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THE STORY OF VINCA ALKALOIDS: NATURE'S CONTRIBUTION TO ONCOLOGY

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ABSTRACT
Vinca alkaloids are important plant-derived compounds that have made a major contribution to modern cancer therapy. Vincristine and vinblastine were discovered from the Madagascar periwinkle (Catharanthus roseus) in the 1950s after researchers unexpectedly observed a reduction in white blood cells rather than the expected antidiabetic effect. These compounds work by interfering with microtubule formation, thereby stopping rapidly dividing cells and leading to cell death. Several bioactive molecules, including vinpocetine, vinflunine, and vinorelbine, are commercially available and are used as medicinal drugs for neurological disorders and various cancers. However, their production is associated with challenges such as low yields, scale-up difficulties, and toxicity concerns. Using endophytes to produce these valuable compounds could be a simpler, more sustainable, and efficient method, and it offers good opportunities for future research.

KEYWORDS: Anti-cancer, vinca alkaloids, vincristine, vinblastine, phytochemicals.

INTRODUCTION

Historical Documentation of Cancer in the Ancient World

Egypt and Greece occupy a landmark position in the historical documentation of cancer, with ancient manuscripts providing definitive evidence of the disease's impact on these civilizations.

The earliest recorded observation of human cancer was discovered in Egypt within the Edwin Smith Papyrus. Believed to be authored by the architect, physician, and statesman Imhotep during the Pyramid Age (around 3000–2500 BC), this landmark document provides the world's first description of a tumour.[1]



Fig. 1: Edwin Smith Papyrus.

Using both sight and touch, ancient Egyptian physicians carefully diagnosed tumours and recorded their cases in hieratic script. Their descriptions paint a vivid picture of the disease, noting visual signs like redness, breast abscesses, pus-filled swellings, and advanced tumours that penetrated deep into the bone.

Following its early documentation in Egypt, the history of cancer shifted to ancient Greece, where Hippocrates—the renowned physician and surgeon—first coined the term karkinoma (carcinoma).[2] The Greek physician Galen later provided a detailed characterization of uncontrolled growths in his treatise On Tumours Against Nature. He posited that while cancer could develop in any part of the body, it occurred most frequently in the breasts of women with abnormal menstruation.[3]

Although cancer had been recognized in India since the ancient Ayurvedic period, it was rarely mentioned in medieval literature. The routine diagnosis of the disease only began in the 19th century as Western medicine gained acceptance. Between 1860 and 1910, doctors from the Indian Medical Service began publishing audits and case series, culminating in the landmark studies of Nath and Grewal (1917–1932), which established cancer as a common cause of death among middle-aged Indians.[4,5]

Milestones and Molecules in Early Cancer Treatment

The earliest therapeutic models emerged in ancient Egypt and Greece, laying a foundation that evolved over centuries into the modern treatments developed by the late 1800s. According to the Edwin Smith Papyrus, ancient Egyptian physicians were highly skilled in bandaging. They used this technique medically to secure topical treatments, like leaves and herbs, over tumours, and surgically to immobilize patients for optimal healing. The Papyrus also details a specific regimen involving wrapping the tumour in fresh meat on the first day—likely to achieve haemostasis—followed by daily applications of grease, honey, and lint as a protective ointment. Additionally, these ancient practitioners utilized astringents to dry exudative tumour wounds.

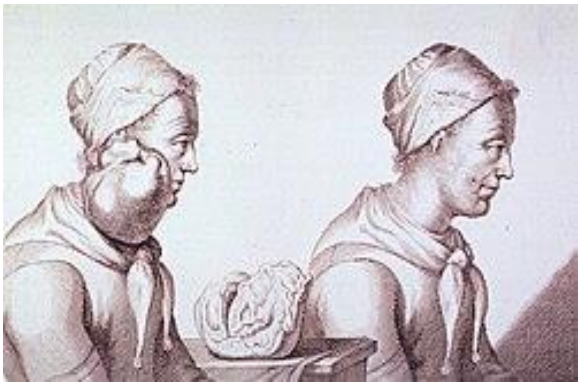


Fig. 4: A tumour removed by surgery in 1689.

Table 1: Milestones of Oncology Research (Before 1900).

Historical Period	Year / Time	Major Discoveries in Oncology
Ancient discoveries and theories of cancer	3000 B.C.	Edwin Smith papyrus describes the first case of human cancer
	1500 B.C.	Ebers papyrus describes tumors of skin, uterus, stomach, and rectum
	400 B.C.	Hippocrates proposes the first theory of tumor development
	130–200	Galen expands theory: black bile → incurable tumors; yellow bile → treatable tumors
	300–400	Oribasius confirms tumors are caused by excess black bile
No significant progress in the study of tumors	527–565	Aëtius of Amida introduces breast tumor treatment via full amputation
	625–690	Paul of Aegina describes uterine tumors and surgical treatments (bladder, thyroid, nasal polyps)
	860–932	Rhazes describes new tumor treatments in *De Chirurgia*
	980–1037	Avicenna introduces surgical removal of rectal tumors
	1070–1162	Averroes describes esophageal and rectal tumors; introduces hysterectomy
	1500	Paracelsus challenges humoral theory; proposes tumors due to "salt" accumulation
	1543	Vesalius publishes *De Humani Corporis Fabrica* with anatomical findings
	1600	Theories suggest tumors arise from coagulation/fermentation of blood or lymph
	1600–1620	Invention of the microscope
	1700	Boerhaave suggests environmental causes (water/soil); links inflammation, trauma, heredity
	1760	Morgagni links cancer to organ-specific pathological lesions

	1775	Percivall Pott links scrotal cancer to soot exposure (first occupational cancer link)
	1858	Rudolf Virchow identifies tumors originate from abnormal cells
	1896	Wilhelm Conrad Röntgen discovers X-rays
Birth of radiotherapy	1896	Emil H. Grubbé uses X-rays to treat breast cancer
	1898	Marie & Pierre Curie discover radiation from radium
	1899	Curie suggests use of radiation for tumor treatment
	1920	Establishment of radiotherapy as a medical field.

CHANCE DISCOVERY OF VINCA ALKALOIDS – ORIGIN & HISTORY

The Origin and Evolution of Vinca Alkaloids

The story of vinca alkaloids - vincristine and vinblastine, spans cosmic biological and medical history. These potent chemotherapeutic compounds derived from the Madagascar periwinkle *(Catharanthus roseus)* are the result of billions of years of chemical evolution planetary formation and biological adaptation.

Secondary Metabolites from plants as drugs

Plants throughout history have provided humans an economical supply of natural compounds which their secondary metabolites contain. These compounds display various bioactivities which include their capability to combat tumours.[6,7] Secondary metabolites exist as small organic compounds which living organisms produce but which do not serve any purpose for their growth or reproduction or development.

The classification system groups compounds according to their synthetic production methods which they use to create their respective products.[8] A basic classification system categorizes substances into three fundamental groups which include terpenoids (polymeric isoprene derivatives which biosynthesize through the mevalonic acid pathway from acetate), phenolics (substances which originate from shikimate pathways and possess one or more hydroxylated aromatic rings) and the highly varied alkaloids (compounds which contain nitrogen but not protein and originate from amino acids like tyrosine and have been utilized in medicine throughout history).[8,9] Each year researchers discover new plant-based secondary metabolites which exhibit cytotoxic properties and these discoveries open up new research directions for developing cancer treatments.



Fig. 5: ***Catharanthus Roseus.***

The medical application of certain natural compounds with anticancer properties becomes impossible because their physical and chemical characteristics limit their bioavailability and they exhibit toxic effects. Drug development efforts benefit from the search for plant secondary metabolites which scientists discover in natural environments.[10,11] The manuscript will showcase plant secondary metabolite research which has produced critical advancements in anticancer drugs with one derivative already used in hospitals and another one undergoing testing and research.

Discovery and Medical Transformation

Researchers Robert Laing Noble and Charles Thomas Beer at the University of Western Ontario started their study of *Catharanthus roseus* in the 1950s because people used the plant for diabetes treatment. The research team found that experimental models showed a significant decrease in white blood cell counts instead of showing the anticipated glucose-lowering results. The research team discovered that the plant extracts blocked cell division because it particularly affected cells that divided at a fast rate. The process of chemical analysis and fractionation created a pivotal moment for drug discovery which established vinblastine and vincristine as natural product-based medications.[12] Vinblastine entered clinical use in the late 1950s while vincristine received U.S. Food and Drug Administration approval in 1963. The compounds became essential medications for chemotherapy treatments which fought haematological malignancies and some solid tumours.[13]

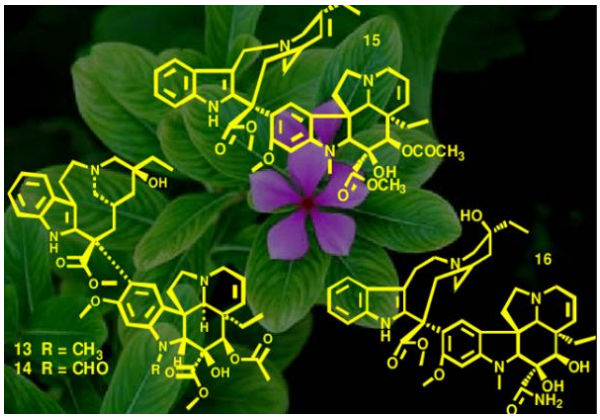


Fig. 6: Chemical Structure of *Catharanthus Roseus.*

Vinca alkaloids achieve their anticancer function through their ability to attach themselves to microtubule proteins which form the structure of tubulin. The substance specifically attaches itself to β-tubulin through the vinca-

binding domain which prevents tubulin dimers from creating microtubules during polymerization. The process creates a barrier that blocks mitotic spindle development which cells need for their chromosome separation during their cell division phase. The process stops cells at the mitosis metaphase point which then triggers their programmed cell death through apoptosis.

Cancer cells experience the greatest vulnerability to this mechanism because their division rate exceeds that of typical human cells. The complete lack of selectivity causes most drug side effects because it affects both cancer cells and normal cells in the gastrointestinal tract, hair follicles and bone marrow which develop rapidly. The discovery of vinca alkaloids shows how unexpected findings created a path to develop new medications which turned out to be important for medical treatment. Today these compounds establish the base for chemotherapy drug combinations which demonstrate how plant-based natural products continue to shape contemporary medical practice.[14]

A Bridge from Evolution to Medicine

The extraordinary biosynthetic sophistication of the periwinkle flower, evolved for ecological defence, became humanity's ally in fighting cancer. From a genomic perspective, these alkaloids represent nature's molecular evolution, where random genetic variation produced metabolically gifted enzymes.

The evolutionary saga of the vinca alkaloids, from the Big Bang to human medicine, underscores the cosmic unity of life: elements from dying stars, organised into living systems, now extend life through science.[13]

EXTRACTION AND ISOLATION OF VINCA ALKALOIDS

Vinca alkaloids have found their use and applications in various important fields such as cancer treatments, and their remarkable anti-cancer properties. In order to extract these valuable alkaloid compounds, from *Catharanthus roseus* or *Vinca rosea* which is the source of important antineoplastic vinca alkaloids like vinblastine and vincristine, several steps must be taken to isolate and purify the alkaloids.[15]

The high aggregated value of Vinca alkaloids is a direct consequence of their exceedingly limited natural occurrence and the rigorous, multi-step extraction techniques necessary to isolate them.

For example, the work of Tikhomiroff and Jolicoeur outlines a detailed process that involves lyophilization and mechanical mashing, followed by a 5-hour methanol extraction in a sonication bath.[16] Similarly, some protocols improve extraction using thermal and chemical methods, extracting with methanol at 50°C before using pH-driven resuspension in 0.1 N of HCl and ethyl acetate at pH 10 to refine the target molecules. Even the traditional aqueous sulfuric acid method requires a challenging four-stage purification process. This includes benzene partitioning and dual-column chromatography, ending with crystallization. Ultimately, while these sonication and partition-based techniques have improved recovery, moving from raw biomass to clinical-grade sulphate salts is still a complicated economic and chemical challenge.

Svoboda's Method

Gordon Svoboda devised an extraction process by which numerous individual Vinca alkaloids have been isolated. Following de-fatting with Skelly B (basically n-hexane), the plant material (ground whole plant, Catharanthus roseus) is extracted with 2% tartaric acid before being extracted with organic solvents in both acidic and alkaline conditions. This first separates the alkaloids whose tartrate is soluble in organic solvents from those that are not.

Some alkaloids unintentionally come from the plant material along with lipids when using Skelly B. This extraction plan, together with the chromatography and gradient pH extractions that followed, might be used to highlight new developments from the traditional extraction method. Some other groupings of alkaloids can be separated using the same techniques.

The flow chart shown in Fig. 1 provides a schematic summary of the first extraction steps. Following chromatography on alumina, the various fractions are eluted using different eluting solvents. To separate specific Vinca alkaloids, some of these column fractions (i.e., eluted from the alumina column) are then subjected to gradient pH extractions.
Along with several other alkaloids, portion A in this scheme contains vinblastine, vinleurosine, vincristine, and vinrosidine.

Chromatography

A Benzene solution of 10 gm of extracted fraction A is loaded onto a chromatographic column packed with 400 gm of alumina Grade F-20, which has been de-activated using 12.5 ml of 10% acetic acid. The elution process follows a systematic polarity gradient (non-polar to more-polar), beginning with benzene, followed by benzene-chloroform and pure chloroform, before concluding with a chloroform-methanol system. This mobile phase is collected in 500 ml fractions. Through the chromatographic separation, Vinleurosine is successfully recovered within fraction 34-42 using a 1:1 mixture of benzene-chloroform, while (0.126 gm) is isolated as a sulphate from fractions 43-45 under the same solvent ratio.

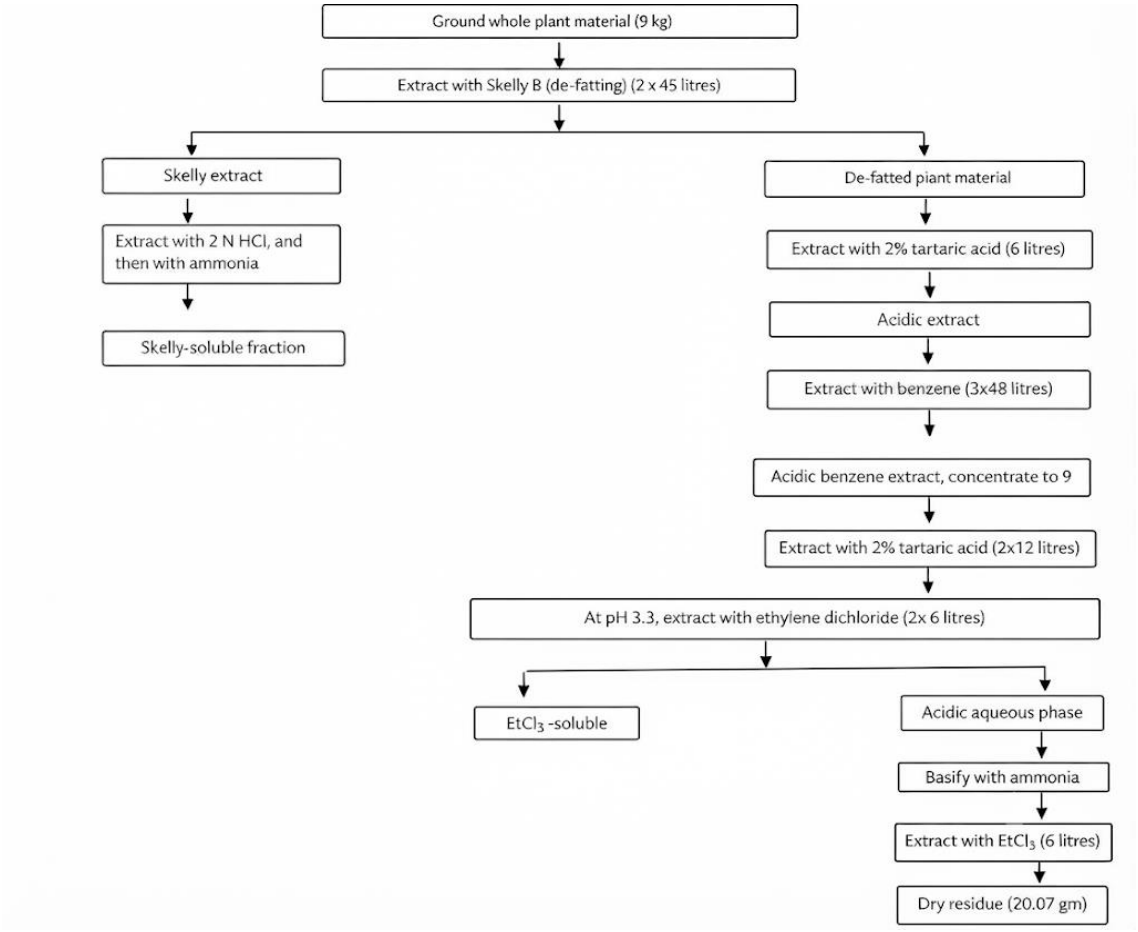
Similar procedures are re-chromatograph for the recovery of vinblastine, the remaining eluent—a 3.6 kg residue obtained from evaporated chloroform fractions-is subjected to a second, high-scale purification on 120 kg of deactivated alumina. The eluting solvents and fractions collected in this re-chromatographed are

benzene (fraction 1), benzene-chloroform 3:1 (fractions 2-15), benzene-chloroform 1:1 (fractions 16-29), benzene-chloroform 1:3 (fractions 3CM3), chloroform (fractions 44-57), and chloroform-methanol 19:1 (fractions 58-67). Vinrosidine and vincristine are separated from fractions 33–45 and 33–42 of these re-chromatographed fractions, respectively. Gradient pH extractions are used to separate these alkaloids from these column fractions.

Gradient pH Extraction

After dissolving the eluted crude fraction (10 gm) in 500 ml of benzene insoluble material is filtered out. After that, the benzene solution is extracted using steam distillation at low pressure into 500 ml of 0.1 M citric acid. The purpose of this steam distillation process is to prevent the creation of emulsions. Any insoluble material is filtered off once all of the benzene has been removed. 500 ml of benzene are used to extract the acidic solution (pH 2.75–2.85). Ammonia is then used to gradually modify the pH of the aqueous phase to 3.54, 3.9, 4.4, 4.9, 5.4, 5.9, 6.4, and 7.5. 500 ml of benzene are used to extract the aqueous solution at each pH level. In each instance, the benzene extract is evaporated to dryness after being dried over sodium sulphate. This process extracts both vinrosidine and vincristine from the acidic solution at pH values between 4.9 and 6.4.[17]

Table 2: Flowchart of Svoboda's extraction.



Isolation of Catharanthine, Vindoline and Vinblastine

Atta-ur-Rahman (1983) Published the significant following rapid procedure for the isolation of catharanthine, vindoline, and vinblastine. This method emphasizes reducing the time and steps compared to the classical Svoboda method.

The process for isolating alkaloids from *Catharanthus roseus* can be arranged into three distinct phases: extraction, purification (initial fractionation), and high-resolution separation.

Extraction Phase: 20 gm of air-dried leaves of Catharanthus roseus are meticulously pulverized with 40 lt. of ethanol. 10 litres of ethanol are used to filter and thoroughly wash the crushed material. Before being condensed to a gum, the ethanolic filtrates are mixed and evaporated in a flash evaporator and a rotary evaporator. 5 litres of 5% HCl are used to acidify the gum, and 3 litres of chloroform are used to wash it. After basification (1 litre, 33% NH solution), the ice-cold solution is extracted using 2 × 3 litres of chloroform. After being dried over anhydrous sodium sulphate, chloroform extracts are concentrated into a crude alkaloidal gum (120 grams).

Purification and Initial Fraction: 1 litre of pH 3 phosphate buffer is used to extract the alkaloids (120 grams) after they have been dissolved in 400 millilitres of chloroform. To obtain 60 grams of the alkaloidal combination, the chloroform layer is dried over anhydrous Na2SO4, filtered, and concentrated under vacuum. 240 millilitres of chloroform are used to dissolve this. Certain alkaloids precipitate out when 480 millilitres of petroleum ether are introduced. The precipitated fraction contains almost no vinblastine, vindoline, or catharanthine. After filtering off the precipitates, the filtrate is once more concentrated to a gum (36 grams). 1 litre of pH 2 phosphate buffer is used to extract the gum after it has been dissolved in 200 millilitres of ethyl acetate. A fraction rich in vindoline and catharanthine (15 grams) is obtained by separating the aqueous layer and extracting it with one litre of chloroform. After basifying the buffer layer with an ammonia solution to a pH of 10, the vinblastine-containing fraction (20 grams) is extracted using one litre of chloroform.

High Resolution Separation

Isolation of Catharanthine and Vindoline: A flash (dry) column chromatographic method is used to extract vindoline and catharanthine. This entails filling a sintered column with silica gel (70–230 mesh) and adding a ground glass bottom junction and tap. A Buchner flask is fitted with this column. Using a vacuum on the collecting Buchner flask, the material is placed into the column and the eluting solvent is dragged down the column. On top of such a column, 150 grams of silica gel (70 230 mesh) are packed with 15 grams of a fraction high in vindoline and catharanthine. Pure catharanthine (0.6 gram) is obtained by first eluting the column with 28% ethyl acetate in petroleum ether (2 litres) and then with 35% ethyl acetate in petroleum ether (5 litres). The other alkaloids are eliminated by elution with 45% ethyl acetate in two litres of petroleum ether. Pure vindoline (2.4 grams) is obtained by further elution with 55% ethyl acetate in petroleum ether (5 litres).

Isolation of Vinblastine: A flash chromatography column filled with 200 grams of alumina (neutral activity 1) is loaded with the vinblastine-containing fraction (20 grams). Seven litres of petroleum ether containing 70% ethyl acetate are used to elute the column. After being condensed to a gum (10 grams), the eluates are once more put onto the same kind of column that has been filled with 30 grams of TLC-grade silica. The faster-moving materials are eliminated by elution with 50% ethyl acetate in petroleum ether. A vinblastine-rich fraction (0.6 gram) is obtained by further elution with 0.5% ethanol in ethyl acetate (2 litres).

A preparative HPLC (column diameter: 2.2 cm; column length: 50 cm; column packing: LiChroprep 15-25 pm silica; solvent pressure: 1000-1200 lb/sq. inch; flow rate: 13 ml/minute) is used to load the vinblastine-containing fraction (0.6 gm). It is then eluted with 50% ethyl acetate in petroleum ether (2 litres), 60% ethyl acetate in petroleum ether (2 litres), and 70% ethyl acetate in petroleum ether (2 litres). Pure vinblastine (60 mg) is the material that moves the slowest during the final elution.

Extraction and Isolation of Vinblastine and Vincristine: The dried leaf material is extracted using a 9:1:1 hot ethanol, water, and acetic acid solution. After removing the solvent, a 2% hot hydrochloric acid solution is applied to the residue. In order to precipitate the non-alkaloidal components, which may be filtered out, the pH of the acidic extracts was adjusted to 4. After bringing the aqueous acidic solution's pH down to 7, benzene is used for extraction. Vinblastine and other alkaloids are obtained by evaporating the benzene layer.

Isolation of Vinblastine and Vincristine: By washing the extract with diluted alkali, the phenolic compounds are eliminated. After the extract has been cleaned, it is chromatographed on alumina and eluted in eighteen fractions, ranging from a combination of benzene and methylene chloride (65:35) to pure methylene chloride. In the tenth fraction, vinblastine was found. The fractions of vincristine are separated by further column elution.[18]

SEMISYNTHETIC PRODUCTION OF VINCA ALKALOIDS

The semi-synthetic production of vinca alkaloids is the solution for the industries to the supply problem. It primarily focuses on coupling the monomeric alkaloids catharanthine and vindoline to produce high amount anti-cancer drug vinblastine and vincristine.

Production of Vinblastine

Dry leaf powder of vinca is first extracted using 0.1M HCl for 30 minutes in an ultrasonic bath. The mixture is then centrifuged for 10 minutes at 2000 rpm. More HCl is used to re-extract the obtained sediment. Combine the two supernatants and strain. To get rid of chlorophyll and lipophilic compounds, treat this filtrate with petroleum ether. To precipitate the alkaloid, separate the acidic fraction and treat it with an alkaline solution (pH 10.5) containing 10% pamoic acid added gradually. Raise the pH to 5.0, then use decantation to extract the precipitate, which can be utilized for vinblastin semi-synthesis. Combine this precipitate with 0.1M HCl and 0.1M citric acid, then use dichloro methane and an ice bath to chill the mixture from 0 to -5°C. For three to five hours, gradually add 30% aqueous hydrogen peroxide, 10% aqueous sodium hypochlorite, and 1% sodium borohydride solution to methanol. Raise the mixture's pH to 9.5, then gradually gather and dry the organic layer.

Production of Vincristine sulphate

Diluted tartaric acid is applied to the dried, uniform ground material, then extract it using benzene. After concentrating the benzene extract, carry out the steam distillation. The residue will be excluded once the benzene is extracted as distillate. After dissolving the residue in methanol, apply a diluted tartaric acid solution

to it. Carry out the distillation. The bottom product will be treated with a diluted ammonia solution after the methanol separates as distillate. After extracting it, let the extract evaporate until it is completely dry. After dissolving the dry powder, separate the vincristine sulfate using an alumina column and elute it with benzene, benzene + chloroform, chloroform, and chloroform + methanol. After isolating vincristine and treating it with sulfuric acid, vincristin sulfate will be produced.[19]

ANALYSIS OF VINCA ALCALOIDS

High performance liquid chromatography-electrospray ionization-mass spectrometry (HPLC-ESI-MS) offers an extremely sensitive and selective way to identify the alkaloids.[20,21]

Alkaloids can be identified with excellent selectivity and sensitivity using high performance liquid chromatography-electrospray ionization-mass spectrometry (HPLC-ESI-MS). Catharanthus alkaloids have also been quickly identified using direct-injection ESI-MS.[22] The melting points of the separated compounds can also be used to verify their identity. Vinblastine and vincristine have melting points of 284–285°C and 273–281°C, respectively. Several chromatographic techniques have been used to separate and detect pure forms of vinblastine and vincristine, including:

- VLC using a silica gel column; aluminium oxide (1:1) combined with VLC using a carbon column; and purification using accelerated radial chromatography using centrifugation (chromatotron).
- Thin Layer Chromatography (TLC) techniques have been used to produce semi-quantitative procedures. Ajmalicine is found at a level of 0.0007% in a volume of 10 µL, demonstrating the increased sensitivity of TLC for alkaloid detection. Vinblastine and vindoline are not sensitive to this approach since their concentrations are both 0.05% in a volume of 10 µL, whereas vincristine is identified at 0.055% in a volume of 10 µL. Cerium Ammonium Sulphate (CAS), a chromogenic reactive that reacts with analyte to give visible colours in the TLC plate,[23] is employed chromatographically in alkaloid detection.
- HPLC is used to measure vincristine and vinblastine sulphate. For the estimation, the following solutions are ready:
  Solution 1: 0.1 percent by volume of the material under investigation. Solution 2: This solution contains 0.2 percent w/v of both vinblastine sulphate RS and vincristine sulphate RS. Solutions 3, 4, and 5 contain 0.1 percent w/v, 0.002 percent w/v, and 0.0001 percent w/v of either vincristine sulphate (if vincristine sulphate is estimated) or vinblastine sulphate (if vinblastine is estimated).
- Column: Static phase LC2 is packed. 1.0 ml/min is the flow rate. The mobile phase for vinblastine is a mixture of 70 volumes of methanol and 30 volumes of 1.5 percent w/v diethylamine (pH adjusted to 7.5 using phosphoric acid).
  The detection wavelength for vinblastine sulphate is 297 nm.
  Mobile phase: 50 volumes of methanol, 38 volumes of 1.5 percent w/v diethylamine (pH adjusted to 7.5 with phosphoric acid), and 12 volumes of acetonitrile (for vincristine sulphate). The wavelength of detection for vincristine sulphate is 262 nm.
- Vincristine Thin Layer Chromatography: Vincristine is dissolved in a 25% water in methanol solution, spotted on a Silica gel-G plate, and developed using the solvent acetonitrile:benzene (30:70). A 1% ceric ammonium sulphate solution in 85% phosphoric acid is sprayed onto the dry plates. The spot that appeared would have an Rf value of 0.39.[24]

MECHANISM OF ACTION

Vinca Alkaloids were the first group of plant derived anti-cancer drug which had clinical applications. Behind this huge prospect of the chemotherapeutic agent, the mechanism of its action should be considered as the most crucial part. Vinca alkaloids, functions, by inhibiting microtubule assembly and arresting the cells (Metaphase Arrest) in mitotic phase of cell cycle. This activity leads to a primary repression against tumour cells.

In mitotic phase of cell division occurs in four subsequent stages

1. Prophase 2. Metaphase 3. Anaphase 4. Telophase

After completing all these phase cells go through Cytokinesis, where cytoplasm divides.

Metaphase and anaphase have major involvement in the mechanism of vinca alkaloids.

1. Metaphase: This is an extremely dynamic part of cell cycle. Metaphase plays a crucial role in understanding the mechanism of vinca alkaloids. Spindle fibres rapidly assemble and dissemble in this stage, seeking out attachment sites at chromosome. To attach the spindle fibres there is a specialized structure called kinetochore, located on centromere. There are two kinetochores on each chromosome facing in opposite direction.
2. Anaphase: each sister chromatid of a metaphase chromosome is attached to kinetochore microtubule via its kinetochore. At anaphase, the kinetochore microtubules pull the kinetochores towards the opposite poles. During this stage separate degrades cohesins. After separation, each chromatid is pulled slowly towards the pole it faces.

Cytokinesis

The division of cytoplasm is known as the cytokinesis.

Mechanism of action of Vinca Alkaloids

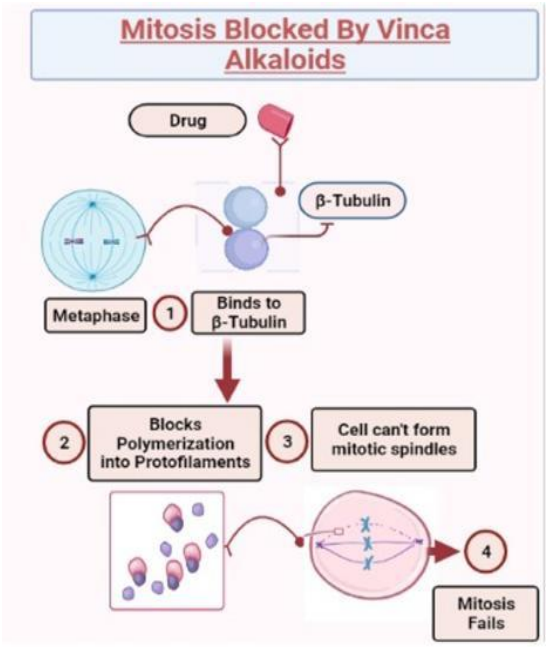


Fig. 7: Mitosis blocked by Vinca Alkaloids.

Microtubules are the target of a large group of natural product anticancer drug. Microtubules are highly dynamic assemblies of protein tubulin. These dynamics have two types of dynamics – treadmilling and dynamic instability. This dynamic is very critical in the process of chromosomal division in mitosis. Microtubule dynamics are regulated by several cellular regulator in metaphase. Moreover, many antitumour drugs like vinca alkaloids inhibit microtubule polymerization high drug concentration. Vinca alkaloids supress the dynamics of microtubules without appreciably changing the mass of microtubules. By this mechanism of repression vinca alkaloids block mitosis at the metaphase transition and leads to cell death.[25]

Cryptophycin works as a potent anticancer agent by targeting tubulin, which protein forms microtubules – essential for cell division. This binds to vinca alkaloid binding site, similar to drugs like vinblastine. This binding does not allow the tubulin from properly assembling into microtubules, leading to breakdown of and disruption of mitotic spindle.[26]

Vinca alkaloids also show anti-angiogenesis ability *in vitro*. Study shows that metronomic administration of vinblastine or vinorelbine in mice bearing tumour cells induce a persistent decrease in circulating endothelial progenitor cell (CEPs) mobilization viability. Vinca alkaloids also work through inhibiting vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) signalling pathway – this hypothesis was proposed by Markus and his colleagues. They assumed that vinblastine down regulates the protein expression of endothelial VEGRF2. Vincristine down regulates the expression of VEGF in human leukaemia T cell lines.

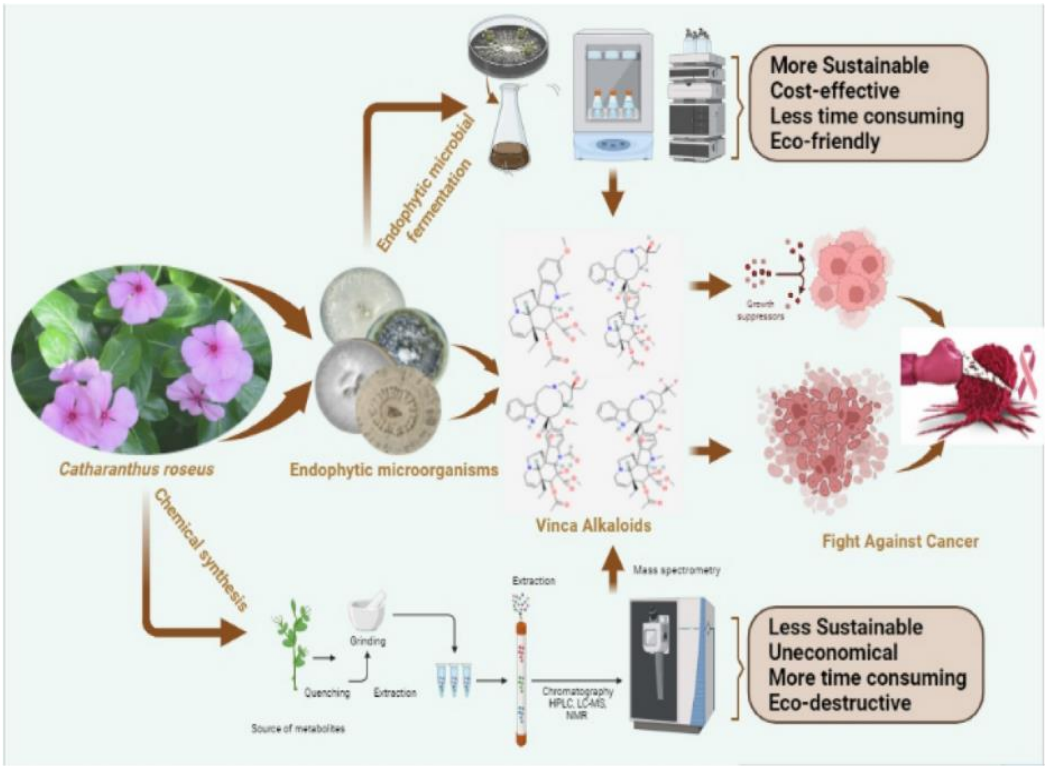


Fig. 8: Function of Vinca Alkaloids in daily life.

Chemical structure of vincristine and vinblastine

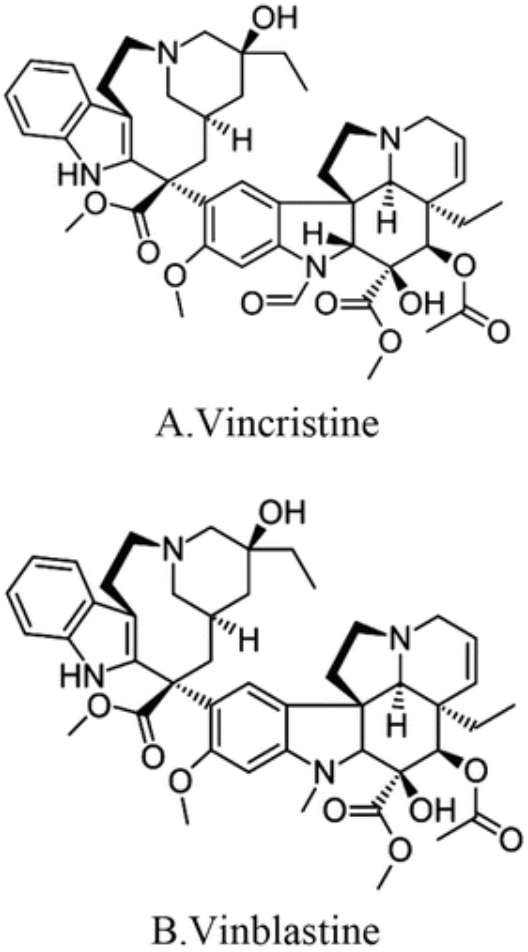


Fig. 9: Chemical structure of (A) Vincristine and (B)Vinblastine.

ABC (ATP- binding cassette) are membrane proteins that use ATP energy to pump substances out of cell. Vinca alkaloids are substrates of P-gp, so the protein can expel these drugs from cancer cells. This P-glycoprotein is encoded by mdr1 gene.[27]

Table 3: Mechanism of action of vinca alkaloids and its impact on cell.

Mechanism of action of vinca alakaloids:	Effects on the cell:
1. bind specifically to β-tubulin proteins in the cell.	prevents normal tubulin function.
2. inhibit polymerization of tubulin into microtubules.	microtubule formation is blocked
3. cause depolymerization and destabilization of existing microtubules.	loss of cytoskeletal structure
4. disrupt formation of the mitotic spindle during mitosis	chromosome can not separate properly
5. arrest cells in metaphase of the M phase	cell division stops
6. activate apoptotic signalling pathway.	leads to programmed cell death.

The scientific efforts still focus on the development of newer microtubule inhibitors, which posses' potential effect on overcoming clinical multidrug resistance to vinca alkaloids. There is huge impact of this drug in our human history and it has a remarkable mechanism. By

using its large-scale effect, we hope to utilize it in nearer future.

CHALLENGES AND CONCERNED AREA FOR THE SYNTHESIS OF VINCA ALKALOIDS

Limitations of Vinca Alkaloids

One of the first plant alkaloids to be produced for use as anti-cancer drugs in humans were vinca alkaloids, which are members of a family of cell cycle phase M-specific anti-tubulin compounds. First-generation vinca alkaloids (vincristine, vinblastine), second-generation semi-synthetic derivatives (vinorelbine, vindesine), and third-generation vinca alkaloids (vinflunine) are obtained from *Vinca rosea* or the periwinkle plant (*Catharanthus roseus*). Vinflunine has also been categorized as a second-generation agent by others.[28] The most recent vinca alkaloid and fluorinated anti-microtubule drug is called vinflunine. Transitional cell urothelial bladder cancer has been treated with the drug. Compared to the previous vinca alkaloid medicines, vinflunine is said to be more potent and to have fewer side effects. As part of multi-drug combination regimens, vinca alkaloids are typically coupled with other medicines since they enhance the anti-cancer effects. These are also known to be well tolerated with manageable adverse events. *Catharanthus roseus* has been thoroughly investigated for the production of various terpene indole alkaloids (TIAs) since the discovery of the anticancer medication vinblastine and vincristine. Alternative methods of production to traditional extraction are required because of their limited quantity in plant tissues and concurrently increasing demand. One of these options may be plant cell fermentation, however decades of study have demonstrated that some product classes have little success. This raises the question of how to maintain the innate capacity to create TIAs (metabolic competence) in cell culture. In order to produce such strains, we employed the developmental potential of mature embryos. It was discovered that two cell strains (C1 and C4) from *Catharanthus roseus* seed embryos differed in both morphology and metabolic competence. Both phytohormone elicitation and feeding with alkaloid pathway precursors caused this differential competence to become apparent. The more active strain C4 had longer mitochondria and produced bigger cell aggregates. In response to methyl jasmonate (MeJA) elicitation, these cellular characteristics were accompanied by increased alkaloid accumulation. Catharanthine levels may be significantly raised while the pathway's concomitant vindoline branch was inhibited, making bisindole alkaloids undetectable. Vincristine was detected by feeding vindoline to MeJA-induced C4 cells, but only in trace levels. These findings demonstrate that cultured cells can differ in their metabolic competence rather than becoming "de-differentiated". In addition to elicitation and precursor feeding, the cellular properties of the “biomatter” are highly relevant for the success of plant cell fermentation.

Physical Toxicity

Central nervous system toxicity

These medications can cause vision loss, seizures, and acute or subacute encephalopathy, usually in cases of overdose or delayed elimination.[29] Other less common adverse effects include parkinsonism, ataxia, visual hallucinations, tremors, unilateral or bilateral optic neuropathy, transient cortical blindness with posterior reversible encephalopathy syndrome, and syndrome of inappropriate antidiuretic hormone production.[30] The latter can cause encephalopathy and widespread convulsions and is more prevalent in individuals getting intravenous hydration. Accidental intrathecal injection has been linked to mortality, unconsciousness, and ascending myelopathy. Vincristine has been used to treat neuropathic jaw pain that does not respond to conventional painkillers. There is a theory that the trigeminal nerve, the fifth cranial nerve, is involved in this discomfort. There have also been reports in the literature of vincristine-induced vocal cord palsy, which is a possibly reversible condition that goes away when the medication is stopped. Vocal cord involvement, which manifests as hoarseness of voice, can be unilateral or bilateral, but the left side has been shown to be more frequently affected.[31] Unilateral involvement is known to result from recurrent laryngeal nerve involvement, whereas bilateral involvement is known to neurologically localize to the vagal nucleus. Vocal cord palsy has also been linked to higher dosages, preexisting hepatic dysfunction, neuropathic illness, a history of drug hypersensitivity, and co-administration of other cancer chemotherapy agents and non-chemotherapy medications like mitomycin-C, allopurinol, azathioprine, phenytoin, isoniazid, and itraconazole. Seizures are a direct consequence of severe toxicity, especially in cases of acute overdose.[32]

Bottle neck

Endophytic microbes produce valuable secondary metabolites that find use in cosmetics, food and pharmaceuticals, yet translating small-scale laboratory success into industrial production remains a persistent bottleneck, with scale-up typically yielding low output and poor performance.[33] The central obstacle to commercialization is the steep decline in metabolite production with repeated subculturing under axenic monoculture, the very approach on which nearly all efforts to date have relied. To overcome this, researchers are turning to genetic engineering and mutagenesis to enhance metabolite output, co-culture fermentation to activate silent gene clusters through microbial interaction, and process optimization of medium composition, pH, temperature, nutrient ratios, incubation time and aeration. Even so, scale-up challenges and potential product toxicity persist,[34] and the development of industrial-scale endophyte co-culture bioprocesses for sustainable biopharmaceutical manufacture remains largely unexplored, an open frontier ripe for further research and innovation.

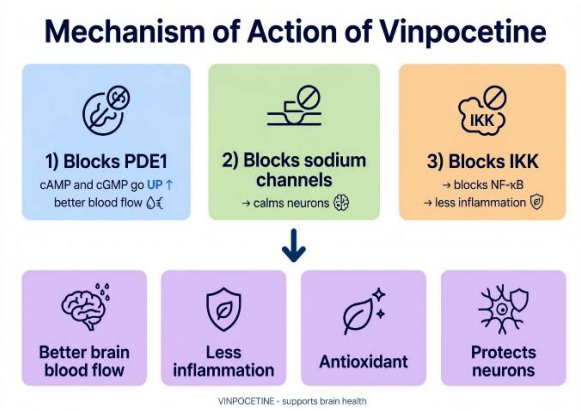
MANUFACTURING AND MARKET STUDY AND GLOBAL BUSINESS

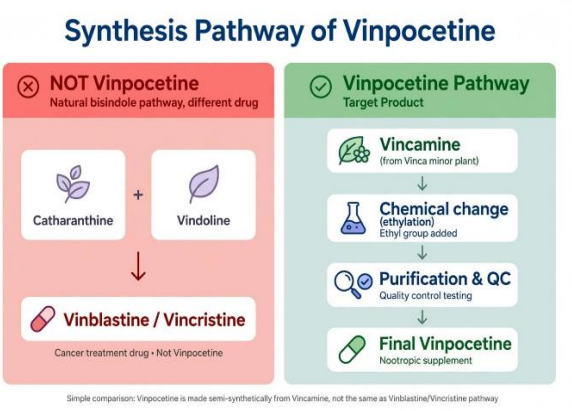
Market Analysis of Vinca Alkaloids

VINPOCETINE

Background: Vinpocetine is a semisynthetic indole alkaloid derived from the periwinkle plant, vincamine, which occurs naturally in *Vinca minor* and used as a multi-action agent in the treatment of neurological disorders like Alzheimer's and Parkinson's diseases. It is also sold as a dietary supplement for improving cognition and memory, as it has anti-inflammatory, analgesic and antioxidant effects.

Market study: Vinpocetine was originally developed and marketed by Gedeon Richter in Hungary in 1978 under the brand name Cavinton. Today, the drug is produced and distributed globally by several major pharmaceutical companies—including Merck KGaA, Sun Pharma, Northeast Pharma, and Micro Labs—alongside various dietary supplement brands, and is sold under regional names like Vinpace, Cerevas, Vinpocare, and Intelectol.[39] Its key producers operate on a massive financial scale, with its original developer Gedeon Richter reporting annual revenues of approximately €2.1 billion ($2.3 billion USD), major generic manufacturer Sun Pharmaceutical Industries maintaining a turnover of around ₹48,497 crore ($5.8 billion USD), and multinational giant Merck KGaA recording group net sales of roughly €21 billion ($23 billion USD).

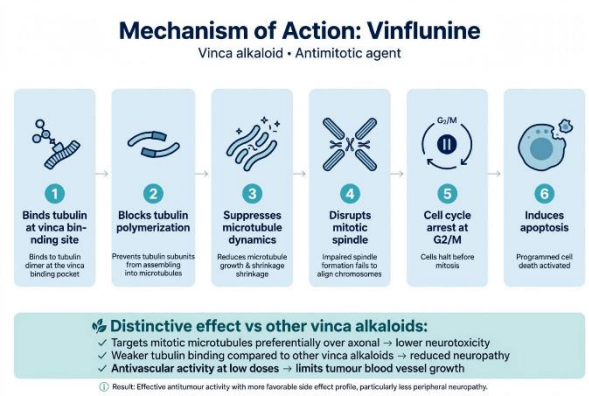


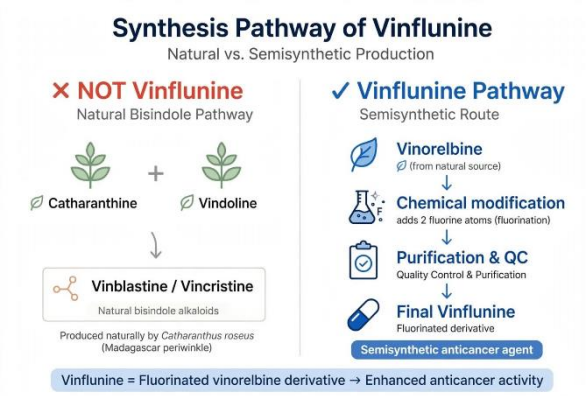


VINFLUNINE

Background: Vinflunine is a semisynthetic, difluorinated vinca alkaloid microtubule inhibitor with antineoplastic activity, administered intravenously. This phase evaluated the feasibility of a weekly oral dosing schedule in patients with advanced malignancies.

Market study: Vinflunine is primarily developed and marketed by the French multinational pharmaceutical company Laboratoires Pierre Fabre under the brand name Javlor, and is approved in regions like the European Union and Australia for treating advanced or metastatic urothelial carcinoma (bladder cancer). Financially, Laboratoires Pierre Fabre supports this production with a total group revenue of €3.2 billion (~$3.5 billion USD).



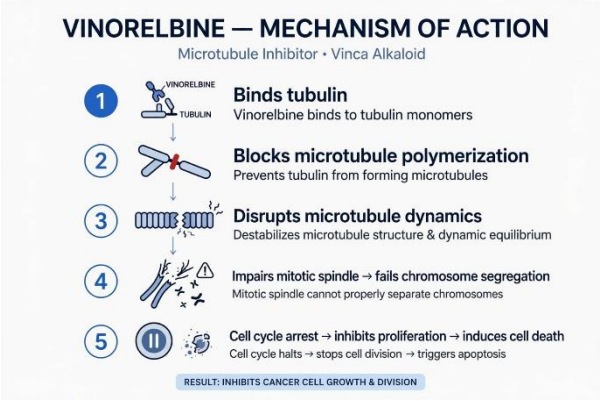


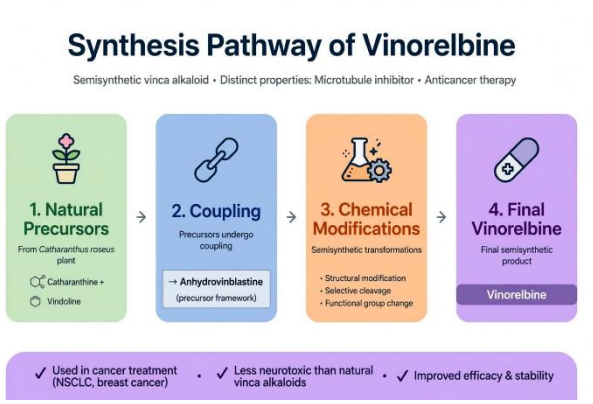
VINORELBINE

Background: Vinorelbine is a semisynthetic vinca alkaloid with antineoplastic activity used parenterally and orally for lung cancer and breast cancer. This study aimed to determine the biotransformation of VRL in humans by applying liquid chromatography-tandem mass spectrometry.

Market study: Vinorelbine, developed in the 1980s by Laboratoires Pierre Fabre, is sold under the innovator

brand Navelbine (generating ~$80M in specialized sales, backed by Pierre Fabre's €3.2B group revenue and €1.4B pharma division). Post-patent, it is widely marketed by major generic players: Teva (~$45M sales; ~$15.8B corporate revenue), Fresenius Kabi (distributed via hospital networks like Vinelbine under an >€8B parent group revenue), Viatris (~$30M sales; ~$15.4B corporate revenue), and Dr. Reddy's (~$15M sales; ~$3.2B revenue).[35]





CONCLUSION

Vinca alkaloids are one of the most important plant-derived anti-cancer drugs discovered from *Catharanthus roseus* (Madagascar periwinkle). From their accidental discovery as anti-diabetic agents to their current use as essential chemotherapy drugs, they have played a major role in the history of oncology.

This review highlights the successful journey of vinca alkaloids from a natural source to a clinically used drug. A bioactive molecule was first isolated from the plant *Catharanthus roseus*, then through extensive research, purification, and structural modification, it was developed and introduced into the market as an effective anti-cancer drug.

Historically, this plant was also used in various indigenous and traditional medicine systems. In Ayurveda and folk medicine, it was known as *Sadabahar* and was used for treating diabetes, insect stings, minor wounds, and other ailments. This traditional knowledge actually guided the initial scientific investigation which later led to the discovery of its anti-cancer properties.

This clearly proves that natural products have huge potential to act as sources of new drugs. Nature contains countless secondary metabolites, and if properly isolated and studied, they can become life-saving medicines. The story of vinca alkaloids is a perfect example of how a natural product can be transformed from a traditional medicinal plant into a modern chemotherapeutic agent, opening the door for future drug discovery from natural sources.

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