Report on

NUX VOMICA ALKALOIDS

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Contents

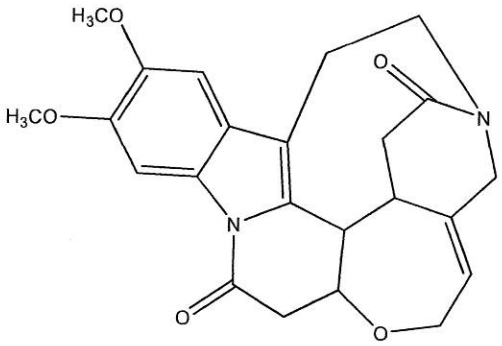
Natural product sources

They are natural plant alkaloids found in Strychnos nux-vomica, the strychnine tree, also known as nux vomica, poison fruit, semen strychnos, and quaker buttons, is a deciduous tree native to India and to southeast Asia. It is a medium-sized tree in the family Loganiaceae that grows in open habitats. The seed is used to make medicine [1].

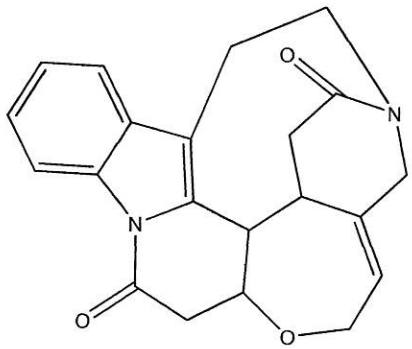
Nux vomica seed

Alkaloids of Nux vomica:

- strychnine and brucine as main constituents
- Minor alkaloids present in the seeds are protostrychnine, novacine, vomicine, n-oxystrychnine, pseudostrychnine, isostrychnine, chlorogenic acid, and a glycoside [2].
- two novel indole alkaloids, strynuxlines A (1) and B (2) [3].



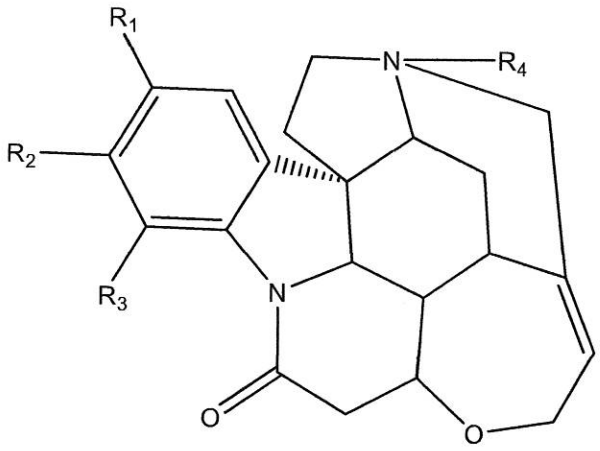
Strynuxline A



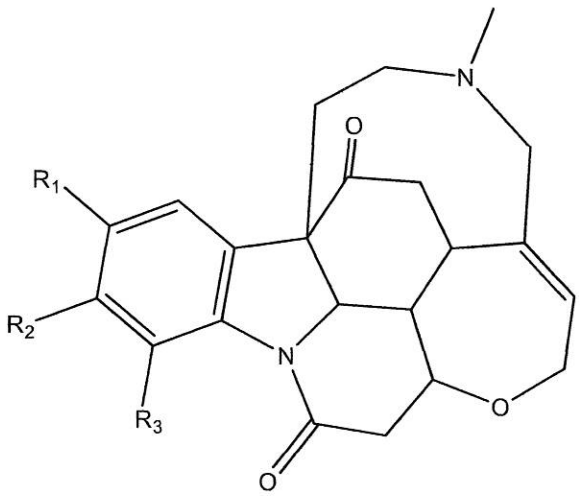
Strynuxline B

Chemistry [4]

Strychnine is a terpene indole alkaloid belonging to the Strychnos family of Corynanthe alkaloids, and it is derived from tryptamine and secologanin.



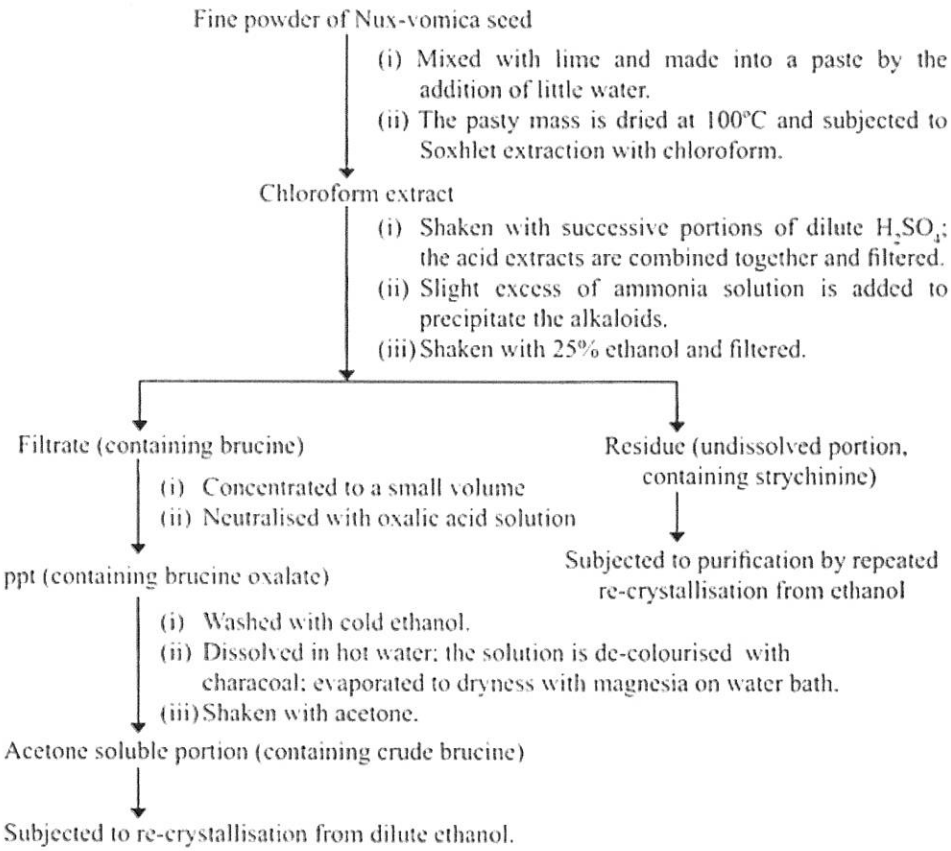
Alkaloid	R_1	R_2	R_3	R_4
Strychnine	H	H	H	H
Brucine	OCH_3	OCH_3	H	H



Alkaloid	R_1	R_2	R_3
Vomicine	H	H	OH
Novacine	OCH_3	OCH_3	H

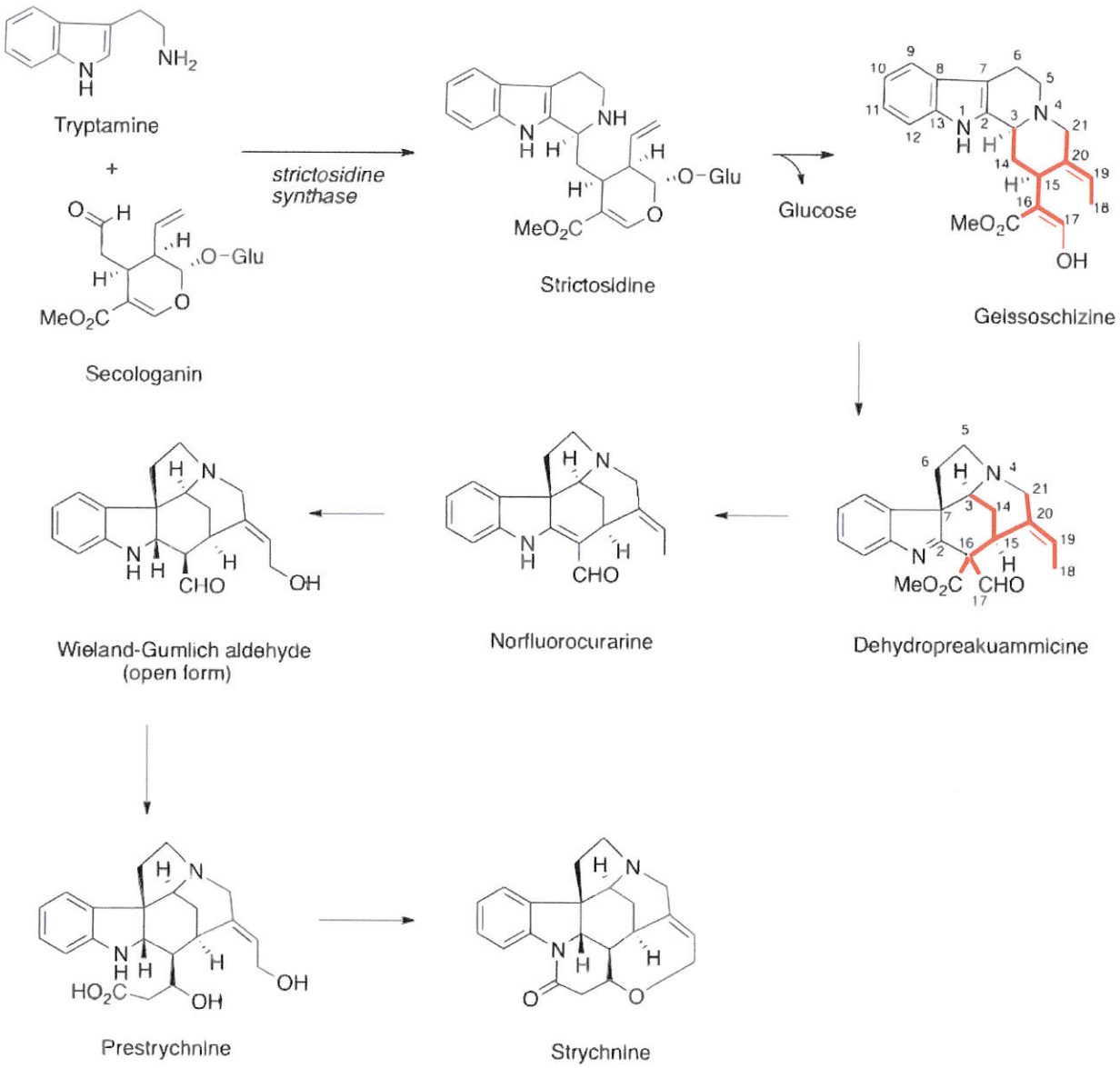
Isolation of nux vomica alkaloids

(Strychnine and Brucine)



1. powdered Nux vomica seeds are mixed with lime, water and dried, extracted with $CHCl_3$ in a soxhlet
2. $CHCl_3$ extract is shaken with successive portions of dil.H_2SO_4
3. Combined acid extracts are filtered, treated with excess ammonia thus precipitating alkaloids
4. Precipitate is treated with 25% ethanol to dissolve brucine
5. Alcohol extract is filtered, and the residue (strychnine) is purified by crystallization repeated from ethyl alcohol. Brucine is crystallized from filtrate as oxalate.

Biosynthesis [5]



Pharmacological effects and Mechanism of action [6]

- ***CNS stimulant***: Strychnine and brucine are the most important alkaloids of Nux vomica. Both are potent stimulants of the spinal cord. Thus, the most characteristic feature of Nux vomica is to render the reflex center in the central nervous system (CNS) more sensitive to afferent stimuli. In addition, strychnine and brucine increase the secretion of gastric juices and heighten sensory awareness.
- ***Analgesic and Anti-Inflammatory Actions***: The mechanism of action of Nux vomica could be related to the inhibition of the release of inflammatory mediators since levels of interleukin-1 (IL-1), prostaglandin E2 (PGE2), interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) were reduced.
- ***Antitumor Effects***: The antitumor mechanisms of Nux vomica include decrease in VEGF, induction of cell apoptosis, cytotoxic effects.
- ***Antimicrobial activity***: with respect to both Gram-positive organisms, such as Staphylococcus aureus, Bacillus subtilis and Streptococcus faecalis, and Gram-negative organisms, such as Escherichia coli, Pseudomonas aeruginosa and Proteus vulgaris.
- ***Effects on the Immune System***: possible application value of S. nux-vomica in allergic conditions and may be helpful in the treatment of many kinds of autoimmune diseases, such as rheumatoid arthritis and myasthenia gravis.
- ***Hepatoprotective activity***: As manifested by increased viability of hepatocytes and reversal of reduced bile.
- ***Potent antipyretic activity***

Uses [6]

Although there is no scientific evidence supporting their use on humans.

Nervous system:

- Nux vomica is used as a stimulant drug in the digestive tract.

Anti-inflammatory action:

- treatment of rheumatism bone pain, muscle and joint injury pains.

GIT disorders

- treatment of constipation, intestinal obstruction, colon and caecum impactions, chronic digestive ailments and it increased the activity of purgative medicines.

Antitumor effects

- Active components and extracts of Nux vomica have inhibitory effects on many types of tumors, both in vitro and in vivo, including liver cancer, breast cancer, colon cancer and multiple myeloma.

Effects on Alcohol Dependence

- Brucine (10, 20, or 30 mg/kg) suppressed voluntary ethanol intake and reduced ethanol preference.

Effects on the Immune System

- In allergic conditions and may be helpful in the treatment of many kinds of autoimmune diseases, such as rheumatoid arthritis and myasthenia gravis.

Rodenticide

- Commercial rodenticide preparations typically contain between 0.3 to 5.0 percent strychnine.

Structure Activity Relationship of Strychnine [7]

Strychnine Analogs with Anticonvulsive and muscle relaxant effects

2-aminostrychnine shows high affinity for the strychnine binding sites of synaptic membranes from brain and spinal cord comparable to that of strychnine. Strychnine derivatives containing the lactam group and the C21=C22 double bond can induce an anticonvulsive effect. Lacking such functional groups led to a remarkable decrease in activity. Strychnidine, lacking the amido group, as well as 21, 22-dihydrostrychnine induces less convulsion compared to that of strychnine and show lethal effects in animal experiments. These findings indicate that the lactam group is responsible for the characteristic strychnine effect. The analog 21,22-dihydrostrychnidine is about twice as active and four times as toxic as strychnidine itself. When hydroxyl groups are introduced at the 21 and 22-positions as in 21,22-dihydroxy-21-22-dihydrostrychnine and 21-hydroxy-22-oxo-21,22-dihydrostrychnine, a combined convulsant and muscle-relaxant effect appears. Introduction of an epoxy function in the 21 and 22-positions decreases the convulsant and toxic activity, but no muscle-relaxant effect appears. The decreased activity indicates that the 21,22-double bond is another important active site for the receptor. The 16-alkoxystrychnine produces both clonic and tonic convulsions. The convulsive activity and lethal effects decrease with increasing size of the alkyl substituent, whereas the unalkylated 16-hydroxy compound is the active in this series. Strychnine N-oxide analog shows a decreased convulsive effect; however, no muscle relaxant effect appears.

Quaternary strychnine and strychnidine derivatives exhibit curiform activity but the potency is low compared to that of the curarines. N-methyl strychnine, N-methyl strychnidine and N-methyl-21-22-dihydrostrychnine could produce muscle relaxant effect only. An explanation for this could be that the charged quaternary compounds

cannot cross the blood brain barrier and hence cannot reach the active site in the CNS.

Toxicology: Causes and Symptoms of Poisoning [6]

Large doses of Nux vomica cause convulsions and death. There have been many reports of poisoning by Nux vomica, and the severe toxicity caused by strychnine and brucine. Strychnine is highly toxic to humans, and it can be rapidly absorbed from the gastrointestinal tract to act upon the CNS, causing general CNS excitation. Death by strychnine poisoning is usually caused by spasmodic fixation of the respiratory muscles or exhaustion of the CNS, particularly the respiratory center.

Pharmaceutical preparation:

- SBL Nux Vomica Dilution 200 CH
- SBL Nux Vomica Dilution 30 CH

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Report on

Vinca Alkaloids

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Contents

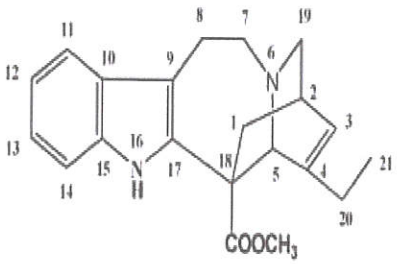
Vinca alkaloids

Vinca alkaloids are isolated from the periwinkle plant Catharanthus roseus, also known as Finca rosea, Family Apocynaceae.

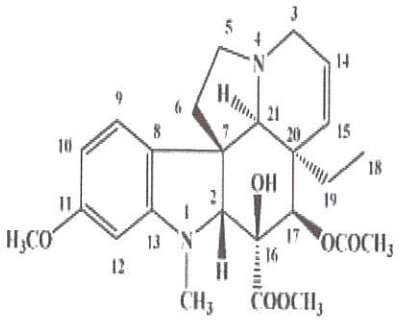
chemistry

The vinca alkaloids are dimerie asymmetrical compounds consisting of two multi-ringed subunits, vindoline and catharantine, linked by a carbon-carbon bridge.

catharantine nucleus



vindoline



1) Vindoline

Molecular Formula

$C_{25}H_{32}N_2O_6$

IUPAC Name

methyl (1R,9R,10S,11R,12R,19R)-11-acetyloxy-12-ethyl-10-hydroxy-5-methoxy-8-methyl-8,16-diazapentacyclo[10.6.1.01,9.02,7.016,19]nonadeca-2(7),3,5,13-tetraene-10-carboxylate

2) Catharantine nucleus

Molecular Formula

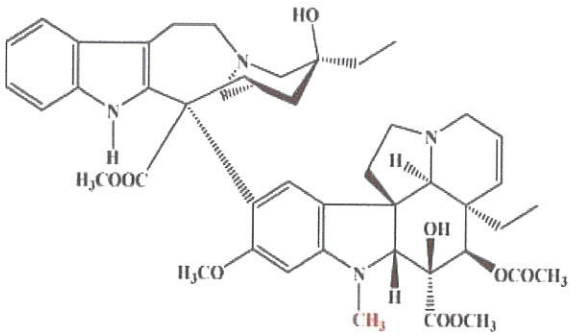
$C_{21}H_{24}N_2O_2$

IUPAC Name

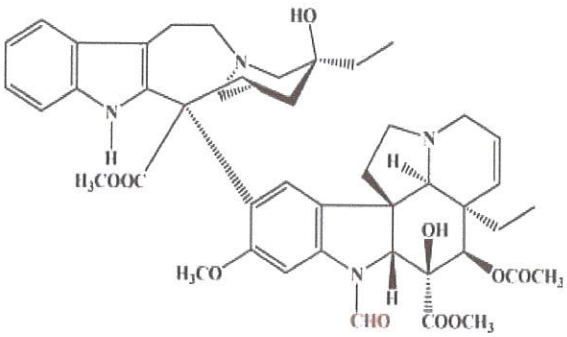
methyl (1*R*,15*R*,18*R*)-17-ethyl-3,13-diazapentacyclo[13.3.1.$0^{2,10}$.$0^{4,9}$.$0^{13,18}$]nonadeca-2(10),4,6,8,16-pentaene-1-carboxylate

Extracts of Vinca rosea possess many therapeutic effects including anti-tumor activity,

Vineristine (Oncovin), vinblastine (Velban) and vindesine (Eldisine) are the first

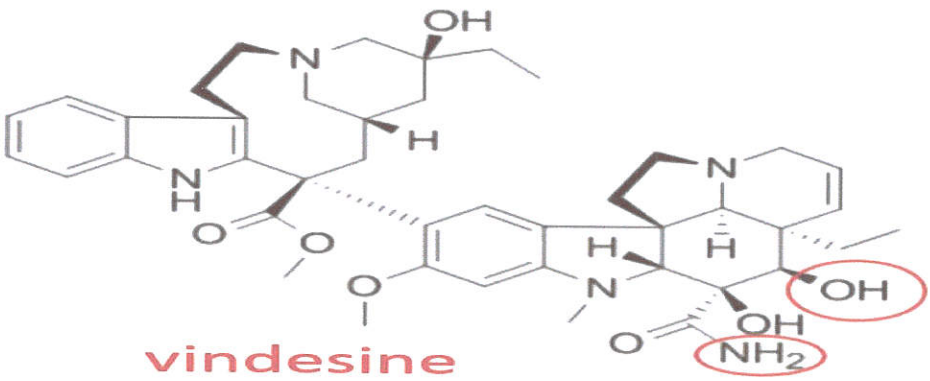


vicristine



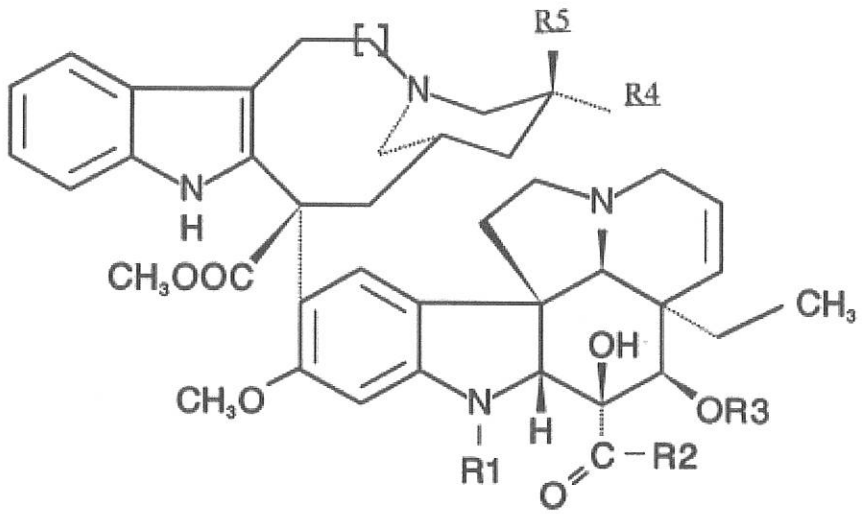
vineblastine

vinca alkaloids with anti-tumor activity to be identified.



vindesine

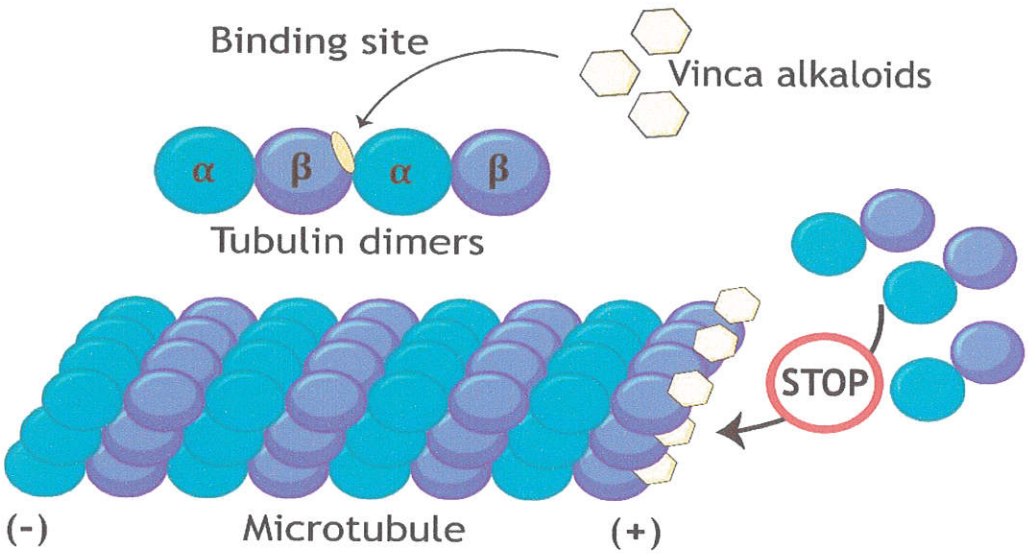
They are different in the group present in the nitrogen of the indole ring, so in vincristine there is a methyl group while in vinblastine there is a formyl group or as in vindesine additional amide group is added and a hydroxyl group is instead of the esoteric group in vincristine and vinblastine as in the following figure :



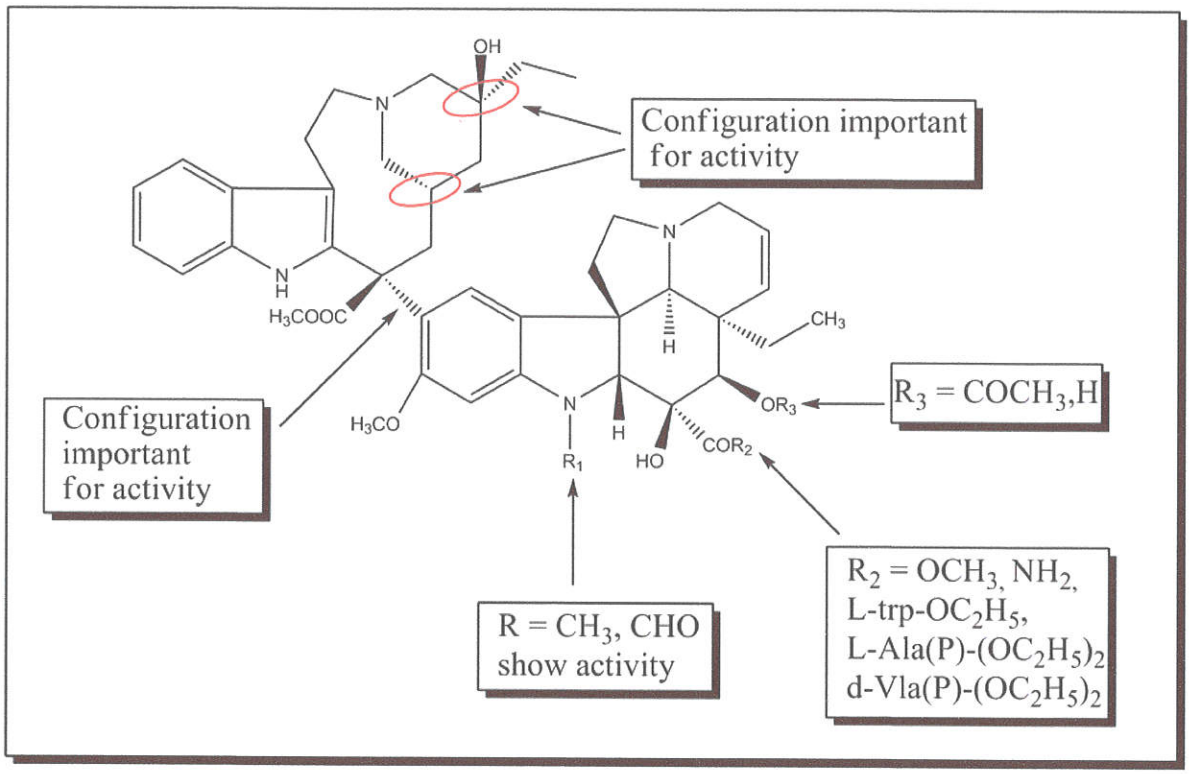
	R1	R2	R3	R4	R5	[ ]
vincristine	CHO	OCH_3	$OCOCH_3$	CH_2CH_3	OH	--
vinblastine	CH_3	OCH_3	$OCOCH_3$	CH_2CH_3	OH	--
vindesine	CH_3	NH_2	OH	CH_2CH_3	OH	--

Mechanism of action and pharmacological effect:

Vincristine and other vinca alkaloids belong to the group of mitotic poisons, particularly tubulin-binding compounds, which derive their biological properties from disrupting the function of microtubules. Microtubules are polymeric fibers composed of tubulin heterodimers. The dimers are formed by α- and β-subunits of the protein tubulin and the binding site for vincristine is located on the β-subunit at the boundary between two heterodimers (**Figure**). Vincristine and other vinca alkaloids are, thus, the only tubulin-binding agents discovered, so far, which do not strictly bind one tubulin heterodimer. This important property plays a crucial role in the specific mechanism of action of vinca alkaloids. In particular, at high doses, the compounds are capable of splitting the microtubule fibers. Subsequently, the fibers join with one another always linked through the vinca alkaloid. Such irregularly ordered, often spiraled fibers are unable to fulfill their function mainly in the mitotic spindle, which is responsible for the separation of chromatids in mitosis. Also, low doses of vinca alkaloids hamper this function, since the compounds bind the ends of the microtubule fibers and stabilize the microtubule dynamics.



Structure activity relationship:



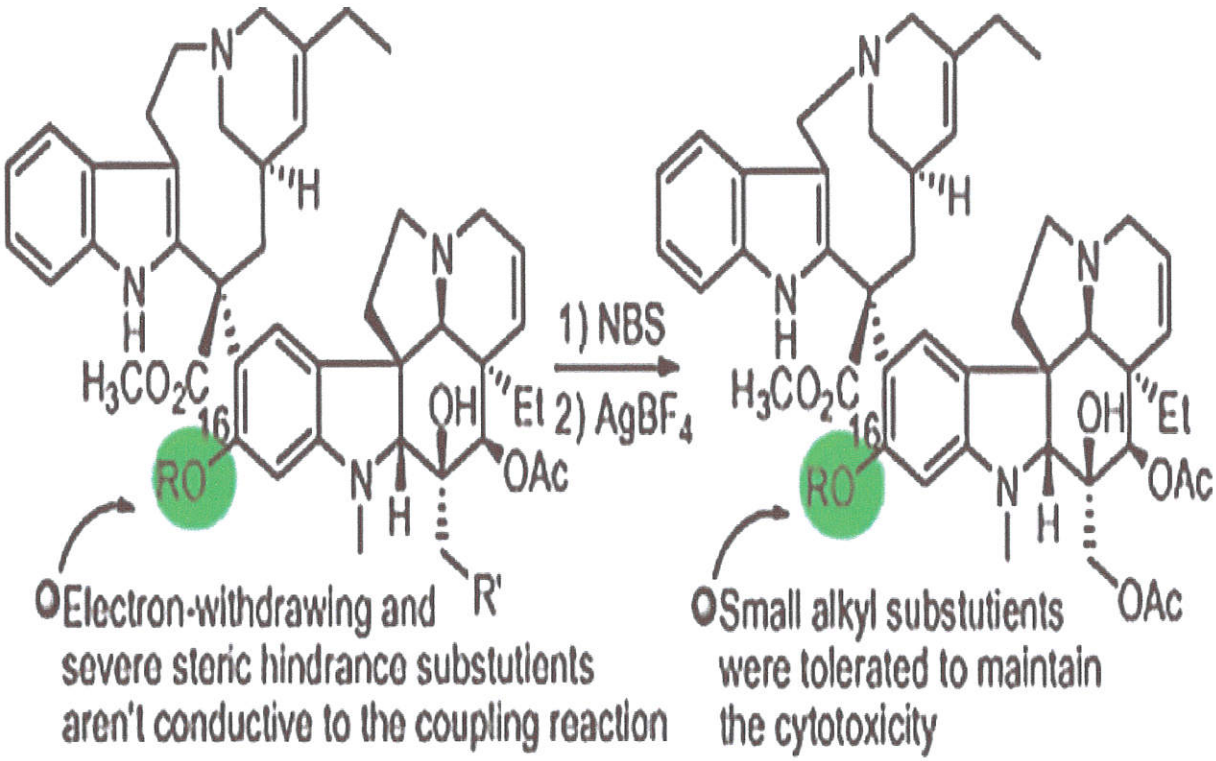
* Configuration is very important in the chiral centers present in carbon number

C2, C4, C18 in the catharantine nucleus.

* n vindoline nucleus R_1 is essential for activity and may be a methyl group as in vincristine or a formyl group as in vinblastine.

* R_2 may be methoxy group forming ester group as in both vincristine and vinblastine or an amino group forming amidic group as in vindesine

* R_3 is responsible for making a prodrug as in vincristine and vinblastine



Uses of vinica alkaloids:

Uses of vincristine:

Recommended for treatment of acute leukemia in children, small cell lung cancer, cervical and vaginal cancers.

Uses of vinblastine:

Recommended for generalized Hodgkin's disease, lymphocytic lymphoma, testicular carcinoma and choriocarcinoma.

Side Effects:

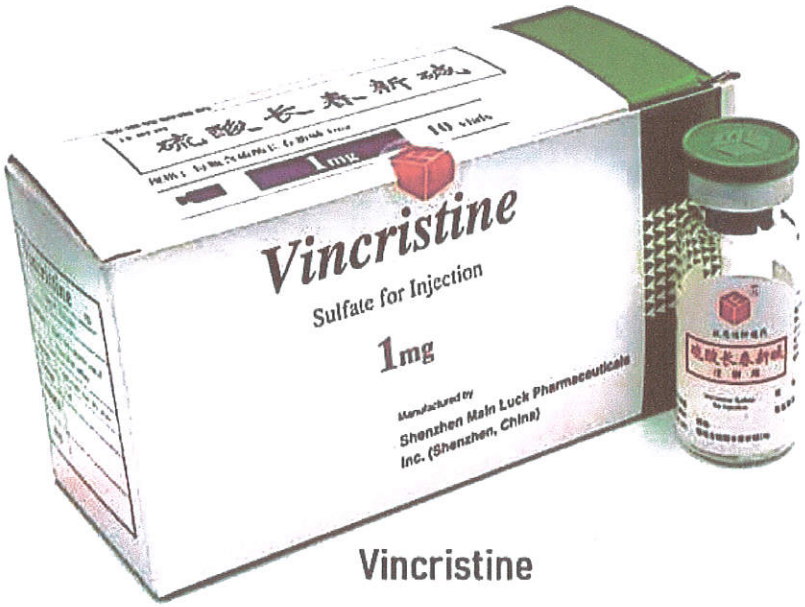
Vincristine may cause these side effects:

- nausea.
- vomiting.
- sores in the mouth and throat.
- loss of appetite or weight.
- stomach pain.
- diarrhea.
- headache.
- hair loss.

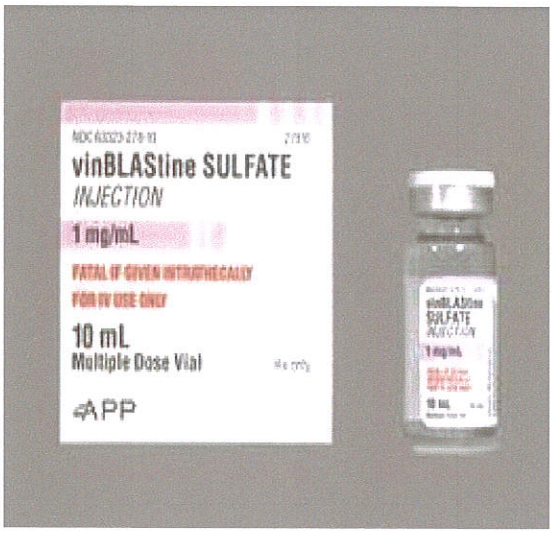
Vinblastine may cause these side effects:

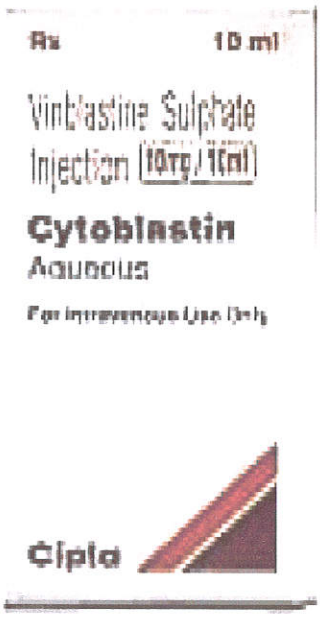
- constipation.
- nausea.
- vomiting.
- loss of appetite or weight.
- stomach pain.
- diarrhea.
- headache.
- dizziness.

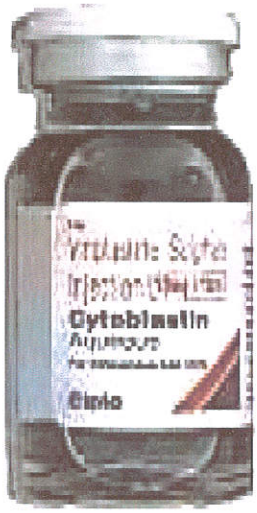
Pharmaceutical preparations:

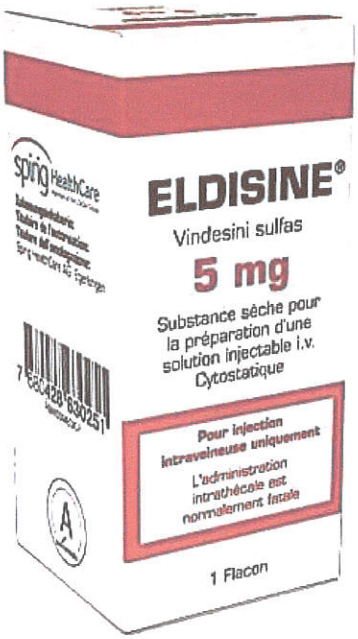


Vincristine









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Report on

Peyote Alkaloids

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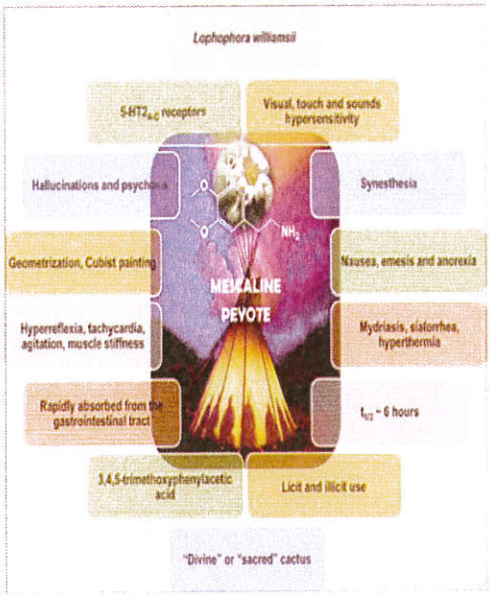
❖ Introduction



Peyote is well known for its hallucinogenic effects; the plant contains at least 28 alkaloids, the principal one of which is mescaline.

Mescaline is regarded as the first of a series of hallucinogens or psychomimetics, in a dose of 400-700 mg by injection. - Habituation and addiction do not result from repeated use of mescaline, so it is not regarded as a narcotic drug.

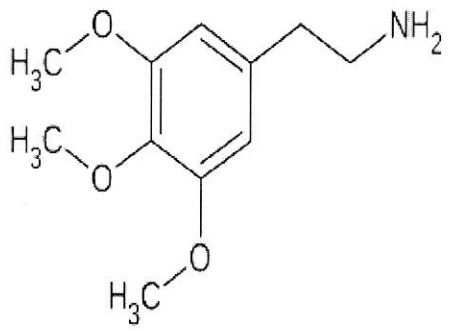
The drug is usually taken orally, without chewing, although it can still be smoked, or even injected.so it is not regarded as a narcotic drug.

It's chemical structure is close to that of an amphetamine (stimulant).

❖ Natural source

Peyote*(Lophophorawilliamsii) (family Cactaceae)*. is a cactus containing the hallucinogen mescaline (2-(3,4,5-trimethoxyphenyl) ethanamine).

❖ Chemical Structure



Mescaline (2-(3,4,5-trimethoxyphenyl)ethanamine).

❖ Structure Activity Relationship :

- Mescaline is orally active, but it is the least potent of all the classical hallucinogens. Despite its low potency, mescaline has served as a prototype hallucinogen because of the similarity of its psychopharmacolgy to other hallucinogens and also because it is extensively used up to the present day in the form of peyote during religious services of the Native American Church. It also has served as the lead molecule in structure-activity relationship studies of the phenethylamines.

- The mono substituted methoxy counterparts are inactive. Also inactive are all disubstituted methoxy isomers.
- All trisubstituted compounds are inactive, except mescaline itself.
- The 2,3,4,5-tetramethoxy derivative is somewhat more active than mescaline.
- The pentamethoxy analog is the most active, indicating that sidechain cyclization to the indole derivative may not be important for mescaline.

- Other SAR studies involved sidechain homologs, such as 3,4,5-trimethoxy-phenyl-isopropyl-amine (3,4,5-trimethoxy amphetamine). It is about twice as potent as mescaline.
- Sidechain homolog of mescaline. The data show that homologation of the sidechain to the isopropyl structure enhances the potency .

❖ Mechanism of action of peyote:

Its pharmacodynamic mechanisms of action are primarily attributed to the interaction with the serotonergic 5-HT2A-C receptors, and therefore clinical effects are similar to those elicited by other psychoactive substances, such as lysergic acid diethylamide (LSD) and psilocybin, which include euphoria, hallucinations, depersonalization and psychoses.

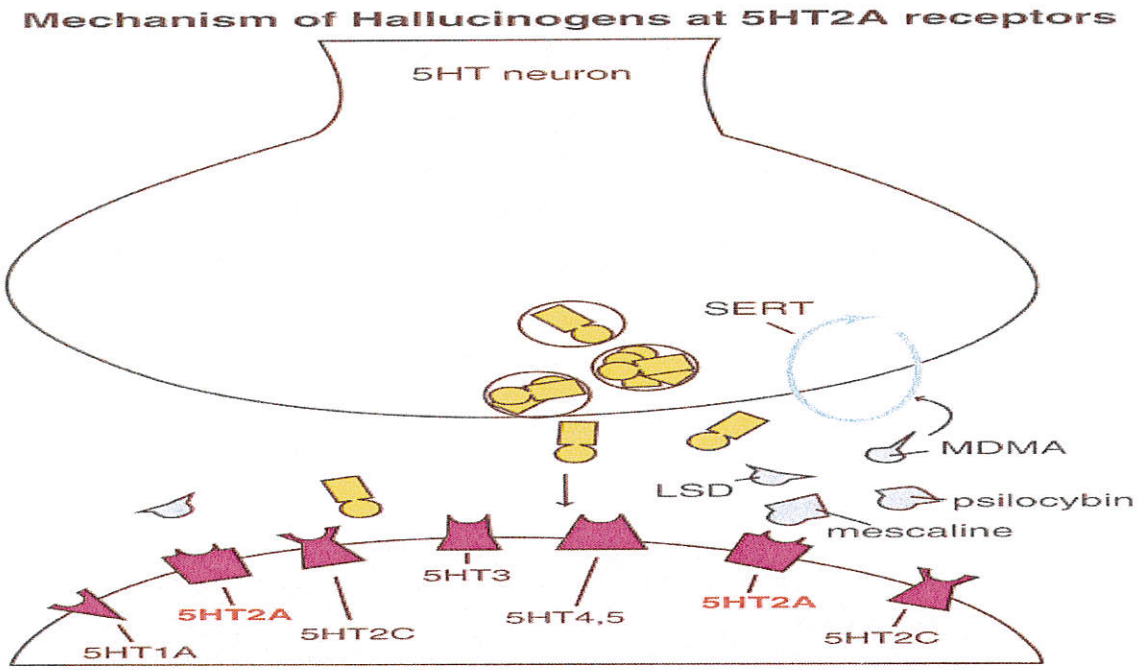


Figure 14-19. Mechanism of hallucinogens at $5HT_{2A}$ receptors. The primary action of hallucinogenic drugs such as LSD, mescaline, psilocybin, and MDMA are shown here: namely, agonism of $5HT_{2A}$ receptors. Hallucinogens may have additional actions at other serotonin receptors (particularly $5HT_{1A}$ and $5HT_{2C}$) and at other neurotransmitter systems, and MDMA in particular also blocks the serotonin transporter (SERT).

❖ Pharmacological effect:

Mescaline is considered a hallucinogen or psychedelic drug and its effects include:

An altered state of consciousness – with altered thinking and changes in time and perception – which is often described as happy, positive, enjoyable and 'illuminating.'

Feeling like you are in a dream-like state.

Prominent changes in visual perceptions with intense visual distortions and possibly hallucinations (where you see things that aren't there).

These can happen with your eyes open or closed. Less common are auditory hallucinations (hearing things that aren't there.

Development of vomiting, headaches and feelings of anxiety.

❖ Mescaline poisoning:

Symptoms are consistent with a sympathomimetic toxidrome, namely hyperreflexia, tachycardia, agitation, muscle stiffness, ataxia, seizures, mydriasis, sialorrhea, hyperthermia and paresthesia .

❖ Side Effects

- Peyote is unsafe for use .
- It can cause nausea and vomiting ,anxiety ,paranoia ,fear and Emotional instability.
- It can also raise blood pressure ,heart rate, and respiratory rate.
- Changing in vision, drooling, headache, dizziness, and drowsiness may also occur.
- Although it is rarely fatal, peyote can cause homicidal, psychotic, or suicidal behavior related tohallucinations.

❖ Special precautions and Warning

❖ Pregnancy and Breast feeding

It is unsafe to use Peyote if you are pregnant.The mescaline in peyote can cause birth defects.

❖ Uses of peyote :-

Peyote is used for treating:

1. Fevers.
2. joint pain (rheumatism).
3. Paralysis.. People apply peyote to the skin for treating fractures, wounds, and snakebite.
4. Peyote is also used as a recreational drug because it can cause hallucinations.

❖ Pharmaceutical Preparation

Exemplified by products like (pomade depeyote).
Such products can be found for treatment of arthritic and muscular pain through topical application.

❖ References

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Assiut University
Faculty of Pharmacy

"PhenylEthylAmine"

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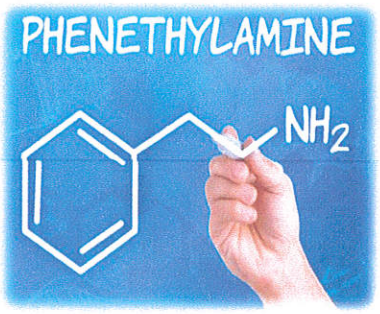

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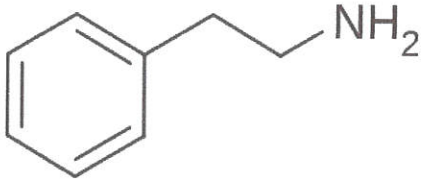
1. Natural Product Source:

- Phenylethylamine is produced by a wide range of species throughout the plant and animal kingdoms, including humans; it is also produced by certain fungi and bacteria (genera: *Lactobacillus, Clostridium, Pseudomonas* and the family Enterobacteriaceae) and acts as a potent antimicrobial against certain pathogenic strains of *Escherichia coli* .
- Certain algae are the sources of phenyl ethylamine, *Desmerestia aculeate* and *Desmerestia viridis* are the phenyl ethylamine containing brown algae, similarly *Cystoclonium purpureum, Polysiphonia urceolata, Delesseria sanguine, Dumontia incrassate,* and *Ceramium rubrum* are the red algae used for extraction of phenyl ethylamine

2. Structure:

Phenyl ethylamine is the first class of **marine alkaloid** which is an aromatic monoamine alkaloid.
Phenyl ethylamine alkaloids consist of an ethylamine side chain on a benzene.

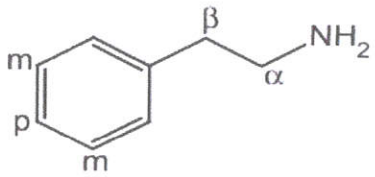


3. Chemistry:

- Color: colorless liquid at room temperature
- Odor: fishy odor
- Solubility: soluble in water, ethanol and ether
- Density: 0.964 g/ml
- Boiling point: 195 °C
- Upon exposure to air, it combines with carbon dioxide to form a solid carbonate salt.
- Phenyl ethylamine is **strongly basic** $pK_b = 4.17$ (or $pK_a = 9.83$), as measured using the HCl salt, and forms a stable crystalline hydrochloride salt with a melting point 217 °C

4. Structure-Activity Relationship:

Many of the sympathomimetic drugs contain β-phenyl ethylamine as parent structure.



β–Phenyl ethylamine

I. Phenyl ring substitution:

- Substitution on the meta and para positions of the aromatic ring and on the amino, α, and β positions of the ethylamine side chain influences the mechanism of sympathomimetic action and the receptor selectivity of the drug.
- Maximal activity is seen in β-phenyl ethylamine derivatives, containing hydroxyl groups in the meta and para positions of the aromatic ring (catechol) and a β-hydroxyl group of the correct stereo- chemical configuration on the ethylamine portion of the molecule.
- Although the **catechol moiety** is an important structural feature to obtain maximal agonistic activity at adrenergic receptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonism.
- For example, replacement of the catechol function of isoproterenol with the resorcinol structure gives the drug metaproterenol, which is a selective β_2-receptor agonist.
- In an other approach, replacement of the meta hydroxyl of the catechol structure with a hydroxymethyl group afforded Salbutamol, which shows selectivity to the β_2 receptor.
- The naturally occurring noradrenaline has 3, 4-dihydroxy benzene ring (catechol) active at both α and β receptors. However, it has poor oral activity because it is rapidly metabolized by COMT, the change in substitution pattern 3, 5-dihydroxy as in metaproterenol gives good oral activity. This is due to its resistance to metabolism by COMT. It also provides selectivity for β_2 receptors.

II. Substitution at nitrogen:

- Amino group in phenylethylamines is important for direct agonistic activity.
- The amino group should be separated from the aromatic ring by **two carbon atoms** found among the potent direct-acting agonists.
- As the bulk of the nitrogen substituent increases, α-receptor agonistic activity decreases and β-receptor activity increases. Thus, NE that is an effective β -receptor agonist is also a potent α-agonist, while epinephrine is a potent agonist at α, β_1, and β_2 receptors. N-tertiary butyl group enhances β_2 selectivity. As the size increases from hydrogen in noradrenaline to methyl in adrenaline, isopropyl in isoproterenol, the activity of α receptor decreases and β receptor increases.
- Primary and secondary amines are more potent direct-acting agonists than 3° or 4° amines.

III. Substitution on the carbon side chain:

- Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct receptor agonist activity at both α and β receptors.
- Importantly, an α-alkyl group increases the duration of action of the phenylethylamine agonist by making the compound resistant to metabolic deamination by MAO.
- α-substitution also significantly affects receptor selectivity.
- Another effect of α-substitution is the introduction of a chiral centre, which has pronounced effects on the stereo-chemical requirements for activity.

5. Mechanism of Action:

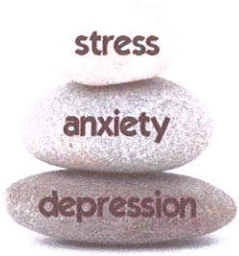
Scientists suspect that phenethylamine may act by:

- Activating a receptor (TAAR-1) in the brain to trigger the release of neurotransmitters. Neurotransmitters send chemical signals to different targets in the body causing various responses e.g., happy, sad, scared, awake.
- Activating TAAR-1, phenethylamine increases the release of serotonin, epinephrine (adrenaline), dopamine, and norepinephrine (noradrenaline) from neurons. These neurotransmitters affect mood, cognitive function, and mental well-being.
- Potentially preventing the same neurotransmitters from taken back up (through reuptake transporters) by neurons, meaning they stay in the spaces between neurons (synapses) longer and they may have more time to exert their effects.

6. Uses and Pharmacological Effects:

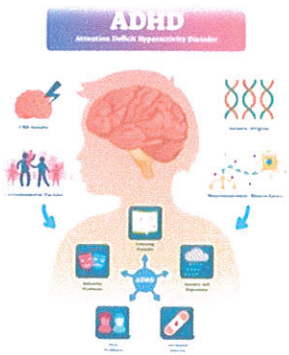
Phenylethylamine helps:

1) **Anxiety & Depression:**
   PEA activates TAAR1 and TAAR2 receptors which in turn prevents the **uptake** and boosts the release of the **'feel- good'** neurotransmitters serotonin & dopamine



2) **Neuroprotector:**.
   Monoamine oxidase inhibits the catecholamines like dopamine and norepinephrine. Decreases in dopamine levels are implicated in diseases like Parkinson's. PEA helps boost dopamine and norepinephrine levels. Reducing the symptoms of neurodegenerative diseases

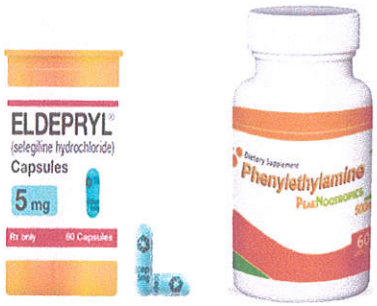
3) **Attention Deficit Disorder (ADHD):**
   PEA prevents the reuptake of dopamine and norepinephrine and inhibits their transport. Like the mechanism of action provided by ADHD stimulant meds. Some have found supplementing with PEA as a nootropic has decreased the symptoms of ADHD.



7. Pharmaceutical Preparations:

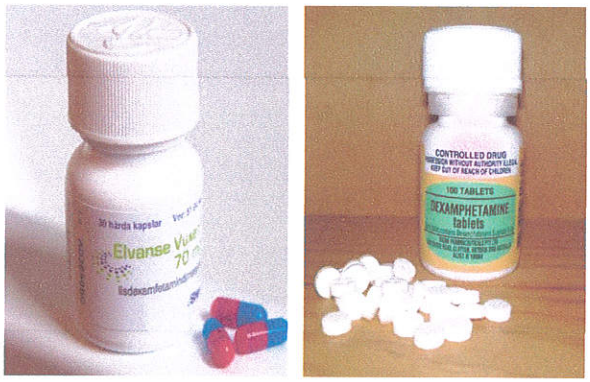
a) Depression:

- ✓ Early research shows that taking 10-60 mg of phenethylamine by mouth per day along with 5 mg of the antidepressant **selegiline** (Anipryl, Eldepryl) twice per day for 4 weeks relieves depression in 60% of people.



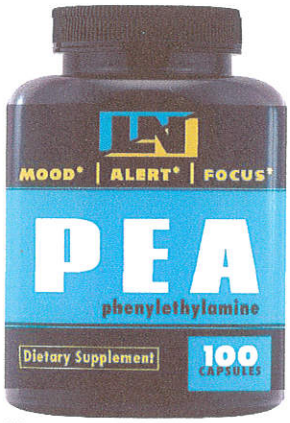
b) Attention Deficit Disorder (ADHD):

- ✓ Different types of amphetamines are available for the treatment of ADHD, such as lisdexamfetamine, dexamphetamine (or dextroamphetamine), and mixed amphetamine salts (MAS), which contain d-amphetamine and l-amphetamine at a ratio of 3:1.



- ✓ Recommended dosages range from 5 mg/d to 40 mg/d for MAS (FDA 2015a), from 30 mg/d to 70 mg/d for lisdexamfetamine (FDA 2015b), and from 5 mg/d to 40 mg/d for dexamphetamine (FDA 2007)

c) Energy Mangment:



- ✓ Phenyl ethylamine, a powerful neurotransmitter shown to induce stimulation, elevate mood, reduce appetite and increase focus. This powerful psycho-stimulant is found in trace amounts in chocolate.

- ✓ Increased metabolic activity: Phenylethylamine, which has been studied extensively for its ability to affect appetite. Indeed, pea, when administered orally, crosses the blood brain barrier and affects the appetite Control center of the brain, essential delaying hunger and preventing cravings for carbs and sweets.

8. References:

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