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CATHARANTHUS ROSEUS AND PROSPECTS OF ITS ENDOPHYTES: A NEW AVENUE FOR PRODUCTION OF BIOACTIVE METABOLITES

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ABSTRACT: *Catharanthus roseus* is a medicinal herb found in many tropical and subtropical regions around the world. This plant produces a diverse array of secondary metabolites that are pharmaceutically important like vinblastine and vincristine used as chemotherapeutic agents in the treatment of several types of cancers. Low yield of these vinca alkaloids from the plant *in vivo* and the challenges to meet their high demand worldwide led researchers to develop various *in vitro* techniques like hairy root culture, callus cultures, shoot cultures, metabolic engineering and regulation studies to increase their production. The present review gives an account of the various phytochemicals derived from the plant and the pharmacological aspects of secondary metabolites studied. Present review also highlights the biotechnological prospects of an efficient and alternative means of production of valuable metabolites from *Catharanthus roseus* and also from rich microflora residing inside the plant tissues. It gives an emphasis on the need of exploration of diverse niches of endophytes.

INTRODUCTION: *Catharanthus roseus* is a medicinal plant belongs to the family Apocynaceae native and endemic to Madagascar. The plant is also known by the names such as *Vinca rosea*, *Ammocallis rosea* and *Lochnera rosea*. The plant has been put to traditional use for the treatment of a wide variety of ailments worldwide since ages [1]. The plant bears active phytoconstituents and exhibits various pharmacological activities like antidiabetic, antioxidant, anti-hypertensive, antimicrobial, cytotoxic etc. *Catharanthus roseus* produces a spectrum of terpenoid indole alkaloids (TIAs) vinblastine and vincristine, the anticancer lead molecules.

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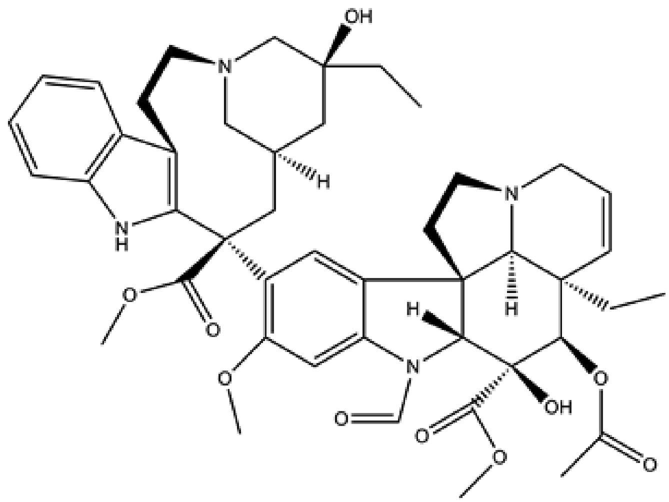
Being a source of these important secondary metabolites, an extensive study has been carried out on *C. roseus.* The present review provides a description of the secondary metabolites derived from this plant, its pharmacological activities, the biotechnological approaches undertaken to enhance the production of TIAs and the prospects of potential endophytes residing inside the host tissue.

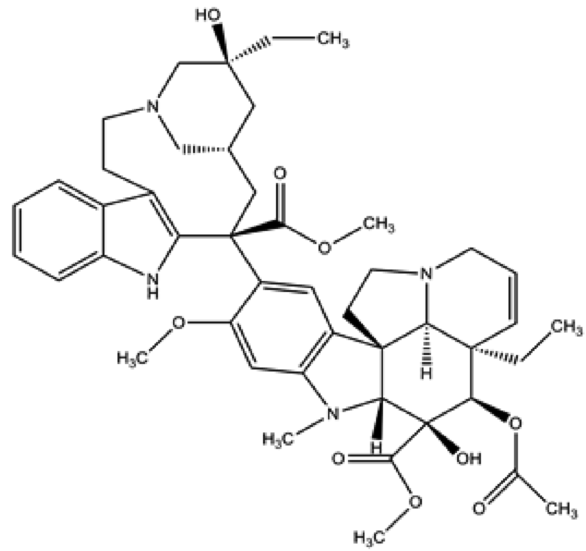
Active Constituents:

Alkaloids: *C. roseus* is known to be a source of about 150 active alkaloids out of which vincristine, vinblastine and vindiscline are of prime importance because of their use in the treatment of Cancer [2]. Vinca alkaloids vincristine and vinblastine are used in chemotherapy with vincristine being used for acute lymphocytic leukemia, both Hodgkin and non-Hodgkin lymphomas and vinblastine being used as the major component in chemotherapy for germ cell, breast, bladder and some types of brain malignancies[3].

Vinblastine and Vincristine shown in (**Figure 1**) are anti-tubulin drugs that act by suppressing the spindle microtubule dynamicity in the cells during mitosis thereby arresting cell division and causing cell death [4].



VINCRISTINE



VINBLASTINE

FIGURE 1: ANTI LEUKEMIC ALKALOIDS ISOLATED FROM *C. ROSEUS*

Vinblastine and vincristine have been isolated in a pure form from *C. roseus* L. Don by the use of several chromatographic techniques like vacuum liquid chromatographic column on silica gel: aluminium oxide (1:1) mixed bed vacuum liquid chromatography (VLC), charcoal column, and finally purified by centrifugally accelerated radial chromatography (Chromatotrone) [5]. Several other methods like high performance liquid chromatography [6, 7] and supercritical fluid extraction[8] have also been devised to efficiently quantify these alkaloids in the plant.

Vinblastine and vincristine are the dimers formed by the coupling of Monoindole alkaloids such as catharanthine and vindoline found abundantly inthe aerial parts of the plant [9]. The biosynthetic pathway of these alkaloids as in (**Figure 2**) has been found to be under strict developmental regulation in the plant[10]. Various studies on the regulation of the biosynthetic pathways as summarised in **Table 1** revealed that terpenoid- indole alkaloid biosynthesis is subjected to different enzymatic and genetic regulation in the plant system.

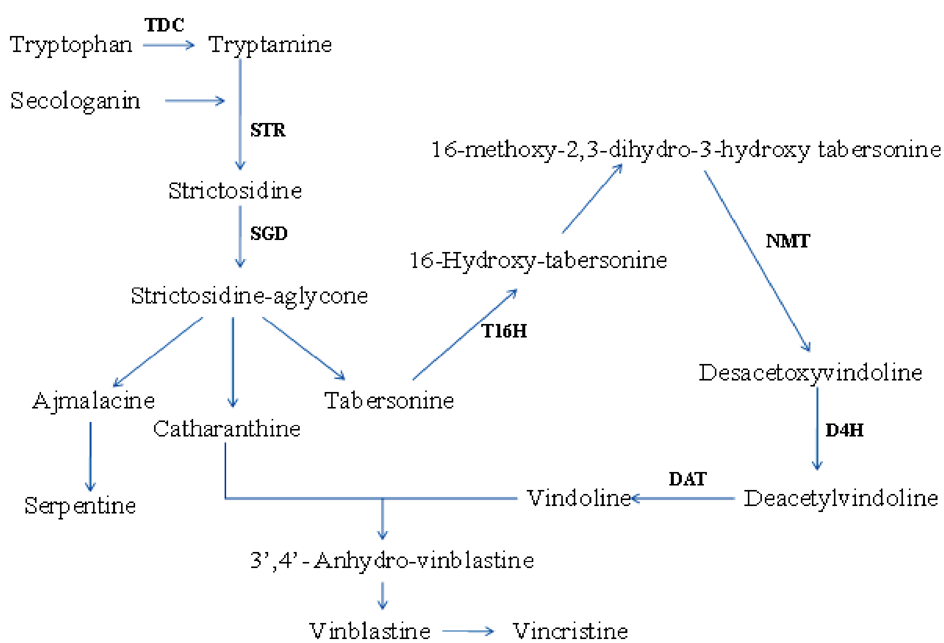


FIGURE 2: TERPENOID INDOLE ALKALOID BIOSYNTHESIS IN PLANT SYSTEM

The enzymes are abbreviated as follows: **TDC** – Tryptophan decarboxylase, **STR** – Strictosidine synthase, **SGD** – Strictosidine glucosidase, **T16H**– Tabersonine 16-hydroxylase, **NMT** - 16-methoxy-2,3-dihydro-3-hydroxy tabersonine *N*-methyl transferase, **D4H** - Vindoline-4-hydroxylase, **DAT**-Deacetylvindoline *O*-acetyltransferase

TABLE 1: STUDIES ON ENZYMES INVOLVED IN TIAS BIOSYNTHESIS IN *CATHARANTHUS ROSEUS*

Study	Reference
Enzymes from *Catharanthus roseus* cell suspension cultures that couple vindoline and catharanthine to form 3′, 4′- anhydrovinblastine.	Endo et al. [11]
Developmental regulation of enzymes of indole alkaloid biosynthesis in *Catharanthus roseus.*	Luca et al. [12]
Isolation and characterization of a 2-Oxoglutarate dependent dioxygenase involved in the second-to-last step in vindoline biosynthesis.	Carolis et al. [13]
Phytochrome is involved in the light-regulation of Vindoline biosynthesis in *Catharanthus.*	Aerts and Luca [14]
Strictosidine synthase from *Catharanthus roseus:* purification and characterization of multiple forms.	Waal et al. [15]
Gene-to-metabolite networks for terpenoid indole alkaloid biosynthesis in *Catharanthus roseus* cells.	Rischer et al. [16]
Rapid identification of enzyme variants for reengineered alkaloid biosynthesis in Periwinkle.	Bernhardt et al. [17]
A vacuolar class III peroxidase and the metabolism of anticancer indole alkaloids in *Catharanthus roseus.*	Sottomayor et al. [18]
Homolog of tocopherol C methyltransferases catalyzes N methylation in anticancer alkaloid biosynthesis.	Liscombe et al. [19]

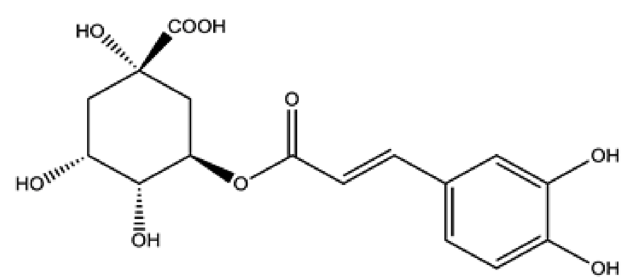
Further, subcellular localization of these enzymes is also implicated in the regulation of the TIA biosynthetic pathway. Tryptophan decarboxylase and strictosidine synthase involved in the synthesis of strictosidine are both found in the cytosol.

16-methoxy-2, 3-dihydro-3-hydroxytabersonine-N-methyltransferase which catalyses the vindoline biosynthesis are localized in the chloroplasts of leaves.

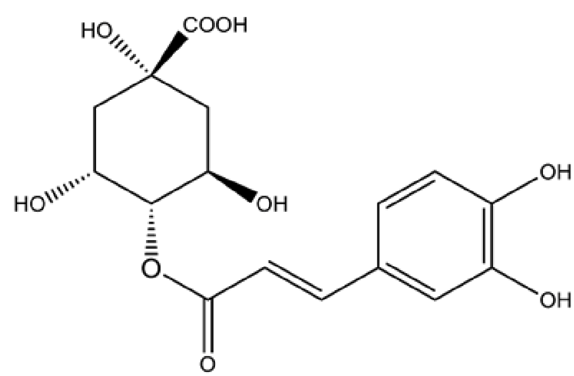
Acetyl-coenzyme-A-deacetylvindoline-O-acetyl transferase catalysing the last step in vindoline biosynthesis is also a cytoplasmic enzyme [20]. Most recently it has been reported that the entire production of catharanthine and vindoline occurs inside young leaves where the former accumulates in the leaf wax exudates and the latter within the leaf cells thus making leaves of this plant an important source of chemotherapeutic drugs [21].

The chemical synthesis involving direct coupling of vindoline and catharanthine and asymmetric total synthesis of vindoline and vindorosine based on a unique intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles have also been studied as a means for the production of terpenoid indole alkaloids like vinblastine, vincristine [22, 23].

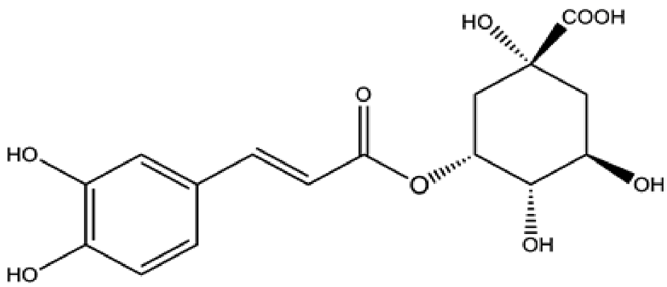
Polyphenolics: Study of non-coloured phenolics from seeds, stems, leaves and petals of *C. roseus* and evaluation of their antioxidant activity led to the characterization of three caffeoylquinic acids and some flavonol glycosides with structures as in **Figure 3**. The scavenging ability of different plant matrices was assessed and a concentration-dependent protective effect was observed for seeds and tissues, with petals found to be most active followed by seeds and leaves, indicating their potential for use in food, pharmaceutical and cosmetic industries [24].



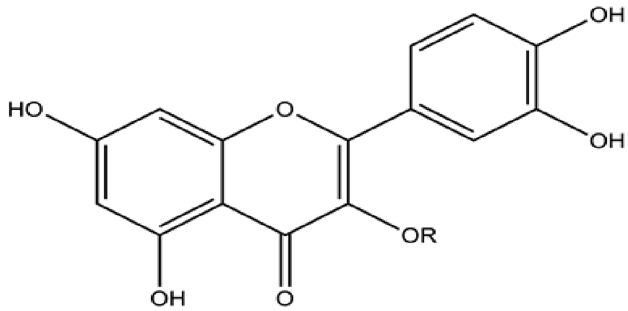
3-O-CAFFEOYLQUINIC ACID



4-O-CAFFEOYLQUINIC ACID



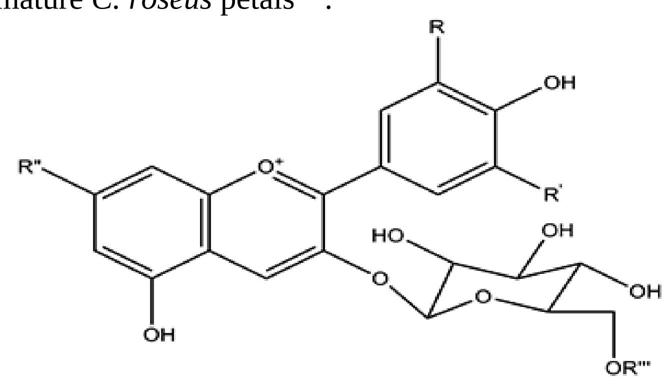
5-O-CAFFEOYLQUINIC ACID



4R= 2,6-di-O-rhamnosyl-galactoside
5R= 2.6-di-O-rhamnosyl-glucoside
6R= 6-O-rhamnosyl-galactoside
7R= 6-O-rhamnosyl-glucoside

FIGURE 3: CHEMICAL STRUCTURES OF THE PHENOLIC COMPOUNDS IDENTIFIED IN *C. ROSEUS*

Anthocyanins: The production of anthocyanins has been described *in vivo* as well as *in vitro* from *C. roseus*. The major anthocyanins have been identified as the 3-O-glucosides, and the 3-O-(6-O-p-coumaroyl) glucosides of hirsutidin, malvidin and petunidin shown in **Figure 4**, respectively both *in vivo* and *in vitro* plant cell cultures [25]. Besides these the presence of tricin, a flavone, was reported in the mature *C. roseus* petals [26].



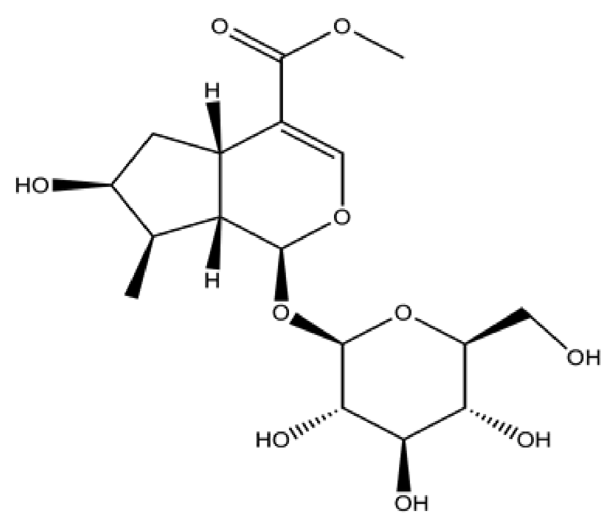
	R	R′	R′′	R′′′
1	OCH_3	OH	OH	H
2	OCH_3	OCH_3	OH	H
3	OCH_3	OCH_3	OCH_3	H
4	OCH_3	OH	OH	p-coumaroyl
5	OCH_3	OCH_3	OH	p-coumaroyl
6	OCH_3	OCH_3	OCH_3	p-coumaroyl

FIGURE 4: ANTHOCYANINS FOUND IN *C. ROSEUS*

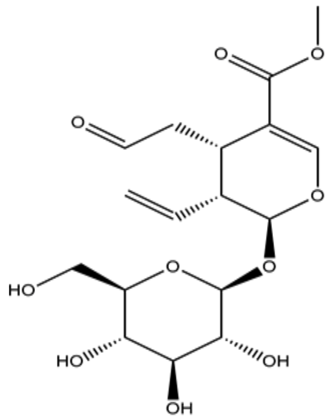
Steroids: Studies have shown that crown gall cells of octopine and nopaline-types derived from *C. roseus* (L.) G. Don produce brassinosteroids with the main components identified as brassinolide and catasterone. Brassinosteroids the steroidal growth-promoting plant hormones have been found to be useful in agriculture for increasing crop production, and improving stress resistance of crops against drought, chilling and pesticides [27].

Flavonoid glucosides: Four new flavonoid glucosides, 3’,4’-di-O-methylquercetin-7-O-[(4”→13”’)-2”’,6”’,10”’,14”’-tetramethylhexadec-13”’-ol-14”’enyl]-β-D-glucopyranoside, 4’-O-methyl kaempferol-3-O-[(4’’→13”’)-2”’,6”’,10”’,14”’-tetramethylhexadecane-13”’-olyl]-β-D-gluco pyranoside,3’,4’-di-O-methylbutin-7-O-[(6”→1”’)-3”’,11”’,-dimethyl-7”’-methylenedodeca 3”’, 10”’ dienyl]-β-D-glucopyranoside and 4’-O-methylbutin-7-O-[(6”→1”’)-3”’,11”’,-dimethyl-7”’-hydroxymethylenedodecanyl]-β-D-glucopyranoside were isolated from the methanol extract of *C. roseus* hairy roots for the first time. These new flavonoids were shown to inhibit MMP-9 activity and TNF-α production in THP-1 cells implying to their use as potential anti-inflammatory medication [28].

Iridoid glucosides: *C. roseus* is known to accumulate monoterpene indole alkaloids that are derived from the coupling of tryptamine and iridoids like loganin and secologanin (**Figure 5**) [29]. The distribution of these iridoids at sub-cellular levels was studied in secologanin accumulating *C. roseus* cells and secologanin was found to be stored exclusively in the vacuoles [30].



LOGANIN



SECOLOGANIN

FIGURE 5: IRIDOID GLUCOSIDES FOUND IN *C. ROSEUS*

Novel metabolites from cell cultures of *C. roseus:* *Catharanthus roseus* is not only an important source of the metabolites discussed above but has also been studied as the source of some novel active metabolites.

Some of the novel metabolites obtained from the cell cultures of *C. roseus* and the approaches used to produce them are discussed in **Table 2**.

TABLE 2: NOVEL METABOLITES FROM *C. ROSEUS* CELL CULTURE

Metabolite	Function	Type of culture	Reference
Phosphatidate kinase	Enzyme of phospholipid metabolism	Plasma membranes of suspension cultured *Catharanthus roseus* cells	Wissing et al. [31]
Trichosetin	Antibiotic	Dual culture of *Trichoderma harzianum* and *Catharanthus roseus* callus	Marfori et al. [32]
Phytic acid	Storage of phosphorus, mRNA export, chromatin remodeling	Suspension cultured cells of *Catharanthus*	Mitsuhashi et al. [33]

Pharmacological Studies:

Antidiabetic activity: Study of a dichlormethane: methanol extract (1:1) of leaves and twigs of *C. roseus* in Streptozotocin-induced diabetic rat models exhibited hypoglycemic activity with the improvement in decreased enzymic activities in liver of diabetic animals. Increased levels of lipid peroxidation caused during oxidative stress were also normalized by extract treatment [34].

The leaf juice of *C. roseus* showed a dose-dependent reduction in blood glucose in both normal and diabetic rabbits when compared to the standard drug, glibenclamide. The mechanism of action was probably due to enhanced secretion of insulin from the ß-cells [35].

Study of *C. roseus*, *Azadirachta indica* and *Allium sativum* showed significant antidiabetic activity for all three medicinal plants compared with the patent drug glimepride supporting their usage as herbal medicines for the diabetes by Ayurvedic physicians[36]. An investigation to study the impact of *C. roseus* leaves on the management of diabetes mellitus in about 20 type-2 diabetics residing in Dharwad city revealed a significant reduction in the fasting blood glucose, post prandial blood glucose, total cholesterol, low density lipoprotein cholesterol and triglyceride levels of the diabetic subjects [37].

A study carried out to investigate the antidiabetic and hyperlipidemic potential of *C. roseus* on alloxan induced diabetes in male albino rats revealed the therapeutic value of the aqueous flower extracts of *C. roseus* to combat the diabetic condition in rats [38].

Anti-tumor activity: A U.S. government screening program incidentally discovered *C. roseus* alkaloids vinblastine and vincristine, as well as some synthetic analogs as highly toxic chemotherapy drugs [39]. Semi synthetic analogs, vinorelbine (VRLB) and vindesine (VDS), obtained from the active compounds showed potential activity against leukemias, lymphomas, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma in combination with other chemotherapeutic drugs [40].

Vinflunine, a bifluorinated derivative of vinorelbine exhibits a superior anti-tumor activity compared to other vinca alkaloids viz. vinorelbine and vinblastine. The mechanism of mitotic block is unknown but it is hypothesised that the anti-tumor activity is due to the decrease in microtubule dynamicity during mitosis and the increase in time centromere spends in the resting state during cell cycle. This novel vinca alkaloid is currently under Phase II clinical trials [41].

Cytotoxic activity: *C. roseus* was investigated for its cytotoxic activity by using MTT assay against Human Colorectal Carcinoma cell line (HCT 116). The study showed dose dependent cytotoxic activity of the methanol extract of *C. roseus* leaves with the chloroform extract showing the highest activity [42]. The aqueous extract of *C. roseus* leaves standardised to Vinblastine was found to inhibit the proliferation of Jurkat cell line indicating the efficacy of the extract for modulating normal and transformed immune cells in leukemia patients [43]. Three new dimeric indole alkaloids isolated from the whole plants of *C. roseus* have been evaluated for their cytotoxic activities against human breast cancer cell line MDA-MB-231 [44].

Antimicrobial activity: Ethanol extract of the *C. roseus* flowers was studied for its wound healing potential in Sprague Dawley rats and the study showed that the extract had properties rendering it capable of promoting accelerated wound healing activity. Besides this the increased wound contraction and tensile strength, increased hydroxyproline content and antimicrobial activity further supported the topical use of *C. roseus* in wound treatment and management [45].

Crude extracts from different parts viz leaves; stem, root and flowers of *C. roseus* were tested for antibacterial activity. The leaf extract showed significantly higher activity suggesting that bioactive compounds of *C. roseus* can be a potentially exploited as antibacterial agents. Gram (-) strains were found to be more sensitive than the Gram (+) bacteria [46].

A study conducted to determine the antibacterial activity of crude extracts from different parts (leaves, stem, root and flower) of *C. roseus* against several bacteria of clinical significance indicated that the extracts prepared from the leaves showed better efficacy, the ethanolic extracts were more active against almost all the test microbes and Gram-positive bacteria were found to be more sensitive than the Gram-negative ones [47].

The plant parts, leaves, stems, roots and flowers of two varieties of *Catharanthus roseus* (L.) G. Don. "rosea" and "alba" were tested for their antibiogram by using different solvents (methanol, acetone and ethyl acetate). The variety "rosea" was found to have a better antibiogram than the alba variety. Of the three solvents ethyl acetate extracts of different plant parts were found to have best antibiogram followed by methanol and acetone extracts [48].

In a study aimed to investigate some of the anti-microbial properties of *C. roseus* against microorganisms like *Pseudomonas aeruginosa* NCIM 2036, *Salmonella typhimurium* NCIM 2501, *Staphylococcus aureus* NCIM 5021 it was found that the extracts from the leaves of this plant can be used as prophylactic agent in many of the diseases, which sometime are of the magnitude of an epidemic [49]. The leaf extract of *C. roseus* has also been shown to have significant fungitoxic activity against *Macrophomina phaseolina* and *Sclerotium rolfsii* the causative agents of the root rot disease in chickpea (*Cicer arietium* L.). The extracts strongly inhibited the mycelial growth in both the fungi at 50, 75 and 100% concentration when compared with the control[50].

In a study to explore the antiplasmodial potential of *C. roseus* L, *Coccinea grandis*, *Thevetia peruviana*, *Prosopis juliflora*, *Acacia nilotica*, *Azadirachta indica* (Abr. Juss) and *Morinda pubescens*, the bark extract of *A. indica* (Abr. Juss) was found to have excellent antiplasmodial activity followed by leaf extract of A. *indica* (Abr. Juss) and leaf extract of *C. roseus* L [51].

Antioxidant potential: The effects of triadmefon treatment, a triazole compound on the antioxidant potentials and root alkaloid ajmalicine content were studied in two varieties of *C. roseus*, *rosea* and *alba*. The treatment with triadimefon increased the antioxidant potential as well as the indole alkaloid ajmalicine (more in the *rosea* variety than the *alba* variety) content. Results suggested that triadimefon may be a useful tool for increasing alkaloid production in medicinal plants [52].

A study to comparatively evaluate the antioxidant potential of ethanolic extracts of the roots of the two varieties of *C. roseus* and *C. alba* using different systems of assay, e.g. Hydroxyl radical-scavenging activity, superoxide radical-scavenging activity, DPPH (2,2-diphenyl-1-picryl-hydrazyl) radical-scavenging activity and nitric oxide radical inhibition method was performed. The results revealed that the root extracts prepared in ethanol exhibited satisfactory scavenging effect in all the radical scavenging assays in a concentration dependent manner and *C. roseus* showed more antioxidant activity than *Catharanthus alba* [53].

Hypotensive activity: The leaf extracts of *C. roseus* were investigated for the hypotensive and hypolipidemic activity in adrenaline induced hypertensive rats in a study. *C. roseus* leaf extract was found to have significant effect on each cardiovascular parameter after investigation with regard to hypotensive and hypolipidemic effect [54]. The dry leaf powder of *C. roseus* was investigated for its antihyperlipidemic and antioxidant efficacy in male albino Wistar rats. The results of the study suggested that *C. roseus* possesses a significant antihyperlipidemic and antioxidant efficacy by attenuating the biochemical and physiological alterations in Streptozotocin induced diabetic rats [55].

Anthelmintic activity: Study of leaves extract of *C. roseus* showed potent antihelmintic activity in experimental adult earthworm *Pheretima posthuma* with the decrease in death time as the concentration increased. In the study, the control drug Piperazine citrate showed more potent anthelmintic activity compared to the methanol, aqueous, ethanol and ethylacetate extract [56]. The anthelmintic property of *C. roseus* was evaluated using *Pheretima posthuma* as an experimental model and Piperazine citrate as the standard reference.

Among the various test concentrations, ethanol extract 250 mg/ml showed significant anthelmintic activity with death time of 46.33 min as compared to the standard drug at 50 mg/ml that showed paralysis at 31.33 min and death time as 40.67 min. The investigation thus revealed that ethanol extract of *C. roseus* showed significant antihelmintic activity against *Pheretima posthuma* supporting the ethnomedical claims of *C. roseus* as an antihelmintic plant [57].

Neuroprotective activity: A study was done to investigate the possible neuroprotective effect of *C. roseus* leaf extract against streptozotocin induced hyperglycaemia in the rat brain demonstrated that *C. roseus* leaf extract is an effective neuroprotective agent against diabetic oxidative damage as treatment with *C. roseus* reduced MDA, XO and Sorbitol DH production and increased glutathione levels significantly when compared to the streptozotocin induced diabetic-untreated rats [58].

Antifertility efficacy: Oral administration of *C. roseus* Linn, leaf extract leading to widespread testicular necrosis, hyalinization of tubules and sertoli cell-only-Syndrome, notable reduction in glycogen and fructose levels in reproductive tissues confirmed the antifertility properties of *C. roseus* extract [59]. The petroleum ether extract of *C. roseus* leaves inhibited the estrogen induced gain in the uterine weight when administered along with estradiol into the female albino mice thus proving to be highly effective in suppressing pregnancy [60].

Biotechnological approaches to enhance *in vitro* production of terpenoid indole alkaloids from *C. roseus*: *Catharanthus roseus* has been of much interest among the scientific and medical communities because of its pharmacological potential. The interest can be traced back to the mid-1950, when researchers began to study the plant for its reported antidiabetic properties. The pharmacological potency of the plant as discussed earlier is due to its varied active constituents and the plant being a sole commercial source of anti-cancer alkaloids vincristine and vinblastine [61] has made it an important subject of research.

Most of the scientific research done on *C. roseus* in the past years had been focussed towards the isolation and characterisation of TIAs, testing their bioactivity and study of their biosynthetic pathways. Low yield of these vinca alkaloids from the plant *in vivo* (0.0005%) [62] and the challenge to meet their high demand worldwide (3kg/annum) has led to the development of various *in vitro* techniques like hairy root culture, callus cultures, shoot cultures for their increased production. Besides these classical tissue culture techniques, metabolic engineering aspects have also been studied to improve the production of terpenoid indole alkaloids [63].

Metabolic and biochemical engineering have been studied as a perspective for the creation of new cell lines producing TIAs in large scale bioreactors combined with efficient upstream and downstream processing [64]. Recently, a study to investigate the effect of various elicitors of hydroxylase, peroxidase, acetyltransferase and inhibitors of oxygenase on regulation of vinblastine biosynthesis in cell suspension cultures of *C. roseus* showed Hydrogen peroxide, Acetyl CoA, Benzotriazole to be very effective in enhancing the production of vinblastine[65].

Table 3 summarises some of the biotechnological approaches used to increase the terpenoid indole alkaloid production.

TABLE 3: BIOTECHNOLOGICAL APPROACHES TO INCREASE TIAS PRODUCTION

Plant species/family	Method Used	Yield	References
Catharanthus roseus (Apocyanaceae)	Biofilm culture (biofilm thickness-6mm)	% Alkaloids – 0.18	Kargi et al. [66]
	Catharanthus roseus immobilized cells	Serpentine - 300 μg/L	Archambault et al. [67]
	Hairy root culture (indole alkaloids)	2- to 3-fold higher than untransformed culture	Cau-uitz et al. [68]
	Cell suspension culture (addition of loganin and tryptamine)	TIAs-350 mmol/L	Whitmer et al. [69]
Catharanthus roseus (Apocyanaceae)	Cell suspension culture + Chemicals Betaine n-propyl gallate Tetramethyl ammonium bromide Linoleic acid Arachidonic acid Succinic acid Malic acid	Ajmalicine - 55.4 mg/l Ajmalicine - 26.8 mg/l Ajmalicine - 63.6 mg/l Serpentine – 32mg/l Serpentine - 8.5 fold increase Serpentine – 16 mg/l Ajmalicine – 23 mg/l Ajmalicine – 31 mg/l Ajmalicine – 60 mg/l Catharanthine – 24 mg/l Serpentine – 19mg/l	Zhao et al. [70]
	Cell suspension culture (addition of 10.0 mmol/L Sodium nitroprusside)	Total Catharanthine 40.3 mg/L	Xu et al. [71]
	Application of Gibberellic acid (1000 g m–3)	Total alkaloids [% DM] 3.44	Srivastava and Srivastava [72]
	Combined treatment of Arbuscular Mycorrhizal Fungi (AMF) and P_2O_5 (200 kg P_2O_5/ha+AMF)	Ajmalicine (1.22±0.66, 1.68±0.44 mg/g/plant)	Karthikeyan et al. [73]
	Suspension culture (UV B irradiation)	Catharanthine – 0.12 ±0.0054 mg/g DW Vindoline – 0.06 ± 0.0023 mg/g DW	Ramani and Jayabaskaran [74]
	Hairy root culture Metabolic engineering	Total TIAs (9.51mg/g DW)	Zhou et al. [75]
	Callus	Vincristine (20.38 mg/g)	Kalidass et al. [76]
Catharanthus roseus (Apocyanaceae)	Hairy root culture Over expression of transcription factor CrWRKY1 Repression of transcription factor CrWRKY1	Serpentine - 291.5 6 ± 73.2 μg/g DW Ajmalicine - 15.4 6 ± 1.6 μg/g DW Catharanthine - 100.2 ± 15.1 μg/g DW Tabersonine - 19.3 6 ± 1.6 μg/g DW	Suttipanta et al. [77]
	Co-cultivation in 1/2 MS medium containing 100 μ Macetosyringone	Vindoline1.42 ~ 2.72 μg/mg (DW)	Wang et al. [78]
	Hairy root culture (co-cultivation with A. rhizogenes A4. B5 medium)	Catharanthine 0.17 mg/g FW	Zhou et al. [79]
	Cell suspension culture Regulation by elicitors and inhibitors	Tabesonine (9.02mg/g DW), Vindoline (0.42mg/g DW) Vinblastine (0.81mg/g DW)	Guo et al. [65]

Endophytes:

A new avenue for production of bioactive metabolites: Despite these continuous efforts, the desired level of production of these metabolites has still not been achieved at optimum level, thereby making it necessary to bioprospect their new sources. Taking into consideration the limitations associated with the production of these metabolites *in vivo* and the need to preserve the world's ever-diminishing biodiversity, a microbial source of a valued product may be easier, sustainable and more economical for the production of valuable metabolites, effectively reducing their market price. Endophytes, the microbes that colonize the internal tissues of the plants without causing any overt negative effects, could thus be the potential sources of these valuable bioactive metabolites [80]. The endophytes are a diverse group of microbes owing to the fact that almost all vascular plants examined to date have been found to colonize these microbes [81, 82]. Due to varied ecological niches of *C. roseus*, there is also a probability of diversity in endophytic localisation inside the plant tissues. The endophytes are sources of bioactive compounds like alkaloids, terpenoids, flavonoids, steroids etc that have importance in medicine, agriculture and industries as well [83, 84]. **Table 4** gives an account of the bioactive compounds obtained from the endophytes islolated from *Catharanthus roseus* till date.

TABLE 4: **BIOACTIVE COMPOUNDS OBTAINED FROM ENDOPHYTES ISOLATED FROM *C. ROSEUS***

Endophyte	Plant part used	Compound	Bioactivity	Reference
Alternaria sp.	Inner bark	Vinblastine	Antitumor	Guo et al. [85]
Fusarium oxysporum	Stem	Vincristine	Antitumor	Zhang et al. [86]
Unidentified	Leaves	Vincristine (0.205 µg/L)	Antitumor	Yang et al. [87]
Pestalotiopsis sp.	Leaves	Taxol (92µg/L)	Antitumor	Srinivasan and Muthumary [88]
Vrb46 similar to *Bacillus coagulans*	Stem	-	Antimicrobial	Roy and Banerjee [89]
Actinomycetes sp.	Leaves	-	Antimicrobial	Kafur and Khan[90]

Endophytes isolated from *C. roseus* not only yield these valuable therapeutic molecules but have recently been studied to improve the *in planta* content of terpenoid indole alkaloids like serpentine, ajmalacine, vindoline and vinblastine. The study showed that the bacterial endophytes isolated from this plant identified as *Staphylococcus sciuri* and *Micrococcus* sp. could possibly be used as bio-inoculants to increase the plant biomass and the content of key terpenoid indole alkaloids within the plant thus providing an efficient and economic means to overcome the gap between high demand and low supply of these vinca alkaloids globally [91].

CONCLUSION: *Catharanthus roseus* is an important medicinal plant with a wide range of uses. The dried plant extracts contain many alkaloids of medicinal use. These alkaloids are produced in very small quantities inside the plant although attempts have been made over the past years to increase their production through various biotechnological applications. The plant has been proven useful not only in the field of medicine but has also been recently put into use for the phytoremediation of radiocesium ^{137}Cs from low level nuclear waste [92].

The leaves of this plant have been found to be of immense medicinal use as most of the pharmacological activities of this plant are attributed to its leaves. So the cultivation as well as the conservation of this plant must be promoted on a large scale. Besides this alternative means, that are less time consuming, sustainable and more economical, must be developed and adopted for the production of these active constituents.

In the present times, when the emphasis is being placed on the use of natural materials in the control and treatment of various diseases and infections because of the undesirable side effects of synthetic drugs there is a need for further research especially on bioactive compounds, their production from alternative sources, methods for increasing their production, herbal remedies, effectiveness of plants for various uses and bioprospecting new sources of natural bioactive products which can provide unlimited scope for the development of new drug leads. Endophytes could thus be exploited as the sources of the valuable secondary metabolites of medicinal, agricultural and industrial importance.

Owing to the huge microbial biodiversity of endophytes, these are still the less investigated group of microorganisms that need to be explored for their huge potential of being used as the sources of pharmacologically active therapeutic lead compounds.

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