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Review Article

A Systematic Review: Antihyperglycemic Properties of *Catharanthus roseus* Linn.

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ABSTRACT

Background: Diabetes mellitus is a term for several diseases that affect how your body regulates blood sugar. Ayurveda has long used *Catharanthus roseus* Linn., to cure diabetes. This review aims to summarise existing scientific studies investigating this plant's potential to manage diabetes. **Methodology:** The review concentrated on current, significant research that was discovered using academic databases such as PubMed, SpringerLink, Web of Science and Google Scholar and that addressed the antihyperglycemic and antidiabetic effects of *C. roseus*. Only English research articles from January 2001 to May 2024 were included in the analysis. **Results:** After reviewing 192 publications from January 2001 to May 2024, this article focus to 15 research studies on the effects of *C. roseus* on blood sugar regulation and diabetes management. **Conclusion:** Interestingly, all the studies concurred that *C. roseus* appeared to have blood sugar-lowering effects in the test subjects. This potential antidiabetic benefit may be due to the plant's ability to Increase insulin production from previously impaired beta cells in response to glucose and enhance the activity of genes involved in sugar uptake (GLUT-2 and GLUT-4).

Keywords: Antidiabetic, *Catharanthus roseus*, Diabetes management, Streptozotocin, *Vinca rosea*.

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INTRODUCTION

An elevated blood sugar level is a symptom of a group of metabolic disorders called diabetes mellitus. This may be the result of either insufficient insulin production by the pancreas (Type 1) or ineffective insulin utilisation by the body (Type 2).[1] The exact causes of Type 1 are still unknown, but it's believed to involve the immune system attacking insulin-producing cells.[2] In contrast, factors like being overweight or having a family history increase the risk of Type 2.[3] Common symptoms include increased hunger, urination and thirst. Uncontrolled, hyperglycemia can result in life-threatening consequences such as heart attacks, insulin resistance DM, strokes, blindness and amputations.[4] long-term usage of insulin therapy might have adverse effects such as fatty liver, problems with eating and insulin resistance.[5] Ayurvedic practitioners have long used the flowering plant *C. roseus* to treat Type 1 and Type 2 diabetes, along with other conditions. Its flowers, leaves and roots are known for their medicinal properties.[6] It is essential to investigate the effectiveness of *C. roseus* in the management of Diabetes Mellitus (DM) and to examine the phyto-constituents that may contribute to the control of this condition. Various health disciplines should be informed about the potential efficacy of *C. roseus* in the regulation of DM. This review aims to analyze existing research on *C. roseus* to see if it can effectively lower blood sugar and manage diabetes-related complications.

METHODOLOGY

Methods

The systematic review followed the quality standards outlined in the PRISMA guideline and the protocol was not recorded in the PROSPERO database.

Ethics

The utilization and welfare of laboratory animals are subject to guidelines established by relevant ethics committees and these guidelines were adhered to in all research studies included in this analysis.

Search strategy

We conducted a comprehensive search in PubMed and SpringerLink, Google Scholer for relevant studies published in English from the databases' inception from January 2001 to May 2024 (Table 1). We also examined reference lists of key reviews to identify additional articles. Our search terms included combinations of "*Catharanthus roseus* Antidiabetic Animal

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Study" and "*Vinca rosea* antidiabetic activity" This initial search yielded 192 articles. After removing duplicates and excluding studies in languages other than English or those not relevant to our topic based on their abstracts, in this article, the selection was reduced to 24 original research publications.

Study selection and data gather

The evaluation of research articles and academic works was based on their impact, importance and relevance. In the situation of investigations related to the antidiabetic and antihyperglycemic effects of *C. roseus* and comprehensive scrutiny of appropriate publications was carried out without any text restrictions on keywords used in the search methodology. Research that investigated the effects of *C. roseus* extracts or constituents on diabetic animal models or pancreatic cells, including mice, rats, rabbits, or pancreatic cells, was incorporated in the review. Exclusion criteria includes, article that was not written in English, literature with technical error, literature that where not meaningful to our search. Figure 1, represents inclusion/exclusion of study.

Diabetes was induced in the experimental groups using the method extracted from each study, when applicable. Additionally, to determine the mode or route of administration of *C. roseus*, the studies were reviewed. and to collect data on the animal samples utilized. This included details such as sample size, type, the specific form of diabetes mellitus induced, as well as the sex and age of the animals. If one or more sample characteristics were missing, the studies underwent a second screening. Should the necessary data still be absent after this second review, the missing sample characteristics were noted by the reviewer. Importantly, these studies were not excluded from the overall analysis. Characteristics of studies were summarized in Table 2.[7-19]

RESULTS

A total of 192 publications were discovered, encompassing research conducted until May 2024. Among these, 24 publications were selected for inclusion as they specifically examined the antihyperglycemic and antidiabetic properties of *C. roseus*.

Assessment of risk of bias

Use SYRCLE's RoB tool to conduct animal experiments to assess risk of bias.[20] Figure 2 below provides an overview of areas contributing to bias in included studies. However, inadequate guidance is provided regarding lack of accommodation, blindness and blindness of assessment results for the majority of the population. Sections were found to be at low risk for sequential design, baseline characteristics, blinded allocation, incomplete outcome assessment, missing data, selective teaching and other inequities. Conclusion of SYRCLE's bias risk presented in Table 3 and Figure 2.[21-23]

DISCUSSION

The research on the use of *C. roseus* in the treatment of diabetes has shown that it can be effective in tackling the complex issues that are associated with the disease, especially in both type 1 and Type 2 diabetes mellitus. The reviewed studies offer strong support for the *C. roseus* is ability to regulate the essential physiological processes that are involved in diabetes, such as enzymatic activities, lipid metabolism and oxidative stress.

Mechanisms of Antidiabetic Action

C. roseus have antidiabetic effects in several ways that are interrelated in some way. Rasineni *et al.* (2017) showed that *C. roseus* has alpha-amylase inhibitory activity which prevents the conversion of starch to glucose and thus decrease the postprandial hyperglycemia. This enzymatic inhibition reduces the uptake of glucose from the gut and therefore it reduces hyperglycemia which is a major issue in diabetic patients.[7,24]

Also, the antioxidant activity of *C. roseus* as pointed out by Rasineni *et al.* (2017) and Alkreathy *et al.* (2020) helps in the reduction of oxidative stress which is usually worsened in diabetes.[7,25] Oxidative stress results in the loss of the pancreatic β-cells that are responsible for the production of insulin. *C. roseus* reduces oxidative stress by quenching ROS and thus maintains the proper functioning of these cells and possibly enhancing insulin release.[26,27]

C. roseus has been shown to inhibit alpha-amylase,[28] an enzyme responsible for breaking down starch into simple sugars. This inhibition can help reduce the absorption of glucose from the gut, thereby lowering blood glucose levels.[29]

Enhancement of Insulin Secretion and Sensitivity

Another significant aspect of the antidiabetic effect of *C. roseus* is its capacity to modulate the secretion of insulin. Espejel-Nava *et al.* (2018) found that the phenolic compounds, especially chlorogenic acid and gallic acid, found in the *C. roseus* plant may help in improving the insulin secretion due to the increased sensitivity of the β-cells to glucose.

In addition, vindoline, vindolidine and other alkaloids described by Tiong *et al.* (2013) have been found to possess hypoglycemic effects, suggesting that they enhance the function of β-cells. The aqueous leaf extract showed significant effects in reducing blood glucose levels among all extracts tested.[11] Vindoline

Table 1: Search strategy from 2001 to May 2024.

Number of Searches	Hits	Search
1	*Catharanthus roseus* Antidiabetic Animal Study.	65
2	*Vinca rosea* antidiabetic activity.	76
3	1 or 2	51

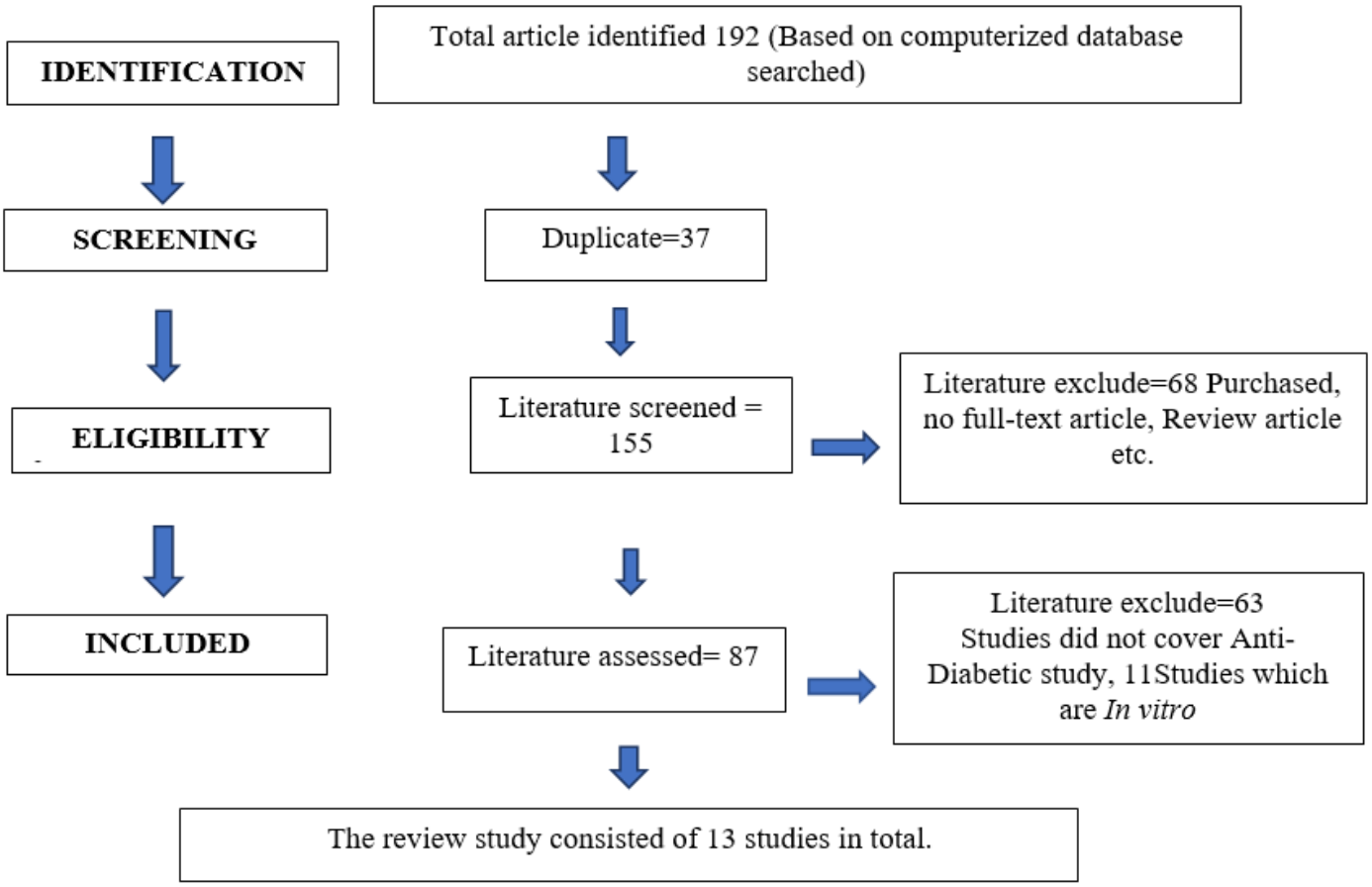

Figure 1: Schematic Diagram for Inclusion/Exclusion of Studies.

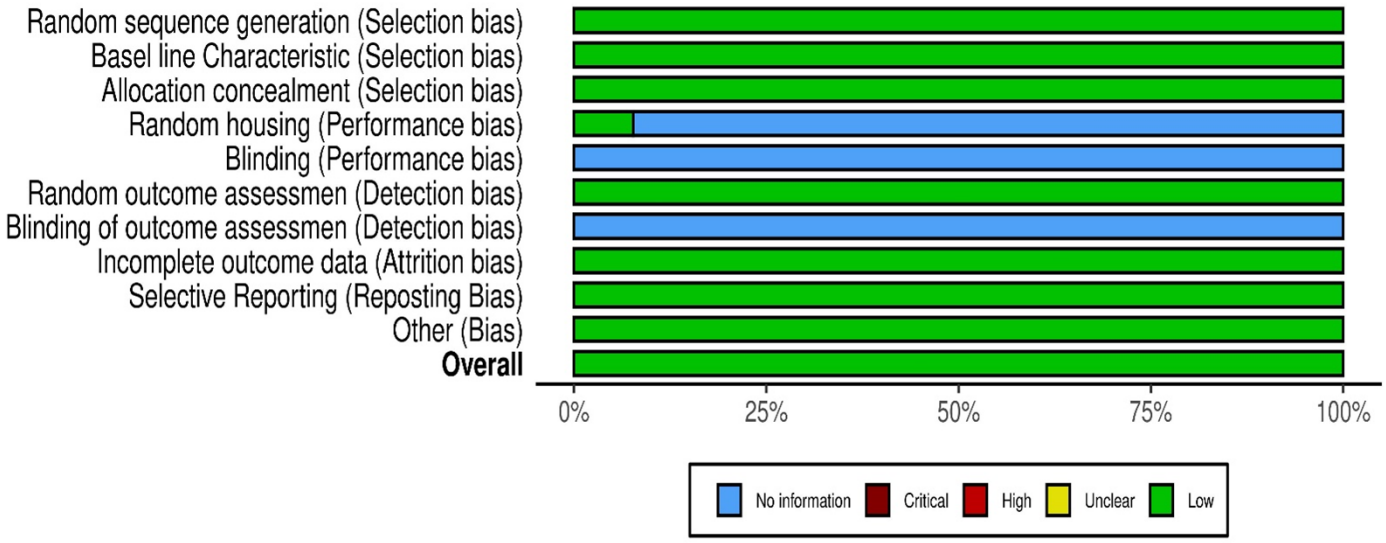

Figure 2: Conclusion of SYRCLE's bias risk.

Table 2: Characteristics of Study.

Author/Year	Size of Sample	Characteristics of Population	Aims/Findings
Rasineni, *et al.* (2017)[7]	*n*=48	Type of Induce Diabetes Mellitus=Type 1 and Type 2 Diabetes. Sex and Age=Male (Wistar rats), 6-7 weeks.	The study thus provides evidence for the therapeutic role of *C. roseus* treatment in correcting enzymatic activities, lipid accumulation and oxidative stress during Type 1 DM as well as Type 2 DM. These findings pave the way for further exploration and potential clinical application of *C. roseus* in diabetes management, offering hope for improved treatment outcomes in the future.
Alkreathy, *et al.* (2020)[8]	*n*=6	Type of Induce Diabetes Mellitus=Type 2 Diabetes. Sex and age=Male (Wistar rats), Age is 5-6 months.	All rats from the six different groups were then injected with streptozotocin to induce diabetes, after which these diabetic/normal groups received *C. roseus* ethanolic extract and Ursolic Acid during 28 days; Treatment of *C. roseus* ethanolic extract in association with Ursolic Acid lowered effective doses and had the best effect on control diabetes as well as regulation of level blood glucose.
Espejel-Nava JA, *et al.* (2018)[9]	*n*=8	Type of Induce Diabetes Mellitus=Type 2 Diabetes Sex and Age=Male (*Mus musculus*) and Age not mentioned.	These six experimental groups had diabetes by the use of streptozotocin and administration of the phenolic fraction that was isolated from *C. roseus*. The phenolic fraction was made of chlorogenic and gallic acid had the highest hypoglycemic effect and, there is a possibility that it stimulated the secretion of insulin.
Waleed, *et al.* (2015)[10]	*n*=30	Type of Induce Diabetes Mellitus=Type 2 Diabetes. Sex and Age=Male (Wistar rats), Age is 6 weeks.	30 rats were split into 6 distinct groups for the experiment. The ethanol extract of the *C. roseus* plant demonstrated a notable anti-hyperglycemic effect in diabetic rats induced by STZ. The findings from the analysis of serum biochemical levels, blood glucose levels and mRNA expression of Glucose Transport genes (GLUT-2 and GLUT-4) suggested that *C. roseus* possesses regenerative and a therapeutic properties, as it was able to reverse the majority of the physiological and tissue alterations induced by streptozotocin-induced diabetes in rats.
Tion, *et al.* (2013)[11]	*n*=1.5 ×10	Type of Induce Diabetes Mellitus=Type 1 Diabetes Sex and Age=NA (Mouse β-TC6 pancreatic cells) and Age is not mentioned.	Extracted from *C. roseus*, the alkaloids vindolicine, vindoline, vindolinine and vindolidine were isolated and utilised in cell experiments. The findings showed these alkaloids' hypoglycemic effect on mouse pancreatic cells, that is β-TC6.
Srinivas, *et al.* (2003)[12]	*n*=10	Type of Induce Diabetes Mellitus=Type 1 Diabetes. Sex and Age=male and female (Albino rabbits) and Age is not mentioned.	To induce diabetes, a dose of alloxan was given to ten groups of five rabbits each. After that, the rabbits were given *C. roseus* leaf juice, which drastically decreased their blood sugar and caused significant hypoglycemia. This could be explained by the release of insulin from the remaining β-cells in the rabbits.

Author/Year	Size of Sample	Characteristics of Population	Aims/Findings
Elisa, *et al.* (2012)[13]	*n*=36	Type of Induce Diabetes Mellitus=Type 2 Diabetes. Sex and Age=male (*Mus musculus* CD-1 strain) and Age is not mentioned.	The experiment involved the division of the mice into 6 groups, each consisting of six individuals. To induce diabetes, a dose of alloxan was administered to all the mice. After that, several extracts from the leaves, flowers, roots and stems of *C. roseus* were given to the mice. Notably, a drop in blood glucose levels was indicated by the hypoglycemic action shown by all of these extracts. The extract with the greatest significant effect on lowering blood glucose levels was the aqueous leaf extract.
Ahmed, *et al.* (2007)[14]	*n*=NA	Type of Induce Diabetes Mellitus=Type 1 Diabetes. Sex and Age=(Wistar rats) Sex and Age is not mentioned.	To induce diabetes, a dose of streptozotocin was given to develop diabetes and then they were given an aqueous extract of *C. roseus* leaves. Over the course of a 24 hr observation period after the extract was administered, the rats' serum glucose levels significantly decreased.
Xin-gang, *et al.* (2013)[15]	*n*=NA	Type of Induce Diabetes Mellitus=Type 1 Diabetes Sex and Age=(Wistar rats) Sex and Age is not mentioned.	All Wistar rats are injected with streptozotocin to induce diabetes. Subsequently, they were treated with vindoline, an alkaloid found in *C. roseus*. Following close observation, it was found that the rats treated with vindoline exhibited increased insulin secretion in response to glucose stimulation.
Somnath Singh, *et al.* (2001)[16]	*n*=NA	Type of Induce Diabetes Mellitus=DM type 1.	The antidiabetic effects of a plant extract from *C. roseus* were tested on diabetic rats. Given orally at 500 mg/kg for seven and fifteen days, the extract decrease blood sugar levels by 49% and 58% respectively. The extract totally prevented diabetes after 30 days of treatment. Additionally, it reduces oxidative stress and enhanced liver enzyme activity in the rats.
Eman H. Altaee, *et al.* (2020)[17]	*n*=40	Type of Induce Diabetes Mellitus=DM type 2 Sex and Age=Male (Swiss albino mice) and Age is 10-12 weeks.	The present study findings showed that the extracts of *Vinca rosea* had profound influence on blood sugar levels leading to a higher number of ß cells being released in the pancreas thereby causing increased insulin levels in treated group compared to diabetic mice. Conversely, treatment with Streptozotocin & *Vinca rosea* exhibited similar values as for control group with no significant differences observed. On the other hand, histopathological evaluation on diabetes treatment using only *Vinca rosea* on the pancreas lesions indicated an increase in beta-cells hypercellularity. In this context, it can be inferred that traditional medicine may adopt *Vinca rosea* extract as a probable option for diabetes prevention.
Khadija Azam, *et al.* (2022)[18]	*n*=40	Type of Induce Diabetes Mellitus=DM type 2 Sex and Age=Male (Albino mice), Age is 2-3 months.	According to the study, *C. roseus* leaf ethanolic extract has strong anti-hyperlipidemic and anti-diabetic effects. When used with atorvastatin, it did not show additional benefits for anti-hyperlipidemic effects. However, when combined with sitagliptin, it notably improved its anti-diabetic effects.

Author/Year	Size of Sample	Characteristics of Population	Aims/Findings
Riya Liak, *et al.* (2023)[19]	*n*=NA	Type of Induce Diabetes Mellitus=DM type 2 Sex and Age=Male (Swiss albino mice) and Age is 2-3 months.	The results obtained after 14 days of treatment indicate that the high dose (500 mg/kg) of methanolic whole plant extract is more effective compared to the low dose (300 mg/kg). It is evident that the high dose exhibits similar therapeutic effects to the standard drug, glibenclamide (5 mg/kg). This observation could be attributed to the presence of viable β-cells that are responsive to the insulin-releasing properties of *Vinca rosea* extract. Furthermore, histopathological examinations support the hypothesis that *V. rosea* extracts possess antidiabetic properties by promoting the healing of the pancreas.

Table 3: Conclusion of SYRCLE's bias risk.

Study	Random sequence generation (Selection bias)	Basel line Characteristic (Selection bias)	Allocation concealment (Selection bias)	Random housing (Performance bias)	Blinding (Performance bias)	Random outcome assessment (Detection bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective Reporting (Reposting Bias)	(Other Bias)
Rasineni, *et al.*	+	+	+	?	?	+	?	+	+	+
Alkreathy, *et al.*	+	+	+	+	?	+	?	+	+	+
Espejel-Nava JA, *et al.*	+	+	+	?	?	+	?	+	+	+
Waleed, *et al.*	+	+	+	?	?	+	?	+	+	+
Tiong, *et al.*	+	+	?	?	?	+	?	+	+	+
Srinivas, *et al.*	+	+	+	?	?	+	?	+	+	+
Elisa, *et al.*	+	+	+	?	?	+	?	+	+	+
Ahmed, *et al.*	+	+	+	?	?	+	?	+	+	+
Xin-gang, *et al.*	+	+	+	?	?	+	?	+	+	+
Somnath Singh, *et al.*	+	+	+	?	?	+	?	+	+	+
Eman H. Altaee, *et al.*	+	+	+	?	?	+	?	+	+	+
Khadija Azam, *et al.*	+	+	+	?	?	+	?	+	+	+
Riya Liak, *et al.*	+	+	+	?	?	+	?	+	+	+

Key: +=Low risk of bias; ?= No information.

administration to rats led to increased insulin secretion upon glucose stimulation, further supporting its potential role in addressing β-cell dysfunction for more effective type 2 diabetes treatment.[28]

C. roseus with Ursolic Acid as discussed by Alkreathy *et al.* (2020) has revealed that the two compounds have a synergistic effect on lowering blood glucose and lipid profiles. This combination not only improves the hypoglycemic effect, but also indicates a decrease in the doses, which will help to reduce the negative impact on the body.[25]

C. roseus significantly enhances the distribution of insulin, glucagon and glucose transport genes (GLUT-2 and GLUT-4), restoring their mRNA levels to near normal. A decrease in these glucose transport gene levels leads to hyperglycemia due to reduced glucose uptake. By restoring these levels, *C. roseus* improves glucose uptake in the liver, aiding in the management of hyperglycemic conditions associated with type 2 diabetes.[10,30]

C. roseus holds promise as a therapeutic agent for managing diabetes by improving enzymatic activities, reducing lipid peroxidation levels and normalizing oxidative stress markers while showcasing hypoglycemic properties across various animal models studied.[31]

CONCLUSION

The antihyperglycemic activity of *C. roseus* Linn. supports the therapeutic role of the plant in diabetes mellitus management. A number of experimental investigations have demonstrated a significant reduction of blood glucose levels in animals and even better results than standard treatment drug glibenclamide, proving the efficiency of *C. roseus*. This plant not only enhances insulin release from damaged beta cells on exposure to glucose but also stimulates the genes of GLUT-2 and GLUT-4. In addition, *C. roseus* has the ability to increase the activity of key glycolytic enzymes and decrease diabetes mediated damage in both blood and tissue. The presence of bioactive compounds including gallic acid, vindoline and chlorogenic acid supports the hypoglycemic effect of the plant. These findings suggest that *C. roseus* could be a potential source of an alternative treatment for diabetes and more research should be carried out to test the efficacy of the plant in human subjects. If these positive effects are further observed in humans, *C. roseus* can be a natural remedy for diabetes with an ability to reduce the risk of complications and enhance the therapeutic strategies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DM: Diabetes Mellitus; ***C. roseus:*** *Catharanthus roseus* linn; **GLUT-2:** Glucose transporter 2; **GLUT-4:** Glucose transporter 4; **PRISMA:** Preferred Reporting Items for Systematic reviews and Meta-Analyses; **ROS:** Reactive oxygen species; **N:** Number; **Mg:** milligram; **Kg:** kilogram

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