

## Review Article

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## CATHARANTHUS ROSEUS: A MEDICINAL PLANT WITH POTENT ANTI-TUMOR PROPERTIES

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#### ABSTRACT

Ayurveda is the Indian traditional system of medicine which focuses on the medical potential of plants. *Catharanthus roseus* is one plant recognized well in Ayurveda. It is known for its anti-tumour, anti-diabetic, anti-microbial, anti-oxidant and anti-mutagenic effects. It is an evergreen plant first originated from islands of Madagascar. The flowers may vary in colour from pink to purple and leaves are arranged in opposite pairs. It produces nearly 130 alkaloids mainly ajmalcine, vinceine, resperine, vincristine, vinblastine and raubasin. Vincristine and vinblastine are used for the treatment of various types of cancer such as Hodgkin's disease, breast cancer, skin cancer and lymphoblastic leukemia. It is an endangered species and need to be conserved using techniques like micro propagation. It has high medicinal values which need to be explored extensively.

Keywords: Alkaloids, Catharanthus roseus, vinblastine, vincristine, anti-cancer.

## INTRODUCTION

The importance of medicinal plants has been renowned since 2600 BC in Mesopotamia<sup>1</sup>. World Health Organization (WHO) have prepared a list of 21000 medicinally important plants. One such plant is Catharanthus roseus (L.) G. Don which is also known as sadabahar or Periwinkle. The other names for C. roseus are Old-maid, Cape periwinkle, Vinca rosea, Rosy periwinkle, Rose periwinkle, Ammocallis rosea and Lochnera rosea<sup>2</sup>. It belongs to family Apocynaceae and is a rich source of alkaloids. These alkaloids are the secondary metabolites of plants which differ in their chemical structure. These are used for the various purposes such as pharmaceuticals, food additives; dye etc.<sup>3</sup> Being cultivated for hundreds of year C. roseus is an evergreen, perennial sub shrub with a height of 30 cm to 1 m. It is known to be originated from island of Madagascar due to which it is also known as Madagascar periwinkle. But now it is found in most of the warm places of the world. It is also considered to be annual as it has the capabilities to tolerate high temperatures, drought conditions as well as heavy rainfall. The flower consist of five petal lobes which form a corolla of 2-5 cm diameter and these are white to pink-purple in colour. The centre is dark red in colour and the basal tube is 2.5-3 cm long<sup>4</sup>. It possesses fruits which are follicle pairs of about 2-4 cm in length and 3 mm in breadth. The fruit is many seeded and the seeds are small, black, oblong or cylindrical<sup>4,5</sup>. The leaves are 1-3 inches long and arranged in opposite pairs. They may be oval, oblong or elliptic with pale midrib and rounded apex. These are glossy, dark green and hairless with a short petiole<sup>2,6</sup>. These plants are mostly found in warm places but they have also adapted to cold conditions. It can grow in different types of soils such as slightly acidic or soils with high moisture content and in low to full sunlight'. Different alkaloid are produced by different parts of this plant such as roots and basal stems produce reserpine, vinceine, raubasin and ajmalcine

whereas antineoplastin dimeric vinblastine and vincristine are produced by aerial parts<sup>8</sup> (Table 1). Maximum amount of these alkaloids is present in the root barks which rounds to nearly 0.15-1.34 % and even 1.79 % in some strains<sup>9</sup>. Out of the 130 different alkaloids produced by this plant 25 are dimeric in nature. Two such main examples of dimeric alkaloids are vinblastine and vincristine which are produced by aerial parts and used for the treatment of human neoplasma. Ajmalicine is a monomeric alkaloid produced by roots and used to treat circulatory diseases. Similarly other different alkaloids are used for many diseases such as lymphoblastic leukemia, Hodgkin's disease, skin cancer, breast cancer and Reticulum cell sarcoma, neuroblastoma, Wilkin's disease, diabetes, sore mouth, mouth ulcers, etc. These alkaloids are in great demand due to their medicinal importance and India is the third largest producer of vinblastine and vincristine. The production of these alkaloids depends on the developmental stage and physiological stage of the plant and these are obtained mostly from wild plants. Techniques such as tissue culture technique, media optimization and control of pH, temperature, light aeration, phytohormones, etc. are being employed to increase their productivity. These techniques have various advantages such as dimeric alkaloids can be produced in large quantity which reduces their cost, even the slow growing plants can be used<sup>13</sup> and different alkaloids can be produced in various quantities by bioengineering plants 14-16. *C. roseus* has been used since long times for the treatment of various diseases in different parts of the world. It was used as diuretic, astringent and to treat cough in China and wasp stings in India<sup>17</sup>, nose bleed, sore throat, mouth ulcers and bleeding gums. It was used to get relief from lung congestion and inflammation in Central and South Asia, in Europe to treat diabetes18. It also had some superstitious aspects with it such as in Europe people believed that it could help to get rid of evil spirits and it was called "violet of the sorcerers"

by the French. Then the Western researchers found that the plant produces a number of alkaloids which has the medicinal values such as vindoline, catharanthine, lochnerine, vindolinine and leurosine sulphate lowers blood sugar levels, reserpine and serpentine are powerful tranquilizers and vincristine, vinblastine have anticancerous properties. Alkaloids are the nitrogen containing compounds produced by the plant which are usually bitter in taste and they possess anticancer and pain relieving properties. Vincristine and vinblastine are produced by the leaves<sup>19,20</sup> whereas vindoline is mainly produced by the green parts of the plant<sup>21</sup> and catharanthine by the roots. Out of the various alkaloids

produced by this plant more than 100 are monoterpenoid indole alkaloids (MIAs) which have anticancer properties<sup>22</sup>. Enzymatic and non-enzymatic antioxidants are also produced by this plant<sup>23,24</sup>. Wound healing, hypoglycaemic, analgesic and vasodilatory effects are some of the other medicinal applications of *C. roseus*<sup>25</sup>. High blood pressure and cardio-vascular diseases can be treated using ajmalicine and serpentine which are found in the roots. A large amount of phytochemical compounds are present in the leaves and stem of this plant which makes it plant of medicinal value. Its conservation is the point of concern as it comes under the endangered species<sup>7</sup>.

Anti-Diabetic Properties

Produced by	Alkaloids	Properties
	Ajmalicine	Cardio-Vascular Diseases And High Blood Pressure
Roots	Catharathine	Anti-Diabetic Properties
	Raubasin	Pain Relieving Properties
	Reserpine	Tranquilizers
	Serpentine	Cardio-Vascular Diseases And High Blood Pressure
Aerial parts like leaves	Vinblastine	Anti-Tumour Properties
	Vincristine	Anti-Tumour Properties

Vindoline

Table 1: Different Alkaloids Produced By Catharanthus roseus

# Medicinal Properties of *Catharanthus roseus* Anti-Cancerous Effect

C. roseus produces vinblastine and vincristine which are well known for their anti-cancerous properties.<sup>26</sup> El-Merzabani et al., 1979 injected ethanol (70 %) extract of leaves intra peritoneally to female mice. As a result the alkaloids showed great responses against different types of cancers especially those that are multi-drug resistant. The nineteen patients suffering from plantar, genital, flat or Verruca vulgaris warts were cured. When the chloroform extract was injected to the patients suffering from Leuk-P3887 then only one was resistant to the treatment, five showed 50 % response and six were completely treated<sup>27</sup>. Both the malignant and nonmalignant, platelet and platelet-associated disorders are effectively treated using the C. roseus alkaloids<sup>28</sup>. In recent studies it has been found that growth of blood vessels that enhance tumour growth is inhibited by alkaloids secreted by C. roseus<sup>29</sup>. These alkaloids, vincristine and vinblastine are used as injectable anticancer drugs<sup>30</sup> such as vinblastine as Velban and vincristine as Oncovin<sup>7</sup>. The division of cancer cells is interfered by these drugs along with their derivatives such as vinflunine. Vincristine is used in the treatment of leukemia in children and vinblastine for choriocarcinoma and Hodgkin's disease<sup>7</sup>.

## **Anti-Microbial Effect**

A number of anti-microbial agents have been used to prevent the adverse effects caused by various microbes. It is very important to discover new antimicrobial agents<sup>31</sup> because the rate of antibiotic production is much lower than the rate at which the microbes are becoming resistant to them<sup>32</sup>. The plant extracts are useful in attaining the long term health response and also reducing the ill effects of various chemotherapeutic agents<sup>33</sup>. Plants like *C. roseus* provide a broad spectrum of resistance against microbial agents and can be used as a prophylactic agent

in the treatment of number of diseases. It has proved to possess efficient anti-viral<sup>34</sup>, anti-bacterial<sup>35</sup> antifungal<sup>36</sup> compound. Tobacco Mosaic Virus (TMV) was inhibited by water extract of callus culture of micro propagated plant<sup>37</sup>. Bacillus megatarium Staphylococcus albusi did not grow on agar plates with 70 % ethanol extract of dried leaves but B. cereus and S. aureus were resistant to same extract<sup>38</sup>. Proteus, Staphylococcus, Shigella and Pseudomonas species are inhibited by the benzene extract of dried flowers (50 %) whereas the same concentration of benzene extract of dried leaves inhibited Salmonella species in addition to the above mentioned bacterial species<sup>39</sup>. Antifungal effect was shown using different plant part extracts and each of them was active against different fungi. Trichophyton mentagrophytes was inhibited by hot water extract of both leaves and stem<sup>40,41</sup>. There was no effect on *Neurospora* crossa by the acetone and water extract (70 %) of aerial parts of plant<sup>42</sup>. A study by<sup>43</sup> Khalil, 2012 has shown the antimicrobial activity of C. roseus against bacteria (S. aureus and E. coli) and fungus (Candida albicans). The antibacterial activity of C. roseus was also shown by 44 Govindasamy and Srinivasan in 2012 in which they studied the effects of extracts from leaf, stem, root, and flower against a number of bacteria. The maximum antibacterial activity was shown against S. typhi and minimum against S. aureus and E. coli. The antimicrobial activity of C. roseus was studied against B. fusiformis, C. albicans, E. coli and Aspergillus fumigatus using agar well disc diffusion assay and paper disc diffusion assay. The methanolic extract of stem was active against B. fusiformis, leaves against A. fumigates and flowers against B. fusiformis<sup>45</sup>. The crude extract from different parts of this plant was used to study the antibacterial activity against Salmonella typhimuruimi (NCIM2501), S. aureus (NCIM5021) and Pseudomonas aeruginosa (NCIM2036). The results showed that it was a potent antibacterial agent<sup>7</sup>. Stem extracts of *C. roseus* were used to save rubber trees (*Hevea brasiliensis*) from White rot disease caused by *Rigidoporus microporus* named fungus. It was found that the extract proved to be an efficient healing agent for the infected trees<sup>46</sup>.

## Anti-Mutagenic and Anti-Mitotic Effect

The anti-mitotic effect was shown by administrating the female mice with ethanol (70 %) extract of dried leaves which showed positive results on CA-Fhrlich ascites vs. induction of metaphase arrest in ascites cells<sup>47</sup>. In a study conducted by 48 Sharma et al., 1982 it was found that when the red blood cells (RBCs) were subjected to hot water extract of dried leaves the number of micro-nucleated polychromatic RBCs decreased which proved the antimutagenic effect of C. roseus. The mutagenic effect of vincristine, an alkaloid secreted by C. roseus was studied using sex linked recessive lethal (SLRL) test system in Drosophilla melanogaster. The results thus obtained showed that vincristine produced many chromosomal effects, arrest cells at metaphase with highly contracted chromosomes and inhibition of tubulin polymerization<sup>49</sup>. When the root tips of C. roseus were treated with ethylmetahne sulphonate (EMS) then a number of chromosomal anomalies were observed such as persistent nucleolus, condensation, fragmentation, laggered, bridge, cleft and binucleolated cells<sup>50</sup>

## **Anti-Oxidant Effect**

Tannins, phenolics and flavonoids are the anti-oxidants produced by medicinal plants which are more potent than the anti-oxidants secreted by dietary plants<sup>51</sup>. Reactive oxygen species (ROS) are the harmful compounds that our body generates during normal aerobic respiration and anti-oxidants are helpful in eradicating these compounds<sup>52</sup>. C. roseus is known to produce many different alkaloids such as flavonol glycosides, caffeovlquinic acids, etc. 53-55 Phenolic compounds are the products of secondary metabolism of plants and act as anti-oxidants, anti-inflammatory, anti-microbial, cardioprotective and anti-allergic agents. Their anti-oxidant potential is because they are efficient hydrogen donors. reducing agents, metal chelators or singlet oxygen quencher<sup>56-58</sup>. When a number of medicinal plants were screened for their oxygen radical absorbance capacity (ORAC) it was found that C. roseus has the highest ORAC value i.e. 22.30 µmol Trolox equivalent (TE)/g of fresh weight<sup>59</sup>. C. roseus has also been shown to scavenge the nitric oxide, superoxide and DPPH (1,1-diphenyl-2picrylhydrazyl) radicals<sup>54</sup>. In 2011 Rasool<sup>60</sup> and his collogues demonstrated through their research that C. roseus is a viable source of natural antioxidants which can be exploited for food and nutraceutical applications. The anti-oxidant activity of C. roseus was studied in different regions of Rajasthan and it was found that plants of Bikaner region had highest phenolic content followed by Kota and Jaipur, India<sup>61</sup>. C. roseus is free of side effects and cost effective and efficient means to get rid from oxidative stress mediated diseases. The antioxidant effect of C. roseus (pink flowers) and C. alba (white flowers) was checked and it was found that C. roseus has higher antioxidant activity than C.  $alba^7$ .

#### **Anti-Diabetic Effect**

Diabetes, malaria, dementia, etc. can also be treated by using the different extracts of this plant. Vinca rosea has the ability to improve the blood supply to brain which results in increased supply of oxygen and glucose to brain and also preventing the abnormal coagulation of blood. V. rosea also helps in increasing the levels of serotonin whose deficiency may cause diseases like migraine, bulimia, phobias and schizophrenia. This plant helps in increasing the insulin production and utilization of sugar from food which helps in curing diabetes. An alkaloid named alstonine which is mainly present in its root bark helps in regulating the blood pressure. In a case study in Malaysia the diabetes patients who took decoctions of this plant in combination with regular medications showed better response as compared to those who undergone only oral medications and insulin<sup>62,63</sup>. Maximum of the reported work about anti-diabetic potential of this plant is being conducted using the crude extract rather than the pure bioactive compounds<sup>64-67</sup>. In streptozotocin induced diabetic rat this plant induces hypoglycemic effect<sup>68,69</sup>. From this plant four alkaloids: vindolie I, II, III and IV were extracted which enabled high glucose uptake in pancreatic β-TC6 or myoblast C2C12 cells and elicited their use against type 2 diabetes<sup>70</sup>. The alkaloid vincamine helps in the treatment of vascular dementia, a disease caused by the plaque development of arteries carrying blood to brain. Vincamine also causes blood thinning and helps to enhance the memory properties<sup>2</sup>. C. roseus lowers the blood sugar levels in a dose dependent manner<sup>7</sup>. The anti-diabetic potential of *C. roseus* was evaluated by studying the protein content in its different parts with highest content in half mature leaves<sup>71</sup>.

## **CONCLUSION**

Catharanthus roseus is one of the 21000 important medicinal plants found. It is used for the cure of a number of diseases such as diabetes, sore mouth, mouth ulcers. and leukemia. It produces about 130 alkaloids such as reserpine, vinceine, raubasin and aimalcine. Antileukemic activity is shown by vinblastine and vincristine. Different parts of this plant produce different amounts of alkaloids, out of which root bark produces the maximum i.e. nearly 1.79 %. There are a number of reports anti-microbial supporting its activity Staphylococcus albusi, Bacillus megatarium, Shigella, Pseudomonas, etc. Its anti-oxidant and anti-mutagenic effects have also been reported. Further studies need to be done to explore its anti-tumour effects.

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