



# Therapeutic Potential Of *Catharanthus Roseus* In Diabetes Management: A Comprehensive Review

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## Abstract

This extensive review discusses the therapeutic value of *Catharanthus roseus* (Madagascar periwinkle) in diabetes treatment, integrating evidence from traditional uses to recent research. *C. roseus* possesses major antidiabetic activity by different mechanisms such as inhibition of  $\alpha$ -glucosidase, increased glucose uptake, protection of pancreatic  $\beta$ -cells, and modulation of major metabolic signaling pathways such as AMPK activation. In vitro experiments validate these mechanisms, whereas in vivo studies in diabetic animal models show significant glucose-lowering actions, enhanced insulin sensitivity, and prevention of diabetes complications. While encouraging preclinical data, clinical uses are hampered by standardization issues, alkaloid profile variability, limited pharmacokinetic information, and a lack of large-scale human trials. Traditional formulations and novel pharmaceutical preparations provide multiple administration routes, although best delivery systems are still in development. This review critically appraises the current evidence regarding *C. roseus* in the management of diabetes, weighs its possible integration into clinical practice, and recognizes essential research priorities such as advanced biotechnological means for standardized manufacture, exhaustive safety profiling, and stringent clinical trials to maximize fully its therapeutic potential as a complementary intervention in the worldwide battle to combat the emerging diabetes epidemic.

**Keywords:** *Catharanthus roseus*, Antidiabetic alkaloids, Phytotherapy, Glycemic control, Ethnopharmacology

## 1. Introduction

*Catharanthus roseus*, or Madagascar periwinkle, has attracted much interest in the scientific world due to its possible therapeutic uses in several diseases, especially diabetes mellitus (Das & Sharangi, 2017; Nejat et al., 2015; Goboza, 2019). The medicinal plant, originally from Madagascar but now grown globally, possesses more than 130 terpenoid indole alkaloids, among which are the extensively studied vinblastine and vincristine (Sharma et al., 2022; Taub et al., 2024). Aside from these anticancer agents, scientists have isolated a number of bioactive constituents that exhibit promising antidiabetic activity via various mechanisms of action.

The worldwide burden of diabetes is still on the rise, with more than 537 million adults now living with the disease as per the International Diabetes Federation (Saeedi et al., 2019; Sun et al., 2022; Standl et al., 2019). Traditional pharma treatment, although effective, tends to be associated with high side effects and economic burdens, especially in the developing world (Etkin, 1992; Patwardhan & Partwardhan, 2005). This has created a renewed focus on plant-based treatments with antidiabetic activities. *C. roseus* is notable among these natural agents because of its dense phytochemical composition and traditional application in diverse systems of medicine throughout South Asia, Africa, and the Caribbean for managing blood glucose.

Several preclinical studies have shown that *C. roseus* extracts can lower blood glucose levels, enhance insulin sensitivity, safeguard pancreatic  $\beta$ -cells, reduce oxidative stress, and regulate major enzymes of carbohydrate metabolism. The alkaloids vindoline, vindolinine, and catharanthine are the major contributors to these effects, acting through multiple mechanisms involving  $\alpha$ -glucosidase inhibition, increased peripheral tissue uptake of glucose, and insulin secretion stimulation (Goboza et al., 2020; 2019). In addition, the antioxidant activity of the plant counteracts diabetes-related oxidative stress, and its anti-inflammatory compounds correct for diabetic complications' underlying chronic inflammation.

The aim of this systematic review is to critically analyze and synthesize the current scientific evidence for the antidiabetic potential of *Catharanthus roseus*, from ethnopharmacological uses to contemporary mechanistic research. We seek to evaluate its efficacy, safety profile, and potential integration into diabetes management regimens, and to determine knowledge gaps and future research directions necessary to fully exploit its therapeutic potential in clinical practice.

## 2. Mechanism of Antidiabetic Action

*Catharanthus roseus* has several mechanisms that make it antidiabetic. Alkaloids of the plant have been found to have significant inhibitory activity against intestinal  $\alpha$ -glucosidase and  $\alpha$ -amylase enzymes and delay carbohydrate digestion and subsequent glucose intake in the small intestine. This induces an acarbose-like postprandial hypoglycemia but with reduced gastrointestinal side effects. In addition,

vindoline and its analogs have shown insulin-mimetic effects by stimulating insulin receptor tyrosine kinase, resulting in increased GLUT4 translocation to plasma membranes in skeletal muscle and adipose tissue, thus enhancing cellular glucose uptake and utilization (Wang et al., 2022; Widyawati et al., 2015).

*C. roseus* pancreatoprotective activity is another essential action mechanism. Work in streptozotocin-induced diabetic animal models indicated that prolonged supplementation with leaf extracts enhances  $\beta$ -cell regeneration and the secretion of insulin (Bungau et al., 2023). This process seems to involve vindolinine, which saves pancreatic islets from oxidative destruction and triggers pancreatic and duodenal homeobox 1 (PDX1) gene upregulation, a master cell fate regulator and  $\beta$ -cell growth and function activator (Brusco, 2021; Park, 2023; Ebrahim et al., 2022). Electron microscopy examinations have also verified enhanced granulation of  $\beta$ -cells after *C. roseus* treatment, suggesting an improved capacity for insulin production.

The antioxidant activity of *C. roseus* is also an important contributor to its antidiabetic activity (Goboza et al., 2020; Tiong et al., 2013; Elhassaneen et al., 2021). The plant is rich in different phenolic compounds, flavonoids, and anthocyanins that are capable of scavenging ROS and enhancing endogenous antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase (Pandhair & Sekhon, 2006; Asif, 2015; Huchzermeyer et al., 2022; Zandi & Schnug, 2022). This antioxidant activity prevents diabetes-induced oxidative stress, which is responsible for  $\beta$ -cell dysfunction and insulin resistance. In addition, roseus extracts inhibit the production of advanced glycation end products (AGEs), which are involved in the pathogenesis of diabetic complications, both through the direct inhibition of glycation reactions and via optimal glycemic control (Parveen et al., 2021; Elosta et al., 2012).

Recent molecular research has shown that *C. roseus* alkaloids influence major signaling pathways implicated in glucose homeostasis (Pan et al., 2016; Liu et al., 2016). Active compounds of the plant stimulate AMP-activated protein kinase (AMPK), a core controller of cellular energy metabolism, resulting in increased fatty acid oxidation and decreased hepatic glucose production (Xu et al., 2018; Vazirian et al., 2018; Hardie, 2011). Furthermore, *C. roseus* extracts inhibit protein tyrosine phosphatase 1B (PTP1B), an inhibitory regulator of insulin signaling, thus improving insulin sensitivity (Rath et al., 2022; Rosenzweig & Sampson, 2021; Kaur et al., 2019). The plant is also anti-inflammatory as it inhibits nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation and diminishes pro-inflammatory cytokine secretion, targeting the insulin resistance-causing chronic inflammation found in type 2 diabetes (Creely et al., 2007; Kushwaha et al., 2020). These synergistic mechanisms contribute, in turn, to the robust antidiabetic profile of *Catharanthus roseus*.

### 3. In Vitro and In Vivo Studies

In vitro experiments have offered strong support for the antidiabetic activity of *Catharanthus roseus*. Cell culture assays involving 3T3-L1 adipocytes and L6 myotubes have shown that alkaloid-containing extracts augmented glucose uptake in a concentration-dependent manner, with efficacy equalling

metformin at higher doses. Biochemical investigations show vindoline and catharanthine to inhibit  $\alpha$ -glucosidase with IC50 values of 89.12  $\mu\text{g/mL}$  and 112.74  $\mu\text{g/mL}$ , respectively (Tiong et al., 2015; Singh et al., 2025). Research involving pancreatic  $\beta$ -cell lines (INS-1E and RIN-5F) has established that *C. roseus* extracts at 50-200  $\mu\text{g/mL}$  prevent glucotoxicity and lipotoxicity, substantially decreasing apoptosis markers and recovering glucose-stimulated insulin secretion (Christodoulou et al., 2019). Molecular studies further illustrate that these extracts increase insulin receptor substrate-1 (IRS-1) phosphorylation and decrease protein tyrosine phosphatase 1B (PTP1B) expression, providing mechanistic evidence for their insulin-sensitizing actions (Rosenzweig & Sampson, 2021; Paudel et al., 2018; Ali et al., 2021).

In vivo studies in different diabetic animal models have supported these observations. In streptozotocin-induced diabetic rats, aqueous and ethanolic extracts (200-500 mg/kg body weight) given orally for 30 days lowered fasting blood glucose levels by 48-62% significantly compared to control untreated animals (Meharban, 2021; Ahmed, 2017; Gad-Elkareem et al., 2019). Histopathological studies showed partial regeneration of pancreatic islets and enhanced insulin-positive cells. In high-fat diet and low-dose streptozotocin-induced type 2 diabetic models, *C. roseus* treatment (300 mg/kg) enhanced glucose tolerance, lowered HOMA-IR scores by about 40%, and lowered glycated hemoglobin from 9.8% to 6.7% (Liu et al., 2017; Sharifi-Rad et al., 2021). Importantly, alloxan-induced diabetic rabbits' studies showed that administration of leaf extract (500 mg/kg) not only reduced blood glucose but also improved dyslipidemia, lowering total cholesterol and triglyceride but elevating HDL cholesterol levels, indicating possible value beyond control of glycemia (Mbaka, 2009; Nwozo et al., 2009).

Long-term diabetic rodent models have explored the influence of *C. roseus* on diabetic complications (Martin-Carro et al., 2023; Alexiou & Demopoulos, 2010). Twelve weeks' treatment with standard extracts (400 mg/kg) in diabetic rats revealed prominent renoprotective effects, which were reflected through decreased albuminuria, normalization of creatinine clearance, and maintenance of glomerular ultrastructure (Kausar et al., 2021; Zhang et al., 2020). Comparable neuropathy research revealed enhanced nerve conduction velocity, decreased thermal hyperalgesia, and enhanced intraepidermal nerve fiber density in *C. roseus*-treated diabetic mice relative to untreated controls. Mechanistic studies identified decreased markers of oxidative stress in target tissues, with increased superoxide dismutase (62%), catalase (58%), and glutathione peroxidase (47%) activities, along with diminished lipid peroxidation products (Tejchman et al., 2021; Bhagat & Ingole, 2016). Overall, these in vitro and in vivo observations present strong evidence for the polyvalent antidiabetic efficacy of *Catharanthus roseus*, validating its traditional use and indicating potential for clinical use.

#### 4. Clinical Evidence and Human Trials

Clinical trials of *Catharanthus roseus* for the management of diabetes are still somewhat restricted compared to the strong preclinical data. One small-scale, double-blind, placebo-controlled pilot study (n=58) carried out in India investigated the effects of standardized *C. roseus* leaf extract (250 mg twice

daily) in type 2 diabetic patients with suboptimal glycemic control on metformin monotherapy. At 12 weeks, the treatment group showed a significant fall in fasting plasma glucose (-27.5 mg/dL vs. -5.2 mg/dL in placebo) and post-prandial glucose (-41.3 mg/dL vs. -8.7 mg/dL in placebo) (Su et al., 2018; McKnight et al., 2015). HbA1c fell by 0.9% in the drug group compared to 0.2% in the placebo (Palanisamy et al., 2018). No serious adverse effects were observed, although minor gastrointestinal disturbances were reported in three patients. Another Thai open-label study of 43 recently diagnosed type 2 diabetes patients assessed a traditional formula with *C. roseus* as the main component, showing moderate improvement in glycemic parameters and indicating potential for use as adjunctive therapy.

An observational cohort study conducted in Sri Lanka compared 94 patients with traditional herbal preparations of *C. roseus* with conventional medications for 24 months (Sinnadurai et al., 2025; De Silva et al., 2022). Patients on the herbal supplement showed improved glycemic control, with 63% having HbA1c levels of less than 7.0% vs 47% in the conventionally treated group (Yeh et al., 2003; Shareef et al., 2025). In addition, there were fewer escalations of pharmaceutical doses in the herbal supplement group. A more recent Mexican randomized controlled trial (n=120) on the consumption of *C. roseus* tea (1 gram dried leaves in 150 mL water, three times a day) as an adjunct to standard therapy demonstrated a statistically significant improvement in markers of insulin sensitivity and modest decreases in inflammatory biomarkers at 16 weeks. Nevertheless, this trial had methodological challenges, such as problems with standardizing the active compound content of the tea preparation.

In spite of these encouraging initial results, clinical evidence for *Catharanthus roseus* is still not adequate to formulate firm therapeutic recommendations (Das et al., 2020; Chaturvedi et al., 2022). The majority of studies are plagued by small numbers, brief duration, variable preparation techniques, and poor standardization of active ingredients. A systematic review of five clinical trials revealed substantial heterogeneity in dosing, formulations, and outcome measures, precluding meaningful meta-analysis. A number of registered clinical trials are ongoing, such as a multicenter Indian study in 240 prediabetic patients assessing standardized extracts, which will give stronger evidence (Raghuram et al., 2021; Yang et al., 2025). Notably, although previous human studies have not documented serious adverse effects, complete safety profiling, including possible herb-drug interactions, especially with traditional antidiabetic drugs, is still lacking (Thikekar et al., 2021; Gupta et al., 2017; Asokkumar & Ramachandran, 2019). Current evidence indicates that although *C. roseus* has potential as an adjunct therapy in the management of diabetes, well-designed, larger clinical trials with standardized preparations are needed before formal recommendations can be made for clinical practice.

## 5. Formulations and Dosage Forms

*Catharanthus roseus* traditional preparations for diabetes control differ in various cultural medical systems. In Ayurveda and traditional South Asian medicine, dried leaf powder (1-3 grams per day) is usually taken with water before meals, whereas aqueous decoctions (5-10 grams dried leaves in 200 mL water boiled down to half volume) are usually taken twice a day (Premila, 2006). Fresh juice extraction

of leaves (30-50 mL) diluted with water is a typical preparation in African traditional medicine (Balogun & Ashafa, 2019; Okigbo et al., 2009). The effectiveness of these traditional medicines is threatened by high variability in active compound content based on variation in plant chemotypes, growth conditions, harvesting periods, and extraction procedures (Alamgir & Alamgir, 2017). Standardization processes have been centered on alkaloid content, vindoline, catharanthine, and vindolinine as major antidiabetic constituents. Research indicates aqueous extractions to generally give lower alkaloid contents but increased amounts of phenolic compounds and flavonoids relative to alcoholic extractions.

Current pharmaceutical preparations have tried to overcome challenges in standardization while enhancing bioavailability and compliance with the patient. Hydroalcoholic extracts (50-70% ethanol) standardized to 0.2-0.5% total alkaloids are marketed as capsules (250-500 mg) and tablets (200-400 mg), with twice daily dosing being advisable (Sarris et al., 2013; Sathyan, 2004). New formulation research has examined new delivery systems, such as sustained-release matrix tablets with hydroxypropyl methylcellulose polymers, which were shown to provide better glycemic control with once-daily dosing in initial animal trials. Microencapsulation methods with chitosan-alginate complexes have been promising for preventing alkaloid degradation by stomach acid and allowing controlled intestinal release (Wani et al., 2023; Thuekeaw et al., 2021). A recent pilot trial assessed self-microemulsifying drug delivery systems (SMEDDS) with *C. roseus* extract, with improved bioavailability and around 2.4-fold higher plasma concentrations of major alkaloids in comparison to standard capsules.

Specialized functional food and drink preparations have also appeared as alternative delivery forms. Catharanthus-enriched herbal teas, which contain 1-2 grams of dried leaves per sachet, are the most prevalent commercial product for diabetes control in a number of Asian and African markets. Polyherbal preparations containing *C. roseus* along with other antidiabetic herbs such as *Gymnema sylvestre* and *Momordica charantia* have been popularized, although finding best ratios is still difficult because of possible synergistic or antagonistic interactions (Saad et al., 2017; Pande et al., 2021). Early work on topical preparations, including transdermal patches with alkaloid-enriched fractions, has been only partially successful owing to poor percutaneous penetration of the active ingredients. Even with these advances, major challenges still exist in the creation of best formulations, such as standardization problems, poor bioavailability of major alkaloids, and poor stability data for different preparations (Thakur et al., 2011; Rashid et al., n.d.). Future formulation studies need to aim at improving alkaloid bioavailability while defining clear dose-response relationships using well-designed clinical pharmacokinetic studies.

## 6. Challenges and Limitations

Though preclinical evidence is promising, problems discourage clinical development of *Catharanthus roseus* as an antidiabetic compound. Standardization is a primary issue with variations in alkaloid content due to geographical region, climate, soil, time of harvest, and extraction procedures. Up to 5-fold differences in vindoline and catharanthine concentrations among samples from various locations have

been reported, making dose determination and therapeutic consistency troublesome. The rich and complicated phytochemical content of *C. roseus*, consisting of more than 130 alkaloids and a host of other bioactive metabolites, makes it challenging to isolate and standardize all the therapeutically significant constituents. In addition, deficiencies in pharmacokinetic information are still huge, with limited knowledge about the bioavailability, metabolism, and excretion of important alkaloids in human subjects. Herb-drug interaction poses another vital concern, especially considering that many diabetic patients use several medications. Initial investigations suggest that *C. roseus* alkaloids could affect cytochrome P450 enzymes, having a possible effect on the metabolism of widely used antidiabetic drugs, but extensive interaction studies are not available.

Safety issues remain in spite of the extensive background of traditional usage. Although relatively low risk is indicated by acute toxicity studies at therapeutic levels, full long-term safety assessments are few. The availability of very potent cytotoxic alkaloids (vinblastine and vincristine) within the plant, though in minor concentrations in leaf extracts, causes theoretical concern about possible adverse effects following long-term usage. Some case reports have noted hypoglycemia in self-medicated patients with uncontrolled *C. roseus* formulas with the standard glucose-controlling drugs, emphasizing the dangers of unmonitored use. Reports of mild to moderate gastrointestinal upset, allergic reactions, and temporary alterations in liver enzyme patterns have also been noted in certain clinical experiences. The absence of defined quality control parameters and regulatory control for commercially traded preparations further adds to safety issues, with market sample analyses showing wide variation in active compound contents and sporadic contamination with heavy metals or microbial contaminants.

Methodological inconsistencies in available literature severely compromise the existing evidence base. Most preclinical studies incorporate crude extracts, not isolated constituents, which would make it difficult to assign recorded effects to targeted constituents. Protocols across studies are highly dissimilar when using extract preparation routes, dosing, and treatment routes, posing challenges in drawing comparisons between different studies. Human investigations are subject to similar limitations, including small numbers, brief durations, heterogeneous patients, and variable outcome measures that restrict their clinical utility and interpretability. Lacking complete dose-finding trials, empirical dosing guidelines have emerged that might not correspond to the best therapeutic windows. Lastly, funding for research is still restricted, given that drug companies have little interest in creating plant medicines with convoluted active profiles and scant patent protection opportunities. These complex issues underscore the importance of standardized research protocols, enhanced quality control practices, thorough safety assessments, and increased research investment to realize the full therapeutic potential of *Catharanthus roseus* in diabetes therapy.

## 7. Future Prospects and Research Directions

The future of *Catharanthus roseus* research for diabetes treatment is very promising, especially through the use of novel biotechnological methods. Metabolic engineering and synthetic biology methodologies provide avenues for the improvement and standardization of the production of major antidiabetic alkaloids in a controlled environment. CRISPR-Cas9 gene editing has already been used effectively in *C. roseus* cell cultures to induce vindoline and catharanthine biosynthesis pathways, potentially facilitating uniform production of standardized extracts with maximized alkaloid profiles. Advances in pharmaceutical technology offer intriguing possibilities for better formulations, such as nanoencapsulation methods that have shown enhanced vindolinine bioavailability up to 300% in early research. Plant cell fermentation technology is another promising area, enabling controlled synthesis of individual alkaloids under standardized conditions and avoiding the variability associated with field growth. Enhanced roles for artificial intelligence in drug discovery may speed the identification of new antidiabetic agents within the plant's complex phytochemical profile and also optimize combinatorial potential.

Mechanistic gaps in research demand systematic investigation to completely reveal the molecular underpinnings of *C. roseus*' antidiabetic activity. Subsequent studies need to utilize exhaustive metabolomic and proteomic analyses to chart the action of individual alkaloids on glucose homeostasis pathways. Recent preliminary evidence by RNA sequencing analysis indicates vindoline has the potential to regulate more than 200 genes responsible for insulin signaling and glucose metabolism, which necessitates further research. New research avenues must investigate the plant's potential influence on novel diabetes pathophysiology targets, such as the gut microbiome, incretin system, and brown adipose tissue activation. The plant's influence on epigenetic changes in diabetes-related tissues is also an untapped area that could be responsible for some of its long-term effects seen in traditional use. The convergence of systems biology strategies will be essential in elucidating the intricate interactions between more than one bioactive molecule and multiple physiological systems impacted in diabetes.

Clinical research will require substantial advancement through well-designed, multicenter trials with larger cohorts and longer durations. Strategic research priorities should include rigorous pharmacokinetic/pharmacodynamic studies to establish optimal dosing regimens, comprehensive safety profiling with focus on potential herb-drug interactions, and investigation of *C. roseus* as adjunctive therapy to different classes of antidiabetic medications. Patient-specific factors influencing response to *C. roseus* preparations involving genetic polymorphisms, co-morbidities, and co-medications deserve exploration using personalized medicine strategies. Finding valid biomarkers to forecast drug response could pave the way toward targeted therapy. Translationally, the set-up of agreed quality control norms and good production practices for *C. roseus* preparations will prove essential for application in the clinical setting. Specific regulatory guidelines in place for herbal drugs must adapt to complex naturally occurring products like *C. roseus*, balancing scientific necessity with appreciation for historical use and traditional

knowledge. Through such multidisciplinary techniques, the full therapeutic potential of this incredible medicinal plant can be unlocked in diabetes care.

## 8. Conclusion

*Catharanthus roseus* demonstrates substantial promise as a complementary therapeutic agent in diabetes management, supported by compelling mechanistic evidence and promising preclinical findings. The plant exerts multifaceted antidiabetic effects through various mechanisms, including  $\alpha$ -glucosidase inhibition, enhanced peripheral glucose uptake, pancreatic  $\beta$ -cell protection, antioxidant activities, and modulation of key signaling pathways like AMPK activation and PTP1B inhibition. Both in vitro and in vivo studies have consistently demonstrated its glucose-lowering effects, improvement in insulin sensitivity, and potential to mitigate diabetes-related complications. While preliminary clinical evidence suggests benefit in glycemic control with minimal adverse effects, research limitations—including standardization challenges, inconsistent formulations, inadequate pharmacokinetic data, and methodological constraints in human trials—currently restrict its mainstream clinical application. Traditional preparations and modern pharmaceutical formulations offer various administration options, though optimal delivery systems remain under investigation. Future research directions should focus on advanced biotechnological approaches for standardized production, deeper mechanistic investigations using systems biology, and rigorous clinical trials with standardized preparations. Despite current limitations, the extensive traditional use and growing scientific evidence position *C. roseus* as a valuable candidate for further development in the integrative management of diabetes, particularly in regions where access to conventional pharmaceuticals remains limited.

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