

A Critical Analysis of Drugs Used in Anticancer Therapy Isolated from the *Catharanthus roseus* : A Review

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ABSTRACT

Cancer is an abnormal pattern of growth which has ability to spread to the other parts of the body. Many treatment options are available currently such as chemotherapy, radiotherapy and surgery. Presently increasing number of cancer cases globally has made responsible community and researchers to pay attention to establish a sustainable therapy option which is effective both in terms of cost and treatment. Medicinal plants could be the best option for extracting anticancer drugs. Majority of the anticancer drugs currently being used are extracted from natural sources. *Catharanthus roseus* also known as “Madagascar periwinkle”, belongs to the family Apocynaceae. This splendid and marvelous shrub is a good source of indole monoterpenes and alkaloids which are used as anticancer, antiproliferative and antimitotic drugs. Anticancer drugs extracted from *C. roseus*, their mechanisms of action, their potential and complications associated with them are discussed.

Figures : 04

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Introduction

Cancer is one the deadliest diseases in the world which is responsible for increasing mortality rate. There were 19.3 million cancer cases and 10 million deaths recorded in 2020⁵⁵. This alarming statistics has made scientists to come up with immediate and effective solutions to prevent this fatal disease. Treatment of cancer depends upon the facts that what factors are involved as causative agents and at what stage cancer is? Initially, at the start of cancer, normal cells after developing mutations (being called neoplastic cells) grow and formation of tumor occurs. Later on, it spreads to other normal body cells through metastasis⁴⁷. Breast cancer,

colorectal cancer, lung cancer, stomach cancer and liver cancer are major types of cancer¹¹. Statistics taken from WHO say that almost 400,000 cases are recorded in children each year. Most common type of cancer among children is leukemia. Lack of patient care is one of the biggest reasons of this prevalence, particularly in developing countries. In developed countries with good health care facilities, 80% cure rate is observed while in countries with poor health care system, it is 30%⁶². This mortality rate can be decreased by taking steps in terms of educating people, providing them health care facilities, and (specially) moral support to the patients who are fighting this deadliest disease. On 15th of February each

year, International Childhood Cancer Day is celebrated around the globe to create awareness among people^{34, 64}. In India, situation is getting worse. Each year a million new cases are registered and the number is speculated to be doubled in coming years. Among men, oral cancer and lung cancer are more common while among women, breast and cervix cancer are seemed to be prevailed. While elderly people have been observed with prostate cancer. Even though, there is an effective treatment available in an Indian subcontinent, but the massive expenditures make this inaccessible to millions of patients. Moreover, increasing number of doctors per patient could also be a milestone in improving health care facilities and decreasing mortality rate^{22, 30}.

Globally, the boom in number of cancer cases has been seen due to modernization and urbanization. Even though the officials and responsible community are concerned and are making people aware, but the situation is getting worse as if it were inevitable. The triggering causes of cancer could be external as well as internal factors. The onset of abnormal growth could be arisen due to mutations in genetic material, compromised immune system and hormonal imbalance. These are among internal factors. External factors include change in lifestyle, unhygienic food, smoking, exposure to hazardous or deadly chemicals. Preventive measures such as adopting good lifestyle, periodic health checkups, daily physical activity, proper sleep and nutrition and consumption of no alcohol and tobacco can ameliorate cancer risk. These careful steps can reduce the number of cancer cases even to half. This cannot even be possible without educating people and urge them to quit smoking. It was observed that increasing physical exercise and maintaining healthy lifestyle can decrease the risk of 26 types of cancers. Furthermore, various types of cancers can be protected by taking some preventive measures like, vaccinations can prevent those cancers caused by microbes, skin cancer can be prevented by not getting direct sun exposure; by not going out without applying sunscreens on skin. Regular clinic checkups can prevent colorectal, breast cancers^{16, 41, 54}.

Currently available treatments are chemotherapy, radiotherapy and surgery⁶⁵ and the application of these methods entirely depend upon the type and the stage of cancer. For primary stage cancer, chemotherapy is an effective option; it does not let cancerous cells to diffuse to the normal cells that is very important for the spread of cancer. Along with this fact of it being expensive, it does also have certain side effects that are demerits of the method⁶⁸. Being that expensive and having side effects, scientists are looking for an alternative option that may



Fig. 1 : Common *C. roseus*

be more effective and affordable for people from poor countries¹⁷

'Medicinal plants' could be an alternative and effective option. The thing which makes them a better treatment option is that they carry no side effects. Secondary metabolites produced from them are being used as drugs against various ailments. Beside fighting microorganisms (bacteria, fungi, protozoa), effective against various types of cancers is also one of the best usefulness of these secondary products. They act on cancer cells and interfere with their process of mitosis^{8,40,59}. Now a days, most of the anticancer drugs are being extracted from natural sources : plants¹⁰. Plants' secondary products are bioactive compounds such as alkaloids, monoterpenes, indole alkaloids¹⁵.

Catharanthus roseus

A perennial, medicinal plant that grows in tropical weather condition from Apocynaceae family is a wonderful, splendid creature which gives many MIAs (Monoterpenes Indole Alkaloids) as its secondary products which are proven to be very useful drugs against many diseases (asthma, constipation, blood pressure) more importantly against cancer²¹. Based on its flower color, there are two varieties of *C. roseous*, pink flowered, and white flowered ("Rosea" and "Alba" respectively). There are various names for this same plant; Madagascar periwinkle, *Vinca rosea*, *Ammocallis rosea*, *Rose periwinkle* and Old Maid are some of them.

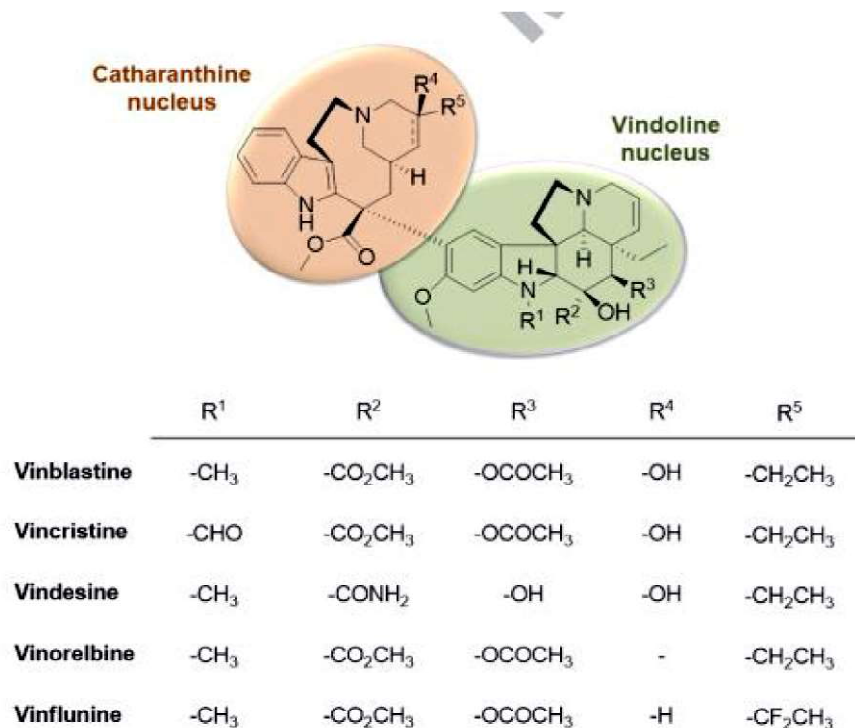


Fig. 2 : The general structure of *Vinca* Alkaloids (VAs) in clinical use. R groups in the structural formula are given in the Table below with respect to each type of VA.

Anticancer drugs extracted from *C. roseus*

For the development of anticancer drugs, natural products are recognized as wonderful source^{20,33}. Almost 60% of anticancer drugs, in fact, are extracted from natural products, plants and microorganisms (doxorubicin, paclitaxel)². Extracted medicines/molecules, by different mechanisms of actions (inhibition of enzymes involved in mitosis, DNA alkylation and different anti-proliferative pathways), induce cancer cell apoptosis³⁷. They do not, as well, let the cancerous cells to diffuse into normal growing healthy cells which is very important for spreading of cancer (metastasis)^{44,66}.

Alkaloids extracted from *C. roseous* are also called *Vinca* (vinka) alkaloids (VAs); it is because of the name *Vinca rosea*. These alkaloids are ultimately used as drugs. These drugs are attributed safe and effective medicines and were one of those firsts drugs that were brought into the market from plant source⁶³. Two Canadian scientists, Robert Noble and Charles Thomas, extracted *Vinca* Alkaloids (VAs) for the first time in 1950 from *C. roseus* (Madagascar periwinkle or *Vinca rosea*)⁵⁰. This marvelous plant has been exploited for its potential against malaria and diabetes¹³. Initially, when it was discovered, it was hypothesized as if it had hypoglycemic effects, but this hypothesis was rejected within no time²⁶.

Because it did not have any role in reduction of blood sugar level when rabbits were treated with these extracted alkaloids. Soon, correlation of these molecules with cancer was speculated¹⁸. Myelosuppression was observed in leukemia mouse model when treated with Vinblastine- a type of VAs. This discovery was a milestone in cancer research, and it paved the scientific community new routes to treat cancer.

There are five VAs currently available in the market and have been approved by FDA as an effective drugs against various types of cancer³⁵. Two of them, vincristine (VCR) and vinblastine (VBN), are natural VAs and approved by FDA in 1961 and 1963 respectively. Three of them are semisynthetic VAs, vinorelbine (VRL)_ approved by FDA in 1994, vindesine (VDS)_ currently being used in some countries, and vinflunine (VFN)_ approved by European Medicine Agency (EMA) in 2012 for the treatment of cancer^{7,67}.

In Fig. 1. As General structure of VAs includes catharanthine (an indole nucleus) and vindoline (dihydroindole nucleus)and these two nuclei are linked by C-C bridge.

VAs have been shown to be effective against neoplasticity as well as against solid tumors (lung cancer, breast cancer *etc.*)⁵¹. Antiproliferative activity of VAs have yet to be known completely, however, evidence is

TABLE-1 : Commonly used anticancer drugs extracted from *C. roseus*

VAs-based Anticancer drugs	Cancers	Side effects	
VBL (Vinblastine)	Lung cancer, testicular carcinoma, Ewing's sarcoma, breast cancer, germ cell tumor, Hodgkin's, and non-Hodgkin's lymphoma	Fever, vomiting, constipation, dyspnea, weight loss, nausea, white blood cells toxicity, hormonal imbalance	
VCR (Vincristine)	B-cell lymphoma, breast cancer, colorectal cancer, Hodgkin's, and non-Hodgkin's lymphoma, metastatic melanoma, Philadelphia chromosome-negative acutelymphoblastic leukemia, Wilms' tumors	Headache, hair loss, stomach pain, dizziness, diarrhea, bloating, neuropathy, constipation, weight loss, taste change	
VDS (Vindesine)	Colorectal, renal, and esophageal cancers, breast cancer, lymphocytic leukemia, Pediatric solid tumors,	Fatigue, weight loss, depression, diarrhea, sore mouth, swallowing difficulty, convulsion, nerve pain	
VRL (Vinorelbine)	Broad spectrum anticancer activity; breast cancer (advanced), metastatic non-small cell lung cancer, rhabdomyosarcoma	Anaemia, weakness, nausea, neuropathy, diarrhea, vomiting, constipation	
VFN (Vinflunine)	Urethral cancer (advanced and metastatic)	Abdominal pain, fatigue, constipation, vomiting, nausea, neuropathy, anaemia, loss of appetite and weight	

found to have the involvement of bcl-x, p53, and bcl-2 genes in the regulation of cell division and cell apoptosis equilibrium²³.

Therapeutic relevance of extracted anticancer drugs

As a single agent or in combination with other drugs, *Vinca* alkaloids are being effectively used in the treatment of various types of cancers (bone marrow cancers, breast cancer, leukemia etc.). Childhood cancers were, initially, treated by these medicines, then adult and solid malignancies have also been started to be tackled^{27,43}. Various alkaloids are being mentioned in Table-1 along with their toxicology and clinical usage. It is hereby important to add that WHO has included VBL, VCR and VRL in its list of Essential Medicines⁴⁶.

VBL is being used as an essential component of various chemotherapy courses and one the most keenly studied VAs. Various cancers viz. lung cancer, melanoma, brain cancer, Hodgkin's lymphoma, and testicular cancers

are being treated with VBL^{32, 38}.

VCR though has been used as an anticancer drug and has proven to be useful in various neoplastic conditions, but its usage is restricted and has become limited due to its rigorous neurotoxicity.

VDS_ semisynthetic VAs; vindesine is being, though, used in various chemotherapy strategies. Due to having its side effects, its usage is limited and approved in some countries¹².

VRL is being furnished with special quality of having broad spectrum antiproliferative activity in many types of advanced cancer stages. It is said to be more effective than VBL and VRL because it carries less toxicity⁵¹. VRL are being widely available and are administered intravenously.

VFN_ a fluorinated, third generation VAs carries the least amount toxicity which makes it the best anticancer treatment option. It is approved and currently being used in Europe⁶⁷ to treat advanced carcinoma and



Fig. 3 : General mechanism of action of *Vinca* Alkaloids-based anticancer drugs.

urethral cancer⁶.

Mode of action of anticancer drugs isolated from *Catharanthus roseus*

As it has been mentioned above, *C. roseus* is a splendid shrub and is being used to extract various indole alkaloids (also called *Vinca* alkaloids) which are anticancer drugs due to their antimitotic and antiproliferative activity¹.

Microtubules (MTs) are composed of tubulin proteins and an essential component of cytoskeleton which are involved in various crucial processes of cell that are essential for survival such as formation of spindle fibers for chromosomes separation during meiosis and mitosis, transport, and giving overall structure to the cell. *Vinca* alkaloids-based anticancer drugs interfere with mitotic potential and make alterations in the microtubular dynamics of cell division and induce cell death⁶⁰.

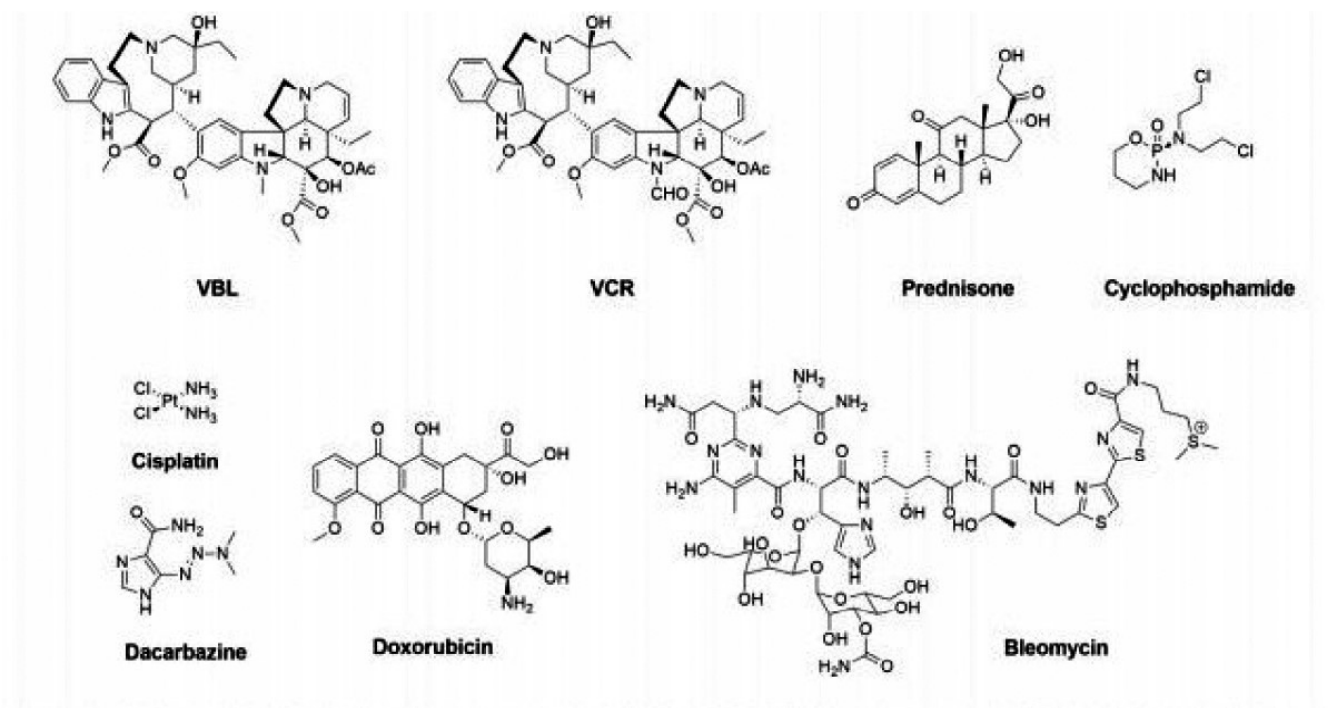
Microtubules are composed of heterodimers of α -tubulin and β -tubulin subunits that continuously interchange between polymerization and depolymerization forms (also called "treadmilling"). This continuous interchangeable process is regulated by the binding of GTP over tubulins. Any interruption in this regulated phenomenon can lead to cell cycle arrest and ultimately cell death²⁸. There are two groups of compounds which can cause disruption in mitosis; those compounds which prevent depolymerization and secondly those which prevent polymerization^{24, 48}. *Vinca* alkaloids interfere with microtubule dynamics by binding themselves at place

between these two α and β subunits beside GTP binding site⁴². Both natural and synthetic alkaloids have almost equal binding affinity for microtubules heterodimers, but their equilibrium constants appear to be as in the following order^{19, 45}.

vincristine > vinblastine > vinorelbine > vinflunine

Interaction of these alkaloids with heterodimers is through electrostatic forces (Van der Waals forces). In case of VFN, this interaction gets stronger because of it contains two fluorine atoms and this one of the reasons VFN is best anticancer treatment option^{9, 39}. Vindoline moiety of the *Vinca* alkaloids is responsible for the binding of them with microtubular heterodimer, on the other hand, toxicity of VAs is due to the catharanthine moiety⁵³. It has been reported by many researchers that antiproliferative mechanism is dose dependent. High concentration of VAs quickly induces cell death by the formation large polymers of tubulin proteins (para-crystals) as compared to low concentration of VAs administration^{3, 56}. There are other mechanisms of actions too, which have been reported by many researchers in recent past. It was reported that amino acid metabolism can be affected/inhibited by the interaction of VAs with calmodulin (CaM; calcium modulated protein)⁵. With this mechanism of action, it is seen that vinflunine's (VFN) antiproliferative activity against tumors is more than vinblastine (VBN) and vincristine (VCR). It might be due to VFN interacts with calmodulin protein instead tubulin proteins⁵⁸.

There are also various other alkaloids extracted



Examples of combination therapies

CVP (cyclophosphamide, vincristine and prednisone): First-line therapy for follicular B-cell lymphoma

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone): Front line therapy for follicular or diffuse large B-cell lymphoma

VCRT (vinblastine, cisplatin and radiation therapy): III A and III B stages of non-small cell lung cancer

CISCAVB (cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin): Non seminomatous germ-cell tumors

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine): Standard chemotherapy for Hodgkin's lymphoma

Fig. 4 : Combination therapies in which *Vinca* Alkaloids are used in combination with other anticancer drugs.

from *C. roseus*, but their mode of action is yet to be discovered. Workers⁶⁰ extracted an alkaloid, catharoseumine, which showed mild cytotoxic effect against HL-60 human cell line. Vinposidin was patented by Eli Lilly Company in 1974 as an antimitotic/anticancer drug²⁹.

Current issues with VAs-based anticancer drugs

One of the drawbacks which limits the potential of *Vinca* alkaloids (VAs) against neoplastic cells is their mechanism of resistance against VAs⁵⁷. Activity of P-glycoprotein (Pgp) creates resistance against drugs effect within cell, this Pgp-modulated resistance reduces the antiproliferative potential of VAs. There are also some other drug resistance mechanisms found in cells which participate in decreasing anticancer potential of VAs, such as multidrug resistance proteins, alteration in the structure of α -tubulin protein and apoptotic response impairment⁶⁹.

Use of VAs in combination therapy could be the solution that scientists came up with to overpower the resistance mechanisms of cells. In Fig 4, some of the examples of combination therapies are described. Facts which support this strategy are: it makes the use of less dosage of VAs which in turn reduces toxicity, usage of sole VAs whose mechanism of action is to disturb MTs which may cause sensory impairment because of decreased axonal transport, but combination therapy can prevent this problem by having different mode of actions. Generally associated health problems with the prolonged use of VAs are neuropathic pain, motor dysfunction, paralysis, gastrointestinal toxicity and neutropenia²⁵. Other less common effects of prolonged use of VAs are constipation, headache, fatigue, dizziness, vomiting, diarrhea *etc.*

Conclusion

Indole monoterpenes and *Vinca* alkaloids extracted

from *C. roseus* are great and effective antiproliferative drugs against various types of cancers. Though, these drugs stop cancer cell proliferation by interfering with microtubules dynamics during cell division, but there are

also severe side effects such as neuropathy, axonal degradation *etc.* associate with them. If we, somehow, make ourselves enable to eliminate associated side effects, these drugs could be the best option for cancer treatment regimens.

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