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ANTICANCER POTENTIAL OF ALKALOIDS: A KEY EMPHASIS TO COLCHICINE, VINBLASTINE, VINCRISTINE, VINDESINE, VINORELBINE AND VINCAMINE

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ABSTRACT

One of the main causes of death globally, cancer continues to be a significant public health concern. The identification of anticancer drugs has been greatly aided by natural compounds made from medicinal plants. The Vinca plant, or Catharanthus roseus (L.) G. Don, is a significant medicinal plant with a high concentration of bioactive alkaloids. Because of their strong anticancer effects, vincristine and vinblastine are the most important of these substances. These alkaloids work therapeutically by blocking the synthesis of microtubules during cell division, which stops cancer cells from proliferating and causes cell death. Vinca alkaloids have been used extensively in the treatment of lung cancer, breast cancer, leukaemia, lymphoma, and other solid tumours. The phytochemistry of Catharanthus roseus, the processes underpinning Vinca alkaloids' anticancer action, their therapeutic value, clinical uses, and new developments in cancer research are all highlighted in this paper. A variety of promising alkaloids, including colchicine, vinblastine, vincristine, vindoline, vinorelbine, and vincamine, are covered in this review in various areas of thorough information about these compounds, including their traditional and modern medical uses, their mechanism of antitumor action, and possible in-vitro scale-up biotechnological research. Future research on Vinca-derived chemicals may help create safer and more potent anticancer treatments. In both industrialized and developing countries, plant-based medications have appeared as promising preventive chemotherapy treatments. Alkaloids and other secondary plant metabolites have proved acceptability and effectiveness in the treatment of cancer.

KEYWORDS: chemotherapy, medicinal plants, anticancer activity, Colchicine vinca alkaloids, vincristine, vinblastine, and Catharanthus roseus.

1. INTRODUCTION

Cancer, a rapid formation of abnormal cells in an uncontrolled manner due to various modifications in gene expression, is one of the leading illness-related deaths worldwide. In 2020, it accounted for nearly 10 million deaths globally, forming a major part of breast cancer > Lung cancer > Colon and rectum cancer > Prostate cancer > Skin cancer > and Stomach cancer related new cases. N comprehensive treatment of cancer is generally available in 90% of high-income countries, but it is only 15% in low-income countries, thus putting a tremendous economic cost on treatment (WHO, 2020). In 2010 alone, the total economic cost of cancer was estimated to be US$ 1.16 trillion. Nevertheless, many cancers have a high chance of being cured if diagnosed early and treated appropriately A 30–50% of cancers can be prevented by avoiding risk factors and implementing evidence-based preventive strategies.[2-4]

For cancer treatment, plant secondary metabolites as chemo-preventive agents are well classified and recognized as bioactive compounds for primary and secondary prevention. Consequently, many pieces of evidence prove that higher consumption of secondary metabolites can lower cancer development. These

compounds have a regulatory effect on metabolic and signalling pathways, thus controlling the angiogenesis, and inhibition of microtubule assembly formation in cells and its apoptosis. The secondary metabolites can be broadly classified into alkaloids, terpenes, flavonoids, lignans, steroids, curcumins, saponins, phenolics, and glucosides. These secondary metabolites, either in individuals or in a group can be used for designing personalized cancer prevention programs as these plants based bioactive compounds present much required Geno-protective effects such as DNA damage protection in healthy cells. This review covers various anticancer alkaloid compounds, including (i) colchicine, (ii) vinblastine, (iii) vincristine, (iv) vindesine, (v) vinorelbine, and (vi) vincamine,[1] in various areas of current knowledge about these compounds, including their traditional and modern medical uses, their mechanism of antitumor action, and possible scale-up biotechnological research on in vitro studies. The review will be a useful tool for the creation of various alkaloids used in plant-based anticancer therapy.[5-7]

During the mid-twentieth century, the UAE rose to become one of the fastest growing economies globally. This growth leads to economic, sociodemographic, and lifestyle changes of the population, paralleled by an epidemiological increase in the rates of non-communicable diseases (NCD) and cancer. Later studies in the UAE linked this increase in cancer with an exposure to several risk factors, including physical inactivity and sedentary lifestyles, the consumption of high-caloric and poorly nutritive meals, an increase in obesity, an increase in smoking, and elevated air pollutant levels. There is an impact of improved cancer diagnostics. The reported deaths due to NCD in 2016 were 77.3% of all deaths. The main causes of deaths are cardiovascular diseases (40%) and cancer (12%).[1-2]

Communicable, maternal, perinatal, and nutritional conditions cause around 6% of all deaths, while chronic respiratory diseases and diabetes represent about 5% each Approximately 90% of head and neck cancers are squamous cell carcinomas. Worldwide, tobacco and alcohol use are the most prevalent risk factors.

In the US and Europe, 60% to 70% of newly diagnosed oropharynx cancers (a subset of head and neck cancers) are caused by human papillomavirus (HPV) infection. At presentation, approximately 30% of patients with head and neck cancer have early-stage or localized disease (tumour <4 cm without regional lymph nodes involvement), 60% have locoregionally advanced disease (tumour ≥4 cm with local invasion and/or regional lymphadenopathy) and 10% have metastatic disease. Up to 10% of oropharynx squamous cell carcinomas present as squamous cell carcinomas of unknown primary.[2]

Standard treatment for localized head and neck cancer is surgery or radiotherapy, which are each associated with a 5-year overall survival rate of 70% to 90%. For locoregionally advanced head and neck cancer, multimodality treatment includes surgery followed by postoperative radiation with or without chemotherapy or concomitant chemotherapy (with cisplatin as the preferred agent), and radiation with surgery is reserved for persistent or recurrent disease. With these treatments for locoregionally advanced head and neck cancer, 5-year overall survival rates are 25% to 60% and more than 80% for HPV-associated oropharynx cancer.[2,3]

Choice of treatment for locoregionally advanced head and neck cancer should involve shared decision-making and consideration of effects on speech and swallow function and appearance. First-line treatment for patients with incurable locoregional recurrences or distant metastatic disease is immunotherapy with programmed death ligand-1 inhibition (i.e., pembrolizumab) alone or in combination with platinum-doublet chemotherapy. With treatment, patients with incurable locoregional recurrences or distant metastatic disease have a median survival of 12 to 15 months, and 5-year survival rates are less than 20%. Surgery, radiotherapy, and chemotherapy from the conventional approaches are used to treat cancer.[4]

Surgery was the first modality used successfully in the treatment of cancer. It is the only curative therapy for many common solid tumours. The most important determinant of a successful surgical therapy is the absence of distant metastases and no local infiltration. Chemotherapy is the administration of cytotoxic agents (orally or intravenously, usually in combinations) resulting in cytotoxicity to both resting and dividing cells. The aim of cancer chemotherapy is to prevent cancer cells from multiplying, invading, metastasizing, and killing the patient. Systemic chemotherapy is the main treatment available for given malignant diseases. Radiation therapy is a local modality used in the treatment of cancer. Other conventional techniques used in the treatment of cancer including bone marrow transplantation, peripheral stem cell transplantation, hormone therapy, photodynamic therapy, cryosurgery, immunotherapy, and gene therapy.[4]

Is cancer curable? The short answer to this question is “Yes.” In fact, all cancers are curable if they are caught early enough. That is the justification for screening tests (such as mammograms, colonoscopies, and Pap smear examination). When cancers are caught early, they tend to be smaller; they are thus either easier to remove surgically or more likely to shrink in response to chemotherapy or radiation therapy.

When cancer is localized, it can be totally removed by surgery but in most of the cases, it is practically impossible to detect cancer at such an early stage. Early detection is often the key to surviving any form of cancer.

The diagnosis and treatment of cancer have come a long way in the last 50 years. In the past, cancer, the "C-word," was a death sentence. Today, we can treat and cure several types of cancer; however, these cancers need to be found at an early stage. More than 7 out of 10 children are cured of cancer. Testicular cancer, Hodgkin's lymphoma and many cases of leukaemia can all be cured in adults with current treatments. Most skin cancers are cured with surgery. Moreover, many cases of thyroid cancer and cancer of the larynx are cured with radiotherapy. Many other types of cancer are also cured if they are found early enough – for example, 75% of breast cancers found at an early stage. Of course, there is still a long way to go before we can cure most cancers. The difficulty is that different cancers are caused by different things, so there is not one strategy that can prevent them.[5-7]

They also respond to different treatments, so not one kind of treatment can cure them all. Even though we can cure several types of cancers, it is important to maintain vigilance about screening for cancer.

Cancer is a key threat to people's health and life, accounting for ∼13% of all disease-causing deaths in the world. In 2007, 7.6 million people died of cancer world-wide. In the U.S, over 1.4 million new cancer cases were reported each year in the past few years, and cancer becomes the second leading cause of death following heart disease. Statistics from the SEER reports write down that the mortality rate across all cancer types in the U.S. went from 195.4 per 100,000 cases in 1950, continued an upward trend till 1978 reaching 204.4, and then steadily decreased to 184.0 in 2005. This decreasing trend has been mostly due to the improved diagnostic techniques for detecting the early stage of cancer. General survival statistics of cancer show that early detection and treatment are the key to longer survival across all cancer types.

Challenges in early cancer detection arise mainly from the reality that most patients are asymptomatic in the first stages of cancer, and only a few effective cancer-screening tests are clinically available. While some tests have proved to be effective in detecting cancer at its early stage, they are often too invasive, such as colonoscopy, to be routinely used during regular physicals and are currently limited to only a small number of cancer types. Often a cancer is already in an advanced stage when diagnosed; clearly, more effective techniques for early cancer detection are needed.[7]

A few genetic markers have been proposed for various cancers, such as BRCA1 and BRCA2 for breast cancer and CDH1 for gastric cancer. In addition, a few promising serum markers for cancer have been used clinically. Among them, PSA (prostate-specific antigen) is the most well-known and has been widely used for diagnosing prostate cancer through blood tests. However, its effectiveness of detection is far from adequate, widely considered as having a false positive rate that is too high to be a reliable cancer-indicator. Similar observations have been made about other serum markers such as CA125 for ovarian cancer.[7]

Herein we present a computational study on prediction of both genetic and serum markers for seven cancer types, based on public microarray gene-expression data and a computer program for prediction of blood-secretory proteins. Compared to earlier studies on cancer marker identification, including meta-analyses on multi-types of cancers, the present study has the following unique features: (i) a focus on identification of multi-gene markers through exhaustive analysis of all possible combinations of genes, taking full advantage of the available high-level computing power, rather than using heuristic approaches that may not necessarily find the optimal markers; (ii) an attempt to find markers for groups of cancers in addition to those for individual cancers; (iii) an attempt to link the information derived from transcriptomic data of tissues to marker prediction in serum using the novel prediction program ; and (iv) identification of pathways that are abnormally regulated, either common across multiple cancer types or specific to individual cancer types.[7,8] We believe that these novel data will prove highly valuable in elucidating the genetic alterations in various cancers, as well as offering potential directions for new approaches in diagnostics and therapeutics. A class of organic compounds obtained from plants, which has hydrogen, oxygen, nitrogen, carbon groups and has the alkaline properties they are known as the alkaloids. The group of alkaloid plants used in the treatment of cancer are the vinca alkaloids. It is a class of anti-mitotic agents and anti-microtubule alkaloids; it blocks the beta-tubulin polymerization in dividing cell. Which helps in treating the cancer growing cells. Types of vinca alkaloids some of them are Vinblastine (VBL), Vincristine (VCR), Vinorelbine (VRL), Vindesine (VDS), Vinflunine, etc. are majorly used in clinical treatments Vindesine, a vinca alkaloid that has broad spectrum antitumor activity in-vitro also less neurotoxicity. VDS administered with methotrexate in L1210 leukaemia cells which result in 200% increment in the life span of mice, while vindesine administered with Epirubicin didn't affect the efficacy of the drug. Vindesine has antineoplastic activity reported in acute lymphocytic leukaemia, malignant melanoma, breast, oesophageal and colorectal carcinomas. Vinflunine, the first fluorinated microtubule inhibitor that belongs to the vinca alkaloids. It used as the first line advanced breast cancer treatment.

Table 1: Some major patents on vinca alkaloids and its derivatives used in cancer therapy.

S.No.	Patent No.	Title	Inventor	Year/ [ref.]
1.	US4,210,584A	Vindesine synthesis	Gloria c. Paschal, Gerald L. Thompson	Jul.1,1980
2.	US4,375,432A	Method of preparing vincristion	Robert A. Conrad	Mar.1,1983
3.	US4910138A	Use of an organ culture of catharanthus roseus to produce vincristion and vinblastion	Yoshiharu Miura, Kazumasa Hirata.	Mar.20,1990
4.	US5047528A	Process of synthesis of vinblastion and vincristion	James P. Kutney, Lewis S. L. Choi, Jun Nakano, Michel McHugh	Sep.10,1991
5.	US 6,365,735 B1	Vinca – alkaloid derivatives and preparation method	Patrice Rool	Apr.2,2002
6.	US 7,235,564 B2	Vinorelbine derivatives	Ian L. Scott, Jeffery M. Ralph, Matthew E. Voss	Jun.26,2007

Introduction Catharanthus is a perennial tropical medicinal plant belonging to the Family Apocynaceae which forms eight species, seven endemic to Madagascar (C. coriaceus, C. lanceus, C. longifolius, C. ovalis, C. roseus, C. scitulus, C. trichophyllus), and one, C. pusillus, from India. Specifically, C. roseus is a decorative and curing plant of enormous pharmaceutical interest because it is nothing less than a chemical factory, producing more than 130 different terpenoid indole alkaloids (TIAs), some of which show strong and important pharmacological activities. Vinca alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant. They are naturally extracted from the pink periwinkle plant Catharanthus roseus G. Don and have a hypoglycaemic as well as cytotoxic effect. The vinca alkaloids are also important for being cancer fighters.[9]

There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VCR, VBL and VRL have been approved for use in the United States. Vinflunine is also a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium is being developed for other malignancies. Vinca alkaloids are the second-most used class of cancer drugs and will stay among the original cancer therapies. Vinca alkaloids were found out in the 1950's by Canadian scientists, Robert Noble and Charles Beer for the first time.

Medicinal applications of this plant lead to the monitoring of these compounds for their hypoglycaemic activity, which is of little importance compared to their cytotoxic effects.[9]

The leaves and stems are the sources of dimeric alkaloids, vincristine and vinblastine that are indispensable cancer drugs, while roots have antihypertensive, ajmalicine and serpentine. Alkaloids that are isolated from C. roseus are found to be hypotensive, sedative and have tranquilising and anti-cancerous properties. Traditionally, the plant has been used for relieving muscle pain, depression of the central nervous system and wasps' stings. It is used in the cases of nosebleed, bleeding gums, mouth ulcers and sore throats.

It has also been used internally for the treatment of the loss of memory, hypertension, cystitis, gastritis, enteritis, diarrhoea and ~ 723 the raised blood sugar levels. Catharanthus roseus L. is found to be an important source of the indole alkaloids that are present in all plant parts. The plant has been used for the treatment of diabetes, fever, malaria, throat infections, chest complaints and regulation of menstrual cycles and as a euphoriant.[9,10]

The physiologically important antineoplastic alkaloids such as vincristine and vinblastine are present in the leaves, and the antihypertensive alkaloids are found in the roots such as ajmalicine, serpentine, and reserpine. Vinka Alkaloid Vinca alkaloids belong to an important class of anti-cancer drugs.

The mechanism of action of Vinca alkaloids is that they inhibit the cell proliferation by affecting the microtubular dynamics during mitosis, and this causes a characteristic block during mitosis leading to apoptosis. Vinka alkaloids include, Vinblastine (VLB) and Vincristine (VCR), Vinorelbine (VRLB) and Vindesine (VDS) are obtained from the Madagascar periwinkle, Catharanthus roseus G. Don. (Apocynaceae).

2. TYPES OF CANCER

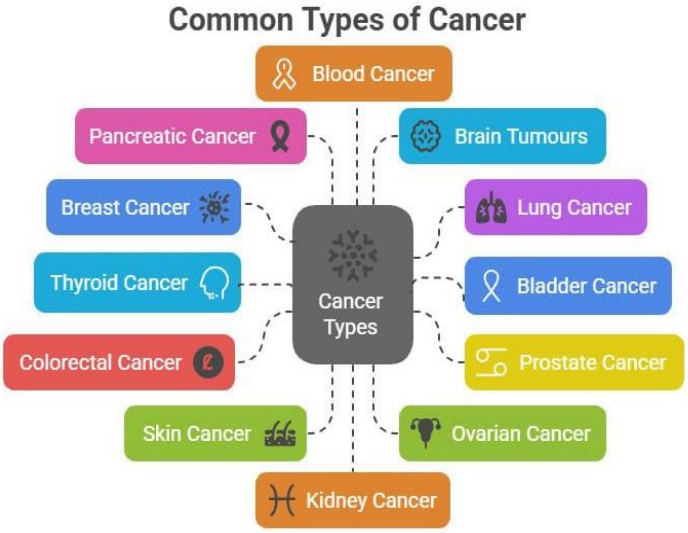

Fig. 1: Types of Cancer.

3. CATEGORIES OF CANCERS

Cancer is a complex disease that can arise from diverse types of tissues in the body. The 31 diverse types of cancer can be broadly categorized into five main groups: carcinomas, sarcomas, leukemias, lymphomas, and central nervous system cancers.[10]

3.1 Carcinomas

Carcinomas are the most common type of cancer, accounting for about 80-90% of all diagnosed cases. They develop from cells that make up the skin or the lining of internal organs and glands. Examples of carcinomas include lung cancer, breast cancer, colon cancer, and prostate cancer.

3.2 Sarcomas

Sarcomas are cancers that develop from cells in the body's connective tissues, such as bone, cartilage, fat, and muscle. They are relatively rare, accounting for only about 1% of all cancer cases. Examples of sarcomas include osteosarcoma, chondrosarcoma, and liposarcoma.

3.3 Leukemias

Leukemias are cancers that begin in blood-forming cells in the bone marrow, which produce abnormal white blood cells that don't function properly. Leukemia is the most common cancer in children, and the eighth most common cancer in adults. Examples of leukemias include acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML).

3.4 Lymphomas

Lymphomas are cancers that begin in the lymphatic system, which is part of the body's immune system. They occur when abnormal lymphocytes (a type of white blood cell) grow out of control. There are two main types of lymphomas: Hodgkin lymphoma and non-Hodgkin lymphoma.

3.5 Central nervous system

cancers Central nervous system (CNS) cancers are those that develop in the brain and spinal cord. They are relatively rare, accounting for only about 2% of all cancer cases. Examples of CNS cancers include glioblastoma, astrocytoma, and ependymoma. Understanding the distinct categories of cancer can help in the development of targeted and effective treatment strategies.[10-12]

4. CENTRAL NERVOUS SYSTEM CANCERS

Central nervous system (CNS) cancers are a group of cancers that affect the brain and spinal cord. They are relatively rare, accounting for about 1.4% of all diagnosed cancers. There are two main types of CNS cancers: primary CNS cancers, which start in the brain or spinal cord, and metastatic CNS cancers, which spread to the brain or spinal cord from other parts of the body. Primary CNS cancers can be further divided into two main types: gliomas and meningiomas. Gliomas develop from glial cells, which provide support and protection for neurons in the brain and spinal cord. There are several subtypes of gliomas, including astrocytomas, oligodendrogliomas, and ependymomas.[12]

4.1 All Treatment Methods

There are several treatment methods for cancer, which may be used alone or in combination depending on the type and stage of cancer, as well as the patient's overall health and preferences. These treatments include:

4.2 Surgery

Surgery is a common treatment for cancer that involves the removal of the tumor and surrounding tissue. It is most effective for solid tumors that have not spread to other parts of the body.

4.3 Radiation therapy
Radiation therapy uses high-energy radiation to kill cancer cells and shrink tumors. It can be used as the main treatment or in combination with surgery or chemotherapy.

4.4 Chemotherapy
Chemotherapy uses drugs to kill cancer cells throughout the body. It may be used before or after surgery, or as the main treatment for cancers that have spread to other parts of the body.

4.5 Immunotherapy
Immunotherapy works by boosting the body's immune system to recognize and attack cancer cells. It is often used to treat cancers that have spread to other parts of the body and is sometimes combined with other treatments.

4.6 Targeted therapy
Targeted therapy uses drugs or other substances to find and attack specific cancer cells without harming normal cells. It is often used for cancers that have specific genetic mutations.

4.7 Hormone therapy
Hormone therapy is used to treat cancers that are hormone-sensitive, such as breast and prostate cancer. It works by blocking the hormones that fuel the growth of cancer cells.

4.8 Stem cell transplant
Stem cell transplant, also known as bone marrow transplant, may be used to treat certain types of cancer, such as leukemia, lymphoma, and multiple myeloma. It involves replacing diseased or damaged bone marrow with healthy stem cells to promote the growth of new, healthy blood cells. It is important to note that the best treatment approach for cancer depends on many factors, including the type and stage of cancer, the patient's overall health, and their individual preferences. A multi-disciplinary team of doctors and specialists will work together to create an individualized treatment plan for each patient.[12]

5. THE CHEMICAL STRUCTURES OF THE MOST REPRESENTATIVE NATURAL ALKALOIDS AND THEIR SEMISYNTHETIC DERIVATIVES ARE USED AS ANTICANCER AGENTS

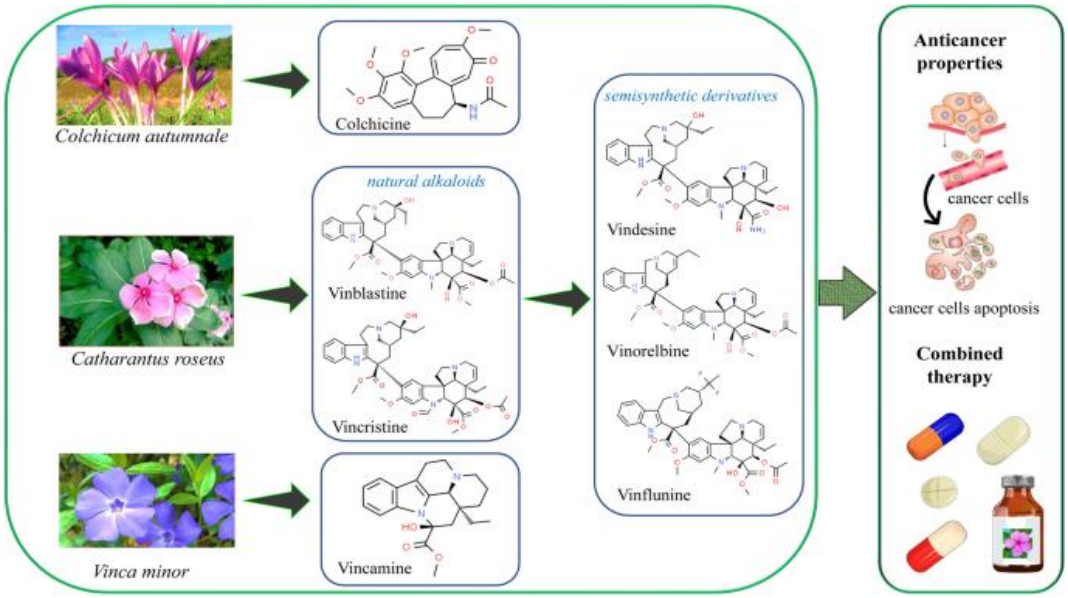

Fig. 2: Chemical constituents and their structures.

6. TRADITIONAL USES OF NATURAL ALKALOIDS

6.1 Colchicine
Colchicine is an alkaloid derived from the colchicum genus, derived from the autumn crocus (*Colchicum autumnale*) and Glory Lilly (*Gloriosa Superba*) plants, found primarily in Europe and North America (Additional file 1). Colchicine has been used in medications approved by the US Food and Drug Administration since 2009. It is a plant water-soluble alkaloid, odourless, with pale yellow needles or powder. The IUPAC name for Colchicine is *N*-[(7*S*)-1,2,3,10-tetramethoxy-9-oxo-6,7-dihydro-5*H*-benzo[a]heptalen-7-yl] acetamide with molecular formula of $C_{22}H_{25}NO_6$. Colchicine is biosynthesized by phenylalanine and tyrosine which process 4-hydroxy-dihydro cinnamaldehyde (4-HDCA) and dopamine. A Pictet–Spengler reaction-based joining of 4-HDCA and dopamine results in a 1-phenethyl isoquinoline scaffold. This scaffold through a series of methylations and phenyl ring hydroxylations produces (S)-autumnaline. The (S)-autumnaline by phenol coupling and methylation results in *O*-methyl andro cymbine, which results in Colchicine by ring expansion and modification of nitrogen atom. This water-soluble alkaloid has been most used as a secondary treatment for gout, working as an anti-inflammatory agent. Derivatives of colchicine, like thio colchicine, deuterium enriched colchicine is also used for

the treatment of pain or inflammation, bone-related disorders, Mediterranean fever (FMF), gout, scleroderma, secondary amyloidosis, Behcet's disease, pericarditis, coronary artery disease, and other inflammatory and fibrotic disease conditions. Several reports proved the efficiency of colchicine in chronic infections, autoimmune, allergic, cardiovascular syndrome, and neurodegenerative diseases. The colchicine drug prevents DNA synthesis and tubulin polymerization, thus halting mitosis.[13]

6.2 Vinblastine

Vinblastine is a natural Vinca alkaloid that was initially found from *Catharanthus roseus* (Fig. 1) (Additional file 1). When the extract was administered to rabbits to explore the plant's putative anti-diabetic function, its potential as a chemotherapeutic agent was first revealed. In the experiment, rabbits died of a bacterial infection due to a lack of white blood cells, and vinblastine was therefore thought to be beneficial against malignancies of the white blood cells, such as lymphoma. Since then, alkaloids have become clinically useful for their antitumor properties. Due to putative hypo-glycemic properties, initially, it was isolated from extracts of *Catharanthus roseus.* It is structurally similar to two compounds of multi-ringed units: vindoline and catharanthine. It clings to tubulin and prevents microtubule formation, causing mitotic spindle assembly to be disrupted and tumour cells to be arrested in the M phase of the cell cycle. Bio molecules like amino acid, cyclic AMP, and glutathione metabolism; calmodulin-dependent Ca++-transport ATPase activity; cellular respiration; and nucleic acid and lipid biosynthesis may all be affected by this molecule. (NCI04). It's used to treat Hodgkin's and non-Hodgkin lymphomas, breast cancer, Kaposi sarcoma, renal cell carcinoma, and testicular cancer. Due to adverse reactions, it causes typical side effects such as myelosuppression, mucositis, fever, anemia, and alopecia.

6.3 Vincristine

Vincristine, also known as leurocristine, is a Vinca alkaloid with formula $C_{46}H_{56}N_4O_{10}$ obtained from *Catharanthus roseus* (Madagascar periwinkle. It appears as a white crystalline solid with a melting point of 218 °C. The IUPAC name of the compound is methyl (1*R*,9*R*,10*S*,11*R*,12*R*,19*R*)-11-acetyloxy-12-ethyl-4-[(13*S*,15*S*,17*S*)-17-ethyl-17-hydroxy-13-methoxycarbonyl-1,11 diazatetracyclo[13.3.1.$0^{4,12}$.$0^{5,10}$] nonadeca-4(12),5,7,9-tetraen-13-yl]-8-formyl-10-hydroxy-5-methoxy-8,16diazapentacyclo [10.6.1.$0^{1,9}$.$0^{2,7}$.$0^{16,19}$] nonadeca-2,4,6,13-tetraene-10-carboxylate. It is commonly used as a chemotherapy drug for the treatment of leukemia, lymphoma, myeloma, breast, head, and neck cancer. It played a vital role as a tubulin modulator, a microtubule-destabilizing agent, a plant metabolite, an antineoplastic agent, and a drug. It is a methyl ester, acetate ester, and tertiary alcohol, a member of formamides, an organic hetero-pentacyclic, and organic hetero-tetracyclic compound. It's injected as an intravenous infusion and can be used in a variety of chemo programs. Its principal applications include non-lymphoma Hodgkin's treatment with CHOP, Hodgkin's lymphoma treatment with MOPP, COPP, BEACOPP, or the Stanford V chemotherapy treatment in acute lymphoblastic leukaemia (ALL), and nephroblastoma treatment. It's likewise used with dexamethasone and l-asparaginase to promote recovery in ALL, as well as in combination with prednisone to manage juvenile leukaemia. Vincristine is used as an immunosuppressant in the treatment of thrombotic thrombocytopenic purpura (TTP) and chronic idiopathic thrombocytopenic purpura (CITP).

6.4 Vindesine

Vindesine is a Vinca alkaloid obtained from vinblastine that is being used to treat a variety of cancers, the most common of which being acute lymphocytic leukemia (Additional file 1). It works by preventing cells from entering metaphase mitosis by inhibiting tubulin mitotic function. The molecular weight of compound is 753.9 and molecular formula is C43H55N5O7 having IUPAC name, methyl (13*S*,15*S*,17*S*)-13 [(1*R*,9*R*,10*S*,11*R*,12*R*,19*R*)-10-carbamoyl-12-ethyl-10,11-dihydroxy-5-methoxy-8-methyl-8,16 diazapentacyclo[10.6.1.$0^{1,9}$.$0^{2,7}$.$0^{16,19}$]nonadeca-2,4,6,13-tetraen-4-yl]-17-ethyl-17-hydroxy-1,11 diazatetracyclo [13.3.1.$0^{4,12}$.$0^{5,10}$] nonadeca-4(12),5,7,9-tetraene-13-carboxylate (Fig. 1). Vindesine is used to treat non-small cell lung cancer and juvenile chronic lymphocytic leukemia that is resistant to vincristine. Vindesine prevents cells from entering metaphase mitosis. In vitro experiments, it is three times more effective than vincristine and approximately ten times more effective than vinblastine at concentrations intended to block 10 to 15% of cells from entering mitosis. At tested doses that block 40 to 50% of cells in mitosis, vindesine and vincristine are nearly equal. In contrast to vinblastine, vindesine produces a small number of post-metaphase cells. Vindesine has shown promise in patients who relapsed after receiving vincristine as part of a multi-agent treatment regimen.

6.5 Vinorelbine

Vinorelbine suppresses cell proliferation by attaching to tubulin, and this distinguishes it from other alkaloids in its field of anticancer activity. Slowing of the growth rate of microtubules, an increase in the length of growth and a decrease in the shortening period are all evidence obtained in vitro on the dynamic instability of cancer cells.

6.6 Vincamine

Vincamine is a monoterpenoid indole alkaloid isolated from the foliage of *Vinca minor* (lesser periwinkle). It accounts for around 25–65% of the indole alkaloids in Vinca minor (Additional file 1). The molecular formula of compound is $C_{21}H_{26}N_2O_3$ and IUPAC name, methyl (15*S*,17*S*,19*S*)-15-ethyl-17-hydroxy-1,11 diazapentacyclo [9.6.2.$0^{2,7}$.$0^{8,18}$.$0^{15,19}$] nonadeca-

2,4,6,8(18)-tetraene-17 carboxylate (Fig. 1). The alkaloid is often used to prevent and cure cerebrovascular diseases and inabilities. It has pharmacological properties in both the central nervous system and the cardiovascular system, but its principal effect is on the brain vessels. It is often used for circulatory disorders, cerebral circulatory illness, assistance for brain metabolism and improved oxygen supply, strengthen prophylaxis, concentration impairment and betterment of memory and cognitive capacity, psychological productivity, prevention of aging of brain cells, improvement of immune function, diarrhoea, throat ailments, vaginal flux, tonsillitis, sore throat, intestinal inflammation, toothache, dropsy, diuretic, and blood-purifying and blood-purifying and wound healing.[13]

7. ANTICANCER/CYTOTOXIC POTENTIAL OF ALKALOIDS: PHARMACOLOGICAL MECHANISMS OF ACTIONS

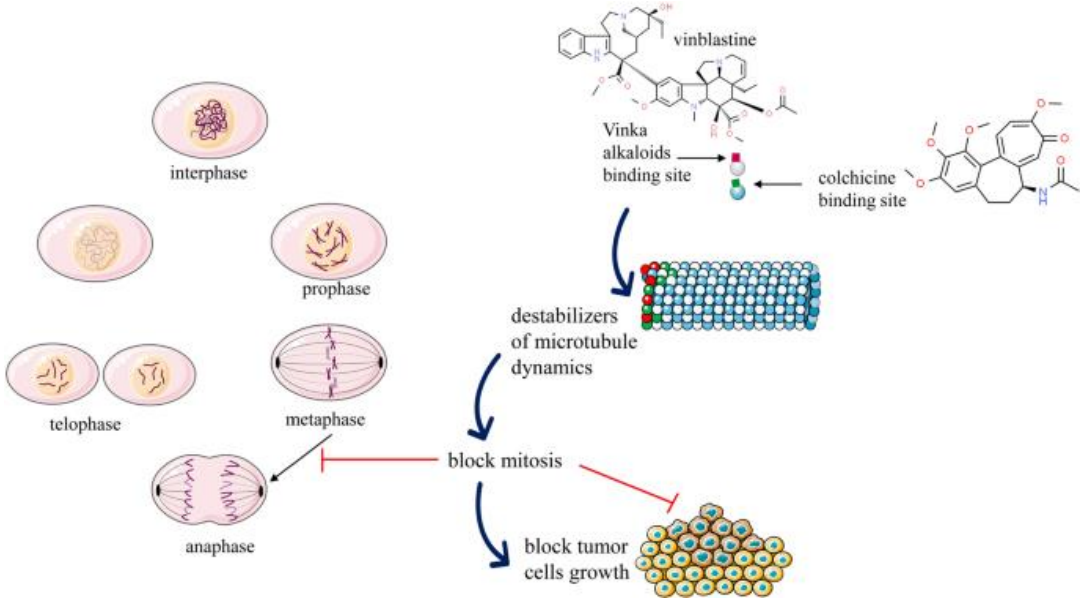

Fig. 3: Mechanism of action of Vinca alkaloids.

Vinca alkaloids act directly on the mitotic phase of cell cycle and stops the further division of the cell division (Figure 3). It binds with the tubulins of spindle fibres and disrupters the micro tubules formation which arrest the cell into the metaphase(Figure 3). Vinca alkaloids depolymerize the micro tubules and destabilized the mitotic spindles which resulting in cell death. Microtubule-targeted antimitotic drugs are classified into two main groups like microtubule-destabilizing agents and microtubule-stabilizing agents. Vinca alkaloids (vinblastine, vincristine, vinorelbine) are examples of microtubule-destabilizing agents.

8. MEDICINAL USES

A source of natural products (Madagascan periwinkle) produces chemotherapy agents (vincristine, vinblastine) which are driven from vinca alkaloids, vindoline and catharanthine. Clinical efficacy of these vinca alkaloids for anticancer properties is broad spectrum by sole use or in combination. Vinca alkaloids shows their effect on both malignant and non-malignant cells.[14-16]

Vinca alkaloids are used for the treatment of several types of cancer therapy, they are given in combined form with other drugs as they did not show any side effect or any cross resistance to the drug molecules. Vinblastine has widely use in the treatment of several types of cancer and use as the major medical treatment in the therapy of testicular 797 World Journal of Advanced Research and Reviews, 2022, 16(03), 794–800 carcinoma. Vincristine is one of the drugs in PCV (Procarbazine, Carmustine, and Vincristine) chemotherapy used for the treatment of brain tumor. VBL can also be used as in the treatment of tumor in germ cells and for the breast cancer treatment.

Some of the side effect of vinblastine, which shows toxicity to white blood cells, vomiting, dyspnea, nausea, tumor pain, wheezing and fever. Vinorelbine shows similar effect as the vinblastine, VRL shows the greater antitumor activity among the patient suffering from breast cancer and shows effect on bone cells tumor, osteosarcoma. Vinorelbine affect the lipid bilayer membrane and decreases the stability. Vincristine can be useful in the treating the acute leukemia, neuroblastoma, wilm's tumor and other lymphomas. It has some common side effect peripheral neuropathy, suppression of bone marrow activity, constipation, nausea and vomiting.

Vindesine, a vinca alkaloid that has broad spectrum antitumor activity in-vitro also less neurotoxicity. VDS administered with methotrexate in L1210 leukemia cells which result in 200% increment in the life span of mice, while vindesine administered with Epirubicin didn't affect the efficacy of the drug.[14,15]

9. TOXICITY

Vinca alkaloids has toxicity profiles in different extensive properties but all the vinca alkaloids has characteristic toxic effect of peripheral neurotoxicity. VBL and VRL shows less frequency towards the severity of neurotoxicity then VCR. VCR shows rare conditions of hematologic toxicity and severs cases with myelosuppression condition. Vinorelbine have a heavy risk of adverse drug reaction to haematological and non-haematological in patients. VBL, VDS, VRL they show main dose limiting toxicity in neutropenia.[16]

Pregnant women should avoid the use of such vinca alkaloid drugs and should not take any vaccine during the treatment with these drugs. Vincristine induces neuropathy; however, it also studies to use an animal model for induction of neuropathy in mice or rat by various authors.[17]

10. CONCLUSION

Alkaloids such as Colchicine from *Colchicum autumnale*; vinblastine, vincristine, vindesine, and vinorelbine (Vinca alkaloids) from *Catharanthus roseus*; and Vincamine from *Vinca minor* are promising anticancer properties. These alkaloids through their binding to microtubulins, one of the key components of the cytoskeleton, form the tubulin-alkaloid complex. These complexes thereof inhibit cancer cell migration and metastatic potential of the cell resulting in Programmed Cell Death and apoptosis of cancer cells.[18] These alkaloids can be used in combination with chemotherapy regimens, as they do not impart cross-resistance to commonly used DNA alkylating drugs. However, a strong spectrum of biotechnological studies on in vitro production of these compounds is needed, to which plant callus suspension cultures with different biotic and abiotic elicitors in bioreactors may have the potential to be new frontiers to produce compounds with anticancer activity. For primary and secondary chemoprevention as well as cancer management, a comprehensive research program is warranted for the discovery of new alkaloids along with their metabolic effects and molecular actions such as vinca alkaloids, to develop novel anticancer drugs followed by clinically relevant recommendations for dose and efficacy, which is often underrepresented.[19]

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