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Anti-diabetic properties of sadabahar plant

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Abstract
Diabetes is a rapidly escalating health problem. Researchers have discovered novel strategies for the treatment of diabetes. Since ancient times, Sadabahar has been utilised to control diabetes in many regions of the world. Also known as *Catharanthus roseus*, it has been used in Ayurveda and Chinese medicine for centuries and is claimed to be a tried-and-true herbal remedy for chronic illnesses like diabetes. Over 120 alkaloids are produced, with 70 of them being pharmacologically active. Beneficial flavonoids and hypoglycemic alkaloids like catharanthine, leurosine, lochnerine, tetrahydroalstonin, vindoline, and vindolinine, vindogentianine are found in the plant. Researches have shown that the ethyl acetate fraction of the ethanolic extract of *C. roseus* has the best glucose lowering effect. This study focuses on the various biotechnological methods being adopted with constant advancements towards the role of sadabahar in treatment of diabetes and its future prospects.

Keywords: Alkaloids, anti-diabetic agents, *Catharanthus roseus*, diabetes, phytotherapy

Introduction
Diabetes mellitus is a complex disorder that affects a large portion of the global total. It is the world's major cause of mortality, and its trend is growing. It is a multifactorial disease in which the blood glucose level rises due to insulin action and secretion defects (Kumar *et al*., 2011) [22]. The World Health Organization (WHO) predicts that the diabetic population will reach 300 million or more by 2025. Diabetes is responsible for about 10% of all deaths. As a result, chronic hyperglycemia causes neuropathy, retinopathy, nephropathy, and cardiovascular disease. These are the most common causes of mortality and morbidity in diabetics. (World Health Organisation Tech Rep Ser 1980; 646: 1-80, World Health Organ Tech Rep Ser 1985, Mayfield J, 1998) [10, 29, 28]. Herbal medicines are thought to have a bright future in the treatment of type 2 diabetes. According to ethno - botanical data, approximately 800 plants have anti-diabetic potential and have shown beneficial effects in the treatment or preventative measures of diabetes - related complications. The ability of medicinal plants to restore pancreatic cell function by increasing insulin release or inhibiting intestinal glucose absorption is primarily responsible for their anti-diabetic activity. Polyphenols, terpenoids, flavonoids, carotenoids, and coumarins are the primary active constituents of plants (Matalqah *et al*., 2025) [26]. Among ancient cultures, India has long been known as a great storehouse of natural remedies. *Catharanthus roseus* is an annual herb in the Apocynaceae family. It has traditionally been used to control diabetes in many parts of the globe. *Catharanthus roseus* (synonym: *Vinca rosea*; Madagascar periwinkle; Apocynaceae) is a perennial plant native to Madagascar and Southern Asia (Sharma Sk, 1998, Council of Scientific and Industrial Research 3 (1985): 391-395) [43, 47]. The plant has stretched throughout India's tropical and subtropical regions, growing wild on the plains and lower westernghats of the Northern and Southern hills. Pink, purple, and white flowers are produced by these plants, which are planted for aesthetic reasons. Madagascar periwinkle has traditionally been used to treat a variety of conditions including high blood pressure, infection, and diabetes mellitus. The stem generates a milky sap that contains over 70 indole alkaloids. Vincristine and vinblastine, both secluded from such a plant, are well-known anti-cancer drugs for Hodgkin's lymphoma and childhood cancer. The mode of action is tubulin binding, which inhibits the metaphase of cellular mitosis. The most common side effects of this medication are hair loss, peripheral neuropathy, constipation, and hyponatremia (Johnson IS., *et al*. 1963, Loh KY, 2008) [19, 24]. Its leaf extracts significantly reduced blood sugar levels in normal and streptozotocin-induced diabetic model rats. In animal models, the

blood sugar-lowering potential of the leaf extract was equivalent to that of the commercially available drug Tolbutamide (Tiong SH *et al*., 2013, Chattopadhyay RR *et al*.,1999) [48, 9]. In diabetic animals, the enzymic activities of glycogen synthase, glucose 6-phosphate-dehydrogenase, succinate dehydrogenase, and malate dehydrogenase were found to be lower than in normal animals, but significantly higher after 7 days of treatment with dichloromethane–methanol (DCMM) extract of *C. roseus* leaves and twigs at 500 mg/kg p.o.It has been proposed that *C. roseus* exerts anti-diabetic activity in treated rats by increasing glucose metabolism (Singh SN.; *et al*., 2001) [45]. Between many crude extracts, alkaloids such as vindoline, vindolidine, vindolicine, and vindolinine secluded from *Catharanthus roseus* leaves stimulated enhanced uptake of glucose in myoblast C2C12 or pancreatic b-TC6 cells, with vindolicine displaying the greatest efficacy. Even at the highest dose of 25.0g/mL, the first three compounds had no cytotoxicity against pancreatic b-TC6 cells. Vindolicine, vindolidine, and vindolinine also demonstrated enhanced protein tyrosine phosphatase-1B (PTP-1B) inhibition behaviour, which may be important in the treatment of type 2 diabetes (Tiong SH *et al*., 2013) [48]. Thus, *Catharanthus roseus'* mechanism of action increases insulin synthesis from Langerhans beta cells (Verma S.; *et al*; 2018) [50]. Thus, we will conclude in the following review article that the leaves of the *C. roseus* plant have many therapeutic uses, and we can use the leaves in many pharmacological activities, particularly its anti-diabetic property.

Source: https://www.scientificworld.in/2015/04/sadabahar-medicinal-plant-hindi.html

Fig 1: Sadabahar Plant

Classification

Kingdom - Plantae
Division - Magnoliophyta
Class - Magnoliopsida
Order - Gentianales
Family - Apocynaceae
Genus - *Catharanthus*
Species - *roseus*

Morphology of Sadabahar

Catharanthus roseus commonly known as Sadabahar is a lengthy (perennial) sub-shrub plant that is normally erect, 30-100 cm tall, and rigid at the base, occasionally spreading. A white latex is present in it (Henderson, L.; 2001) [15]. Stems are tubular (terete), lengthwise ridged or broadly winged, dark green crimson in colour, and pubescent when in juvenile state. Leaves are alternate, borne on short pedicels, 2.5-9.0 cm in length, elliptic to ovate (egg-shaped in design but smaller at the base), greenish with whiter veins, and borne on short pedicels. With a little point protruding from the rhizome, the leaf tip is rounded to sharp (Henderson, L.; 2002) [16]. Hairy leaves and stems are common, yet bald stems and leaves do exist. Flowers are borne singly or in pairs on very short stalks on the leaf axils (pedicels). Sepals are 5 to 6 mm long, thin, and usually hairy (pubescent).Corolla tube greenish, generally at least 2.2 cm long, with both the interior of the mouth frequently dark pink or yellow, glandular within the neck with rings of stiff hairs beneath the mouth and anthers; corolla lobes 5, pinkish to white or pinkish purple, 1.0-2.8 centimetres long, obovate. Anthers 5, hooked to the inner of the upper portion of the corolla tube and hidden within it (J N Mishra *et al*., 2017, S Siti *et al*., 2019) [18, 40]. The fruit is a spindle with countless little black seeds that is 2.0-4.7 cm long.

Source:https://link.springer.com/article/10.1007/s00253-020-10592-1

Fig 2: Morphological features of leaf, stem, flower and fruit

Geographical Distribution

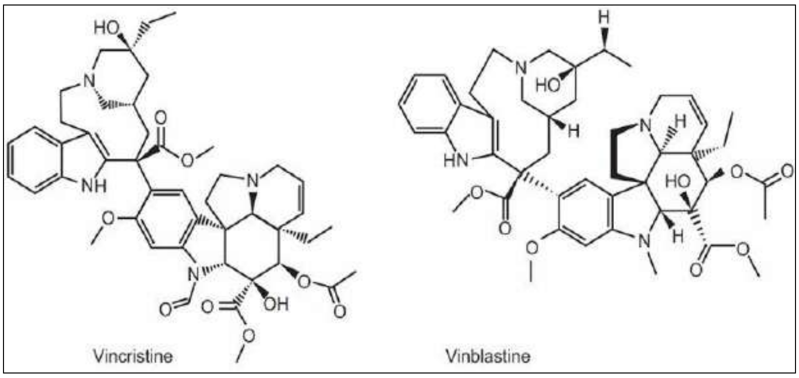
Catharanthus is a genus with around eight species. Seven of the life forms are unique to Madagascar, and one is only found in India and Sri Lanka. *C. roseus* is grown and naturalised throughout the tropical regions and every now and then in the subtropics of both hemispheres, particularly along the coast, but also inland on dunes in savannas and on dry, waste places, sometimes on rocky soil. *C. roseus* has a high salt sensitivity, up to 2000 ppm, and is typically found close to sea level, though it can be found at slightly high latitudes on occasion. (Plaizier AC; 1981) [39]

Cultivation

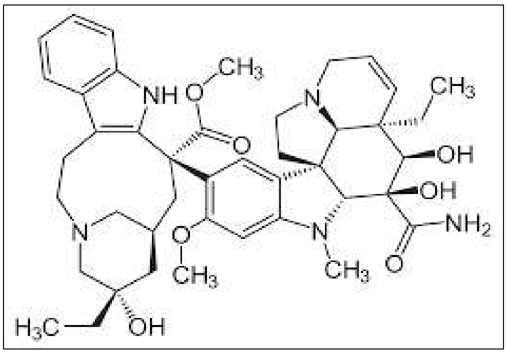
Catharanthus cultivation necessitates both moist and dry soil. It can also withstand dry conditions. During cultivation, seeds are visible in the soil. In the months of February and March, the nursery sells fresh seeds. After 2 months, the obtained plant seedling grows to a height of 5-8 cm when transplanted into soil at a distance of 45 cm. After cultivation, the entire plant is gathered and cut 10 cm just above the stem; afterward, the stem, leaves, and seeds are separated and dried out during organisation. The roots are rinsed before being packed. (Maurya S, *et al*., 2021) [27]

Alkaloids of Sadabahar

Alkaloids are heterocyclic organic compounds of plant origin that contain nitrogen and have a variety of pharmacological properties (Sato *et al*., 2001; Buckingham *et al*., 2010) [42, 8]. The majority of alkaloids are colourless, crystalline solid particles that are partially soluble in neutral or alkaline aqueous solutions but easily and quickly soluble in organic solvents. The major bioactive constituents of various alkaloids have been shown to have various activities such as anaesthetic, analgesic, antipyretic, anti-inflammatory, anti-tumor, inhibition of linoleic acid peroxidative damage, 2,2-diphenyl-picrylhydrazyl (DPPH) radical scavenging, antibacterial, antifungal, antiviral, and anti-diabetic activity (Benabdesselam *et al*., 2007; Kucukboyaci *et al*., 2010) [7, 21]. Although alkaloids are toxic, they may be used to cure diseases. Some of the common indole alkaloids of sadabahar plant are described here. Vincristine, also recognised as Leuro-Cristine and marketed as Oncovin, is a chemotherapeutic agent for treating a number of cancers. It is linked to lymphocytic leukaemia, atypical myeloid leukaemia, Hodgkin disease, neuroblastoma, and small cell lung degradation. (Hejaz *et al*., 2006). Vinblastine (VBL), also widely recognized as Welban, is a chemotherapy drug that is widely used in many prescriptions for the treatment of numerous threatening types of cancer. It is comparable to Hodgkin lymphoma, small cell lung damage, bladder risk, cortical disease, carcinoma, and testicular congenital abnormalities (Ravina *et al*., 2011) [40]. Vindesine is a synthetic supplicant of vinblastine, a naturally occurring vinca alkaloid. Vindesine works by binding to and resolves tubulin, preventing tubulin polymerization and the game plan of the cell division shaft and cell division; cells treated can't go through cytokinesis and are stuck in metaphase. This analyst also disturbs complex molecular mixture (Mondal *et al*., 2019) [30]. Tabersonine is a cytotoxic monoterpenoid indole alkaloid. It has a section as an anti - neoplastic expert and a metabolite. It is an alkaloid derivative, a monoterpenoid indole alkaloid, a methyl ester, and a distinctive heteropentacyclic compound. It is the foundation of a tabersoninium structure. (Leeuwenberg *et al*., 1985) [23].

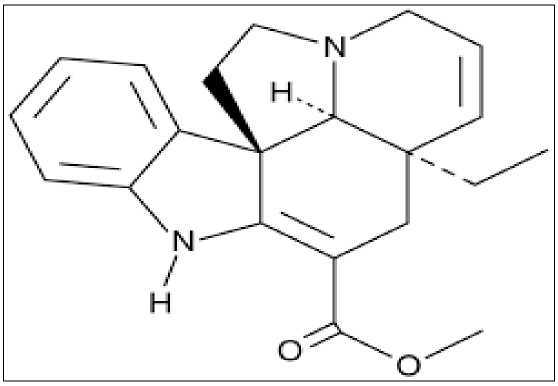


Source 1: https://solutionpharmacy.in/vincristine-and-vinblastine/



Source 2: https://en.wikipedia.org/wiki/Vindesine

Vindesine



Source 3: https://www.caymanchem.com/product/26848

Tabersonine

Fig 3: Potential alkaloids of sadabahar

Mechanism of alkaloids and their anti - diabetic role

The alkaloids vindoline, vindolidine, vindolicine, and vindolinine were isolated and identified from *Catharanthus roseus* dichloromethane leaf extract. Leave extract, as well as the chemicals vindoline and vindolicine, had no harmful effect on pancreatic -TC6 cells at a concentration of 25.0 g/mL. Vindolicine had the highest action in pancreatic -TC6 or myoblast C2C12 cells. Vindolidine and vindolinine demonstrated good inhibitory effects against tyrosine phosphatase 1B in type 2 diabetes mellitus. Vindolicine demonstrated the highest antioxidant potential in ORAC and DPPH assays, and increased H2 O2-induced oxidative damage in -TC6 cells at concentrations of 12.5 and 25.0 g/mL (Ijaz Muhammad *et al*., 2021) [31]. Anti-diabetic alkaloids help to prevent hyperglycemia by increasing glucose intake and encouraging glycogen synthesis (Tang *et al*., 2017) [46]. To manage glucose levels in the body, alkaloids use a complex method that involves modulating the activity of many enzymes that are directly or indirectly involved in carbohydrate metabolism. Expression of multiple molecules involved in insulin stimulation such as AMP-activated protein kinase (AMPK), glucose transporter 4 (GLUT4), glycogen synthase kinase-3 (GSK3), sterol regulatory element binding proteins 1 (SREBP1), glucokinase (GK), glucose6-phosphatase (G6Pase), acetyl-CoA carboxylase (ACC), peroxisome proliferator-activated receptor (PPAR) and protein of tyrosine phosphatase 1B (PTP1B) are induced or inhibited by the phytodrugs (Gupta *et al*., 2016) [13]. Several novel monoterpenoid indole alkaloid pathway genes were discovered. There are currently new alkaloids being studied in the Catharanthus plant. For example, vindogentianine, a hypoglycemic metabolite extracted from leaves, demonstrated hypoglycemic activity in -TC6 and C2C12 cells by inducing higher glucose consumption and significant *in vitro* inhibition, implying that vindogentianine's hypoglycemic activity is due to an increase in glucose consumption and PTP-1B-type inhibition, which could be a potential medicinal substance (Barrales-Cureño *et al*., 2019) [6]. The production pathways for triterpenes were discovered, and oleanane-type triterpenes were located in the cuticular wax layer. The production pathways for very long chain fatty acids and flavonoids were also shown to be cell type specific.To increase the production of these alkaloids in the plant, numerous biotechnological tactics are used. VLB and Leurosine-like alkaloids, monomeric alkaloids, and polymeric alkaloids are the three types of alkaloids generated by C.roseus. Vinblastine and vincristine were the first alkaloids to be synthesised spontaneously, and their structures were established using X-rays. These alkaloids are the end products of a variety of biochemical processes. Tryptophan and the monoterpenoid geraniol kickstart the process. Tryptophan decarboxylase (TDC) breaks down the tryptophan and turns it to tryptamine. In the process, anthranilate synthase (ASA) and chorismate mutase play a role. Geraniol-10-hydroxylase transforms geraniol to geraniol-10-hydroxylase, loganic acid, loganin, and lastly secologanin. Strictosidine synthase is a crucial step since it affects both secologanin and tryptamine. Further processes are catalysed by enzymes such as OMT, D4H, and DAT.

Antidiabetic Potential of Sadabahar

Catharanthus roseus (L.). G. Don (Apocynaceae) has been used to manage diabetes in numerous parts of the world, including Nigeria, India, and Trinidad & Tobago (Elisa Vega-Ávila *et al*., 2012). Sadabahar may be used to treat diabetes in some regions of the world. It's an essential component of traditional medicine. According to WHO statistics, diabetes affects over 422 million people worldwide. The ethanolic extracts of *C. roseus* leaves and flowers demonstrated a dose-dependent blood sugar reducing effect that was comparable to the standard medication. In several countries, a water decoction of the leaves and/or the entire plant is used as a household remedy for diabetes. Vindoline and Vindogentianine are anti-diabetic substances found in *Catharanthus roseus*. Vindoline can increase insulin secretion to its maximal level at concentrations greater than 50 M. The ethanolic extract of *Catharanthus roseus* coupled with ursolic acid produces a lot of insulin. In diabetic rats, a mixture of *Catharanthus roseus* ethanolic extract and ursolic acid (25 mg: 25 mg) increased insulin production from 5.93 to 13.65 units per millilitre. This demonstrated the potential of combining *Catharanthus roseus* and ursolic acid as a viable alternative medicine (Arya SS *et al*., 2021) [4]. Previous research has found that hydroalcoholic or dichloromethane-methanol extracts of *C. roseus* leaves have significant blood glucose lowering activity in laboratory animals. Ayurvedic physicians in India have used fresh leaf juice of *C. roseus* with beneficial results (Srinivas Nammi *et al*., 2003) [32]. A study with *Catharanthus roseus* leaf juice on normal and alloxan diabetic rabbits supports ayurvedic physicians' traditional use of fresh leaves for diabetes control. In comparison to control, alloxan-treated animals receiving *C. roseus* leaf juice demonstrated quick normalisation of blood glucose levels, which could be attributed to the likelihood that some -cells are still alive to act on by *C. roseus* to exert its insulin-releasing function (Srinivas Nammi *et al*., 2003) [32]. The beta-cytotoxin alloxan induces extensive death of -cells in the islets of Langerhans, resulting in decreased insulin synthesis and release. It is well known that sulfonylureas cause hypoglycemia by increasing pancreatic insulin secretion, and that these chemicals are active in moderate alloxan-induced diabetes but not in severe alloxan diabetes. Due to the negative effects associated with the use of insulin and oral hypoglycemic medications, the use of herbal remedies for the treatment of diabetes mellitus has grown in popularity around the world, and there is a rising demand for natural products with antidiabetic action.The blood sugar lowering effect is comparable to that of the conventional medication glibenclamide. The increased glucose consumption in the liver has resulted in the hypoglycemic impact. When compared to dichloromethane and methanol extracts, which dropped blood glucose levels by 49-58 percent in diabetic rats, the aqueous extract was found to lower blood glucose by roughly 20%. The enhanced glucose consumption in the liver has resulted in the hypoglycemic impact.In a mouse insulinoma cell line, vindoline was discovered to raise insulin levels (MIN6) (Alkreathy HM and Ahmad A, 2020) [2]. Pharmacological studies of alkaloids obtained from *C. roseus* have been conducted, and a medicine developed from the plant has been sold as a diabetes cure under the brand name Vinculin (Jai Narayan Mishra *et al*., 2017) [18]. In both normal and streptozotocin-induced hyperglycemic rats, the ethyl acetate fraction of the ethanolic extract of *C. roseus* has the best glucose lowering effect (M. A. Islam *et al*., 2009) [17]. Hypoglycemic alkaloids (catharanthine, leurosine, lochnerine, tetrahydroalstonin, vindoline, and vindolinine) may also have a role. Flavonoids and alkaloids have been reported to have significant hypoglycemia and hypolipidemic effects, according to early phytochemical investigation. Other studies have shown that the antidiabetic activity of *C. roseus* on STZ-induced diabetes is due to complex GLUT gene mRNA expression pathways. STZ serves as a nitric oxide donor in pancreatic cells and is a powerful DNA methylating agent. The findings are quite positive, and they strongly support its candidacy for developing a revolutionary herbal medication to treat severe diabetes (Waleed M. Al-Shaqha *et al*., 2015) [3]. Reduced glucose transport gene levels are essentially one of the main causes of hyperglycemia in diabetics, which is caused by impaired glucose uptake. As a result, restoring glucose transport gene levels would improve glucose uptake in the liver and hence aid in the treatment of hyperglycemia. In type 2 diabetes, glucose insensitivity linked to GLUT gene dysfunction is common. In diabetic mice fed with an ethanolic extract of *Catharanthus roseus* leaves in conjunction with sitagliptin, the anti-diabetic benefits were significantly increased (Khadija Azam *et al*., 2022) [5]. Similar studies have revealed that *Catharanthus roseus* extracts were found to reduce hyperglycemia and oxidative stress in diabetic rats. The destruction of the pancreas in diabetic rats treated with alloxan and regeneration of beta-cells in diabetic rats treated with *Catharanthus roseus* was noted. *Catharanthus roseus* extract of 300 mg/kg bw was also effective and produced normal outcomes (Yousif Elhassaneen *et al*., 2021). This result could be related to the potential that certain cells are still alive and can be acted upon by *Catharanthus roseus* extract to release insulin. Histopathological investigations support the repair of the pancreas as a probable mechanism of *Catharanthus roseus* extracts' anti-diabetic action. Long-term use of *Catharanthus roseus* prevents insulin resistance in the body, according to research. As a result, *Catharanthus roseus* could be utilised in conjunction with other treatments to prevent or manage insulin resistance in pre-diabetic patients. The study's findings demonstrated that there was a substantial interaction between metformin and the extract when compared to the medicine alone (Khadija Azam *et al*., 2022) [5]. The leaf extract of *C. roseus* possesses multiple mechanistic considerations on the hypoglycemic activity of alphaglucosidase inhibitors and biguanides, conferring synergism of action and effects, including a glibenclamide-like lowering of glucose concentration in the blood, primarily by stimulating a first-phase release of insulin from beta cells in the functioning pancreas, as well as enhance response to glucose entry into obligatory tissues (Sylvester C Ohadoma *et al*., 2021) [33]. The pharmacodynamics component and pharmacokinetic involvements of interactions such as enzyme inhibition are associated with the manifestation of significant changes in the outcome between combination treatments and monotherapy in the treatment of *C. roseus* with AGIs and biguanides.

Future Prospects

Plant secondary metabolites, or natural bioactive substances, are essential for inter- or intragenus/species competition, defence, attraction, and signalling in plants. C.roseus is the subject of nanotechnology and bioinformatics research in order to establish and carry out a comparative investigation of the plant's anti-diabetic potential. This could pave the way for plant-based natural medications to treat diabetes that are less expensive, have fewer side effects, and are more productive. Green synthesis of nanoparticles is a novel method of producing nanoparticles from biological sources. To assess sadabahar leaves' antidiabetic potential, researchers used an *in vitro* antidiabetic assay (α - Amylase Inhibition Assay) and in-silico molecular docking (M Mall *et al*., 2022) [25]. Due to gaps in our knowledge of the production of pharmacologically significant terpenoid indole alkaloids, the plant remains a mystery (TIAs). The plant has genomic and transcriptomic resources, but these have yet to be fully utilised. Endophytes found in *Catharanthus roseus* have been studied for their ability to produce indole alkaloids such as vinblastine, vincristine, vindoline, vinflunine, vincamine, ajmalicine, ajmaline, serpentine, and reserpine (Prabhjot Kaur *et al*., 2021) [20]. Transgenesis, metabolic engineering, and elicitation are viable biotechnological technologies that have been adopted to meet the desired demand for more efficient and sustainable synthesis of vinca alkaloids from endophytic fungus. Endophytes help host plants survive by boosting defence responses and creating bioactive molecules that are comparable to those produced by their hosts.

Conclusion

Sadabahar plant is a highly potent antidiabetic source. The extracts of various parts of the plant have shown hypoglycemic activity and the alkaloids have been proven beneficial in this aspect. In the treatment of sadabahar with AGIs and biguanides, the pharmacodynamics component and pharmacokinetic involvements of interactions such as enzyme inhibition are associated with the manifestation of significant differences in outcome between combination treatments and monotherapy. Recent breakthroughs, such as the creation of micro, nano formulations, support therapy, and other therapies, are on the rise, as the demand for a safer and more effective alternative to the long-term use of dangerous pharmaceuticals grows.

References

1. Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, *et al*. Antidiabetic Phytochemicals From Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. Front Endocrinol (Lausanne). 2022 Feb 24;13:800714. DOI: 10.3389/fendo.2022.800714. PMID: 35282429; PMCID: PMC8907382.
2. Alkreathy HM, Ahmad A. *Catharanthus roseus* combined with ursolic acid attenuates streptozotocin induced diabetes through insulin secretion and glycogen storage. Oxid. Med. Cell. Longev, 2020.
3. Al-Shaqha WM, Khan M, Salam N, *et al.* Anti-diabetic potential of *Catharanthus roseus* Linn. And its effect on the glucose transport gene (GLUT-2 and GLUT-4) in streptozotocin induced diabetic wistar rats. *BMC* Complement Altern Med. 2015;15:379. https://doi.org/10.1186/s12906-015-0899-6
4. Arya SS, Sonia NS, Nair DS. Functional potential of anti-diabetic medicinal plants. Journal of Pharmacognosy and Phytochemistry. 2021;10(2):1177-1181.
5. Azam K, Rasheed MA, Omer MO, Altaf I, Akhlaq A. Anti-hyperlipidemic and anti-diabetic evaluation of ethanolic leaf extract of *Catharanthus roseus* alone and

in combination therapy. Brazilian Journal of Pharmaceutical Sciences, 2022, 58.
6. Barrales-Cureño HJ, Reyes CR, García IV, Valdez LGL, De Jesús AG, Ruíz JAC, *et al*. Alkaloids of Pharmacological Importance in *Catharanthus roseus* . In (Ed.), Alkaloids - Their Importance in Nature and Human Life. Intech Open, 2019. https://doi.org/10.5772/intechopen.8200.
7. Benabdesselam FM, Khentache S, Bougoffa K, Chibane M, Adach S, Chapeleur Y, *et al*. Antioxidant activities of alkaloid extracts of two *Algerian* species of Fumaria: *Fumaria capreolata* and *Fumaria bastardii*. Rec Nat Prod. 2007;1(2-3):28-35.
8. Buckingham J, Baggaley K, Roberts A, Szabo L. Dictionary of Alkaloids with CD-ROM. Boca Raton: CRC Press, 2nd Ed, 2010.
9. Chattopadhyay RR. A Comparative Evaluation of Some Blood Sugar Lowering Agents of Plant Origin. J Ethnopharmacol. 1999;67:367-72. DOI: 10.1016/s0378-8741(99)00095-1
10. Committee WE. WHO Expert Committee on Diabetes Mellitus Second report. World Health Organization Tech Rep Ser. 1980;646:1-80.
11. De Vos B. Investigating the antidiabetic potential of the combination of *Catharanthus roseus and Portulacaria afra* leaf extracts (Doctoral dissertation, North-West University (South-Africa)), 2021.
12. Elhassaneen Y, Ragab S, Abd El-Rahman A, Arafa S. Vinca (*Catharanthus roseus*) Extracts Attenuate Alloxan-Induced Hyperglycemia and Oxidative Stress in Rats. American Journal of Food Science and Technology. 2021;9(4):161-172.
13. Gupta P, Bala M, Gupta S, Dua A, Dabur R, Injeti E, *et al*. Efficacy and risk profile of anti-diabetic therapies: Conventional vs traditional drugs A mechanistic revisit to understand their mode of action. Pharmacol Res. 2016;113(Pt A):636-74.
14. Hejaz HA, Karaman R. Drug overview. Commonly Used Drugs-Uses, side effects, bioavailability and approaches to improve it, 2015, 1.
15. Henderson L. Alien weeds and invasive plants. A complete guide to declared weeds and invaders in South Africa. Plant Protection Research Institute Handbook. PPR, ARC South Africa. 2001;12:300pp.
16. Henderson L. Problem plants in Ngorongoro Conservation Area. Final Report to the NCAA, 2002.
17. Islam MA, Akhtar MA, Islam MR, Hossain MS, Alam MK, Wahed MII, *et al*. Antidiabetic and Hypolipidemic Effects of Different Fractions of *Catharanthus roseus* (Linn.) on Normal and Streptozotocin-induced Diabetic Rats. Journal of Scientific Research. 2009;1(2):334-344. https://doi.org/10.3329/jsr.v1i2.1075
18. Mishra JN, Verma NK. A brief study on *Catharanthus roseus*: A review, Inter. J of Research in Pharmacy and Pharmaceutical Sciences. 2017;2(2):20-23.
19. Johnson IS, *et al*. The vinca alkaloids: a new class of oncolytic agents. Cancer Research. 1963;23:1390-1427.
20. Kaur P, Dey A, Kumar V, Dwivedi P, Banik RM, Singh R, *et al*. Recent advances and future prospects of indole alkaloids producing endophytes from *Catharanthus roseus*. Volatiles and Metabolites of Microbes, 2021, 449-472.
21. Kucukboyaci N, Adigüzel N, Özkan S, Tosun F. Alkaloid profiles and biological activities of different *Sophora jaubertii* extracts. Turk J Pharm Sci. 2010;7(1):1-7.
22. Kumar R, Pate DK, Prasad SK, Sairam K, Hemalatha S. Antidiabetic activity of alcoholic leaves extract of *Alangium lamarckii* Thwaites on streptozotocin-nicotinamide induced type 2 diabetic rats. Asian Pac J Trop Med. 2011;4(11):904-9.
23. Leeuwenberg AJ. Voacanga Thou. In Series of revisions of Apocynaceae. 1985;15(3):5-80.
24. Loh KY. Know the medicinal herb *Catharanthus roseus* (*Vinca rosea*). Malaysian Family Physician. 2008;3(2):123.
25. Mall M, Singh P, Yadav S, Sundaresan V, Mani DN, Shasany AK, *et al*. Future Prospects for Research on *Catharanthus roseus*. In The Catharanthus Genome. Springer, Cham, 2022, 175-183.
26. Matalqah SM, Al-Tawalbeh DM. Medicinal plants potential against diabetes mellitus. Diabetes. 2025;9(10):11.
27. Maurya S, Yadav P, Prajapati V, Gupta VK, Singh V. A Phytomedicine- *Catharanthus roseus.* 2021;9(1):454-458.
28. Mayfield J. New classification and diagnostic criteria for diabetes mellitus. Am Fam Physician. 1998;58:1355-70.
29. Mellitus D. Report of a WHO study group. World Health Organ Tech Rep Ser. 1985;727:1-113.
30. Mondal A, Gandhi A, Fimognari C, Atanasov AG, Bishayee A. Alkaloids for cancer prevention and therapy: Current progress and future perspectives. European journal of pharmacology. 2019;5:858-172472.
31. Muhammad Ijaz, Rahman Noor, Gul-E-Nayab, Nishan Umar, Shah Mohibullah. Antidiabetic activities of alkaloids isolated from medicinal plants. Brazilian Journal of Pharmaceutical Sciences, 2021, 57. 10.1590/s2175-97902020000419130.
32. Nammi S, Boini MK, Lodagala SD, *et al.* The juice of fresh leaves of *Catharanthus roseus* Linn. Reduces blood glucose in normal and alloxan diabetic rabbits. BMC Complement Altern Med, 2003, 3(4). https://doi.org/10.1186/1472-6882-3-4
33. Ohadoma SC, Akpan JL, Odey PA, Okoro EP. Mechanistic considerations of *Catharanthus roseus* on the hypoglycemic activity of alpha glucosidase inhibitors and biguanides: A review, 2021.
34. Parihar S, Sharma D. A brief overview on Asparagus racemosus. IJRAR. 2021;8(4):96-108.
35. Parihar S, Sharma D. A Brief Overview on *Crinum latifolium*. International Journal of Science and Research (IJSR). 2021;10(12):725-728.
36. Parihar S, Sharma D. Navagraha (nine planets) plants: the traditional uses and the therapeutic potential of nine sacred plants of India that symbolises nine planets. IJRAR. 2021;8(4):96-108.
37. Parihar S, Sharma D, Chirania A, Telrandhe U. To Review on the Pharmacology of the Leaf Extract of *Catharanthus roseus*. Asian Journal of Pharmaceutical Research and Development. 2022;10(1):32-37. https://doi.org/https://doi.org/10.22270/ajprd.v10i1.1075
38. Paul A, Shamim N, Sarkar A, Acharya K, Chakraborty N. Boosting of Bioactive Secondary Metabolites in Anti-Diabetic Plants Through Elicitation: A Simple

Technology for Better Future. In Biotechnology of Anti-diabetic Medicinal Plants Springer, Singapore, 2021, 307-340.
39. Plaizier AC. A revision of *Catharanthus roseus* (L.) G. Don (Apocynaceae). Landbouwhogeschool, 1981.
40. Ravina E. The evolution of drug discovery: from traditional medicines to modern drugs. John Wiley & Sons, 2011 Apr 18.
41. Siti S, Nettyani N, Dian P. Variability of *Catharanthus roseus* based on morphological and anatomical characters, and chlorophyll contents, Biodiversitas, Vol. 2019;20(10):2986-2993.
42. Sato F, Hashimoto T, Hachiya A, Tamura K, Choi K, Morishige T, *et al*. Metabolic engineering of plant alkaloid biosynthesis. PNAS. 2001;98(1):367-72.
43. Sharma SK. Medicinal Plants used in Ayurveda. New Delhi: Rashtriya Ayurveda Vidyapeeth, Ministry of Health and Family Welfare, Govt of India, 1998, 193.
44. Shrinet K, Singh RK, Chaurasia AK, Tripathi A, Kumar A. Bioactive compounds and their future therapeutic applications. In Natural Bioactive Compounds. Academic Press, 2021, 337-362.
45. Singh SN, Vats P, Suri S, Shyam R, Kumria MML, Ranganathan S, *et al*. Effect of an Antidiabetic Extract of *Catharanthus roseus* on Enzymic Activities in Streptozotocin Induced Diabetic Rats. J Ethnopharmacol. 2001;76:269-77.
DOI: 10.1016/S0378-8741(01)00254-9
46. Tang D, Chen QB, Xin XL, Aisa HA. Anti-diabetic effect of three new norditerpenoid alkaloids *in vitro* and potential mechanism via PI3K/Akt signaling pathway. Biomed Pharmacother. 2017;87:145-52.
47. The Wealth of India-Raw Materials New Delhi: Publication and Information Directorate, Council of Scientific and Industrial Research. 1985;3:391-395.
48. Tiong SH, Looi CY, Hazni H, Arya A, Paydar M, Wong WF, *et al*. Antidiabetic and Antioxidant Properties of Alkaloids From *Catharanthus roseus* (L.) G. Don. Mol Basel Switz. 2013;18:9770-84. DOI: 10.3390/ molecules18089770
49. Vega-Ávila E, Cano-Velasco JL, Alarcón-Aguilar FJ, Fajardo Ortíz MDC, Almanza-Pérez JC, Román-Ramos R. Hypoglycemic activity of aqueous extracts from *Catharanthus roseus*. Evidence-Based Complementary and Alternative Medicine, 2012.
50. Verma S, Gupta M, Popli H, Aggarwal G. Diabetes Mellitus Treatment Using Herbal Drugs. International Journal of Phytomedicine. 2018;10(1):1-10.
51. https://www.scientificworld.in/2015/04/sadabahar-medicinal-plant-hindi.html
52. https://link.springer.com/article/10.1007/s00253-020-10592-1
53. https://solutionpharmacy.in/vincristine-and-vinblastine/
54. https://en.wikipedia.org/wiki/Vindesine
55. https://www.caymanchem.com/product/26848