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REVIEW ON CATHARANTHUS ROSEUS: AN EFFECTIVE TREATMENT APPROCH FOR DIABETES

[1] Miss. Pawar Madhuri. R*,[2] Miss. Khandagale Sheetal.S,[3] Dr. Kambale Hemant.V, [4] Mr. Waghmare Santosh. A

[1]Student,[2]Student ,[3]Principal, [4]Assistant Professor
[1]Department of Pharmacology,
[1] Lokenete Shri. Dadapatil Pharate college of Pharmacy, Pune, India

Abstract :
Globally, diabetes mellitus is the most common condition that results from metabolic issues. Hyperglycemia in the blood, which results from improper pancreatic insulin secretion, is the primary sign of diabetes mellitus. The traditional signs of polyuria (frequent urine), polydipsia (increased thirst), and polyphagia are caused by this elevated blood sugar level (increased hunger). The body's inability to create enough insulin causes type 1 diabetes. Previously, this condition was referred to as "juvenile diabetes" or "insulin-dependent diabetes mellitus" (IDDM). There is no known cause. Insulin resistance, a disease in which cells do not respond to insulin as it should, is the first sign of type 2 diabetes. In addition, a shortage of insulin may occur as the condition worsens. Previously, this type was known as "non insulin-dependent diabetes mellitus." (NIDDM) Diabetes has a lot of problems if left untreated. India has a diverse array of medicinal plants, although they have not yet been fully studied. The prevalence of diabetes mellitus is practically universal throughout the world. Plants have been utilised to treat ailments since since the Ayurveda philosophy and practise emerged in India. Although Catharanthus roseus has been utilised for its purported health advantages and to profit from its hypoglycemic impact, diabetics take it as medicine. Many pharmacological properties of Catharanthus roseus, a strong medicinal plant, including antibacterial, antioxidant, anthelmintic, antidiarrheal, and antidiabetic effects, among others. Extracted from the Catharanthus roseus plant, vindoline, vindolicine, vindolinine, and vindolidine showed anti-diabetic or antihyperglycemic properties. Catharanthus roseus, as well as the traits and customary use of this plant's phytoconstituents. In order to support their potential as medicines, the benefits of the bioactive substances discovered in Catharanthus roseus were also examined.

KEYWORDS: Catharanthus roseus, Apocynaceae, Diabetes mellitus, diagnosis, etiology, and therapy

I. INTRODUCTION

Diabetes mellitus (DM) Almost 100 million people (6% of the world's population) globally are affected by diabetes mellitus (DM), the most prevalent endocrine illness. Hyperglycemia, glycosuria, hyperlipidemia, a negative nitrogen balance, and occasionally ketoacidosis are the hallmarks of this metabolic condition. A metabolic illness known as diabetes mellitus is characterised by persistent hyperglycemia and changes in the metabolism of carbohydrates, fats, and proteins as a result of errors in insulin secretion, insulin action, or both. (1) The pancreas's inability to produce enough insulin, which causes glucose levels in the blood to rise or fall, is the cause of this condition. Several biological systems, including the blood vessels, eyes, kidneys, heart, and nerves, have been discovered to be damaged by it. (2)

Table 1: Classification of diabetis mellitus

No.	Type Characteristics	Feature
1	Type 1 ((IDDM)	This type is an autoimmune disease Damage of β-cells there by Secretion of insulin was reduced
s	Type 2 (NIDDM)	Imperfection of ß-cell functions genetically. Failure in insulin secretion genetically
3	Gestational diabetes	It is a temporary and appears during pregnancy usually develops during third trimester of pregnancy. After delivery, blood sugar levels generally return to normal
4	Other specific types	Pancreatic endocrinopathy. Indigenous infections like rubella or chemicals. Other genetic indisposition.

1.

Type 1 diabetes(T1D)/ Juvenile diabetes/ Insulin dependent diabetes	Type 2 diabetes/ Non-insulin dependent diabetes mellitus (T2D or NIDDM)	Gestational diabetes
This type is an autoimmune disease, meaning your body attacks itself. In this case, the insulin-producing cells in your pancreas are destroyed.	There is no loss or moderate reduction in B cell mass; insulin in circulation is low; normal or even high,	This type develops in some women during their pregnancy.
It's usually diagnosed in children and young adults (but can develop at any age).	This is the most common form of diabetes that most often occurs in adulthood.	Gestational diabetes usually goes away after pregnancy.
It was once better known as "juvenile" diabetes.	Over 90% cases of diabetes are type 2 DM.	Weight gain and changing hormones that occur during pregnancy can impair insulin function, resulting in high blood sugar
People with Type 1 diabetes need to take insulin every day	In T2D, fat, muscle and liver cells do not respond correctly to insulin. This is called insulin resistance	
This is why it is also called insulin-dependent diabetes.	Diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM	
Insulin replacement therapy is the mainstay for patients with type 1 DM .		

Hormones as a cause of diabetes (Type1 IDDM)

This type of diabetes, formerly known as juvenile-onset or ketosisprone polygenic disease, is also referred to as reaction diabetes. If a person has Graves' disease, Hashimoto's thyroiditis, or Addison's disease, they may also request if they have those conditions. The majority of people with type I diabetes, also known as insulin-dependent diabetes (IDDM), are children and young adults. (5)

Etiology

Auto immune response: It takes the form of an autoimmune disorder [11–15], in which the body's own immune system eventually kills the beta cells in the pancreas, lowering insulin production. It is still unclear how exactly environmental and genetic risk factors relate to the development of type 1 diabetes. (6)

2. Mellitus, a polygenic condition that is not insulin-dependent (Type2 NIDDM)

Ketosis-resistant diabetes mellitus is another name for type 2 diabetes (5)

Almost 90% of all instances of diabetes are Type 2 diabetes mellitus (T2DM). Insulin resistance is the term used to describe the reduced insulin response in T2DM. When insulin is useless in this condition, the body produces more insulin to maintain glucose homeostasis at first, but over time, this diminishes, leading to T2DM. T2DM is most frequently diagnosed in those over the age of 45. Nonetheless, it is becoming more common in kids, teenagers, and young adults as a result of increased obesity rates, inactivity rates, and calorie-dense diets. (7)

Etiology

1. Genetic Factors: Genetic research is more crucial for type II diabetes than type 1 If one of the identical twins has type II DM, the other twin has an 80% risk of developing the condition.
2. Constitutional Factors: These include environmental influences as well as other problems including obesity, high blood pressure, and a lack of exercise.
3. Insulin Resistance: The lack of responsiveness to the insulin released is the most obvious symptom of type II diabetes (peripheral tissues including skeletal muscle and the liver become resistant to insulin). Insulin resistance and obesity are closely related.
4. Impaired Insulin Secretion: Insulin is secreted in substantial amounts in the early stages of type II diabetes to counteract rising blood glucose levels. Later on, however, it can happen that beta cells are unable to secrete enough insulin.

The pancreas is unable to produce enough insulin to combat insulin resistance because of the continued development of insulin resistance and -cell malfunction.

Gestational diabetes mellitus (GDM)

One of the most prevalent medical problems during pregnancy is gestational diabetes mellitus (GDM), whose incidence is rising as more women of older ages are getting pregnant. The higher incidence is also brought on by the rising rates of maternal inactivity and obesity. GD often manifests between 24 and 28 weeks into pregnancy. Hormonal changes and the body's process of turning food into

energy are the causes of gestational diabetes. Hormones during pregnancy can affect how insulin functions. There is a chance that it won't control your blood sugar levels as it should, which can result in gestational diabetes. (8) In contrast to type 1 diabetes, gestational diabetes results from additional hormones released during pregnancy that may reduce the effectiveness of insulin, a condition known as insulin resistance. After birth, gestational diabetes symptoms go away. (9)

Other certain kind (Monogenic diabetes)

"Other Particular Types" refers to a classification of recognised etiologically diverse types of diabetes mellitus. Less than 10% of people in this group have pancreatic dysfunction brought on by drugs, chemicals, or infections. The remaining 90% have diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis, dysfunction associated with other endocrinopathies (such as acromegaly), or pancreatic dysfunction brought on by genetic defects of beta-cell function (this type of diabetes was formerly known as MODY or maturity-onset diabetes in youth).

Pathophysiological aspects

Patients with type 1 diabetes who initially experience symptoms are typically young (children or teenagers) and not obese.

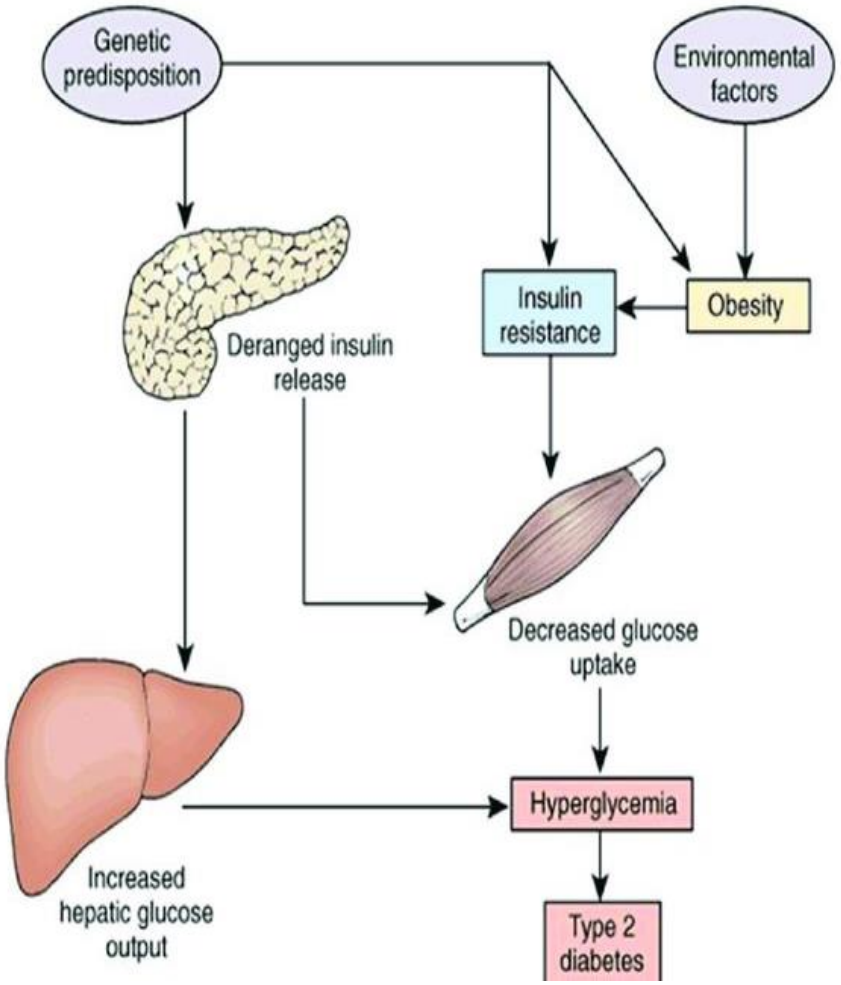
This kind of diabetes is a chronic autoimmune illness in which insulin-producing pancreatic beta-cells are specifically destroyed. When CD4+ and CD8+ T lymphocytes and invading macrophages attack the insulin-producing cells in the pancreas, Type 1 Diabetes is characterised. (11) The metabolic abnormalities associated with T1DM are caused by the autoimmune death of pancreatic beta-cells, which results in a lack of insulin production.

In addition to the reduction in insulin secretion, T1DM patients also have aberrant pancreatic beta-cell activity and increased glucagon release.

In healthy people, hyperglycemia reduces glucagon secretion; however, in those with T1DM, hyperglycemia has no effect on glucagon secretion. (12)

Pathophysiological aspects

As a result of insulin resistance, decreased insulin production, and eventually failing pancreatic beta cells, type 2 diabetes is characterised by insulin insensitivity. As a result, less glucose is transported into the liver, muscles, and fat cells. With hyperglycemia, there is an increase in the breakdown of fat. (13,14) When insulin resistance is prevalent, the mass of -cells goes through a change that can increase the insulin supply and make up for the excessive and abnormal demand.



Diabetes type 1 treatment

The initial line of treatment for type 1 diabetes is insulin, which can be given intravenously or through an insulin pump. There are three types of insulins: intermediate acting, long acting, and quick acting.

Certain insulins (HUMULIN 70/30, NOVOLIN 70/30) are similar to ordinary insulin. (6)

The goal of insulin therapy should be to replicate nature, which is very effective at preventing between-meal hypoglycemia and minimising postprandial hyperglycemia.(5)
The use of insulin is not without risks and side effects.
The most significant negative effects include weight gain and hypoglycemia when an improper insulin dose is given and when meals and insulin injections are not timed properly.(16, 17)

Pharmacological treatment for type 2 diabetes:

Oral hypoglycaemic medications, including sulphonylureas, alpha glucosidase inhibitors, biguanides, and thiazolidenediones, are helpful in the management of type 2 DM. The primary goal is to treat metabolic disorders such insulin resistance and inadequate insulin secretion.
They are administered along with a proper diet and lifestyle adjustments. They demonstrate weight loss, improved glycemic management, and a reduced risk of cardiac issues. (18)

Table 3: Pharmacological therapy

No.	Type of drug	Drug generic	Brand name
1	Sulfonylureas	Tolbutamide Glipizide, Gliclazide, Glimepiride	AMARYL DIABETA GLYNASE GLUCOTROL
2	Biguanides	Metformin	GLUCOPHAGE
3	Thiazolidinediones	Pioglitazone	ACTOS, AVANDIA
4	α-Glucosidase inhibitors	Acarbose	Acarbose PRECOSE, GLYSET
5	Phenylalanine analogues	Nateglinide	PRANDIN, STARLIX

Antidiabetic Potential of Phytochemicals Derived from Catharanthus roseus

In order to avoid the adverse effects of the pharmaceuticals used to treat Type II diabetes, which have several side effects on the body and interact with other medications, we should utilize herbal medications instead, which are widely available and have few unwanted effects on the body.
Adverse effects include gaining weight, black urine, upset stomach, rashes on the skin, elevated LDL values, etc.
Fluconazole and ketoconazole, as well as other azole antifungals, may interact with other medications. NSAIDs, sulfonylureas, oral contraceptives, nitrates, and certain antibiotics like chloramphenicol.
We can utilise herbal medicines made from various plants, such as Catahranthus roseus, to stop this impact. (22)
More than 180 million people globally are estimated to have diabetes as of right now, and that number is expected to quadruple by 2030, with India, China, and the United States expected to have the highest numbers of affected people (19). Many plants and their chemical constituents have proven effective in treating a variety of illnesses (20). More than 800 plants are utilised as traditional treatments in some capacity for the management of diabetes, according to ethnobotanical data (21).
India gains access to a priceless herbal legacy. (23) Together with homoeopathy and folk medicine, the traditional medical system in India continues to be essential to the nation's total healthcare system (24). Humans have employed medicinal plants as necessary components in diets, beverages, and remedies since the dawn of time. There are numerous industrial uses for the nutritional, pharmacological, biological, and toxicological traits of medicinal plants (25). Traditional medicine has always made use of medicinal herbs.
Access to a priceless herbal legacy is gained by India. (23) The traditional medical system in India continues to be crucial to the country's overall healthcare system, along with homoeopathy and folk medicine (24). Throughout the beginning of time, humans have used medicinal plants as essential ingredients in foods, drinks, and treatments. The nutritional, pharmacological, biological, and toxicological characteristics of medicinal plants have a wide range of industrial applications (25). Herbal remedies have historically been used in traditional medicine.

Several hypoglycemic plants are well-known through folklore, but their inclusion in the current medical system will have to wait until the development of animal test systems that are closely related to the pathological development of diabetes in humans. Several plants have been implicated with hypoglycemic activity throughout the past 20 years. (26)
The Rig-Veda, a collection of Hindu sacred scriptures, and the Ayurveda medical system it inspired, which is still widely used in India today, are the sources of herbal remedies in that country. Catharanthus roseus is a member of the apocynaceae family (27) Periwinkle, Madagascar periwinkle, and Sadabahar are some of the common names for Catharanthus roseus; the word catharanthus means "pure flower" in Greek. Roseus, on the other hand, is Latin for red, rose, or rosy (34). It spreads throughout India and can be found in waste areas and sand dunes as a refuge. The National Cancer Council of Malaysia uses the periwinkle emblem as a representation of hope for people with cancer.

There have been reports of around 130 distinct substances, including about 100 monoterpenoid indole alkaloids (28). Under drought stress, it has strong antioxidant potential across its entire body as a significant medical plant (29). Catharanthus roseus leaves have been shown to maintain blood sugar (30), reduce excessive blood pressure (31) and treat Hodgkin's disease (32) in addition to acting as an antioxidant (33).

Scientific classification (35)

Kingdom: Plantae
Division: Magnoliophyta (Flowering plants)
Class: Magnoliopsida (Dicotyledons)
Order: Gentianales
Family: Apocynaceae
Genus: *Catharanthus*
Species: roseus

Vernacular names (36)

Sanskrit: Nityakalyani, rasna, sadampuspa, sadapushpi
English: Cayenne jasmine, old maid, Madagascar periwinkle, Red periwinkle
Hindi: Sada suhagan, sadabahar
Kannada: Batla hoo, bili kaasi kanigalu, ganeshana hoo, kempu kaasi kanigalu

FIG.2: *CATHARANTHUS ROSEUS (COPIED FROM GOOGLE.COM*

Chemical constituents

The most significant alkaloids range from 0.74 to 0.82%, with vincristine, vinblastine, catharanthamine, and vincoline being among them. There are also isolated forms of other alkaloids, including deoxyvinblastine, leurosine, pleurosin, leurocristine, leuroidine, vincolinine, vinacardine, roseadine, vindolicine, and rosicine (37-41).
Vinca alkaloids are valuable as medications since they contain both physiological effects and toxic properties. The alkaloids are found throughout the entire plant. The root bark, particularly during blossoming, contains the most. The antineoplastic dimeric alkaloids vinblastine and vincristine in the aerial portions and ajmalicine and serpentine in the roots are the most physiologically significant alkaloids.

Vinflunine is another alkaloid that is only widely used in Europe and is thought to have anti-tumor properties. The alkaloids catharanthine and vindoline are biosynthesized to produce the chemotherapeutic drugs vinblastine and vincristine, which are used to

treat many forms of cancer. Vinorelbine, a more recent semi-synthetic chemotherapeutic drug used to treat non-small-cell lung cancer, can be made from the vinca alkaloid leurosine or from vindoline and catharanthine, both of which need the usage of anhydrovinblastine. Anthocyanidin pigment known as rosinidin can be discovered in the flowers of C. roseus (42-45)

Table no.4 Traditional utilization of Catharanthus roseus (46)

Plant Components	**Preparation**	**Diseases**
Whole plant	Soaked and steamed in water	Diabetes, Hypertension, Dysentry, Cancer
	Dried, soaked and steamed in water	DM
	Dried, ground into a fine powder and diluted in regular cow milk	DM
Leaf	Dried and prepared an extract by decoction	DM
Roots	Crushed and added with water	Stomach pain
Stem	Boiled in water	DM

Antidiabetic activity

Catharanthus roseus has historically been utilized to control diabetes throughout many countries all over the world. The ethanolic extracts of C. roseus's leaves and flowers demonstrated a dose-dependent decrease in blood sugar that was comparable to that of the prescribed medication. Blood sugar lowering is comparable to the common medication glibenclamide. The increased hepatic glucose utilisation has led to the appearance of the hypoglycemic impact. In comparison to the dichloromethane and methanol extracts, which reduced blood glucose levels in diabetic rats by 49–58% and 20%, respectively, respectively, the aqueous extract was found to lower blood glucose by roughly 20%. Due to the liver's increased use of glucose, the hypoglycemic effect has shown. Pharmacological research on the C. roseus alkaloids' hypoglycemic action has led to the commercialization of Vinculin, a medicine produced from the plant, as a diabetes cure.(35)

Using a streptozotocin-induced diabetic rat model, a dichloromethane:methanol extract (1:1) of the plant's leaves and twigs was reported to have hypoglycemic effect when given orally for 7 and 15 days at a dose of 500 mg/kg. The hypoglycemic activity was between 48.6 and 57.6%, and further treatment for 30 days completely protected the subjects from the STZ challenge (75 mg/kg/i.p.).

The livers of diabetic rats were observed to have lowered enzyme activity for glycogen synthase, glucose 6-phosphate dehydrogenase, succinate dehydrogenase, and malate dehydrogenase, which would dramatically improve after treatment with extract at doses of 500 mg/kg p.o. for 7 days. Findings showed that treated rats had higher levels of lipid peroxidation and enhanced glucose metabolization.(36)

Using 2-NBDG glucose uptake and PTP-1B down regulation, which impede the insulin signalling pathway, researchers examined the in vitro anti-diabetic effects of four distinct bioactive chemicals isolated from Catharanthus roseus leaves.

Glycemic management in people with T2DM can be improved by increasing glucose absorption in pancreatic cells. In mouse -TC6 pancreatic and myoblast C2C12 cells, four alkaloids were found to increase glucose absorption while inhibiting PTP-1B. The four alkaloids were most active in vindolicine.

The findings highlighted Catharanthus roseus as a prospective source for more research into anti-diabetic drugs and showed its traditional use for therapeutic purposes in diabetes patients.

Conclusion:

Catharanthus roseus has long been used as a universal remedy for a wide range of illnesses. It has emerged as one of the strongest plants in the world. The powerful source of numerous innovative pharmaceutical compounds with pharmacological effects on humans came from medicinal plants. Instead than employing chemical treatments that have adverse effects, researchers might look into ancient medicine to find new drug formulations that are more effective, have less side effects, and are less expensive. The above plant has been studied for its phytochemical elements and pharmacological effects since ancient times. The plant contains a large number of phytochemical components with potential medical benefits. Because Catharanthus roseus contains phytochemicals such alkaloids and flavonoids, it has hypoglycemic properties. As a result, it may aid in preventing diabetic complications and act as a useful adjuvant in the current arsenal of anti-diabetic medications. There is hope that in the near future, since their role in immunology is still poorly understood, significant new information will become available.

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