

## A Review on Vinca Alkaloids in Cancer Therapy: Mechanisms, Cultivation and Future Prospects

**Priti Bhure\*, Rajashri Wagh, Trupti Bankar, Shital Karhale, Vikram Saruk, Manoj Garad**

*Jagdamba Education Society's SND College of Pharmacy, Yeola, Maharashtra, India*

### ABSTRACT

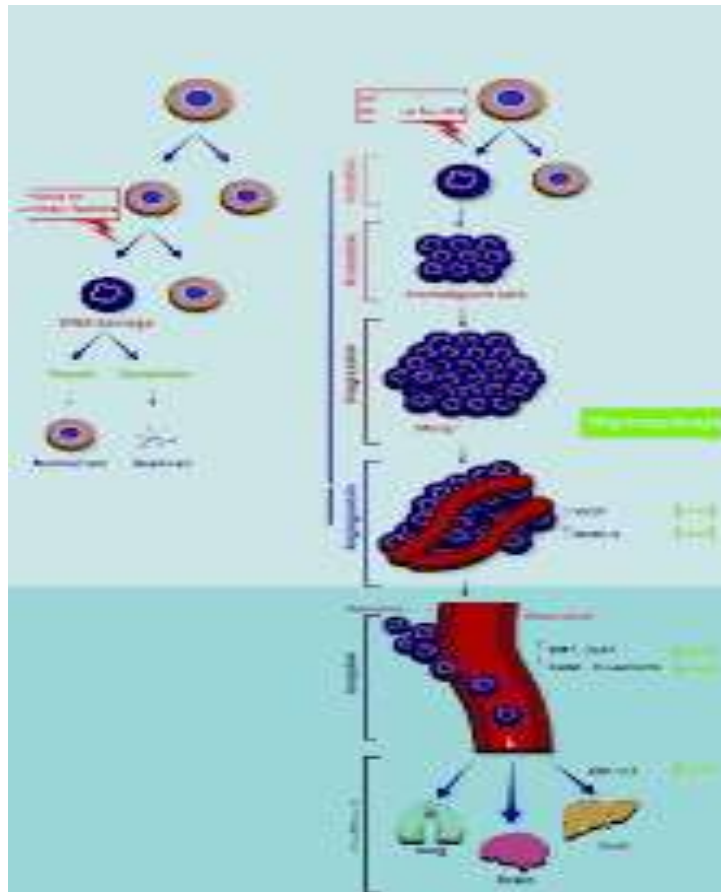
Cancer remains a leading global health burden, responsible for millions of deaths annually. Therapeutic strategies such as surgery, chemotherapy, radiation, and pharmacological agents are widely utilised. Among the chemotherapeutic agents, The Madagascar periwinkle (*Catharanthus roseus*) serves as a natural source of vinca alkaloids, a group of compounds widely recognized for their therapeutic applications. They have gained prominence due to their potent cytotoxic and hypoglycemic properties. Traditionally used for managing hypertension and diabetes, these alkaloids are now critically important in oncology. The four principal vinca alkaloids used in clinical settings include vincristine, vinblastine, vinorelbine, and vindesine. Additionally, vinflunine, a synthetic analogue, has been approved in Europe for treating advanced transitional cell carcinoma. This review presents an in-depth analysis of the pharmacological potential, extraction methods, clinical relevance, and recent advances in the therapeutic use of vinca alkaloids. By exploring both traditional uses and contemporary research findings, this article aims to support the integration of these plant-based compounds into cost-effective cancer treatment strategies.

**Keywords:** Alkaloids, Vinca, *Catharanthus*, *Colchicum*, Anticancer, Microtubule-targeting agents, Antimitotic, Apoptosis

### INTRODUCTION

How Cancer Grows? Normal Cell Cycle Diagram & Cancerous Cell Cycle

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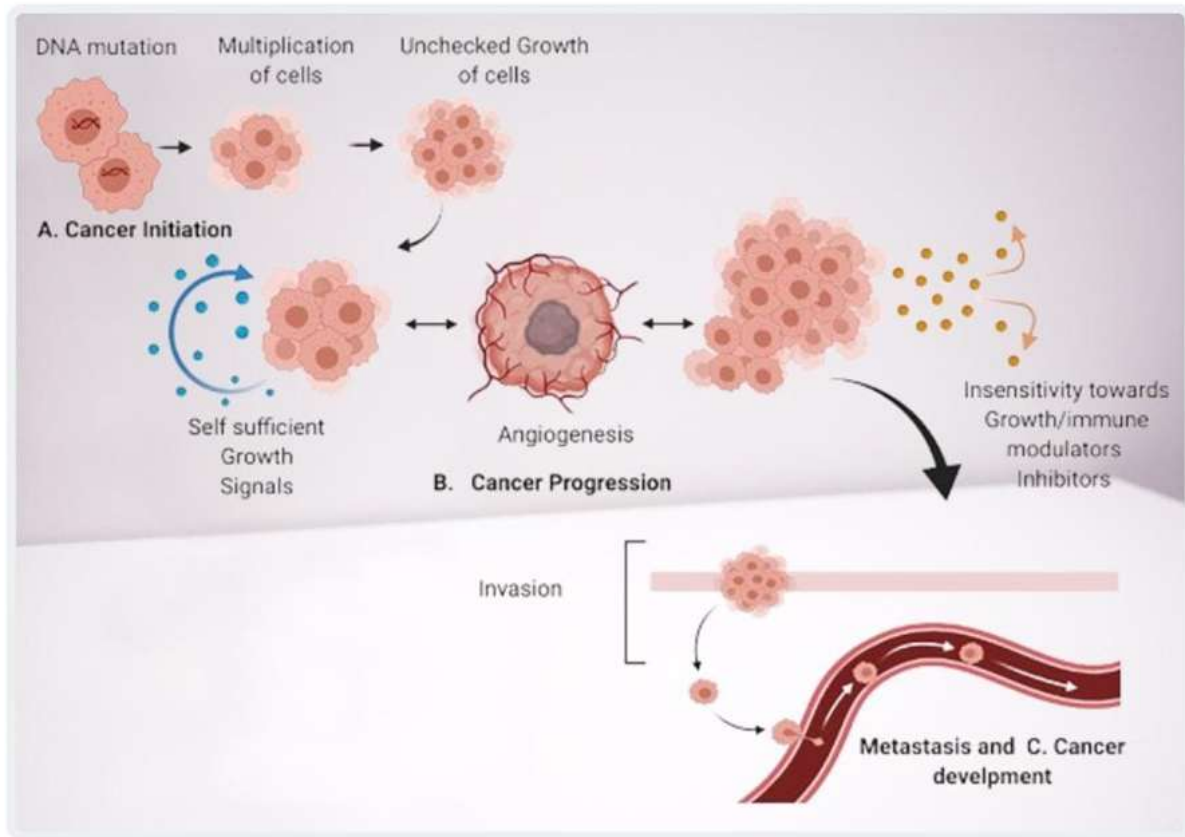


Cancer ranks among the foremost causes of death worldwide, characterised by the abnormal and uncontrolled proliferation of cells triggered by genetic and epigenetic alterations. According to global health statistics, nearly 10 million deaths in 2020 were attributed to various forms of cancer, including breast, lung, colorectal, prostate, skin, and stomach cancers. [1] Cancer cells differ from normal cells primarily in their rapid division and ability to evade natural cell death mechanisms. As these malignant cells accumulate, they form tumours, which demand a continuous supply of nutrients and oxygen. In order to maintain their rapid expansion, cancer cells trigger the development of new blood vessels, a mechanism known as angiogenesis. This not only supports tumour expansion but also facilitates metastasis, allowing cancer to spread to other parts of the body. Current therapeutic research is exploring angiogenesis inhibitors as a strategy to restrict tumour progression and improve patient outcomes. [2]

### MECHANISM OF ACTION

The therapeutic effectiveness of vinca alkaloids in cancer treatment is primarily attributed to their interaction with tubulin, a key structural protein in

microtubules. These alkaloids disrupt the microtubule network by binding to specific sites on  $\beta$ -tubulin, particularly within the region referred to as the "vinca domain." [3] This binding interferes with the dynamic equilibrium of microtubule assembly and disassembly, essential for mitotic spindle formation during cell division. [4] As a result, the treated cells experience arrest at the metaphase stage of mitosis, ultimately leading to programmed cell death or apoptosis. Interestingly, even at low concentrations, vinca alkaloids can significantly alter microtubule dynamics by reducing both their growth and shrinkage rates. This stabilises the microtubules in a dysfunctional state, halting cell proliferation. [5] Beyond their role in mitosis, vinca alkaloids also impact non-dividing cells by affecting other microtubule-associated cellular processes. This includes intracellular transport and cell signalling pathways. Moreover, these compounds have shown potential in inhibiting tumour angiogenesis, thereby limiting the blood supply essential for tumour survival and growth. Such effects further enhance their anti-cancer potential, especially when used in combination with other chemotherapeutic agents or anti-angiogenic therapies. [6]



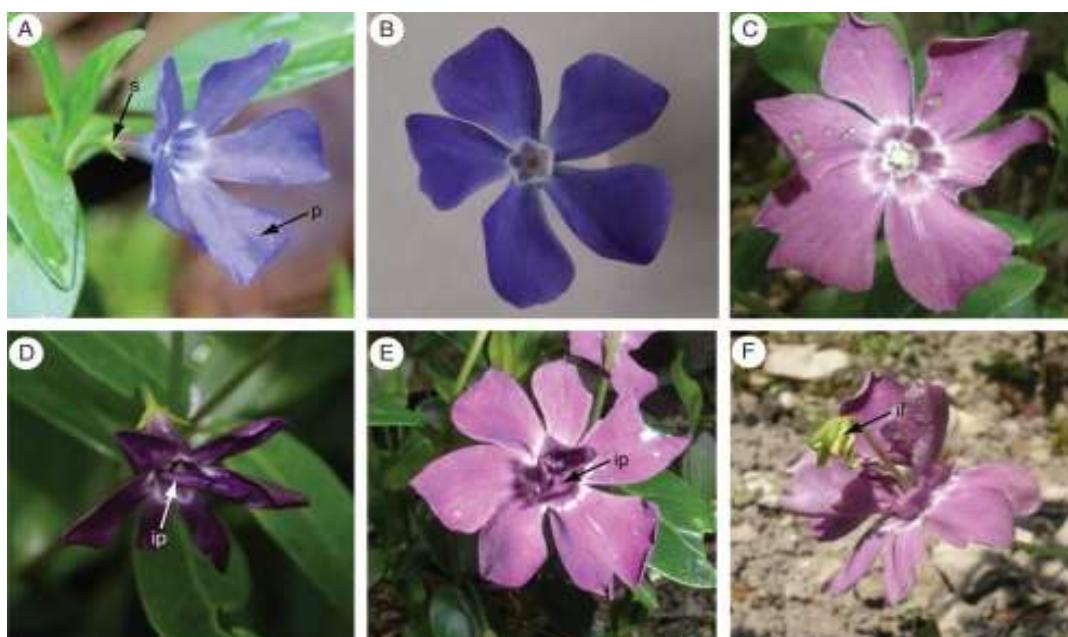
**Fig.1 Cancer growth [7]**

### Plant species, plant part content, history of development of vinca alkaloid, and activity evidence

Alkaloids, a type of phytochemical, have shown promise as anticancer drugs. Alkaloids are an extremely diverse collection of chemicals, with around 3000 different alkaloids identified from plants, fungi, and mammals. Although the term implies alkali, some do not have alkaline qualities. Many alkaloids with toxic properties also have physiological effects, making them useful as medications. Vinca alkaloids are the oldest plant alkaloid group that has been utilised to treat cancer. [8]

### History

It has a long history of use in pharmacology, particularly in relation to its phytochemical makeup. Alkaloids, essential oils, phenols, sugars, saponins, and flavonoids are among the many phytochemicals found in *C. roseus*; nevertheless, alkaloids are the most abundant phytochemicals with therapeutic potential. It's interesting to note that vinblastine (VLB) and vincristine (VCR), two major, pricy, medicinally sound anti-cancer bis-indole alkaloids that exhibit mitotic poisoning activity, are only found in *C. roseus*. [9][10]



**Fig 2. Floral morphology variations in *Vinca minor*.**

(A, B) Wild-type flowers displaying the typical floral structure with clearly visible sepals (s) and petals (p). (C–F) Floral phenotypes observed in the *florepleno* variety. (D, E) Show the presence of an additional inner whorl of petals (ip), characteristic of double-flowered forms. (F) A particularly notable case where an internal flower (if) arises from within the primary floral structure, indicating an altered floral meristem identity. Images (C, E, F) were captured following transplantation into a cultivated garden environment.

Abbreviations: s - sepal, p. petal, ip - extra (inner) petals, f - stalked flower within flower.

*Vinca* alkaloids have been traditionally used for managing conditions such as diabetes and

hypertension, and they have also demonstrated efficacy as antimicrobial agents. However, their most significant medical application lies in oncology. Currently, four major *vinca* alkaloids are utilized in clinical settings: vinblastine (VBL), vincristine (VCR), vinorelbine (VRL), and vindesine (VDS). Among these, vincristine, vinblastine, and vinorelbine are approved for therapeutic use in the United States. Additionally, vinflunine, a semi-synthetic derivative, received regulatory approval in Europe in 2008 for its anticancer properties. [11]

#### Individual alkaloid content chart with concentration

| Alkaloids         | concentration |
|-------------------|---------------|
| Vincristine (VCR) | 0.1%          |
| Vinblastine (VBL) | 0.2%          |
| Vinorelbine (VRL) | 0.05%         |
| Vindesine (VDS)   | 0.05%         |
| Vinflunine        | 0%            |

#### Biological Source

*Vinca* refers to the whole dried plant of *Catharanthus roseus* Linn., a species classified under the Apocynaceae family. [13] [14]

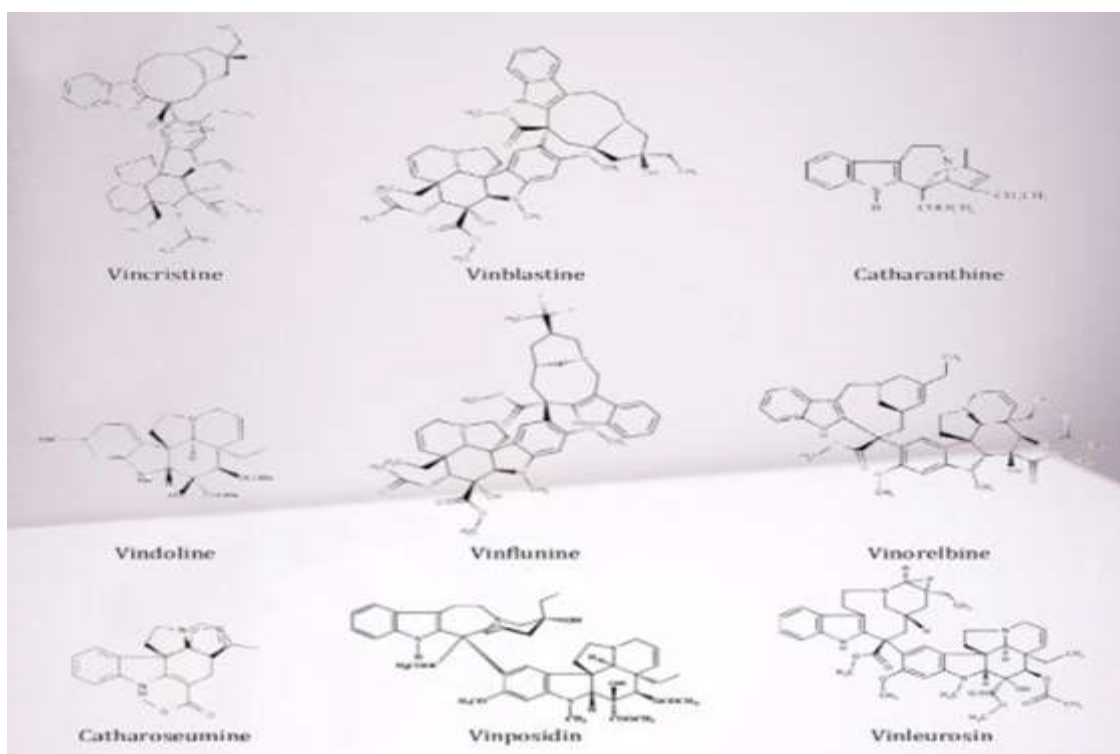
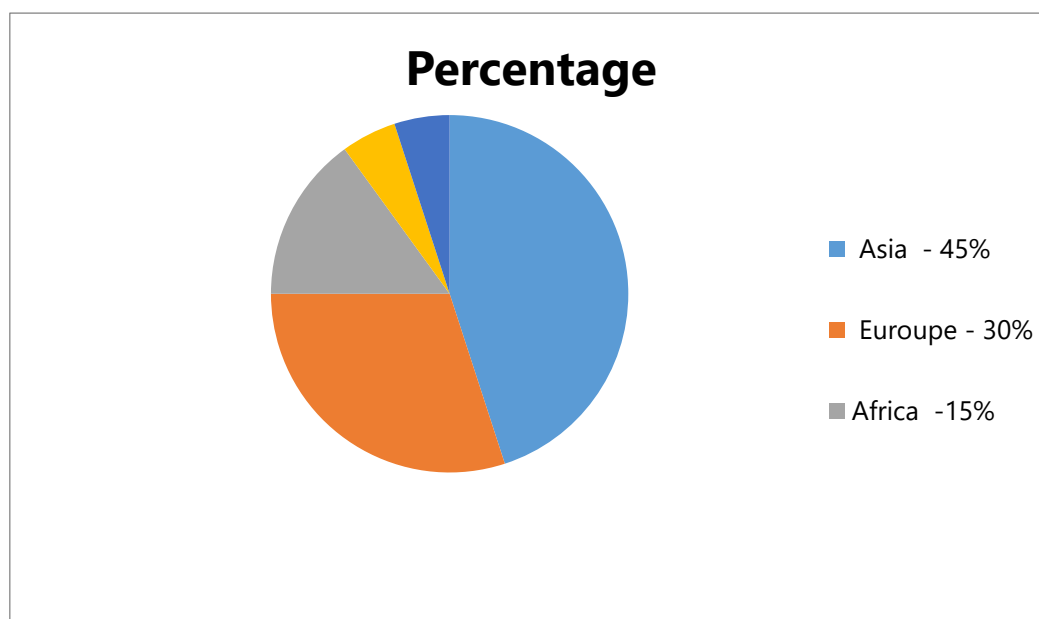


Fig.3 Structure of chemicals present in Vinca. [15]

### Geographical Source Chart



### Cultivation and Collection

*Catharanthus roseus* is a perennial plant known for retaining its glossy foliage even during winter. It adapts well to a range of soil types, including sandy, loamy, and even heavy clay soils. It thrives in soils of varying pH—acidic, neutral, or alkaline—and can be grown under diverse light conditions, such as full shade, partial shade, or direct sunlight. The plant is

tolerant of both dry and moist environments and shows resilience to drought conditions. Propagation can be done either through direct seed sowing or via nursery-raised seedlings. Among these methods, nursery sowing is considered more cost-effective. Fresh seeds are typically sown in nurseries during February or March. After about two months, the seedlings reach a height of 5–8 cm and are then transplanted into fields with a spacing of 45 cm × 30

cm. To ensure optimal growth, timely fertilization and weeding are essential. Harvesting begins approximately nine months after planting. Leaves are removed manually, and for full plant collection, stems are cut about 10 cm above the soil surface. The harvested parts—leaves, seeds, and stems—are separated and dried. Roots are extracted by digging, followed by washing, shade drying, and packing for storage or further processing. [18]

### **Vincristine and vinblastine**

Vinca alkaloids are plant-derived secondary metabolites with significant therapeutic applications (Moudi et al., 2013). Among them, vincristine (VCR) and vinblastine (VBL) were among the first compounds identified to exert anti-cancer effects by disrupting microtubule dynamics. The ability of these agents to inhibit tubulin polymerization was first reported in 1965. They function by rapidly and reversibly binding to the  $\beta$ -subunit of tubulin at a specific site known as the Vinca binding domain, thereby halting the cell cycle during metaphase. Clinically, vincristine is commonly administered in combination regimens for the treatment of acute lymphoblastic leukemia and Hodgkin's lymphoma. [19] [20]

### **Recently synthetic Vinflunine**

Vinflunine is a next-generation, synthetic derivative of the vinca alkaloid family, designed for improved efficacy and safety in cancer treatment. It has been primarily investigated for its potential in managing advanced or metastatic transitional cell carcinoma of the urothelial tract (TCCU), particularly in patients unresponsive to platinum-based chemotherapy. [21] A pivotal Phase III clinical trial assessed vinflunine in combination with best supportive care (BSC) versus BSC alone. [22] The study revealed a notable survival advantage in the vinflunine group, with a median overall survival of 6.9 months compared to 4.6 months in the control group [23]. Statistical analysis confirmed vinflunine's independent association with improved patient survival, highlighting its role as a viable second-line treatment option [24]. Real-world observational studies further support its clinical benefits. In a retrospective analysis involving patients with metastatic TCCU, vinflunine achieved a disease control rate of over 80%, with a median progression-

free survival of approximately 3.5 months. The treatment was generally well-tolerated, with most adverse effects being mild to moderate in severity. Noteworthy grade 3–4 toxicities included anaemia and febrile neutropenia, though these were relatively uncommon. [25] Additional research has validated vinflunine's safety and effectiveness across diverse patient populations, including those with poor prognostic factors. Side effects such as fatigue, abdominal discomfort, and constipation were manageable, reinforcing its potential for broader clinical application. [26] These findings position vinflunine as a promising therapeutic agent, especially for patients requiring alternatives after first-line treatments have failed. [27]

### **Real-World Observational Studies**

In a retrospective analysis of 27 patients diagnosed with metastatic or recurrent transitional cell carcinoma of the urethra (TCCU) and treated with vinflunine, a disease control rate of 81.4% was observed [28]. The study reported a median progression-free survival (PFS) of 3.45 months and a median overall survival (OS) of 3.22 months. Importantly, patients who responded to the treatment exhibited a longer median OS of 7.24 months. Vinflunine was generally well-tolerated, with only mild side effects in most cases. However, grade 3–4 adverse events were documented, including anemia in 11.1% of patients and febrile neutropenia in 4% [29].

### **Efficacy in Specific Populations**

A study focusing on patients with metastatic/recurrent TCCU found that vinflunine is effective even in populations with unfavourable risk factors. The study observed that clinicians can administer vinflunine confidently to unselected patients, with fatigue, constipation, and abdominal pain being the most frequent non-hematologic side effects. [30]

### **Comparative Efficacy**

A long-term survival analysis of a Phase III trial reported a median OS of 6.9 months for the vinflunine plus BSC group compared to 4.6 months for BSC alone. This study supports the use of vinflunine as a valuable second-line treatment option for advanced TCCU after failure of platinum-based regimens. [31]

## Common Extraction Methods for Vinca Alkaloids

Various techniques have been reported for the extraction and identification of vinca alkaloids; however, methanol-based extraction is the most widely adopted method compared to aqueous extraction. Several studies have favored methanolic extracts for better efficiency and yield (Gupta et al., 2005; Verma et al., 2007; Paul et al., 2022), whereas water extracts have shown comparatively lower efficacy (Abdul-Rahim et al., 2018) [32]. For detection and quantification, advanced chromatographic techniques are predominantly employed. High-performance liquid chromatography (HPLC) remains one of the most commonly used methods (Verma et al., 2007; Abdul-Rahim et al., 2018; Zafari et al., 2020), along with liquid chromatography–mass spectrometry (LC–MS), which offers enhanced sensitivity and specificity for alkaloid profiling (Jin et al., 2021; Paul et al., 2022) [33].

## Mechanism of Action of Vinca Alkaloids

The cytotoxic activity of vinca alkaloids primarily arises from their ability to bind tubulin, thereby disrupting microtubule dynamics—especially those critical for the formation of the mitotic spindle. This interference results in the arrest of cell division at metaphase [34]. In addition to their mitotic effects, vinca alkaloids exhibit several other biochemical actions, some of which are independent of their interaction with microtubules [35]. However, many of these non-microtubule-related effects are observed only at concentrations that exceed clinically relevant levels. Notably, vinca alkaloids impact both cancerous and healthy cells during non-mitotic phases of the cell cycle, as microtubules are essential for various interphase cellular functions [36]. These alkaloids interact with tubulin at specific binding domains distinct from those of taxanes, colchicine, podophyllotoxin, and GTP. The binding process is rapid and reversible [37]. Research indicates that each tubulin dimer has two high-affinity binding sites for vinca alkaloids, and approximately 16–17 such sites are located at the ends of each microtubule [38]. At low drug concentrations, vinca alkaloids do not significantly reduce microtubule mass but rather suppress dynamic instability by decreasing the rates of both polymerization and depolymerization at the

microtubule plus-end. This creates a “kinetic cap,” thereby impairing microtubule functionality [39]. The disruption of microtubule dynamics—especially at spindle extremities—leads to mitotic arrest even at sub-cytotoxic concentrations [40]. Furthermore, vinca alkaloids exhibit anti-angiogenic effects. For instance, vinblastine (VBL) at picomolar concentrations (0.1–1.0 pmol/L) has been shown to inhibit endothelial cell proliferation, migration, and fibronectin-mediated adhesion—key steps in angiogenesis. Interestingly, these concentrations had minimal effects on fibroblasts and lymphoid malignancies. The combination of low-dose VBL with anti-VEGF antibodies has demonstrated enhanced antitumor efficacy, particularly in tumors resistant to direct cytotoxic action. Overall, vinca alkaloids, such as vincristine (VCR), suppress cell division by binding to tubulin, destabilizing microtubules, and inducing mitotic arrest followed by apoptotic cell death. [41] [42]

## USES

1. Combination chemotherapy regimens for medical medications have frequently used vinca alkaloids. They work differently from medications that cross-react with deoxyribonucleic acid (DNA) and are not cross-resistant [43]
2. Along with Hodgkin and non-Hodgkin lymphomas, VBL has been used to treat testicular cancer. Breast cancer and germ-cell tumours are also treated with it. Antidiuretic hormone secretion is also rarely associated with it [44]
3. VBL and VRL are equivalent. It exhibits a potent anticancer effect in breast cancer patients and can affect osteosarcoma cells. Moreover, VRL reduces the stability of lipid bilayer membranes. [45]
4. In the US, VRL is now approved for use as the initial line of treatment for patients with advanced lung cancer [46]
5. Loss of hair and allergic reaction. Acute leukaemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumour, Hodgkin's disease, and several lymphomas can all be treated with VCR. Numerous non-malignant hematologic disorders, such as hemolytic uremic syndrome, refractory autoimmune thrombocytopenia, and thrombotic thrombocytopenia purpura, have also been reported to be treated by VCR. [47]

## SIDE EFFECTS

1. Constipation, nausea, vomiting, dyspnea, wheezing, fever, chest or tumour discomfort, and white blood cell poisoning are among the side symptoms associated with VBL [48]
2. Anaemia, constipation, diarrhoea, nausea, tingling or numbness in the hands and feet, fatigue (sometimes referred to as peripheral neuropathy), bleeding or bruising, and inflammation at the injection site are among the side effects of VRL. Less often, allergies and hair loss have negative effects [49]
3. The most common side effects of VCR include nervous system, constipation, peripheral neuropathy, and suppression of bone marrow function. [50]

## CONCLUSION

Vinca alkaloids continue to serve as a cornerstone in the development of anti-cancer therapies. Their unique ability to target microtubules and disrupt mitotic activity has made them valuable components in combination chemotherapy regimens. Unlike many conventional drugs, vinca alkaloids are not cross-resistant with DNA-alkylating agents, which enhances their utility across a wide spectrum of malignancies. In addition to their cytotoxic effects, these compounds exhibit therapeutic potential in managing various non-malignant conditions, such as autoimmune and hematologic disorders. Among the clinically significant vinca alkaloids—vincristine, vinblastine, vinorelbine, and vindesine—each demonstrates distinct efficacy profiles against specific cancer types. Vinflunine, a synthetic analogue, has expanded treatment possibilities, especially in refractory urothelial cancers. Its inclusion in second-line treatment regimens reflects ongoing progress in optimising cancer therapy. Overall, continued research into the mechanisms, synthesis, and clinical applications of vinca alkaloids is essential for maximising their therapeutic potential. These compounds not only exemplify the power of plant-derived molecules in oncology but also underscore the importance of innovation in developing cost-effective, targeted.

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