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Vinca Alkaloids – Anti cancer drugs

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Abstract: ***Cancer, one of the most common disease, is responsible for nearly 10 million deaths annually. The treatment of cancer typically includes surgery, chemotherapy, radiation therapy, and drug therapy which have a significant financial impact on patients. Also, over the time, patients may develop drug resistance. By applying evidence-based preventative techniques, a significant number of cancer cases can be avoided or treated. Plant-based medications have emerged as hopeful alternatives to chemotherapy in both developed and developing countries.***

Alkaloids are the secondary plant metabolites that have shown to be effective and acceptable for treating cancer. The second-most popular family of cancer medications is vinca alkaloids, and they will continue to be utilised for cancer treatment. These medications, which include vinblastine, vincristine, vindesine, and vinorelbineare frequently used either alone or in combination with other medications. These cell cycle-dependent drugs work by preventing tubulin from polymerizing into microtubules, which causes cell death. There have been several studies looking at the pharmacological behaviour of this family of antitumor drugs in both humans and animals utilising diverse in vivo and in vitro models.

Despite tremendous improvements in the prevention and control of cancer progression, there are still many flaws and space for growth. Several undesirable side effects might occasionally happen when receiving chemotherapy. Natural treatments, and hence the use of cancer therapy agents produced from plants, may reduce negative side effects.

Keywords: vinca alkaloids; Catharanthus Roseus; chemotherapy; Vinblastine; Vincristine

I. INTRODUCTION

Cancer is a family of diseases in which cells in the tissues of the body grow and divide without normal control. [1] This uncontrolled division of cells forms a mass or lump called tumor. These tumors may be cancerous or non-cancerous, which is also called as malignant and benign respectively. Malignant tumours can grow continuously and spread to distant areas of the body [2].

Chemotherapy and surgery are now accepted treatments for cancer, but they have not yet been completely effective. Although there has been some improvement in cancer diagnosis and treatment, there are still reports of high cancer incidence rates and poor patient survival rates on a global scale [3]. Cancer is also known for being a significant cause of death worldwide [4]Traditional medicine and it's secondary metabolites are being increasingly recognized as useful complementary treatments toward the cancer.[5] Alkaloids are the most remarkable plant secondary metabolites with potential toxicity proving remarkable therapeutic actions against a wide variety of malignancies and other diseases in vitro and in vivo .[4]They are naturally occurring organic nitrogen-containing bases that have ability of preventing or inhibiting the process of carcinogenesis. Due to their well-defined anticancer drug mode of action, herbal anticancer drugs made from Catharanthus Roseus are widely employed. [4], [6]

Vinca alkaloids are indole compounds with anticancer properties. [7] They are naturally extracted from the pink periwinkle plant of Catharanthus roseus G. Don. [6] Vinca roseus is a perennial flowering plant that is indigenous to the Mediterranean region and is mainly found in the northern hemisphere. They are indigenous to countries in southern Asia and the tropics. There are several uses for the Madagascar-grown Catharanthus Roseus L. [8] The leaves and stems are the sources of dimeric alkaloids,while roots have antihypertensive, ajmalicine and serpentine[6]Alkaloids that are isolated from C. roseus are found to be hypotensive, sedative and possess tranquilising and anti-cancerous properties.The vinca alkaloids are also important for being cancer fighters .Specifically, C. roseus is a decorative and curing plant of enormous pharmaceutical interest as it is nothing less than a chemical factory, producing more than about 130 different terpenoid indole alkaloids (TIAs), some of which are exhibiting strong pharmacological activities [9] .Even in varieties selected for the highest alkaloid content, the concentrations of these antitumor agents are very low, as much as 1 kg of dried leaves are being needed to obtain 3 mg of vincristine [7]

II. PLANT PROFILE

1) *Biological Source:* It is dried whole plant of vinca roses.
2) *Geographical Source:* It is indigenous to Madagascar. Vinca plant is cultivated for the decorating plant and found in tropical regions like Africa, Australia, Eastern Europe Taiwan, India and Thailand.

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A. Botanical Classification

Botanical Name(s): Vinca Rosea (Catharanthus Roseus)
Family Name: Apocynaceae
Kingdom: Plantae
Division: Magnoliopsida (Flowering plants)
Class: Magnoliopsida (Dicotyledons)
Order: Gentianales
Family: Apocynaceae
Genus: Catharanthus
Species: C. roseus. Coriaceus, C. lanceus, C. Longifolius, C. ovalis, C. scitulus, C. trichophyllus, C. pusillus [10]

B. Synonyms

1) Vinca rosea L.
2) Pervinca rosea (L.) Gaterau
3) Lochnera rosea (L.) Rchb. Ex Spach
4) Ammocallis rosea (L.) Small

C. Morphological Character

A Vinca is found in blue, purple And white color.It is a specific kind of corneal or annular plant.Vinca is near about 0.52 to 1 cm in length and its leaves is oblong, ovate, glossy and bitter in taste with slight odour. [10]



Figure 1 the flowers of Catharanthus roseus G. Don. Catharanthus roseus (syn. Vinca rosea) **[**6**]**

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III. CHEMICAL CONSTITUENTS

Table1 The pharmacology of major alkaloids used for cancer treatment, their mode of action, oncological applications and side effects

Type of alkaloid	Plant part	Pharmacological mechanism	Therapeutic indication	Side effects	Reference No.
Vinblastine	Leaf stem root	Clings to tubulin prevents microtubules from developing anti-mitotic	Breast cancer Lung cancer head and neck cancer Hodgkin's lymphoma Testicular cancer	Increase Gastrointestinal toxicity, potent vesicant extravasation injury	[10] ,[11] [1]
Vincristine	Leaf stem root	Binds to tubulin dimer prevents microtubule structures from forming mitotic inhibitor anti-mitotic	Non-Hodgkin's lymphoma lymphoblastic leukemia nephroblastoma	Peripheral neuropathy hyponatremia, constipation paralysis, spinal nerve demyelination, lung spasm	[10], [11], [1]
Vindesine	Leaf stem root	Anti-mitotic	Melanoma Lung cancers Uterine malignancies	Spinal nerve demyelination, hyponatremia, constipation, hair loss, nerve demyelination, breathing problems, lung spasm	[2],[5], [11]
Vinorelbine	Leaf stem root	Anti-mitotic	Breast cancer non-small cell lung cancer	Inflammation of the veins, constipation, poor resistance to infection, bleeding, anaemia, nausea, diarrhoea, numbness or tingling in hands or feet	[10], [12], [1]
Vinflunine	Leaf stem root	Decrease Transition from metaphase to anaphase, preventing cancer cells from entering mitosis Enhanced apoptosis	Transitional cell carcinoma breast cancer	Hair loss Weariness Overall sensation of weakness	[13] ,[11], [14], [1]

IV. DISCOVERY OF C. ROSEUS AS AN ANTICANCER AGENT

Vinca alkaloids were the first plant based antimitotic medicines belonging to the plant kingdom to be introduced in the drug market [11]. Two teams, one Canadian and one American, independently discovered the antitumor properties of C. roseus. One of the founding members of the university of Toronto's insulin team, Clark Noble, sent C. roseus leaves to his brother Robert Noble in Jamaica to treat diabetes in the early 1950s. The challenge for R. Noble, who was working in Collip's Laboratory at the University of Western Ontario, was to find substances that could have impact on blood glucose levels. In place of these properties, R. Noble discovered a significant impact on white blood cell counts and bone marrow. [15] They observed that a considerable reduction in white blood cells, granulocytopenia and bone marrow destruction in rats instead of the anti-diabetic actions. [11]

This theory was soon rejected, because there were no reduction in blood sugar levels in treated rabbits was observed. On the other hand, leukopenia caused the animals to die from septicaemia. [11] And further research shown that they could extend the lives of transplanted rats with lymphocytic leukaemia. This unexpected finding indicates that vinca alkaloids and cancer may be related .Possibilities of vinca alkaloids as potent anticancer drugs were investigated and evaluated .[16]Consequently, he isolated the active ingredient, then known as vincaleukoblastine but now known as vinblastine, along with the scientist Charles T Beer.[15]

When Svoboda, Johnson, and collaborators at Lilly laboratories noticed a repeatable anti-tumor activity of extracts of C. roseus leaves, their other research also contributed to the isolation of vinblastine. Other bioactive alkaloids were also discovered as a result of these studies. As a result, periwinkle leaves were used to isolate luiocristine, also known as vincristine [15].

Accordingly, a phytochemical study led to the separation and the identification of Vinblastine (VBL) The prototype of vinca alkaloids – this compound is able to cause myelosuppression in xenograft mouse models of leukemia. This outstanding discovery opened the door toward a new therapeutic approach against cancer. Thus, the Food and Drug Administration (FDA) approved vinca alkaloids as pharmaceutical strategy against different tumor types (i.e. leukemia,Hodgkin's lymphoma, lung cancer, breast cancer) [11]

V. MECHANISM OF ANTITUMOUR ACTION

The main mechanisms of vinca alkaloids cytotoxicity is due to their interactions with tubulin and disturbs the function of microtubule, particularly of those microtubules that make the mitotic spindle apparatus, directly causing metaphase arrest in dividing cells [17]

Tubulin heterodimers (α- and β tubulin subunits) make up the basic skeleton of microtubules, which develop into the mitotic spindle and bind to the chromosomes during mitosis. Chromosomes are either pulled or pushed toward the cell poles by microtubules, depending on whether they are in a state of rapid shrinkage or slow expansion [16] Binding sites are connected by the vinca alkaloids about tubulin [18] Vinca alkaloids typically attach to microtubules at two different locations: Tubulin binds to the surface of microtubules with a high affinity at the plus ends and a low affinity along the sides [16]. Binding happens quickly and can also reverse. There are two vinca alkaloid binding sites per mole of tubulin dimer, according to the evidence currently available [19] Each microtubule has close to 16–17 high-affinity binding sites, which are found at the ends of each microtubule.Binding of the vinca alkaloids to these sites disrupts microtubule congregation. One of the most significant effects of low drug concentrations can be a decrease in the rates of both growth and shortening at the assembly end of the microtubule, which can produce a "kinetic Cap" and suppress function [20].

Vinca alkaloids cause metaphase arrest by disrupting microtubule dynamics, especially at the ends of the mitotic spindle, at drug concentrations lower than those that cause a reduction in microtubule mass. [21] Vinca alkaloids are classified as destabilising substances that disrupt microtubule polymerization, cause microtubule depolymerization, and finally stop mitotic progression, which eventually causes cell cycle arrest and cell death. [16]

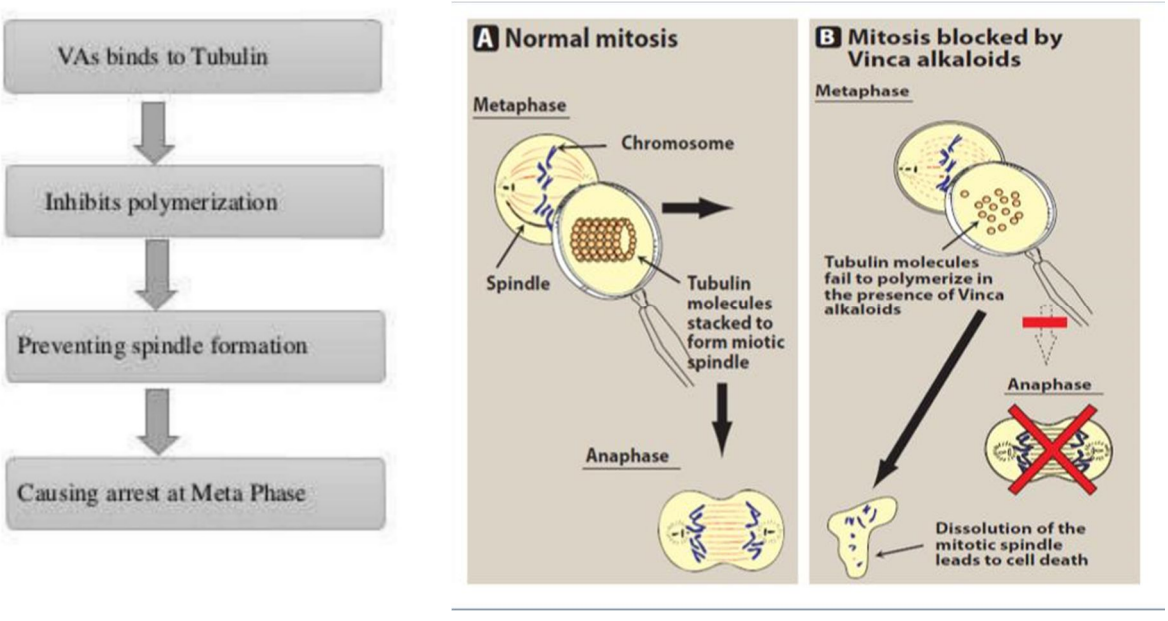


Figure 2 mechanism of action of vinca alkaloids [8]

A. Case Studies

Vincristine was administered to 40 individuals with malignant neoplastic disease in an effort to determine its toxicity, tolerable dose, the impact of varied dose schedules, and antitumor characteristics. The weekly schedule tolerable dose for the majority of patients is 0.05 mg per kg due to the dose-related toxicity of vincristine. The tolerable dose per unit time is unrelated to the delivery schedule. The neuromuscular system and the gastrointestinal tract are predominantly affected by the toxic symptoms. These manifestations are transitory and non-accumulative at the tolerable dose or lower. Rare cases of hematologic toxicity and thrombocytosis can occur in patients.

In the majority of patients with lymphoma, vincristine causes tumour regression, and its activity compares favourably to that of the alkylating agents. [22]

In phase II investigation of vinblastine, 51 patients were prospectively enrolled (range: 1.4 to 18.2 years; median: 7.2 years). Ten patients had previously received radiation therapy, and fifty patients had at least one prior chemotherapy cycle. Thirty-one patients finished a full year of treatment out of fifty patients who were evaluable for response; 18 patients (36%) had a complete, partial, or modest response. 23 patients had not progressed at a median follow-up of 67 months, and three patients had passed away. Five-year progression-free survival was 42.3% 7.2%, and five-year overall survival was 93.2% 3.8%. Despite a few individuals needing blood transfusions, toxicity was primarily hematologic and treatable. For juvenile LGG patients who have received treatment, weekly vinblastine appears to be a viable substitute for radiation.[23]

When xenografts were evaluated, vinflunine demonstrated definite (high or moderate) antitumor Activity in 64% (seven out of 11), but vinorelbine only demonstrated moderate activity in 27% (three out of 11). (Kruczynski et al, 1998a, b; Hill et al, 1999). Additionally, vinflunine clearly showed cytotoxic action in a preclinical study on a murine bladder cancer cell line (MB-49) (Bonfil et al, 2002). Thus, vinflunine was seen to be a promising option for additional clinical research on bladder cancer. The 3 weekly plan was chosen for phase II examination after the single drug vinflunine was examined in numerous clinical phase I trials using various schedules (Delord et al., 2001; Bennouna Et al., 2003; Johnson et al., 2005).[24]

Gasparini et al. evaluation shows that the efficacy and toxicity of Vinorelbine in patients with breast cancer who have previously treated with other chemotherapeutic regimens for metastatic disease showing that vinorelbine is an efficient and well-tolerated treatment for individuals with advanced breast cancer who have already received treatment. Drug does not seem to present cross-resistance with earlier chemotherapeutic regimens. [12]

VI. SIDE EFFECTS AND COMPLICATIONS OF CANCER THERAPY

Nowadays chemotherapy , radiations surgery are standard methods for treatment of cancer, but they haven't always been completely effective .Although some improvement has been made in cancer diagnosis and treatment, but high incidence rate of cancer and low survival rate of patient Are still being reported on a global scale[5]However, the drug resistance is a common problem of chemotherapy which strictly restrict the cancer therapeutic effect[16]The development of side effects from chemotherapy and radiotherapy, on the other hand, restricts therapeutic utilization.[4]

Since cancer cells lose many of the regulatory functions present in normal cells, they continue to divide when normal cells do not. Because of this feature cancer cells are more susceptible to chemotherapeutic drugs. [25]chemotherapy's intended purpose is to kill the tumor cells, diverse range of normal cells is also affected, leading to many adverse side effects on multiple organ systems .[5]

Table 2. Cancer treatment and their side effects [7]

Cancer Treatment	Side effects
Surgery	Bleeding, blood clots, damage to nearby tissues, pain, and infection
Radiation therapy	Fatigue, skin irritation, fever/chills, and mild-faint
Chemotherapy	Damage in many organ cells like the bladder, heart, kidneys, lungs, and nervous system, as well as hair follicles
Targeted cancer therapy	Skin problems, intense itching, allergies in the skin, trouble breathing, and dizziness

Taxanes—paclitaxel (Taxol), docetaxel (Taxotere), Dalbumin-bound paclitaxel (Abraxane), Anthracyclines—doxorubicin, pegylated liposomal doxorubicin, epirubicin, Platinum agents—cisplastin, carboplastin, etc.—are among the effective chemotherapeutic medicines. These medications all have severe adverse effects that can affect the kidneys, the liver, the nerves, and the blood vessels. Damage, loss of hearing, decreased blood count, etc. localised toxicity affecting mucosa cells that results in irritable urinary and blood loss [26], [27], [28]

Over 75% of cancer patients experience side effects from their treatment, such as fatigue, nausea, vomiting, pain, rashes, infections, and headaches, which significantly lowers their quality of life. They also have an impact on the patients' nutritional state, which can lead to malnutrition, which is one of the main causes of cancer patient mortality [5].By applying evidence-based preventative techniques, a significant number of cancer cases can be avoided or treated.

Both in developing and industrialised countries, plant-based medications have become potential alternatives to chemotherapy. Alkaloids are secondary plant metabolites that have shown efficacy and acceptability in the treatment of cancer. [1] Although there are many chemotherapeutic Procedures being used to treat cancer, which are the primary cause for high mortality is cancer relapse and drug resistance.

Research on numerous phytochemicals, the organic substances derived from plants, has shown that they have anticancer properties and are useful for treating other diseases. [4]

Vindesine is the first analogue of vinblastine for clinical use. It is a second-generation semi-synthetic vinca alkaloid having broad-spectrum anti-tumor activities with lower neurotoxicity. Vindesine is preferred over vinblastine due to its lesser liver toxicity in combination drug therapy [1] Vinflunine is also a brand new synthetic vinca alkaloid, which has been approved and licensed in Europe for the treatment of second-line transitional cell carcinoma of the urothelium is being developed for other malignancies. [9]In essence, rigorous control over the administration of these medications is required to minimise their side effects. Some anticancer treatments are consumed in smallest doses or given topically. A superior method for reducing the local action of cancer cells at an externally affected portion is topical treatment. [29]

The most recent one, vinflunine, develops drug resistance more gradually than vinorelbine and has higher in vivo activity than vincristine, vinblastine, and vinorelbine. As a result, vinflunine appears to be a viable option and active against lung cancer. [16]Cancers typically have many mutations, but they can also become dependent on one particular mutation to drive tumour growth. Therapeutic agents with higher specificities of action and efficacy than chemotherapy that target specific critical molecules involved in tumour growth and progression. While either mutations or target modifications provide resistance, much like chemotherapeutic drugs. Clinically, the use of targeted medicines in combination with chemotherapy would seem to be promising [16].

VII. COMBINATION THERAPY OF VINCA ALKALOIDS [30]

Combination therapy is a viable approach for lessening the negative effects of vinca alkaloids and overcoming cancer treatment resistance.

Which are coupled with other chemotherapy medications to increase their anticancer effects. To enhance their therapeutic impact, drugs are frequently taken in a cocktail form or in a sequential order.

CVP, a first-line therapy for follicular B-cell lymphoma, is vincristine coupled with cyclophosphamide and prednisone. Patients with either follicular or diffuse large B-cell lymphomas are treated in the first instance with cyclophosphamide, doxorubicin, vincristine, and prednisone (also known as CHOP). For individuals with diffuse large B-cell lymphoma and follicular lymphoma, rituximab coupled with CVP or CHOP gives another first-line treatment. When combined with other chemotherapy drugs, vinblastine can be used to treat a variety of tumour types.

The VCRT regimen, also called as vinblastine, cisplatin, and radiation treatment, is used to treat non-small-cell lung cancer stages IIIA and IIIB. Patients with disseminated nonseminomatous germ-cell cancers are treated with CISCA/VB, which is a combination of cisplatin, doxorubicin, cyclophosphamide, vinblastine, and bleomycin.

For Hodgkin's lymphoma, doxorubicin, bleoycin, vinblastine, and dacarbazine combination therapy is the usual chemotherapy regimen.

The chemotherapeutic drug vinorelbine is also used to treat different malignancies. Non-small-cell lung cancer is treated with vinorelbine with cisplatin. In 2014, a novel thoracic radiotherapy plan combining vinorelbine and cisplatin was created; patients with stage III A and stage III B non-small-cell lung cancer who had this form of chemotherapy showed promising outcomes.

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Table 3 Examples of combination therapies for anti-cancer [11]

Combination therapy	Application
CVP (cyclophosphamide, vincristine and prednisone)	First-line therapy for folicular cell tymphoma
CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)	Front line therapy for follicular or diffuse large B-cell lymphoma
VCRT (vinblastine, cisplatin and radiation therapy	Treat IIIA and IIIB non-small Cell lung cancer
CISCAVB (cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin)	Non seminonuous germ cell tumors
ABVD (doxorubicin, bleomycin, vinblastine and Dacarbazine	Standard chemotherapy for Hodgkin's lymphoma
Rituximab combines with CVP or CHOP	first-line therapy for diffuse large B-cell lymphoma and follicular lymphoma
vinorelbine and cisplatin	adjuvant chemotherapy for non-small cell lung cancer
a thoracic radiation scheme, vinorelbine and cisplatin	stage III A and stage III B non-small cell lung cancer

VIII. ADMINISTRATION, DOSE, AND SCHEDULE [31]

It is advised that the vinca alkaloids be supplied via quick intravenous injection, possibly through a continuous parenteral infusion. To prevent injection site responses after treatment, the vein should continue to be flushed. The catheter shouldn't be taken out before the vein has been flushed since insufficient flushing may raise the risk of phlebitis.

Children over 10 kg are frequently given VCR as a bolus intravenous injection at a dose of 1.5 to 2.0 mg/kg per week, whereas smaller kids are given 0.05 to 0.65 mg/kg every week. The typical weekly dose for adults is between 1.4 and 2.0 mg/kg. Early reports of significant gastrointestinal toxicity in a small number of patients treated at larger dosages led to a general adoption of "capping," or limiting the absolute dose of VCR to 2.0 to 2.5 mg in children and 2.0 mg in adults. Additionally, studies on adults show the safety and effectiveness of treatment plans without "capping" at 2.0 mg.

In any case, doses shouldn't be decreased for mild peripheral neurotoxicity, especially if the drug is being taken in a setting where it could be therapeutic. Instead, until toxicity resolves, doses should be adjusted for symptoms suggestive of more severe neurotoxicity, such as extreme symptomatic sensory alterations, motor and cranial nerve impairments, and ileus. It is also advised to follow a regular prophylactic practise to avoid the negative effects of severe autonomic poisoning, especially severe constipation.

The VBL schedule that is the most popular Rapid intravenous injections at a dose of 6 mg/m2 per week are used in combination chemotherapy regimens. For children and adults, the recommended weekly doses are 2.5 and 3.7 mg/m2, respectively, with hematologic tolerance determining a gradual increase in dose by weekly increments of 1.8 and 1.25 mg/m2. Weekly VBL doses of 18.5 mg/m2 for adults and 12.5 mg/m2 for children should not be exceeded as a single drug; however, even on less frequent schedules of administration, most patients cannot tolerate these doses because of myelosuppression. Given the significant variation in the severity of leukopenia that may result from identical VBL doses, VBL should generally only be administered once per week.

Many other intravenous administration regimens, such as weekly and biweekly bolus and longer infusion programmes, have been used to administer VDS. As an intermittent or continuous infusion over the course of 1 to 5 days, the medication has also been administered in fractionated dosages. Every 7 to 14 days, a single intravenous dosage of 2 to 4 mg/m2 of VDS is typically delivered. VDS dosages of 1.2 mg/m2/d for five days every three to four weeks or 1 to 2 mg/m2/d for one to two days are typically used in intermittent or continuous infusion regimes.

VRL is typically given on a weekly or biweekly schedule at a dose of 30 mg/m2 through a side-arm port as a 6- to 10-min intravenous injection into a running infusion (or, alternatively, as a slow bolus injection followed by flushing the vein with 5% dextrose or 0.9% sodium chloride solutions), or as a brief infusion over 20 min.

22–25 It seems that decreased local venous toxicity is linked to faster infusions. Although weekly oral dosages of 80 to 100 mg/m2 are often well tolerated, no suitable oral formulation has yet received approval. Other dosing regimens that have been examined include long-term intravenous infusion schedules, occasional high doses, and chronic oral delivery of modest doses.

The Vinca alkaloids shouldn't be given intramuscularly, subcutaneously, intravesically, or intraperitoneally due to their outstanding vesicant properties. Direct intrathecal injection of VCR and other vinca alkaloids causes a severe myeloencephalopathy that is characterised by ascending motor and sensory neuropathies, encephalopathy, and quick death. This has happened accidentally during clinical mistakes.

IX. CONCLUSION

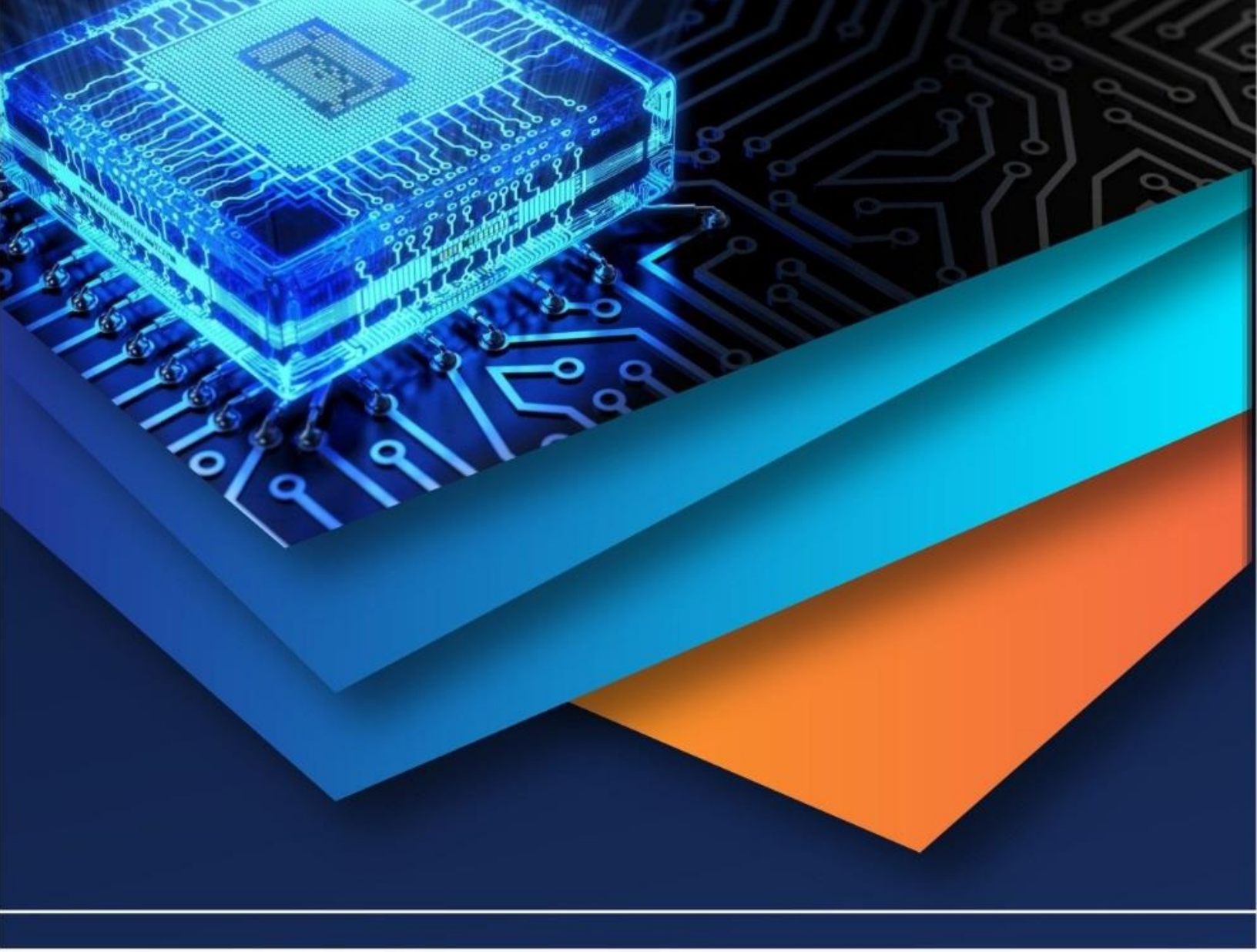
Both developed and developing nations are beginning to place a high priority on the condition of cancer, and both have experienced some progress with treatment.However, the chemotherapeutic medications created through synthesis have limits, primarily because of their harmful effects on non-targeted tissues, which exacerbate human health problems. Modern cancer treatments come with a multitude of undesirable side effects and occasionally don't operate as intended. As a result, there is a need for alternative therapies, with organically produced anticancer medicines being the preferred option.The development of new clinical medications with novel anticancer mechanisms of action Is made possible by the fact that secondary metabolites are themselves suitable anticancer agents. Some of these have already achieved success in the pharmaceutical industry. At the moment, alkaloids are powerful substances that can be used either alone or in conjunction with other anticancer drugs to treat cancer.

Probably because of their potential to be utilised as medications against the treatment of various cancer types, these alkaloids' therapeutic characteristics have drawn scientists' attention for thousands of years. Vinca alkaloids remain among the first cancer treatments and are currently the second most commonly used family of anti-cancer drugs.

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