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THERAPEUTIC EFFECTS OF GRAVEYARD PLANT (*CATHARANTHUS ROSEUS*): A REVIEW

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ABSTRACT

In India *Catharanthus roseus* is commonly known as 'Sadabahar' and its common name varies with the location. It is the evergreen dicotyledonous plant used for the therapeutic use and also used as an ornamental plant. The plant is loaded with variety of alkaloids which have numerous therapeutic properties. It is reported that the plant had been widely used in Chinese and Ayurvedic medicines since ancient times. Looking at the present scenario most of the population of the world is suffering from hypertension and diabetes, Sadabahar can be the natural solution to these leading diseases as it is known to have wonderful property of lowering the blood sugar level making it anti-diabetic agent and also possess neurosedative properties which result in lowering the blood pressure. *Catharanthus roseus*is the magical plant which do wonder against cancer due to the presence of the Vinca alkaloids which are well known anti cancerous agents. Some of the Vinca alkaloids are commercially available in the market and used in the process of chemotherapy to reduce its after affects such as nausea. Seeing the potential of *Catharanthus roseus*it can do miracles against variety of diseases including cancer and can take the ayurvedic medic to new heights.

Keywords **:** Cancer, graveyard, Catharanthus, plant and extract.

Introduction

Ayurveda is traditional system of medicine which is helpful to cure many diseases. The main focus of this system of medicine is to treat diseases with help of the plants and the plant products. Various plants are known all over the world which are beneficial for the humankind and are helpful in treatment of various diseases. The commonly found spices in the Indian kitchen like clove, turmeric, cinnamon etc. are also loaded with the beneficial properties like anti-tumor, anti-diabetic, anti-microbial and anti-oxidative. They are helpful in the treatment of the various diseases like different types of cancer, obesity, cold and cough, diabetes, hypertension, dysentery etc. Various herbs are also useful and one of the commonly found medicinal herb is *Catharanthus roseus*, this herb belongs to the Apocynaceae family and is native to Madagascar, the common name used for this plant are 'Sadabahar' and 'Nayantara' (Mishra and Verma, 2017) . Due to its various beneficial properties this herb is widely used in the treatment of different diseases since ages. There are many traditional and folkloric periwinkle applications that are verified and validated in the confidence of the cultures. The paste made from the leaves is an outstanding wound healer and also tends to alleviate the discomfort of wasp bite. It will stop bleeding and therefore speed up the healing process. Some even claim the periwinkle is effective in relieving stress, headaches and exhaustion.

Catharanthus roseus is fully loaded with numerous phyto-constituents which show many pharm logical activities like anti-cancer, anti-diabetic, anti- microbial, wound healing property, anti-helmenthic, memory enhancement property and anti- hypertensive (Koul *et al*., 2013). Apart from all these properties the leaves of this plant are used to calm the menstrual pains. *Catharanthus roseus* consist of around 130 different varieties of alkaloids (Tolambiya and Mathur, 2016) and these alkaloids are found in the different parts of the plant, vinblastine and vincristine alkaloids are mainly located in the arial parts of the plant and the roots of the plant contains ajmalicine which is the vasodilating agent. Different alkaloids present in the *Catharanthus roseus* have different function. The phenolic compound of this plant has the anti-oxidative properties. Some alkaloid and other natural compounds found in this plant are reported to have the anti-cancerous properties and are mainly used in the treatment of the colon and the breast cancer. Cancer is the deadly disease and lot of people lose their life while fighting the battle against cancer. The most common cancer that affects the women is the breast cancer, in various developed countries this disease affects many women. Studies show that there are compound like Vincristine and Vinblastine which can be helpful in treating the breast cancer. The extracts are tested on the various breast cancer cell lines and mouse and they give the positive result in treating the disease. It is reported that the dried roots, leaves, flower and stalk of *Catharanthus roseus* are widely used in the treatment of different diseases in Ayurveda as well as in the Chinese medicine. It is also seen that this plant is also beneficial in soothing the after effects cause by the chemotherapy in the patient suffering from cancer. The main focus of this study is to identify the

various parts of the plant which can be beneficial in treating the human breast cancer.

A brief of Catharanthus roseus

Scientific classification

Table 1 : Scientific classification of Graveyard plant.

Kingdom	Plantae
Phylum	Magnoliopsida
Class	Annonidae
Order	Gentianales
Family	Apocynaceae
Genus	Catharanthus
Species	roseus
Botanical Name	*Catharanthus roseus*

Morphology

It is long lived evergreen plant that grows all over the year having an average height of the plant is 30-100 centimeters. It have green stem containing the white sticky latex, leaves and bright pink, yellow and white colour flowers. Its stem is erect having the hard woody appearance at the bottom and green from the top, it also contains the whitish sap inside it. The stem is little hairy in the texture in most of the cases but sometimes can be hairless. The leaves are on the opposite directions mainly dark green in colour and glossy in appearance (Das, S., & Sharangi, A. B. (2017)) with the pale midrib and veins. The flowers are grown in leaf axils having five petals attached to the short stalk.

Distribution

Periwinkle has the capability to grow in different variety of habitats as it is tolerant against the abiotic stresses such as temperature, salinity, water scarcity etc. (Nejat *et al*., 2015). Due to its tolerant nature this plant widely found in many states of India and have different local name across different parts of India but grows slowly in extreme low temperature areas, It is commonly it is known as 'Sadabahar' which means evergreen. It is found in Tamil Nadu, Gujrat, Andhra Pradesh, Madhya Pradesh, Assam,Karnataka, Punjab, and Haryana. This plant grows widely in the sub-tropical region of the North India but is Native to West Indies.

Fig. 1 : Graveyard plant.

Various species of Catharanthus

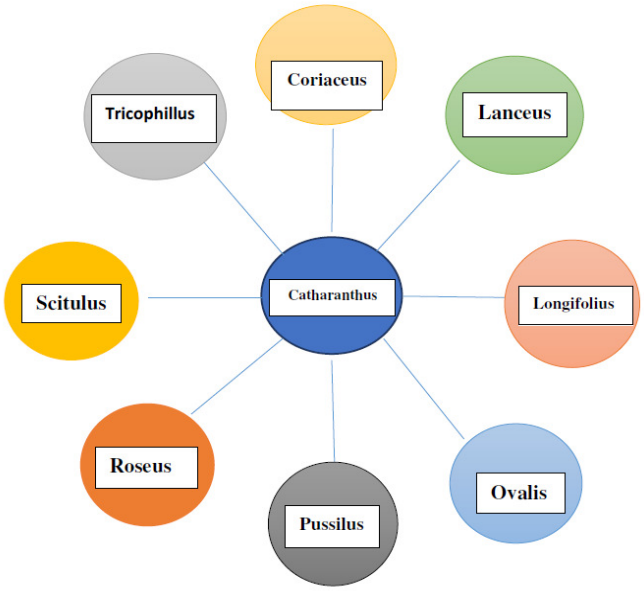

Fig. 2 : Various species of Catharanthus.

Potentially active compounds of *Catharanthus roseus*

Catharanthus roseus is known for containing more than 400 different compounds that have the pharmaceutical importance. This plant is the source of more than 150 active alkaloids which are helpful in treating various diseases. The widely studied alkaloids are Vincristine, Vindiscline and Vinblastine as all of these alkaloids are helpful in the treatment of various types of cancer and tumors. Leave of Catharanthus produces the alkaloids Vincristine and Vinblastine but in low concentration i.e. 0.0004% to 0.0003% of the dry weight (Barrales-Cureño, 2015). Different parts of the plant produces the different alkaloids in different concentrations (Zhao and Verpoorte, 2007) but the market demand is high for roots and leaves as the high amounts of alkaloids are produced in the cortex of the roots (Soleimani *et al*., 2013). Apart from being used in the pharmaceutical industry this plant is widely used in cosmetics and food industry due to its anti-oxidative properties (Kabesh *et al*., 2015).

Majority of the alkaloids produced by the plats are synthesized through secondary metabolism pathways which means the plant produces these types of alkaloids in the stress conditions or this type of mechanism is used by the plant for the self-defense. The anti-cancer alkaloids such as Vinblastine and Vincristine along with their derivatives are produced by the stem of the plant as the milky stick sap (Arora *et al*., 2010). The sap present in the stem of the plant is poisonous if consumed directly, these compounds are being extracted and purified and then finally used for therapeutic purpose. The main issue is that the plant produces these compounds in very quantity, Vincristine is of more importance in therapeutic field but the plant produce more amount of vinblastine as compared to vincristine. So many of the biologists are working to change the production of vinblastine to vincristine by genetic engineering or by using some specialize microorganism which have the ability to convert vinblastine to vincristine within the plant by some specialized mechanism.

Apart from vincristine and vinblastine some other alkaloids such as vinpocetine, produced by the plant are also helpful as these are the compounds which enhances the

human cognitive properties and it is commercially present in the market in its synthetic form. Semisynthetic Catharanthus alkaloids are developed by the researchers as the direct administration the natural alkaloids have some type side effects as used along with chemotherapy resulted in some complications to the patients such as nausea, hair loss and hyponatermia.

Catharanthus roseus is proven to contain some volatile phenolic compounds such as caffeoylquinie acid and flavonal glycosides, these alkaloids are loaded with ant oxidative properties and required by the human body in defense mechanism against variety of pathogens mainly they work as the anti-oxidative agents against reactive oxygen species (Bhutkar and Bhise, 2011). Reactive oxygen species are harmful for the human body as they form some harmful products through respiration resulting in accumulation of free radical in the body and these free radicals are root cause of many deadly health condition such as asthma, Parkinson's disease, arthritis, dementia and mongolism.

i. Vinblastine (VLB)

Vinblastine is the naturally occurring alkaloid first isolated by Robert Noble and Charles Thomas Beer from *Catharanthus roseus*, it is colorless and earlier was known by the name vincaleuko-blastine. In most of the clinical and therapeutic purposes its sulphate derivative is widely used. The sulphate derivative is hygroscopic, crystalline in nature and changes its colour from colourless to yellowish-white. Vinblastine is responsible for many chemotherapy successes but its targeting sites still remains unknown to researchers. (Gigant *et al*., 2005), as the production of vinblastine bt the plant is very low i.e. 0.0005%, so the researchers are continuously working to increase the production of secondary metabolites using techniques like tissue engineering and somatic embryogenesis. It is reported that the production of vinblastine is maximum content of vinblastine was present in the germinating embryos followed by matured embryos which gradually reduce with time and in the initial stages there was complete absence of vinblastine in the embryos (Aslam *et al*., 2010). Vinblastine is reported to be effective in neoplasia treatment and resistant pregnancy choriocarcinoma (Barrales-Cureño, 2015).

Mode of Action of Vinblastine

Vinblastine affects the cancerous cells by binding to the tubulin which further do not allow microtubules to assemble or in interferes in microtubule assembly. Tubulin is mainly composed of α-tubulin and β-tubulin which forms hetrodimers further arranging themselves in long chains and get protected by microtubule associated proteins (MAP's), at last this assembly gets evolved into 13-protofilament spiral microtube. The formed microtubule grows at one end and gets dissociate at the other end. Two types of microtubules are present in the cells i.e. cytoplasmic and spindle microtubule. When the cell enters the M-phase the cytoplasmic microtubule depolymerize and forms microtubule proteins which further assembles into spindle microtubule. In the anaphase these spindle microtubules are responsible to carry the chromatids aligned at the center towards the pole, as soon the process of mitosis is over these spindle microtubules gets depolymerize and changes to cytoplasmic microtubule. This is the continuous process which continues when the cell enters the cell division and comes out of it and even the little alteration in this process can induce apoptosis in the cell. Vinblastine cause the de-polymerization of the microtubules of the rapidly dividing cells which are mostly tumor cells which lead to the apoptosis of tumor cells (Zhou *et al*., 2018). Vinblastine is cell cycle specific alkaloid which works particularly at M-phase and even it is the integral part of various chemotherapy regimens such as ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) which is used for the treatment of Hodgkin's disease. Vinblastine has also been reported to work against cancer by interfering with glutamic acid metabolism (Arora *et al*. 2010).

Toxicity and Side Effects of Vinblastine

- Bone Marrow suppression
- Gastrointestinal toxicity
- Potent Vesicant (ability to form blisters)
- Extravasation injuries (can form deep ulcers)
- Embryotoxicity (cannot be used in pregnancy and not for breast feeding mothers)

ii. Vincristine (VCR)

Vincristine s the colourless alkaloid present in the aerial parts of the plant such as leaves and stem. It is potentially more active than vinblastine and also have on more advantage that it is produce in larger quantities by the plant than vinblastine. Vincristine is commercially available in the market by the brand name 'Oncovin' and 'Leurocristine'. US FDA (Food And Drug Association) has approved Vincristine in the year 1963 for the brand name Oncovin. Vincristine id widely used for the therapeutic purpose and is the part of chemotherapeutic regime as is helpful in soothing the after effects of chemotherapy such as nausea, fever etc.

Mode of Action of Vincristine

Vincristine is cell dependent anti-cancer agent as it bind to the tubulin which lead to microtubule depolymerization, (Van Tellingen *et al*., 1992) Tubulin is the vital component in the process of cell division as it is essential for normal polymerization of mitotic spindle microtubule. A slight alteration in the process of polymerization of the mitotic spindle microtubule can lead to cell death. Vincristine binds to the spindle microtubule which makes the change in the structure and function of the microtubules leading to the metaphase arrest or apoptotic cell death. The anti-cancer ability of vincristine totally depend on it concentration as administration with low concentration stabilize spindal apparatus and do not allow chromosome to segregate which causes the cell to get stuck in metaphase and could not able to perform mitosis, on the other hand when the high concentration of vincristine is administered the complete depolymerization of the microtubule happens which will further induce apoptotic cell death. In-vitro studies have shown that Vincristine also have antivascular and antiangigenic properties, as various angiogenic factore such as vasculature endothelial growth factor (VEGF) is inhibited by vincristine. It is also reported that vincristine do not allow the tumor cells to proliferate, establish capillary network and do not allow tumor cells to migrate from one place to another (Silverman and Deitcher, 2013).

Toxicity and Side Effects of Vincristine

- Peripheral Neuropathy
- Hyponatremia
- Constipation

- Hair loss
- If administered in spinal canal can be lethal
- Breathing problems
- Lung spasm
- Motor weakness
- Depression

Apart from Vincristine and Vinblastine there are other alkaloids such as Vindestine, Vinorelbine, and Vinfluvin which are also extracted from Catharanthus roseus and have diverse importance in therapeutic field. All of above mentioned alkaloids are helpful in curing variety of cancers and tumors such as lung cancer, breast cancer, leukemia, lymphoma and melanoma. Researchers are continuously working to enhance the bioavailability and target tumors, limiting multi-drug resistance (Wang *et al*. 2014) and toxicological profile of all the Vinca alkaloids. FDA (Food and Drug Association) approved the sphingo-myelin and cholesterol based nanoparticles formulation of vincristine sulfate in the year 2012 for the treatment of Philadelphia chromosome negative acute lymphocytic leukemia (Martino *et al*., 2018).

Therapeutic importance of *Catharanthus roseus*

i. Anti-microbial properties

It is reported that the ethanolic plant extract of *Catharanthus roseus* is effective against various fungal stains like A. *fumigatus*, A. *niger*, C. *albicans* and *F. monliforme* (Kumari and Gupta, 2013). It is also reported that the plant extract is also efficient against bacterial strains i.e. *Pseudomonas aeruginosa* NCIM2036, *Salmonella typhimuruim* NCIM2501, *Staphylococcus aureus* NCIM5021 and was found that the extracts could be used as the prophylactic agent in the treatment of many of the disease (Mishra and Verma, 2017).

ii. Anti-oxidant properties

It is reported that the water extract of *Catharanthus roseus* have anti-oxidative properties at level concentration 0.5% resulted 71.87% as it scavenge DPPH free radical activity (Widowati *et al*., 2011), but the ethnolic extract of the plant show satisfactory levels of anti-oxidative properties.

iii. Anti-helminthic activity

Human beings get infected by variety of helminthes and the diseases caused by these infections can even be lethal in some cases. *Catharanthus roseus* is used as anti-helminthic agent. The ethanol extract, at a concentration of 250 mg/mL showed significant anti-helminthic activity at 46.3 min, while the standard drug showed activity at a concentration of 50 mg/mL at 40.7 min. This ethno-medical research considers *C. roseus* as an effective anti-helminthic drug (Agarwal *et al*., 2011; Barrales-Cureño, 2015).

iv. Anti-tumor activity

As described above there are variety of alkaloids present in different parts of the plant i.e. Vincristine, Vinblastine, Vindesine and Vinflunine that have shown wonderful results against variety of cancer and tumors. Extracts from Catharanthus roseus have reported to be effective when investigated in-vitro using different cell lines such as MCF-7 and Caco2 (Asmah *et al*., 2005).

Conflict of Interest:

There is no conflict of interest among the authors.

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