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A BRIEF STUDY ON CATHARANTHUS ROSEUS VINCA I.E ANTICANCER OR ANTINEOPLASTIC DRUG

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ABSTRACT
Vinca alkaloids are acts as a antineoplastic drugs obtained from the "Madagascar Periwinkle plant and it is naturally extracted from the Periwinkle plant, Cathranthus roseus. Vinca is blue, purple and also white in colour and it is generally produce in summer and grown anywhere in the garden. The Vinca alkaloids have lots of medicinal value such as Anticancer drug (antineoplastic drug), antidiabetic, antimicrobial and acts as a disinfectant. Vinca alkaloids have hypoglycemic as well as cytotoxic effects and given in targeted and combination therapy. Anticancerous drug Vinca have ability to inhibit the cancerous cells. Vinblastine (VBL), Vincristine (VCR), Vinorelbine (VRL), and Vindosine (VDS) are the four major Vinca alkaloids but mainly two chemical constituents play a vital role in medicinal field as Vinblastine mainly used to treat Hodgkin lymphomas on the other hand Vincristine used to treat childhood leukaemias. Many times it causes toxic effects in our body such as bone, narrow depression and muscle weakness etc. Vinflunine is now a new synthetic vinca alkaloid. It is also helps in regulation of menstrual cycle. Vinca is known for its antitumour against diabetic, hostile to microbial and against the mutagenic impact.

KEYWORDS: Madagascar Periwinkle, Catharanthus roseus, vinca alkaloid, Vinblastine, Vincristine, Vinorelbine, Vindesine, Vinflunine, Antineoplastic agent, anticancer, antimicrobial etc.

INTRODUCTION

Vinca alkaloids are the class of organic compounds generally made up of carbons, hydrogen, nitrogen and oxygen that is often derived from the plant is named as as alkaloid. Vinca alkaloid is discovered in the 1950's by the Canadian scientist Robert Noble and Charles Beer. Vinca alkaloids are obtained from the Madagascar Periwinkle plant. Vinca alkaloid is naturally occurring and it is extracted from the Pink Periwinkle plant 'Canthranthus roseus G. Don is belonging to the family "Apocynaceae".

Vinca alkaloids producing more than 130 different Terpenoid indole alkaloid (TIA's) and it is the oldest group of the plant alkaloid groups that is used to treat cancer. The species has been long cultivated for herbal and as an Ornamental plant. In Ayurveda, the extract of its roots and shoots, through poisonous, is used against the several diseases such as Diabetes, high blood pressure and the drug which acts as a disinfectant. The species has been long cultivated for herbal and as an Ornamental plant. In Ayurveda, the extract of its roots and shoots, through poisonous, is used against the several diseases such as Diabetes, maleria, high blood pressure, Hodgkin lymphoma and the drug which acts as a disinfectant.

In this review we focused on the application and resistance mechanism of vinca alkaloids such as Vinblastine (VBL), Vincristine (VCR), Vinorelbine (VRL), and Vindesine (VDS) medicinal and clinical use. From 2008, a new synthetic vinca alkaloid Vinflunine which is now currently approved in Europe for medicinal treatment of lung cancer. Vinblastine and vincristine shows a strong antimicrobial activity and also used in the treatment of leukemia and Hodgkin lymphoma.

Vinca alkaloids were first applied into clinical chemotherapy during the 1960's exerting the anti-tumour effects by interfering with microtubules and inhibiting angiogenesis. Vinblastine and Vincristine are commercially terpenoid indole alkaloid (TIAs) used in anticancer chemotherapy. Vinblastine is also involved in the treatment of NSCLC on administration in combination with Cisplatin. Vinca alkaloids are the class of cell cycle-specific cytotoxic drugs that works by inhibiting the ability of cancer cells to divide. Vinorelbine is the most commonly used and extensively tested chemotherapy for lungs cancer alone or in combination. The Cisplatin- Vinorelbine combination had a superior one year survival rate of 35% compared to 30% for Vinorelbine alone and 27% for cisplatin -

vindesine and response rates were 30%, 14%, and 19% respectively.

The latest one, Vinflunine has higher activities than Vincristine, Vinblastine and Vinorelbine in vivo and develops drug resistance more slowly than Vinorelbine. Vinca alkaloids derived from plants and also known as Periwinkle, Cathranthus roseous or semisynthesis have a potent anti-tumour activities by preventing microtubules polymerization. It is grown freely in tropical and subtropical area in South India and North Eastern states in India. The Periwinkle, Cathranthus roseous L produces several commercially valuable secondary metabolites including the anticancer agents, Vinblastine, Vincristine and the hypertension drugs Ajmalicine and Serpentine.

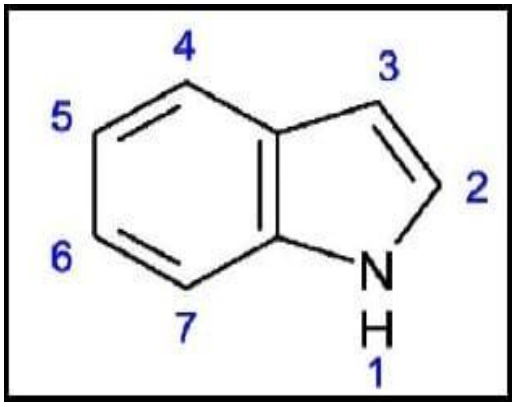
Indole Alkaloid

Figure 1:- The flowers of Catharanthus roseus G.Don Catharanthus roseus (Synonym: - Vinca Rosea) an evergreen shrub, it grows to a height of 1m with a spread of 1m.The stem is short, erect and branching, the leaves are glossy green oval, 5 cm long and opposite acuminate; the flowers are soft pink, 5 petal, open tubular and 4 cm across (three colors: pink,purple ,white).

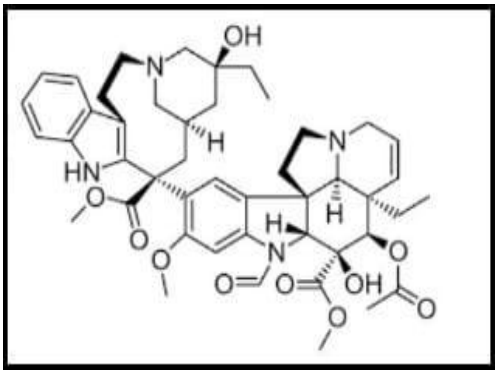
Scientific classification

❖ **Scientific classification**

- **Botanical names:-** Vinca Rosea (Cathranthus roseous) Pisum sativum ,Allium cepa
- **Family Name :-** Apocynaceae
- **Kingdom :-** Plantae
- **Division** :- Magnolipsida (Flowering plant)
- **Class** :- Magnolipsida (Dicotyledons)
- **Order** :- Gentianates
- **Genus :-** Cathranthus
- **Species**: - C.roseus.



Vernacular names



Vinca Alkaloid

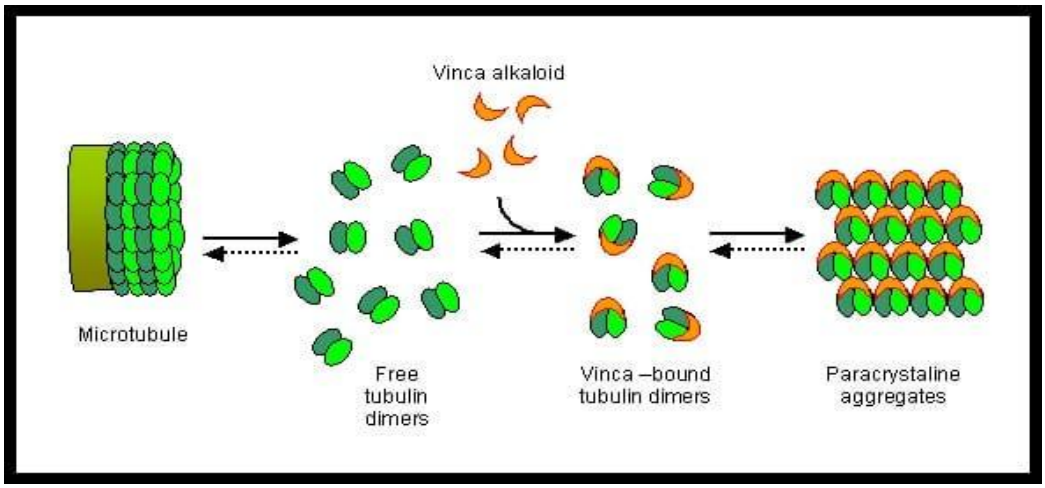
- **English**:- Cayenne, Jasmine, old maid, Periwinkle.
- **Hindi:-** Sada- bahar
- **Malayalam**:- Banappuva, Nityakalyani Savan
- **Marathi**:- Sadaphool, Sadaphuli
- **Sanskrit**:- Nityakalyani, Rusna, Sadampuspa, Sadapushpi.
- **Tamil:-** Chtkattu malli, cutukatta malli, Cutukattuppu
- **Telugu**:- Billaganneru
- **Gujarati**:- Barmasi
- **Bengali**:- Noyontara

❖ **Morphological characters**

- **Colour**

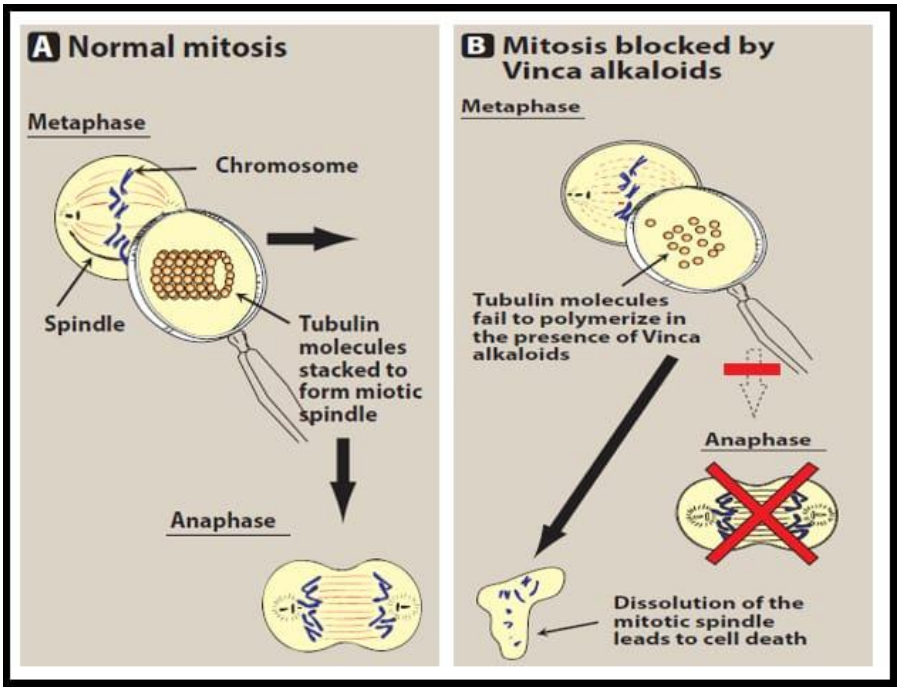
1. **Leaves:-** Green

2. **Flower:-** Pinkish white or Carmin red, voilet
3. **Root:-** Pale grey
- **Odour:-** Characteristics
- **Taste:-** Bitter
- **Leaves :-** Oppositly arranged
- **Fruit :-** Follicles



❖ **Mechanism of Action**

1. The vinca alkaloid cytotoxicity is due to the their interaction with tubulin & disruption of Microtubule function, particularly of Microtubules comparising the mitotic splindle apparatus directly causing metaphase arrest.
2. There are many other biochemical activities of those alkaloids that will or might not be associated with their effects on microtubules. After the treatment of the cells with dose of vina alkaloid, there doesn't show any effect on the microtubules.
3. Vinca alkaloid and other antimicrobial agents shows the effect on non-malignant cell as well as malignant cell in the non-mitotic cell division (Because micro tubules are involved in many non-mitotic function)
4. The vinca alkaloid hook up with binding sites on tubulin that they're break free those of the taxane, colchicine, podophylltoxin and guanonines-5 triphosphate, binding occurs earlier & can reverse too existing evidence maintains the existance of two vinca alkaloid binding sites per mole of tubulin dimer. Normally with reference to 16-17 high affinity binding sites in each microtubules that located at the ends of every microtubules. Binding of the vinca alkaloid to those sites interupts microtubule congregation but one among the foremost.



Mechanism of action of Vinca Alkaloids

❖ **Micropropogation of Catharanthus roseus**

- **Steps involved**

Axillary node or shoot tip

⬇

Wash with tap water 5min.

⬇

Rince with Teepol solution (2min), 70% Ethanol (v/v1min) & 0.1% HgCl2 (5min)

⬇

Wash with water (2-4 times).

⬇

Axillary buds were cultured on sterile M.S medium.

⬇

Shoot multiplication on MS medium supplemented with 1.0 mg

⬇

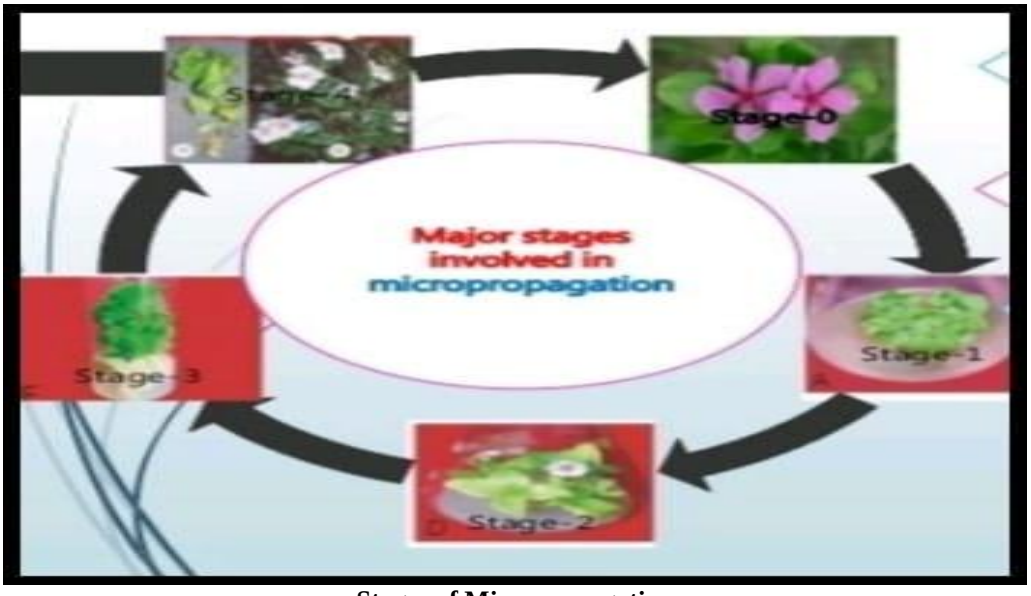
Root induction (¼ of MS with 5.0 mg/IBA)

⬇

4 Weeks old rooted plant for hardening (F)

⬇

Well growing plant in green house (G).



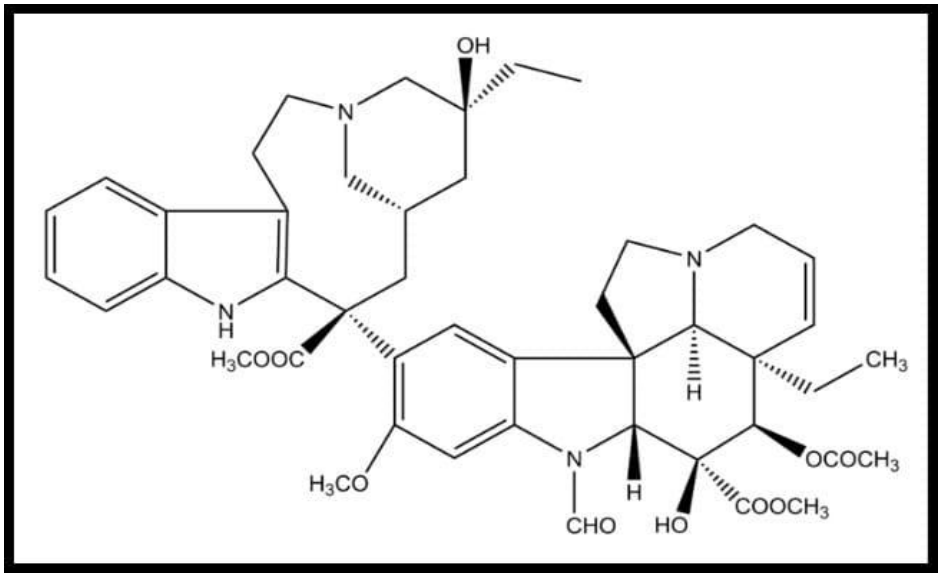
Stages of Micropropagation

There are the following chemical constitutes of Vinca alkaloids as follows

Vinblastine

Vinblastine sold under the marketed brand name Velban among others, is a chemotherapy medications. It is tropically used combined with other medications.

These are used to treat various types of cancers which include Hodgkin lymphoma, non small cell lung cancer, bladder cancer, brain cancer, melanema and Testicular cancer. It is administered by injections into a vein (Vinblastine sulphate 2015).



VINBLASTINE

❖ **Mechanism of action of Vinblastine**

Vinblastine and Vincristine

⬇

Binds to Beta (B) tubulin (Drug Tubulin Complex)

⬇

Disruption of mitotic spindle

⬇

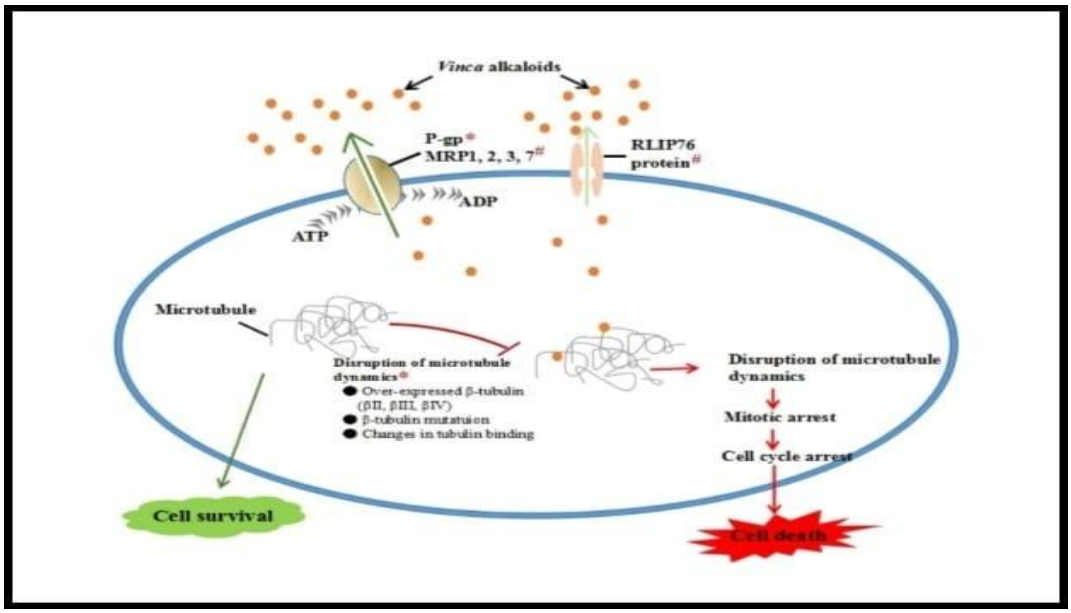
Chromosome fails to move apart during the mitosis

⬇

Metaphase arrest

⬇

Cell division is inhibited



Prevents the formation of microtubules

Side Effects

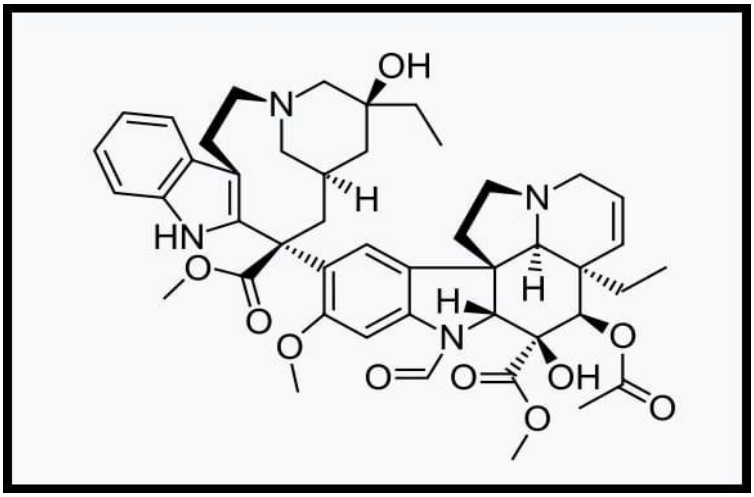
- Commonly it causes a change in sensations, Constipation, weakness, loss of appetite and headache.
- It also causes low blood cell counts and shortness of breath.
- Gastrointestinal problems
- High blood pressure
- Sweating
- Muscle Cramps
- Cause extensive tissue damage.

❖ **Uses of Vinblastine**

- Vinblastine works by blocking the cell division.
- Vinblastine is used to treat Lungs cancer.
- Also, it should not be given to the people who have a current bacterial infection.
- It is used with Bleomycine and Methotrexate in UBM chemotherapy for stage-lA or stage-llA Hodgkin lymphomas.
- It is also used to treat Histiocytosis.

Vincristine

Vincristine was first isolated in 1961'. Vincristine is additionally called Leurocristine and marketed under the name Oncovin among others during a chemotherapy medications wont to treat number of forms of cancers and acts as a Antineoplastic agent. It includes acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin disease, neuroblastoma and small all lungs cancer among others. It is administered by itravenously. These are also used as an immunosuppressant (Vincristine Sulphate 2015).



VINCRISTINE

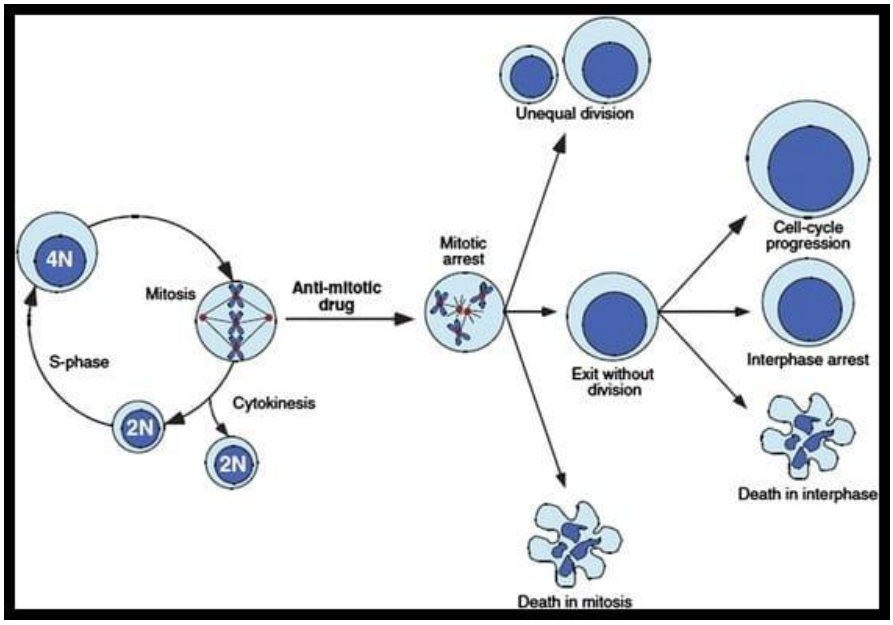
❖ **Side Effects**

- Commonly it causes a change in sensations, hair loss, Constipation, difficulty in walking and headache.
- **Serious Side Effects**

1. Neuropathic pain
2. Lung damage or low white blood cells which increases the danger of infection.

❖ **Therapeutic Uses**

- It is utilized in the treatment for Neuroblastoma.
- It is also wont to induce remission altogether with Dexamethasone and L-asparaginase.
- Vincristine is employed together with presnisone to treat Childhood leukemia.
- It is used for treating Thrombotic Thrombocytopenic Purpura (TTP) or Chronic Idiopathic Thrombocytopenic Purpura (CITP).



Extraction / Isolation Of Vinblastine & Vincristine

Leaves and herbs are extracted with aqueous alcohol in acetic acid solutions (in composition 1:9:1).

Aq.extract concentrated residue extracted with 2% HCL.

Extract with brnzene

Adjust the PH-4 NaOH solution (vicristine)

PH of solution is increased 7 (vinblastine)

Again extract with benzene

When treated dried

Dissolve in benzene to methyl chloride (65:35)

Eluted by using column chromatography

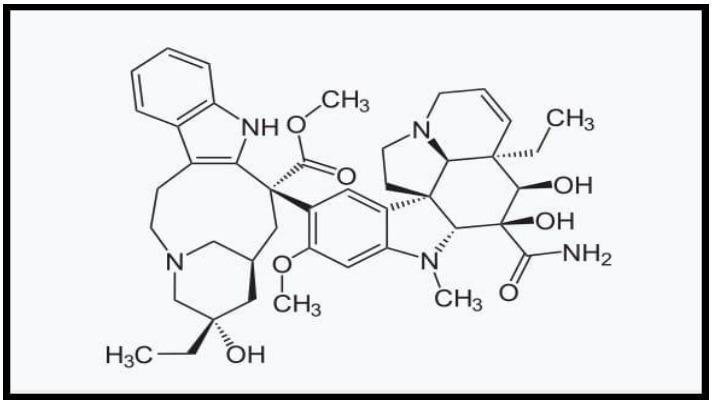
Evaporate to dryness

Vincristine sulphate

Crystalline from alcohol

Vindesine

Vindesine is additionally referred to as Eldisine which is that the Antimitotic Vinca alkaloid. Vindesine is an inhibitor of mitosis that's used as a chemotherapy drug. By inhibiting the mitosis, vindesine blocks the proliferation of cells of certain sorts of cancers. It is used in the treatment of various Malignancies such as leukemia, lymphoma, melanoma breast cancer and lung cancer. It is administered by the intravenous.



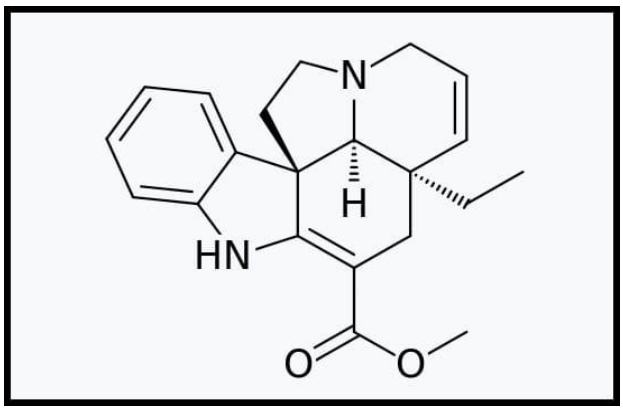
Vindesine

❖ **Side Effects**
- Myelosuppression
- Neurotoxicity
- Alopecia
- Nausea and Vomiting
- Local tissue irritations

Tabersonine

Tabersonine could be a Terpene alkaloid found within the medicinal plant herb and also within the genus Voacanga.

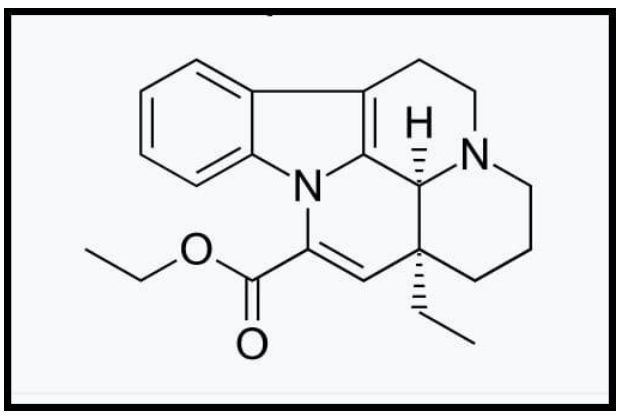
Tabersonine is hydroxylated at the 16-position by the enzyme Tabersonine 16-Hydroxylase (T16H) to make Hadroxy tabersonine. it's the primary intermediate resulting in form the Vindoline one among the 2 precursors required for Vinblastine biosynthesis.



Tabersonine

Vinpocetine

It is a manmade made synthetic derivative chemical of vinca alkaloid Vincamine. Vincamine is extracted from either the seeds of Voacanga africana or the leaves of periwinkle.



Vinpocetine

❖ **Side Effects**

- Use of Vinpocetine during the pregnancy may harm to the baby or results in miscarriage.
- Adverse effects include flushing, nausea, dizziness, dry mouth, Trancient hypo and hypertension, headache, heartburn and decreased blood pressure.
- FDA issued a statement in 2019 warning that "Vinpocetine may cause a miscarriage or harm Fetal development and reduces the immune functions.
- It causes apoptosis (cellular death).

❖ **Dose Range: -** 10 mg, 2 or 3 times/day (with meals).

❖ **USES :-**

- It improves blood flow to the brain.
- It is used at delay onset of Alzheimer's disease.
- It improves cell communication and having a rich Antioxidant activity.

Table 2.1 Properties of the vinca alkaloids

	Vincristine	Vinblastine	Vindesine	Vinorelbine
Mechanism of action	Low concentrations inhibit changes in microtubule length (treadmilling and dynamic instability) whereas high concentrations inhibit polymerization of tubulin			
Standard Dose (mg/m^2)	1–1.4 every 3 weeks	6–8 every week	3–4 every 1–2 weeks	15–30 every 1–2 weeks
Route of administration	Intravenous	Intravenous	Intravenous	Intravenous, oral
Metabolism	Predominantly P450 IIIA	Predominantly P450 IIIA	Predominantly P450 IIIA	Predominantly P450 IIIA
Elimination	Biliary/Fecal	Biliary/Fecal	Biliary/Fecal	Biliary/Fecal
Terminal half-life (h) ($T_{1/2}$)	95 (range 19–155)	25 (range 7–47)	24 (range 12–42)	33 (range 14–44)
Principal toxicity	Peripheral Neuropathy	Neutropenia	Neutropenia	Neutropenia

Table 2.2 Disposition of vinca alkaloids by bolus injection in patients with normal organ function [60]

	Volume of distribution (l/kg)	Elimination half-life (h)	Clearance (l/h/kg)	Fecal Clearance (%)	Renal Clearance (%)
Vincristine	7.2 (3.1–11.0)	45.1 (8.2–144)	0.16 (0.1–0.3)	69	4–13.5
Vinblastine	24.7 (17.3–35.1)	25.6 (19.6–29.2)	0.79 (0.7–0.9)	25–41	5.5–34
Vindesine	8.6 (6.8–10.5)	23.6 (19.0–34.8)	0.22 (0.1–0.3)	ND	4–19
Vinorelbine	54.3 (44.7–75.6)	41.2 (31.2–62.4)	0.95 (0.8–1.3)	40–58	3.3–24.6

Properties & Deposition of Vinca Alkaloid

❖ **Toxicity (Adverse effect)**

A. On Peripheral Nervous System

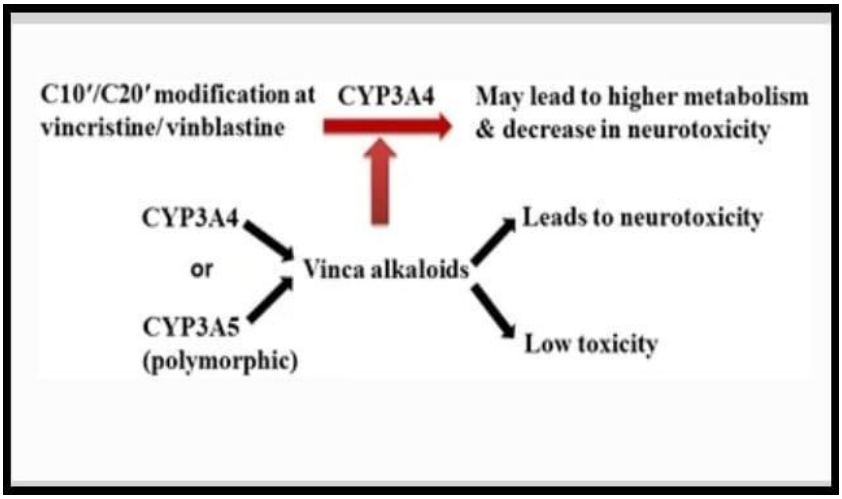
1. The incidence of peripheral neuropathy which are present in the typical glove & Stocking dishibution, & proceeds from a distal To a proximal Fashion with vincristine, is known to range between 35 to 45 %
2. Vincristine induced neurotoxicity is known to present with the sensory, motor, & autonomic symptoms.
3. Dose limiting toxicity of vincristine affecting on extraocular & laryngeal.
4. Neuro toxicity is dose dependent with a dose threshold of 2 to 6 mg / An_2 for the development of sensory symptoms.
5. Guideline Suggest that a single dose of vincristine Should not exceed 2 mg to prevent neurotoxicity.

B. Central Nervous system

1. Acute oR subacute encephalopathy seizures, visual loss can occur with the administration of these drugs
2. Other less Frequent Side effects include transient Cortical blindness with posterior reversible encephalopathy syndrome, unilateral OR bilateral optic neuropathy, visual hallucination Parkinsonism, and Inappropriate antidiuretic hormone secretion.
3. Jaw pain with a neuropathic Component which is non-responsive to traditional pain medication has been reported with the use of vincristine.
4. There is a hypothesis that pain results on the fith cranial nerve i.e. trigeminal nerve involvement
5. Vincristine induced vocal cord palsy which is potentially reversible. Phenomenon & Subsides with the cessation of the drug has been repoted in the literature.

C. Hematological Toxicity

1. Vincrstine is usually a bone marrow Sparing agent.
2. limiting dose of vinblastin exist hematological toxicity.
3. Vinorelbine & vindesine are also known to cause bone marrow toxicity.



D. Renal Toxicity

1. Vinblastine and it's active metabolite desacetyl vinblastine, vincristine and vindesine have a low renal exretion. (between 10 to 15%)
2. No dose adjustment has been advised for vinca alkaloids as a class.
3. Recommendation dose of vinorelbine reduced by 50% in patients undergoing hemodialysis due to an increased risk of adverse effect.

E. Hepatic Toxicity:- Vincristine, is metabolized in liver, dose adjustment is recommended with Hepatic dysfunction with hyperbilirubinemia, but particularly in cases with an elevation of the direct bilirubin fraction

F. Pulmonary Toxicity: - In which the acute dyspnoea and bronchospasm may occure with the concurrent use of vincristine and vinblastine with mitomycin.

G. Gastrointestinal Toxicity: - Vinorelbine and its metabolites are associated with chemotherapy-induced autonomic neuropathy which may present with constipation and urinary retention, through activation of the muscarinic receptors.

H. Cardiovascular Toxicity:- Apart from the cardiovascular autonomic effects which present as disturbances in the hemodynamic parameters, these drugs have also correlated with cardiac ischemic pain presenting with electrocardiographic abnormalities and myocardial infarction.

Local Effects

- Vincristine and vinblastine are known to act as vesicants and cause chemotherapy-associated extravasation.
- Recommendations include caution against the intramuscular, subcutaneous, and intraperitoneal use of vinca alkaloids.
- A bolus injection is recommended whenever possible, due to the risks associated with local administration. Local reactions related to the injection include erythema, pain, and discoloration

❖ **Other Rare Adverse Effects**

➢ Alopecia is a rare adverse effect of these drugs.

Pharmacological Value / Importance

1. **Anticancer Property: -** Vinblastine and Vincrstine inhibit the growth of human tumor's. Vinblastine is used in treatment of neoplasmas and for Hodgkin's disease, chronic carcinoma.Vinca and it's another ingredients are used for treatment of Leukemia in children's.
2. **Memory Enhancement Property: -** Vinpocetine produces various actions which is hypothetically used to treat Alzheimer's disease (AD). It has been given at the doses up to 60 mg/d in clinical trials of dimention and stroke and it has no significant adverse events.
3. **Anti-Ulcer Property: -** Generally Vincamine and Vindoline alkaloids show Anti-Ulcer property. The Vincamine are present in the leaves of vinca plant which shows Cetebrovasco dilatary and Neuroprotective activities.
4. **Hypolipidimic Activity:**-The leaf juice of C.roseus proved significant Anti-Atherosclerotic as observed by decline in the serum level of total cholesterol,t triglycerides, LDL-c ,VLDLc and histology of Aorta , Liver and Kidney.
5. **Antioxidant Property:-** It means which inhibit the Oxidlation.It is a chemical reaction that produce free radical the ethanolic extract of roots of various varieties of Catharanthus roseus such as rosea (pink flower) and alba (white flower) was obtained.
6. **Antihypertensive Property:** Antihypertensive drugs are used to treat Flowering of blood pressure. Leaves extract of vinca plant made significant change in hypotensive.

CONCLUSION

- In this review we are concluded that Vinca alkaloids are acts as a Antineoplastic and Anticancer drugs. It is broadly used in medical field. Vinblastine, Vincristine, Vinorelbine and Vinpocetine are the main chemical constitutes in Vinca alkaloids and every constitutes play a vital role like Vinblastine and Vincristine have Antineoplastic activity.
- Vinca is used to treat many diseases such as kidney cancer lungs cancer etc. It has antibacterial,

antidiarrheal, Hypolipidimic, antihypertensive and Anti-oxidants properties.

- It is also used to regulate the menstrual cycle. So this plant is used for various medicinal purposes.

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