https://doi.org/10.31674/book.2023pcbs003

Role of Paclitaxel and Vinblastine in Modern Cancer Therapy

Suranjana Sarkar
Department of Botany, Surendranath College, Kolkata, West Bengal, India

Corresponding Author's E-mail: drsuranjanasarkar@gmail.com

ABSTRACT

Natural products still account for more than half of all medications in clinical use in the generic age of contemporary biotechnology. According to the World Health Organization, plant extracts are used in 85 percent of out-dated medicine, and around 80 percent of people in underdeveloped nations rely on conventional medicinal substances for their main health care. 62 percent of the 87 anticancer medicines authorised in the last 10 years are natural products. The major drugs among them include paclitaxel and vinblastine, extracted from *Taxus brevifolia* and *Catharanthus roseus* respectively. All of them work by binding to tubulin and altering microtubule dynamics to impede cancer cell proliferation. They trigger apoptosis by causing mitotic arrest. These findings from epidemiological and investigational research emphasise the usefulness of phytochemicals in reducing cancer risk and inhibiting the growth and spread of tumours in investigational animals, which are medically more important. In a range of spontaneous or transplanted lymphocytic leukaemia, paclitaxel and Vinblastine medications have a high inhibitory impact on monozygotic leukaemia, breast cancer, lung cancer, liver cancer, ovarian cancer, solid sarcoma, malignant melanoma, head and neck cancer, and testicular cancer. Anti-tumour effects, on the other hand, still encounter obstacles and have a long way to go. The study and development of these medications will provide more significant results in the future.

Keywords: *Paclitaxel; Vinblastine; Cancer; Taxus Brevifolia; Catharanthus Roseus*

Introduction

Cancer, as a serious public health issue, affects simultaneously both developed and emerging nations globally. In 2018, an estimated 18.1 million new cases of cancer were diagnosed worldwide, with the number expected to rise to 23.6 million new cases per year by 2030 (Bray *et al.,* 2018). Because of this disease's extraordinary notoriety, treating it has been a never-ending battle with mixed results.

Plant phytochemicals and derivatives are promising alternatives to boosting therapeutic efficacy and decreasing unwanted effects in cancer patients. Some of these plant-based, physiologically active substances are naturally occurring. The examination of natural extracts (from dehydrated or wet plant material) is the initial step towards potential biological action against cancer and the creation of effective anticancer therapies based on phytochemicals that have few adverse effects. The effects of the separated active phytochemicals are next examined in vitro and in vivo using bioassay-guided fractionation (Ravina, 2011). Based on their roles, chemotherapeutic drugs that target microtubules are classified into two groups:

Paclitaxel (Taxol) is a microtubule stabiliser that promotes microtubule polymerization, which causes difficulties in chromosomal separation and the cell cycle process. Paclitaxel is commonly used to treat solid tumours such as advanced cases of ovarian and breast cancer, non-small cell lung cancer (NSCLC), and Kaposi's sarcoma (Hennessy, Coleman & Markman, 2009; Takashima *et al.,* 2015). The other is vinblastine, a vinca alkaloid that destabilizes microtubules and prevents cell growth mostly by binding to tubulin and disassembling microtubules. According to Coderch, Morreale and Coderch, Morreale and Gago, (2012) and Koontz *et al*. (2013), vinblastine is frequently used to treat cancers such as choriocarcinoma, Hodgkin's disease, malignant lymphoma, osteosarcoma, breast, ovarian, gastric, and lung cancers. Taxol and Vinblastine consequently interact with tubulin in opposing ways (Shen *et al.,* 2017).

Paclitaxel was found to be a component of the National Cancer Institute screening program launched in 1960 by Dr. Jonathan L. Hartwell, and to have anticancer potential (Wani & Horwitz, 2014). Scientist Wani and his group isolated and identified paclitaxel (which they termed Taxol®) from the bark extract of the Pacific Yew Tree (*Taxus brevifolia*) and conveyed their findings (Wani *et al.,* 1971). Nonetheless, the mechanism of action of paclitaxel as an anticancer medication attracted the interest of cancer pharmacology or pharmaceutical corporations. Dr. Horwitz's laboratory inspected and confirmed that paclitaxel besides having powerful cytotoxic properties capable of inhibiting the developmental development of human cervical cancer cells (HeLa) at nanomolar concentrations, also detained cells in the mitotic (M) phase of the cell cycle while not disrupting the S- phase (Horwitz *et al.,* 1986; Schiff, Fant & Horwitz, 1979). Scientists conducted more biochemical tests and experiments to discover the significant and distinct features of paclitaxel (Rowinsky, Cazenave & Donehower, 1990). Paclitaxel research as an anticancer agent is still ongoing decades later (Barbuti & Chen, 2015).

A vinca alkaloid anti-cancer agent is vinblastine. Vindoline and catharanthine are two multiringed units that make up the structurally related vinca group of alkaloids (Jordan & Kamath, 2007). Since the discovery of the vinca alkaloids' antitumor effects in 1959, they have been effective in clinical settings. The periwinkle plant (*Catharanthus roseus*) extracts were initially looked into for their alleged hypoglycemic characteristics, however it was discovered that they also have antileukemic effects in vitro and marrow suppression in rats. Vinblastine can suppress the immune system in some ways. Cell cycle phase-specificity is thought to apply to vinca alkaloids. The interaction between vinblastine and tubulin, which stops mitosis at metaphase, is considered to be responsible for the majority of the drug's anticancer effects. (Jordan *et al*., 1998; Islam & Iskander, 2004). Vinblastine binds to the proteins in the microtubules of the mitotic spindle, driving the microtubule-crystallisation and causing mitotic arrest or cell death (Gupta & Bhattacharyya, 2003).

Source Plant Material

1. Madagascar periwinkle / Nayantara

   Family: Apocynaceae

Scientific Name: *Catharanthus roseus* (L.) G. Don

Synonym: *Vinca rosea* L.

2. Pacific yew

   Family: Taxaceae

   Scientific Name: *Taxus brevifolia*

Literature Review

Cancer is responsible for approximately 10 million annual deaths worldwide (WHO, 2022). Cancer treatment includes, among other things, surgery, chemotherapeutic treatment, radiation therapy, and medication, all of which not only significantly affect patients' financial situations but also lead to resistance to drugs in patients over time. Implementing evidence-based preventive strategies can prevent or treat a large number of cancer cases. Drugs made from plants have emerged as promising anti-cancer treatments in both developing and developed countries (Garcia-Oliveira *et al.,* 2021). Some alkaloids have already demonstrated efficiency in protecting us against cancer (Dhyani *et al.,* 2022).

***The Pharmacology of Paclitaxel*:**

Microtubules are a dynamic and complex web of tubulin heterodimers comprising and β subunits, participating in many essential cellular activities, including the formation of mitotic spindle fibres required for M-phase cell division (Wilson, 1975). Microtubule-targeting medicines, viz., colchicine and the vinca alkaloids, cause microtubule breakdown. Taxanes, on the other hand, bind to tubulin and prevent microtubule disintegration. Antimicrotubule drugs, whether depolymerizing or stabilising tubulin, alter microtubule dynamics, induce mitotic arrest, and prevent cell division, eventually leading to programmed cell death (Mukhtar, Adhami & Mukhtar, 2014). Paclitaxel, like docetaxel, belongs to the taxane class of anticancer medicines. Though tubulin is the primary target for inducing apoptosis, paclitaxel also targets mitochondria and prevents the apoptosis inhibitor protein B-cell Leukemia 2 (Bcl-2) (Ferlini *et al.,* 2003). Paclitaxel is a very hydrophobic medication that needs appropriate delivery vehicles to properly allocate it into tumour tissues. Paclitaxel is now manufactured and supplied to patients in either polyethoxylated castor oil (Cremophor EL, CrEL) or albumin-bound (nab-paclitaxel, Abraxane®) form for efficient distribution. For many years, intravenous (IV) administration of CrEL-paclitaxel, generally once every three weeks, was a standard method, although it has been linked to hypersensitivity responses and neurotoxicity (Fransson *et al.,* 2011). Fresh paclitaxel preparations incorporating the utilisation of nanoparticles, emulsions, liposomes, and micelles have been investigated to reduce toxicity and improve transport and dispersion (Hennenfent & Govindan, 2006). Because it does not include CrEL, Nab-paclitaxel, a newer albumin-bound paclitaxel nanoparticle version, has been shown to reduce hypersensitivity responses. Indeed, Li et al. revealed variations in the distribution of paclitaxel between CrEL- and nab-paclitaxel. When compared to CrEL-paclitaxel micelles, nab-paclitaxel distribution to peripheral tissue was quicker (4-fold) and more widespread (10-fold) (Li *et al.,* 2015). The study also found that when liberated from the

respective carrier complexes, tissue distribution of free and protein-bound paclitaxel was restricted and sluggish, attesting to the drug's hydrophobic nature.

Taxanes are metabolised by cytochrome P450 enzymes in the liver and removed by biliary excretion (Vaishampayan *et al.,* 1999). Paclitaxel's known metabolites are largely inactive when biotransformed by means of hydroxylation events. These are 6--hydroxypaclitaxel (via CYP2C8), 3′-p-hydroxyphenylpaclitaxel (via CYP3A4), and 6--p-3-dihydroxypaclitaxel (by subsequent CYP3A4 and CYP2C8 metabolism, respectively) (Rowinsky *et al.,* 1993). Paclitaxel's most serious side effects are neutropenia, peripheral neuropathy, and mild cardiotoicity (Vaishampayan *et al.,* 1999). Nonetheless, because paclitaxel is eliminated in the bile, it is frequently the first choice of anticancer treatment in individuals with decreased creatinine clearance or renal illness. The ATP Binding Cassette (ABC) transporter B1 (ABCB1/MDR1/P-gp) has also been discovered to have a function in paclitaxel metabolism (Fransson *et al.,* 2011; Yamaguchi *et al.,* 2006). The involvement of ABCB1 in paclitaxel-treated cells has been linked to drug resistance.

Paclitaxel has been authorised by the FDA to treat AIDS-related Kaposi sarcoma, breast cancer, non-small cell lung cancer (NSCLC), and ovarian cancer, either alone or in combination with other anticancer therapies. It is also being researched for usage in the treatment of various malignancies, including head, neck, esophageal, bladder, endometrial and cervical cancer. Recently, the FDA authorised Abraxane® to treat metastatic pancreatic cancer, non-small cell lung cancer, and breast cancer. The drug management caution that comes with these paclitaxel formulations states that patients' neutrophil counts should be monitored to treat any bone marrow suppression (Barbuti & Chen, 2015). Neutropenia caused by chemotherapy is a typical side effect of numerous anticancer medications.

***Pharmacology of Vinblastin*:**

The natural Vinca alkaloid, Vinblastine, was first discovered in Catharanthus roseus. The plant's potential as a chemotherapeutic agent was initially discovered when the extract was offered to rabbits to investigate the plant's purported anti-diabetic effect. Because the rabbits died of a bacterial infection owing to a huge deficiency of white blood cells in the experiment, Vinblastine was assumed to be useful against white blood cell cancers such as lymphoma (Noble, Beer & Cutts, 1958). It was originally isolated from *Catharanthus roseus* extracts due to its suspected hypoglycemic effects. According to the National Center for Biotechnology Information (2023), it shares structural similarities with two additional multi-ringed compounds, vindoline and catharanthine. It adheres to tubulin and hinders the production of microtubules, disrupting the construction of the mitotic spindle and stopping cancer cells from progressing through the cell cycle's M phase. The metabolism of amino acids, cyclic AMP, glutathione, calmodulin-dependent Ca++-transport, ATPase activity, cellular respiration, and the synthesis of nucleic acids and lipids may all be affected by this molecule. It is used to treat testicular cancer, breast cancer, Kaposi sarcoma, renal cell carcinoma, and Hodgkin's and non-Hodgkin lymphomas. The characteristic side effects, like mucositis, myelosuppression, anaemia, fever, and baldness, are brought on by unfavourable responses.

Vinblastine is rapidly absorbed from the plasma and transported to tissues, notably the lung, liver, spleen, and kidneys (Owellen & Hartke, 1975; Owellen, Hartke & Hains, 1977). Vinblastine, like the other vinca alkaloids, is processed by the hepatic cytochrome P450 3A enzyme. This pathway may be compromised in people with hepatic dysfunction and may be influenced by various medicines that either promote or inhibit cytochrome P450 3A activity. Vinblastine is mostly eliminated in the bile and faeces, with little excretion in the kidney (28).

The pharmacologic behaviour of Vinblastine is similar to that of Vincristine (Owellen, Hartke & Hains, 1977; Zhou *et al.,* 1990). Peak plasma drug concentrations are around 0.4 mol/L following a fast intravenous injection of VBL at normal dosages. Similar to VCR, vinblastine binds extensively to blood components and plasma proteins. Moreover, dispersion is fast, with half-lives of roughly 4 min and 1.6 h for the and β phases, respectively. Similar to VCR, tissue sequestration is significant, with 73% of radioactivity remaining in the body for six days following radiolabelled medication administration (Ratain & Vogelzang, 1986). 20 to 24 hour terminal half-life values have been recorded. Like the VCR, the hepatobiliary system is primarily responsible for vinblastine disposal. Low fecal excretion of the parent substance suggests significant metabolism. Its biotransformation appears to be mostly caused by the cytochrome P450 CYP3A isoform (Zhou *et al.,* 1990; Rowinsky, 2003). The primary metabolite of VINBLASTINE is 4-diacetyl vinblastine, also known as vindesine (VDS), despite the fact that its metabolic destiny has not yet been thoroughly characterized. (Rowinsky & Donehower, 1991; Rowinsky, 2003).

Discussion

Paclitaxel has been used in several anticancer therapy regimens because it is an efficient microtubule stabiliser and radiation sensitizer. However, paclitaxel's therapeutic effectiveness has been proven to promote multidrug resistance (MDR) via numerous cellular contrivances that have yet to be completely comprehended. Resistance to Paclitaxel has been reported to comprise both tubulin mutations, modifications in the binding areas of -tubulin, decreased efficacy of key creator proteins of apoptosis, and variations in cytokine release, in addition to over-expression of the ABCB1 and ABCC10 efflux transporters. Paclitaxel will be delivered to tumour tissue by novel drug delivery technologies such as nanoparticles and targeted drug conjugates, allowing for improved anticancer efficacy and safety. Moreover, novel drugs, as well as already authorised small molecule inhibitors, must be investigated in order to counteract the ABC transport-mediated MDR associated with paclitaxel resistance. Paclitaxel (Taxol®) has been isolated and identified for over 40 years, and its exclusive pharmacokinetic and pharmacodynamic anticancer features continue to support its therapeutic importance. Paclitaxel treatment will continue to transcend the centuries of cancer therapy with additional research focused on identifying the origins of de novo and acquired resistance, together with improved chemotherapy and radiation.

Vinblastine is a mitotic inhibitor used in the treatment of leukaemia, non-lymphoma, Hodgkin's lymphoma, breast malignancies such as breast carcinoma, Wilm's tumour, Ewing's sarcoma, small-cell lung cancer, testicular carcinoma, and germ cell tumours (Dandamudi & Campbell, 2007; Moudi *et al.,* 2013). Vinblastine inhibits not just tumour development but also malignant

angiogenesis and can bind selectively to tubulin, blocking polymerization and following microtubule attachment (Dandamudi & Campbell, 2007; Moudi *et al.,* 2013).

They inhibit microtubule dynamics when administered at very low concentrations and lower microtubule polymer mass when doses are increased. Recent research indicates that they can form microtubule fragments by inducing detachment from microtubule organising centres. These studies show that increased microtubule dissociation from spindle poles correlates best with cytotoxicity (Ganguly *et al.,* 2010). However, research into the process is still ongoing since new findings reveal Vinblastine triggering apoptosis that is phase-independent in some leukemias (Salerni *et al.,* 2010).

In combination with other chemotherapeutic medicines, Vinblastine can treat a wide range of cancers. Vinblastine, cisplatin, and radiation treatment, or VCRT, are used to treat non-small-cell lung cancer stages IIIA and IIIB (Waters *et al.,* 2010). In patients with disseminated non-seminomatous germ-cell cancers, CISCA/VB (cisplatin, doxorubicin, cyclophosphamide, Vinblastine, and bleomycin) is used (Fizazi *et al.,* 2002). As a conventional chemotherapy treatment for Hodgkin's lymphoma it is used along with doxorubicin, bleoycin, and dacarbazine (Schwenkglenks *et al.,* 2010).

Although simple diffusion-like non saturable mechanisms, which are temperature-independent, probably account for the bulk of drug transport (Zhou, Placidi & Rahmani, 1994). This is contrary to the widespread belief that the cellular entry of the Vinca alkaloids occurs through both energy and temperature-dependent transport methods. Drug exposure over a critical threshold concentration is the significant predictor, although drug concentration and treatment time are also significant factors in drug accumulation and cytotoxicity, according to the majority of the evidence now available (Jackson & Bender, 1979). Vinblastine side effects include toxicity to white blood cells, nausea, vomiting, constipation, dyspnea, chest or tumour discomfort, wheezing, fever, and, in rare cases, antidiuretic hormone production (Chen & Zhang, 2004).

Table 1: Comparative Account between Paclitaxel and Vinblastine

	Paclitaxel (Taxol)	**Vinblastine (Velban)**
Chemical Formula:	$C_{47}H_{51}NO_{14}$	$C_{46}H_{58}N_4O_9$
Molecular Weight:	853.9 g/mol (Computed by PubChem, 2019)	811 g/mol (Computed by PubChem, 2019)
Discovery	First isolated in 1971 by Mansukhlal C. Wani, Harold Lawrence Taylor, Monroe E. Wall, Philip Coggon, and Andrew T. McPhail	First isolated in 1958 by Robert Noble, Charles Thomas Beer and Cutts, J.H.
Chemical Nature	Tetracyclic diterpenoid, lipophilic in nature	Natural Vinca Alkaloid comprising of two multiringed units: vindoline and catharanthine
Source Plant Part	Bark of pacific yew tree *Taxus brevifolia*	Mainly obtained from leaves and partly from stems and buds of *Catharanthus roseus*

Physical Nature	This anti-neoplastic drug appears as fine white powder.	White to slightly yellow crystalline solid, melting point is 267˚C
Uses	Ovarian cancer, breast cancer, AIDS related Kaposi's sarcoma cervical cancer, pancreatic cancer and lung cancer.	Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, melanoma, breast cancer and testicular cancer
Mode of Action	Paclitaxel disrupts the normal function of microtubule development by hyper-stabilizing its structure. This robs the cell of its capacity to employ its cytoskeleton flexibly. Paclitaxel specifically targets the tubulin subunit. Tubulin is the "building block" of mictotubules that holds them together. This has a negative impact on cell function since microtubule shortening and lengthening is required for their function as a transportation highway for the cell. Paclitaxel causes programmed cell death in cancer cells by attaching to an apoptosis-inhibiting protein called Bcl-2 (B-cell leukaemia 2) and therefore terminating its action.	The primary mechanism by which vinblastine suppresses mitosis during metaphase is thought to be its interaction with tubulin. Vinblastine interacts to the microtubular proteins in the mitotic spindle, resulting in crystallisation and mitotic arrest or cell death.

Conclusion

The current review aims to assess the anticancer activity of two distinct phytochemicals - Paclitaxel and Vinblastine. Cancer is a constant threat to mankind. These two natural cancer chemo-preventive substances are capable of preventing or suppressing carcinogenesis. Paclitaxel is a medication that is used exclusively or in combination with other medications to address AIDS-type diseases, Kaposi's sarcoma, advanced ovarian cancer, some forms of breast cancer, and non- small cell lung cancer. To treat various forms of cancer, Paclitaxel is being tested. Paclitaxel inhibits cancer cell growth and division, perhaps killing them. Vinblastine has long been used for several forms of advanced lymphomas, and also as a chemotherapy ingredient for germ cell malignancies. Vinblastine has previously been used wholly or in conjunction with other medications to treat different types of cancer. The process of researching and developing these medications will provide additional significant future revelations.

Acknowledgement

The author would like to thank the Government of India's Department of Biotechnology for funding this review study under the DBT-Star College Grant. The author would like to thank the Principal of Surendranath College and the DBT-STAR Coordinator for their assistance and support in carrying out this review project.

References

Barbuti, A. M., and Z. S. Chen. "Cancers, 2015, 7, 2360–2371." Chapter 11–Triazole CBD analogues and Substituted CPPs–References.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 68(6), 394-424. https://doi.org/10.3322/caac.21492

Chen, W., & Zhang, D. (2004). Kinetochore fibre dynamics outside the context of the spindle during anaphase. *Nature Cell Biology*, *6*(3), 227-231. https://doi.org/10.1038/ncb1104

Coderch, C., Morreale, A., & Gago, F. (2012). Tubulin-based structure-affinity relationships for antimitotic Vinca alkaloids. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 12(3), 219-225. https://doi.org/10.2174/187152012800228841

Dandamudi, S., & Campbell, R. B. (2007). The drug loading, cytotoxicty and tumor vascular targeting characteristics of magnetite in magnetic drug targeting. *Biomaterials*, *28*(31), 4673-4683. https://doi.org/10.1016/j.biomaterials.2007.07.024

Dhyani, P., Quispe, C., Sharma, E., Bahukhandi, A., Sati, P., Attri, D. C., ... & Cho, W. C. (2022). Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell International, 22(1), 1-20. https://doi.org/10.1186/s12935-022-02624-9

Ferlini, C., Raspaglio, G., Mozzetti, S., Distefano, M., Filippetti, F., Martinelli, E., ... & Scambia, G. (2003). Bcl-2 down-regulation is a novel mechanism of paclitaxel resistance. Molecular pharmacology, 64(1), 51-58. https://doi.org/10.1124/mol.64.1.51

Fizazi, K., Do, K. A., Wang, X., Finn, L., Logothetis, C. J., & Amato, R. J. (2002). A 20% dose reduction of the original CISCA/VB regimen allows better tolerance and similar survival rate in disseminated testicular non-seminomatous germ-cell tumors: final resultsof a phase III randomized trial. *Annals of Oncology*, *13*(1), 125-136. https://doi.org/10.1093/annonc/mdf005

Fransson, M. N., Green, H., Litton, J. E., & Friberg, L. E. (2011). Influence of Cremophor EL and genetic polymorphisms on the pharmacokinetics of paclitaxel and its metabolites using a mechanism-based model. Drug metabolism and disposition, 39(2), 247-255. https://doi.org/10.1124/dmd.110.035394

Ganguly, A., Yang, H., Pedroza, M., Bhattacharya, R., & Cabral, F. (2011). Mitotic centromere-associated kinesin (MCAK) mediates paclitaxel resistance. Journal of Biological Chemistry, 286(42), 36378-36384. https://doi.org/10.1074/jbc.M110.160820

Garcia-Oliveira, P., Otero, P., Pereira, A. G., Chamorro, F., Carpena, M., Echave, J., ... & Prieto, M. A. (2021). Status and challenges of plant-anticancer compounds in cancer treatment. Pharmaceuticals, 14(2), 157. https://doi.org/10.3390/ph14020157

Gupta, S., & Bhattacharyya, B. (2003). Antimicrotubular drugs binding to vinca domain of tubulin. Molecular and cellular biochemistry, 253, 41-47. https://doi.org/10.1023/A:1026045100219

Hennenfent, K., & Govindan, R. (2006). Novel formulations of taxanes: a review. Old wine in a new bottle?. Annals of oncology, 17(5), 735-749. https://doi.org/10.1093/annonc/mdj100

Hennessy, B. T., Coleman, R. L., & Markman, M. (2009). Ovarian cancer. The lancet, 374(9698), 1371-1382. https://doi.org/10.1016/S0140-6736(09)61338-6

Horwitz, S., Lothstein, L., Manfredi, J. J., Mellado, W., Parness, J., Roy, S. N., ... & Zeheb, R. (1986). Taxol: Mechanisms of Action and Resistance a. Annals of the New York Academy of Sciences, 466(1), 733-744. https://doi.org/10.1111/j.1749-6632.1986.tb38455.x

Islam, M., & Iskander, M. N. (2004). Microtubulin binding sites as target for developing anticancer agents. Mini reviews in medicinal chemistry, 4(10), 1077-1104. https://doi.org/10.2174/1389557043402946

Jackson Jr, D. V., & Bender, R. A. (1979). Cytotoxic thresholds of vincristine in a murine and a human leukemia cell line in vitro. Cancer Research, 39(11), 4346-4349.

Jordan, A., Hadfield, J. A., Lawrence, N. J., & McGown, A. T. (1998). Tubulin as a target for anticancer drugs: agents which interact with the mitotic spindle. *Medicinal research reviews*, *18*(4), 259-296. https://doi.org/10.1002/(SICI)1098-1128(199807)18:4%3C259::AID-MED3%3E3.0.CO;2-U

Jordan, M. A., & Kamath, K. (2007). How do microtubule-targeted drugs work? An overview. Current cancer drug targets, 7(8), 730-742. https://doi.org/10.2174/156800907783220417

Koontz, Michael Zach, Sandra J. Horning, Raymond Balise, Peter L. Greenberg, Saul A. Rosenberg, Richard T. Hoppe, and Ranjana H. Advani. "Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials." Journal of Clinical Oncology 31, no. 5 (2013): 592. https://doi.org/10.1200%2FJCO.2012.44.5791

Li, B. J., Hao, X. Y., Ren, G. H., & Gong, Y. (2015). Effect of lipoic acid combined with paclitaxel on breast cancer cells. Genet Mol Res, 14(4), 17934-17940.

Moudi, M., Go, R., Yien, C. Y. S., & Nazre, M. (2013). Vinca alkaloids. International journal of preventive medicine, 4(11), 1231.

Mukhtar, E., Adhami, V. M., & Mukhtar, H. (2014). Targeting microtubules by natural agents for cancer therapymicrotubule-targeting agents for cancer chemotherapy. Molecular cancer therapeutics, 13(2), 275-284. https://doi.org/10.1158/1535-7163.MCT-13-0791

National Center for Biotechnology Information. (12th June 2023). *Compound Summary: Vinblastine*. https://pubchem.ncbi.nlm.nih.gov/compound/Vinblastine

Noble, R. L., Beer, C. T., & Cutts, J. H. (1958). Role of chance observations in chemotherapy: Vinca rosea. Annals of the New York Academy of Sciences, 76(3), 882-894. https://doi.org/10.1111/j.1749-6632.1958.tb54906.x

Owellen, R. J., & Hartke, C. A. (1975). The pharmacokinetics of 4-acetyl tritium vinblastine in two patients. Cancer Research, 35(4), 975-980.

Owellen, R. J., Hartke, C. A., & Hains, F. O. (1977). Pharmacokinetics and metabolism of vinblastine in humans. Cancer Research, 37(8_Part_1), 2597-2602.

Ratain, M. J., & Vogelzang, N. J. (1986). Phase I and pharmacological study of vinblastine by prolonged continuous infusion. Cancer research, 46(9), 4827-4830.

Ravina, E. (2011). The evolution of drug discovery: from traditional medicines to modern drugs. John Wiley & Sons. 157–159.

Rowinsky, E. (2003). The vinca alkaloids. *Holland-Frei Cancer Medicine*. 6th edition. Hamilton (ON): BC Decker.

Rowinsky, E. K., & Donehower, R. C. (1991). The clinical pharmacology and use of antimicrotubule agents in cancer chemotherapeutics. Pharmacology & therapeutics, 52(1), 35-84. https://doi.org/10.1016/0163-7258(91)90086-2

Rowinsky, E. K., Cazenave, L. A., & Donehower, R. C. (1990). Taxol: a novel investigational antimicrotubule agent. JNCI: Journal of the National Cancer Institute, 82(15), 1247-1259. https://doi.org/10.1093/jnci/82.15.1247

Rowinsky, E. K., Wright, M., Monsarrat, B., Lesser, G. J., & Donehower, R. C. (1993). Taxol: pharmacology, metabolism and clinical implications. Cancer surveys, 17, 283-304.

Salerni, B. L., Bates, D. J., Albershardt, T. C., Lowrey, C. H., & Eastman, A. (2010). Vinblastine Induces Acute, Cell Cycle Phase–Independent Apoptosis in Some Leukemias and Lymphomas and Can Induce Acute Apoptosis in Others when Mcl-1 Is SuppressedAcute Apoptosis Induced by Vinblastine. Molecular cancer therapeutics, 9(4), 791-802. https://doi.org/10.1158/1535-7163.MCT-10-0028

Schiff, P. B., Fant, J., & Horwitz, S. B. (1979). Promotion of microtubule assembly in vitro by taxol. Nature, 277(5698), 665-667.

Schwenkglenks, M., Pettengell, R., Szucs, T. D., Culakova, E., & Lyman, G. H. (2010). Hodgkin lymphoma treatment with ABVD in the US and the EU: neutropenia occurrence and impaired chemotherapy delivery. Journal of hematology & oncology, 3(1), 1-6. https://doi.org/10.1186/1756-8722-3-27

Shen, F., Long, D., Yu, T., Chen, X., Liao, Y., Wu, Y., & Lin, X. (2017). Vinblastine differs from Taxol as it inhibits the malignant phenotypes of NSCLC cells by increasing the phosphorylation of Op18/stathmin. Oncology Reports, 37(4), 2481-2489. https://doi.org/10.3892/or.2017.5469

Takashima, S., Kiyoto, S., Takahashi, M., Hara, F., Aogi, K., Ohsumi, S., ... & Fujita, Y. (2015). Clinical experience with nanoparticle albumin-bound paclitaxel, a novel taxane anticancer agent, and management of adverse events in females with breast cancer. Oncology Letters, 9(4), 1822-1826. https://doi.org/10.3892/ol.2015.2954

Vaishampayan, U., Parchment, R. E., Jasti, B. R., & Hussain, M. (1999). Taxanes: an overview of the pharmacokinetics and pharmacodynamics. Urology, 54(6), 22-29. https://doi.org/10.1016/S0090-4295(99)00451-3

Wani, M. C., & Horwitz, S. B. (2014). Nature as a Remarkable Chemist: A personal story of the discovery and development of Taxol®. Anti-cancer drugs, 25(5), 482. https://doi.org/10.1097%2FCAD.0000000000000063

Wani, M. C., Taylor, H. L., Wall, M. E., Coggon, P., & McPhail, A. T. (1971). Plant antitumor agents. VI. Isolation and structure of taxol, a novel antileukemic and antitumor agent from

Taxus brevifolia. *Journal of the American Chemical Society*, *93*(9), 2325-2327. https://doi.org/10.1021/ja00738a045

Waters, E., Dingle, B., Rodrigues, G., Vincent, M., Ash, R., Dar, R., ... & Yu, E. (2010). Analysis of a Novel Protocol of Combined Induction Chemotherapy and Concurrent Chemoradiation in Unresected Non–Small-Cell Lung Cancer: A Ten-Year Experience With Vinblastine, Cisplatin, and Radiation Therapy. Clinical Lung Cancer, 11(4), 243-250. https://doi.org/10.3816/CLC.2010.n.031

WHO. (3rd February 2022). Cancer. *World Health Organization.https://www.who.int/news-room/fact-sheets/detail/cancer#:~:text=The%20problem Cancer%20is%20a% 20leading %20cause%20of%20death%20worldwide%2C%20accounting%20for,lung%20(2.21%20 million%20cases)%3B*

Wilson, L. (1975). Microtubules as drug receptors: pharmacological properties of microtubule protein. Annals of the New York Academy of Sciences, 253(1), 213-231. https://doi.org/10.1111/j.1749-6632.1975.tb19201.x

Yamaguchi, H., Hishinuma, T., Endo, N., Tsukamoto, H., Kishikawa, Y., Sato, M., ... & Goto, J. (2006). Genetic variation in ABCB1 influences paclitaxel pharmacokinetics in Japanese patients with ovarian cancer. International Journal of Gynecologic Cancer, 16(3). http://dx.doi.org/10.1136/ijgc-00009577-200605000-00004

Zhou, X. J., Martin, M., Placidi, M., Cano, J. P., & Rahmani, R. (1990). In vivo and in vitro pharmacokinetics and metabolism of vincaalkaloids in rat II. Vinblastine and Vincristine. European journal of drug metabolism and pharmacokinetics, 15, 323-332. https://doi.org/10.1007/BF03190222

Zhou, X. J., Placidi, M., & Rahmani, R. (1994). Uptake and metabolism of vinca alkaloids by freshly isolated human hepatocytes in suspension. Anticancer research, 14(3A), 1017-1022.