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VINCA ROSEA IN ANTICANCER ACTIVITY AND ITS FUTURE OUTCOMES

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ABSTRACT

A subclass of medications known as vinca alkaloids is derived from the Madagascar periwinkle plant. They are derived organically from Catharanthus roseus G. Don, the pink periwinkle plant, and exhibit both cytotoxic and hypoglycemic properties. They have been employed as disinfectants, diabetic treatments, and high blood pressure treatments. The vinca alkaloids' ability to combat cancer makes them significant as well. In clinical application, vinblastine (VBL), vinorelbine (VRL), vincristine (VCR), and vindesine (VDS) are the four main vinca alkaloids. The United States has approved the usage of VCR, VBL, and VRL. Ten million people die from cancer each year, making it one of the most common illnesses in the world. Plant-based medications have emerged as viable possibilities for preventive chemotherapy in both affluent and underdeveloped countries. Alkaloids, among other

KEYWORDS: Vinca, alkaloids, Catharanthus, anti-cancer, microtubule targeting agents, apoptosis.

INTRODUCTION

The Madagascar periwinkle plant yields a subclass of medications called vinca alkaloids.[1] They come from the pink periwinkle plant Catharanthus roseus, which is naturally harvested. A perennial species of flowering plant in the family Apocynaceae, Catharanthus roseus is also known as bright eye, cape periwinkle, graveyard periwinkle, and rose periwinkle.[2] Although it is indigenous to and endemic to Madagascar, it is grown elsewhere as a decorative and therapeutic plant. California's southern coast and desert ranges are home to the herb Catharanthus roseus, which has pink flowers and oval-shaped leaves. It is an evergreen shrub that was initially discovered in Madagascar.[3] Today, this plant is widespread throughout many tropical and subtropical regions of the world. It is cultivated both as a medicinal plant and mostly as a decorative plant in gardens, parks, and backyards because of its colorful blossoms.[4] It is a woody, deciduous herb with upright branches. The leaves are oppositely paired and oval to oblong in shape. They are glossy green, hairless, 2.5–9 cm long, 1–3.5 cm wide, with a pale midrib and a short leaf stalk.[5] The blooms have a basal tube that is 2.5–3 cm long, a flower that is 2–5 cm in diameter, and five lobes that resemble petals. They range in color from white to dark pink with a darker red center. The fruit consists of two follicles that are 3 mm wide and 2-4 cm long. When used medicinally, these chemicals are monitored for their hypoglycemic activity, which is less significant than their cytotoxic consequences.[6] They've been employed as disinfectants, diabetes, high blood pressure, and other conditions. The vinca alkaloids are essential for fighting cancer. In clinical settings, there are four main vinca alkaloids. Vindesine, Vinblastine, Vincristine, and Vinorelbine. Additionally, a brand-new synthetic vinca alkaloid called Vinflunine was introduced in 2008 and has now received approval for medical use in Europe.[7]

CANCER

The term "cancer" refers to a group of intricate illnesses brought on by stimuli that alter genetic material, causing unchecked cell division and the emergence of aberrant cells that are capable of attacking nearby or distant cells.[8] Despite the fact that genetic changes in normal tissues can sometimes cause benign and premalignant tumors, there are signs that serious health difficulties brought on by cancer, particularly those without an early diagnosis, are highly related to cancerous or malignant tumors. In 2020, 19.3 million individuals were estimated to be affected, and 10 million more people died from this sickness than originally thought.[9] Additionally, it is anticipated that by 2040, the global health challenge brought on by cancer will rise by 47%. Almost each tissue or organ in the body has the potential to develop cancer. However, the most common forms of this pathology reported globally in 2020 were breast (2.26 million cases), lung (2.21 million cases), prostrate (1.41 million cases), skin (1.19 million cases), and colon (1.14 million cases).[10] If the tumor starts to grow (metastasize) throughout the body, the cancer is highly severe. Cancer comes in a variety of forms. The location of the tumor or the site of its initial growth within the

body determines its nomenclature. Colon, lung, breast, and prostate cancer are the most prevalent types of the disease.

Vinca alkaloids, which are anticarcinogenic substances utilized in numerous chemotherapy regimens, work by attaching to intracellular tubulin. By stopping mitosis, the alkaloids prevent cell division. They also prevent the creation of purines and RNA by causing the death of quickly dividing cells.[11]

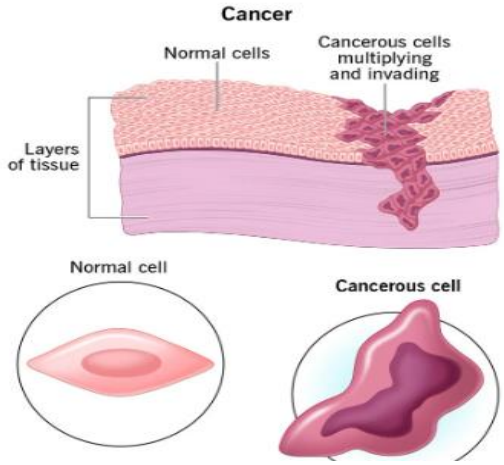

Fig. 1: Diagram of cinereous cell.

VINCA ROSEA

Around us, there are numerous naturally growing plants that can be utilized as medicines. One of those is Catharantus roseus, which is native to tropical regions worldwide.[12] Originally from Madagascar, the perennial plant Catharanthus roseus Linn is primarily found in southern Asia and tropical nations. Catharanthus roseus L. is known by a variety of common names, including vinca rosea, rose periwinkle myrtle, pink periwinkle, graveyard plant, sparkling eyes, and rose periwinkle.[13] It has diverse shades of pink, purple, and white and is used as an ornamental as well as medicinal plant. In Malaysia, the name is referred to as Kemunting Cina. The vinca alkaloids are the first class of plant alkaloids to be employed in the treatment of cancer. Over 70 distinct indole alkaloids can be found in vinca rosea stems, which also yield a milky sap.[14] Two of them, vinblastine as well as vincristine, are plant-based anti-neoplastic substances. Vinblastine is used to treat juvenile leukemia, whereas vincristine is utilized as a chemotherapy regimen for Hodgkin's lymphoma. Vinca alkaloid's primary negative effects include peripheral neuropathy, hair loss, hyponatremia, and constipation, which hinder the metaphase of cellular mitosis. They are mostly used to treat conditions like hypertension, diabetes, blood cancer, malaria, non-small-cell lung cancer, Hodgkin's lymphoma, and to enhance memory.[15] Additionally, it exhibits antibacterial, antioxidant, anti-diarrheal, hypolipidemic, and wound healing properties.

Fig. 2: Vinca Rosea Plant.

The vinca's botanical name, Cartharantus roseus, was established by the Scottish botanist George Don after much discussion and controversy about the plant's classification. Vinca rosea, the first member of his genus, was given the name Carl von Linneanus in 1759 by a Swedish botanist.[16] The genus name Lochnera was suggested by German botanist Heinrich Gottlieb Ludwig Reichenbach in 1828. In 1838, Stephan Ladislaus Endlicher, an Austrian botanist, changed the name of the plant to Lochnera rosea. William Stearn established that the Madagascan periwinkle's official name is Catharanthus roseus.

DESCRIPTION

Periwinkles are a fairly widespread plant that may be found in India.[17] It is a member of the Apocynacea family and has the botanical name Catharanthus roseus. It is a shrub that can reach a height of 1-3 feet and has smooth, glossy, dark green leaves as well as flowers all year long. The periwinkle flower comes in a variety of hues, including blue, purple, violet, pink, and white.[18] These plants are indigenous to China, India, Europe, and North America. Although the plant's entire body has therapeutic value, alkaloids are primarily found in the roots and bark.

CHEMICAL CONSTITUENTS

Vinca alkaloids have a significant role in the creation of novel anticancer medicines since they contain the structural elements indole, pyrrole, and carbazole. The most effective cancer medicines in the majority of cancer treatment classes are vinca alkaloids, which are utilized as a second-line therapy for cell carcinoma. Several phytocompounds of pharmacological significance, including carbohydrates, flavonoids, tannins, saponins, glycosides, terpenes, proteins, phenols, and alkaloids, are present in Catharanthus roseus. 400 alkaloids are found in the plant, and they are the part of the plant that have the greatest potential for activity when it comes to pharmacological effects, flavor and fragrance, ingredients, food additives, insecticides, and agrochemicals.[19] Alkaloids found in the plant's aerial parts include vindesine, vindeline tabersonine, vinblastine, vincristine, and antineoplastidemeric, while those found in the plant's basal or root portions include raubasin, reserpine, catharanthine, vinceine, vincamine, and ajmalicine. C. roseus is abundant in alkaloids,

tannins, coumarin, quinine, carbohydrates, flavonoids, triterpenoids, and phenolic chemicals. Alkaloid and carbohydrate content in leaves is high. Tannins, triterpenoids, and alkaloids found in plant flowers are what give them their ability to cure diabetic wounds.[20] Terpenes or terpenoids, also known as indole alkaloids, have been found to be effective anti-malarial, anti-inflammatory, and anti-bacterial agents in several pharmaceutical studies.

VINBLASTINE

Major naturally occurring active chemicals include vinblastine (VLB). The alkaloid vinblastine sulfate is derived from Vinca rosea Linn., a popular blooming plant also known as periwinkle. Drugs that disrupt microtubules, such as vinblastine, colcemid, and nocodazole, have been found to act in two different ways.[21] Vinblastine side effects include thinning or brittle hair and the potential for sunburn on exposed skin areas. Nausea and vomiting, which often last less than 24 hours, as well as stomach pain, constipation, diarrhea, jaw pain, headaches, and other aches are also possible.[22]

VINCRISTINE

A vinca alkaloid from the Catharanthus roseus (Madagascar periwinkle), originally Vinca rosea, and therefore its name, is vincristine (brand name, Oncovin), also known as leurocristine and frequently abbreviated "VCR". It is a mitotic inhibitor and is employed in chemotherapy for cancer. Vindoline and catharanthine, two indole alkaloids, merge to form vincristine in the vinca plant.[23] The structural protein called tubulin polymerizes to form microtubules. Microtubules are a structural component found in the cytoskeleton and mitotic spindle of cells. Vincristine attaches to tubulin dimers and prevents the construction of microtubule structures. Mitosis is stopped in metaphase by microtubule disruption. Therefore, the intestinal epithelium, bone marrow, and all rapidly dividing cell types, including cancer cells, are all impacted by vinca alkaloids. A vinca alkaloid from the Catharanthus roseus (Madagascar periwinkle), originally Vinca rosea, and therefore its name, is vincristine (brand name, Oncovin), also known as leurocristine and frequently abbreviated "VCR". It is a mitotic inhibitor and is employed in chemotherapy for cancer. Vindoline and catharanthine, two indole alkaloids, merge to form vincristine in the vinca plant.[24] The structural protein called tubulin polymerizes to form microtubules. Microtubules are a structural component found in the cytoskeleton and mitotic spindle of cells. Vincristine attaches to tubulin dimers and prevents the construction of microtubule structures.[25]

VINORELBINE

The first vinca alkaloid to conform to 5'NOR is vinorelbine. The rosy periwinkle, Catharanthus roseus, which contains the alkaloids, is used as a source for semi-synthesis. Under the trade name Navelbine, it is advertised in India by Abbott Healthcare. Vinorelbine's anticancer activity is assumed to be principally caused by its interaction with tubulin, which prevents mitosis at metaphase. Vinorelbine interacts to the mitotic spindle's microtubular proteins, causing the microtubule to crystallize and causing mitotic arrest or cell death.[26] Vinorelbine, like other vinca alkaloids, may impair the metabolism of amino acids, cyclic AMP, glutathione, calmodulin-dependent Ca2+-transport ATPase, cellular respiration, nucleic acid synthesis, and lipids.

VINFLUNINE

A semi-synthetic vinca alkaloid called vinflunine is now being evaluated clinically. Because it is less neurotoxic than vinorelbine and exhibits superior antitumor activity (preclinical) in comparison to other vinca alkaloids, vinflunine is proving to be an effective anticancer drug.[27] Although vindesine and vinflunine are promising anticancer medications utilized in medicine, there has not been much research on related drug delivery systems.[27]

VINDESINE

Vinca alkaloid vindesine, derived from vinblastine, is used to treat a range of malignancies, acute lymphocytic leukemia being the most common. It functions by reducing tubulin's ability to facilitate mitosis, which keeps cells from going through metaphase.[28] Children's chronic lymphocytic leukemia that is resistant to vincristine and non-small cell lung cancer are treated with vindesine. Cells are unable to enter metaphase mitosis when vindesine present. In vitro studies show that, at dosages meant to prevent 10–15% of cells from going through mitosis, it is roughly ten times more effective than vinblastine and three times more effective than vincristine. Tested dosages of vindesine and vincristine that prevent 40–50% of cells from going through mitosis are almost identical. Vinblastine creates large numbers of post-metaphase cells, while vindesine produces very few. When used as a component of a multi-agent treatment strategy for patients who relapsed after receiving vincristine, vindesine has showed potential.[29]

VINCAMINE

Vinca minor (lesser periwinkle) leaf is the source of the monoterpenoid indole alkaloid known as vincamine.[30] It makes up between 25 and 65 percent of Vinca minor's indole alkaloids. Cerebrovascular illnesses and impairments are frequently prevented and treated with the alkaloid. Although it has pharmacological effects on the cardiovascular and central nervous systems, its main effect is on the brain vessels.[31] It's frequently used to treat circulatory problems, cerebral circulation illnesses, support brain metabolism and increased oxygen supply, strengthen prophylaxis, improve memory and cognitive function, prevent brain cell aging, psychological productivity, improve immune function, treat diarrhea, throat ailments, vaginal infections, tonsillitis, sore throats, toothaches, dropsy, diuretics, and blood-purifying and wound-healing conditions.

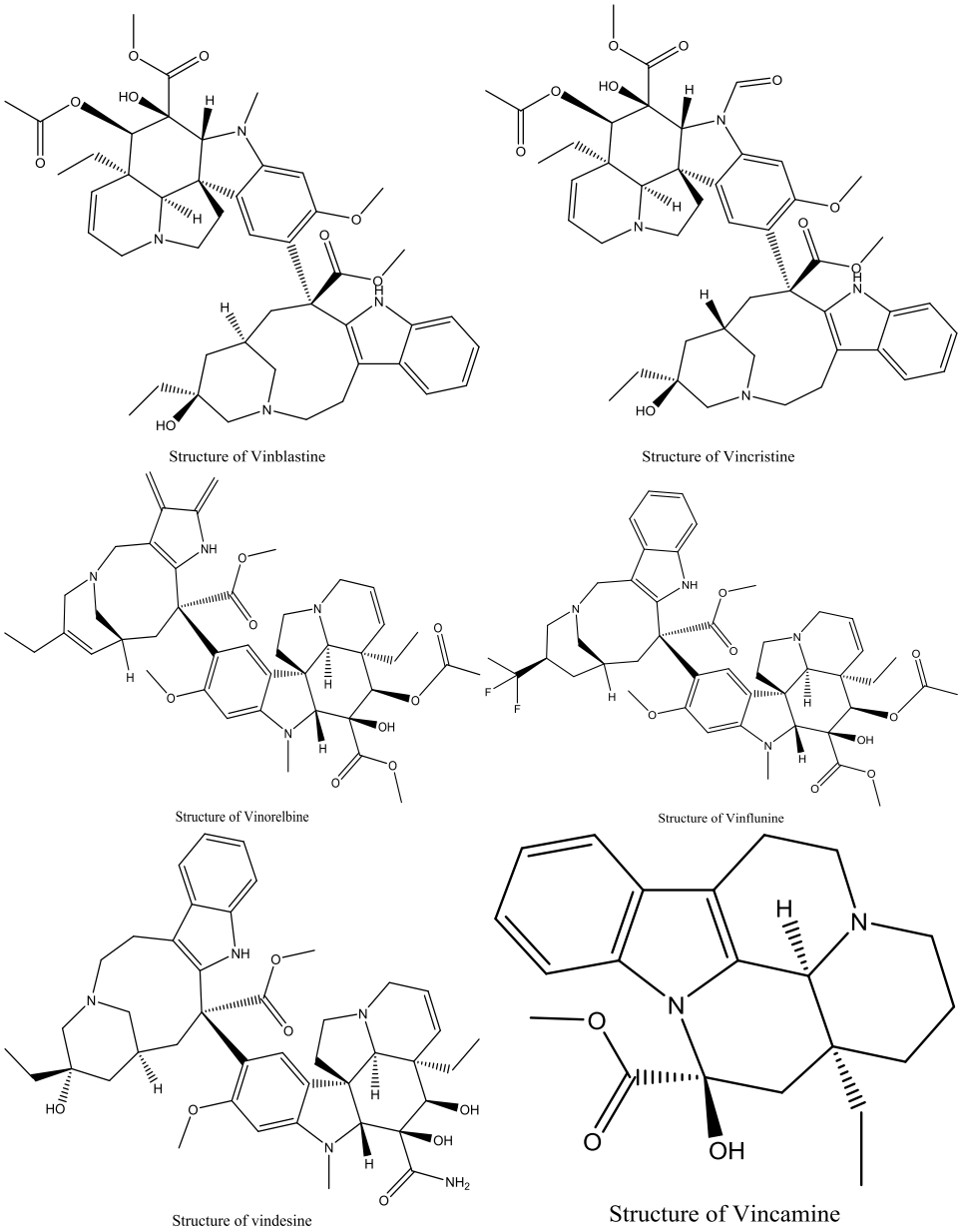

Fig.3: Structure of different chemical constituents.

ANTICANCER/CYTOTOXIC POTENTIAL OF VINCA ALKALOIDS

Vinca alkaloids, such as vincristine and vinblastine, as well as semi-synthetic derivatives like vindesine, vinorelbine, and vinfunine, are abundant in the stem and leaves of C. roses.[32] Using the precursor alkaloids catharanthine and vindoline, vinfunine and vinorelbine have been created to boost the therapeutic action. Vinblastine is specifically used to treat carcinomas, Hodgkin's disease, and neoplasms. Vincristine has been used specifically for pediatric leukemia. Second-line transitional cell carcinoma of the urothelium has been studied in relation to transplantable murine and human cancers using vinfunine and vinorelbine. Known as "mitotic poison," these substances attach to tubulin and have anticancer action. During mitosis, the cell cycle is stopped at the microtubule metaphase.[33]

POTENTIAL USE AS AN ANTICANCER AGENT

It has been shown that Catharanthus roseus contains a broad variety of alkaloids with anticancer activities, including vinblastine, vincristine, vindoline, vindolidine, vindolicine, vindolinine, and vindogentianine. By altering the dynamics of microtubules, they can prevent the growth of cells by inducing apoptosis. Vinblastine sulfate has been used in the treatment of Hodgkin's disease, choriocarcinoma, neuroblastoma, lymphosarcoma, and carcinomas of the breast and lungs.[34] While vincristine sulfate, an oxidized version of vinblastine, aids in the treatment of neuroblastoma, Hodgkin's disease, acute juvenile leukemia, lymphocytic leukemia, reticulum cell sarcoma, and Wilkins' tumor by blocking mitosis in the metaphase. According to theory, vinblastine's interaction with tubulin, which prevents mitosis at metaphase, is what gives it its anticancer properties. Vinblastine binds to the microtubular proteins

of the mitotic spindle, resulting in microtubule crystallization, a stop to mitosis, or both. Vinblastine and its derivatives engage with α and β-tubulin through a double-sided sticking procedure that gives them almost the same affinity regions to become effective anticancer medications against cancer cells. Furthermore, vindoline, the chemical ancestor of vinblastine, is also a cancer-fighting substance derived from tabersonine. Similar to vincristine, which is an organic compound found in nature, vinca alkaloids also occur naturally. By preventing cells from entering the metaphase, this alkaloid (vincristine medication) functions as an anti-microtubule agent to prevent mitosis.[35]

MECHANISM OF ANTITUMOR ACTION OF SUBSTANCES

The presence of vinca alkaloids in C. roseus changes the dynamics of microtubules, which causes regression in cell growth and apoptosis. During mitosis and meiosis, the cytoskeleton mitotic spindle components known as microtubules assist the cell in separating its chromosomes.[36] Numerous cellular functions, including transport and cell shape, depend on microtubules. α-and β-tubulin heterodimers form microtubules, which dynamically polymerize and depolymerize at their ends. Guanosine triphosphate and tubulin binding regulate the processes known as "treadmilling" and "dynamic instability," respectively, in the assembly and disassembly of microtubules.[37] These residences Electrostatic and van der Waals interactions at the same binding site stabilize vinca alkaloids and tubulin heterodimers. Essentially, it is possible to distinguish between two distinct categories of destabilizing chemicals: the first, known as microtubule stabilizing agent, includes preventive depolymerization, and the second group consists of microtubulin destabilizing compounds that hinder the development of microtubulin assemblies. When vinflunine was combined with vinorelbine, the two fluorines present enhanced the electrostatic binding. Vinca alkaloids also decrease amino acid metabolism through their interaction with calmodulin and microtubule-associated protein.[38] This is one of their additional modes of action. The distinct mechanisms of action of several vinca alkaloids may compromise their efficacy. For instance, the interaction between vinblastine and calmodulin best explains the fluctuation in vinflunine's effectiveness relative to vinblastine, even though it has a lower binding affinity for tubulin than either drug. There have also been reports of C. roseus cell growth inhibitors recently, but it's still unclear how they work.

The primary mechanisms of vinca alkaloids' cytotoxicity are caused by their interactions with tubulin and by the disruption of microtubule function, especially of microtubules involved in the mitotic spindle machinery, which directly results in metaphase arrest. But they can also perform a wide range of other metabolic processes that might or might not be connected to how they affect microtubules. Vinca alkaloids attach to binding sites on tubulin that are distinct from those used by taxanes, colchicine, podophyllotoxin, and guanosine 5'-triphosphate. Rapid binding and reversal are both possible. Per mole of tubulin dimer, there are two vinca alkaloid binding sites, according to the available evidence. Vinca alkaloids' binding to these sites disrupts microtubule congregation, but one of the most significant effects of low drug concentrations can be a reduction in growth and shortening rates at the assembly end of the microtubule, which can result in the formation of a "kinetic cap" and suppress function. In vitro, the vinca alkaloids and other microtubule disrupting substances can stop malignant angiogenesis. The vinca alkaloids in C. roseus change the dynamics of microtubules, which causes cell growth to slow down and apoptosis. During mitosis and meiosis, microtubules, which are cytoskeleton mitotic spindle components, aid in the cell's chromosome separation.[39] Microtubules are heterodimers of tubulin that actively polymerize and depolymerize at their ends.

NATURAL VINCA ALKALOIDS: VINBLASTINE AND VINCRISTINE

Due to cell contact, loss of microtubule activity, and tubulin comprising the mitotic spindle machinery, vinblastine and vincristine in particular stop the cell cycle in metaphase.[40] Vinblastine, which binds to the microtubule and inhibits cell proliferation, finally results in mitotic block and apoptosis in the affected cells. There are 16–17 binding sites on each microtubule, which are positioned at the extremities of the tubules. Vinblastine and vincristine bind to these locations and disrupt the assembly of microtubules, slowing growth rates and causing microtubule shortening at the assembly end. This results in kinetic cap and inhibits its function. Vinblastine often causes metaphasic arrest and microtubular dynamic disruption, notably at the extremities of the mitotic spindle, at low drug concentrations.[41] Vinblastine alters the lipid content of the membrane, breaks microtubules, prevents the synthesis of proteins and nucleic acids, increases levels of oxidized glutathione and cyclic adenosine monophosphate (cAMP), and inhibits the calcium-calmodulin-regulated cAMP phosphodiesterase. Vinca alkaloids' anti-cancer effects are mostly ascribed to their capacity to prevent the development of micro spindles, the breakdown of the mitotic spindle, and the arrest of metaphase in diving cells. Vinblastine and vincristine's antitumor effects are brought on by their binding to intracellular tubulin, which prevents DNA repair and RNA synthesis by blocking the enzyme DNA-dependent RNA polymerase.

SYNTHETIC DERIVATIVES: VINDESINE AND VINORELBINE

In order to treat leukemia, non-small cell lung cancer, and lymphoma, vindesine is given in combination with other treatments. Like other Vinca alkaloid compounds, vindesine works by attaching to the microtubular protein tubulin during the metaphase of the cell cycle, preventing tubulin from polymerizing to form a micro spindle, and

then depolymerizing the microtubules that have already been created. In medication combination therapy, vindesine is preferred over vinblastine due to its lesser hepatotoxicity. A semi-synthetic Vinca alkaloid derivative called vinorelbine is a mitotic spindle toxin that interferes with chromosomal segregation and prevents cells from entering the G2/M phase of mitosis.[42] Vinorelbine forms a reversible covalent connection with tubulin by breaking the catharanthine ring. Vinorelbine stimulates the tumor suppressor gene p53 and disrupts the mitotic spindle, which causes the activation or inactivation of several signal pathways including WAF1/CIP1, Ras/Raf, PKC/PKA, and the inactivation of the apoptosis suppressor Bcl2. This inactivation results in a decrease in the formation of the heterodimer between the pro-apoptotic gene BAX and Bcl2, which increases cell death.

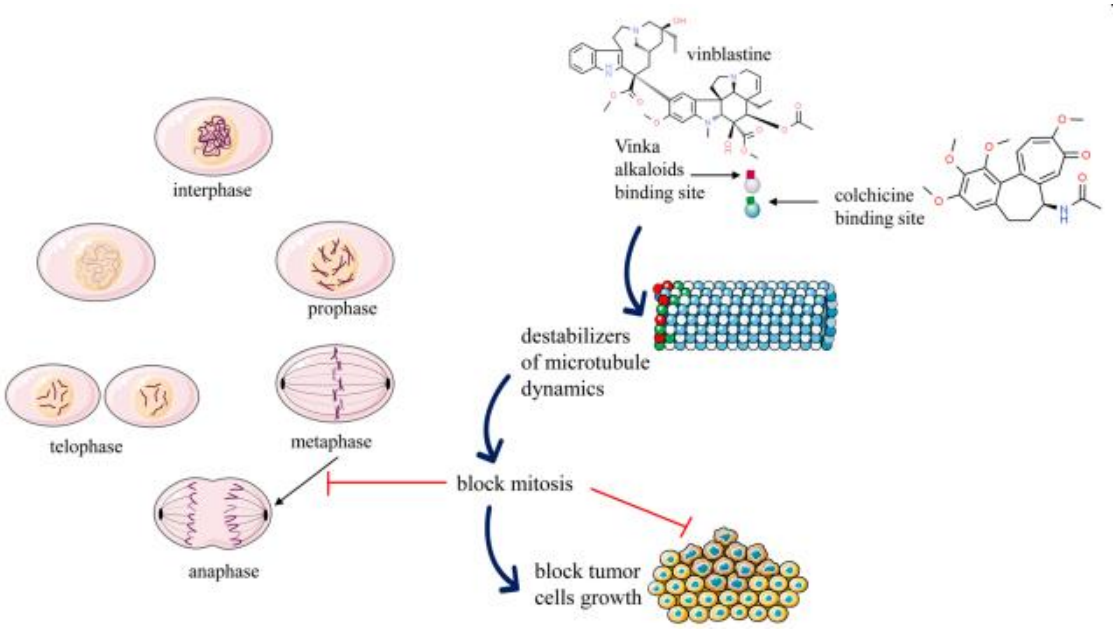

Figure 4: Mechanism of Vinca alkaloids.

SCIENTIFIC STUDIES CONFIRM THE ANTICANCER PROPERTIES

Vinblastine

The alkaloid vinblastine is used to treat a variety of conditions, including neoplasia, breast cancer, Kaposi carcinoma, resistant pregnant choriocarcinoma, metastatic testicular tumors, and Letterer-Siwe disease.[43] Vinblastine derivatives showed potential anti-tumor action in the P388 murine leukemia model, HeLa, and MCF-7 (breast cancer) cell lines. Nitro derivatives of amino vinblastine exhibit anti-cancer properties in non-small cell lung cancer, melanoma, breast cancer, colon cancer, and P388 and L1210 leukemia. Human non-small lung cancer and cervix epithelial adenocarcinoma cell lines treated with carbamate derivatives of vinblastine showed anticancer potential, according to Shao et al.[44] Analogously, amide substituted anhydrous vinblastine derivatives stopped HeLa cells from growing. Vinblastine induces acute, cell cycle phase-independent acute apoptosis in chronic lymphocytic leukemia and certain lymphomas, such as ML-1. Adenocarcinoma-reactive MAb KSI/4S2 conjugate, which has 4-6 desacetyl vinblastine molecules per molecule of KSI/4S2, showed a significant antitumor effect in vivo against human lung and colorectal adenocarcinoma xenografts in nude mice, after coupling its lysine amino group with a 4-hydroxy group of 4-desacetyl vinblastine through a succinate bridge.

Vincristine

Vincristine's cytotoxicity in cancer cells was enhanced by crude methanolic extracts when used in combination therapy with conferone from Ferula schts-churowskiana. By binding to P-gp transporters in a competitive manner, conferone increases vincristine cytotoxicity while reducing vincristine resistance. Intraperitoneal administration of vincristine sulfate was shown to enhance cell death in both in vitro and in vivo clinical investigations. Vincristine sulphate attaches itself to cancerous cells, inhibiting their growth by changing the dynamics of tubulin. It also impacts DNA, RNA, lipid biosynthesis, glutathione metabolism, and calmodulin-dependent ATPase activity in cells. Vincristine and siramesine, two microtubule destabilizing medicines, were tested for their anticancer effects on vincristine-sensitive and -resistant HeLa cervical carcinoma and MCF-7 breast cancer cells. Vincristine-treated HeLa died within 48 hours, exhibiting apoptosis-like chromatin condensation, lysosomal membrane permeabilization, cytochrome c release, Bax and caspase activation, and G2-M cell cycle arrest. MCF-7 cells, on the other hand, chose to enter mitotic arrest, reattached to bottom cells that were metabolically active and had an intact plasma membrane, and continued to exist for several days. Vincristine stimulates caspase-3 and -9 to induce apoptosis and regulates cyclin B and D to induce mitotic cell cycle seizure in human neuroblastoma SH-SY5Y

cells. Vincristine is effective against T cell lymphoblastic leukemia cells in reducing medication resistance when combined with suberoyl anili-dehydroxamic acid (SAHA).[45] When vincristine and SAHA are combined, they inhibit HDAC6, which alters microtubule dynamics and result in M phase arrest, an increase in the amount of cells in the sub-G1 phase, and the start of the apoptotic pathway.

Vindesine

A second-generation semi-synthetic vinca alkaloid with reduced neurotoxicity and broad-spectrum antitumor efficacy in vitro is called vindesine.[46] In preclinical studies, vindesine has been shown to be effective against mouse B16 melanoma, S180 ascites tumor, Ridgeway osteogenic sarcoma, Gardner lympho sarcoma, P154 leukemia, and P388 leukemia in mice. When given intraperitoneally with L1210 leukemia cells, vindesine and methotrexate were shown to improve mouse life span by 200%. In a phase III randomized trial, the combination of vindesine and epirubicin did not improve the medication's efficacy. In a different research, patients with advanced breast cancer who received vindesine (3 mg/m2) and Adriamycin at random showed an overall response of 63% and a 43-week survival.

Vinorelbine

In glial tumors with characteristics of modest proliferation, vinorelbine has been shown to be effective. Combining vinorelbine with nimotuzumab (anti-EGFR monoclonal antibody) has been shown to be an effective treatment for pediatric diffuse pontine glioma. Another study recommended giving a single vinorelbine dose to young children with optic pathway glioma that is advancing.[47] The treatment's overall results indicated improved life quality and low toxicity. When used in conjunction with immune therapy, vinorelbine may be more effective in treating advanced cancers since it alone can cause inflammatory immunity, which can then cause pontine gliomas to respond to immunotherapy treatments. The Karnofsky performance score of patients with malignant glioma and pontine glioma increased from 20 to 60 when they received local treatment with IL-2-stimulated Natural Killer cells. PEGylated IFN-2b treatment was shown in a phase II trial to decrease the course of diffuse intrinsic pontine glioma in children. The trial findings were published in 2012. According to Tuna et al., vinorelbine hindered DNA synthesis in glioblastoma spheroids and caused significant cell death in C6 glioma cells.[48] Vinorelbine stimulates ERK2 in MCF-7 human breast cancer cells. In both uni-variate and multivariate statistical analyses, Shi et al. discovered a correlation between increased phospho-ERK1/ERK2 expression and improved relapse-free survival in lung cancer patients receiving vinorelbine. Vinorelbine and ERK inhibitors together inhibited the in-vivo development of human cancer xenografts. A notable tumor response with manageable toxicity has been observed with vinorelbine and docetaxel combined in the first line of treatment for metastatic breast cancer. Due to its strong affinity for mitotic tubulin and low level of neurotoxicity, vinorelbine has proven effective in the treatment of breast cancer. As such, it is a promising option for phase II clinical trials in patients with advanced breast cancer who have not responded to first- or second-line chemotherapy.[49]

MEDICINAL USES OF VINCA ALKALOIDS

Anti diabetic

The ethanolic extracts found in the flowers and leaves of Vinca rosea bear resemblance to the conventional hypoglycemic medication glibenclamide. The increased hepatic glucose utilization has resulted in the emergence of the hypoglycemic effect.[50] Hypoglycemic activity has been noted as a result of the liver's consumption of glucose. When administered orally for 7–15 days, a 500 mg/kg dose of dichloromethane: methanol extract [1:1] exerts hypoglycemic effect on vinca leaves and twigs in a streptozotocin-induced diabetic rat model. The enzyme activities that cause the liver of diabetic mice to diminish include glucose 6-phosphate dehydrogenase, succinate dehydrogenase, malate dehydrogenase, and glycogen synthase. These enzyme activities have been improved when the animals were treated with extract orally at a dose of 500 mg/kg for seven days. It shows that rats with higher amounts of lipid peroxidation had more glucose metabolized in their bodies.

Anti -microbial activity

With its vast medical properties, vinca aids in the development of new pharmaceuticals as it increases the resistance of most bacterial infections to the majority of anti-microbial medications now on the market. Additionally, the plants contain natural chemical compounds that have a wide range of potential effects, with a focus on prevention.[51]

Anti- oxidant property

Antioxidant properties are primarily found in the roots of pink and white flowers.[52] These roots contain phenolic extracts that are obtained through a variety of assays, including nitric oxide radical inhibition, hydroxyl radical scavenging activity, and peroxide radical scavenging activity.

Anti -helminthic activity

The chronic condition known as helmenthic infections is more common in humans and animals. With piperazine citrate as a standard reference and the Pherithema postuma experimentation model, vinca's anti-helmenthic properties have been assessed. The anti-helimenthic activity of the ethanolic extract is 250 mg/ml.

Hypolipidimic activity

Vinca leaf juice has an anti-artherosclerotic effect by lowering serum levels of LDL-c, VLDL-c, total cholesterol, and triglycerides. Consequently, the flavonoid, vinpocetine-like molecule found in vinca leaf juice had an antioxidant effect.[53]

Anti- diarrheal property
Castor oil and ethanolic leaf extracts are investigated for their anti-diarrheal properties in wistar rats as part of a diarrhoea pretreatment experiment.[54]

Anti- ulcer property
Vincamine and vindoline are two alkaloids that possess anti-ulcer properties. The plant leaves that contain vincamine have neuroprotective and cerebrovasodilatory properties, but they also cause stomach damage in rats.

Hypotensive property
The leaf extract, which has 150 beneficial alkaloids and other chemicals with pharmacological activity, has the hypotensive quality. In lab animals, leaf extracts (hydroalcoholic or dichloromethane-methanol) have been shown to exhibit hypoglycemic and hypotensive effects.

Enhancement of memory
One alkaloid called vinoceptine has the ability to enhance memory and brain function, which is advantageous for Alzheimer's patients.[55] In clinical trials for dementia and stroke, vinpocetine was administered at a well-tolerated dose of up to 60 mg/d with no discernible side effects.

TOXICITY

Despite having structural similarities, the toxicologic profiles of the vinca alkaloids varied greatly from one another. While all vinca alkaloids can cause a typical peripheral neurotoxicity, VCR is the most promising in this situation. The primary indicator of neurotoxicity is a symmetric, peripheral polyneuropathy involving various sensory-motor and autonomic functions.[56] Axonal degeneration and decreased axonal transport are the main pathogenic effects, and these are most likely the result of drug-induced disruptions of microtubule activity. VCR has a poor brain uptake rate and infrequently causes central nervous system side effects such disorientation, altered mental status, depression, agitation, hallucinations, sleeplessness, seizures, coma, syndrome improper antidiuretic hormone production, and visual problems. Additionally, laryngeal paralysis has been discussed. Reversing treatment or reducing dosage or frequency of medication administration is the only known effective countermeasure against vinca alkaloid neurotoxicity. Numerous countermeasures have been used, such as thiamine, vitamin B12, folinic acid, pyridoxine, and neuroactive drugs, but their efficacy has not been conclusively demonstrated. All vinca alkaloids cause similar neurotoxic symptoms; however, compared to VCR, severe neurotoxicity is less common with VBL and VRL.[57] The primary dose-limiting hazard of VBL, VDS, and VRL is neutropenia. Anemia and thrombocytopenia have often been less common. Additionally, there is a rare correlation between VCR and hematopoietic toxicity. Severe myelosuppression has been observed in circumstances that lead to significantly elevated drug exposure and hepatic insufficiency. Patients who are breastfeeding or considering a pregnancy shouldn't use these medications as they may result in birth abnormalities. Immunizations should not be administered to patients who are taking this medicine. VCR has the potential to weaken immunity and result in disease. Patients with chickenpox, herpes zoster infection, gout, kidney stones, infections, liver illness, and nerve or muscle diseases should inform their clinician about any prescription medications they are taking at the same time as the chemotherapy. Overall, medication concentration and treatment length play a significant role in determining drug accumulation and cytotoxicity; however, the majority of the information currently available indicates that the use of drugs above a critical threshold concentration is the most crucial factor. Although the toxicity profiles of vinca alkaloids vary widely, they all have the same lethal impact of peripheral neurotoxicity. Compared to VCR, VBL and VRL exhibit lower frequency in terms of neurotoxicity severity.

Rare instances of hematologic toxicity and severe myelosuppression conditions are displayed by VCR. Patients taking vinorelbine run a significant risk of experiencing both haematological and non-haematological adverse medication reactions. The main dose-limiting toxicity in neutropenia is demonstrated by VBL, VDS, and VRL. Such vinca alkaloid medications should not be used by pregnant women, and vaccinations should not be administered while these medications are being used.[58] However, some writers have also studied the use of an animal model to cause neuropathy in rats or mice using vincristine.

1. Hematological effects, including myelosuppression. Leukopenia develops in the initial days following administration. Trombocytopenia is a minor, temporary condition.
2. Vomiting and queasiness.
3. Severe inflammation, discomfort, and tissue damage can result from extravasation.
4. Alopecia, which is usually partial.
5. Neurotoxicity: Both central and peripheral neurotoxicity, including vegetative neurotoxicity, may be brought on by vinca alkaloids. High doses or prolonged therapy may raise the risk of neurotoxicity. Recovery typically happens weeks or months after treatment discontinuation, although neurotoxicity can happen days or weeks after treatment begins. Compared to vincristine, neurological effects are typically less frequent and severe.[59] The most frequently documented neurological harm is mild paresthesias, which are typically reversible when vinblastine is stopped.

Additional neurological toxicities can include bone pain, paralysis of the vocal cords, profound immediate or delayed pain at the tumor site, headache, malaise, weakness, convulsions, depression, psychosis, numbness, neuritis, cramping in the muscles, loss of deep tendon reflexes, ocular toxicity, including ptosis, and autonomic system dysfunction. Doses too high may result in

orthostatic hypotension, constipation, and urine retention due to vegetative neuropathy. Vinblastine patients should use opioid analgesics sparingly since they run the risk of developing additive vegetative neuropathy, which can cause extreme constipation. Vinblastine exposure increases the risk of respiratory toxicity in patients with preexisting pulmonary impairment. Patients who already have renal impairment, particularly ureteral blockage, may be at higher risk. Alkaloids also have limited water solubility and low bioavailability, which makes it difficult to obtain effective therapeutic doses in the tumor target.[60] Therefore, novel approaches are required to boost their bioavailability, including structural modifications, the creation of nanotechnologies, and new therapeutic target transport systems.

RECENT STUDY

Using an Agrobacterium tumefaciens infection, the antitumor activity of methanol leaf extracts of Catharanthus roseus (L.) G. Don was evaluated using the potato disc bioassay method.[61] Used as a positive control was camptothecin. There was a significant ($P<0.05$) percentage of tumor inhibition at leaf extract concentrations of 10 ppm, 100 ppm, and 1000 ppm. Agrobacterium tumefaciens strains AtSI0105, AtAc0114, and AtTA0112 showed maximum tumor inhibition of 80.96, 82.68, and 84.96% at 1000 ppm, respectively. Additionally, it was noted that the strain AtSI0105 (28.06±0.29) was more dominant than other strains in terms of tumor production. The findings of the sensitivity test indicated that none of the tested strains of A. tumefaciens was affected by the extracts in terms of viability. A time- and dose-dependent way, the aqueous extract caused Jurkat cells to die 24, 48, and 72 hours after treatment. The half maximum inhibitory concentration (IC50) values of 2.55µg/ml and 2.38µg/ml, respectively, indicated that the cells treated at 48 and 72 hours exhibited more cytotoxic effects. Conversely, after a 24-hour treatment with 1000 µg/ml, the extract caused normal PBMC proliferation. This finding suggests that the crude aqueous extract of C. roseus exhibited distinct effects, acting to both promote and hinder the growth of PBMCs and the proliferation of the Jurkat cell line. The findings indicate that the extract might have potential for regulating both normal and altered immune cells in individuals with leukemia. obtained from suspension cultured cells of C. roseus was assessed in this study. The cells were stimulated with methyl jasmonate (MJ) and cyclodextrins (CDs). Only catharanthine and ajmalicine were quantified out of the four indole alkaloids that were identified: tabersonine, lochnericine, ajmalicine, and catharanthine. For the JURKAT E.6 and THP-1 cell lines, the concentration of the indole alkaloid-enriched bioactive extract that inhibited cell growth by 50% was 211 and 210 ng/mL, respectively. The newly discovered vinca alkaloid vinflunine is specifically fluorinated in a small, underutilized area of the catharanthine moiety with the application of super acid chemistry. Vinflunine shares qualities with other Vinca alkaloids, including tubulin interaction and mitotic arrest. These properties have been validated by in vitro research.[62]

However, distinctions have been found between vinflunine and the other vinca alkaloids regarding the inhibitory effects on microtubule dynamics and tubulin binding affinities. Vinflunine produced smaller spirals with a shorter relaxation period, potentially indicating a decrease in neurotoxicity. Research looking at the in vitro cytotoxicity of vinflunine in combination therapy has shown that vinflunine works very well in conjunction with 5-fluorouracil, doxorubicin, mitomycin C, or cisplatin. Additionally, even while vinflunine seems to play a component. Vinflunine belongs to the vinca alkaloid class and is a novel microtubule inhibitor with unique tubulin-binding characteristics.

When compared to previous vinca alkaloids, preclinical testing of this new microtubule inhibitor has demonstrated greater anticancer effectiveness against a wide range of tumor types both in vitro and in vivo. Vinflunine's ability to cause apoptosis in target cells is what mostly accounts for its anticancer impact, which is mediated by its manipulation of microtubule dynamics.[63] Vinflunine also has antiangiogenic and antivascular effects at non-cytotoxic doses. Vinflunine's positive preclinical profile and its ability to work in concert with a number of different therapy modalities support the need for this molecule to undergo additional clinical research. In comparison to other Vinca alkaloids, such as vinorelbine, from which it was synthesized, vinflunine had more anticancer activity. Vinca alkaloids appear to prevent cell division by altering spindle microtubule dynamics. In patients with advanced non-small cell lung cancer, a randomized comparison trial was carried out between 254-S plus Vindesine VDS and CDDP plus VDS. At least twice, at intervals of four weeks, 90 mg/m2 of 254-S, also known as CDDP, was injected intravenously. Intravenous VDS at a dose of 3 mg/m2 was given on Days 1 and 8 of either 254-S or CDDP treatment. 121 patients (64 from the 254-S/VDS group and 57 from the CDDP/VDS group) out of the 136 registered patients could be evaluated for tumor response (full cases). The tumor response rate (254-S/VDS group: 12.5% [8/64], CDDP/VDS group: 15.8% [9/57]) did not differ significantly across the groups, nor did cancer stage, histological type, or survival. Regarding adverse effects, the 254-S/VDS group had considerably lower rates of leukopenia and thrombocytopenia, respectively. Compared to 8.9% of patients in the VDS arm, 31.1% of patients in the VRB arm showed an objective response ($P = 0.0002$). The reaction to VRB took an average of 18.5+ weeks (range: 7.9 to 107.5+ weeks) on average, while the response to VDS took an average of 11.7+ weeks (range: 6.0 to 35.0+ weeks). Thirteen patients (26.5%) out of the 49 patients who were initially on VDS and received subsequent VRB + P responded, while 33 patients in the VRB group who received VDS + P later on did not respond to the first monotherapy. In the two monotherapy arms (VRB, 55.3% vs. VDS, 48.5%), the

rates of grades 3 and 4 leukopenia were comparable. On the other hand, patients on VRB experienced grade 3 anemia more frequently than those on VDS. With VDS, peripheral neurotoxicity occurred much more frequently. Relative to VRB (P = 0.002), yet relative to VDS (P = 0.012), VRB caused a marginally greater rate of local cutaneous reactivity. The VRB group experienced peripheral neurotoxicity less frequently than the VDS group when cisplatin and these vinca alkaloids were combined. Vinorelbine VNR had greater anticancer activity in comparison to other vinca alkaloid antitumor medicines. Additionally, VNR's neurotoxicity was shown to be lower than that of other vinca alkaloids.[64] VNR demonstrated anticancer effectiveness against eight out of eleven tumor models (non-human) in naked mice xenografted tumor models. Breast cancer: 2/3, colon cancer: 0/2, stomach cancer: 2/2) and small cell lung cancer: 4/4. In particular, VNR demonstrated tumor-regressive efficacy against MX-1 breast cancer and LC-6 non-small cell lung cancer. Vindesine (VDS), one of the main medications used to treat non-small cell lung cancer in the clinic, was not as effective against non-small cell lung cancer as VNR was. VNR plus cisplatin (CDDP) was a more effective combination chemotherapy than VDS plus CDDP, which was one of the conventional regimens for chemotherapy for non-small cell lung cancer. The reason behind VNR's high anticancer impact with less neurotoxicity was its greater activity on mitotic microtubules as opposed to axonal microtubules.[65] Less activity of VNR against mitotic microtubules was thought to be associated with the two types of microtubules having differing compositions of microtubule-associated TAU isoforms. Compared to VDS, VNR produced a noticeably greater response rate in non-small cell lung cancer. When paired with CDDP, VNR produced a significantly longer survival than VDS in the log-rank test. VNR produced a high response rate in first- and second-line treatment for advanced breast cancer. When used with chemotherapy drugs like Taxol, Fluorouracil, and Anthracycline, VNR is beneficial.

There were distant metastases in the lung (29.3%), bone (20.2%), and retroperitoneal nodes (58%). When vinflunine was first introduced, the ECOG 0, 1, and 2 performance statuses were, respectively, 31.3%, 60.6%, and 8.1%. Each patient received a median of four cycles of vinflunine (range: one to eighteen). The overall and progression-free survival median for all patients (N = 102) were, in turn, 3.9 months (2.5–5.5) and 10 months (7.3–12.8). The tumor progressed during a period of 4.3 months (2.6–5.9). 42 patients (41.2%) had SD as their best response, 23 patients (22.5%) had PR, and two patients (2%) had CR. Vinflunine had a clinical benefit rate of 65.7%. T47D cell growth was inhibited by C. roseus with a median inhibitory concentration (IC50) of 2.8%, D. petandra at 1.2%, P. betle at 2.8%, and C. mangga at 74.8%. The necroptosis the analysis's findings indicated that 36.77% of C. roseus, 24.03% of D. petandra, 9.45% of P. betle, and 0.41% of C. mangga caused apoptosis. As for 36.06%, doxorubicin at 10 µg/ml caused apoptosis. P. betle extract had the highest DPPH scavenging activity, measuring 83%; D. petandra, 75.11%; C. roseus, 71.87%; and C. mangga, 38.45%. The highest anticancer efficacy was shown by the aqueous extracts of C. moseus and D. petandra, which inhibited cell proliferation and induced apoptosis. The extract from P. betle exhibited the highest level of antioxidant activity. C. mangga extract showed only weak antioxidant activity and no anticancer properties.[66]

CONCLUSION

Cancer is the result of unchecked cell proliferation combined with malignant invasion and metastasis. It results from the interplay of environmental variables and genetic vulnerability. These elements cause genetic alterations in tumor suppressor and oncogene genes to accumulate, giving cancer cells their malignant traits, like unchecked proliferation. For pharmaceutical treatments, vinca alkaloids have typically been a part of combination chemotherapy regimens. They have been employed as disinfectants, anti-cancer agents, and to treat diabetes and high blood pressure. The cytotoxic properties of vinca alkaloids can stop cell division and result in cell death. Vinca alkaloids remain one of the original cancer medicines and are currently the second most used family of anti-cancer pharmaceuticals. Vinca alkaloids, derived from Catharanthus roseus, include vinblastine, vincristine, vindesine, and vinorelbine; vincamine, derived from Vinca minor, exhibits potential anticancer effects. The cytotoxic properties of vinca alkaloids can stop cell division and result in cell death. In clinical application, there are four main vinca alkaloids: VBL, VRL, VCR, and VDS. The United States has approved the usage of VCR, VBL, and VRL. Additionally, a novel synthetic vinca alkaloid called vinflunine is being explored for different cancers and has been approved for use in Europe for the treatment of second-line TCCU. Vinca alkaloids remain one of the original cancer medicines and are currently the second most used family of pharmaceuticals for the disease.

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CONFLICT ON INTEREST

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