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Research Article

A Review: Importance of *Catharanthus roseus* in the treatment of Cancer

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Abstract: *Catharanthus roseus* , commonly known as Vinca rosea, an important medicinal plant and a member of the family Apocynaceae is well known for its medicinal properties and ornamental attributes [1]. *C. roseus*, one of the most valuable medicinal plant species has traditionally been used since many ages in the treatment of a number of diseases including cancer [4]. The plant has gathered increased attention over the recent years because of its rich varieties of phytochemicals having numerous biological activities such as anti-oxidant, anti-fungal, anti-diabetic and anti-cancerous property. Till now, 344 bioactive photochemical is isolated and identified from *Catharanthus roseus* [2]. Among the various secondary metabolites isolated from this plant, Vincristine and Vinblastine are remarkably the first plant-derived compounds with anti-cancerous property applied for clinical use. Various types of anti-cancerous agent extracted from Catharanthus roseus and their role in the treatment of cancer has been mainly focused in this review article.

Keywords- *Catharanthus roseus* , cancer, anti-cancerous, drugs, alkaloids, antioxidant, vincristine , vinblastine

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INTRODUCTION

Botanical Description

Catharanthus roseus is an annual evergreen, herbaceous, dicotyledonous ornamental flowering plant having medicinal importance, belonging to the family Apocyanaceae and grows about height of 1 meter. Leaves of these plants are 2.5 cm to 9 cm long and 1-3.5 cm broad, hairless, glossy and green in color and midrib is pale in color and shape is oval to oblong, petiole is short and they are appositively arranged in pairs. The flowers are pale pink, white, red and pink in color stems are usually green in color often permeated with red or pink [8].

This plant has gathered significant importance not only recently but from many ages, because of its effectiveness in the treatment of a number of diseases affecting the human population which may include diabetes, hypertension, asthma, blood pressure, constipation, menstrual problems and most importantly in the treatment of cancer, which is the topic mainly focused in this review article.

Chemical Constituents of *C. roseus* :

Despite the presence of numerous bioactive compounds of pharmacological significance including carbohydrates, flavonoids, tannins, saponins, glycosides, terpenes, proteins and phenols, alkaloids are considered to be the potentially active constituent of this plant. The plant of *C. roseus* contains more than 400 different alkaloids with its wide application in

pharmaceuticals process, flavor and fragrance, ingredients , food additives, insecticides etc. More than 100 monoterpenoid indole alkaloids has been identified to be present in various parts of this plant. Vindeline, vindesine, tabersonine, vinblastine, vincristine are the alkaloids mainly present in aerial parts of the plant. The roots of this plant contains various alkaloids like raubasin, reserpine, catharanthine, vinceine, vineamine and ajmalicine etc. The flower of the plants are very high in tannins, triterpenoids and alkaloids and helpful in healing diabetic wounds [2]. According to many pharmacological research, this terpenes, terpenoids and alkaloids are the potent anticancer, antibacterial, anti-inflammatory and antimalarial medicines [14]. Among the various bioactive secondary metabolites, two major alkaloids namely vincristine and vinblastine has been deployed widely in cancer treatment. Such types of drugs exerts their effectiveness by interfering with the proliferation of tumor cells, thus preventing the progress of cancer at an immature stage.

Cancer is considered to be one of the most life-threatening diseases associated with serious health problems which causes about 10 billion deaths worldwide due to various external and internal factors. There are various treatment developed for the treatment of cancer such as drug therapy, chemotherapy, surgery, radiation therapy etc. which not only provide economic impact on patients but also increases the resistance against many drugs in patients with time. So, by implementing evidence based preventive strategies, a significant number of cancer cases can be prevented. Now a days, plant based drugs have evolved as a promising and preventive chemotherapeutic alternative [2]. The anti-cancerous compound extracted from this plant are synthesized via Shikimate, Mevalonate and Methyl-erythritol phosphate (MEP) pathways [4]. The importance and anti-cancerous properties of *C. roseus* with its application in different fields of chemotherapy are discussed next in this review article. A recent significant development in cancer treatment includes the identification of various cytotoxic compounds to be applied in chemotherapy. Although these drugs have positive role in targeting tumor cells but these drugs also induce genotoxic, carcinogenic and teratogenic impacts in non-cancerous cells [6, 7]. Despite having high efficacy in the destruction of malignant cancerous cells, the application of these drugs are limited because of these associated side effects. Therefore, there is an increasing need to search for some alternative or complementary drugs for the cancer cells which would be effective only on the cancerous cell, without imposing any toxicity towards the normal cells. According to WHO, 80% of the world population depends on plant based drugs. This medicinal plant has been reported to be used widely in traditional medicines by various tribes and communities to treat diabetes, hypertension, cancer and fever. It contains more than 120 terpenoids, indole alkaloids and these alkaloid exhibits strong pharmaceutical activities. A significant number of bioactive compounds has been identified from *C. roseus* including vincristine, vinblastine (anticancer) and ajmalicine (antihypertensive), serpentine (sedative) etc. which are reported to be produced in small amounts and are used in combination with other therapeutic compounds to treat cancer [8]. The flower of *C. roseus* is used for fragrance and brain stimulating odour. The compounds extracted from different parts of this plant has different pharmacological properties such as antimicrobial, antioxidant, anthelmintic, antifeedant, anti-sterile, antidiarrheal and antidiabetic [9].

Importance of Herbal medicine in cancer :

Cancer is a general term applied for the malignant diseases that affect different parts of body. These diseases are characterized by a rapid and uncontrolled growth of abnormal cells which cluster together to form a mass of rapidly proliferating growth or tumor throughout the body. Continuous proliferation of these malignant cells ultimately leads to the death of an individual, if the process is not arrested at an immature stage. In order to prepare anticancer medicines from natural resources like plants, cytotoxic compounds and screening raw extracts of plants is very important. Plants produce a various range of bioactive compounds, commonly known as secondary metabolites that apparently have no direct role in organisms, however they are reported to have many indirect role in sustaining the health of the plant. Alkaloids, terpenoids flavonoids, pigments and tannins etc. are the commonly obtained plant secondary metabolites with a number of significant biological properties like anti-inflammatory, anti-cancerous, contraceptive with different effects on hematopoietic cells, lipids and cardiovascular systems [4].

Traditional uses :

Catharanthus roseus has wide application in traditional medicinal practices for the treatment of many different type of diseases. Historically, *C. roseus* was used in the treatment of disease such as diabetes mellitus, high blood pressure and infection. About 90 alkaloids were isolated in the leaf part and the most important monomers are catharanthine and vindoline. The derivatives of vincamine known as vinpocetine were used widely used in blood thinning, memory enhancing activities and in vaso-dilation. In India, leaf juice of the plant is used in the treatment of bee sting and wasp sting. Flower extract of the plant was used for eye wash in infants in Cuba and Jamica. Infusion of the leaves were used in Menorrhagia and Rheumatism. Leaves were used for the treatment of diabetics, stomach cramps and roots in intestinal parasitism in Philippines. Crude extract of roots and leaves were used in cancer .In Madagascar, astringent and bitter leaves were used in prevention of vomiting, roots were used as purgative and for toothache. Bleeding was prevented by applying boiled extract of the plant. The people in Brazil used whole plant extract for treating diabetics and leaves are used to control scurvy, hemorrhage, for healing and cleaning of Chronic wounds. Leaf extract was taken orally for menorrhagia and diabetes in South Africa. In Taiwan, they used orally the whole plant extract for diabetics [10]. In different countries of the world, *Catharanthus roseus* has been used as traditional medicine. The traditional remedy of dried leaf of plant boiled with water then that used orally to treat the diabetes in northern India. This plant also used to treat cancer patients in Kenya. Holdsworth (1990) stated that the people of Kancheepuram in Tamil Nadu, India prepared powder of whole plant and combined with cow's milk and used orally to cure diabetes [11]. Muthu et al, (2006) stated that *C. roseus* helps to prevent urogenital infections in Venda region [12]. People of Zimbabwe used the plant to cure stomach ache infection [10].

Plant part	Name of the alkaloid present.
Flower	Catharanthine, Vindoline, Neurosine, Lochnerine, Tricin
Stem	Leurosine, Lochnerine, Catharanthine, Vindoline
Leaf	Catharanthine, Vindoline, Vindolidine, Raubasine , Vinblastine etc.
Root	Ajmalacine, Serpentine, Catharanthine, Vindoline, Reserpine, Tabersonine.

Table: Plant parts used for extraction of alkaloids. [4]

Pharmacological uses -

Anticancer activity-

In clinical practice, use of *C. roseus* is carried out intravenously and after this they are eventually metabolized by liver and excreted. Major side effects of these drugs are hair loss, peripheral neuropathy, constipation and hyponatremia. To improve this situation, semi synthetic alkaloids such as vinorelbine and vinflunine were developed which alkaloids exert their anti- tumor effect by binding to tubulin. These alkaloids have growth inhibition effect on tumors. Vinca alkaloids also called as mitotic spindle poisons as they inhibit assembly of the spindle forms from microtubules, there by inhibit mitosis in cell cycle. Vinca alkaloids have successfully prevented cancer cells from dividing.

Antimicrobial activity

Phytochemical and antibacterial studies revealed that the presence of active compounds like steroids, phenolics, tannins and saponins. Antibacterial activity was shown against common human pathogens such as *Staphylococcus aureus, Escherichia Coli, Vibrio*. Aldehydes and phenolics compounds of the plant extract show antibacterial activities. Catharanthus roseus is an important medicinal plant for the creation of the novel medicine as most of the bacterial pathogens were developing resistance against many of the anti-microbial drugs. Plants are proved to be valuable natural resources for the active chemotherapeutic agents and give emphasis on the preventive action. It is experimented that the mutant leaf extract had good antibacterial potential against S. aureus and E. coli .Wang et al, isolated a monoterpenoid indole alkaloids named Catharoseumine from whole plant that showed potent inhibitor against protozoans parasite falcipain-2 showing an IC50 value of 4.06 um.[8]**.** Antimicrobial activity of the leaf extract of the plant was tested *against Pseudomonas aeruginosa , Salmonella typhimurium and staphylococcus* and found that the extract could be used as the Prophylactic agent in the treatment of many microbial diseases[15].

Antidiarrheal activity

Kyakulaga et al, showed that leaf ethanolic extract of the *Catharanthus roseus* showed potent anti-diarrheal activity [16] .The in vivo anti-diarrheal action of *C. roseus* ethanolic leaf extract was tested in the wister rats with castor oil as an anti-diarrhea including agent. Loperamide and atropine sulphate are used as the standard bags. The anti-diarrheal activity of the plant ethanolic leaf extracts in the wister rats with castor oil as a experimental diarrhea inducing agent in addition to the pretreatment of the extract. The ethanolic extract of *Catharanthus roseus* showed the dose inhibition of the castor oil induced diarrhea [17].

Anti-helminthic activity

Helminthic infections are responsible for the chronic diseases in cattle and human beings [18]. *Catharanthus roseus* has traditionally been used as an anti-helminthic agent since many ages. The anti-helminthic activity of *Catharanthus roseus* has been tested using piperazine citrate as the standard reference and *Pheretima posthuma* as experimental model.

Hypotensive activity

Among the other known pharmacologically active compounds, about 150 alkaloids of medicinal importance have been identified in the leaves of *C. roseus*. The alkaloids isolated from the leaves are found to have hypotensive, sedative, tranquilizing as well as anti-cancerous effect. Significant antihyperglycemic and hypotensive activity have also been reported in the leaf extract of *C. roseus*. The extract of this plant could also be used to treat hypertension. The leaves extract of the *Catharanthus roseus* was reported with hypotensive effects in adrenaline- induced hypotensive rats. Animals treated with the extract of this plant has been found to show hypotensive effects. A number of significant changes in cardiovascular parameter has been reported after further investigation.

Antidiabetic activity-

Diabetes mellitus is a leading cause of death now a days due to which large number of population died. It have been reported that *Catharanthus roseus* is used in the treatment of controlling diabetes. Vinculin, a plant derived natural remedy for curing diabetes was extracted from *Catharanthus roseus* which showed hypoglycemic activity and it have commercial value. Antihyperglycemic activity is significantly showed by whole plant extract at (500 mg/kg) of high dose. Blood sugar level of body and beta cell number were reversely effected due to extract of *Catharanthus roseus* . Leaf and flower ethanol extract of this plant reduce blood sugar. *Catharanthus roseus* is used in the treatment of diabetes in different parts of the world. After being treated with *C. roseus* leaf juice both healthy and diabetic rabbits blood glucose level were observed decrease in a dose dependent manner [19]. The dichloromethane extract of Catharanthus leave contains all four of the alkaloids vindoline, vindolidine, vindolicine and vindolinine . According to experts, these substance increased glucose absorption in vindolicine. Vindolicine experts had the strongest anti-oxidant properties in both the oxygen radical absorption capability.

Wound healing activity-

The extract flower extract in rats showed antibacterial and wound healing activity. Rats wound healing activity was assessed. Rats were used to test the ethanol extract of *Catharanthus roseus* at 100 mg/kg/day for ability to check healing wounds. The use of the management of wound healing includes wound contraction, enhanced tensile strength and

hydroxyproline content. Nayak et al, showed that ethanolic compound extracted from *Catharanthus roseus* have wound healing capacity when treated to wounded rats. The Wound healing property was carried using 100 mg kg/day of *Catharanthus roseus* ethanol extracts in rats [20].

Antioxidant activity-

Aerobic respiration and other metabolic activities create free radicals and ROS which are very harmful for our body. Antioxidant are the element that eliminate these free radicals and protect the body cells from damage. *C. roseus* contains different type of natural antioxidants which are used in nutraceutical and food industry. According to the comparative study of antioxidant activity of *C. roseus* and C. alba it is showed that the antioxidant activity is present more in *C. roseus* than C. alba. *C. roseus* exhibit antioxidant property due to presence of phenolic compounds. In leaf juice of *Catharanthus roseus* vinpocetine like compounds was present which antioxidant activity similar to flavonoid . The antioxidant capacity of the two types of *catharanthus roseus* were discovered by two methods-hydroxyl radical scavenging activity which have capacity to scavange superoxide radicals and nitric oxide radical scavenging activity[1]**.** Bhutke and Bhise reported that ethanol root extract when tested for antioxidant activity in two different varieties of cathranthus then it shows scavenging effect for *Catharanthus roseus* [21].

Memory enhancement capacity- Nayak et al, showed that vinpocetine that made from vincamine alkaloid is the most important Dietary supplement because of its action to improve brain function and memory which are particularly beneficial in treatment of Alzheimer's disease [20].

Antiulcer activity

Antiulcer activity is caused due to the presence of vincaline and vindoline alkaloids. Vincaline alkaloids present on the leaves is due to cerebro vasodilatory and neuroprotective capacity. Babulova et al, described that the vincamine and vindoline present on the leaves of the plantshow prevented nature againsty experimentally induced gastric damage in rats [2].

Role of Alkaloids extracted from *Catharanthus roseus*

Catharanthus roseus contains various alkaloids which have diverse medical properties. Vinblastine and Vincristine are very important for cancer treatment. While another alkaloids named ajmaline has antihypertensive, antimicrobial and antirrhythmic effects and serpentine and reserpine also manages hypertension.

1.**Ajmaline**- Medicinal properties of these alkaloids includes anticancer potential, anti-rhythmic properties , cardiovascular and antioxidant properties.

1. It hinders cancer cell growth which helps in anti-cancer drug development.
2. It aids in clot prevention and lower heart disease risks.
3. It helps in neutralizing free radicals, protecting cells and lowering chronic disease risks [4].

2**. Alstonine** - It has antispasmodic activity by aiding conditions involving muscle spasms like in the gut.

3. **Apovincamine** - It has cardiovascular activity and memory enhancement and vasodilatory properties, can widen blood vessels leading to improved blood circulation.

4**. Reserpine** - It has antihypertensive properties and lower blood pressure by acting as a calcium channel nlocker.

5. **Tabersonine** - It acts as a precursor for the semi-synthesis of anti-cancer drugs due to its role in the biosynthesis of vincristine.

6. **Vindoline**- It has anticancer properties and involved in the biosynthesis of vinblastine, a potent anti-tubulin agents.

7. **Vinblastine and vincristine**- These have anticancer properties by disrupts the formation of microtubules during cell division and effectively inhibit the growth of cancer cells.

8. **Isovincoside** – It is acts like precursor to chemotherapeutic alkaloids. According to research, it can be metabolized into Vincristine, particularly important for leukamia and lymphoma treatments. [2]

Mode of action of Vinblastine and Vincristine-

Alkaloids derive from *C. roseus* belongs to an important class of anticancer drugs. The mechanisms of action of these alkaloids that they inhibit the cell proliferation by effecting the microtubules during mitosis which leads to apoptosis. Vinblastine can cause side effects including bone pain, depression, constipation, hair loss, stomach pain and loss of appetite. These alkaloids have two mechanisms- at very low concentration, they suppress microtubule dynamics and at higher concentration, they reduce microtubule polymer mass. Vinblastine is an anticancer medication prescribed in various cancers such as Hodgkins lymphoma, breast cancer, testicular cancer. Vinblastine is also used to prevent bladder cancer , non-small cell lung cancer , head and neck cancer and cervical cancer. It acts as a amitotic inhibitor and thus used in cancer chemotherapy. Vincristine can be created by the coupling of the indole alkaloids such as vindoline and catharanthine. Tubulin is a structural protein that polymerizes to microtubules. Vincristine binds to the tubulin dimers by inhibiting assembly of microtubule structures. Disruption of the microtubules leads to arrests of mitosis in metaphase. Therefore the alkaloid extract from *C. roseus* effects all rapidly dividing cells.

Adverse Effects :

Exposure to nervous tissues to Vinca alkaloids inhibits axonal transport, causing neurotoxicity, secretory processes as a result of perturbations in membrane trafficking with disruption of cytoskeleton. As result of treatment with vinca alkaloids, platelets which depends on integrity of the peripheral ring of microtubules for their different shape become spherical [22].

Conclusion :

Present day drugs have many side effects which adversely affect the human health. In the current situation, the issue of multi drug resistance become worldwide clinical danger and challenging for scientific society. Understanding the principles engaged with the screening of bioactive compound becomes challenges for the researchers. The decrease of adequacy and increment of toxicity of engineered drugs are further increase the complexity of problems. Taking all this into consideration, there is a need to proceed with research models to help the

improvement of plant medicinal plants products to drug discovery[23] .Due to the presence of various bioactive compounds, traditionally used medicinal plants play an essential role in health sector. This plants were widely used in folk remedy for treatment of several diseases. In recent years, the demand of *Catharanthus roseus* is increased due to its alkaloids contains and used for curing of cancer and other diseases. To fulfill the increased demand, it is necessary to focus on the pharmacological study and also its conversation. This plant ranks highly as a popular ornamental plants in the horticulture sector and as a model plant to study phytopathology and biotechnology. In addition to its natural supply as a anticancer treatment in the global market [2].

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