



REVIEW ARTICLE

Therapeutic Efficacy and Antihyperglycemic Properties of *Catharanthus roseus* for Diabetes Mellitus: A Systematic Review

Dhrithi Tummala*

Department of Center for Molecular and Translational Medicine, Georgia State University, USA

*Corresponding author: Dhrithi Tummala, Department of Center for Molecular and Translational Medicine, Georgia State University, USA



Abstract

Background: Diabetes mellitus refers to a group of metabolic diseases, in which the patient experiences high levels of blood glucose due to an insufficient production of insulin by the pancreas (Type I diabetes) or an inability of his/her body to respond to the insulin produced (Type II diabetes). *Catharanthus roseus* (*C. roseus*) is a plant that belongs to the *Apocynaceae* family, and has long been used as a natural medicine for Type-1 and Type-2 diabetes in the Ayurvedic system of medicine. This systematic review aims to summarize and provide an overview of the results of several studies that have been conducted to evaluate the plant's antidiabetic efficacy.

Methods: Publications from the databases PubMed and SpringerLink were searched up until August 2020. Publications and studies were considered based upon their relevance, impact, and recency. Studies that analyzed the antihyperglycemic and antidiabetic effects of *C. roseus*, and that had an English title and abstract were included. Extraction and content analysis were performed systematically.

Results: In total, 169 publications were identified that had been published up to August 2020, of which 9 publications that analyzed the antihyperglycemic and antidiabetic effects of *C. roseus* were included after being assessed for eligibility and undergoing an exclusion process based on finding duplicates and assessing content.

Conclusion: The results from all the studies were consistent in that they corroborated hypoglycemic activity by *C. roseus* and decreased/controlled blood glucose levels in their experimental subjects. These antidiabetic properties of *C. roseus* are accounted for by the augmented production of glucose-stimulated insulin from beta cells that were otherwise impaired and augmented the expression of GLUT-2 and GLUT-4 genes in the experimental subjects.

Keywords

Systematic review, *C. roseus*, Diabetes, Preclinical, Natural medicine

Introduction

Diabetes mellitus refers to a group of metabolic diseases, in which the patient experiences high levels of blood glucose due to an insufficient production of insulin by the pancreas (Type 1 diabetes) or an inability of his/her body to respond to the insulin produced (Type II diabetes) [1]. The etiological factors for type I diabetes have not been confirmed; however, scientists have identified autoimmune causes, in which the immune system attacks the insulin producing beta cells [1]. On the other hand, those who are overweight or have familial history of type II diabetes are more disposed to the condition [1]. Symptoms may include increased appetite, frequent urination, and increased thirst [1]. Prolonged periods of high blood sugar levels as characterized by diabetes may lead to severe complications when untreated. This disease is a significant determinant of heart attacks, blindness, kidney failure, stroke, and amputations of limbs [1]. In 2019, approximately 9.3% of the global population, which equates to about 463 million people worldwide, suffered from diabetes mellitus, whilst the disease also accounted for about 1.92 million deaths in the same year [2,3]. As morbidity rates for diabetes augmented over the decades, new medications and treatment procedures tailored for each type of diabetes came about. Glucose lowering

medications, such as metformin, NPH insulin, and GLP-1 agonists, are administered in the form of oral drugs or injections [1]. Although insulin therapy is effective, it can result in various side effects after prolonged periods of treatment, such as insulin resistance, fatty liver, anorexia nervosa, and brain atrophy [4].

Catharanthus roseus (*C. roseus*) is a flowering plant that belongs to the Apocynaceae family, and its flowers, leaves, and roots have long been used as a natural medicine for Type-1 and Type-2 diabetes as well as other ailments in the Ayurvedic system of medicine [4].

Aims

This systematic review aims to provide an overview of the results of several studies that have been conducted to evaluate the plant's efficacy in lowering blood sugar levels as well as its ability to treat other blood glucose related illnesses.

Methods

This systematic review was conducted in accordance with the quality requirements of the PRISMA guideline, and the protocol was not pre-registered in the PROSPERO database.

Ethics

All included research studies were carried out by adopting the guidelines of a relevant ethics committee on the use and care of laboratory animals.

Consent

No human studies were included.

Search strategy

The searched databases were PubMed and SpringerLink, and publications from the inception of the database to August 2020 with an English title and abstract were included. The reference lists from applicable reviews were also screened for additional articles. Search terms used included "*Catharanthus roseus* Diabetes", "*Catharanthus roseus* Glucose", and "*Catharanthus roseus* Diabetes" OR "*Catharanthus roseus* Glucose". The database search resulted in 169 articles, and a total of 74 duplicates were removed. Three non-English articles were excluded, and 81 non-pertinent articles were excluded after abstract screening, leaving a total of 9 primary research articles.

Study selection and data extraction

Publications and studies were considered based upon their relevance, impact, and recency. Full texts of relevant articles were screened for studies that analyzed the antihyperglycemic and antidiabetic effects of *C. roseus*. The search strategy was set up using free-text terms. Studies were included if they involved the testing of *Catharanthus roseus* extracts or components on diabetes induced test subjects, including strains of rabbits, mice, rats, or pancreatic cells. Studies in which *C. roseus* extracts or organic compounds were not

Table 1: Search strategy in PUBMED from 1989 to August 2020.

Search step	Hits	Search
1	36	<i>Catharanthus roseus</i> Diabetes
2	59	<i>Catharanthus roseus</i> Glucose
3	73	1 or 2

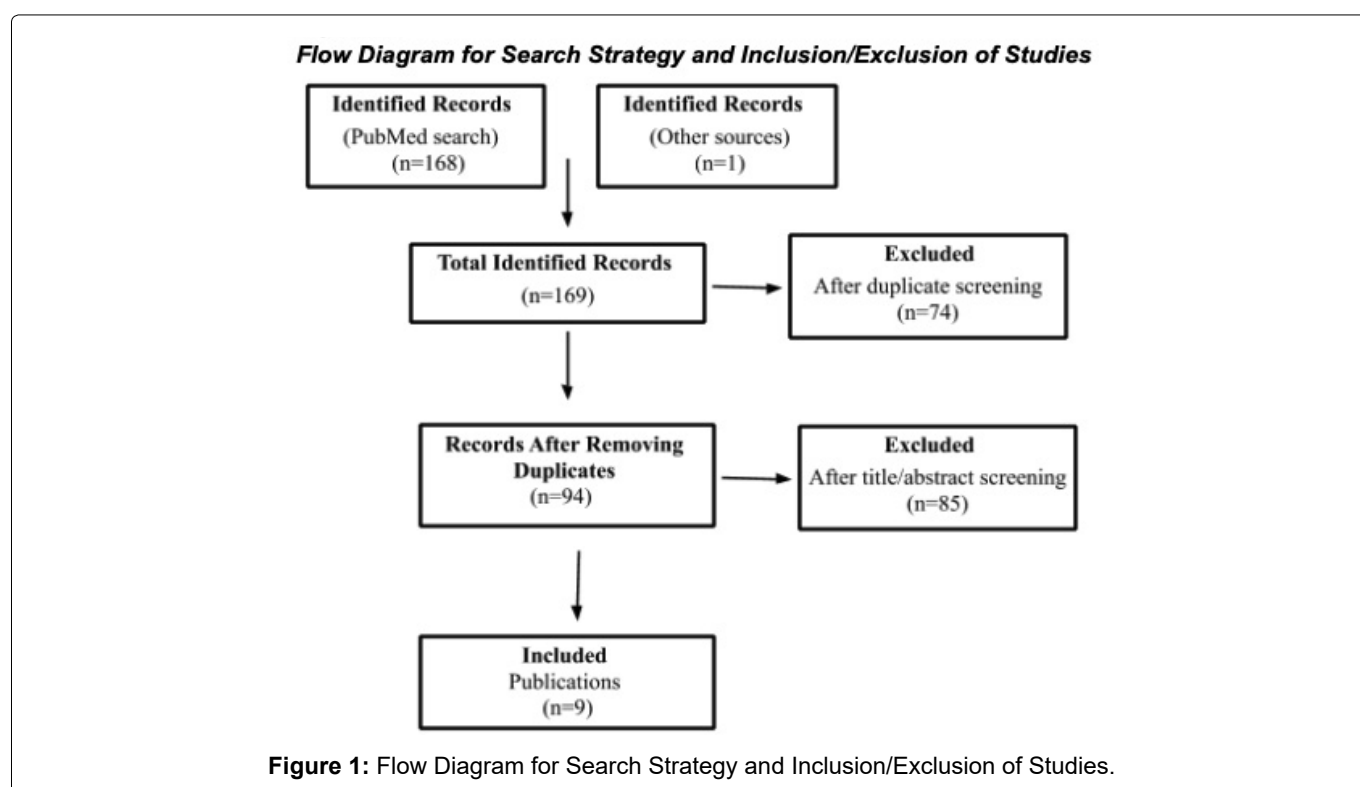


Figure 1: Flow Diagram for Search Strategy and Inclusion/Exclusion of Studies.

administered, or those without appropriate controlled groups were excluded. Studies were excluded if full English language texts were not available. Studies that focused on the efficacy of *C. roseus* to treat other diabetes-induced secondary diseases were not included.

When relevant, the method of inducing diabetes in the experimental groups was extracted from each of the studies. The studies were also screened for the method or route of administering *C. roseus* and characteristics of the animal samples, including sample size, sample type, type of diabetes mellitus that was induced, sex, and age. Studies in which one or more sample characteristics were not found were screened again, and if the data was not found after a second screening, the reviewer made note of the specific sample characteristics that were not found; those studies were not excluded (Table 1 and Figure 1).

Assessment of risk of bias

Risk of Bias was assessed for each study with the use of SYRCLE's RoB tool for animal studies [5]. The author (DT) independently assessed the risk of bias of the included studies across domains of sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessment, incomplete outcome data, and selective outcome reporting. Each domain had three possible judgments: "low risk", "high risk" or "unclear risk".

Results

In total, 169 publications were identified that had been published up to August 2020, of which 9 publications that analyzed the antihyperglycemic and antidiabetic effects of *C. roseus* were included (Table 2).

Table 2: Study Characteristics.

Author/Year	Sample Size	Population Characteristics	Aims/Findings
Rasineni, et al. [4]	n = 48 (Wistar rats)	DM type = Type 1 and Type 2 Diabetes Sex = Male Age = 6-7 weeks	The study treated both STZ-induced Type 1 and fructose diet-induced Type 2 rats with <i>C. roseus</i> for 60 days. At the end of the 60 days, the rats were found to have ameliorated the defects in the activities of key enzymes of glycolytic, gluconeogenesis and polyol pathway, and intestinal disaccharides.
Alkreathy, et al. [6]	n = 6 (groups of Wistar rats)	DM type = Type 2 Diabetes Sex = Male Age = 5-6 months	The six groups were given a dose of streptozotocin to induce diabetes, and were then treated with <i>C. roseus</i> ethanolic extract and Ursolic Acid for 28 days. The results showed that low dose combinations of <i>C. roseus</i> ethanolic extract and Ursolic Acid were optimal for treatment of diabetes and showed the greatest control of blood glucose levels.
Espejel-Nava, et al. [7]	n = 8 (groups of <i>Mus musculus</i>)	DM type = Type 2 Diabetes Sex = Male Age = NA	The six groups were given a dose of streptozotocin to induce diabetes, and were then treated with a phenolic fraction of <i>C. roseus</i> . The particular phenolic fraction of <i>C. roseus</i> , which contained gallic acid and chlorogenic acid had the greatest hypoglycemic effect that may account for an increase in insulin secretion.
Chaudhary, et al. [8]	n = 30 (Wistar rats)	DM type = Type 2 Diabetes Sex = Male Age = 6 weeks	The 30 rats were divided into six groups and were given a dose of streptozotocin to induce diabetes, and were then treated with <i>C. roseus</i> plant ethanol extract. The results showed that the <i>C. roseus</i> extract exhibited antihyperglycemic activity and reversed most blood and tissue changes caused by STZ-induced diabetes in the rats.
Tiong, et al. [9]	n = 1.5 × 10 ⁴ (Mouse β-TC6 pancreatic cells)	DM type = Type 1 Diabetes Sex = NA Age = NA	Vindoline, vindolicine, vindolidine, and vindolinine, which are alkaloids present in <i>Catharanthus roseus</i> , were isolated and administered to the cells. The results showed hypoglycemic activity of the alkaloids in the β-TC6 mouse pancreatic cells.
Nammi, et al. [10]	n = 10 (groups of adult albino rabbits)	DM type = Type 1 Diabetes Sex = male and female Age = NA	The rabbits were divided into ten groups of five and were administered a dose of alloxan to induce diabetes. They were then given leaf juice of <i>C. roseus</i> , which resulted in significant antidiabetic and hypoglycemic activity in the rabbits, which could be accounted for the release of insulin from the surviving β-cells.

Vega-Avila, et al. [11]	n = 36 (Mus musculus CD-1 strain)	DM type = Type 2 Diabetes Sex = male Age = NA	The mice were divided into six groups of six and were administered a dose of alloxan to induce diabetes. They were then administered aqueous stem, leaf, root, and flower extracts of <i>C. roseus</i> ; they all resulted in hypoglycemia activity, with the aqueous leaf extract resulting in the most significant blood glucose decreasing activity.
Ahmed, et al. [12]	n = NA (Wistar rats)	DM type = Type 1 Diabetes Sex = NA Age = NA	The rats were administered a dose of streptozotocin to induce diabetes, and were then given an aqueous leaf extract of <i>C. roseus</i> . After being monitored for a period of 24 hours following the administration of extract, the rats exhibited a significant decrease in serum glucose levels.
Yao, et al. [13]	n = NA (Wistar rats)	DM type = Type 1 Diabetes Sex = NA Age = NA	The rats were administered a dose of streptozotocin and a high-fat diet to induce diabetes, and were then given vindoline, which is an alkaloid present in <i>C. roseus</i> . The rats were monitored, and the results showed that the vindoline increased the secretion of glucose-stimulated insulin in the rats.





























































































Key:	Random sequence generation (selection bias)	Baseline characteristics (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 (reporting bias)	Other bias
 = Low risk of Bias										
 = Unclear Risk of Bias										
Rasineni, et al. [12]										
Alkreathy, et al. [4]										
Espejel-Nava, et al. [5]										
Chaudhary, et al. [6]										
Tiong, et al. [7]										
Nammi, et al. [8]										
Vega-Avila, et al. [9]										
Ahmed, et al. [10]										
Yao, et al. [11]										

Figure 2: SYRCLE's Risk of bias summary.

Risk of bias

Risk of Bias was assessed for each study with the use of SYRCLE's RoB tool for animal studies [5]. Risks of bias in each of the domains for each included study is summarized in Figure 2 and each risk of bias item is presented as percentages across all included studies in Figure 3. The studies were at low risk of bias for random sequence generation, baseline characteristics, allocation concealment, random outcome assessment, incomplete outcome data, selective reporting, and other bias. Details of random housing conditions, blinding, and blinding of outcome assessment were poorly described across the majority of the studies.

Discussion

Summary of findings

This is the first systematic review that analyzes the existing research regarding the efficacy of *Catharanthus roseus* to treat diabetes; nine studies were identified. Four of the studies evaluated the efficacy of *C. roseus* to treat Type 1 diabetes, four of the studies evaluated the efficacy of *C. roseus* to treat Type 2 diabetes, and one study tested the plant's efficacy to treat both types. Eight of the studies utilized strains of rats or mice to test the plant on, while one study utilized pancreatic rat cells *in vitro*. Two of the studies isolated particular alkaloids present in the plant and tested those on their experimental groups, while the other seven studies administered extracts from the entire plant or from particular parts of it, such as from its flowers, leaves, roots, and/or stem. The results from all the studies

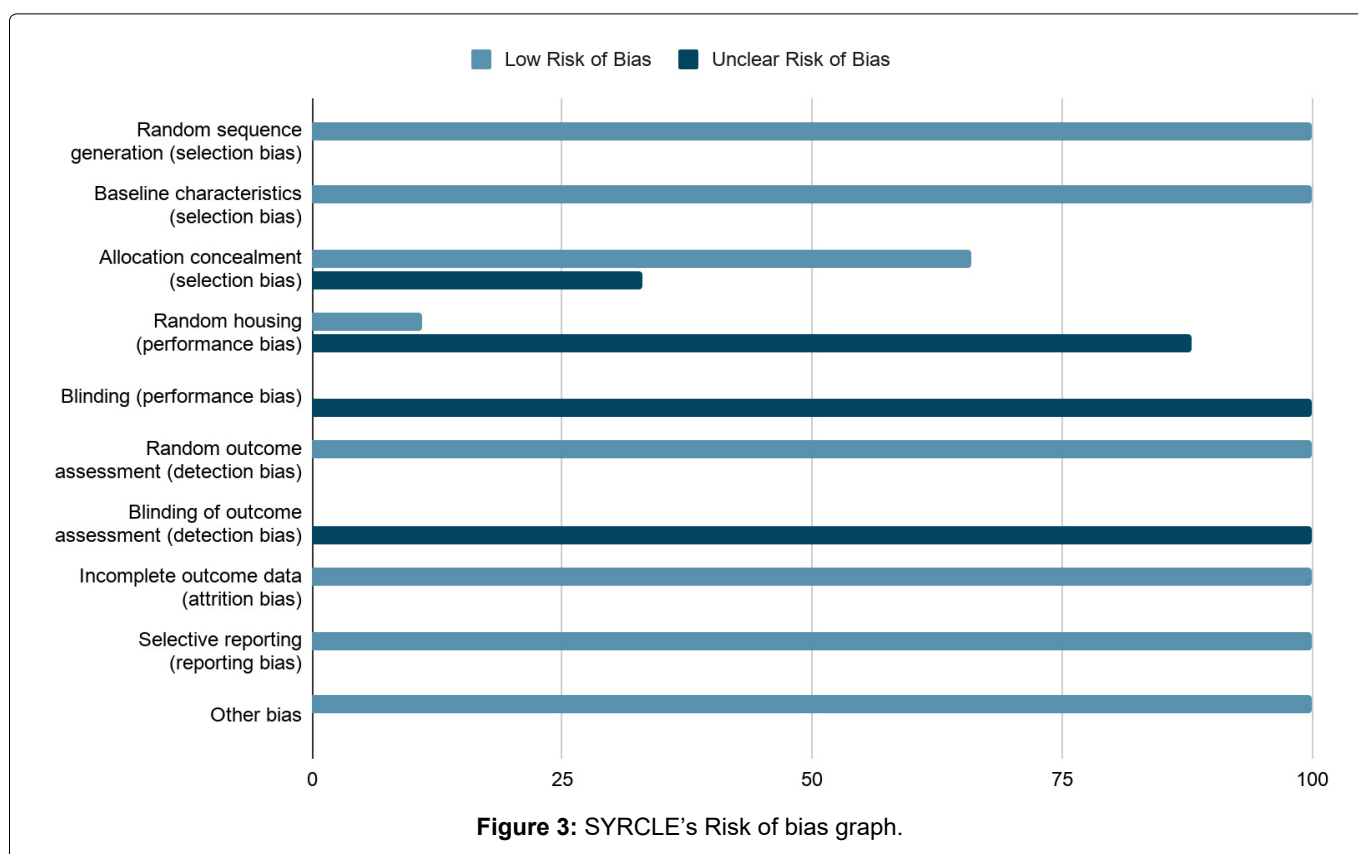
were consistent in that they corroborated hypoglycemic activity by *C. roseus* and decreased/controlled blood glucose levels in their experimental subjects.

Limitations

Although full texts could be found for most of the studies identified, only the abstracts could be found for two of them. As a result, those particular studies could not be scrutinized in as great detail as the others. Withal, all of the studies identified were performed on animals resulting in a lack of data regarding the plant's effects on humans.

Conclusions

In overall establishment, *C. roseus* exhibited antihyperglycemic activity and significantly decreased blood glucose levels in the test subjects; administration of the plant resulted in prolonged action of reduction of blood glucose in comparison to standard diabetes drugs, such as glibenclamide. It, in fact, induced the secretion of glucose-stimulated insulin from beta cells that were otherwise impaired and augmented the expression of GLUT-2 and GLUT-4 genes. Defects in the activities of key enzymes of glycolytic pathways were ameliorated, whilst diabetes-induced damage to blood and tissue in the subjects were reversed. Specific components of *C. roseus*, such as vindoline, vindolicine, vindolidine, vindolinine, gallic acid, and chlorogenic acid were isolated and identified as having hypoglycemic properties. The propitious and consistent results of the studies examined could provide as a basis for further studies of the efficacy of the plant in human trials. *C.*



roseus could be utilized as a prevention of diabetes complications and as a possible herbal/natural cure for diabetes mellitus.

Funding

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Declaration of Conflict of Interest

The Author, Dhriti Tummala, declares that there is no conflict of interest.

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