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Review Article

An Updated Review on Phytochemical and Pharmacological Properties of *Catharanthus rosea*

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Abstract

Catharanthus roseus is an important evergreen medicinal herb of Apocynacea family used mainly for treatment of cancer and diabetics. The plant was 1 m in height and commercially grown widely in India, Australia, Africa and Southern Europe. Alkaloids such as vincristine and vinblastine, flavonoids and phenolic are the main components of plant. The plant exhibits various biological properties such as antibacterial, anticancer, antioxidant, antihyperglycemic, anti-hypertensive, antidiabetic and wound healing. In the present study we have tried to collect traditional uses, phytochemical constituents and pharmacological properties of plant. This study should be used to understand the health promoting properties of this multipurpose plant and it may also provide clues for discovery of new lead compound of pharmaceutical importance.

Keywords: *Catharanthus rosea*, Apocynaceae, phytochemical, pharmacological, alkaloids.

INTRODUCTION

Nowadays plant derived natural products are widely used in treatment and prevention of various diseases for improving the longevity and achieving the positive health care and also reducing the adverse effect of chemotherapeutic agent. Herbal extracts contain various phytocompounds or secondary metabolites that act against various diseases and their mode of action is different for each extract and compound respectively. *Catharathus rosea* (L.) known as *Vinca rosea* is an important evergreen herb belongs to dogbane family-Apocynaceae generally known as "Nayantara" or "Sadabahar". *C. roseus* have two common cultivars which are differentiated based on their flower color "Rosea" for pink flower and "Alba" for white colored flowers. The plant is popularly known as Madagascar periwinkle because it is endemic to Madagascar. The synonyms of plant include Lochnera rosea, Ammocallis rosea, Rosy Periwinkle Cape Periwinkle, Rose Periwinkle and "Old Maid". Traditionally *C. roseus* was used to cure various types of diseases such as hypertension, cancer, skin disease, diabetes, menstrual disorders, indigestion, rheumatism, dyspepsia. The plant is rich in bioactive compounds and possesses vast range of pharmacological properties. [1] Reported that the plant is cultivated widely for its alkaloids which have anticancer properties. [2] Reported that *Catharanthus roseus* contain more than 130 different types of alkaloids broadly used in curing various types of cancer including breast cancer, lung cancer, melanomas due to the presence of vincristine and vinblastine. Leaves of *Catharanthus roseus* contain 70 different types of chemical compound such as ajmalicine, reserpine, and serpentine. Alkaloids are the main constituents of *C. roseus* which is being used for the treatment of diabetes, blood pressure, menstrual problem, asthma, constipation, and cancer. The plant synthesizes two main terpene indole alkaloids namely vincristine and vinblastine that act against cancer [3]. *Catharanthus roseus* contain significant amount of volatile and phenolic compounds such as caffeoylquinic acids and flavonal glycosides which act as antioxidants against reactive oxygen species and play important role in plant defense system [4]. These compounds also exhibit anti-inflammatory, antimicrobial, antithrombotic, anti-allergic, vasodilatory effects and cardio-protective properties [5]. The plant possess good antioxidant, antifungal, antibacterial and antiviral activity [6, 7]. The present review focuses on ethanobotanical, phytoconstituents and pharmacological aspects of *C. rosea.*

METHODOLOGY

In this review the complete information of the plant has been collected from various peer reviewed research articles retrieved from many online databases such as Scopus, Pub Med, Med Line, Springer Link, Google Scholar, Research Gate, Google and Science Direct .The keywords used for online search includes *Catharanthus rosea*, Apocynacea family, biology, distribution, diversity, ethanobotanical importance, pharmacological properties, bioactive constituents, antidiabetic activities, antioxidant activities, antimicrobial activities, adverse and anticancer activities. As *C. rosea* is used for medicinal purpose for long time in acute and chronic diseases, it should be therapeutically safe for clinical purpose.

Botanical Description

Morphology

Catharanthus roseus is an annual, herbaceous, evergreen, dicotyledonous ornamental flowering plant growing to a height of 1m. Leaves of the plant are 2.5-9.0 cm long and 1- 3.5 cm broad, hairless, glossy, and green in color and midrib is pale and shape is oval to oblong, petiole is short about 1- 1.8 cm, long and they are appositively arranged in pairs. The flowers are dark white or pink with dark red in centre. Basal tube is 2.5-3 cm long and diameter of corolla was 2-5 cm with 5 petals like lobes. Fruits are arranged in follicle shaving length of 2-4 cm and width of 3 mm broad. The chromosome number for all *Catharanthus* species is 2n= 16. However, tetraploid plants grow faster and the flowers are reported to be bigger in size [8].

Fig-1: Showing *Catharanthus rosea*

Table-1: Vernacular names of *Catharanthus roseus*

Language	Vernacular names of *C.rosea*
English	Cayenne Jasmine, Old Maid, Periwinkle
Hindi	Sada Bahar, Sadabahar
Kannada	Batla Hoo, Bili Kaasi Kanigalu, Ganeshana Hoo, Kempu Kaasi Kanigalu
Malayalam	Banappuvu, Nityakalyani, Savanari, Usamalari
Marathi	Sadaphool, Sadaphul, Sadaphuli
Sanskrit	Nityakalyani, Rasna, Sadampuspa, Sadapushpi
Bengali	Noyontara
Gujarati	Barmasi
Telugu	Billaganneru
Tamil	Cutkattu Malli, Cutukattu Malli, Cutukattuppu

Taxonomy

Kingdom : Plantae
Division: Magnoliophyta (Flowering plants)
Class : Magnoliopsida (Dicotyledons)
Order : Gentianales
Family : Apocynaceae
Genus : *Catharanthus*
Species : *roseus*
Botanical name: *Vinca Rosea*
Binomial name*: Catharanthus roseus* [9]

Cultivation Principles

Catharanthus roseus prefers sunny and hot conditions and grown widely in sandy loams in full sunlight to part shade. The flower blooms throughout the summer season until frost appears. Vinca minor and Vinca major are evergreen veining ground plants and there are propagated through cuttings. The plant requires regular moisture but avoid over head of watering. Seeds are produced in the plant 12-16 weeks before the last frost. The plants are self propagated in nature from seeds and the seeds require total darkness to germinate. Cutting of the plants were taken in late summer and they were also capable to develop roots. Flowering is not encouraged in high fertility soil and flowers drop off after blooming.

Geographical Distribution

Catharanthus roseus is a native plant Indian Ocean, Island of Madagascar cultivated widely in tropical and subtropical areas worldwide including Southern United states, Philippines, Cuba Jamica, Bahamas, Mauritius and Malaysia. The plant was grown commercially in Australia, Africa, India and Southern Europe for medicinal purpose and throughout the tropical and subtropical regions of world as ornamental purpose [10].

Ethno Medicinal Importance

Catharanthus roseus is an important traditional medicinal plant used for treatment of several types of diseases. Historically, *C. rosea* was used for various treatments such as diabetes mellitus, high blood pressure and infection. About 90 alkaloids were found in leaf part and the most abundant monomers are catharanthine and vindoline. The derivatives of vincamine known as ethyl-apovincaminate or vinpocetine were widely used as medicine in blood thinning, vaso-dilating, memory-enhancing actions and atherosclerotic plaques [11]. In India, leaf juice of the plant is used as application in bee sting and wasp sting. Extract of flower was used for eye wash in infants in Cuba and Jamica. Menorrhagia and rheumatism is treated by the infusion of leaves [12]. In Philippines leaves were used for treatment of diabetics, stomach cramps and roots in intestinal parasitism. Crude extract of leaf and root was used for treatment of cancer. In Madagascar astringent and bitter leaves were used in prevention of vomiting, roots were used as purgative and also used remedy for toothache. Leaf juice is used for dyspepsia and indigestion in Mauritius. The plant was used in tuberculosis, asthma and flatulence in Bahamas. West Indies and Nigeria people used the plant for treating diabetes. The plant was used in Malaysia for hypertension, diabetes, insomnia and cancer. Bleeding was prevented by applying boiled extract of plant. In Africa rheumatism and menorrhagia is treated by the leaves of the plant [13]. In British West Indies the plant is used to cure diabetic ulcer and in Philippines it is used as hypoglycemic agent. In India the leaves of the plant was traditionally used to control diabetes, cancer, menorrhagia and Hodgkin's diseases [8, 14]. De Mollo [15] reported that in Brazil people used dried hot water whole plant extract for treating diabetics and leaves of the plant are used to control scurvy, hemorrhage, for healing and cleaning of chronic wounds, as a mouth wash for toothache. Bhandari *et al.*, [16] reported that in South Africa leaf extract was taken orally for menorrhagia and diabetes. In Taiwan whole plant extract was used orally for treatment of diabetes [17]. Leaf extract was smoked as euphoriant in USA [18]. Holdsworth [19] reported that in Cook-Island dried leaves of plant was used to treat cancer, hypertension and diabetics. In Dominica boiled leaves were used by pregnant women during pregnancy to combat primary inertia in childbirth [20]. Thomson [21] reported that whole plant extract was used by people of England for diabetics. In European countries the plant was used as folk remedy for curing of diabetes and headache. In rural areas dried or wet extracts of flower and leaves were applied as paste on wounds. In India ayurvedic physicians used fresh juice from flowers of *C. rosea* for treatment of skin diseases e.g. dermatitis, eczema and acne. The plant contain more than 400 known alkaloids approved as anti-neoplastic agents and used for treatment of leukemia, Hodgkin's disease, neuroblastoma, rhabdomyo-sarcoma, malignant lymphomas, wilms' tumor and other cancers [22] .

Economic Values

In the year 1990 the world market consumed 5-10 kg of vincristine and vinblastine with a total value of US$25-50 million. In the year 1991 the world market consumed 3-5 t of ajmalicine, with a total value of US$4.5-7.5 million. It was estimated that in 2005 the world market was at US$150-300 million. Oncovin® and Velban® are the two most important anticancer drug isolated from *C. roseus* are sold for a total of US$100 million per year [23].

Chemical Constituents

Catharanthus roseus contains several phytocompounds of pharmacological importance such as carbohydrate, flavonoid, tannin, saponin, glycoside, terpenoid, protein, phenol and alkaloids [24]. The plant contains about 400 alkaloids and alkaloids are the most potentially active chemical components of the plant used in pharmacological activities, flavor and fragrance, ingredients, food additives, pesticides and agrochemicals. More than 100 monoterpenoid indole alkaloids (TIA) are produced by these plants in different organs. Ariel parts of the plant contain several alkaloids like vindesine, vindeline tabersonine, vinblastine, vincristine, actineoplastidemeric whereas basal or root parts of the plant contains raubasin, reserpine, catharanthine, vinceine, vineamine, and ajmalicine. Heijden *et al.*, [25] reported that vindoline (0.5%) is the principle component other compounds are reserpine, vincamine, alstonine, 22-oxovincaleukoblastine (vineristine), leurocristine, ajmalicine, vinine, vincaleukoblastine (vinblastine), vintsine, leurosine, vinomine, vinoxine. *C. roseus* is rich in alkaloids, tannins, coumarin, quinine, carbohydrates, flavonoids, triterpenoids and phenolic compounds [26]. Leaves are rich in alkaloids and carbohydrates. Flowers of plant were rich in tannins, triterpenoids and alkaloids were responsible for diabetic wound healing property [27]. Flowers of *C. roseus* contain an anthocyanidin pigment rosinidin [28]. Terpenes or terpenoids indole alkaloids have been identified as active anti-cancer, anti-inflammatory and anti-bacterial anti-protozal and anti-malarial agents in many pharmacological studies [29, 30]. Table-2 showed different types of alkaloids produced by *Catharanthus roseus*.

Table-2: Alkaloids present in different organs of the plant

Plant organ	Name of Alkaloids present.
Leaf	Catharanthine, Vindoline, Vindolidine, Vindolicine, Vindolinine, ibogaine, yohimbine, raubasine, Vinblastine, Vincristine, Leurosine, Lochnerine.
Stem	Leurosine, Lochnerine, Catharanthine, Vindoline
Root	Ajmalacine, Serpentine, Catharanthine, Vindoline, Leurosine, Lochnerine, Reserpine, Alstonine, Tabersonine, Horhammericine,Lochnericine, echitovenine.
Flower	Catharanthine, Vindoline, Leurosine, Lochnerine, Tricin (Flavones).
Seeds	Vingramine, Methylvingramine.

Pharmacological Applications

The plant showed broad spectrum of pharmacological properties which signifies its medicinal importance. Vinblastine and vincristine are active components isolated from the leaf and stem parts and showed inhibition property against human tumours. Vinblastine an alkaloid isolated from plant used significantly in treatment of neoplasmas and recommended for treatment of hodgkins disease, chorio carcinoma. Vincristine is used experimentally for curing leukemia in children. Vinblastine is commercially sold as velban or vincristine as oncovin. The leaf extract was tested and is being used as prophylactic agent against several diseases. The cerebro-vasodilatory and neuro-protective activity was found on vincamine alkaloid present on plant leaf. Experimentally leaves of the plant extract showed antiulcer activity and was proved against gastric damage in rats. Due to presence of vast phytochemical constituents the plant can be used as an important therapeutic aid in future.

Anti-Oxidant Activity

Aerobic respiration and other normal metabolic activities create free radicals or ROS which are very harmful for our body. Antioxidants eliminate these free radicals and protect the body cells from damage. *C. roseus* contain viable source of natural antioxidants used in nutraceutical and food industry. The comparative study of antioxidant activity of *C. roseus* pink flowered and *C. alba* white flower showed that the antioxidant activity is present more in *C. roseus* than *C. alba* [31]. Salah *et al.,* [32] reported that *C. roseus* exhibits antioxidant property due to presence of phenolic compounds. The antioxidant activity of extracts of *C. roseus* was determined by DPPH method and found that plant extract was able to inhibit T47D cell proliferation with IC_{50} (55.2) µg/ml and (26.22) µg/ml respectively which indicated its potent antioxidant property [33]. Bhutkar and Bhise [34] reported that ethanol root extract was tested for anti oxidant activity in two varieties of *Catharanthus roseus,* rosea (pink flower) and alba (white flower) by using different assay and found that plant ethanol root extract exhibited potent scavenging effect for *C. roseus*. Patel *et al.,* [35] reported that in leaf juice of *C. roseus* vinpocetine like compound was present which showed antioxidant activity similar to flavonoid. It has been studied that methanol and dichloromethane leaf extracts and ethanol root extracts showed antioxidant activity in β-TC6 cells [36].

Anti-Diarrheal Activity

Kyakulaga *et al.,* [37] reported that leaf ethanolic extract of the *Catharanthus roseus* showed potent anti-diarrheal activity as tested on wistar rats with castor oil as an experimental diarrhea inducing agent in addition to pretreatment of the extract. Loperamide and atropine sulphate was taken as standard and ethanolic extracts of *Catharanthus roseus* at the doses of 200 and 500 mg/kg showed the dose dependent inhibition of castor oil induced diarrhea. It has been reported that in wistar mice at 200 and 500 mg/kg of ethanol leaf extracts of *C. rosea* showed antidiarrheal activity [38].

Anti-Diabetic Activity

Diabetes mellitus is a leading cause of death nowadays a large population depends on herbal drugs for curing of diseases. Several authors have reported that *Catharanthus rosea* was used for controlling diabetics. It has been reported that vinculin a plant derived natural remedy used for curing of diabetes was isolated from *C. roseus* which showed hypoglycemic activity and has been marketed commercially [39]. Anti hyperglycemic activity is significantly showed by whole plant alcoholic extract at a (500 mg/kg) of high dose. Blood sugar level and the beta-cell number were reversed effectively due to extract of *C. roseus*. The phyto constituents responsible exactly for the anti-diabetic effect were not yet known [40]. Leaf and flower ethanol extract showed reduction in blood glucose and is comparable to the standard drug. Reduction of blood sugar is similar to the standard drug glibenclamide [41, 42]. In the liver hypo glycemic effect has observed due to the result of the enhanced glucose utilization. In laboratory animals it has been observed that leaf extract of *C. rosea* possess anti-hyperglycemic and hypo-tensive activity [43]. The fresh leaf juice of *C. rosea* helps to reduce blood glucose levels in normal and alloxan diabetic rabbits [44]. The hypoglycemic activity was observed after administration of leaves and twigs of *C. rosea* in streptozocin induced diabetic rats [45]. Venter *et al.,* [46] studied that plant extract was used for stimulated glucose utilization in hepatocytes. Aqueous leaf extract of *C.rosea* showed hypolipidemic effects in alloxan induced diabetic rats [47]. Muralidharan [48] reported

antidiabetic activity of dicloromethane extracts of leaves and twings of *C. rosea* in streptozotocin (STZ) induced diabetic rat model.

Anti-Microbial Activity

Phytochemical and antimicrobial studies revealed the presence of active compounds like steroids, phenolics, tannins and saponins, alkaloids and flavonoids in *Catharanthus roseus*. Antibacterial activity was shown against common human pathogens such as *Styphylococcus aureus, Escherichia coli, Vibrio cholerae* and *Streptococcus faecalis* in the methanol, ethanol, acetone and chloroform extracts. Aldehydes and phenolic compounds of the plant extract showed significant antimicrobial activities [49]. Patil and Ghosh [50] reported antibacterial activity from the crude extracts from different parts of *Catharanthus roseus* against *Pseudomonas aeruginosa* NCIM2036, *Salmonella typhimuruim* NCIM2501, *Staphylococus aureus* NCIM5021 and found that the leaf extract showed high antibacterial activity. The antibacterial activity of *C. rosea* was tested in ethanolic leaf, stem, root and flower extracts and found highest activity in leaf part [51]. *C. rosea* extract showed antiviral activity against herpes simplex virus (type1) [52]. Yohimbine exhibits antifungal activity against *Candida albicans* [53]. It has been reported that vincristine and vinblastine compound isolated from *C. rosea* showed antiparacitic activity against *Trypanosoma cruzi* that causes trypanosomiasis in humans [54]. Wang *et al.*, [55] isolated a mono terpenic indole alkaloid, catharoseumine from whole plant of *C. rosea* that showed potent inhibitor against protozoan parasite falcipain-2 (that causes malaria) showing an IC50 value of 4.06 μM.

Anticancer Activity

Catharanthus rosea is well known for its anticancer activity. The anti tumour activity investigated in *C. roseus* is due to presence of dimeric alkaloids such as vinblastine, vincristine and anhydrovinblastine which are already in use. Vinca alkaloids are the rich source of life saving drugs which are widely used to produce anti-cancer drugs. It has been reported that spindle formations from microtubules are inhibited by vinca alkaloids which are also known as mitotic spindle poisons that act by inhibiting mitosis in cell cycle. Dividing of cancer cell was prevented successfully by vinca alkaloids. Microtubule formation is especially powerful inhibited by vincristines. Among the cancer drugs vinca alkaloids are one of the second most-used classes [56]. In 1990 Noble reported that vinca alkaloids known for their anti-cancer properties are produced from *C. roseus*. Jordan [57] reported that anti-cancer drugs derived from the plant act us inhibitors of tubulin by binding to α/β- – tubulin and thus prevents its association into microtubules which provide cells both the structure and flexibility they need to divide and replicate. Microtubules are the main component or building block of protein and is vital to the proper functioning of the mitotic spindle in mitosis i.e., cell division. Moudi *et al.*, [58] reported anticancer activity of vinca alkaloids as they represses the cell growth and alter micro tubular dynamics and promotes apoptosis. Vincristine is oxidized form of vinblastine that is very effective for treating acute lymphoblastic leukaemia in both children and adults as it arrests mitosis in metaphase stage. Vincristine is also used against Hodgkin's disease, Wilkins's tumour, neuroblastoma, and reticulum cell sarcoma. Some semi synthetic compounds similar to vincristine and vinblastine have been developed to increase the therapeutic action against cancer treatment [59]. Vinblastine isolated from *C. rosea* was used for treatment of several diseases such as Hodgkin's disease, besides lymphosarcoma, choriocarcinoma, neuroblastoma, carcinoma of breast and lung, and lymphocytic leukemia [60, 61]. The anhydro-vinblastine the direct precursor of vinblastine showed significant *in vitro* cytotoxic activity against human non-small cell lung cancer C4 and human cervical carcinoma, human leukemic cells, and A431 human carcinoma cells [62].

Memory Enhancement Activity

Nayak *et al.*, [63] reported that vinpocetine, made from the alkaloid called vincamine is the most interesting dietary supplement because of its action to improve brain function and memory which are particularly beneficial in treatment of Alzheimer's disease. In clinical trials it has been studied that in dementia and stroke, vinpocetine at doses up to 60 mg/d has been well tolerated and no significant adverse events were observed. Warfarin, aspirin as well as some dietary supplements like ginkgo, vitamin E and garlic the blood thinning agents should not be combined with vinpocetine [64].

Wound-Healing Activity

Nayak *et al.*, [63] reported that ethanolic extract of *Catharanthus roseus* have wound healing property when treated to wounded rats and this property was due to increased tensile strength and hydroxyproline content of the granulation tissues. It supports the use of plant extract in the management of wound healing. *C. roseus* leaf juice was reported to be effective in reducing total cholesterol, triglycerides, LDL-c, VLDL in serum levels and histology of liver arota and kidney and showed significant atherosclerotic activity. Singh *et al.*, [65] reported that methanol leaf extract of *C. rosea* showed wound healing activity in Streptozotocin-induced diabetic mice at a concentration of 200 and 400mg/kg.

Antiulcer Activity

The antiulcer activity is exhibited by vincamine and vindoline alkaloids. Cerebro vasodilatory and neuroprotective activity was showed

by vincamine alkaloid present on leaves of the plant [43]. Babulova *et al*., [66] reported that the antiulcer property was exhibited by the alkaloid vincamine and vindoline present on plant *Catharanthus roseus* as proved against experimentally induced gastric damage in rats.

Hypotensive Activity

Pharmacologically active compounds are present on the leaves of the plant. About 150 alkaloids of pharmacological importance are present on plant leaves. In laboratory animals significant antihyperglycemic and hypotensive activity was reported by the leaf extracts of *C. roseus*. It has been reported that the leaf extract of *C. roseus* showed significant hypotensive activity on laboratory animals [43].

CONCLUSION

Traditionally used medicinal plants play an essential role in health sector due to its wide abundance source of bioactive compounds. The plants were widely used in folk remedy for treatment of several diseases. In the past few years the demand of *C. rosea* is being increased due to its alkaloid contains and used for curing of cancer and other diseases. To fulfill the demand of plant at commercial level researchers might focus on the pharmacological study and also its conservation. This review may be beneficial for analysis of active phytocompounds and to investigate the plant for development of new drug for the betterment of human kind.

Conflict of interest: The authors declare no conflict of interests.

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