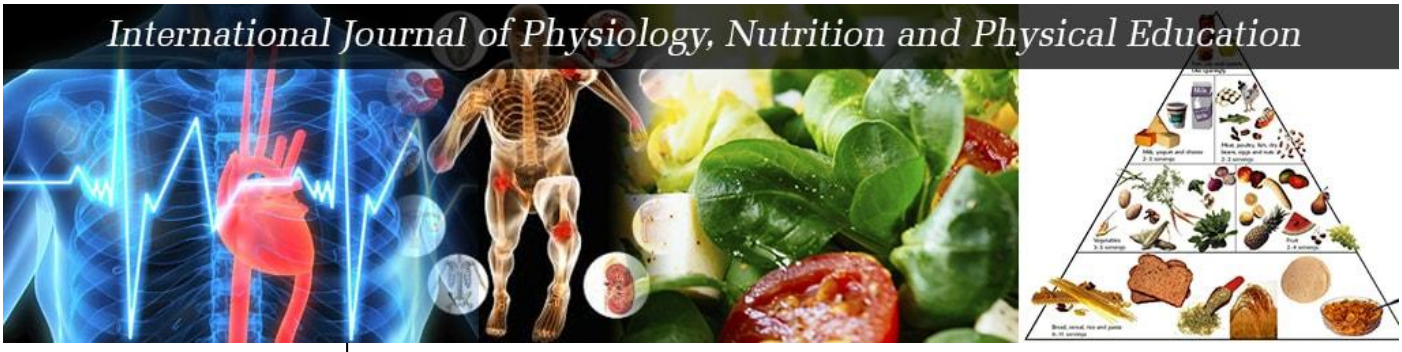

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Vinca alkaloid- the second most used alkaloid for cancer treatment- A review

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Abstract
This review is aimed at conferring the efficacy of anticancer property of different phytochemicals from Nayantara (*Catharanthus roseus*). Cancer is one of public health burden in developed and developing country. Cancer chemo preventive agents, many of which are natural products, are capable of preventing or inhibiting the process of carcinogenesis. Herbal anticancer drug are obtained from *Catharanthus roseus* is wildly used because of their well defined mechanism of action as anticancer drug. The main alkaloids of *Catharanthus roseus* is vinca alkaloids which is important for being cancer fighters. There are four major vinca alkaloids in clinical use: vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). Recently vinflunine is discovered as new anticancer agent of vinca alkaloids. In this review, an attempt has been made to summarize the pharmacological effect of the above plant against anticancer property in a precise way to help the scientist and learners to understand the basis medicinal value of the plant.

Keywords: Nayantara (*Catharanthus roseus*), vinca alkaloid, vinblastine (VBL), vincristine (VCR), and anticancer drug

Introduction
Catharanthus is a perennial tropical medicinal plant belonging to the Family Apocynaceae which comprises 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 exhibit strong and important pharmacological activities [1]. 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 hypoglycemic as well as cytotoxic effect. The vinca alkaloids are also important for being cancer fighters. 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 [2]. 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 hypoglycemic activity, which is of little importance compared to their cytotoxic effects [3]. The leaves and stems are the sources of dimeric alkaloids, vinacristine and vinblastine that are indispensable cancer drugs, while roots have antihypertensive, ajmalicine and serpentine[4]. Alkaloids that are isolated from *C. roseus* are found to be hypotensive, sedative and possess 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 nose bleed, 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

the raised blood sugar levels [5]. *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 [6]. 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 [7].

Fig 1: Tree and flowers of *Catharanthus roseus*. Vinka Alkaloid [8]

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 alkaloid include, Vinblastine (VLB) and Vincristine (VCR), Vinorelbine (VRLB) and Vindesine (VDS) are obtained from the Madagascar periwinkle, *Catharanthus roseus* G. Don. (Apocynaceae).

1. Vinblastine: Vinblastine (VLB) is major naturally occurring active compounds. Vinblastine sulfate is the salt of an alkaloid extracted from Vinca rosea Linn., a common flowering herb known as the periwinkle (more properly known as *Catharanthus roseus* G. Don). Previously, the generic name was vincaleukoblastine, abbreviated VLB. It is a stathmokinetic oncolytic agent. When treated *in vitro* with this preparation, growing cells are arrested in metaphase.
2. Vincristine: Vincristine (brand name, Oncovin), formally known as leurocristine, sometimes abbreviated "VCR", is a vinca alkaloid from the *Catharanthus roseus* (Madagascar periwinkle), formerly Vinca rosea and hence its name. It is a mitotic inhibitor, and is used in cancer chemotherapy. Vincristine is created by the coupling of indole alkaloids vindoline and catharanthine in the vinca plant.
3. Vinorelbine: Vinorelbine is the first 5´NOR semi-synthetic vinca alkaloid. It is obtained by semi-synthesis from alkaloids extracted from the rosy periwinkle *Catharanthus roseus*.
4. Vinflunine: Vinflunine is one of a group of drugs known as the vinca alkaloids
5. Vindesine: Vindesine is an anti-mitotic vinca alkaloid used in chemotherapy.

Recent Study

Antitumor activity of methanol leaf extracts of *Catharanthus roseus* (L.) G. Don was assayed using potato disc bioassay through *Agrobacterium tumefaciens* infection. Camptothecin used as a positive control. Significant ($P<0.05$) percentage of tumor inhibition was observed at 10ppm, 100ppm and 1000ppm of leaf extracts. Maximum tumor inhibition 80.96, 82.68 and 84.96% were observed at 1000ppm for *Agrobacterium tumefaciens* strains AtSI0105, AtAc0114 and AtTA0112, respectively. It was also observed that the strain AtSI0105 (28.06±0.29) was more dominant for producing tumor than other strains. The sensitivity test results showed that the extracts had no effect on the viability of all the tested strains of *A. tumefaciens* [9].

The aqueous extract induced cell death of Jurkat cells at 24, 48 and 72 hours post-treatment in a time- and dose-dependent manner. However, cells treated at 48 and 72 hours produced higher cytotoxic effects with half maximal inhibitory concentration (IC_{50}) values of 2.55µg/ml and 2.38 µg/ml, respectively. In contrast, the extract induced normal PBMC proliferation, especially after 24 hours treatment with 1000 µg/ml. This result indicates that the *C. roseus* crude aqueous extract showed differential effects of inhibiting the proliferation of the Jurkat cell line and promoting the growth of PBMCs. These data suggest that the extract may be applicable for modulating the normal and transformed immune cells in leukaemia patients [10].

This study evaluated the cytotoxic activity of the indole alkaloid-enriched *bioactive* extract obtained from suspension cultured-cells of *C. roseus* elicited with methyl jasmonate (MJ) and cyclodextrins (CDs) in three cell lines: JURKAT E.6 human lymphocytic leukemia, THP-1 human monocytic leukemia and BL 1395 non-tumor human B-cell line. Four indole alkaloids were identified (catharanthine, ajmalicine, tabersonine and lochnericine) but only catharanthine and ajmalicine were quantified. The concentration of the indole alkaloid-enriched bioactive extract that inhibited cell growth by 50% was 211 and 210 ng/mL for the JURKAT E.6 and THP-1 cell lines, respectively [11].

Vinflunine is a new Vinca alkaloid uniquely fluorinated, by the use of super acid chemistry, in a little exploited region of the catharanthine moiety. *In vitro* investigations have confirmed the mitotic-arresting and tubulin-interacting properties of vinflunine shared by other Vinca alkaloids. However, differences in terms of the inhibitory effects of vinflunine on microtubules dynamics and its tubulin binding affinities have been identified which appear to distinguish it from the other Vinca alkaloids. Vinflunine induced smaller spirals with a shorter relaxation time, effects, which might be

associated with reduced neurotoxicity. Studies investigating the *in vitro* cytotoxicity of vinflunine in combination therapy have revealed a high level of synergy when vinflunine was combined with either cisplatin, mitomycin C, doxorubicin or 5-fluorouracil. Furthermore, although vinflunine appears to participate in P-glycoprotein-mediated drug resistance mechanisms, it has proved only a weak substrate for this protein and a far less potent inducer of resistance than vinorelbine [12].

Vinflunine is an innovative microtubule inhibitor of the vinca alkaloid class with distinct tubulin-binding properties. Preclinical evaluation of this novel microtubule inhibitor has shown superior antitumor activity against a broad spectrum of tumor types *in vitro* and *in vivo*, in comparison with other vinca alkaloids. The antitumor effect of vinflunine is largely attributable to its modulation of microtubule dynamics, and is mediated by its ability to induce apoptosis in target cells. At non-cytotoxic concentrations, vinflunine also exerts antiangiogenic and antivascular activity. The favorable preclinical profile of vinflunine, in addition to its synergism with a variety of other therapeutic modalities, justifies further clinical development of this compound [13].

Vinflunine exhibited superior antitumor activity to that of other Vinca alkaloids, including vinorelbine from which it was synthetically derived. Vinca alkaloids appear to inhibit cell proliferation by affecting the dynamics of spindle microtubules [14].

A randomized comparative study of 254-S plus Vindesine VDS vs. CDDP plus VDS was conducted in patients with advanced NSCLC. 254-S or CDDP was intravenously administered at 90 mg/m^2, at least 2 times at 4-week intervals. VDS was intravenously administered at 3 mg/m^2 on Days 1 and 8 of each treatment of 254-S or CDDP. Of 136 patients registered, 121 (64 of the 254-S/VDS group and 57 of the CDDP/VDS group) were evaluable for tumor response (complete cases). There was no significant intergroup difference in the tumor response rate (254-S/VDS group: 12.5% [8/64], CDDP/VDS group: 15.8% [9/57]), nor by cancer staging, histological type or survival. As for toxic effects, leukopenia was significantly less frequent in the 254-S/VDS group while thrombocytopenia was significantly less frequent in the CDDP/VDS group. Nephrotoxicity such as an elevation of BUN and a decrease in serum creatinine was significantly less frequent in the 254-S/VDS group in spite of the lower volume hydration performed. Based on these results, it was concluded that combination treatment with 254-S and VDS is a safe and useful regimen for treatment of NSCLC, generating antitumor effects equivalent to the CDDP/VDS regimen [15].

Objective response was observed in 31.1% of patients in the VRB arm versus 8.9% of those in the VDS arm (P = 0.0002). The median duration of response to VRB was 18.5+ weeks (range, 7.9 to 107.5+ weeks) compared with 11.7+ weeks (range, 6.0 to 35.0+ weeks) for VDS. Of the 69 patients who failed to respond to initial monotherapy, 33 in the VRB group who subsequently received VDS + P did not respond and 13 (26.5%) of 49 initially on VDS who received subsequent VRB + P responded. The rates of grades 3 and 4 leukopenia were similar in the two monotherapy arms (VRB, 55.3% vs. VDS, 48.5%). However, grade 3 anemia was more frequent in the patients on VRB than in those on VDS. The incidence of peripheral neurotoxicity was significantly higher with VDS than with VRB (P = 0.002), but VRB induced a slightly higher rate of local cutaneous reaction than VDS (P = 0.012). With the combination of cisplatin and these vinca alkaloids, peripheral neurotoxicity was less frequent in the VRB group than in the VDS group [16].

The antitumor activity of Vinorelbine VNR was superior to other vinca alkaloid antitumor agents, and the neuro-toxicity of VNR was weaker than those of other vinca alkaloids. In nude mice xenografted human tumor models, VNR showed antitumor activity against eight of eleven tumor models (non-small cell lung cancer: 4/4, breast cancer: 2/3, colon cancer: 0/2, stomach cancer: 2/2). Especially, VNR showed tumor-regressive activity against LC-6 non-small cell lung cancer and MX-1 breast cancer. The antitumor activity of VNR against non-small cell lung cancer was superior to that of vindesine (VDS), which had been one of the key drugs of non-small cell lung cancer in the clinic. In combination chemotherapy, VNR plus cisplatin (CDDP) was better than VDS plus CDDP, which had been one of the standard regimens of non-small cell lung cancer chemotherapy. The potent antitumor effect of VNR with minor neurotoxicity was explained by VNR having stronger activity on mitotic microtubules than axonal microtubules. It was supposed that less activity of VNR against mitotic microtubules would be related to different composition of microtubule-associated TAU isoforms in the two types of microtubules. In non-small cell lung cancer, VNR resulted in a significantly higher response rate than VDS. In combination with CDDP, VNR resulted in longer survival than VDS with a significant log-rank test. In advanced breast cancer, VNR resulted in a high response rate in 1st line and 2nd line treatment. VNR is effective in combination with chemotherapeutic agents such as anthracycline, fluorouracil and Taxol [17].

Distant metastases were present in retroperitoneal nodes (58%), lung (29.3%), and bone (20.2%). The ECOG 0, 1 and 2 performance status at the start of vinflunine were 31.3%, 60.6% and 8.1%, respectively. A median of 4 cycles of vinflunine was administered per patient (range 1–18). Median progression free and overall survival for all patients (N = 102) were 3.9 months (2.3-5.5) and 10 months (7.3-12.8), respectively. Time to tumor progression was 4.3 months (2.6-5.9). Two patients (2%) achieved CR, 23 (22.5%) patients had PR, and 42 (41.2%) presented SD as best response. The clinical benefit rate with vinflunine was 65.7% [18].

C. roseus was able to reduce T47D cell proliferation with a median inhibition concentration (IC50) of 2.8%; *D. petandra* 1.2%; *P. betle* 2.8%; and *C. mangga* 74.8%. The apoptotic analysis result showed that *C. roseus* induced apoptosis for 37.67%; *D. petandra* 24.03%; *P. betle* 9.45%; and *C. mangga* 0.41%. Meanwhile doxorubicin at 10 µg/ml induced apoptosis for 36.06%. The highest DPPH scavenging activity was recorded for *P. betle* extract as to be 83%; *D. petandra* 75.11%; *C. roseus* 71.87%; and the lowest for *C. mangga* as 38.45%. *C. moseus* and *D. petandra* aqueous extracts presented the highest anticancer activity by means of cell proliferation inhibition and inducing apoptosis. *P. betle* extract represented the strongest antioxidant activity. *C. mangga* extract exhibited no anticancer and only low antioxidant activity [19].

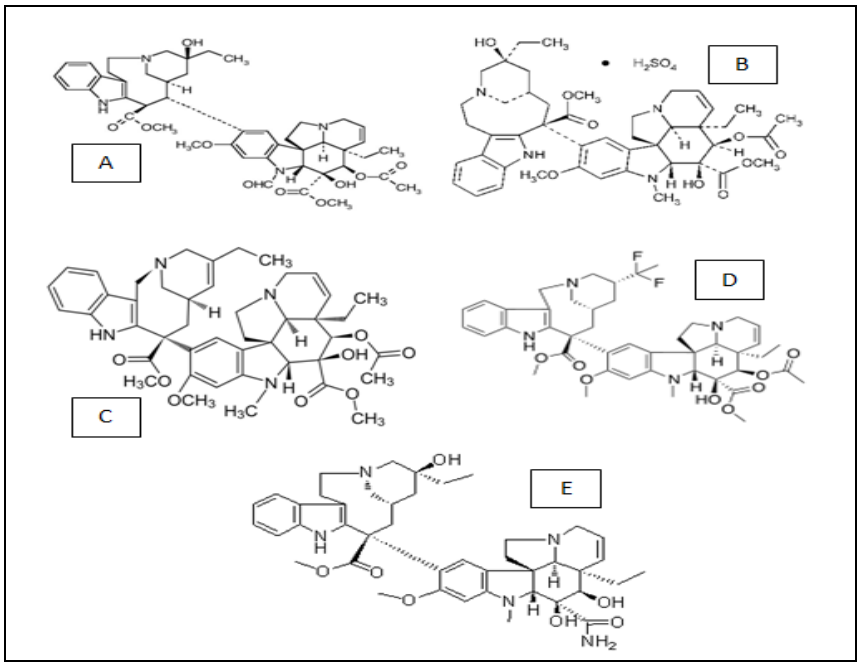

Fig 2: Chemical structures of the four Vinca alkaloids vincristine (A), vinblastine (B), vinorelbine (C), vinflunine (D) and vindesine (E)

Conclusions

Cancer is the uncontrolled growth of cells coupled with malignant behavior: invasion and metastasis. It is caused by the interaction between genetic susceptibility and environmental factors. These factors lead to accumulations of genetic mutations in oncogenes and tumor suppressor genes, which give cancer cells their malignant characteristics, such as uncontrolled growth. Vinca alkaloids have been generally included in combination chemotherapy regimens for medicinal therapies. They have been used to treat diabetes, high blood pressure and have been used as disinfectants and anti-cancer. The vinca alkaloids have cytotoxic effects that can arrest the division of cells and causes cell death. Overall, vinca alkaloids have the second most-used class of anti-cancer drugs and will stay among the original cancer therapies. Different researches and studies for new vinca alkaloid applications will be carried out in this regard.

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