

# Immunomodulatory and Pharmacological Properties of *Catharanthus Roseus*: A Comprehensive Review

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**Abstract:** *Catharanthus roseus* (*C. roseus*), known as the factory of medicine, is a tropical plant species native to Madagascar but has been introduced and naturalized in many other parts of the world. It is known for its medicinal properties and has been used for centuries to cure a variety of illnesses in different parts of the world. *C. roseus* is a well-known medicinal herb that provides a variety of outstanding health advantages. It consists of various bioactive compounds, including polyphenols, alkaloids, flavonoids, phytosterols, and carotenoids. Some signature compounds, including vincristine, vinblastine, ajmalicine, reserpine, serpentine, lochnericine, strictosidine, and vindoline, added more value to this plant. These bioactive compounds have several bioactive functions, such as anti-diabetics, antimicrobials, anthelmintics, antioxidants, antiulcer bactericides, anti-hypertensives, and anti-cancer agents. In this review, we summarize the most recent pharmacological activities, conventional uses, phytochemistry, medicinal functionality, bioactive compounds, immune-modulatory activities, and toxicological effects of *C. roseus*.

**Keywords:** *Catharanthus roseus*; cancer; diabetes; immunomodulation; alkaloids.

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## 1. Introduction

*Catharanthus roseus* (*C. roseus*), commonly known as the factory of medicine, is also named Madagascar periwinkle [1]. It is a flowering plant member of the family Apocynaceae and is broadly cultured as a pretty plant due to its attractive, long-lasting flowers [2]. It was found in Madagascar, in the Indian Ocean Island. Worldwide, it is found in tropical and subtropical regions like India, Pakistan, Malaysia, Bangladesh, and Australia [3]. It is native to Madagascar, though it has grown somewhere else as an ornamental and medicinal plant. *C. roseus* is a significant medicinal plant with abundant sources of amazing health benefits. It contains more than 350 bioactive compounds in pharmaceuticals, agrochemicals, food additives, and pesticides [4,5]. These bioactive compounds have several functions, including anti-diabetic, bactericide, antiviral, anti-helminthic, anti-hypertensive, anti-cancer, anti-malaria etc [6]. Ajmalicine is a significant compound utilized as an anti-hypertensive, and another compound named serpentine is used against neuro-inflammatory drugs. Vindolicine is utilized for the production of antidiabetic medicines, while yohimbine, a product of *C. roseus*, is primarily used in erectile dysfunction treatments. The *Catharanthus* alkaloids protect against

microbial infection and have a broad impact on clinical medicine due to the treatment of hypertension. This plant contains two important compounds, vincristine and vinblastine, which are constituents of drugs used to treat cancer [7,8]. *C. roseus* become a preferred area of research interest because of its broad range of pharmacological activities along with its history of treating life-threatening diseases. In this review, we summarize pharmacological activities and analyze the traditional applications, phytochemistry, pharmacological activities (in vitro, in vivo, and clinical studies), and toxicity of various extracts, established medicine, and compounds from *C. roseus*.

**Traditional uses and ethnopharmacology:** *C. roseus* has been used for medicinal purposes for centuries, particularly in traditional Ayurvedic and Chinese medicine. Its extracts have been utilized to treat various ailments, including diabetes, cancer, etc. In 1910, Peckolt recorded the usage of an infusion of the leaves in Brazil to prevent hemorrhage and scurvy, as a mouthwash for toothache, and to treat and clean chronic wounds. It has been used to treat diabetic ulcers in the British West Indies and has been described as an effective oral hypoglycemic medication in the Philippines [9]. *C. roseus* G. Don contains vinca alkaloids, which are broadly used for their medicinal value. Vinca alkaloids found in *C. roseus* G. Don are widely used for their therapeutic potential. Vinca alkaloids have been employed as disinfectants for diabetic and high blood pressure treatments [10]. Vinca alkaloids are the second-most popular class of cancer drugs, and they will continue to be used for cancer [11].

## 2. Methodology

A literature-based search was performed to reclaim information on the phytochemistry, health effects, molecular pharmacology, herb-drug interaction, and safety of *C. roseus*, and literature was collected from accessible online databases, such as PubMed, Web of Science, Scopus, and Google Scholar, using the key search terms of '*Catharanthus roseus*', and chemical constituents, antioxidant, anti-inflammatory, immunomodulatory, neuroprotective, cardio-protective, anticancer, etc. This review covers those articles that describe the pharmacological properties of *C. roseus* alone or its compounds or both.

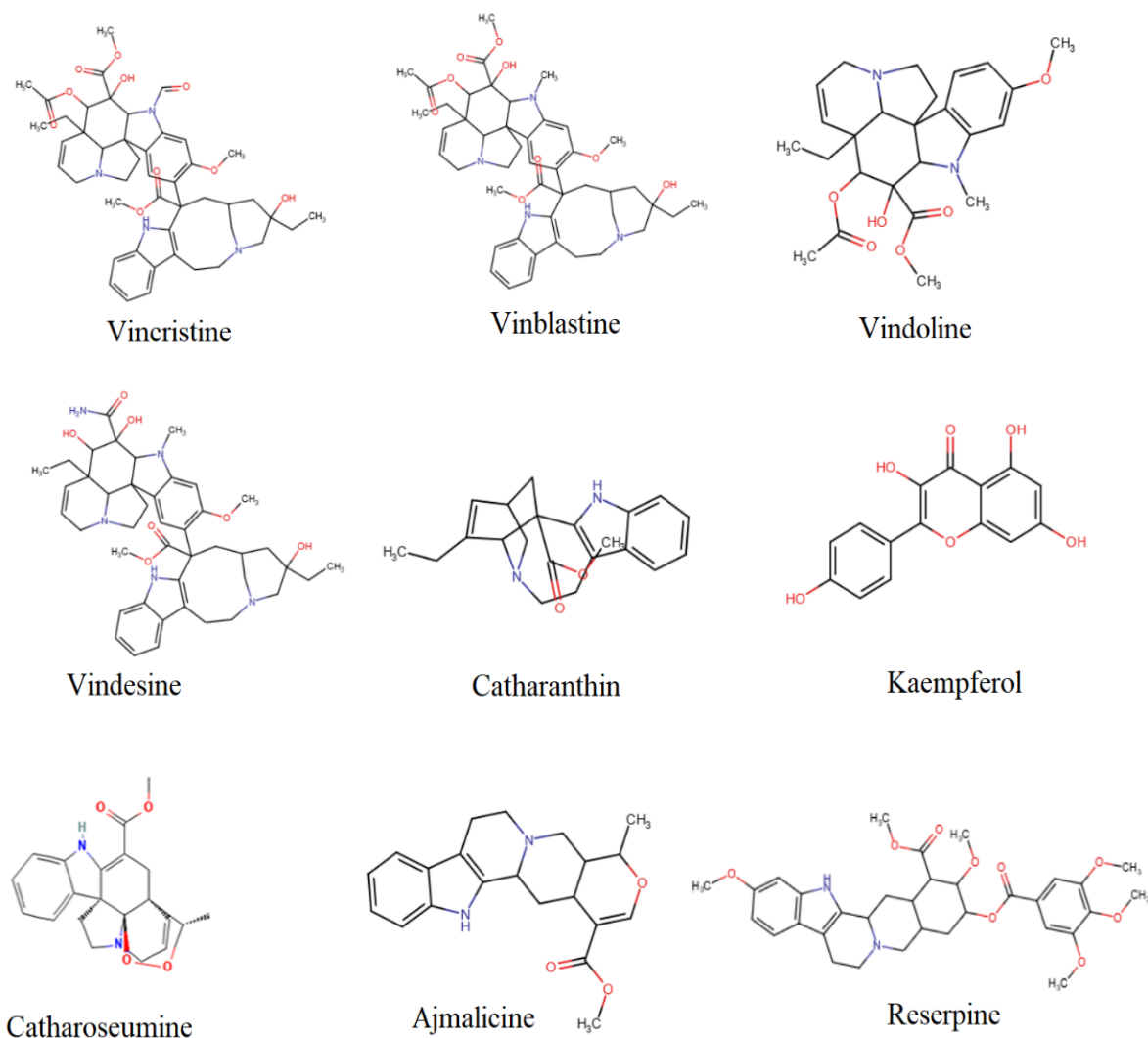
## 3. Evolution of Trends in Research with *C. roseus*

*C. roseus* has a long history of traditional use in treating various ailments, including diabetes, malaria, cancer, and Hodgkin's lymphoma. Researchers found many alkaloids in *C. roseus* in the 1950s and 1960s, including vincristine and vinblastine. These alkaloids were discovered to have powerful anti-cancer capabilities, and they were later developed into chemotherapeutic medications for treating leukemia and other cancers [12]. Vinorelbine and vindesine are two vinca alkaloids that were partially synthesized by researchers in the 1980s and 1990s. Potier's team discovered the anti-cancer medication Navelbine, another name vinorelbine, ten years after discovery was commercialized in 1989 [13]. In comparison to the original alkaloids, it was discovered that these derivatives had enhanced anti-cancer effectiveness and decreased toxicity.

The biosynthesis processes of the Vinca alkaloids found in *C. roseus* were first studied in the 1990s and 2000s. The results of this study gave information on the control of these pathways as well as the identification of numerous important enzymes involved in the production of alkaloids [14]. In the 2010s and 2020, researchers have concentrated on enhancing the synthesis of vinca alkaloids in *C. roseus* using genetic engineering and synthetic

biology [15]. This involves initiatives to enhance the expression of genes involved in the biosynthesis of alkaloids, enhance the growth and development of plants, and design new manufacturing routes for novel alkaloids [16,17].

Phytochemical profile: *Cantharanthus roseus* is rich in alkaloids, carbohydrates, flavonoids, triterpenoids, tannins, saponins, coumarin, quinone, and phenolic compounds [18,19]. Different parts of this plant, like roots, stems, leaves, flowers, etc., contain the essential chemical constituents. Many essential phytoconstituents of *C. roseus* such as vinblastine, vindoliscine, vincristine, Vindensine, leurosine, ajmalicine, reserpine, vincoline, leurosidine, vinacardine, catharanthamine, vincardine, tabersonine, etc [3]. *C. roseus* contains significant types of alkaloids (Table 1), among them vinblastine and vincristine, two alkaloids that are used in chemotherapy to treat different tumors [20]. These alkaloids impede cell division, which is important for developing cancer cells. Flavonoids like quercetin and kaempferol have been discovered in *C. roseus* antioxidants, and their anti-inflammatory and anti-cancer properties have been attributed to these compounds. Ajmalicine is used as anti-hypertensive [1,21]. The anthocyanins in *C. roseus* include anthocyanins found in *C. roseus*, which are responsible for the plant's pink and purple coloration. Some of the key compounds are illustrated in Figure 1. These compounds have been found to have antioxidant properties and may help protect against certain diseases.



**Figure 1.** Crucial compounds of *C. roseus* (vincristine, vinblastine, vindoline, vindesine, catharanthin, kaempferol, catharoseumine, ajmalicine, reserpine).

**Table 1.** Key functions of significant compounds in *C. roseus*.

Compounds	Function	References
Vinoceptine derivative	Vinopocetine has the functional property of improving brain function and memory	[40]
Catharoseumine	considered as a potential inhibitor against falciparum-2 protozoa parasites (causes of malaria)	[38]
Vinolbine, vincristine, vinblastine, vindesine.	act as cancer-fighting agents	[11,29,41]
vindoline	utilized in the development of antidiabetic drugs	[34]
Vincristine	inhibits the formation of microtubules, which leads to cellular death and the arrest of mitosis	[42,43]
Vincamine and Vindoline	Have properties to treat ulcer	

## 4. Pharmacological Activities

### 4.1. Anti-cancer activity.

Worldwide, cancer is a mortal illness that hurts people in the most heinous manner, the most common cause of death. Although there has been great improvement in recent decades, cancer treatment is still a mystery. However, nature always finds a way to keep things in balance, and we have the good fortune of plants providing incredibly promising anti-cancerous properties. *C. roseus* alkaloids have proven to be the most effective higher plant substance in cancer like breast cancer, leukemia, and Hodgkin’s lymphoma [22,23]. *C. roseus* alkaloids are the most successful plant drugs (Table 2) utilized in cancer treatment. *C. roseus*, in particular, contains vinca alkaloids, the second most popular class of cancer drugs, and they will continue to be used to treat cancer [24]. The vinca alkaloids are essential as anti-cancer agents. In clinical settings, there are some main vinca alkaloids: Vinolbine, vincristine, vinblastine, and vindesine. Additionally, the European Union has approved the use of vinflunine, a new synthetic vinca alkaloid, to treat second-line urothelial transitional cell carcinoma [11]. Vinblastine is sold as Velban and Vincristine as oncovin drugs [25].

**Table 2.** Marketed drugs derived from *C. roseus* are used in cancers.

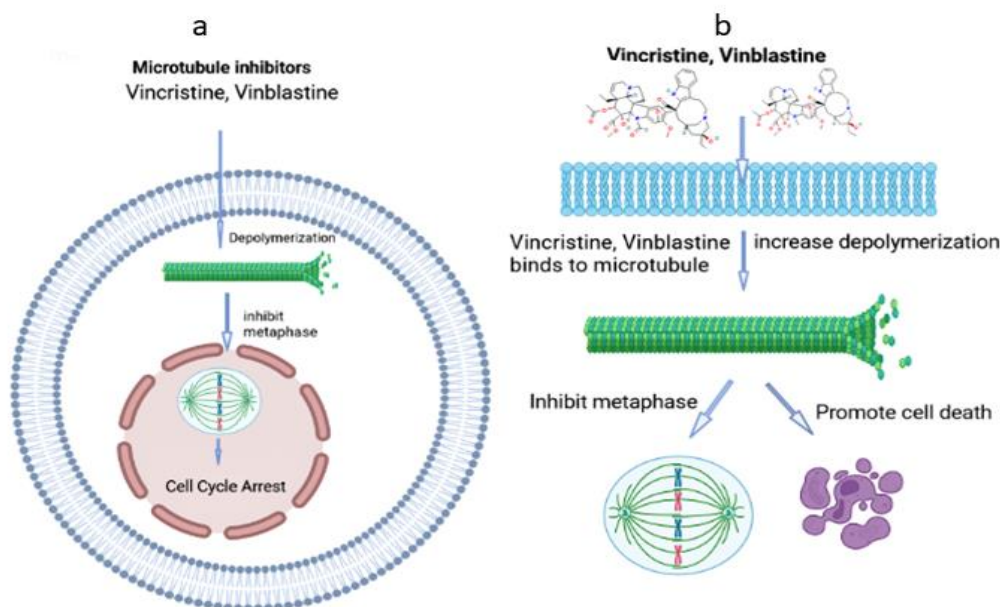
Alkaloids	Mode of action	Trade name	Function	References
Vinblastine	Binds to tubulin prevent microtubules from developing anti-mitotic	Velban	Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, melanoma, and testicular cancer	[44]
Vinblastine sulphate		Oncovin		[41]
Vincristine	Clings to tubulin prevent microtubules from developing anti-mitotic	Marqibo	Hodgkin's lymphoma, breast cancer	[43]
Vindesine	Antibiotic	Eldisine	Cancer	[45]

The mechanism of the action of these alkaloids has been disclosed by scientists. Microtubules have long been seen as an excellent target for anticancer medications due to their crucial function in mitosis, where they construct the dynamic spindle apparatus [26]. Microtubules constitute the majority of the cytoskeleton of eukaryotes. These heterodimers of alpha and beta tubulin interconvert between stages of rapid growth (polymerization) and shrinking (depolymerization). Microtubules are essential for maintaining cell shape and motility, properly segregating chromosomes during mitosis, and intracellular transport of macromolecules and organelles during the interphase [27]. Microtubules play special roles in both mitotic and interphase cellular functions.

The major mechanisms of vinca alkaloid cytotoxicity include interactions with tubulin and disruption of microtubule function, particularly of microtubules that comprise the mitotic spindle machinery, resulting in metaphase arrest. Vincristine inhibits the formation of microtubules, which results in cellular death and mitosis arrest, as shown in Figure 2. Existing research suggests that two vinca alkaloid binding sites exist per mole of tubulin dimer [11]. Vincristine binds to the tubulin-beta subunit at a distinct region called the Vinca-binding domain, the precursor protein of microtubules responsible for mitosis and other vital cellular functions like substrate transport, cellular mobility, and structural integrity [28].

Per mole of tubulin dimer, there are two Vinca alkaloid-binding sites. Depending on whether the binding sites are found at the microtubule ends or on the microtubule surface, vinca alkaloids bind to their binding sites in intact microtubules with varied affinities. There are around 16 to 17 high-affinity binding sites at the ends of each microtubule. Vinca alkaloids disrupt microtubule assembly by attaching to these sites. However, the main effect of low drug concentrations is to slow down the rates of growth, also shortening at the assembly (plus) end of the microtubule, producing a "kinetic cap" and inhibiting function. The Vinca alkaloids have disruptive effects on microtubule dynamics, leading to metaphase arrest at doses below those that decrease microtubule mass [29].

In addition to lymphosarcoma, choriocarcinoma, neuroblastoma, and carcinoma of the breast, lungs, and other organs in acute and chronic leukemia, vinblastine sulfate is used to treat Hodgkin's disease. Vincristine sulfate inhibits mitosis in the metaphase and is particularly successful in treating pediatric acute leukemia and lymphocytic leukemia. It is also used to treat Hodgkin's lymphoma, Wilkins' lymphoma, neuroblastoma, and reticulum cell sarcoma. Vinblastine has also been structurally changed to produce diacetyl vinblastine amide (Vindesine), which was recently released as Eldisine for the treatment of pediatric acute lymphoid leukemia. Catharanthine and Vindoline alkaloids are also biochemically coupled to form dimeric molecules [30].



**Figure 2.** Mechanism of action of microtubule inhibitory drugs on cell cycle arrest against cancer treatment.

#### 4.2. Anti-diabetic activities.

A worldwide condition, diabetes mellitus impairs quality of life and triggers a number of other serious illnesses. Moreover, Natural products have a variety of molecular pathways,

including those that promote cell regeneration, inhibition of alpha-glucosidase, insulin mimicking, sodium-glucose co-transporters, and oxidative stress [31]. Glycogen synthase, glucose 6-phosphate dehydrogenase enzyme activities were discovered to be decreased in the liver of mice with diabetes; however, following 7 days of treatment with extract at doses of 500 mg/kg, these enzyme activities would considerably improve. Results indicated the increased metabolization of glucose in treated rats 'As a result of the liver's increased glucose utilization, hypoglycemic activity has developed. The extracts of leaves and flowers from ethanol solvent showed that a dose-dependent lowering of blood sugar is comparable to the effect of the marketed medication [22].

Another preclinical investigation into the anti-hyperglycemic activity of *C. roseus* was conducted. Male Wistar rats were injected intraperitoneally with 55 mg streptozotocin for 1kg body weight to induce diabetes. Four groups of animals were created: control, control-treated, diabetic, and diabetic-treated. Every day, 100 mg/kg of body weight was given for 60 days via oral administration of *C. roseus* leaf powder suspension in 2 ml of distilled water to diabetic and control rats. In diabetic rats (D-group), plasma glucose was steadily increased while plasma insulin progressively increased. After 15 days, an increase in plasma insulin and a drop in plasma glucose were detected in the diabetic-treated group. At the end of the study period, plasma glucose had nearly returned to normal levels, but insulin had not. In diabetic-treated rats, the considerable increase in plasma total cholesterol, triglycerides, LDL, and VLDL-cholesterol was corrected. *C. roseus* administration reduced the decreased hepatic and muscular glycogen content and changes in the activity of enzymes of glucose metabolism found in diabetic control rats. These findings suggest that *C. roseus*, with its anti-diabetic and hypolipidemic qualities, could be a promising natural treatment for diabetes [32].

The study aimed to investigate the anti-diabetic effects of an ethanolic extract of *C. roseus* and the expression of the GLUT-2 and GLUT-4 genes in diabetic Wistar rats. The doses were delivered orally to STZ-induced diabetic rats treated with extract of *C. roseus* 100 mg/kg and 200 mg/kg, and one group was treated with Metformin 100 mg/kg. After four weeks of treatment, fasting blood samples were taken, and body weights (BW's) were determined. The glucose transport system in the liver was detained for four weeks. In isolated islets of Langerhans, the observed association between intracellular calcium and insulin release levels was strong and positive. The supplementation of *C. roseus* extracts dramatically increased GLUT gene mRNA expression detected by real-time PCR in the livers of diabetic rats [33].

In a different investigation, the pancreatic RIN-5F cell line was grown in the absence of glucose, at low and high glucose concentrations, and extracts of *C. roseus* and vindoline were tested for alpha-glucosidase and alpha-amylase inhibitory activities as well as insulin secretory effects. Vindoline dramatically increased insulin secretion in vitro and had detectable antioxidant action compared to ascorbic acid [10]. When glucotoxicity-induced cells were treated with vindoline, methanolic, and dichloromethane extracts, intracellular reactive oxygen species formation was considerably reduced compared to the high glucose untreated control. Compared to acarbose, plant extracts had weaker inhibitory effects on the activity of enzymes that help break down carbohydrates. Additionally, the plant extracts had little alpha-glucosidase and alpha-amylase inhibitory effects [34].

Alkaloids extracted from *C. roseus* have been examined pharmacologically for their ability to lower blood sugar levels, and a product made from the plant that treats diabetes is marketed under the brand name Vinculin [9].

Vincristine, one of the important alkaloids found in *C. roseus*, has been demonstrated to have insulin-mimetic effects. The cells take up and use more glucose due to it attaching to the insulin receptor and activating the same signaling pathways as insulin. Another alkaloid called vinblastine inhibits enzymes alpha-glucosidase and alpha-amylase, which break down complex carbs into glucose. Vinblastine decreases postprandial hyperglycemia by blocking these enzymes, which slows down the rate at which glucose is absorbed from the gut.

In addition, *C. roseus* contains flavonoids such as quercetin and kaempferol, which have been shown to have antioxidant and anti-inflammatory properties. Chronic inflammation and oxidative stress are known to contribute to the development of diabetes and its complications. By reducing inflammation and oxidative stress, these flavonoids may help to lower the incidence of diabetes complications and increase insulin sensitivity.

#### 4.3. Antioxidant property.

Antioxidant properties are mostly present in the roots and also present in the leaf, flower, and stem as determined by several assays such as DPPH radical-scavenging, peroxide radical-scavenging activity, and nitric oxide radical inhibition. Complementary antioxidant activity can be found in *C. roseus*. Diseases brought on by free-radical oxidative stress may benefit from this treatment [35,36]. *C. roseus* has the capacity for oxidative defense. Increases in oxidative stress correlate with changes in oxidative stress indicators, such as decreased glutathione levels. *C. roseus* was discovered to have a somewhat beneficial effect (15%) on increasing glutathione levels in several experimental circumstances [23].

#### 4.4. Antimicrobial activity.

Since most bacterial infections increase their resistance to many of the known antimicrobial medications, vinca has tremendous therapeutic potential and aids in developing innovative pharmaceuticals. Additionally, the plants include natural chemotherapeutic agents that imply a wide range of actions focusing on prevention. Significant amounts of substances, including coumarin and quinones, are thought to have antibacterial activity in the stem and root of *C. roseus* [18].

#### 4.5. Antiviral activity.

The findings showed that the *C. roseus* extract included a phytochemical component with potential antiviral action that was not cytotoxic to cells.

The *C. roseus* extract contains a phytochemical component with potential antiviral action that is not cytotoxic to cells but has antiviral activities. Plaque reduction experiments against HSV-1 revealed that the extract of *C. roseus* had 36, 20, and 4.7 as its selective indices (SI = CC50/EC50), respectively, in post-treatment, pre-treatment, and virucidal assays [37]. Catharanthus has been shown to have antiviral properties against the herpes simplex virus (type I). In this case, antiviral characteristics with a cytopathogenicity effect were at 0.8 g/mL. With an IC<sub>50</sub> value of 4.06 M, the monoterpenoid indole alkaloid catharoseumine has been found as a possible inhibitor against falciparum-2 protozoa parasites (malaria causes cytotoxicity test against Vero cells revealed that the CC50 value for the crude extract of *C. roseus* was 0.5 mg/mL using MTT assay [38].

#### 4.6. Enhancement of memory.

*C. roseus* was shown to have AChE-inhibitory effects comparable to those of galantamine and other already approved AD therapies and is of special interest to AD sufferers. Leaf extracts were demonstrated to have anti-cholinesterase action, with an inhibitory effect on AChE at a concentration of 422 g/ml [23,39]. Vinoceptine is a synthetic analog of the vinca alkaloid vincamine. Alzheimer's disease can be helped by an alkaloid called vinoceptine, which has the ability to enhance memory and brain function [40]. In clinical studies for dementia and stroke, vinpocetine at a dosage of up to 60 mg/d was well tolerated and showed no signs of serious side effects.

### 5. Immunomodulatory Effects of *C. roseus*

The immune system is essential for defending the body against viruses and other dangerous elements. Yet, immune-related illnesses, including cancer, allergies, and autoimmune disorders, can develop as a result of immune system dysregulation. Thus, one of the most important treatment approaches for many disorders is immune system modification. Alkaloids, flavonoids, terpenoids, and phenolic compounds, among others, have been demonstrated to have immunomodulatory effects among the bioactive substances found in *C. roseus* (Table 3).

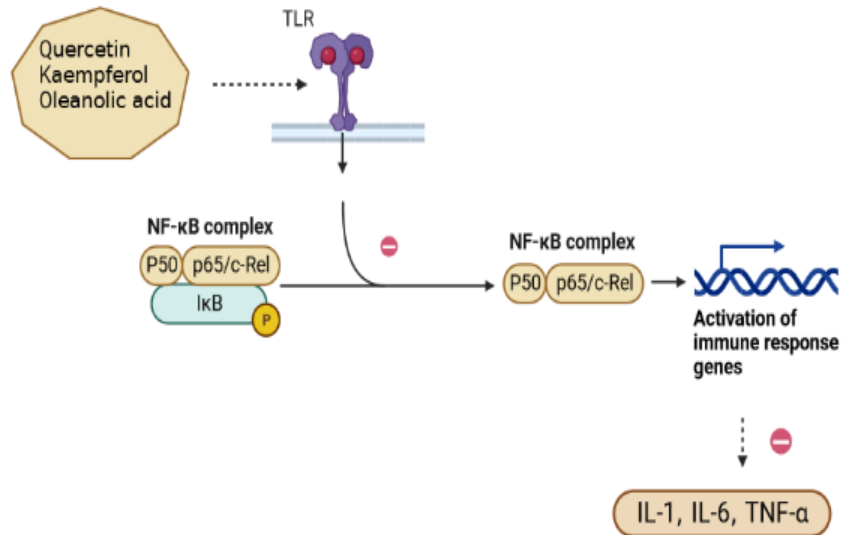
**Table 3.** Compounds from *C. roseus* exhibit immunomodulation.

SI	Immunomodulators	Chemical class	Mechanism	References
1	Capsaicin	Hydrophobic alkaloid	inhibits antigen-specific T cells in pancreas-draining lymph nodes and the nF- $\kappa$ B pathway.	[49]
2	Kaempferol	Flavonoid	inhibits STAT-1 and NF-B activation	[51,52]
3	Quercetin	Flavonoid	inhibits wnt1, c-Myc, cyclin d1 and axin1. downregulates the expression of nF- $\kappa$ B. Mitigates phosphorylation of akt, s6, and P70s6K.	[52,53]
4	Oleanolic acid	Pentacyclic triterpenoid	inhibits MaPK and nF- $\kappa$ B pathways	[48]

Nowadays, cytotoxic drugs are used for cancer chemotherapy. With the advantages of these drugs in treating tumor cells, most of them can also affect non-tumor cells by showing carcinogenic and teratogenic effects. In an effort to find chemotherapeutic treatments with minimal or no adverse effects, *C. roseus* showed promise in a trial. Few studies have examined the effects of crude aqueous extract of *C. roseus* on peripheral blood mononuclear cells (PBMCs). A study analyzed the anticancer chemicals found in the crude extracts to determine whether this drug may potentially act on Jurkat cells (cancer cells, a leukemic T-cell line). The cytotoxic effects of the extract on PBMCs were also investigated. *C. roseus* crude extract strongly suppressed the growth of Jurkat cells, but it promoted the proliferation and activation of normal PBMCs [46]. Extracts of *C. roseus* exhibited immunomodulatory effects in mice by boosting the generation of white blood cells and improving the phagocytic activity of macrophages.

For instance, it has been shown that flavonoids like kaempferol and quercetin have anti-inflammatory effects (Figure 3) by preventing the synthesis of pro-inflammatory cytokines like interleukin-1 and tumor necrosis factor [47]. The potential of *C. roseus* in immune-related disorders has been looked at in a number of research studies. Extract of *C. roseus* exerted immunomodulatory effects on human dendritic cells by raising the expression of co-stimulatory molecules and improving cytokine production.

Another study discovered that *C. roseus* extract reduced the production of pro-inflammatory cytokines, including IL-1 and IL-6, in lipopolysaccharide-stimulated RAW264.7 macrophages. IL-1, IL-6, and TNF- $\alpha$ , which are crucial immune response mediators, have all been observed to be produced in greater quantities when vincristine is administered. Vincristine, one of the main alkaloids present in *C. roseus*, has been demonstrated to have immunomodulatory effects. Vincristine is not the only alkaloid found in *C. roseus*; vinblastine and ajmalicine have also been shown to have immunomodulatory effects.



**Figure 3.** Compounds of *C. roseus* preventing the synthesis of pro-inflammatory cytokines Immunomodulatory effects of compounds.

### 5.1. Oleanolic acid.

Oleanolic acid is a pentacyclic triterpenoid that occurs naturally in many different plants and has various pharmacological effects. It is also present in *C. roseus*. In a recent study, OA inhibited Caspase-1 and Caspase-3 activation and increased Bcl-2 expression to prevent apoptosis in a SCI mice model. This experiment was also carried out in LPS-stimulated HT22 cells and exhibited the same result. Additionally, by blocking the MAPKs and NF-B signaling pathways, OA treatment boosted IL-10, Arg1, and SOCS3 and decreased pro-inflammatory mediators such IL-1, IL-6, TNF-, IL-8 and IL-12, and p-JNK, p-IB pathways [48].

### 5.2. Capsaicin.

Recent research has elucidated the CD11b + F4/80+-macrophages with regulatory phenotype in the mesenteric lymph nodes of a mouse model for autoimmune diabetes treated with oral capsaicin, which results in the inhibition of a continuous immune response and autoimmune diabetes prevention [49]. Though capsaicin is the major compound of chili, it is also found in *C. roseus*.

### 5.3. Chelerythrine.

It is a phenanthridine alkaloid extracted have anticancer, antibiosis, and anti-inflammatory properties. An investigation revealed that therapy with chelerythrine significantly decreased the invasion of inflammatory cells, edema, and oxidative stress in mice produced with LPS. By decreasing inflammatory cytokines and activating the NF-B pathway

through the Nrf2 transcription factor, chelerythrine reduced the inflammation caused by LPS in RAW264.7 cells [50].

#### 5.4. Kaempferol.

In the current investigation It was shown that kaempferol significantly and dose-dependently inhibited IDO-1-mediated Trp breakdown as well as neopterin formation in mitogen-stimulated PBMC and human monocytic THP1-Blue-CD14/THP1-Blue cells stimulated by LPS. Both pathways are extremely responsive to oxidative stimuli and activate concurrently in response to IFN- or LPS activation. As a result, it is hypothesized that kaempferol's antioxidative capabilities not only significantly contribute to the phytochemical's immunosuppressive activity but also influence pro-inflammatory signaling cascades. Results imply that rather than changing mRNA or protein levels. Inhibiting the enzyme's activity mediates the inhibitory action on Indoleamin 2,3- dioxygenase (IDO) [51,52].

#### 5.5. Quercetin.

Quercetin is a flavonol. Experiments have demonstrated that kaempferol and quercetin have anti-inflammatory properties while inhibiting STAT-1 and NF-B activation. Nitric oxide (NO) is produced in significant amounts during inflammation thanks to an enzyme called inducible nitric oxide synthase (iNOS). Certain substances have the ability to decrease NO generation while also having anti-inflammatory properties. Flavone, isoflavones, flavonols, kaempferol, and quercetin inhibited iNOS protein and mRNA expression as well as nitric oxide (NO) generation in a dose-dependent manner. The activation of NF-kappaB, an important transcription factor for iNOS, decreased by each of the eight active substances. Another crucial transcription factor for iNOS, the activator of transcription 1 (STAT-1), was also suppressed by kaempferol and quercetin. The present study describes how naturally occurring phenolic chemicals affect the expression of iNOS and NO synthesis in activated macrophages. The findings partially explain the pharmacological effects of flavonoids as anti-inflammatory substances [52].

#### 5.6. Anti-covid activity.

Research on the possible application of *C. roseus* in creating COVID-19-fighting medications has recently been conducted. One study examined the molecular interactions between alkaloids contained in *C. roseus* and the major protease of SARS-CoV-2, the virus that causes COVID-19 [54]. Ajmalicine was discovered in the in-silico approach to exhibit substantial binding affinity (-8.28 kcal/mol) with the major protease, indicating their potential as COVID-19 treatment candidates [55].

The effectiveness of an ethanolic *C. roseus* extract as an in vitro antiviral against SARS-CoV-2 was investigated in a study. The study demonstrated that the extract inhibited viral replication significantly, with an IC<sub>50</sub> value of 79.2 g/mL, showing its potential as a COVID-19 antiviral medication. While these investigations imply that *C. roseus* may have the potential for developing anti-COVID-19 medicines, additional study is required to validate these findings and assess the safety and efficacy of such treatment.

### 5.7. Toxicity.

Several methods were applied in many studies to discover the acute oral harmful effects of *C. roseus* leaf extract. A cytotoxicity test established the maximum non-toxic dose of *C. roseus* extracts. Several extract concentrations were applied to confluent Vero cells cultured on 96-well microtitre plates. Each well was added 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT). The MTT assay's cytotoxicity test against Vero cells revealed that the crude extract of *C. roseus* showed a CC50 value of 0.5 mg/mL [37]. A study was designed to assess the kidney, liver, and heart organ toxicity in Wistar albino rats. The finding was that a 2000 mg dosage of *C. roseus* extract had no fatal effects. When given in doses of 300 mg and 2000 mg, creatinine phosphatase, serum glutamic-oxaloacetic transaminase, lactate dehydrogenase, urea, serum glutamic pyruvic transaminase, and creatinine were all raised. A cytotoxicity test established the maximum non-toxic dosage of the plant extracts. Though there was no mortality, more than 300 mg extract of *C. roseus* can cause the liver, kidney, and heart to exhibit biochemical and histopathological damage. It is recommended that the treatment be administered at lower doses than those examined [56].

## 6. Future Recommendations

Future research on *C. roseus* should prioritize elucidating molecular mechanisms underlying the pharmacological and immunomodulatory effects of its diverse bioactive compounds, such as vincristine, vinblastine, ajmalicine, reserpine, and vindoline. Detailed studies on the specific biochemical pathways and cellular targets these compounds interact with can significantly enhance their therapeutic efficacy and safety profiles. Advanced techniques in genomics, proteomics, and metabolomics could be employed to discover and characterize new bioactive compounds, further expanding the medicinal potential of this plant. Additionally, exploring sustainable and optimized cultivation methods, including genetic modification and tissue culture, can help increase the yield and consistency of these valuable compounds. Comprehensive toxicological assessments are essential to ensure the safe application of *C. roseus* extracts, considering their potent bioactivity. Investigating the synergistic effects of these compounds in combination with other medicinal plants or synthetic drugs could also provide new insights into developing more effective multi-target therapies. Collaboration between ethnobotanists, pharmacologists, immunologists, and biotechnologists will translate traditional uses of *C. roseus* into scientifically validated, globally accessible medical treatments.

## 7. Conclusion

*C. roseus* is a valuable and adaptable plant with various applications in contemporary pharmacology and traditional medicine. Overall, *C. roseus* remains a significant and fascinating research topic for scientists and plant enthusiasts. Due to its numerous pharmacological qualities, this plant has a long history of being used traditionally in various medical procedures. *C. roseus* has a lot of potential for creating new medications and therapies thanks to its strong alkaloids, which have demonstrated potential as anticancer agents, as well as its antidiabetic, antibacterial, anti-cancer, and anti-inflammatory properties. Additionally, this plant is simple to grow and adaptable to various environments, making it a strong contender for sustainable agriculture and complementary medicine. To sum up, *C. roseus* is a fascinating and adaptable plant species that has drawn the interest of researchers, scientists, and herbalists

alike. As *C. roseus* research progresses, we might anticipate learning more about its benefits in several diseases.

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## Conflicts of Interest

The authors declare no conflict of interest.

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