancy.



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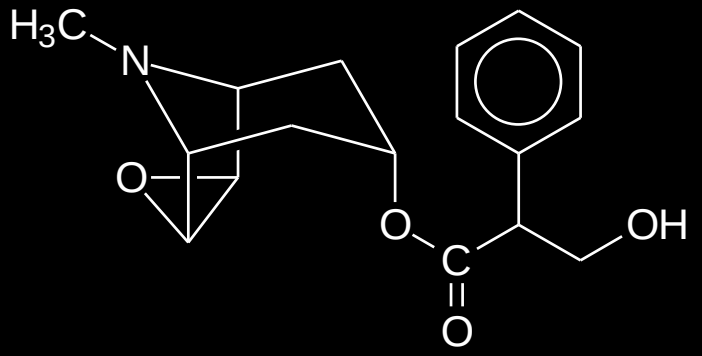


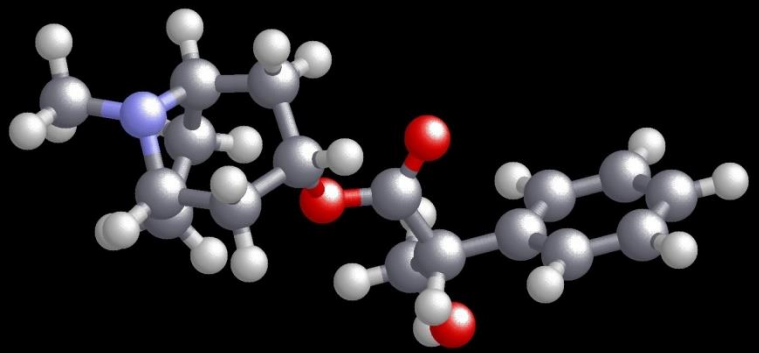
Witches Sabbath (1789) Goya

Magic

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.

Magic

The scopolamine from mandrake has a similar structure, but a more potent activity, compared to *atropine* which is extracted from the plant *Atropa belladonna*.



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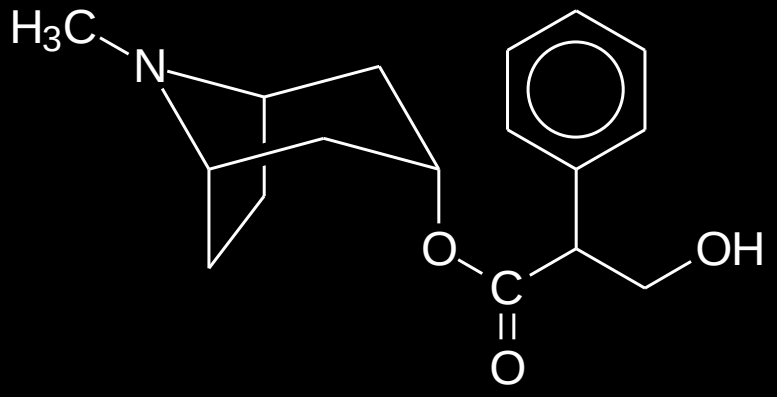
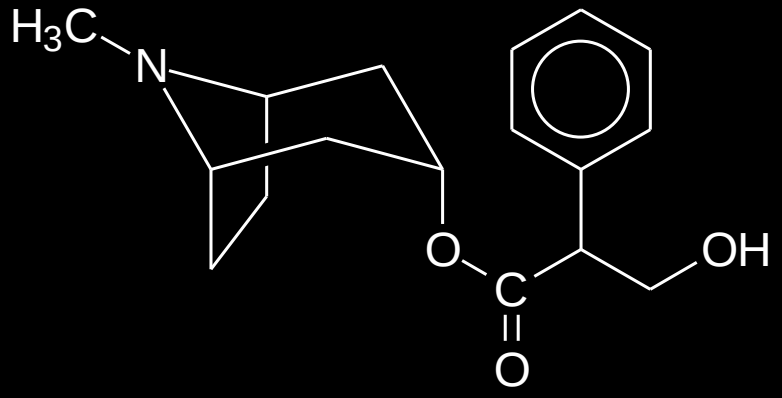


Magic

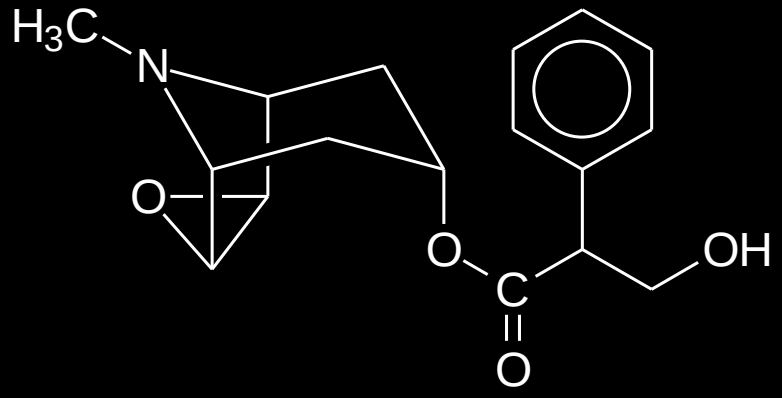
Extracts of Atropa belladonna were the major ingredient in witches salves. These salves were applied under the arms and to other parts of the body where the skin is quite thin and delicate.

Under the influence of the atropine, the witches would hallucinate that they were flying around on the broomsticks which they had originally used to apply the salve!

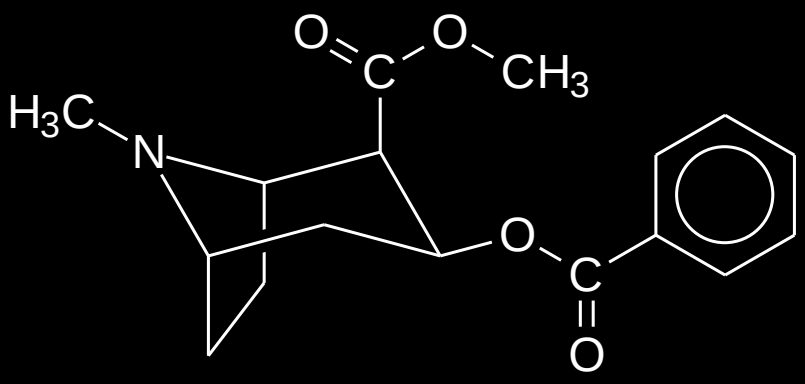
Magic



Scopolamine

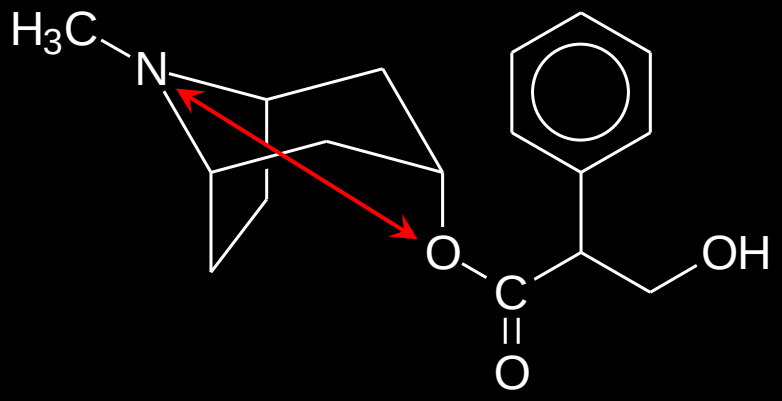


Atropine

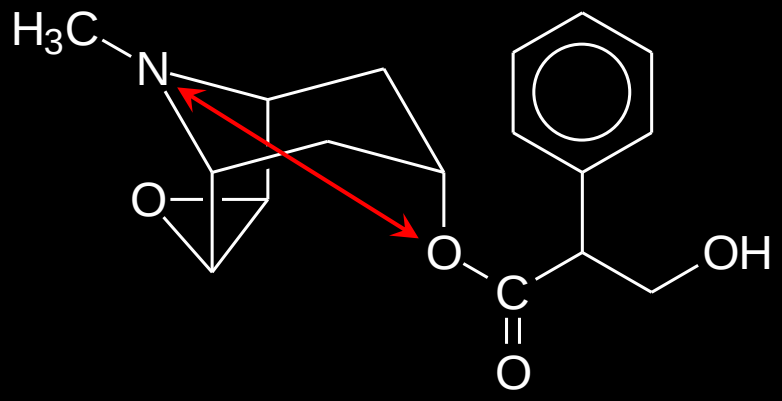


Cocaine

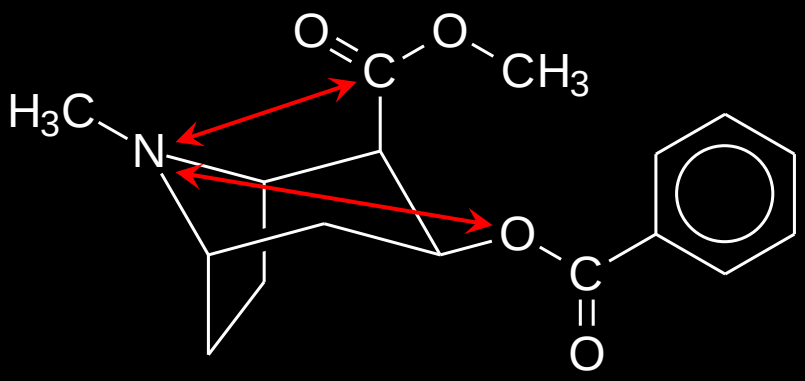
Magic



Scopolamine



Atropine



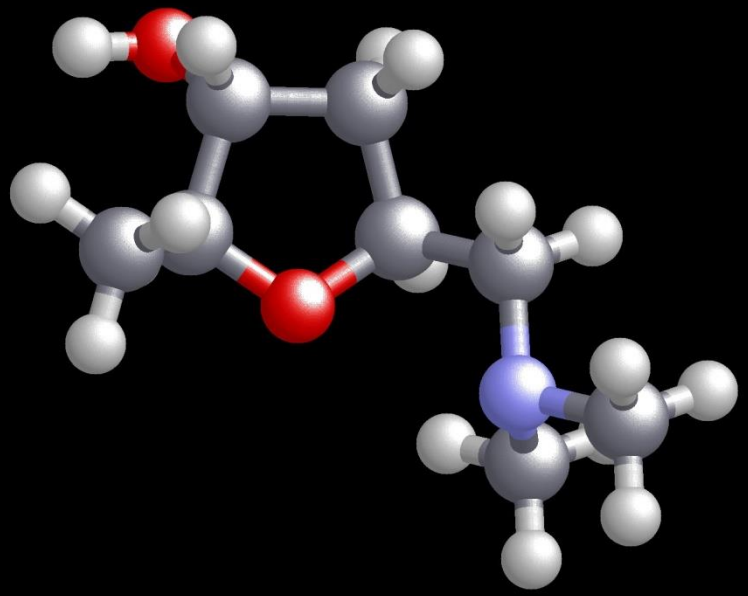
Cocaine

Magic

“Come, my head’s free at last!” said Alice in a tone of delight, which changed into alarm in another moment, when she found that her shoulders were nowhere to be found: all that she could see, when she looked down, was an immense length of neck, which seemed to rise like a stalk out of a sea of green leaves that lay far below her.

Magic

The hallucinogenic effects of the *fly agaric mushroom*, *Amanita muscaria*, have been attributed to the chemistry of several different compounds. One of these chemicals is *muscarine* which can mimic the effects of the neurotransmitter *acetylcholine* at nerve endings.



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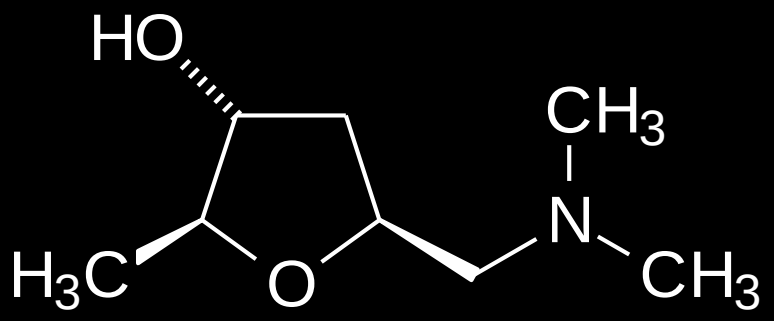
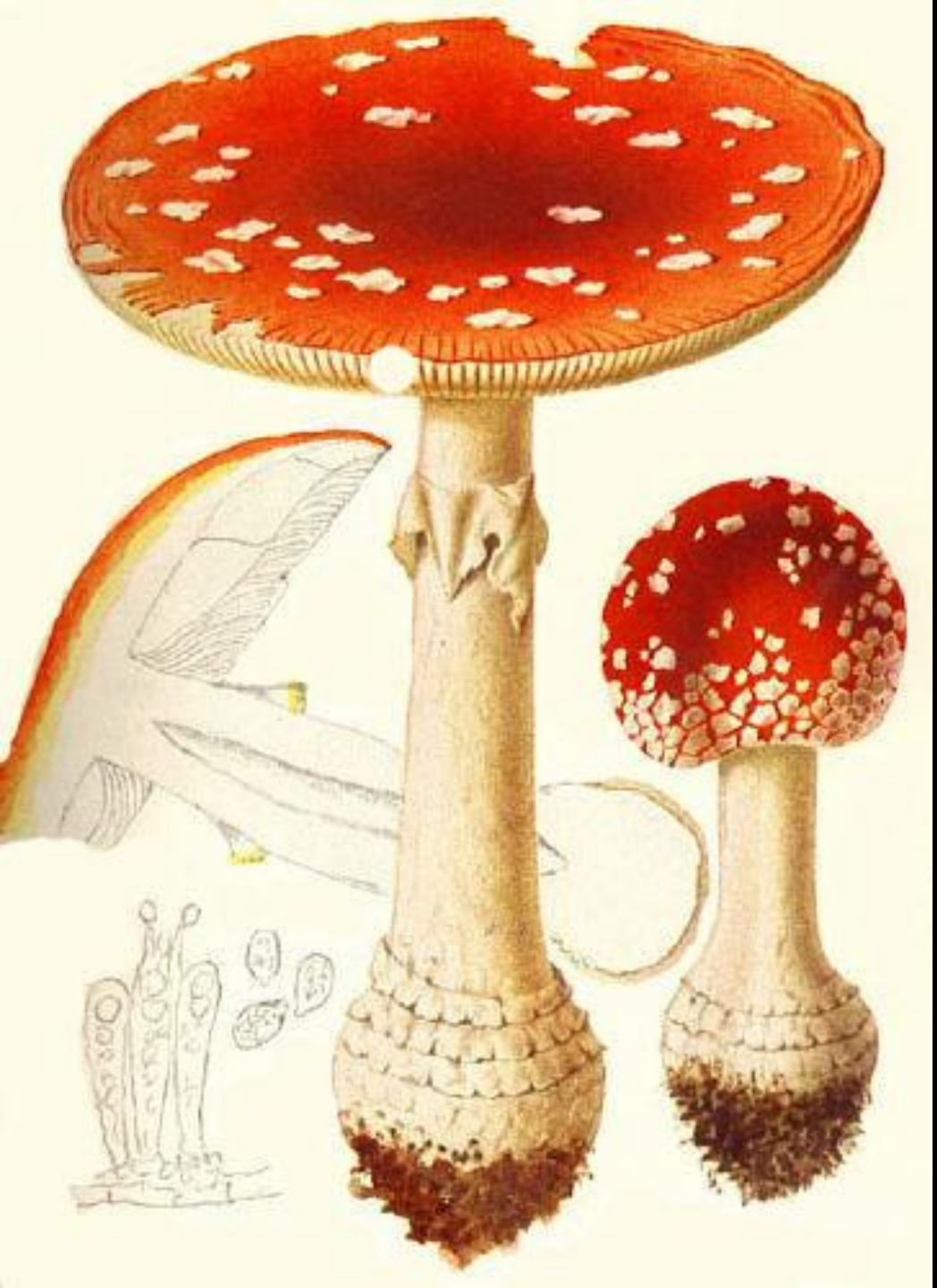
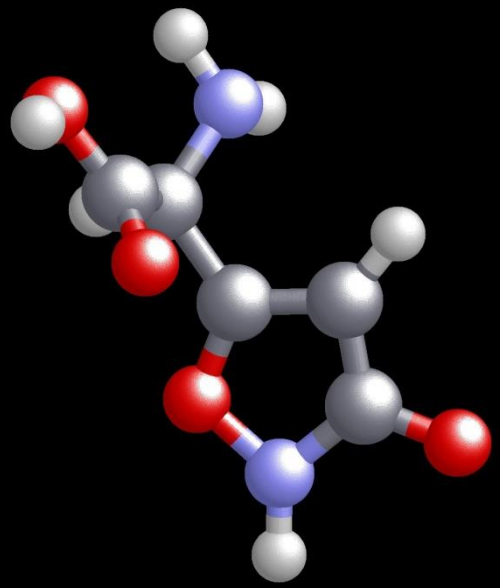
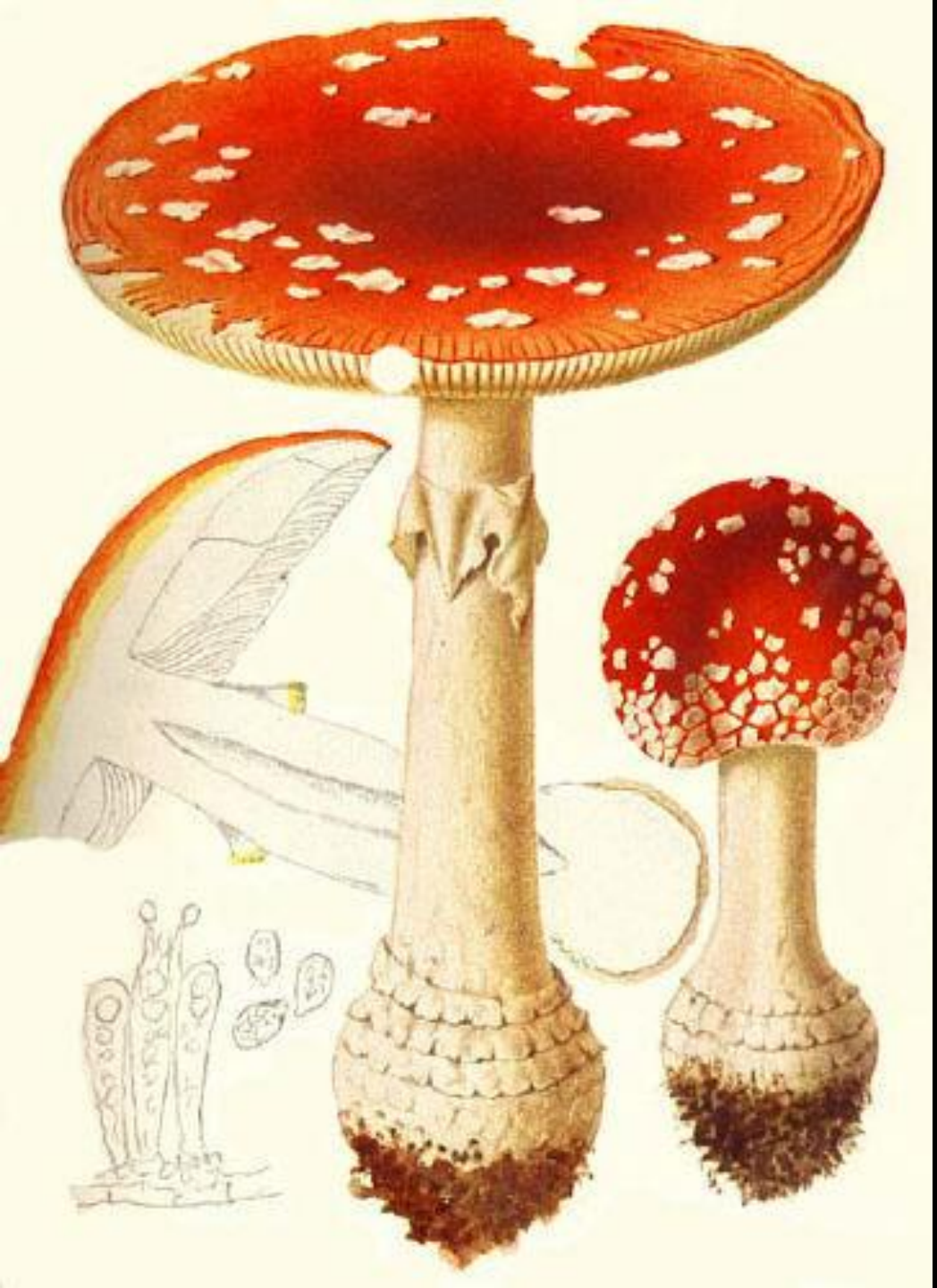




Magic

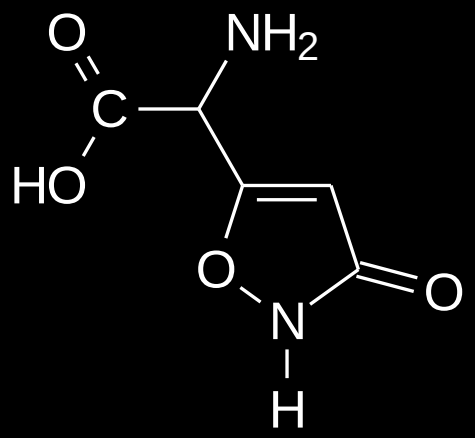
Ibotenic acid is another hallucinogenic component of the fly agaric mushroom. It exerts its pharmacological effect by interfering with the normal functioning of the brain neurotransmitter *γ-aminobutanoic acid*.





Magic

γ-aminobutanoic acid is an inhibitory neurotransmitter, which is active at up to 40% of the brain's synapses. It functions by opening channels in the neuronal membrane specific to chloride ions. This makes the inside of the neuron more negative, so more sodium ions must enter before depolarisation can occur.

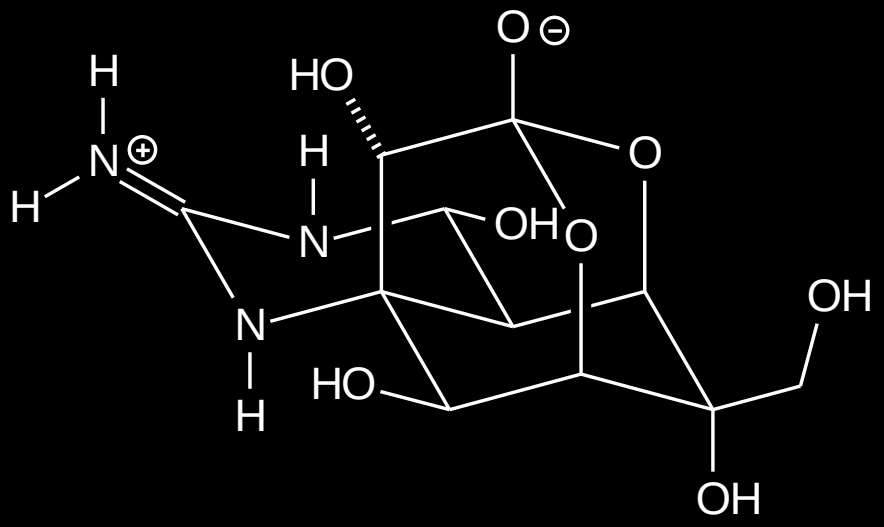


Magic

Georg Steller, who spent several years with the *Koryak tribe* of north-eastern Siberia wrote this account of them in 1774:

"The fly agarics are dried, then eaten in large pieces without chewing them, washing them down with cold water. After about half-an-hour the person becomes completely intoxicated and experiences extraordinary visions. Those who cannot afford the fairly high price of the mushrooms drink the urine of those who have eaten it, whereupon they become as intoxicated, if not more so. The urine seems to be more powerful than the mushroom, and its effect may last through to the fourth or fifth man."

Magic



Tetrodotoxin

Magic

Tetrodotoxin is extracted from the liver and ovaries of the *puffer fish*, and other members of the family *Tetraodontoidea* and is used in various parts of the world to create the illusion of *zombies*.

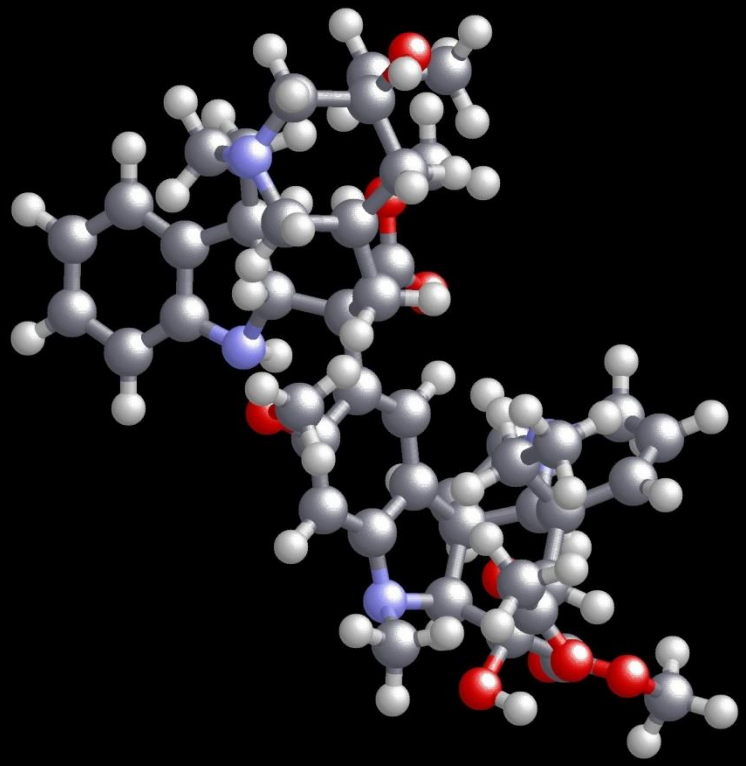
Tetrodotoxin halts nerve transmission by deactivating the uptake of sodium ions via the sodium channels in neuronal membranes. Given to a person in very small quantities, tetrodotoxin can create the illusion of death because it slows the victims breathing and heart rate.

Medicine

Windflowers (1903)
John William Waterhouse

Medicine

The anti-cancer drugs *vinblastine* and *vincristine* are extracted from the *Madagascan Periwinkle*, *Catharanthus roseus*.



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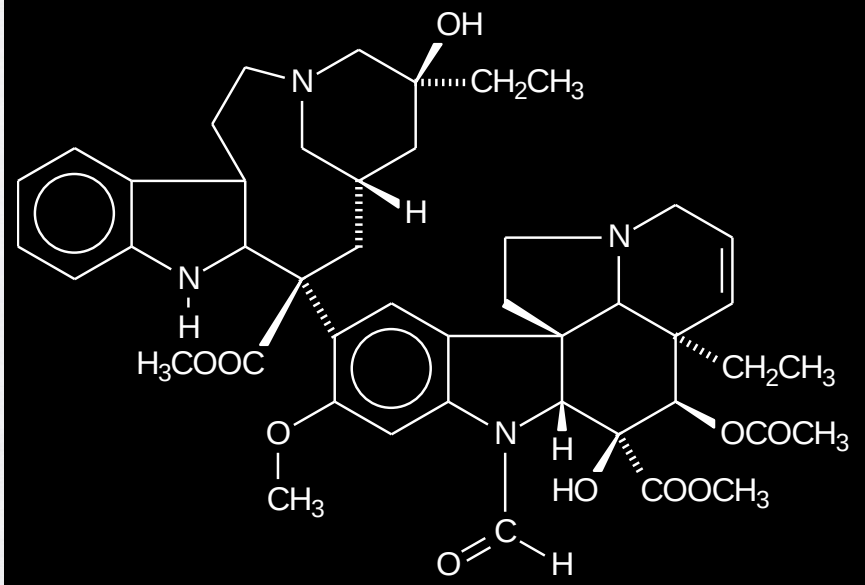
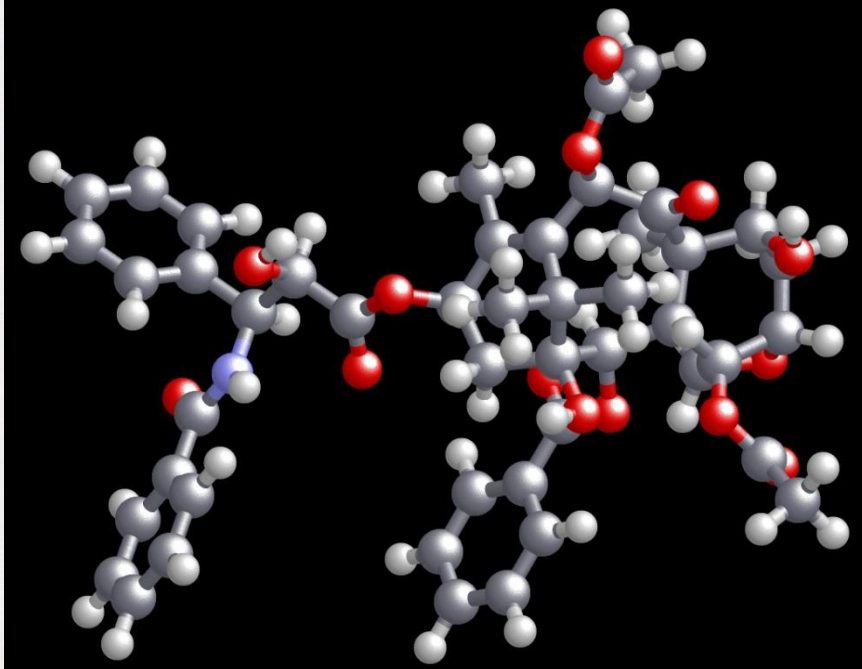


Medicine

The anti-cancer drug *taxol* is extracted from the *yew tree*, *Taxus brevifolia*.



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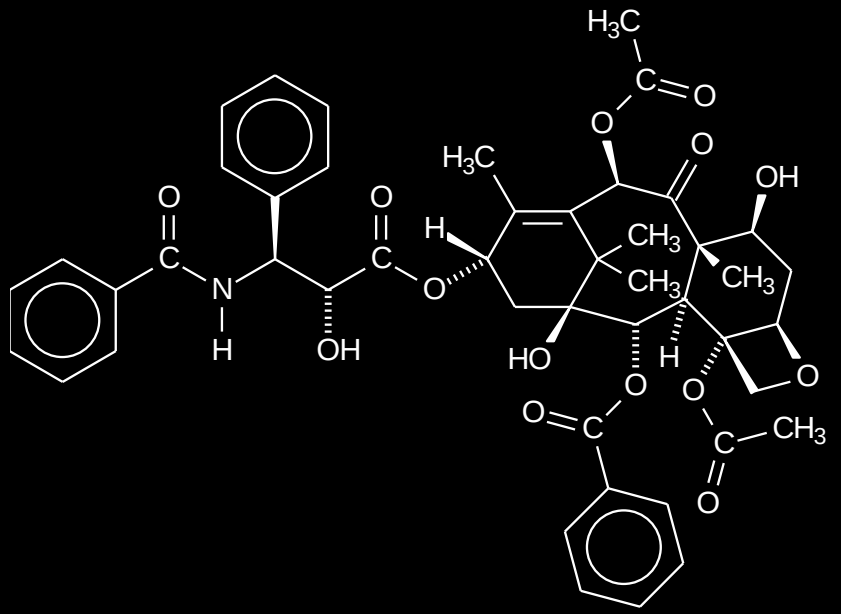
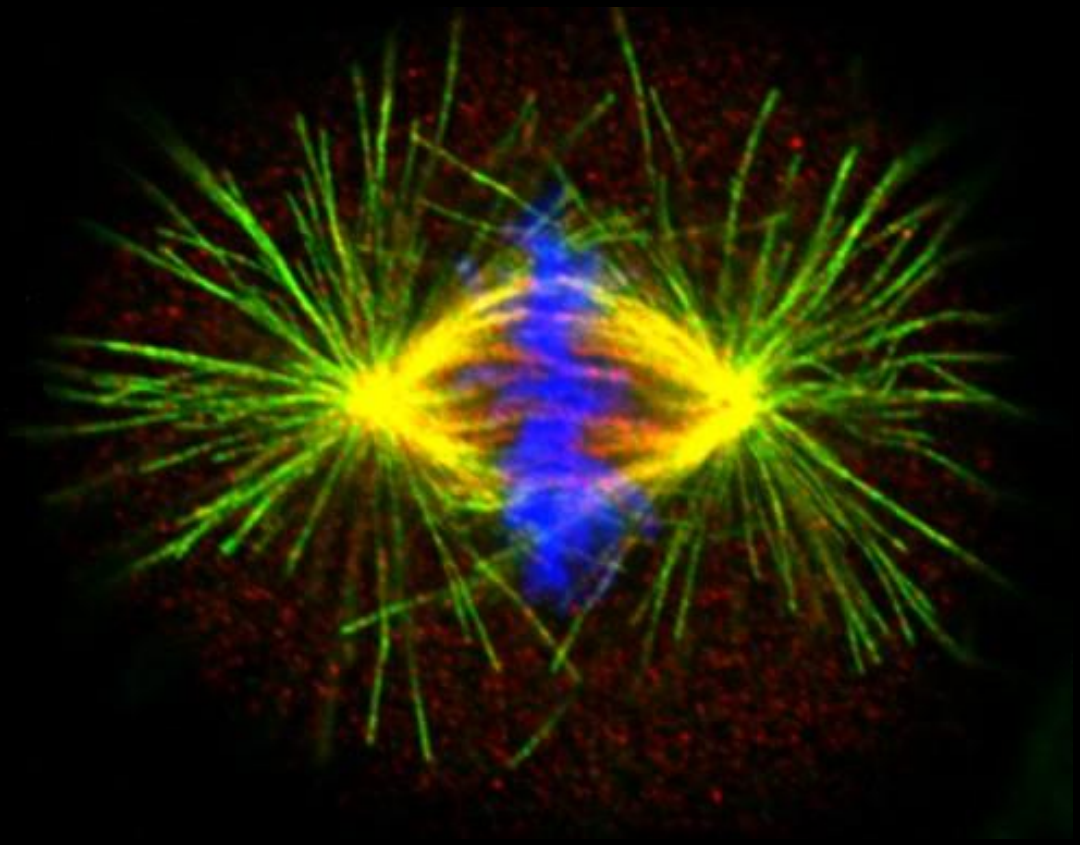


Medicine

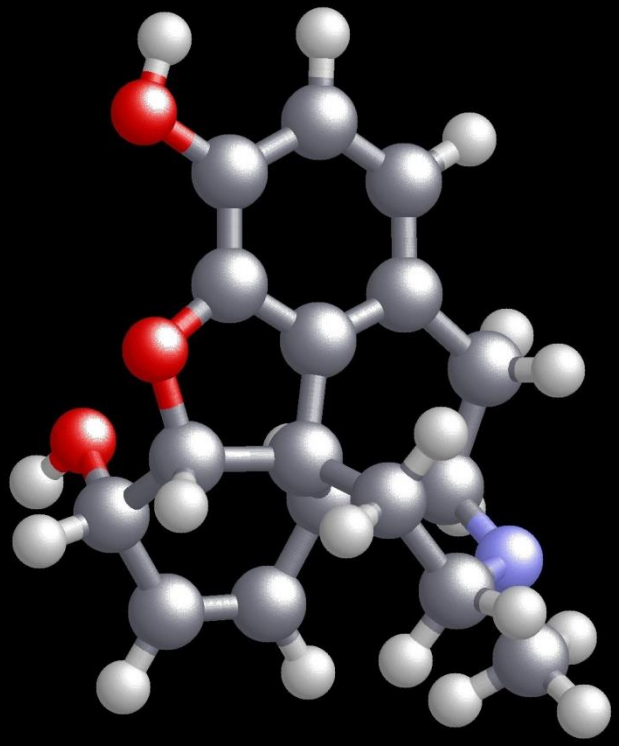


Fluorescence microscopy photograph of a cell undergoing mitosis:
DNA = Blue.
Tubulin (various) = yellow and green and red.

During mitosis, vinblastine, vincristine and taxol bind to *tubulin* and consequently interfere with its polymerisation / depolymerisation. This in turn interferes with the formation of structures called *spindles* which serve to push apart the two new cells and act as a framework on which the chromosomes of the original cell are transferred to the nuclei of the daughter cell.

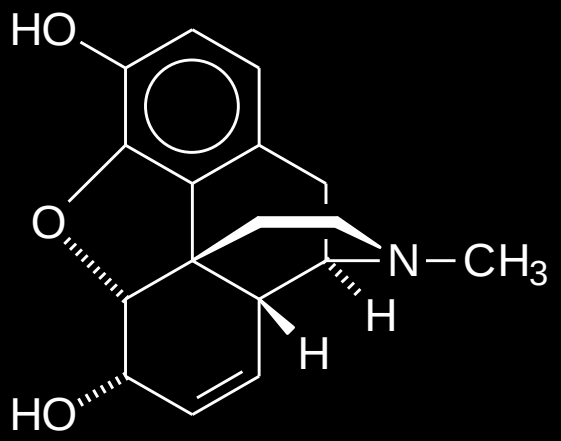
Medicine

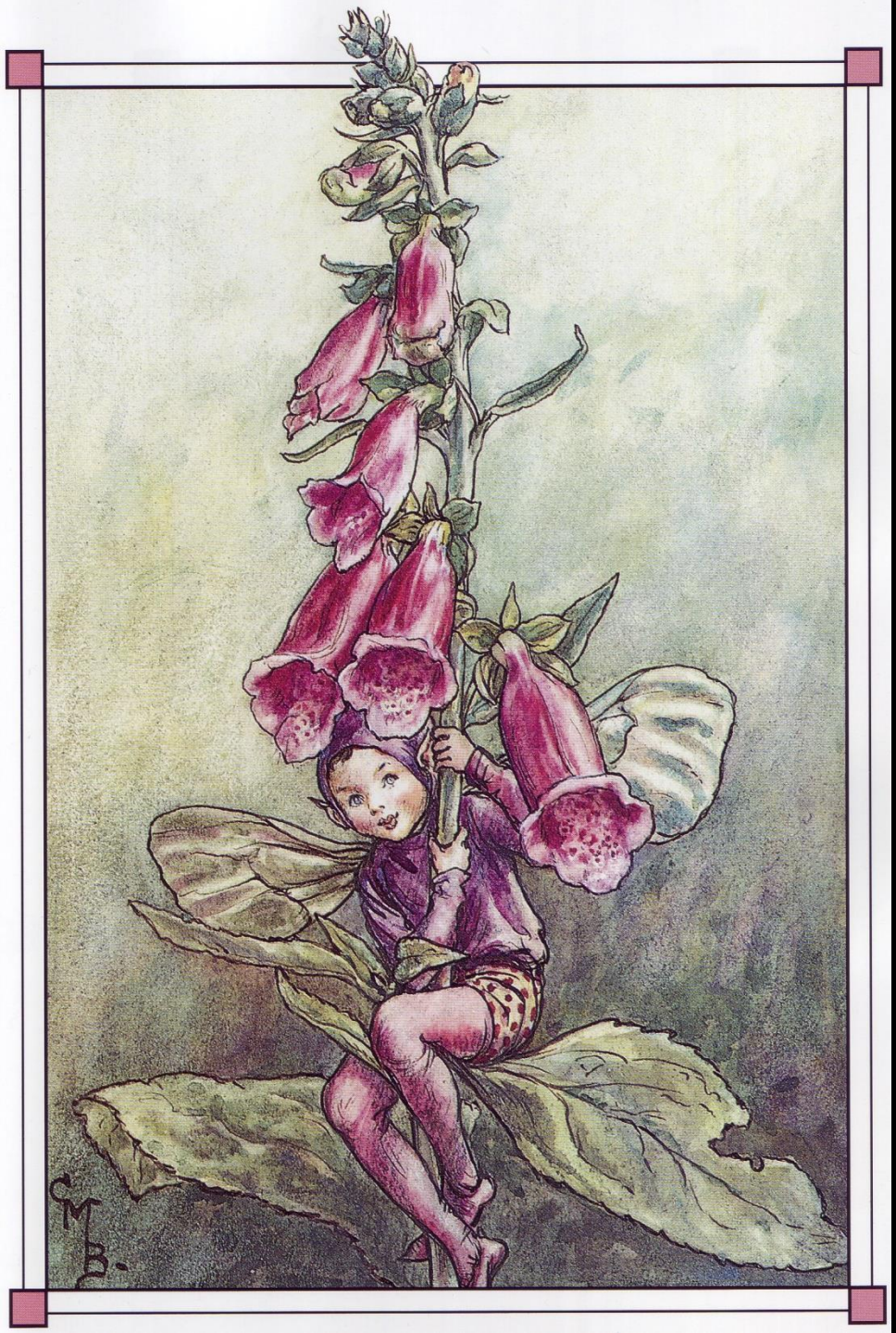
The analgesic drug *morphine* is extracted from the *opium poppy*, *Papaver somniferum*.



Medicine

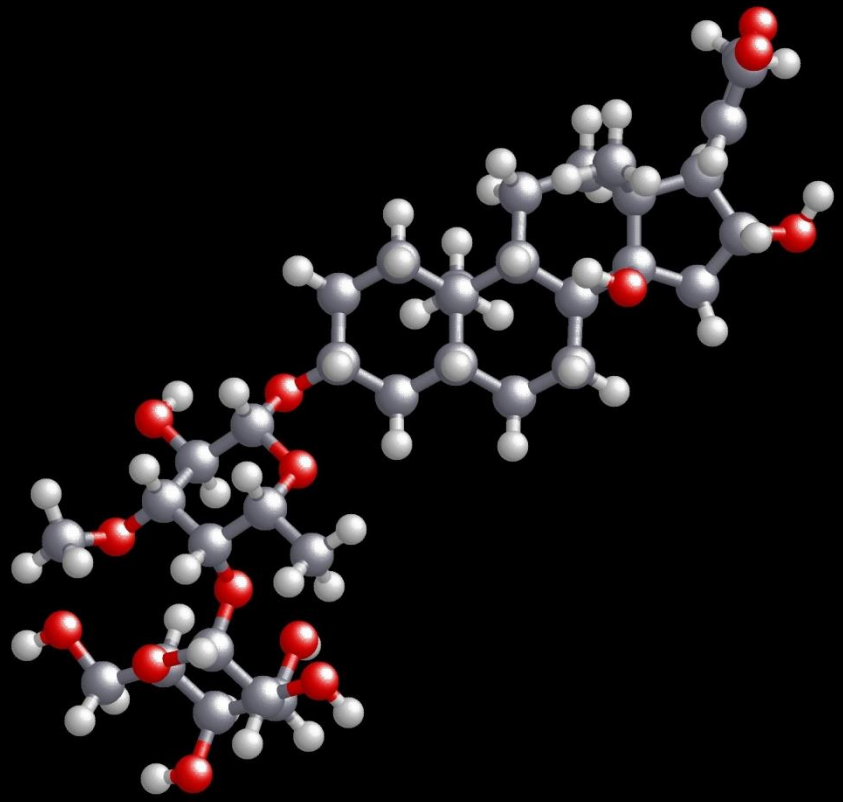
Morphine is named after the ancient god of sleep – *Morpheus*. Pure morphine was isolated in 1803, but it was not until 1833 that chemists were able to isolate it and purify it on a commercial scale. However, since morphine is poorly absorbed orally, it was of little use in medicine until the hypodermic syringe was invented in 1853, allowing doctors to inject morphine directly into the blood.

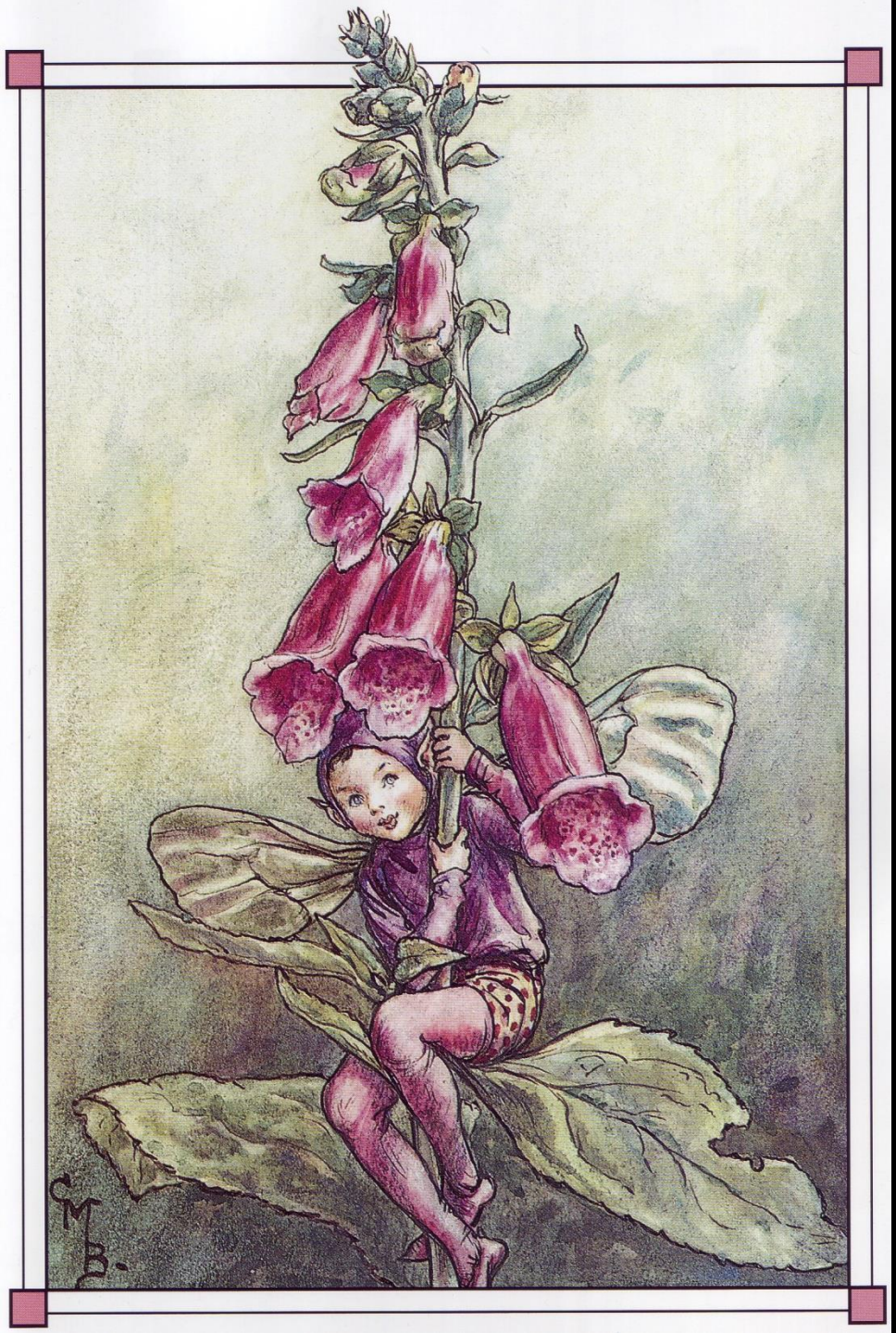




Medicine

The cardiac glycoside digitalin is extracted from the *foxglove*, Digitalis purpurea.





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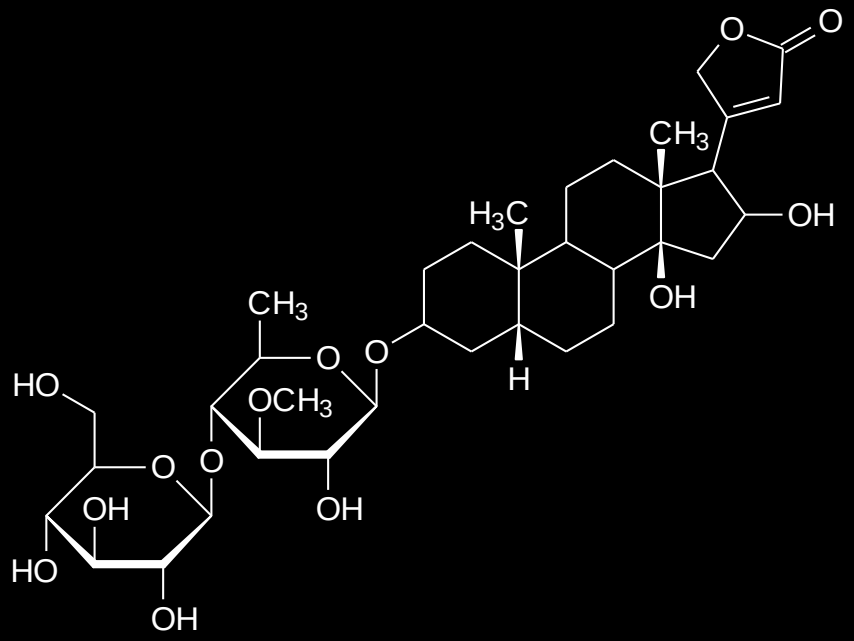
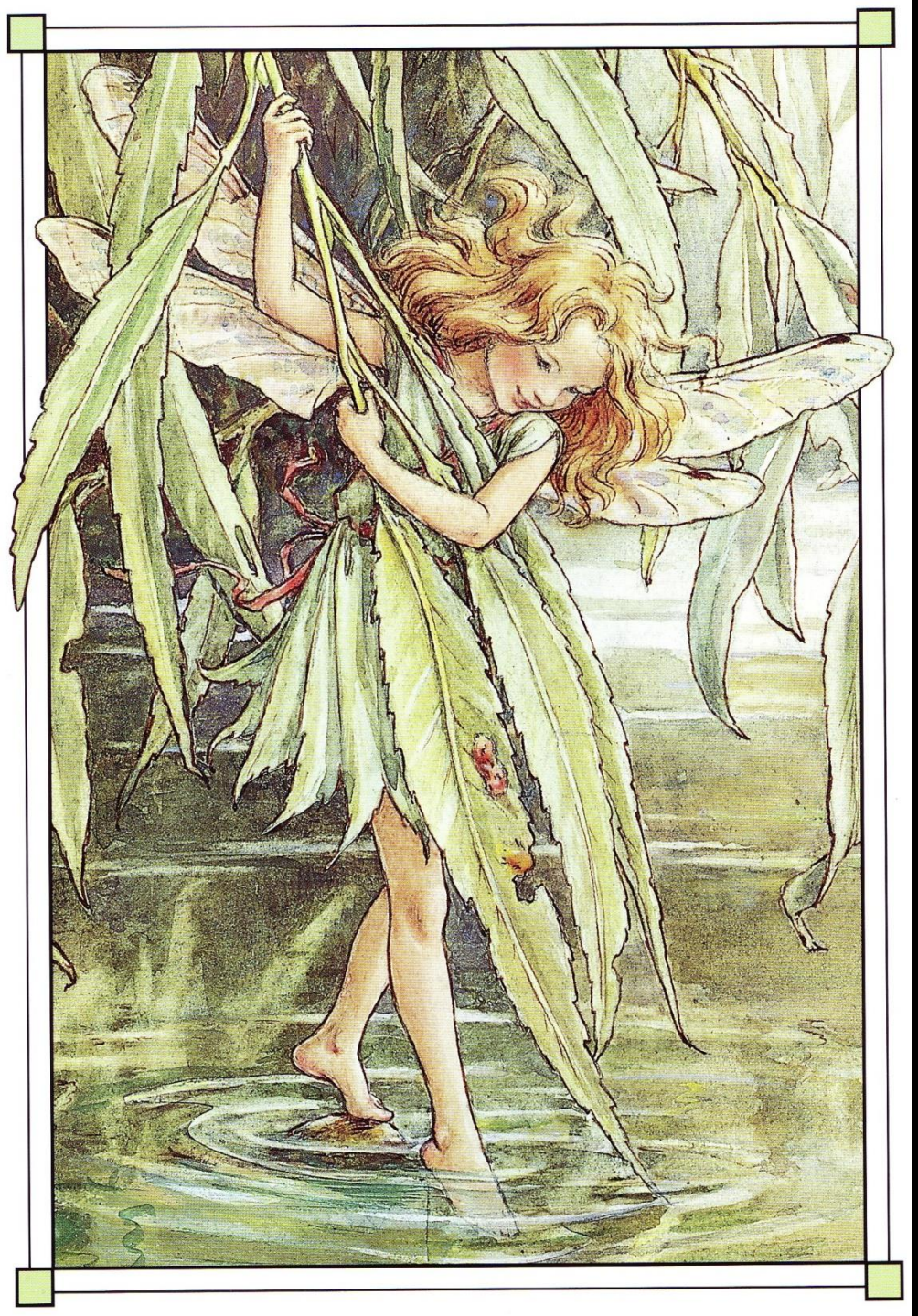
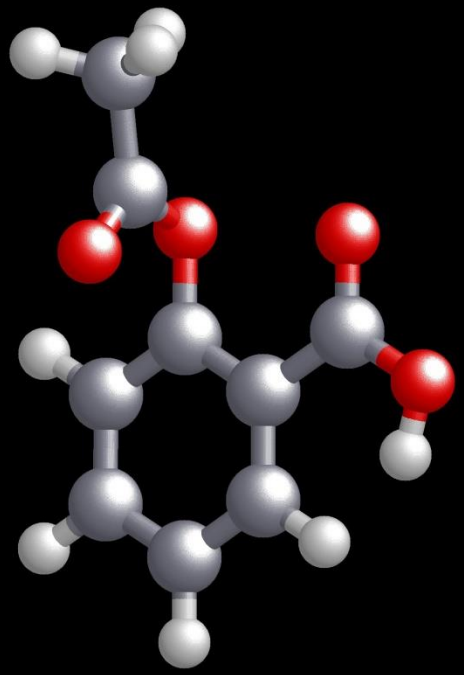
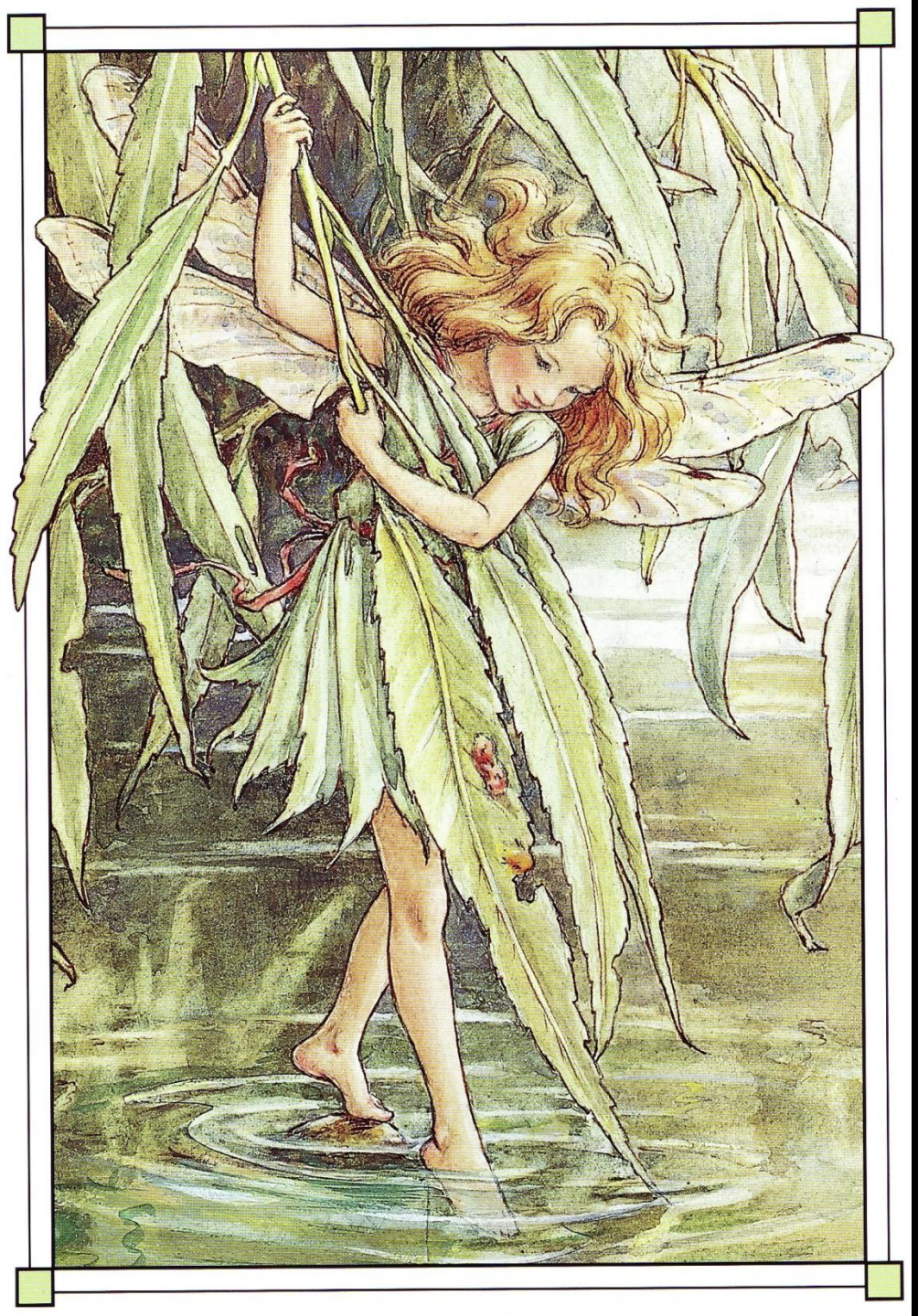




Medicine

The analgesic and anti-inflammatory properties of aspirin were first realised when similar chemicals in *willow tree*, *Salix alba*, bark were found to alleviate the symptoms of rheumatoid arthritis.





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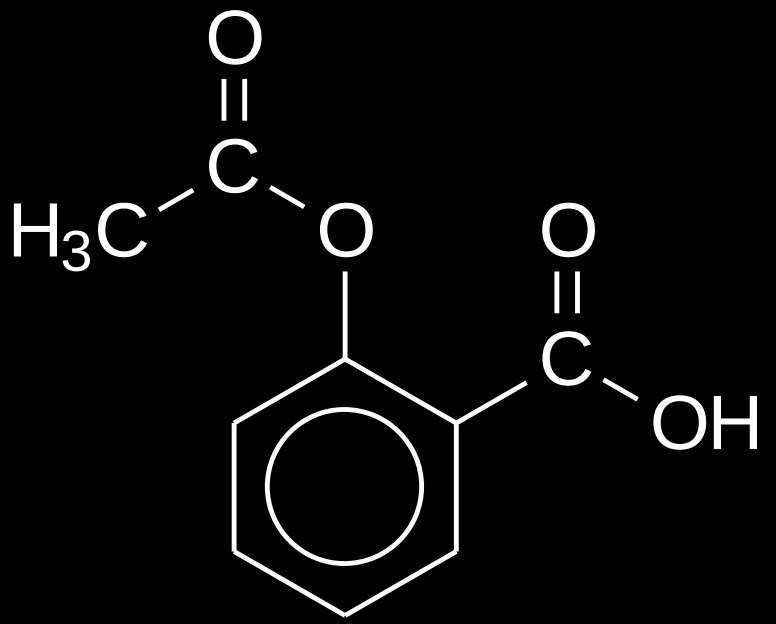

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