

REVIEW ARTICLE

Periwinkle- A contingent crop for barren and scanty rainfall areas

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ABSTRACT

Periwinkle has been cultivated as a garden plant in India, and it is acclimatized to local conditions. The plant has been used in traditional medicine since ages in various parts of the world. The plant has been catapulted into the international limelight of modern medicine owing to utilization of vincristine series of alkaloids from its leaves which have been used extensively for the treatment of various types of cancer and malignant growth. Indian farmers have been looking for better alternative crops due to gradual reduction in profitability owing to decline in productivity, increased incidence of disease and pest attack in traditional crops. Their hardy nature and higher returns make periwinkle cultivation a better option. There is immense scope for cultivating periwinkle in barren land areas, with minimum availability of irrigation water. In India, this drought tolerant annual plant is cultivated under rain-fed condition in barren land by small and marginal farmers of Gujarat, Rajasthan, Assam, Madhya Pradesh, Maharashtra, Andhra Pradesh, Telangana, Karnataka and Tamil Nadu states of India. There is an increasing demand worldwide for its alkaloids making its cultivation profitable in India.

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INTRODUCTION

Periwinkle (*Catharanthus roseus* (L) G. Don) is a perennial tropical herb, belongs to the family Apocynaceae and is cultivated as an ornamental plant. This medicinal shrub or herbaceous plant sprawling along the ground or standing erect to 1m (2 feet) in height is native and endemic to Madagascar where its natural habitat has almost been lost. This herb is now common worldwide as an ornamental-cum-medicinal plant (Husain, 1993). The plant is also known as the source of chemical compounds used in the treatment of cancer. Their discovery led to one of the most

important medical breakthroughs of the twentieth century. Plant species *Vinca minor* L., *Vinca major* L., (blue periwinkle), *Cantharanthus cariacetrs* L.; edible species of sea snails & Ittorini littoren L, *Littorini obtusata* L.) and shell fish (*Tympanostomus fuscatus*) are also known by the name periwinkle. The interest in this plant emanates due to the fact that it contains more than 120 terpenoid indole alkaloids (TIAs), several of which exhibit strong pharmacological properties. The plant has been used in traditional medicine since ages in various parts of the world (Arora et al., 2010; Paula Santos et al., 2010).

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It has been catapulted into the international limelight of modern medicine owing to utilization of vincristine series of alkaloids, which can be extracted from leaves of the young plants. The alkaloids have been used extensively in the pharmaceutical industry for the treatment of various types of cancer and malignant growth. Ajmalicin is another type of alkaloid which is extracted from the roots of periwinkle that has therapeutic value in controlling hypertension and capillary fragility. Pharmaceutical companies like M/s Eli Lilly, USA and M/s CIPLA, India are among the leading organizations in the production and utilization of alkaloids from this plant. India is one of the major producers and principal exporters of its crude drug and Mozambique, Malaysia as well as Madagascar are its competitors. Seven species of the genus are known from Madagascar; one is restricted to India and Sri Lanka, while another species is cultivated in China. The plant is believed to be a native of the West Indies. *Catharanthus* is more commonly known as Madagascar periwinkle (Gurib-Fakim, 2006)

Europeans used the plant for minor ailments like headache and as remedy for diabetes. Some of its alkaloids are approved as antineoplastic agents to treat leukaemia, malignant lymphomas, neuroblastoma, Hodgkin's disease, Wilms' tumor, rhabdomyosarcoma, and other cancers (Nayak, 2006). Its vasodilating and memory-enhancing properties have experimentally been indicated to alleviate vascular dementia and Alzheimer's disease. The plant also has antihypertensive and antispasmodic properties (Retna and Ethalsa, 2013).

Area and production

It is naturalized in most tropical and subtropical regions being escaped from cultivation, spreading in rocky outcrops and roadsides in dry savanna, urban open spaces and in cultivated areas. In India, it is being grown in Tamil Nadu, Andhra Pradesh, Karnataka, Gujarat, Madhya Pradesh and Assam in an area of about 2000-3000 ha. Global production of root alkaloids (Ajmalicine) is to the tune of 3600 kg per year, whereas that of leaf alkaloids (Vinblastine and Vincristine) is only a few kilograms.

The market value of these alkaloids, however, is in the range of several hundred million US dollars (Mishra et al., 1996).

Table 1: Common names of *Catharanthus* in different countries

Country	Common names
Bangladesh	Nayantara
Brazil	Boa-noite, Cong orca
Cook Islands	Tiare-tupapaku-kimo
Dominica	Caca poule
French Guiana	Pervenchede de Madagascar
Guatemala	Chatilla
Guyana	Periwinkle
India	Ainskati, Billaganneru, Nayantara, Nityakalyani, Periwinkle, Sadabahar, Sadaphul, Ushamanjairi
Jamaica	Periwinkle
Japan	Nichinich-so, Nichinichi-so
Kenya	Maua
Madagascar	Madagascan periwinkle
Mexico	Ninfa
Pakistan	Sada-bahar
Peru	Chavelita
Philippines	Atay-biya, Chichirica, Kantotan, Periwinkle, Tsitsirika
Rodrigues islands	Saponaire
Sri Lanka	Mini-mal, Patti-poo
Thailand	Phaeng phoi farang, Phang-puai-fa-rang
USA	Periwinkle

Composition

Periwinkle produces more than 100 terpenoid indole or bisindole alkaloids. Most important among these are the dimeric leaf alkaloids; Vinblastine and Vincristine and the monomeric root alkaloid "Ajmalicine". The alkaloids vindoline, catharanthine, cathenamine, strictosidine, serpentine, secologanin and leurosine have also been detected in this plant. The alkaloids are distributed in all parts of the plant in varying proportions: roots 0.7-2.6%, root bark 4.5-9.0%, stem < 0.1-0.5%, leaves 0.3-7.5%, flowers < 0.1-0.8%, fruits < 0.10.4%, seeds up to 0.2% (Krishnan, 1995).

The root contains 0.01-0.1% ajmalicine, while the leaves yield 0.001-0.002% vinblastine and 0.000002-0.005% vincristine. Factors such as genotypes, crop age, nipping tops or pruning,

defloration, soil moisture regime, fertilizers application, PGRs, climatic conditions etc., influence the total alkaloid concentration in the leaves and roots.

Medicinal uses

Vinblastin, vincristin, leurosidine and leurosine are oncolytic alkaloids are effective against leukaemia. Vinblastin sulphate is used particularly to treat choriocarcinoma, neuroblastoma, Hodgkin's disease beside lymphosarcoma, and carcinoma of breast, lung and other organs, in acute and chronic leukaemia. Vincristin sulphate arrest mitosis in metaphase and is very effective for the treatment of acute leukaemia in children and lymphocytic leukaemia's. It is used against Hodgkin's disease, Wilm's tumor, neuroblastoma, rhabdosarcoma and reticulum cell sarcoma (Beni et al., 2012)

Chloroform fraction of crude drug showed significant and sustained hypotensive action and sedative and tranquilizing properties similar but more marked than total alkaloids of *Rauvolfia serpentina*. The alkaloid also causes relaxant and antispasmodic effect on smooth muscles of the intestine and uterus, and direct myocardiac and central nervous system depression (Dey et al., 2020; Morrone et al., 2016).

Mode of action of vincristine and vinblastin

Vincristine (VCR), also known as leurocristine is a Vinca (*Catharanthus roseus*) alkaloid and hence its name. In most commercial preparations vincristine appears as a colourless fluid (Verma et al., 2017). It is a mitotic inhibitor, and is extensively used in cancer chemotherapy. Vincristine was approved by the United States Food and Drug Administration (FDA) in July 1963 (Farnsworth, 1988) as Oncovin (Brand name). Vincristine binds to tubulin dimer, which is a structural protein, inhibiting assembly of micro tubule structures. Disruption of the microtubules arrests mitosis in metaphase stage of the cell cycle (Sorger, 1997). The *Catharanthus* alkaloids affect all rapidly dividing cell types including cancer cells, intestinal epithelium and bone marrow. Both Vincristine (VCR) and Vinblastine (VLB) are active at

submicromolar concentrations ranging from 10 nM upto 1 μ M. These drugs bind to the growing ends of microtubules resulting in an "end-capping" or the "poisoning" effect. It has also been noticed that at higher concentrations ($>10 \mu$ M) these compounds also cause tubulin aggregation, which results in the formation of tubulin par crystals (Arora et al., 2010; Verma et al., 2017).

Vinblastine is the official generic name for the alkaloid formerly known as vincleukoblastine is a colourless compound. Vinblastine sulfate (VLB) is a white to slightly yellow, hygroscopic crystalline compound, soluble in water and methanol, is an anti-mitotic drug widely used medically to treat different kinds of cancers, like breast cancer, lung cancer, head and neck cancer, Hodgkin's lymphoma and testicular cancer. Vinblastine was first isolated by Robert Noble and Charles Thomas Beer from the Madagascar periwinkle plant. Vinblastine's utility as a chemotherapeutic agent was first discovered when it was crushed into a tea. Consumption of this tea led to a decreased number of white blood cells; therefore, it was hypothesized that vinblastine might be effective against cancers of the white blood cells such as lymphoma. Vinblastine is a chemical analogue of vincristine. It binds to tubulin, thereby inhibiting the assembly of microtubules. (Arora et al., 2010)

It is M phase cell cycle-specific and is an integral component of a plethora of chemo-therapy regimens, including ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) for Hodgkin's lymphoma. Vinblastine is a component of the regimen of choice for the treatment of metastatic testicular cancer. In the treatment of testicular carcinomas, vinblastine in association with other antitumor agents often results in a cure rate of over 90% in patients. In adult Hodgkin's lymphoma, *Catharanthus* alkaloids have raised the remarkable survival chances to 98%. Vinblastine has been shown to combat cancer by interfering with glutamic acid metabolism. Vinblastine has also been successfully used in the treatment of Kaposi's sarcoma, mycosis fungoides and carcinoma of the breast (Einhorn and Donohue, 1977; Jones and Vasey, 2003).

Side effects

Catharanthus roseus is poisonous if ingested or smoked. It has caused poisoning in grazing animals. Even under a doctor's supervision for cancer treatment, products from this plant produce undesirable side effects (Kintzios and Barberaki, 2004).

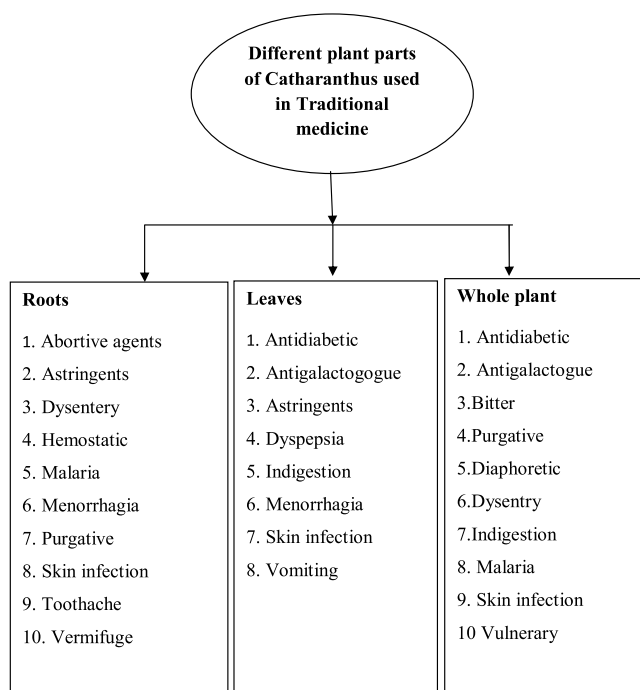


Figure 1: Different plant parts of *Catharanthus* used in traditional system of medicine for curing different types of diseases

Advantages of cultivating periwinkle in barren lands

Cultivating of periwinkle of the following advantages:

1. Periwinkle is not eaten by domestic animals or damaged by birds.
2. Low incidence of pests and diseases.
3. Low labour requirement.
4. Less exhaustive and require less nutrients.
5. Periwinkles easily grow on poor and marginal soil.
6. Resistant to drought and pest.
7. It is easily cultivated with minimum availability of irrigation water.



Rose-purple flowers type variety



White flowers type variety



White flowers with rose purple spot in the centre type variety

Figure 2: Different type of flower variants of periwinkle

Cultivation practices for periwinkle

Soil and climate

The plant grows well in tropical and sub-tropical areas up to an altitude of 900 m. Rain fed crop can be raised in areas with 70-100 cm well distributed rainfall. It can be grown on any type of soil except alkaline and waterlogged soils. Well drained, light soils are best suited for cultivation of this crop.

Type of varieties

There are three variants in periwinkle (Figure 2) those with (i) rose-purple flowers (ii) white flowers, and (iii) white flowers with rose purple spot in the centre. The rose-purple is being cultivated because of its higher alkaloid content (Nejat, 2015; Senbagalakshmi, 2017). The CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow has released two white flowered high yielding varieties, Nirmal and Dhawal (a mutant) (Kulkarni et al., 2005).

Season and sowing

Periwinkle crop can be raised either by direct seeding or by transplanting nursery grown seedlings. Direct seeding is generally adopted for growing a rain fed crop either through broadcasting (seed rate 5 kg/ha) or by drilling the seeds (seed rate 3 kg/ha) in rows 45 cm apart, at a depth not exceeding 2 cm (due to shorter plumule length, deeper sowing results in poor crop stand) and

thinning the seedlings a month after germination of the seeds, to maintain 15-30 cm plant to plant distance. Seeds are mixed with sand ten times up to their weight for even sowing, owing to the small size of the seeds.

For transplanting the crop, a nursery is raised during the summer months using 0.5-1.0 kg seeds per ha. Nursery beds are prepared by mixing equal quantities of sand and leaf mold with native soil. Seeds are sown in rows 10-15 cm apart at a depth of 1.5-2.0 cm and watered regularly. Seeds germinate in about 10 days and attain 15-20 cm height in 45-60 days, when they are ready for transplanting in the main field at 30-45 x 15-30 cm² spacing. Closer spacing produces thinner roots and wider spacing, thicker roots. Spacing needs to be adjusted based on the requirements of the industries for thinner or thicker roots. Treating the seedlings with Naphthalene Acetic Acid (NAA) 0.25 mg per liter, prior to transplanting is beneficial for trickery recovery from transplant shock. A nursery area of about 200 m² is sufficient to raise seedlings for one hectare. This method of planting is recommended for areas with well distributed rainfall or with proper irrigation facilities.

Thinning and weeding

Periwinkle requires two weedings in the initial stage. First Weeding is done about 60 days after sowing/transplanting and the second weeding is done after 60 days.

Irrigation

Places where rainfall is evenly distributed throughout the year, the plants do not require any irrigation. However, the areas where the monsoon is restricted to a particular period, 4-5 irrigation once in 15 days during February, March and April months are needed for obtaining the optimum yield.

Fertilizer application

The seeds should preferably be treated with bacterial inoculants of the green manure crop prior to sowing to increase the development of root nodules which absorb atmospheric nitrogen and fix it in the soil. In case organic manure is not applied. It is advisable to apply a basal dose of 25

kg N, 50 kg P₂O₅ and 75 kg K₂O per hectare per year.

Pests and diseases

The seeds are treated with Captafol/Captan @ 2 g/kg seeds for controlling damping off disease of seedlings (*Pythium* and *Rhizoctonia* species). Field spray of Captafol/Mancozeb (0.3%) to control die back disease (*Pythium aphanidermatum*) at 15 days interval for 2 to 3 times. Spraying Rogor (0.06%) to control insect pests such as leaf hoppers.

Harvesting and drying

Roots: The crop is harvested after about 12 months from sowing. The crop is cut at about 7.5 cm above the ground and dried in shade. The field is then copiously irrigated and when it reaches at proper moisture level, it is ploughed and the roots are collected. The roots are washed thoroughly and dried in shade.

Leaves, stems and seeds: If there is demand for leaves, two leaf-strippings can be taken, the first one after 6 months and the second one after 9 months from sowing. Third stripping of leaves is also obtained when the whole plant is harvested. After harvesting, the whole plant is dried in shade. At this stage, light threshing will separate the seeds, which can be used for the next sowing. The leaves and stems are also then separately collected. Seeds are collected this way will have fruits of various degrees of maturity and hence will have poor percentage of germination. It is, therefore, advisable that only mature pods should be collected during two or three months before the crop is harvested. This may be quite expensive, but is good result oriented in terms of yield of the crop. The aerial part of the plant between 7.5 cm and about 25 cm above ground level is taken as stem for the purpose of marketing.

Yield and agro-economics

The production of root alkaloids of ajmalicine series varies from 0.1-0.2 per cent. Rainfed crop yields 1500-2000 kg of leaves and 600-700 kg roots and a net profit of more than Rs. 1,50,000 per hectare. Likewise, irrigated crop yields 3000-3500

kg leaves and 800-1000 kg roots and a net profit of more than Rs. 2,50,000 - 3,00,000 per hectare (Considering cost of the leaves @ Rs. 60 per kg and roots @ Rs. 80 per kg).

Conclusion and future prospects

Catharanthus alkaloids and their semi synthetic derivatives have been used in the clinic since a long time and continue to benefit innumerable cancer patients. Several other anticancer drugs of plant origin have yielded success stories, e.g. Taxol, combretastatin's, camptothecin, etc., but the case of *Catharanthus* stands apart in view of its serendipitous discovery. There is a need to discover several such agents from nature's storehouse, given to us in the form of gift as plants. In view of export and in-house demand, several new factories are coming up in South India for manufacture of raubasine from *Cantharanthus* roots. Thus, there is increasing scope for cultivation of *Cantharanthus roseus* in India.

There is need to develop need-based package of practice in periwinkle crop. Proper training and skill knowledge to the periwinkle farmer regarding value addition in periwinkle crop to increase income of the farmer is also needed. The development of suitable variety of periwinkle with high yield and alkaloid content for different types of climatic locations is also a need of country like India. The government has to create organized market for sale of produce without interference of middlemen for the ease of periwinkle growers. A holistic management action plan is also necessary for the assessment and management of resource base, best harvesting and processing practices and trade issues if raised, in this crop. The gaps between the grower and the traders/buyers/entrepreneurs need to be minimized as these are at present very wide and often inequitable.

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REFERENCES

- Arora R, Malhotra P, Mathur AK., Mathur A, Govil CM, Ahuja PS. 2010. Anticancer alkaloids of *Catharanthus roseus*: transition from traditional to modern medicine. In: Rajesh R, Mathur AK, (Eds.) *Herbal Medicine: A Cancer Chemopreventive and Therapeutic Perspective*. Jaypee Brothers Medical Publishers Pvt. Ltd, New Delhi, India, pp 292-310.
- Beni, Z, Háda V, Dubrovay Z, Szántay Jr C. 2012. Structure elucidation of indole-indoline type alkaloids: a retrospective account from the point of view of current NMR and MS technology. *J Pharm Biomed Anal* **69**: 106-124.
- Dey P, Kundu A, Kumar A, Gupta M, Lee BM, Bhakta T, Dash S, Kim HS. 2020. Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). In: Kumar A, Gupta M, (Eds.) *Rec Adv Nat Prod Anal*. pp 505-567. <https://doi.org/10.1016/B978-0-12-816455-6.00015-9>.
- Einhorn LH, Donohue J. 1977. Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Internal Med* **87**: 293-298.
- Farnsworth NR.1988. Screening plants for new medicines. *Biodiversity*, **15**: 81-99.
- Gurib FA. 2006. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med* **27**: 1-93.
- Husain A. 1993. Medicinal Plants and their cultivation. Central Institute of Medicinal and Aromatic Plants, Council of Scientific and Industrial Research, Lucknow, India.
- Jones RH, Vasey PA. 2003. Part II: testicular cancer-management of advanced disease. *The Lancet Oncol* **4**: 738-747.
- Kintzios SE, Barberaki MG, 2004. Plants and cancer. In: Kintzios SE, Barberaki MG, (Eds.) *Plants that fight cancer*. CRC Press. pp 26-45.

- Krishnan SS, Jing SL, Kurtz DL, Zweifel M, Portoghese PS, Li TK, Froehlich JC. 1995. The delta opioid receptor antagonist naltrindole attenuates both alcohol and saccharin intake in rats selectively bred for alcohol preference. *Psychopharm* **120**: 177-185.
- Kulkarni RN, Baskaran K, Chandrashekhra RS, Khanuja SPS, Darokar MP, Shasany AK, Uniyal GC, Gupta MM, Kumar S. 2005. Improved varieties and genetic research in medicinal and aromatic plants (MAPs). In: Proceedings of Second National Interactive Meet on Medicinal & Aromatic Plants: pp 53-61.
- Mishra N, Luthra R, Kumar S. 1996. Enzymology of indole alkaloid biosynthesis in *Catharanthus roseus*. *Ind J Biochem Biophys* **33**: 267-273.
- Morrone LA, Rombolà L, Amantea D, Mizoguchi H, Corasaniti MT. 2016. Contribution of Herbal Medicine to Human Health. In: Rombolà, L, Amantea D, (Eds.) *Herbal Medicines: Development and Validation of Plant-derived Medicines for Human Health, A Brief History*. pp 381-411.
- Nayak S. 2006. Influence of ethanol extract of *Vinca rosea* on wound healing in diabetic rats. *Online J Biol Sci* **6**: 51-55.
- Nejat N, Valdiani A, Cahill D, Tan YH, Maziah M, Abiri R. 2015. Ornamental exterior versus therapeutic interior of Madagascar periwinkle (*Catharanthus roseus*): the two faces of a versatile herb. *The Scientific World Journal*. Hindawi Publishing Corporation. <https://doi.org/10.1155/2015/982412>.
- Paula SA, Rogero MM, Bastos HMD. 2010. Edible plants, their secondary metabolites and ant obesogenic potential. *Rec Pat Food Nutr Agri* **2**: 195-212.
- Retna MA, Ethalsa P. 2013. A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Catharanthus roseus* (Apocyanaceae). *Int J Eng Res Tech* **2**: 3899-3912.
- Senbagalakshmi P, Rao MV, Kumar TS. 2017. In vitro studies, biosynthesis of secondary metabolites and pharmacological utility of *Catharanthus roseus* (L.) G. Don.: a review. In *Catharanthus roseus* Springer, Cham. pp 153-199.
- Sorger PK, Dobles M, Tournebize R, Hyman AA. 1997. Coupling cell division and cell death to microtubule dynamics. *Curr Opin Cell Biol* **9**: 807-814.
- Verma P, Khan SA, Parasharami V, Mathur AK. 2017. Biotechnological Interventions to Modulate Terpenoid Indole Alkaloid Pathway in *Catharanthus roseus* Using In Vitro Tools and Approaches. In *Catharanthus roseus*, Springer, Cham. pp 247-275.