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A REVIEW OF CATHARANTHUS ROSEUS: AFRICAN MADAGASCAR PERIWINKLE

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Abstract: *Catharanthus roseus* is an evergreen plant that originated from the islands of Madagascar. It is known for its antitumor, anti-diabetic, and anti-microbial effects. Many famous phytochemicals, such as vincristine and vinblastine, were isolated from the plant. It possesses various pharmacological properties, including antioxidant, antimicrobial, and antidiabetic effects. The purpose of the current study is to document updated data about its traditional uses. The endangered species needs to be conserved using techniques like micropropagation.

Keywords: Vincristine, Vinblastine, Antitumor effects, Antidiabetic effects, antimicrobial effects, Pharmacological properties, Antioxidant effects, Endangered species, Micropropagation.

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INTRODUCTION

Medicinal plants have a long history of usage in traditional medicine. Ethno-botanical information on medicinal plants and their usage by indigenous cultures is useful in the conservation of traditional cultures, biodiversity, community health care, and drug development. The history of the use of medicinal plants in India has been passed down from one generation to another (Ullah et al., 2020). Folk recipes are prepared from the whole plant or from its different parts, like leaf, stem, bark, root, flower, seed, etc., and also from secondary products such as gum, resins, and latex. In the human body, medicinal plants interact directly or indirectly with the body's chemistry through their chemical constituents. Trace elements have significant roles in combating a variety of human ailments and diseases, as observed by the study of elements with respect to indigenous medicinal plants. Catharanthus roseus is an evergreen sub-herb plant growing to 1 m tall. The leaves are oval to oblong, 2.5- 9.5 cm. long and hairless with a pale midrib.

TRADITIONAL USES

Periwinkle has historically been used to treat a wide range of diseases. Western researchers noticed the plant in the 1950s when they learnt of a tea that Jamaicans were drinking to treat diabetes. It contains alkaloids that lower blood sugar levels and prevent bleeding. Another traditional way of using the *Catharanthus roseus* is Ayurveda. Ayurveda is an Indian traditional medical practice that focuses on the medicinal properties of plants. The periwinkle has been used in traditional medicine to treat muscle pain, depression of the central nervous system, and wasp stings (Kumar et al.,2022). It is also used for applying to apply to wounds and to heal wounds (Gajalakshmi *et al.*, 2013). Ajmalicine, vinceine, resperine, vincristine, vinblastine, and raubasin are among the roughly 130 alkaloids produced. Hodgkin's disease, breast cancer, skin cancer, and lymphoblastic leukemia are among the cancers that vincristine and vinblastine are used to treat (Dubey et al., 2020).

- **Botanical Name(s)**: *Vinca Rosea* (*Catharanthus roseus)*
- Family name: *Apocynaceae*
- Kingdom: *Plantae*
- Division: *Magnoliopsida* (Flowering plants)
- Class: *Magnoliopsida* (Dicotyledons)
- Order: *Gentianales*
- Family: *Apocynaceae*
- Genus: *Catharanthus*
- Species: *C. roseus*
- **Vernacular names:** English: cayenne jasmine, old maid, periwinkle
- Hindi: sada bahar, sadabahar.

POTENTIALLY CHEMICAL ACTIVE CONSTITUENTS

Catharanthus roseus contains alkaloids that could have potential uses in cancer treatment. More than 400 alkaloids are present in the plant, which are used as pharmaceuticals, agrochemicals, flavor and fragrance, ingredients, food additives, and pesticides. Actineo plastidemeric, Vinblastine, Vincristine, Vindesine, Vindeline Tabersonine, and other alkaloids are mostly found in the aerial portions, whereas ajmalicine, vinceine, vineamine, raubasin, reserpine, catharanthine, and other alkaloids are mostly found in the roots and basal stem. The anthocyanin pigment rosindin is present in the flower of C. roseus (Sertel et al., 2011). According to Ethalsha and Retna (2014), these alkaloids, some of which have been categorized as antineoplastic agents for inhibiting or preventing the growth and spread of tumors or malignant cells. These active substances are anti-carcinogenic, anti-oxidative, hypoglycemic, anti-allergic, and antibiotic in nature, thus essential for the healthy functioning of the body. Studies reveal that most of the vinca alkaloids were first isolated from

Catharanthus roseus. Also, alkaloids that are isolated from the plant are found to be hypotensive, sedative, and possess a tranquilizing effect on the blood pressure. Periwinkle alkaloids are found to be used for the treatment of both malignant and nonmalignant diseases and in the platelet and platelet-associated disorders (Jacobs et al., 2004).

TRANSCRIPTOME ANALYSIS

Each plant tissue of periwinkle produces a unique spectrum of terpenoid indole alkaloids. However, they are only present in the plant's aerial portions, not in its subterranean tissues. The anticancer bisindole alkaloids were discovered exclusively in the aerial regions. As a result, identifying the structural and regulatory variables that operate specifically in the plant's shoot/leaf would be a common requirement for modulating bisindole alkaloid production. The differential gene expression in the two main tissues (leaf and root) of the plant, which are well known for their distinct terpenoid indole alkaloid profiles, was elucidated indirectly through the construction and characterization of separate cDNA libraries and directly through a strategically designed suppression subtractive hybridization using the leaf and root cDNA populations. The direct method generated one EST for (SDG) (strictosidine b-D-glucosidase) and 16 new ESTs out of a total of 155 ESTs submitted to homology-based categorization.

Polyamines and the cell cycle of Catharanthus roseus cells in culture

Flow cytometry was used to investigate the effect of partial depletion of polyamines (PAs) caused by treatment with inhibitors of PA production on cell distribution at each phase of the cell cycle in periwinkle cells in suspension cultures. Inhibitors of arginine decarboxylase (ADC) and ornithine decarboxylase (ODC) were shown to accumulate more cells in the G phase, whereas spermidine synthase inhibitors did not affect cell distribution. During the cell cycle, two maxima in the endogenous level of PAs, specifically PUT and SPD, were detected. Before the event, PA levels were found to be much higher than PAs.

PHARMACOLOGICAL ACTIVITIES

Anti-cancer /antineoplastic/anticarcinogenic effects

Vinblastine and Vincristine are anticancer alkaloids produced from the stem and leaves of *Catharanthus roseus*. Some human cancers respond to these alkaloids by slowing down their growth. Vinblastine is a neoplastic therapy that has been tested in clinical trials and is indicated for Hodgkin's disease and choriocarcinoma. Another alkaloid, vincristine, is used to treat childhood leukemia (Patharajan and Abirami, 2004). In vitro, different percentages of methanolic crude extracts of *Catharanthus* were discovered to have substantial anticancer activity against a variety of cell types, with the greatest activity against multidrug-resistant tumor types. Velban or Vincristine are two brands of vinblastine that are offered as oncovin. (Quideau *et al.*, (2011). *Catharanthus* extracts were antineoplastic in vitro, which ultimately led to the licensing of the alkaloids as chemotherapies.

Anti-diabetic activity

The ethanolic extracts of the leaves and flowers of *C. roseus* showed a dose-dependent lowering of blood sugar comparable to the standard drug. Lowering of blood sugar is comparable to the standard drug glibenclamide. Because of the increased glucose consumption in the liver, a hypoglycemic effect has developed. The impact of daily oral administration of *Catharanthus roseus* (CR) leaf dichloromethane: methanol (1:1) extracts (500 mg/ body weight) on blood glucose and liver enzymes in normal and Alloxan-induced diabetic rats was investigated for 20 days. The extract caused the test animals' body weight to rise while their blood glucose, urea, and cholesterol levels decreased. Hepatic enzyme activity, such as hexokinase, was enhanced, but glucose 6-phosphatase and fructose 1 6 1,6-bisphosphate activity was considerably reduced. Because of the increased glucose consumption in the liver, a hypoglycemic effect has developed. The International Journal of Pharmacy and Pharmaceutical Sciences is a peer-reviewed journal that publishes research in the fields of pharmacy and hypoglycemic actions of alkaloids extracted from *C. roseus* have been investigated pharmacologically, and a medicine produced from the plant has been sold as a therapy for type 2 diabetes under the trademarked name Vinculin.

ANTI-MICROBIAL ACTIVITIES OF CATHTARANTHUS ROSEUS

As most bacterial pathogens have developed resistance to many of the current antimicrobial medicines, *Catharanthus roseus* was discovered to be an essential medicinal plant for the creation of new pharmaceuticals. Plants are a valuable natural resource for effective chemotherapeutic drugs, and they have a wide range of activities, with a focus on prevention. The goal of this study is to look at some of the plant's antimicrobial characteristics. Crude extracts from different parts of the plant were tested for anti-bacterial activity. Extract from leaves showed significantly higher efficacy. The anti-bacterial activity of the leaf extract of the plant was checked against microorganisms like *Pseudomonas aeruginosa* NCIM2036, *Salmonella typhi* NCIM2501, and *Staphylococcus aureus* NCIM5021, and it was found that the extracts could be used as a prophylactic agent in the treatment of many diseases.

Anti-fungi activity

Kumari and Gupta (2013) investigated the African periwinkle for its antifungal activities against a number of therapeutically important fungal species, including *Fusarium moniliform*, *Candida albicans*, *Aspergillus niger*, and *Aspergillus fumigatus*. The experiment was carried out utilizing the paper disc diffusion method, which employed three different extraction media (acetone, aqueous, and ethanol).

The results revealed that the inhibition pattern is strongly reliant on the extraction solvent. Unlike the aqueous extracts, the organic extracts showed more substantial antifungal action. In ethanol extracts, the leaves demonstrated considerable inhibition against *Fusarium moniliform*. The study supports that the rosy periwinkle plant contains antifungal properties.

Anti-viral activity

Periwinkle *(Catharanthus roseus L.)* contains about 100 alkaloids, including vincristine and vinblastine, which are used to treat leukemia. Natural infections in periwinkle are caused by members of the Potyviridae family, notably *Catharanthus* mosaic virus (CatMV). The presence of CatMV in collected samples was verified using a reverse transcription polymerase chain reaction with appropriate primers and a double antibody sandwich enzyme-

linked immunosorbent assay. Chromatographic methods were used to assess the effect of CatMV infection on vincristine and vinblastine. High-performance liquid chromatography was used to analyze all of the separated mixtures. A charcoal column was used to separate vinblastine and vincristine. We looked at the possibility of using plant growth-promoting rhizobacterial isolates (*Bacillus subtilis* and *Bacillus pumilus*) to induce resistance in host plants against viral infection.

Anti-bacteria activity

Catharanthus roseus is selected to evaluate the possibility of novel pharmaceuticals. Most of the bacterial pathogens are developing resistance against currently available antibiotics. Dry powder extracts of all plant parts demonstrated more antibacterial activity than extracts prepared from fresh parts. The ethanol extract was found to be most active against almost all the bacterial species tested.

Anti-oxidant property

The antioxidant potential of the ethanolic extract of the roots of the two varieties of *C. roseus*, namely rosea (pink flower) and alba (white flower), was obtained by using different systems of assay, such as Hydroxyl radical-scavenging activity, peroxide radical-scavenging activity, DPPH radical-scavenging activity, and nitric oxide radical inhibition method. The result obtained proved that the ethanolic extract of the roots of Periwinkle varieties has exhibited a satisfactory scavenging effect in the entire assay in a concentration-dependent manner, but *C. roseus* was found to possess more antioxidant activity than that of *C. alba*.

Anti-helminthic activity

Helminth infections are a chronic illness, affecting human beings and cattle. *Catharanthus roseus* was found to be used from the traditional period as an anti-helminthic agent. *Catharanthus roseus'* anti-helminthic properties were assessed using *Pherithema posthuma as* an experimental model and Piperazine citrate as a standard reference. The ethanolic extract at 250 mg/ml was shown to have substantial anthelminthic action with a death time of 46.33 minutes, whereas the reference medication at 50 mg/ml had a death time of 40.67 minutes. The ethnomedical claims of *Catharanthus roseus* as an anthelminthic herb were supported by this study.

Anti-ulcer property

Vincamine and Vindoline alkaloids of the plant showed anti-ulcer properties. The alkaloid vincamine, present in the plant leaves, shows cerebro-vasodilatory and neuroprotective activity. The plant leaves showed anti-ulcer activity against experimentally induced gastric damage in rats. Hypotensive property: Extract of leaves of the plant made a significant change in hypotension. The leaves have been known to contain 150 useful alkaloids, among other pharmacologically active compounds. Significant antihyperglycemic and hypotensive activity of the leaf extracts (hydroalcoholic or dichloromethane-methanol) has been reported in laboratory animals. In forced swim-induced mice, the methanolic leaf extract of *Catharanthus roseus* at doses of 250 and 500 mg/kg Per Oral (P.O.) significantly reduced the occurrence of ulcers. The ulcerative index increased in forced swim-induced rats as compared to the control group. At a dosage of 500 mg/kg, the methanolic leaf extract of *Catharanthus roseus* exhibited a substantial decrease in the aforementioned parameter, equivalent to the standard medication Ranitidine (5 mg/kg). *Catharanthus roseus* extract had a 62.56 percent protection index, whereas conventional medication Ranitidine had a 78.26 percent protection rating.

In-vivo Antidiarrheal Property

The anti-diarrheal activity of the plant ethanolic leaf extracts were tested in the Wistar rats with castor oil as an experimental diarrhea-inducing agent, in addition to the pretreatment of the extract. The anti-diarrheal effect of ethanolic extracts of *C. roseus* showed the dose-dependent inhibition of castor oil-induced diarrhea.

Wound healing property

Rats treated with 100 mg /kg/day of the *Catharanthus roseus* ethanol extract had a high rate of wound contraction significantly decreased epithelization period, a significant increase in dry weight, and hydroxyproline content of the granulation tissue when compared with the controls. Wound contraction, together with increased tensile strength and hydroxyproline content, supports the use of *C. roseus* in the management of wound healing. *C. roseus* has been used for relieving muscle pain, depression of the central nervous system, and wasp stings.

Hypolipidemic effect

In a study, significant anti-atherosclerotic activity, as suggested by a reduction in the serum levels of total cholesterol, triglycerides, histology of the aorta, liver, and kidney, was observed with the leaf juice of *Catharanthus roseus*. This resulted from the antioxidant effect of flavonoid, and probably, a vinpocetine-like compound present in the leaf juice of *Catharanthus roseus.*

Memory enhancement activity

Vinpocetine has been reported to have a variety of actions that would hypothetically be beneficial in Alzheimer's disease (AD). The only study investigating this agent in a well-defined cohort of AD patients found no benefit. Metal analysis of older studies of vinpocetine in poorly-defined dementia populations concluded that there is insufficient evidence to support its clinical use at this time. Vinpocetine has been well tolerated at doses up to 60 mg/d in clinical trials of dementia and stroke, and no significant adverse events.

Support for the Brain

Researchers have discovered that taking daily pills containing the active compounds found in the Periwinkle plant helps to improve blood flow to the brain. It also raises the levels of oxygen and glucose in the brain, which are necessary for proper brain function. These daily doses have also been shown to be beneficial in preventing and suppressing aberrant blood coagulation in the brain. They also aid in the rise of serotonin levels in the brain (a substance present in serum and blood platelets that functions as a neurotransmitter and closes blood vessels).

Antifeedant activity on lepidopterous insect

Five fractions that were obtained from the root of the common periwinkle were evaluated for their antifeedant activity, growth regulatory potential, and their effect on the fecundity and fertility against various stages of a lepidopterous insect, *Spilarctia obliqua*. The chloroform and ethyl acetate fractions were found to be highly effective as antifeedants, growth inhibitors, and was found to caused sterility in the treated male adults. Initial instars of

the test insect were found to be quite susceptible to the chloroform fraction at the concentration of 5%, whereas the late instar larvae were found to be unaffected. Moreover, little work has been done on anti-insect properties.

Bio-fungicide effects

Researchers have found that the stem extract of *Catharanthus roseus* can be used as a biofungicide to control white root disease, which is the most destructive disease found in a rubber plantation in Malaysia and Indonesia. The research was carried out by Zaini and Halimoon (2013) at the University of Malaya. The chlorophyll content, height, number of leaves, and diameter were all measured. Only Group C of rubber trees showed that the extract could stop *Rigidoporus microporus* from growing. The *Rigidoporus microporus* fungus was suppressed by *Kemunting cina* stem extracts, which were antagonistic. The stem extracts of Catharanthus roseus were shown to be effective in reducing the effects of white root infections in the research.

Anti-Mutagenic and Anti-Mitotic Effect

The anti-mitotic action was demonstrated by giving female mice a 70% ethanol extract of dried leaves, which produced favorable outcomes in CA-Fhrlich ascites vs. activation of metaphase arrest in ascites cells. (Sharma et al., 1982). They discovered that when red blood cells (RBCs) were exposed to a hot water extract of dried leaves, the number of micronucleated polychromatic RBCs reduced, proving *C. roseus'* anti-mutagenic activity. The mutagenic effect of vincristine, an alkaloid secreted by *C. roseus*, was studied using sex linked recessive lethal (SLRL) test system in *Drosophila melanogaster*. The results thus obtained showed that vincristine produced many chromosomal effects, arrested cells at metaphase with highly contracted chromosomes, and inhibited tubulin polymerization. When the root tips of *C. roseus* were treated with ethyl methane sulphonate (EMS) then several chromosomal anomalies were observed, such as persistent nucleolus, condensation, fragmentation, lagging bridge, cleft, and binucleated cells.

Vincristine, an alkaloid derived from *Catharanthus roseus*, exerts significant mutagenic effects by disrupting cellular processes during cell division in *Drosophila melanogaster*, as evidenced by the sex-linked recessive lethal test system (Taghizadehghalehjoughi et al., 2019). This compound interferes with microtubule dynamics, a critical component of cell division, leading to metaphase arrest characterized by highly condensed chromosomes (Verma et al., 2022). Vincristine's mechanism of action involves the inhibition of tubulin polymerization, thereby preventing the formation of functional microtubules that are essential for chromosome segregation during mitosis (Verma et al., 2022). Similar to vincristine, other anti-tubulin agents can face resistance from cancer cells through mechanisms such as the overexpression of efflux pumps, which prevents them from accumulating to toxic levels inside cells, or structural changes to microtubules that reduce drug binding (Dumontet & Šikić, 1999; Kŕause, 2019). The disruption of microtubule dynamics is a well-established strategy in cancer chemotherapy, where agents like vinblastine bind to microtubule ends, suppressing their dynamic instability and causing depolymerization (Castle et al., 2017; Salerni et al., 2010).

The exposure of *C. roseus* root tips to ethyl methane sulphonate, a potent alkylating agent, induces a range of chromosomal aberrations (Basu et al., 2015). These aberrations include persistent nucleoli, chromosome condensation, fragmentation, lagging bridges, cleft formation, and binucleated cells, all indicative of disrupted cell division. Alkylating agents like diethylsulfate and dimethylsulfate induce significant physicochemical and morphological alterations in DNA, leading to detectable changes in its structure and behavior (Kubiński et al., 1981).

CONCLUSION

Even though many conventional medicines were taken without knowing the underlying mechanism, their effectiveness may be further shown using current technologies and instruments. The active ingredient that causes the pharmacological action may be easily identified and commercialized as a drug product with the necessary permission from the appropriate organizations. One of the 21000 significant therapeutic plants discovered is *Catharanthus roseus*. It's used to treat a variety of ailments, including diabetes, sore mouth, oral ulcers, and leukemia. About 130 alkaloids are produced, including reserpine, vinceine, raubasin, and ajmalicine. Vinblastine and vincristine have anti-leukemic action. The quantity of alkaloids produced by different sections of this plant varies, with the root bark producing the most, almost 1.79 percent. Several studies have shown that it has antimicrobial action against *Staphylococcus aureus, Bacillus megaterium, Shigella, Pseudomonas,* and other bacteria. It has also been found to have antioxidant and antimutagenic properties. To learn more about its anti-tumor properties, more research is needed. Ancient medicine could be explored to identify novel drug formulations that are more effective with fewer side effects and also cheaper cost. More work could be done on the above plant to reveal the unknown mysteries, which would help the needs of the present pharmaceutical world in the future.

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