

## REVIEW ARTICLE

# A Review on Oncolytic and Antimicrobial Properties of *Catharanthus roseus*



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**Abstract:** *Catharanthus roseus* (L.) G. Don, a member of the Apocynaceae family, serves as a primary reservoir for high-value terpenoid indole alkaloids, most notably the oncolytic dimers vinblastine and vincristine. These compounds occupy a critical role in clinical oncology by disrupting mitotic spindle dynamics, leading to cell cycle arrest and apoptosis in various malignancies, including leukemias and lymphomas. Beyond its established anticancer efficacy, the plant exhibits significant antimicrobial potential against a diverse range of bacterial, fungal, and viral pathogens. This biological activity is mediated by a complex chemical profile involving flavonoids, phenolics, and tannins that target microbial membrane integrity and enzymatic functions. Traditional therapeutic applications across various cultures for diabetes and inflammatory conditions provide a foundation for modern pharmacological investigations. Despite the therapeutic utility of its secondary metabolites, the extremely low natural yield of dimeric alkaloids remains a significant challenge. Advanced biotechnological strategies, including hairy root cultures, elicitation, and metabolic engineering, offer pathways to enhance the production of these bioactive molecules. A thorough assessment of the botanical features, biosynthetic pathways, and safety profiles provides the necessary framework for optimizing the clinical and industrial utilization of this medicinal species.

**Keywords:** *Catharanthus roseus*; Terpenoid Indole Alkaloids; Vincristine; Oncolytic activity; Secondary metabolism.

## 1. Introduction

Medicinal plants act as the foundation of global healthcare, serving as both direct therapeutic sources and structural templates for the development of modern pharmaceuticals. Among the most pharmacologically significant species is *Catharanthus roseus*, commonly referred to as the Madagascar periwinkle or Sadabahar. This perennial herb belongs to the Apocynaceae family and originated in Madagascar, though its ornamental and medicinal value has led to widespread naturalization in tropical and subtropical zones across the globe [1]. The pharmaceutical prominence of *C. roseus* arises from its ability to produce over 130 distinct secondary metabolites, with the terpenoid indole alkaloid (TIA) class being the most prominent. The isolation of vincristine and vinblastine from the plant's aerial parts marked a pivotal moment in oncology, introducing potent microtubule-disrupting agents into standard chemotherapy protocols [2]. These alkaloids are indispensable in treating Hodgkin's disease, acute lymphocytic leukemia, and various solid tumors.



Figure 1. Leaves and Flowers of *Catharanthus roseus*

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In addition to its role in cancer treatment, *C. roseus* demonstrates a broad spectrum of antimicrobial activity. Extracts derived from various plant organs show inhibitory effects against pathogenic microorganisms, attributed to a synergistic interaction between alkaloids, flavonoids, and phenolic compounds [3]. These metabolites function through several mechanisms, including the disruption of microbial cell walls and the inhibition of metabolic enzymes. Historically, traditional medical systems such as Ayurveda and Unani have utilized the plant for managing glucose levels, wound healing, and inflammatory pathologies [4].

The increasing prevalence of drug-resistant cancers and microbial strains has prompted a resurgence in the study of natural products. *C. roseus* currently serves as a primary model for investigating secondary metabolite biosynthesis and metabolic flux [5]. Recent progress in plant biotechnology, specifically in the realms of genetic engineering and tissue culture, aims to address the limitations of low alkaloid yields in wild populations [6]. By integrating botanical data with modern molecular techniques, researchers continue to optimize the extraction and production of these life-saving therapeutic agents [7,8].

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## 2. Botanical Characteristics

*Catharanthus roseus* (L.) G. Don is characterized by its resilience and distinct morphological features that facilitate its survival in diverse environments. As a member of the Apocynaceae family, it shares the characteristic of producing latex and a rich variety of alkaloids [9].

### 2.1. Growth Habit and Stem Morphology

The species typically grows as an erect or decumbent perennial herb or subshrub, reaching heights between 30 and 100 cm. The stem is cylindrical, often woody at the base, and displays a green or reddish-purple hue in younger plants, which transitions to a pale brown as the plant matures [10]. Branching is frequent, providing the plant with a dense, bushy appearance. The internodes are clearly defined, contributing to a symmetrical architecture that supports the heavy foliage and flowering clusters.

### 2.2. Foliar Structure

The leaves of *C. roseus* are arranged in an opposite, decussate pattern. Each leaf is simple, elliptic to obovate, and measures approximately 2.5–9 cm in length and 1–3.5 cm in width [11]. The leaf surface is notably glossy with a waxy cuticle that serves to minimize transpirational water loss, an adaptation for survival in tropical climates. The venation is pinnate, with a prominent light-colored midrib. Specialized secretory tissues within the leaf lamina are the primary sites for the accumulation of terpenoid indole alkaloids, making the foliage the most pharmacologically active part of the plant for anticancer extraction [12,13].

### 2.3. Floral and Reproductive Morphology

The flowers are actinomorphic and highly ornamental, featuring a salverform corolla with five lobes. Common color variants include pink, white, and white with a red center [14]. The flowers are typically solitary or found in pairs in the leaf axils. A slender corolla tube, roughly 2–3 cm long, houses the reproductive organs and terminates in spreading lobes that create a pinwheel effect [15]. Flowering occurs throughout the year in tropical regions, with pollination primarily facilitated by long-tongued insects such as butterflies and moths.

### 2.4. Fruit, Seed, and Root Systems

The fruit consists of two narrow, cylindrical follicles, 2–4 cm in length, which dehisce longitudinally upon maturity to release numerous small, black, oblong seeds [16]. The root system is a well-developed taproot with numerous lateral branches. These roots are particularly rich in specific alkaloids like ajmalicine and serpentine, which differ from the alkaloid profile found in the aerial tissues [17].

### 2.5. Ecological Requirements and Habitat

The plant is exceptionally hardy and adaptable, thriving in sandy soils and coastal environments. It prefers temperatures between 20°C and 30°C and exhibits high drought tolerance [18,19]. However, the concentration of bioactive metabolites is highly sensitive to environmental stressors. Soil nutrient availability, light intensity, and water status significantly influence the metabolic flux toward alkaloid biosynthesis, which is a critical consideration for commercial cultivation [20].

### 3. Phytochemical Diversity and Secondary Metabolism

The therapeutic efficacy of *Catharanthus roseus* is the result of its intricate chemical composition. The plant synthesizes a vast array of compounds including alkaloids, terpenoids, flavonoids, and phenolic acids. The distribution of these metabolites is tissue-specific and developmentally regulated [21,22].

#### 3.1. Terpenoid Indole Alkaloids (TIAs)

The TIAs represent the most significant class of phytochemicals in *C. roseus*. These nitrogenous compounds are derived from the condensation of tryptamine and secologanin [23]. Over 100 TIAs have been identified, categorized based on their structural complexity and biological function.

##### 3.1.1. Dimeric Oncolytic Alkaloids

Vincristine and vinblastine are the most prominent dimeric TIAs. These molecules are formed through the coupling of the monomeric precursors vindoline and catharanthine. Because this coupling is a complex, multi-step process, these alkaloids are produced in extremely low concentrations in the plant, often requiring tons of dry material to produce a few grams of the purified drug [24].

##### 3.1.2. Monomeric and Antihypertensive Alkaloids

Monomeric alkaloids such as catharanthine and vindoline serve as precursors but also possess independent biological activities. Other significant TIAs include ajmalicine and serpentine, which are primarily concentrated in the roots. These compounds are known for their antihypertensive and sedative properties, functioning through the modulation of the nervous system and vascular tone [25,26].

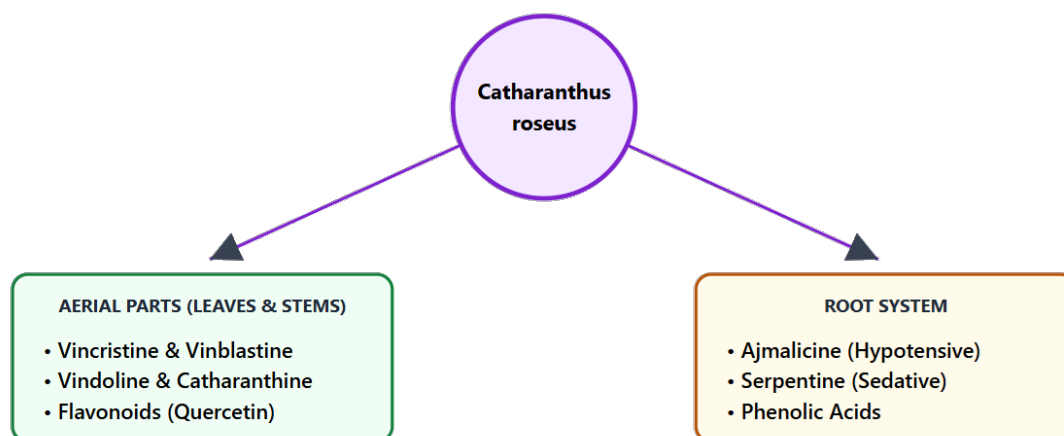


Figure 2. Organ-Specific Distribution of Therapeutic Alkaloids

#### 3.2. Flavonoids and Phenolic Compounds

In addition to alkaloids, *C. roseus* contains high concentrations of flavonoids, including quercetin, kaempferol, and their glycosidic derivatives. These polyphenolic compounds are powerful antioxidants that protect plant tissues from oxidative damage [27]. In a clinical context, they contribute to the anti-inflammatory and cardioprotective effects associated with plant extracts.

Table 1. Major Phytochemical Constituents and their Biological Activities

Compound Class	Specific Metabolites	Primary Biological Activity	Reference(s)
Dimeric TIAs	Vincristine, Vinblastine	Antineoplastic, Microtubule inhibition	[2, 24]
Monomeric TIAs	Catharanthine, Vindoline	Precursors for dimerization, Antimicrobial	[23]
Root Alkaloids	Ajmalicine, Serpentine	Antihypertensive, Sedative, Neuroprotective	[25, 26]
Flavonoids	Quercetin, Kaempferol	Antioxidant, Anti-inflammatory, Cardioprotective	[27]
Phenolic Acids	Caffeic acid, Ferulic acid	Antimicrobial, Free radical scavenging	[28]

Phenolic acids, such as caffeic and ferulic acids, are also present in significant quantities. These compounds possess inherent antimicrobial properties and contribute to the plant's defense against herbivory and pathogens [28]. The interaction between these phenolics and the alkaloid content is believed to produce the synergistic therapeutic effects observed in whole-plant extracts [29].

### 3.3. Other Bioactive Constituents

The plant also contains various terpenoids, steroids, and organic acids. Saponins and tannins have been identified in the leaf and root extracts, contributing to the wound-healing and astringent properties of the species [30,31]. These secondary metabolites collectively form a multifaceted chemical defense system that has been successfully repurposed for human medicine.

## 4. Oncolytic and Pharmacological Mechanisms

The transition of *Catharanthus roseus* from a traditional remedy to a cornerstone of modern oncology followed the discovery of its potent leukopenic effects during early pharmacological screenings for antidiabetic agents [32]. The isolation of vinca alkaloids provided a new class of chemotherapeutic agents that specifically target the structural components of the cell during division.

### 4.1. Molecular Mechanisms of Action

The therapeutic efficacy of the primary alkaloids, vincristine and vinblastine, is primarily defined by their high affinity for tubulin, the protein subunit of microtubules.

#### 4.1.1. Inhibition of Microtubule Dynamics

Microtubules are dynamic polymers essential for various cellular functions, including the formation of the mitotic spindle during cell division. Vincristine and vinblastine bind specifically to the  $\beta$ -subunit of tubulin heterodimers at a site distinct from the binding sites of other antimetabolic agents like taxanes. This binding prevents the polymerization of tubulin into microtubules, leading to the depolymerization of existing structures at higher concentrations [33-36]. By disrupting the dynamic instability of the mitotic spindle, these alkaloids prevent the proper alignment and segregation of chromosomes during the metaphase of mitosis. Consequently, the cell becomes arrested in the M-phase, preventing further proliferation of malignant tissues.

#### 4.1.2. Induction of Programmed Cell Death

Prolonged mitotic arrest induced by TIA exposure triggers signaling cascades that lead to apoptosis. This process involves the phosphorylation of the B-cell lymphoma 2 (Bcl-2) protein family, which regulates the permeability of the mitochondrial membrane [37]. The resulting release of cytochrome c into the cytoplasm activates the caspase cascade, specifically caspase-9 and caspase-3, which execute the systematic dismantling of the cell. Research indicates that *C. roseus* alkaloids activate both intrinsic mitochondrial pathways and extrinsic death receptor pathways, ensuring the elimination of damaged or abnormal cells [38].

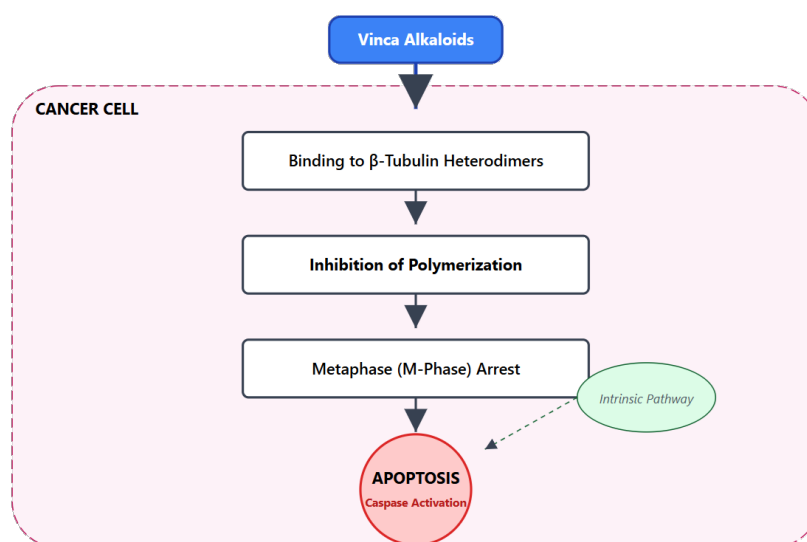


Figure 3. Cellular Mechanism of Action and Apoptotic Induction

## 4.2. Clinical Applications in Oncology

The clinical utility of purified *C. roseus* alkaloids is well-established across a broad range of malignancies. Vincristine is frequently utilized in the treatment of acute lymphoblastic leukemia, particularly in pediatric patients, as well as in regimens for Hodgkin and non-Hodgkin lymphomas [39,40]. Vinblastine finds extensive application in treating testicular cancer, Kaposi's sarcoma, and advanced breast cancer. These agents are rarely used as monotherapy; instead, they serve as vital components of combination chemotherapy regimens, where they work alongside other agents to overcome multi-drug resistance and minimize overlapping toxicities.

**Table 2. Clinical Indications and Regimens for Purified Vinca Alkaloids**

Alkaloid	Primary Clinical Indications	Typical Combination Regimen (Examples)	Targeted Malignancy	Reference(s)
Vincristine	Acute Lymphoblastic Leukemia (ALL)	VAMP (Vincristine, Amethopterin, Mercaptopurine, Prednisone)	Pediatric and Adult Leukemias	[39, 40]
Vincristine	Hodgkin's Lymphoma	MOPP (Mustargen, Oncovin, Procarbazine, Prednisone)	Lymphatic system tumors	[32, 39]
Vinblastine	Testicular Cancer	PVB (Platinol, Vinblastine, Bleomycin)	Germ cell tumors	[38, 40]
Vinblastine	Kaposi's Sarcoma	Monotherapy or with Doxorubicin	AIDS-related malignancies	[33, 40]

## 4.3. Synergistic Interactions and Cytotoxicity

While purified alkaloids are the standard for clinical use, crude extracts of *C. roseus* often demonstrate higher cytotoxicity in vitro compared to isolated compounds at equivalent concentrations. This phenomenon suggests a synergistic interaction between the various TIAs, flavonoids, and phenolic acids present in the plant matrix [41]. Such interactions may enhance the bioavailability of the primary alkaloids or modulate different signaling pathways simultaneously, potentially offering a broader range of therapeutic targets [42].

## 5. Antimicrobial Properties

Beyond its oncolytic applications, *C. roseus* demonstrates significant potential as a source of natural antimicrobial agents. This activity is a result of the plant's diverse chemical defense system designed to combat environmental pathogens.

### 5.1. Antibacterial Activity

Extracts from the leaves, stems, and roots of the plant exhibit broad-spectrum antibacterial efficacy against both Gram-positive and Gram-negative bacteria.

#### 5.1.1. Mechanisms of Bacterial Inhibition

The antibacterial action of *C. roseus* is mediated by several classes of metabolites. Flavonoids and tannins are known to form complexes with bacterial cell wall proteins and extracellular enzymes, leading to the disruption of membrane integrity. This disruption results in the leakage of essential intracellular contents and the eventual death of the bacterium [43-45]. Alkaloids such as vindoline and catharanthine also contribute to this effect by interfering with nucleic acid metabolism and protein production within the bacterial cell [46,47].

#### 5.1.2. Activity Against Pathogenic Strains

Experimental data consistently show that methanolic and ethanolic extracts are particularly effective against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [48]. These pathogens are frequently associated with hospital-acquired infections and have developed resistance to many conventional antibiotics. The ability of *C. roseus* metabolites to inhibit these resistant strains highlights its value as a reservoir for novel antibiotic leads.

**Table 3. Antimicrobial Spectrum of *C. roseus* Extracts Against Pathogens**

Pathogen Type	Microbial Species	Extract Type	Mode of Action	Reference(s)
Gram-positive	<i>Staphylococcus aureus</i>	Methanolic/Ethanollic	Cell wall protein complexation	[1, 3, 4, 48]
Gram-positive	<i>Bacillus subtilis</i>	Aqueous/Methanolic	Membrane permeability disruption	[5, 42, 44]
Gram-negative	<i>Escherichia coli</i>	Ethanollic	Inhibition of DNA/protein synthesis	[3, 26, 48]
Gram-negative	<i>Pseudomonas aeruginosa</i>	Methanolic	Efflux pump inhibition	[1, 4, 11]
Fungal	<i>Candida albicans</i>	Ethanollic	Ergosterol synthesis interference	[12, 15, 49]

## 5.2. Antifungal and Antiviral Potential

The antifungal properties of *C. roseus* are primarily attributed to the presence of specific phenolic acids and terpenoids. Studies have documented significant inhibitory activity against common fungal pathogens such as *Candida albicans* and *Aspergillus niger* [50]. Furthermore, preliminary investigations into the antiviral properties of the plant suggest that its extracts may inhibit the replication of viruses like the Herpes simplex and Influenza viruses. These effects are thought to occur through the prevention of viral attachment to host cells or the inhibition of viral proteases required for maturation.

## 6. Metabolic Pathways and Biosynthetic Formation of TIAs

The production of complex alkaloids in *C. roseus* involves one of the most intricate metabolic networks found in the plant kingdom. The formation of these compounds requires the spatial and temporal coordination of multiple enzymatic steps.

### 6.1. Origins of the Indole and Terpenoid Moieties

The biosynthetic framework for TIAs is built upon two primary metabolic pathways: the shikimate pathway and the methylerythritol phosphate (MEP) pathway.

#### 6.1.1. The Shikimate Pathway

The shikimate pathway provides the indole precursor, tryptamine. This process begins with the conversion of chorismate to the amino acid tryptophan, which is subsequently decarboxylated by the enzyme tryptophan decarboxylase (TDC) to yield tryptamine [51-53]. This step is a critical regulatory point in the pathway, as it provides the nitrogen-containing scaffold for all TIAs.

#### 6.1.2. The MEP Pathway and Secologanin Formation

Simultaneously, the MEP pathway produces the terpenoid component, secologanin. This involves a series of enzymatic reactions starting from primary metabolites like pyruvate and glyceraldehyde-3-phosphate, eventually leading to the formation of geraniol. Geraniol undergoes multiple oxidations and cyclizations to produce loganin, which is then cleaved to form secologanin [54,55].

### 6.2. Assembly of the Dimeric Alkaloids

The convergence of the indole and terpenoid branches occurs through the action of the enzyme strictosidine synthase (STR), which catalyzes the condensation of tryptamine and secologanin to form strictosidine. Strictosidine serves as the universal precursor for over 2,000 different indole alkaloids [56,57]. In *C. roseus*, strictosidine is converted through numerous intermediates into vindoline and catharanthine. The final and most complex stage is the enzymatic coupling of these two monomers to form the dimeric oncolytic agents, vinblastine and vincristine. This dimerization is a rate-limiting process, which explains the low natural accumulation of these compounds in the plant tissues.

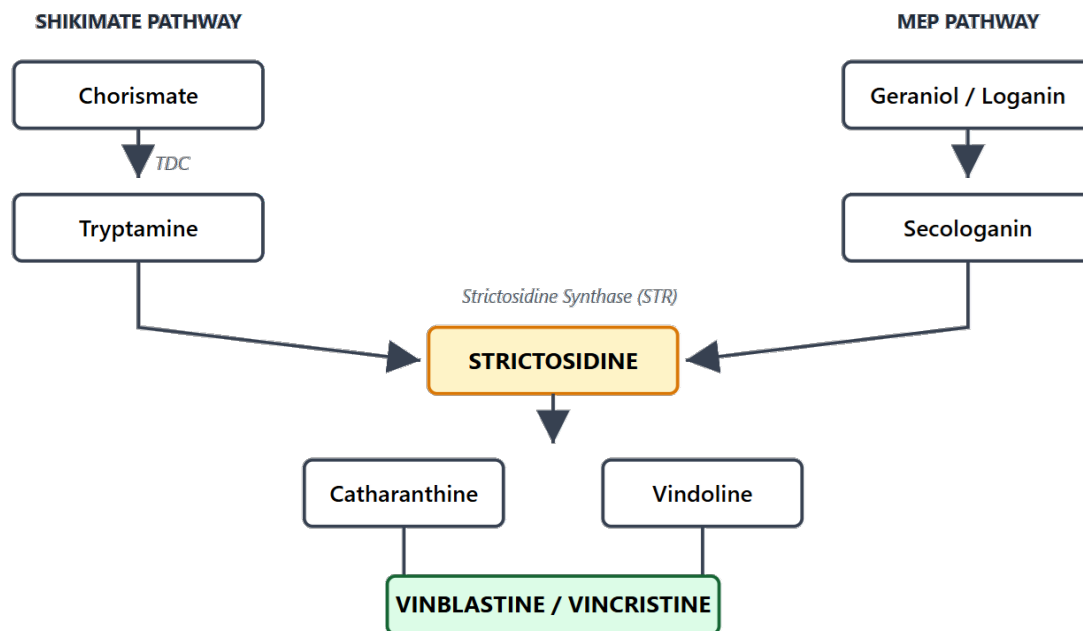


Figure 4. Biosynthesis of the Shikimate and MEP Pathways

## 7. Biotechnological Strategies for Enhanced Alkaloid Production

A primary constraint in the industrial utilization of *Catharanthus roseus* is the extremely low natural concentration of dimeric TIAs, such as vincristine and vinblastine, which often constitute less than 0.0005% of the dry leaf weight [58]. To address this supply challenge, several biotechnological interventions have been developed to bypass traditional agricultural limitations and optimize metabolic output.

### 7.1. Plant Tissue Culture Systems

In vitro culture techniques provide a controlled environment for biomass production and the biosynthesis of secondary metabolites, independent of seasonal variations or geographical constraints [59].

#### 7.1.1. Callus and Cell Suspension Cultures

Callus cultures are initiated from various explants, such as leaves or stems, using specific ratios of plant growth regulators like auxins and cytokinins [62]. While undifferentiated callus tissues can accumulate monomers like ajmalicine, they often lack the specialized cellular structures required for complex dimeric TIA assembly [63-65]. Transitioning these cells into liquid suspension cultures allows for larger-scale production in bioreactors. Optimized carbon-to-nitrogen ratios and precise agitation speeds enhance nutrient uptake and oxygenation, leading to improved yields of catharanthine and serpentine [69-71].

Table 4. Comparison of *In Vitro* Systems for Enhanced TIA Production

Culture System	Primary Advantages	Targeted Alkaloids	Limitations	Reference(s)
Callus Culture	Ease of initiation; high biomass	Ajmalicine, Serpentine	Low yield of dimeric TIAs	[62, 65]
Cell Suspension	Scalability in bioreactors; rapid growth	Catharanthine, Serpentine	Genetic instability over time	[68, 69, 71]
Hairy Root Culture	Genetic stability; high biosynthetic capacity	Vindoline, Ajmalicine	Difficult to scale due to root mass	[73, 75, 76]
Elicited Cultures	Rapid induction of defense genes	Vincristine, Vinblastine (traces)	May inhibit overall biomass growth	[80, 81]

### 7.1.2. Hairy Root Cultures

Hairy root cultures, established through infection with *Agrobacterium rhizogenes*, offer superior genetic stability and biosynthetic capacity compared to undifferentiated cells [73-75]. These roots grow rapidly in hormone-free media and maintain the metabolic profile of the parent plant. In *C. roseus*, hairy roots have been successfully utilized to produce high concentrations of ajmalicine and vindoline, providing a reliable platform for studying the genetic regulation of TIA pathways [76,79].

## 7.2. Elicitation and Metabolic Engineering

Elicitation involves the use of biotic or abiotic agents to trigger the plant's defense-related secondary metabolism.

### 7.2.1. Application of Signal Molecules

The use of jasmonic acid (JA) and methyl jasmonate (MeJA) has proven highly effective in upregulating the expression of key biosynthetic genes, such as tryptophan decarboxylase (TDC) and strictosidine synthase (STR). These signal molecules mimic the plant's response to herbivory, thereby diverting metabolic flux toward alkaloid production [80]. Synergistic effects have also been observed when JA is combined with salicylic acid (SA), leading to a significant amplification of alkaloid accumulation in cultured tissues [81-83].

### 7.2.2. Genetic and Synthetic Biology

Recent advancements in CRISPR/Cas9-mediated genome editing and transient gene expression systems allow for the precise modulation of the TIA pathway. By overexpressing rate-limiting enzymes or silencing competing pathways, researchers aim to create "bio-factories" capable of producing therapeutic alkaloids at commercially viable levels [84-86].

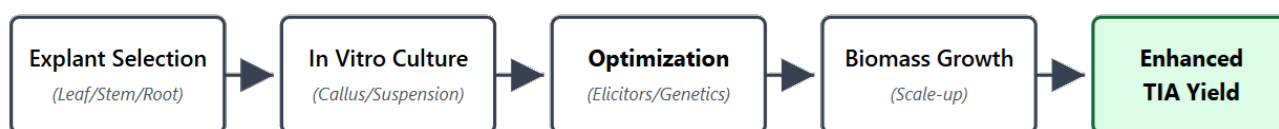


Figure 5. Process for Enhancement of Secondary Metabolites

## 8. Toxicology and Clinical Safety Considerations

Despite the profound therapeutic benefits of *C. roseus* metabolites, their potent biological activity necessitates a thorough understanding of their toxicological profile to ensure safe application in clinical and traditional settings.

### 8.1. Cytotoxicity of Unstandardized Extracts

The use of raw plant material or unverified extracts carries significant risks due to the variable concentration of highly toxic alkaloids. Accidental overconsumption or improper administration can lead to severe gastrointestinal irritation, characterized by nausea and mucosal ulceration [90,91]. More critically, the microtubule-disrupting nature of these compounds can cause systemic neurotoxicity, often manifesting as peripheral neuropathy, muscle weakness, and paresthesia [92].

Table 5. Toxicology and Safety of *C. roseus* Constituents

Organ System	Type of Toxicity	Clinical Manifestation	Management Strategy	Reference(s)
Nervous System	Neurotoxicity	Peripheral neuropathy, paresthesia	Dose reduction; neuroprotective agents	[87, 90, 92]
Hematological	Myelosuppression	Leukopenia, Neutropenia, Anemia	G-CSF administration; blood monitoring	[93]
Gastrointestinal	Mucosal Irritation	Nausea, vomiting, abdominal pain	Antiemetics; mucosal barriers	[90, 91]
Reproductive	Teratogenicity	Embryonic cell arrest	Contraindicated in pregnancy	[92, 93]

## 8.2. Hematological and Teratogenic Risks

Bone marrow suppression is a primary side effect of TIA exposure, resulting in leukopenia, anemia, and thrombocytopenia. This necessitates regular hematological monitoring during clinical treatment [93-95]. Furthermore, the interference of these alkaloids with cell division makes them highly teratogenic. Consequently, the use of *C. roseus* derivatives is strictly contraindicated during pregnancy, as they can impede normal embryonic development and organogenesis [96].

## 8.3 Clinical Management and Environmental Safety

When administered under medical supervision, purified alkaloids like vincristine and vinblastine are manageable through precise dosing and supportive care, such as the use of neuroprotective agents and growth factors to mitigate marrow suppression [97-99]. In laboratory and industrial settings, rigorous biosafety protocols are required to prevent accidental skin contact or inhalation. Furthermore, the disposal of alkaloid-rich waste must be carefully regulated to prevent toxic contamination of aquatic and soil ecosystems [100-102].

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## 9. Conclusion

*Catharanthus roseus* stands as a paradigm of the successful integration of ethnobotany into modern pharmaceutical science. The transition of its alkaloids from traditional healers' kits to the forefront of oncology has fundamentally altered the prognosis of several previously fatal malignancies. Beyond its well-documented oncolytic efficacy, the plant's broad-spectrum antimicrobial activity provides a promising avenue for addressing the global challenge of drug resistance. Current research into the complex biosynthetic pathways of terpenoid indole alkaloids, coupled with sophisticated biotechnological tools, is paving the way for sustainable and enhanced production of these high-value metabolites. While the narrow therapeutic index of its primary constituents requires strict clinical oversight, the ongoing exploration of its diverse phytochemical profile continues to hold the potential for discovering novel therapeutic leads. The continued scientific focus on this species ensures its enduring relevance as a vital natural reservoir for future drug discovery and development.

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