The Physician’s Garden

Instructor: Dr. Alan Jones
Transfer Student Seminar Course taught in the fall semester as needed
Course is limit 20 students, must be a first year transfer student
Meets Tuesdays 2-3:15 and Thursdays 2-4:45 for 4 instructor-student contact hr/wk
Credits 3 hours

Week 1
Tuesday, Aug 18th Introduction (overview, expectations, assignments)
Thursday, Aug 20th UNC Botanical Garden

Week 2
Tuesday, Aug 25th How the Pacific Yew, the Periwinkle, and the Autumn Crocus Cured Cancer (Taxus brevifolia, Colchicum autumnale, Catharanthus roseus, colchicine, tubulin and microtubules)
Thursday, Aug 27th UNC Herbarium, Plant Systematics. Learn to use a key to identify plants.

Week 3
Tuesday, Sept 1st The Weed that Killed Lincoln’s Mother (Eupatorium rugosum, white snakeroot, The Milk Sickness, tremetol, citric acid cycle)
Thursday, Sept 3rd Interview UNC research faculty

Week 4
Tuesday, Sept 8th Holy Hot Pepper! (Capsicum, the deadly nightshade family, Capsaicin, vanilloid receptor subtype 1, ion transport)
Thursday, Sept 10th Visit Medicago, Inc.
Closed shoes, lab coats, and eye protection required

Week 5
Tuesday, Sept 15th EXAM 1
Thursday, Sept 17th  work on the UNC Medicinal Garden, Part I: planning

Week 6

Tuesday, Sept 22nd  **The Death of Socrates** (*Conium maculatum, Strychnos toxifera*, hemlock alkaloids, curares, poison arrows, neuromuscular synapse, nicotinic acetylcholine receptor)

Thursday, Sept 24th  Purification of a plant metabolite

Week 7

Tuesday, Sept 29th  **Opiates and µ** (*Papaver somniferum*, poppy, opium, morphine, mu 2 receptors, G-protein coupled signaling)

Thursday, Oct 1st  work on the UNC Medicinal Garden, Part II: implementing

Week 8

Tuesday, Oct 6th  **The Death Angel** (*Amanita*, amanitin, mRNA, RNA polymerase II, transcription)

Thursday, Oct 8th  Guest Mycologist,  Culture fungi

Week 9

Tuesday, Oct 13th  **The Hound of Hades** (The dog named Cerberus, *Cerbera*, Suicide Tree, Kerala India, Oleander, spies with poisons, cardiac glycosides, the heart, Na+/K+ pump)

Thursday, Oct 15th  Fall Break 2015

Week 10

Tuesday, Oct 20th  **EXAM 2**

Thursday, Oct 22nd  UNC School of Pharmacy- Medicinal Chemistry Research

Closed shoes, lab coats, and eye protection required

Week 11

Tuesday, Oct 27th  **Homer’s Cyclops** (California corn lily, *Veratrum californicum*, the teratogen cyclopamine and the hedgehog signaling pathway)

Thursday, Oct 29th  A taste of undergraduate research at UNC Part I
Week 12
Tuesday, Nov 3rd  A Walk in the Woods of the Human Immune System
(Toxicodendron [poison ivy], urushiol oils, human immune system and the allergic reaction)

Thursday, Nov 5th  A taste of undergraduate research at UNC Part II

Week 13
Tuesday, Nov 10th  Discovery of the Salvia Receptor and Addiction in Teenagers
(Dr. Brian Roth, Dept of Pharmacology)

Thursday, Nov 12th Final work on the UNC Medicinal Gardens- Complete tasks

Week 14
Tuesday, Nov 17th  The Arts and Death by Poison  (a look at the history that plant poisons plays in the arts)

Thursday Nov 19th  Design a T shirt displaying compound, plant, and target molecule

Week 15
Tuesday Nov 24th  Review

Thursday Nov 26th Thanksgiving- no class

Week 16
Tuesday Dec 1st  EXAM 3
Assignments:

An article on a UNC researcher related to this course will be assigned. It will be publishable for Carolina Scientific, a UNC undergraduate managed magazine.

You are required to spend 1 ½ h service to the UNC herbarium (mounting specimens)

Reading:

Course pack assembled by the instructor plus Wicked Plants by Amy Stewart- to be purchased from student stores

Grading:

Grading: Exams 1 through 3 will account for 25% each of the final grade, the magazine article is 10%, and 15% for the remaining projects. The grading is not curved. Missing or late assignments will not be graded and given a score of zero.

Final letter grade assignments are based the following

A - Mastery of course content at the highest level of attainment that can reasonably be expected of students at a given stage of development. The A grade states clearly that the student has shown such outstanding promise in the aspect of the discipline under study that he/she may be strongly encouraged to continue.

B - Strong performance demonstrating a high level of attainment for a student at a given stage of development. The B grade states that the student has shown solid promise in the aspect of the discipline under study.

C - A totally acceptable performance demonstrating an adequate level of attainment for a student at a given stage of development. The C grade states that, while not yet showing any unusual promise, the student may continue to study in the discipline with reasonable hope of intellectual development.

D - A marginal performance in the required exercises demonstrating a minimal passing level of attainment for a student at a given stage of development. The D grade states that the student has given no evidence of prospective growth in the discipline; an accumulation of D grades should be taken to mean that the student would be well advised not to continue in the academic field.

F - For whatever reasons, an unacceptable performance. The F grade indicates that the student's performance in the required exercises has revealed almost no understanding of the course content. A grade of F should warrant an adviser's questioning whether the student may suitably register for further study in the discipline before remedial work is undertaken.
How the Pacific Yew, the Periwinkle, and the Autumn Crocus Cured Cancer

(*Taxus brevifolia*, *Colchicum autumnale*, Catharanthus roseus, colchicine, tubulin and microtubules)

The plants

*Taxus brevifolia* (Pacific yew or western yew) is a conifer native to the Pacific Northwest of North America. It ranges from southernmost Alaska south to central California, mostly in the Pacific Coast Ranges, but with isolated disjunct populations in southeast British Columbia and in north to central Idaho.

https://en.wikipedia.org/wiki/Taxus_brevifolia

http://www.worldbotanical.com/taxus_brevifolia_var_reptaneta.htm
Discovery of taxol

The chemotherapy drug paclitaxel (taxol), used in breast, ovarian, and lung cancer treatment, is derived from *Taxus brevifolia*. As it was already becoming scarce when its chemotherapeutic potential was realized, the Pacific yew was never commercially harvested from its habitat at a large scale; the widespread use of the paclitaxel (taxol) was enabled when a semi-synthetic pathway was developed from extracts of cultivated yews of other species.

*Colchicum autumnale*, commonly known as *autumn crocus*, *meadow saffron* or *naked lady*, is a flower that resembles the true crocuses, but blooms in autumn. The name "naked lady" comes from the fact that the flowers emerge from the ground long after the leaves have died back.

https://en.wikipedia.org/wiki/Colchicum_autumnale
**Colchicine**

The bulb-like corms of Colchicum autumnale contain colchicine, a useful drug. Colchicine is approved by the US FDA for the treatment of gout and familial Mediterranean fever. Colchicine is also used in plant breeding to produce polyploid strains. A synthetic chemical compound, called ICT2588, which is similar to one from the autumn crocus, is in the early stages of drug development for the treatment of some types of cancer. In experimental testing it was successfully used to treat breast, bowel, lung and prostate cancers. [https://en.wikipedia.org/wiki/Colchicum_autumnale](https://en.wikipedia.org/wiki/Colchicum_autumnale)

They are deadly poisonous due to their colchicine content. The symptoms of colchicine poisoning resemble those of arsenic, and no antidote is known.

![Colchicine molecule](http://flipper.diff.org/app/items/6183)

**Catharanthus rosea**

*Catharanthus roseus*, commonly known as the *Madagascar periwinkle* or *rosy periwinkle*, is a species of *Catharanthus* native and endemic to Madagascar. It was formerly classified in the *Vinca* genus as *Vinca rosea*.
**Vincristine** (marketed under the brandname **Oncovin**) is a chemotherapy medication used to treat a number of types of cancer.° It is given intravenously and works by inhibiting mitosis (stopping cells from dividing properly), causing the cells to die. The drug accomplishes this by binding to the tubulin protein, stopping the cell from separating its chromosomes during the metaphase; the cell then undergoes apoptosis. Because cancer cells divide more rapidly than healthy cells, they are affected more by the drug.

Most people experience some side effects from vincristine treatment. Commonly it causes a change in sensation, hair loss, constipation, difficulty walking, and headaches. It will likely cause harm to an infant if given during pregnancy.

Vincristine is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system. It is a vinca alkaloid from the Madagascar periwinkle *Catharanthus roseus* (formerly named *Vinca rosea*).

https://en.wikipedia.org/wiki/Vincristine

**Site of action**

**Microtubules** are a component of the cytoskeleton, found throughout the cytoplasm. These tubular polymers of tubulin can grow as long as 50 micrometres and are highly dynamic. The outer diameter of a microtubule is about 24 nm while the inner diameter is about 12 nm. They are found in eukaryotic cells and are formed by the polymerization of a dimer of two globular proteins, alpha and beta tubulin.

Microtubules are very important in a number of cellular processes. They are involved in maintaining the structure of the cell and, together with microfilaments and intermediate filaments, they form the cytoskeleton. They also make up the internal structure of cilia and flagella. They provide platforms for intracellular transport and are involved in a variety of cellular
processes, including the movement of secretory vesicles, organelles, and intracellular macromolecular assemblies (see entries for dynein and kinesin). They are also involved in chromosome separation (mitosis and meiosis), and are the major constituents of mitotic spindles, which are used to pull apart eukaryotic chromosomes. [https://en.wikipedia.org/wiki/Microtubule](https://en.wikipedia.org/wiki/Microtubule)

**Spindle apparatus – mitosis**
The Weed that Killed Lincoln’s Mother

(Ageratina altissima (formerly known as Eupatorium rugosum), white snakeroot, The Milk Sickness, tremetol, citric acid cycle)

The plant

*Ageratina altissima*, also known as **white snakeroot, richweed, white sanicle, or tall boneset**, is a poisonous perennial herb in the family Asteraceae, native to eastern and central North America. An older binomial name for this species is *Eupatorium rugosum*, but the genus *Eupatorium* has undergone taxonomic revision by botanists and a number of the species once included there have been moved to other genera.

Plants are upright or sometimes ascending, growing to 1.5 meters tall, producing single or multi-stemmed clumps. They are found in woods and brush thickets where they bloom mid to late summer or fall. The flowers are a clean white color and after blooming, small seeds with fluffy white tails are released to blow in the wind. This species is adaptive to different growing conditions and can be found in open shady areas with open bare ground; it can be weedy in shady landscapes and in hedgerows.

[Tremetol](https://en.wikipedia.org/wiki/Ageratina_altissima)

White Snakeroot contains the toxin tremetol; when the plants are consumed by cattle, the meat and milk become contaminated with the toxin. When milk or meat containing the toxin is consumed, the poison is passed on to humans. If consumed in large enough quantities, it can cause tremetol poisoning in humans. The poisoning is also called milk sickness, as humans often ingested the toxin by drinking the milk of cows that had eaten snakeroot.
During the early 19th century, when large numbers of European Americans from the East, who were unfamiliar with snakeroot, began settling in the plant's habitat of the Midwest and Upper South, many thousands were killed by milk sickness. Notably, milk sickness was possibly the cause of death in 1818 of Nancy Hanks Lincoln, mother of Abraham Lincoln.

It was some decades before European Americans traced the cause to snakeroot, although today Dr. Anna Pierce Hobbs Bixby is credited with identifying the plant in the 1830s. Legend has it that she was taught about the plant's properties by a Shawnee woman. The Shawnee woman's name is lost to history, but she and her people would have had deep knowledge of the herbs and plants in the area.

The plants are also poisonous to horses, goats, and sheep. Signs of poisoning in these animals include depression and lethargy, placement of hind feet close together (horses, goats, cattle) or held far apart (sheep), nasal discharge, excessive salivation, arched body posture, and rapid or difficult breathing.

This plant does serve a medical purpose. Root tea has been used to treat ague, diarrhea, kidney stones, and fever. A root poultice can be used on snakebites.


**Tremetone** is a chemical compound found in tremetol, a toxin mixture from snakerooot (*Ageratina altissima*) that causes milk sickness in humans and trembles in livestock. Tremetone is the main constituent of at least 11 chemically related substances in tremetol. Tremetone is toxic to fish, but not to chicken, and is therefore not the major toxic compound in tremetol.

**Benzofuran** is the heterocyclic compound consisting of fused benzene and furan rings. This colourless liquid is a component of coal tar. Benzofuran is the "parent" of many related compounds with more complex structures.

**Milk Sickness**

**Milk sickness**, also known as tremetol vomiting or, in animals, as trembles, is a kind of poisoning, characterized by trembling, vomiting, and severe intestinal pain, that affects individuals who ingest milk, other dairy products, or meat from a cow that has fed on white snakeroot plant, which contains the poison tremetol.

[https://en.wikipedia.org/wiki/Milk_sickness](https://en.wikipedia.org/wiki/Milk_sickness)
**Figure 13-2 Essential Cell Biology, 2/e. (© 2004 Garland Science)**
Holy Hot Pepper!

(*Capsicum*, the deadly nightshade family, Capsaicin, vanilloid receptor subtype 1, ion transport)

The plant

*Capsicum* is a genus of flowering plants in the nightshade family Solanaceae. Its species are native to the Americas, where they have been cultivated for thousands of years. In modern times, it is cultivated worldwide, and has become a key element in many regional cuisines. In addition to use as spices and food vegetables, *Capsicum* species have also found use in medicines. [https://en.wikipedia.org/wiki/Capsicum](https://en.wikipedia.org/wiki/Capsicum)

Deadly Night Shade belongs in the same family

*Atropa belladonna*, commonly known as *belladonna* or *deadly nightshade*, is a perennial herbaceous plant in the family Solanaceae, native to Europe, North Africa, Western Asia, and some parts of Canada and the United States. The foliage and berries are extremely toxic, containing tropane alkaloids. These toxins include scopolamine and hyoscyamine, which cause a bizarre delirium and hallucinations,[1] and are also used as pharmaceutical anticholinergics. The drug atropine is derived from the plant. [https://en.wikipedia.org/wiki/Atropa_belladonna](https://en.wikipedia.org/wiki/Atropa_belladonna)
The compound

Capsaicin; chemical name 8-methyl-N-vanillyl-6-nonenamide) is an active component of chili peppers, which are plants belonging to the genus Capsicum. It is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. Capsaicin and several related compounds are called capsaicinoids and are produced as secondary metabolites by chili peppers, probably as deterrents against certain mammals and fungi.[2] Pure capsaicin is a volatile, hydrophobic, colorless, odorless, crystalline to waxy compound. https://en.wikipedia.org/wiki/Capsaicin

Mode of action

The transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the capsaicin receptor and the vanilloid receptor 1, is a protein that, in humans, is encoded by the TRPV1 gene. It was the first isolated member of the transient receptor potential vanilloid receptor proteins that in turn are a sub-family of the transient receptor potential protein group.[2][3] This protein is a member of the TRPV group of transient receptor potential family of ion channels. The function of TRPV1 is detection and regulation of body temperature. In addition, TRPV1 provides sensation of scalding heat and pain (nociception). https://en.wikipedia.org/wiki/TRPV1
The Death of Socrates

(Conium maculatum, Strychnos toxifera, hemlock alkaloids, curares, poison arrows, neuromuscular synapse, nicotinic acetylcholine receptor)

The Death of Socrates by Jacques-Louis David (1787)

The plant

Conium maculatum is known by several common names. In addition to the English poison hemlock, the Australian Carrot Fern, and the Irish devil's bread are used. The plant should not be confused with the coniferous tree Tsuga, also known by the common name hemlock even though the two plants are quite different. Conium comes from the Greek konas (meaning to whirl), in reference to vertigo, one of the symptoms of ingesting the plant.

Poison hemlock is a plant that grows quite large...in fact, they often grow over 6 feet tall! One of the most distinguishing features of the plant is the purple spots that can be found on the hollow stem. The plant also has white flowers, which are found in small clusters. The plant is part of the parsley family, and as a result smells like parsnip when it is damaged.

https://en.wikipedia.org/wiki/Conium_maculatum

Geographic Locations

This plant can be found throughout the United States and Canada. It usually prefers to grow in moist, rich soils, so it will most often be found in woodlands and along fence rows.

Toxic Plant Components

The entire young plant, including roots and seeds are toxic. However, as the plant matures, the toxic component is stored in the seeds, leaving them the most toxic. The plants are toxic fresh or dried, so it can cause problems if baled into your hay.
Toxicity Cause and Symptoms

The onset of poisoning by this plant is extremely quick, with death often occurring in hours. Unfortunately, usually the most common sign of poisoning is finding the dead animal in the pasture.

Signs that appear shortly after consumption of the plant include:

- Burning in the mouth
- Salivation
- Loose stools
- Frequent urination and defecation
- Muscle tremors
- Muscle weakness
- Impaired vision and dialated pupils
- Disorientation
- Extreme nervousness
- Coma
- Death

The compound

Coniine has a chemical structure and pharmacological properties similar to nicotine and disrupts the workings of the central nervous system through action on nicotinic acetylcholine receptors. In high enough concentrations, coniine can be dangerous to humans and livestock. Due to high potency, the ingestion of seemingly small doses can easily result in respiratory collapse and death. Coniine causes death by blocking the neuromuscular junction in a manner similar to curare; this results in an ascending muscular paralysis with eventual paralysis of the respiratory muscles which results in death due to lack of oxygen to the heart and brain. Death can be prevented by artificial ventilation until the effects have worn off 48–72 hours later. For an adult, the ingestion of more than 100 mg (0.1 gram) of coniine (about six to eight fresh leaves, or a smaller dose of the seeds or root) may be fatal.
Mode of action

Acetylcholine

http://thebrain.mcgill.ca/flash/a/a_06/a_06_m/a_06_m_mou/a_06_m_mou_2a.jpg
Opiates and $\mu$

(*Papaver somniferum*, poppy, opium, morphine, mu 2 receptors, G-protein coupled signaling)

The plant

![Before the Morphine by Santiago Rusiñol](http://upload.wikimedia.org/wikipedia/commons/f/f7/Papaver_somniferum_(2).jpg)

*Papaver somniferum*, the opium poppy, is the species of plant from which opium and poppy seeds are derived. Opium is the source of many drugs, including morphine (and its derivative heroin), thebaine, codeine, papaverine, and noscapine. The Latin botanical name means the "sleep-bringing poppy", referring to the sedative properties of some of these opiates.

The opium poppy is the only species of Papaveraceae that is an agricultural crop grown on a large scale. Other species, *Papaver rhoeas* and *Papaver argemone*, are important agricultural weeds, and may be mistaken for the crop.

![Poppy flower with capsule](http://farm4.static.flickr.com/3134/4302781826_3e1a4f53df_o.jpg)

Poppy seeds of *Papaver somniferum* are an important food item and the source of poppyseed oil, a healthy edible oil that has many uses.

**The compound**

Morphine is the predominant alkaloid found in the varieties of opium poppy plant cultivated in most producing countries.

The seed pod of the opium poppy is the principal source of most naturally occurring $\mu$-opioid receptor agonist opioids.
Incisions are made on the green seed pods, the latex which oozes from the incisions is collected, and dried to produce "raw opium". Opium is about 8-14% morphine by dry weight, although specially bred cultivars reach 26%.

**Morphine** sold under many trade names, is a pain medication of the opiate type. It acts directly on the central nervous system to decrease the feeling of pain. It can be used for both acute pain and chronic pain.

Potentially serious side effects include a decreased respiratory effort and low blood pressure. Morphine has a high potential for addiction and abuse. If the dose is reduced after long term use withdrawal may occur. Common side effects include drowsiness, vomiting, and constipation. Morphine was first isolated between 1803 and 1805 by Friedrich Sertürner. This is generally believed to be the first isolation of an active ingredient from a plant. Merck began marketing it commercially in 1827. Sertürner originally named the substance *morphium* after the Greek god of dreams, Morpheus, for its tendency to cause sleep.

The primary source of morphine is isolation from poppy straw of the opium poppy. In 2013 an estimated 523,000 kilograms of morphine were produced. About 45,000 kilograms were used directly for pain, an increase over the last twenty years of four times. Most use for this purpose was in the developed world. About 70% of morphine is used to make other opioids such as hydromorphone, oxycodone, heroin, and methadone. It is a Schedule II drug in the United States. It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system. [https://en.wikipedia.org/wiki/Morphine](https://en.wikipedia.org/wiki/Morphine)
Mode of action

http://onlinelibrary.wiley.com/store/10.1111/jnc.12071/asset/image_m/jnc12071-toc-0001-m.png?v=1&s=0542385f57b14c3183a47d461be23ec2c79844349
The Death Angel

*(Amanita, amanitin, mRNA, RNA polymerase II, transcription)*

**The plant**

The genus *Amanita* contains about 600 species of agarics including some of the most toxic known mushrooms found worldwide, as well as some well-regarded edible species. This genus is responsible for approximately 95% of the fatalities resulting from mushroom poisoning, with the death cap accounting for about 50% on its own. The most potent toxin present in these mushrooms is α-amanitin.

https://en.wikipedia.org/wiki/Amanita

*Amanita phalloides* commonly known as the death cap, is a deadly poisonous basidiomycete fungus, one of many in the genus *Amanita*. Widely distributed across Europe, *A. phalloides* forms ectomycorrhizas with various broadleaved trees. In some cases, the death cap has been introduced to new regions with the cultivation of non-native species of oak, chestnut, and pine. The large fruiting bodies (mushrooms) appear in summer and autumn; the caps are generally greenish in color, with a white stipe and gills. https://en.wikipedia.org/wiki/Amanita_phalloides

**The compound**
**alpha-Amanitin** or **α-amanitin** is a cyclic peptide of eight amino acids. It is possibly the most deadly of all the amatoxins, toxins found in several species of the *Amanita* genus of mushrooms, one being the death cap (*Amanita phalloides*) as well as the destroying angel, a complex of similar species, principally *A. virosa* and *A. bisporigera*. The oral LD₅₀ of amanitin is approximately 0.1 mg/kg for rats.


**Mode of action**

α-Amanitin can also be used to determine which types of RNA polymerase are present. This is done by testing the sensitivity of the polymerase in the presence of α-amanitin. RNA polymerase I is insensitive, RNA polymerase II is highly sensitive (inhibited at 1μg/ml), RNA polymerase III is moderately sensitive (inhibited at 10μg/ml), and RNA polymerase IV is slightly sensitive (inhibited at 50μg/ml).

![RNA polymerase II](https://en.wikipedia.org/wiki/RNA_polymerase_II)

**RNA polymerase II (RNAP II and Pol II)** is an enzyme found in eukaryotic cells. It catalyzes the transcription of DNA to synthesize precursors of mRNA and most snRNA and microRNA. A 550 kDa complex of 12 subunits, RNAP II is the most studied type of RNA polymerase. A wide range of transcription factors are required for it to bind to upstream gene promoters and begin transcription.

The Hound of Hades

(The dog named Cerberus, Cerbera, Suicide Tree, Kerala India, Oleander, spies with poisons, cardiac glycosides, the heart, Na+/K+ pump)

The plant

*Cerbera odollam* is a dicotyledonous angiosperm, a plant species in the Family Apocynaceae and commonly known as the *suicide tree*, *pong-pong*, and *othalanga*. It is a species native to India and other parts of southern Asia, growing preferentially in coastal salt swamps and in marshy areas but also grown as a hedge plant between home compounds. It yields a potent poison that has been used for suicide and murder.

https://en.wikipedia.org/wiki/Cerbera_odollam

http://fa13ethnobotany.providence.wikispaces.net/file/view/Cerbera%20odollam.JPG/473536656/457x254/Cerbera%20odollam.JPG

The kernels of *C. odollam* contain cerberin, a digoxin-type cardenolide and cardiac glycoside toxin that blocks the calcium ion channels in heart muscle, causing disruption of the heart beat, most often fatally. The difficult in detecting cerberin in autopsies and its the ability of strong spices to mask its taste make it an agent of homicide and suicide in India: in 2004, a team led by scientist Yvan Gaillard documented more than 500 cases of fatal *Cerbera* poisoning between 1989 and 1999 in the southwest Indian state of Kerala alone.

Digitalin, aka digoxin, another cardiac glycoside

*(from Digitalis, foxglove)*
Thus by inhibiting the Na⁺/K⁺-ATPase, cardiac glycosides cause intracellular sodium concentration to increase. This leads to an accumulation of intracellular calcium via the Na⁺/Ca²⁺-exchange system with the following effects:

- In the heart, increased intracellular calcium causes more calcium to be released, thereby making more calcium available to bind to troponin-C, which increases contractility (inotropy).
- Inhibition of the Na⁺/K⁺-ATPase in vascular smooth muscle causes depolarization, which causes smooth muscle contraction.
**Homer’s Cyclops**

(California corn lily, *Veratrum californicum*, the teratogen cyclopamine and the hedgehog signaling pathway)

https://upload.wikimedia.org/wikipedia/commons/0/0e/Polyphemus.gif

The plant

http://research.vet.upenn.edu/Portals/76/Gallery/Album/141/1557lg.jpg

https://facultystaff.richmond.edu/~jhayden/recent_travels/recent_travels_chico-butte_co_CA/veratrum_californicum_BUTTE_CO_CA_04s.JPG

© W J Hayden
The compound

Cyclopamine (11-deoxojervine) is a naturally occurring chemical that belongs to the group of steroidal jerveratrum alkaloids. It is a teratogen isolated from the corn lily (*Veratrum californicum*) that causes usually fatal birth defects. It can prevent the fetal brain from dividing into two lobes (holoprosencephaly) and cause the development of a single eye (cyclopia). It does so by inhibiting the hedgehog signaling pathway (Hh). Cyclopamine is useful in studying the role of Hh in normal development, and as a potential treatment for certain cancers in which Hh is overexpressed.

Cyclopamine was named for one-eyed lambs which were born to sheep which grazed on wild corn lily at a farm in Idaho. In 1957 the US Department of Agriculture started an eleven-year investigation which led to the identification of cyclopamine as the cause of the birth defect.
Mode of action

Cyclopia is a rare form of holoprosencephaly and is a congenital disorder (birth defect) characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities. Its incidence is 1 in 16,000 in born animals and 1 in 250 in embryos.

Typically, the nose is either missing or replaced with a non-functioning nose in the form of a proboscis. Such a proboscis generally appears above the central eye, or on the back. Most such embryos are either naturally aborted or are stillborn upon delivery.

Although cyclopia is rare, several cyclopic human babies are preserved in medical museums (e.g. The Vrolik Museum, Amsterdam).[3]

Some extreme cases of cyclopia have been documented in farm animals (horses, sheep, pigs, and sometimes chickens). In such cases, the nose and mouth fail to form, or the nose grows from the roof of the mouth obstructing airflow, resulting in suffocation shortly after birth.

https://imanithom10.files.wordpress.com/2013/03/cyclops51.jpg
The (Sonic)Hedgehog pathway

A Walk in the Woods of the Human Immune System

(Toxicodendron [poison ivy], urushiol oils, human immune system and the allergic reaction)

The plant

Toxicodendron is a genus of flowering plants in the sumac family, Anacardiaceae. It contains woody trees, shrubs and vines, including poison ivy, poison oak, and the lacquer tree. All members of the genus produce the skin-irritating oil urushiol, which can cause a severe allergic reaction. The generic name is derived from the Greek words toxikos, meaning "poison," and dendron, meaning "tree". The best known members of the genus in North America are poison ivy (T. radicans), practically ubiquitous throughout most of eastern North America, and western poison oak (T. diversilobum), similarly ubiquitous throughout much of the western part of the continent. https://en.wikipedia.org/wiki/Toxicodendron

The compound

urushiol

\[
R = (\text{CH}_2)_{14}\text{CH}_3 \text{ or } \\
(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_5\text{CH}_3 \text{ or } \\
(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_5\text{CH}_3 \text{ or } \\
(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}=\text{CHCH}_3 \text{ or } \\
(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}_2 \text{ and others}
\]
Mode of action

Once absorbed by the skin it is recognized by the immune system's dendritic cells, otherwise called Langerhans cells. These cells then migrate to the lymph nodes, where they present the urushiol to T-lymphocytes and thus recruit them to the skin. Once in the skin, the T-lymphocytes cause pathology through the production of cytokines and cytotoxic damage to the skin.

Langerhans cells are dendritic cells (antigen-presenting immune cells) of the skin and mucosa.
fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell.

They act through receptors, and are especially important in the immune system; cytokines modulate the balance between humoral and cell-based immune responses, and they regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways. They are different from hormones, which are also important cell signaling molecules, in that hormones circulate in much lower concentrations and hormones tend to be made by specific kinds of cells.

They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction.

An antigen-presenting cell (APC) or accessory cell is a cell that displays foreign antigens complexed with major histocompatibility complexes (MHCs) on their surfaces; this process is known as antigen presentation. T-cells may recognize these complexes using their T-cell receptors (TCRs). These cells process antigens and present them to T-cells.

Mango skin is also full of urushiol oils