THE MEDICINAL PROPERTIES OF PHYTOCHEMICALS IN CATHARANTHUS ROSEUS - A REVIEW

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ABSTRACT
Plants have been a rich source of compounds for the development of clinically useful therapeutic agents. Catharanthus Roseus, also known as Madagascar Periwinkle is a pretty ornamental plant of Apocyanaceae family. Medicinal value of this plant has been known from ancient Mesopotamian age. The plant contains enormous phytoconstituents which are used in traditional Indian system of Ayurvedic medicine and conventional Chinese medication and other curative systems. All parts of the plant are reported to contain alkaloids. More than 400 unique alkaloids had been isolated and named from this plant. Its curative action is due to the presence of alkaloids like Ajmalicine, serpentine and reserpine which are known for hypotensive, anti-diabetic, anti-microbial, anti-oxidant and anti-spasmodic properties. With the presence of cancer fighter Vinca alkaloids vincristine, vinblastine, vinorelbine and vindesine, it became eminent anticancer herb along with many other therapeutic effects. Vincristine is in the List of Essential Medicines of World Health Organization's, the most important medication needed in a basic health system. This review gives an overview of the medicinal properties of the phytochemicals present in Catharanthus Roseus.

KEYWORDS: Catharanthus Roseus; Phytochemicals; Vinca Alkaloids; Anticancer; Vincristine; Vinblastine.

INTRODUCTION
The growing demand for novel drugs that can overcome the problem of drug resistance contribute to a revival of interest in plant based compounds for drug discovery. Nature has given many medicinal plants for our health and survival.[1] A great part of herbal composites are used as main particle in drug discovery to produce synthetic molecular analog. This indicates the significance of study of phytochemicals in diversity oriented synthesis (DOS) of natural product-like pharmacompounds.[2] Catharanthus roseus is very common in Madagascar - an Indian ocean island plant which is one of the few pharmacological plants that have a quite long history.[3] It plays considerable role in herbal and traditional medicine for treatment of various diseases like diabetes, hypertension, asthma, constipation, cancer, depression, muscle pain, bleeding gums, mouth ulcers, sore throats, cystitis, menstrual problems, gastritis, enteritis, diarrhea, urogenital infection, menorrhagia, rheumatism, stomach ache and skin problems like dermatitis, eczema and acne.[4,5] Based on the flower color there are two major cultivars in C. roseus. One is pink flowered “Rosea” and another white colored “Alba”.[6] Over the past two decades there are more than 100 varieties are developed though breeding technique. They have not only improved floral traits but also it is tolerant to disease and have boosted herbage and alkaloid yield.[7] Figure 1. Madagascar periwinkle-Rosea.
Morphology

*C. roseus* is an annual evergreen sub herb or herbaceous plant growing to 1 m. tall and secretes milky latex. The roots extend to 70 cm. in depth. Stems are cylindrical (terete), longitudinally ridged or narrowly winged, green or dark red, pubescent at least when young. The leaves are oval to oblong, 2.5-9.0 cm. long and 1-3.5 cm. broad, glossy green above and pale green below with a pale midrib and a short petiole about 1-1.8 cm. long. They are arranged in the opposite pairs. The flowers are pentamerous, actinomorphic and white to dark pink with a dark red center, with a basal tube about 2.5-3 cm. long and a corolla about 2-5 cm. diameter with five petal like lobes. The fruit is a pair of follicles about 2-4 cm. long and 3 mm broad, with numerous black seeds.

**Classification**

*Domain:* Eukarya: eukaryotes.

*Kingdom:* Plantae: plants.

*Subkingdom:* Tracheobionta: vascular plants.

*Superdivision:* Spermatophyta: seed plants.

*Division:* Magnoliophyta: flowering plants.

*Class:* Magnoliopsida: dicotyledons.

*Subclass:* Asteridae.

*Superorder:* Gentiananae.

*Order:* Gentianales.

*Family:* Apocynaceae: dogbane.

*Subfamily:* Rauvolfioideae.

*Tribe:* Vinceae.

*Genus:* Catharanthus G. Don.

*Specific epithet:* Roseus (Linnaeus) G. Don.

**Geographical Distribution**

The plant is distributed all through subtropical Asia, Africa and also in America and has been utilized both for decoration and medicine. All parts of the plant are useful including the roots, leaves, flowers and stems. It prefers well drained sandy loams soil and moisture with excellent soil drainage. It can be propagated by Cuttings and seeds and it has tolerance of cooler growing condition in temperate regions.

**Table 1. Folkloric Uses of Catharanthus Roseus and its vernacular names in different countries.**

<table>
<thead>
<tr>
<th>Country (Vernacular name)</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippines (Tsitsirika)</td>
<td>Decoction of leaves used in diabetes &amp; stomach cramps.</td>
</tr>
<tr>
<td></td>
<td>Root decoction for intestinal parasitism; as emmenagogue; may produce abortion.</td>
</tr>
<tr>
<td></td>
<td>Infusion of leaves used for treating menorrhagia.</td>
</tr>
<tr>
<td></td>
<td>Crude leaf extract has anticancer activity.</td>
</tr>
<tr>
<td></td>
<td>Recent use of roots for anticancer applications.</td>
</tr>
<tr>
<td></td>
<td>Roots used for dysentery.[16]</td>
</tr>
<tr>
<td>Madagascar</td>
<td>The bitter and astringent leaves used as vomitive; roots used as purgative, verminfuge, depurative, hemostatic and toothache remedy.</td>
</tr>
<tr>
<td>Mauritius</td>
<td>Infusion of leaves used for indigestion and dyspepsia.</td>
</tr>
<tr>
<td>India, West Indies, Nigeria &amp; Jamaica (Kannedood)</td>
<td>Used for diabetes.</td>
</tr>
<tr>
<td>Cuba and Jamaica</td>
<td>Flower extract used for eyewash in infants</td>
</tr>
<tr>
<td>Bahamas</td>
<td>Flower decoction used for asthma.</td>
</tr>
<tr>
<td>Malaysia (KemuntingCina)</td>
<td>Plant decoction used for diabetes, hypertension, insomnia and cancer.</td>
</tr>
<tr>
<td>China (Yan laihong, Riricao, Ririxin, San wan hua, Zhang chunhua).[17]</td>
<td>Used for dysmenorrhea, diabetes &amp; malaria.</td>
</tr>
<tr>
<td>India (Sadabahar, Baramassi, Ainskati, Ushamanjairi).[18]</td>
<td>Juice of leaves used for bee stings.</td>
</tr>
</tbody>
</table>

**Phytochemical Components**

Phytoconstituents present in *C. roseus* mainly include carbohydrates, alkaloids, glycosides, flavonoids, tannin, saponins, proteins, amino acids, fats and oils.[19] This plant produces more than 100 monoterpeneindole alkaloids (TIA) in different organs.[20] Among this principal component is vindoline(up to 0.5%). Other compounds arevincaleukoblastine (vinblastine), 22-oxovincaleukoblastine (vineristine), reserpine, vincamine, alstonine, leurocristine, ajmalicine, vinine,
vinonine, vinoxine, vintsine, leurosine. Alkaloids present in different organs can be summarized below.

**Table 2: It explains the name of Alkaloids present in different organs of the plant.**

<table>
<thead>
<tr>
<th>Plant organ</th>
<th>Name of Alkaloids present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaf</td>
<td>Catharanthine, Vindoline, Vindolidine, Vindolicine, Vindolinine, ibogaine, yohimbine, raubasine, Vinblastine, Vincreistine, Leurosine, Lochnerine.</td>
</tr>
<tr>
<td>Stem</td>
<td>Leurosine, Lochnerine, Catharanthine, Vindoline.</td>
</tr>
<tr>
<td>Root</td>
<td>Ajmalicine, Serpentine, Catharanthine, Vindoline, Leurosine, Lochnerine, Reserpine, Alstonine, Tabersonine, Horhammericine, Lochnericine, echitovenine.</td>
</tr>
<tr>
<td>Flower</td>
<td>Catharanthine, Vindoline, Leurosine, Lochnerine, Tricin (Flavones).</td>
</tr>
<tr>
<td>Seeds</td>
<td>Vingramine, Methylvingramine.</td>
</tr>
</tbody>
</table>

Among this vinca alkaloids present in Catheranthusare bulky molecule with closely related structure, containing both an indole nucleus (catharanthine portion) and a dihydroindole nucleus (vindoline portion) connected by a carbon-carbon ring. Naturally occurring Vincristine and vinblastine, semi -synthetic Vindesine and Vinorelbineare Vinca alkaloids extracted from periwinkle plant are effective against different types of cancers.

**Pharmacologicalactivities**

1. **Anti-oxidant activity**
   
   Reactive oxygen species are the harmful byproducts created in our body in normal aerobic respiration and other metabolic activities. Antioxidants are found to be effective against these harmful free radicals. C.roseus produce phenolic compounds which is an effective antioxidant. Oxygen radical absorbing capacity (ORAC) of C. roseusin 2011, Rassoland colleagues demonstrated that C.roseus is a viable source of natural antioxidants which can be applied in food and nutraceuticalindustry. The anti-oxidant properties of two varieties of C.roseus that is pink flowered and Calba were compared and was found that C.roseus possess more antioxidant activity than that of C. alba.

2. **Anti-diarrheal activity**
   
   The anti-diarrheal activity of the plant ethanolic leaf extract was tested in the wistar rats with castor oil as an experimental diarrhea inducing agent in addition to the pretreatment of the extract. Loperamide and atropine sulphate was used as the standard drugs. The anti-diarrheal effect of ethanolic extracts C. roseus showed the dose dependent inhibition of the castor oil induced diarrhea at the doses of 200 and 500 mg/kg.

3. **Anti-diabetic activity**

   The ethanolic extracts of the leaves and flower of C. roseus showed a dose dependent lowering of blood sugar comparable to the standard drug glibenclamide. The Hyperglycemic effect is due to the increased glucose utilization in the liver. The hypoglycemic activity of alkaloids isolated from C.roseus have been studied pharmacologically and a natural remedy derived from the plant has been marketed under the proprietary name Vinculin® as a treatment for diabetes.

Alcoholic whole plant extracts at high dose (500 mg/kg) exhibited significant antihyperglycemic activity without acute toxicity. The extract effectively reverses the changes in the blood sugar level and the beta-cell population. The exact phytoconstituents responsible for the anti-diabetic effect are not known yet.

4. **Anti-microbial activity**

   The phytochemical and antimicrobial studies made on C. roseus have shown that it has very important antimicrobial components alkaloids, flavonoids, steroids, phenolics, tannins and saponins. The methanol, ethanol, acetone and chloroform extracts of these plants have shown antibacterial activity against common human pathogens Staphylococcus aureus and Streptococcus faecalis. The discovery of a potent remedy from plant origin will be a great advancement in bacterial infection therapies as most of the bacterial pathogens were developing resistance against many of the available anti-microbial drugs. The antimicrobial activities of plant extracts may reside in a variety of different components, including aldehydes and phenolic.

5. **Anti-Cancer activity**

   C.roseus produces Vinca alkaloids which are well known for their anti-cancer properties. Some of the alkaloids are vinblastine, vincristine, vinorelbineand vindesine. Following table shows the alkaloid name, the branded drug name and its therapeutic uses.

**Table 3: It shows the name of Vinca alkaloids, branded drug names and its therapeutic uses.**

<table>
<thead>
<tr>
<th>Vinca alkaloid</th>
<th>Related drug</th>
<th>Therapeutic uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>Oncovin[35]</td>
<td>Leukemia, lymphomas</td>
</tr>
<tr>
<td>Vinorelbine[34]</td>
<td>Navelbine</td>
<td>Solid tumors, lymphomas, lung cancer</td>
</tr>
<tr>
<td>Vindesine[37]</td>
<td>Eldisine[38]</td>
<td>Acute lymphocytic leukemia</td>
</tr>
</tbody>
</table>
Anti-cancer drugs derived from *C. roseus* act as inhibitors of tubulin by binding to α/β–tubulin. This prevents its association in to microtubules which provide cells with both the structure and flexibility they need to divide and replicate.\(^{39,40}\) That is microtubules are the building block of protein and is vital to the proper functioning of the mitotic spindle in mitosis i.e., cell division. Vinca alkaloids known as mitotic spindle poisons as they inhibit further assembly of the spindle forms from microtubules, there by inhibiting mitosis in cell cycle.\(^{41}\) Vinca alkaloids thus successfully prevent cancer cells from dividing. Different Vinca alkaloids have their own unique properties. Among this Vincristine’s inhibition of microtubule formation is especially powerful. Overall, Vinca alkaloids are in the second most-used class of cancer drugs. Though, it will remain on top among the fundamental cancer remedies. Research for new Vinca alkaloid applications is ongoing.\(^{42}\) Currently Niosomes are used as drug carriers for vincristine and its toxicity was reduced after encapsulation and anti-cancer activity was improved.\(^{43}\) For many years scientists have involved in the process to synthesize new derivatives of vinblastine and vincristine. Modification in vindoline skeleton or catharanthine moiety produced a number of new selective, less toxic antitumor agents.\(^{44}\)

5. Anthelmintic activity

*C. roseus* was found to be used from the traditional period as an anthelmintic agent. The anthelmintic property of *C. roseus* has been tested by using Pherithemaposthuma as an experimental model and with Piperazine citrate as the standard reference. Then theethanolic extract of the concentration of 250 mg/ml was found to show the significant anthelmintic activity. This analysis reinforced the ethnomedical claims of *C. roseus* as an anthelmintic plant.\(^{45}\)

6. Anti-ulcer activity

The plant leaves proved for anti-ulcer activity against experimentally induced gastric damage in rats.\(^{46}\) Vincamine and Vindoline alkaloids of the plant showed anti-ulcer property. The alkaloid vincamine, present in the plant leaves shows cerebrovasodilatory and neuroprotective activity.\(^{47}\)

7. Hypotensive activity

Extract of leaves of the plant shows significant change in hypotensive. The leaves have been known to contain many useful alkaloids among other pharmacologically active compounds. Significant hypotensive activity of the leaf extracts (hydroalcoholic or dichloromethane-methanol) have been reported in laboratory animals.\(^{48}\)

8. Hypolipidemic effect

Significant anti-atherosclerotic activity of *C. roseus* was observed in a study with reduction in the serum levels of total cholesterol, lipid profiles, triglycerides and histology of aorta, liver and kidney with the leaf juice of *C. roseus*.\(^{49}\)

9. Memory enhancement activity

Vinpocetine the most intriguing dietary supplement madefrom the alkaloid called vincamine. It has been reported to have a variety of actions to improve brain function and memory, particularly beneficial in Alzheimer’s disease. Vinpocetine has been well tolerated at doses up to 60 mg/d in clinical trials of dementia and stroke and no significant adverse events were observed.\(^{50}\) Vinpocetine should not be combined with any blood thinning agents such as warfarin, aspirin as well as some dietary supplements like ginkgo, vitamin E and garlic.\(^{51}\)

10. Wound-Healing activity

When wounded Rats treated withethanolic extract of the *C. roseus* shows high rate of wound contraction. This is due to increased tensile strength and hydroxyproline content of the granulation tissues. It supports the uses of *C. roseus* in the management of wound healing.\(^{52}\)

Toxicity and Side effects

*C. roseus* is not recommended for oral administration because may worsen the side effects including psychological influences. The advised route for *C. roseus* and its derivatives are intravenous. Vinca alkaloids have been applied clinically since the end of the 1950s as major drugs in the treatment of Hodgkins disease, testicular germ cell cancer, lymphomas, Solid tumors, lung cancer and acute lymphocytic leukemia etc.\(^{53}\) In spite of their extraordinary benefits, all of the *C. roseus* alkaloids have neurotoxic activity, particularly vincristine, affecting neurotransmission.\(^{54}\) Vincristine and vinblastine are highly toxic antimitotic, blocking mitosis in metaphase after binding to the microtubules.\(^{55}\) Moreover, many side effects have been reported for these drugs comprising abdominal pains, constipation, nausea/vomiting, ulcerations of the mouth, celldestruction, kidney damage, pulmonary fibrosis, urinary retention, amenorrhea, hypotension and hypertension.\(^{55,56}\) Hence the dosage and administration must be cautiouslymeasured to reduce side-effects.

CONCLUSION

*Catharanthus roseus* is a rich source of lifesaving drugs especially Vinca alkaloids which are widely used to produce anti-cancer drugs. They continue to be an important therapeutic aid in future due to the proximity of vast phytochemicals present. Several researches are going on recently to decrease the toxicity of Vinca alkaloids, increase the yield of alkaloids in the plant by developing new varieties and to improve its therapeutic effects.\(^{57}\) Some successful results are also derived. For instance vincristine encapsulated nanoparticles have promising future in drug delivery as its toxicity was reduced and anti-cancer activity was improved after encapsulation.\(^{43}\)
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