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Exploring the cancer-fighting properties of *Catharanthus roseus*: A natural powerhouse

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ABSTRACT

Catharanthus roseus contains high-value medicinal properties, which are widely used in treating diabetes, kidney, liver, cardiovascular, and other life-threatening diseases. This study aims to explore the potential properties of *C. roseus* that are used as cancer-fighting agents and update the prospects and pharmacological significance of *C. roseus*. This study highlights the screening of anticancer properties, *in vitro* phytochemicals, and pharmacological advancements through biological cell culture approaches. The updated findings further suggest the potential pathways of inhibiting cancer cells and prospect of the medicinal properties in healing life-threatening diseases. The findings together open new insights into using C. *roseus* properties in pharmaceutical significance, cancer treatment, and patient care.

INTRODUCTION

Cancer is a life-threatening disease caused by abnormal rapid cell division in a part or organ of the body. The primary cause of mortality from cancer is metastasis, where the abnormal cells rapidly increase in the body [1]. According to the World Health Organization (WHO), cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or 1 in 6 deaths, in 2018 [2]. The American Cancer Society (ACS) published a Global Cancer Statistics report in 2024. The report revealed that approximately 20 million new cancer cases were diagnosed globally in 2022, and the disease claimed the lives of 9.7 million people worldwide [3]. As cancer detection and treatment improve in high-income countries, it is expected that over the next decade, more than 75% of cancer-related deaths will occur in low- and middle-income countries [4].

Catharanthus roseus, commonly known as Madagascar periwinkle, is a perennial plant from the Apocynaceae family [5, 6]. The plant's name is derived from Greek and means "pure flower." This plant thrives in tropical regions and is cultivated both as an ornamental and medicinal plant. The plant extracts potential properties of *C. roseus* demonstrate a variety of pharmacological activities being used as anticancer, antidiabetic, antimicrobial, antioxidant, and other patient cures [7]. *C. roseus* synthesizes more than 120 alkaloids, with 70 exhibiting pharmacological activity, including indole alkaloids such as ajmalicine, serpentine, and reserpine [6]. These alkaloids possess anti-hypertensive and antispasmodic properties, which are valuable in clinical treatments.

Plant compounds play showed defense against microbial infections and environmental stressors like UV radiation [6].

Among the alkaloids found in *C. roseus*, vincristine, and vinblastine are particularly notable for their anticancer properties [8]. These compounds, present in the plant's leaves, inhibit tumor growth by preventing cell division. Vincristine and vinblastine achieve this by binding to tubulin, a fundamental protein in the cytoplasm, thereby suppressing the formation of microtubule structures. These alkaloids are commonly prescribed to treat various cancers, including leukemia, Hodgkin's lymphoma, and breast cancer [8, 9].

It is not clear how *C. roseus* alkaloids interact with cancer cells at the molecular level. Recent studies have begun to explore tentative pathways, but comprehensive insights are still lacking. A study highlighted newly isolated indole alkaloids from *C. roseus*, such as catharoseumine and 14′,15′-didehydrocyclovinblastine, which have shown effective inhibition of human cancer cell lines *in vitro* [10]. Another research assessed the anticancer effects of incensole acetate, a terpenoid molecule isolated from *C. roseus* essential oil, using *in silico* docking studies and *in vivo* models [11]. Nevertheless, a study explored the regulation of genes coding for enzymes involved in the synthesis of terpenoid indole alkaloids (TIA) and elucidated some molecular mechanisms controlling gene expression in cell suspension cultures of *C. roseus* [6].

Potential clinical trials are required to validate the efficacy and safety of *C. roseus*-derived compounds in diverse patients. A study emphasized the importance of clinical trials for these compounds, which suggests their potential in cancer treatment [12]. Research highlighted the need for improved formulations to enhance the bioavailability and pharmacokinetics of these compounds [9]. This is crucial to explore their therapeutic potential. The efficiency of the compounds has been identified as their role in resistance mechanisms in cancer cells [13], but further research is needed to develop strategies to overcome this resistance. In contrast, it has been studied that cancer cells can develop resistance to alkaloids [9].

Moreover, the synergistic effects of combining these alkaloids with other treatments suggested that combining *C. roseus* alkaloids with other therapeutic agents could enhance efficacy, but it is necessary to clarify optimal doses for therapeutic [12]. *C. roseus* produces a unique set of alkaloids, including vinblastine and vincristine, which have been used in cancer treatment. A recent study identified new alkaloids such as catharoseumine and 14′,15′-didehydrocyclovinblastine, which exhibit significant anti-cancer properties [10]. These compounds show potential therapeutic benefits, particularly in inhibiting the growth of cancer cell lines.

Pham *et al.* also provided deeper insights into three mechanisms of *C. roseus* alkaloids. Firstly, apoptosis induction triggers programmed cell death in cancer cells. Secondly, cell cycle arrest halts the proliferation of cancer cells at specific stages of the cell cycle. (3) Inhibition of Angiogenesis: Preventing the formation of new blood vessels that supply nutrients to tumors. Compounds derived from *C. roseus* can have synergistic effects when used in combination with other cancer therapies. This synergy can enhance the efficacy of treatment protocols, potentially leading to better outcomes for patients [10]. Advances in targeted delivery systems have significantly improved the precision and efficacy of *C. roseus*-derived treatments. These systems allow the delivery of alkaloids to cancer cells, minimizing side effects and enhancing therapeutic outcomes [10, 14].

Research from 2020 has proposed new strategies to overcome resistance mechanisms in cancer cells. These strategies involve using *C. roseus* alkaloids in combination with other agents to bypass or counteract resistance pathways, making them a promising candidate for combination therapies [10].

In order to address these research gaps and highlight the insights and prospects of the cancer-fighting properties in *C. roseus*. In this review, we focus on the isolation of cancer-fighting properties from *C. roseus*, the insights underlying the molecular mechanism of cancer cell inhibition, and use of the components as potential therapeutics and their further pharmacological significance.

CANCER-FIGHTING PROPERTIES IN *C. roseus*

Several potential metabolites have been isolated from *C. roseus*, which are presented in Figure 1. Vinblastine and Vincristine are the primary bioactive alkaloids derived from *C. roseus*. Vinblastine has been used in treating Hodgkin's lymphoma, breast cancer, and testicular cancer [12]. Vincristine is effective against acute lymphoblastic leukemia and Hodgkin's disease [15]. Both vinblastine and vincristine were involved in inhibiting the formation of the mitotic spindle, which is crucial for cell division [16]. This action prevents cancer cells from proliferating, thereby slowing down or stopping tumor growth [16].

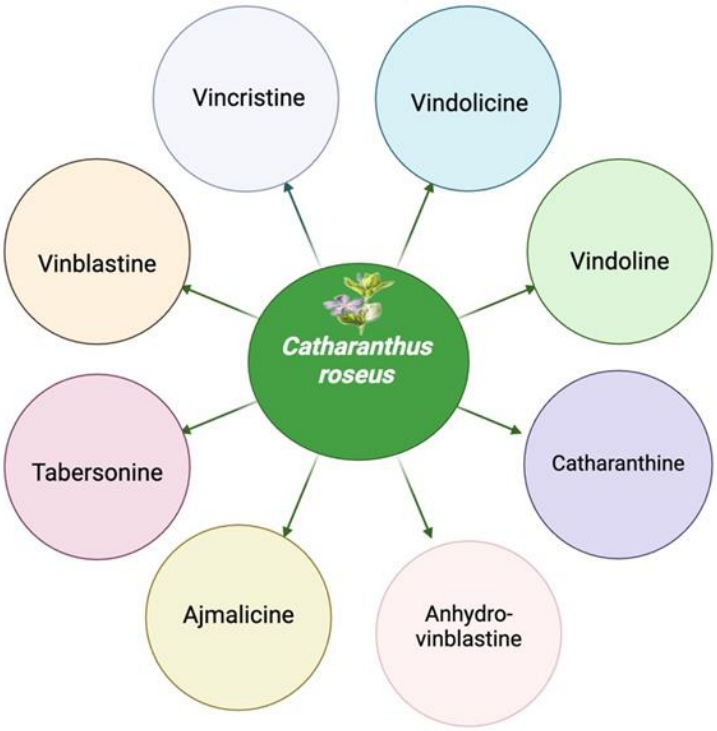

Figure 1. The potential metabolites found in *Catharanthus roseus*. The representative figure presents a total of nine metabolites, which are involved in anticancer and antioxidant potential. This figure was drawn with the BioRender tool (https://www.biorender.com/).

Vinblastine works by binding to tubulin, a protein that is essential for microtubule formation. Microtubules are crucial for cell division as they form the mitotic spindle, which separates chromosomes during mitosis. Vinblastine prevents the formation of microtubules that lead to tubulin polymerization, thereby arresting cells in the metaphase of mitosis (Figure 2). This disruption leads to cell death, particularly in rapidly dividing cancer cells. Vincristine has a similar mechanism of action to Vinblastine (Figure 2). It also binds to tubulin and inhibits microtubule formation. However, Vincristine is particularly effective in treating certain types of leukemia and lymphomas. By preventing microtubule assembly, Vincristine disrupts the mitotic spindle, leading to cell cycle arrest and apoptosis (programmed cell death) in cancer cells (Figure 2).

Table 1. List of key cancer-fighting properties in *C. roseus.*

Metabolites/properties	Extraction process	Key outputs	References
Vinblastine	Alkaloid extraction from leaves	Used in chemotherapy for Hodgkin's lymphoma and breast cancer	[12]
Vincristine	Alkaloid extraction from leaves	Effective against leukemia and lymphoma	[17]
Vindoline	Solvent extraction	Precursor for vinblastine and vincristine synthesis	[18]
Catharanthine	Solvent extraction	Precursor for vinblastine and vincristine synthesis	[18]
Ajmalicine	Alkaloid extraction from roots	Antihypertensive and anticancer properties	[18]
Serpentine	Solvent extraction	Anticancer and antimicrobial properties	[19]
Vindolicine	Solvent extraction	Potential anticancer activity	[20]
Vindogentianine	Solvent extraction	Potential anticancer activity	[21]

EXTRACTION PROCESSES AND PHYSICOCHEMICAL PROPERTIES OF *C. roseus*

The toxic solvent wastes produced by several industrial operations have negative impacts on thyroid, hematological, and respiratory health [22]. Thus, the proper extraction processes of potential compounds are highly demandable. The separation of the bioactive component using water as the solvent is an alternate technique. Nevertheless, the component must be extracted using water that is heated to a high temperature. The purity of the extract and the targeted bioactive component may both suffer from the extraction's increased temperature. Additionally, the water extraction procedure took an extended period to finish the extraction procedure [23].

Vinblastine and vincristine are the key dimeric indole alkaloids that are frequently employed in cancer treatment, are produced in low quantities by *C. roseus*. Eli Lilly originally discovered techniques for extracting and purifying a number of the alkaloids present in *C. roseus* using organic solvents [24]. There are four processes in these sulphuric acid and water extraction techniques, including fractionation by partition with benzene, two chromatographic columns, and crystallization in ethanol. Extensive progress has been made related to extracting vindoline, catharanthin, and vinblastine from *C. roseus* leaves utilizing ultrasonic extraction, methanol, heat, boiling, and refluxing. The use of supercritical fluid extraction (SFE) to extract phytochemicals from *C. roseus* has also been used [24].

MECHANISM OF BIOACTIVE COMPOUNDS OF *C. roseus* AGAINST CANCER

Indole alkaloids produced by *C. roseus* are known as Vinka alkaloids and are frequently used as antimitotic medications to treat cancer. Natural compounds like vincristine and vinblastine are anticancer compounds applied in clinical trials [25]. Vinca alkaloids change the kinetics of the microtubules, causing apoptosis and suppressing the development of cells. These microtubules (MTs), known as cytoskeleton elements and important parts of the spindles that separate the chromosomes amid meiosis and mitosis, are also crucial for preserving cell shape, transport, and a variety of other cellular functions [26]. Tubulin and tubulin heterodimers, which dynamically polymerize and depolymerize at the edges, are the fundamental building blocks of the MTs; The interaction of tubulin and guanosine 5-triphosphate (GTP) controls the formation and breakdown of the MT polymers, also known as treadmilling and dynamic instability, and any destabilization or interruption of this interactions can stop the cell cycle and cause programmable cell death or apoptosis [27]. Due to this, two categories of destabilizers

have been identified. The first category includes substances that stabilize MTs and hinder depolymerization, whereas the second category includes substances that depolymerize MTs and hinder their formation [28]. Vinca alkaloids and their analogy work by attaching to two tubulin heterodimers at the outermost layer near the convertible GTP-binding region and depolymerizing the MTs to stop the progression of tumor cells amid mitosis [29](Figure 2). Although the apparent propensity of the two indigenous Vinca alkaloids from *C. roseus* or their partially synthetic counterparts and analogy for tubulin heterodimers is identical, it is distinguished by an additional sequence of a reduction in the overall equilibrium constants: Vincristine is followed by Vinblastine, Vinorelbine, and Vinflunine. Via shared docking premises, van der Waals forces and electrostatic interaction energy consolidate the combined structures of these alkaloids with, α, β-tubulin.

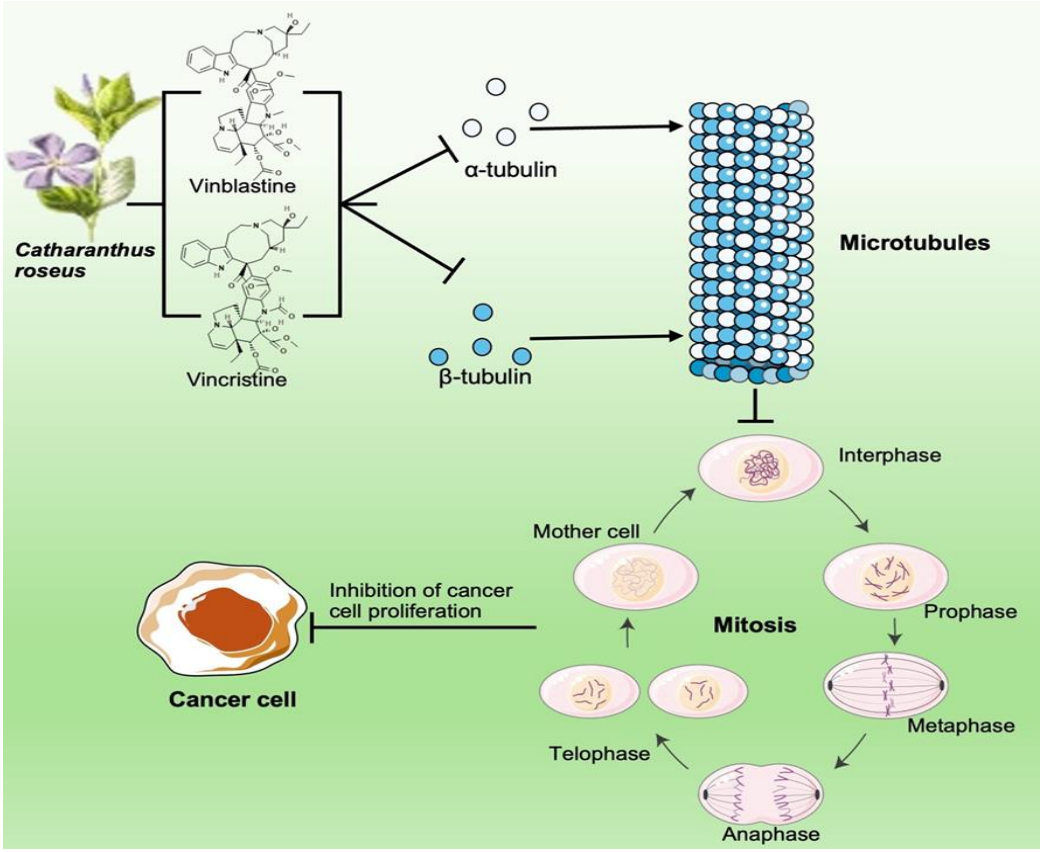

Figure 2. Mechanism of action of Vinblastine and Vincristine against cancer cells. Vinblastine and 86 vincristine combat cancer by targeting microtubules within the cell. They bind to tubulin, an 87 protein that forms microtubules, disrupting their dynamics. This interference halts cell division, 88 leading to mitotic arrest and ultimately causing cancer cell death. The chemical structures are adapted from the National Center of Biotechnology Information (https://pubchem.ncbi.nlm.nih.gov/).

Additionally, the two fluorine atoms that distinguish vinflunine from vinorelbine increase this electrostatic connection in the context of vinflunine [30], the vindoline region then ensures tubulin heterodimers' interaction, as the catharanthine region provides the cytotoxic impact [22]. According to some publications, vinca alkaloids work in a dose-dependent manner, preventing cell division when present in low concentrations. The cells then perish over an extended period of incubation. Nevertheless, at high concentrations, vinca alkaloids cause cell death by causing the production of paracristals (giant tubulin polymers), which prevent tumoral cells from undergoing mitosis [31]. Numerous scientists have lately reported on new modes of action for these

alkaloids, which include interactions with MTs-associated proteins, calmodulin, and the inhibition of amino acid metabolism [32]. Using this novel method of action, nevertheless, variations in Vinca alkaloids' potency were found. Then, although having a lesser affinity for tubulin than vinblastine or vincristine, vinflunine's superior activity against murine tumors and human tumor xenografts can be explained by its interaction with calmodulin. The monoterpenoid indole alkaloid catharoseumine, which was isolated from the *C. roseus* plant, has a distinctive peroxy bridge moiety and exhibits cytotoxicity when tested on human tumor cell lines, albeit with modest cytotoxicity when tested on the HL-60 cell line.

SYNTHESIS OF ANTI-CANCER AGENTS FROM *C. roseus*

Extensive progress has been made in the culture of plant cells for more effective synthesis of anticancer substances. These approaches open several new benefits, including the ability to produce bioactive pharmaceuticals with purification processes, a highly effective production system in short duration, and a well-controlled manufacturing process under sterile circumstances. The *C. roseus* has shown potential to produce high-value pharmaceuticals in recent years utilizing submerged growth techniques that either use shake flasks or various forms of bioreactors [33]. It has been demonstrated that hairy root lines of *C. roseus* may be grown in bioreactors of various sizes for the large-scale synthesis of ajmalicine, serpentine, and catharanthine [34]. Vincristine and vinblastine, two more promising anticancer bioactive agents, were effectively synthesized in stirred tank bioreactor system. These alkaloids were produced at their maximum levels when the pH was unregulated, and the aeration rate was 0.5 v/v/min. The vincristine and vinblastine were produced 13.47 and 7.94, respectively [35].

The synthesis of alkaloid compounds rises with the presence of a chemical that induce stresses to cells. According to the report, the addition of relatively small amounts of chromium to culture media (between 10 and 100 M), was found to decrease cell proliferation, while vinblastine and vincristine synthesis also significantly increased [36]. The incorporation of sodium chloride into cultures to induce osmotic pressure can also result in different stress signaling, enzyme functions, and a rise in the generation of vinblastine and vincristine [37]. Another study revealed the addition of the *Aspergillus flavus* fungal elicitor significantly stimulated cell proliferation and increased the synthesis of vinblastine and vincristine [38]. However, one recent study showed that the supplementation of yeast extract to culture media, even at low concentrations (1.5g/L), significantly increased the levels of vinblastine and vincristine in suspension cultures of *C. roseus* [39].

PROSPECTS AND LIMITATIONS OF USING *C. roseus*

The current study confirms the extraction and isolation processes of several alkaloids including vinblastine, and vincristine, which have potent anticancer and antidiabetic properties. However, further study is required on their anticancer activities and underlying molecular mechanisms. Nanotechnology-based synthesis of these properties and formulations opens new prospects for enhancing the efficacy of cancer treatment. In contrast, toxicity concerns of the potential alkaloids and the limitations of their application should be screened properly. The extraction process of bioactive compounds should be improved, and a strategy needs to be applied to reduce pharmaceutical costs, although it remains a challenge to optimize. In addition, the alkaloid-associated side effects must be addressed properly. The solution to these limitations with the potential

development of disease suppression or inhibition of cancer cell growth could open new horizons for *C. roseus*-based therapy against cancer.

CONCLUSIONS

This study explored the potential vinca alkaloids found in *C. roseus*, and their prospects of use as anticancer compounds, and mechanical insights of vincristine and vinblastine involving inhibition of cancer cell proliferation, and the prospects of enhancing potential alkaloid synthesis using bioreactor approach. This updated study further suggests the potential alkaloids isolated from *C. roseus*, show their pharmaceutical significance with the development of *C. roseus*-derived cancer drugs. The prospect of efficient cultivation in bioreactor-based large-scale production of these potential compounds would be an excellent source of sustainable raw materials supply for the pharmaceutical industry in producing high-quality anticancer agents. Considering these potential benefits of C. *roseus*, might be considered a natural powerhouse and used as a cancer therapeutics and patient care.

AUTHOR CONTRIBUTIONS

MJI and MK designed the study. SS and SRS wrote the initial draft and prepared tables and figures. MJI edited and reviewed the whole manuscript. All the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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