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Chapter- 1

Anticancer and antidiabetic potential of phytochemicals derived from *Catharanthus roseus*: a key emphasis to vinca alkaloids

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Abstract:

Catharanthus roseus is a widely used medicinal herb in several regions of the world. It has already gained popularity because of the discovery of numerous phytoconstituents with diverse biological properties like anti-oxidant, antimicrobial, antifungal, hypoglycaemic, and anticancer properties. Cancer treatments involve surgical intervention, chemotherapy, radiotherapy, as well as pharmacotherapy, among other things, that not just have a significant financial impact on the patients. Still, it also leads to chronic drug resistance in patients over time. Plant-based drugs have emerged as effective precautionary chemotherapies in both developing and advanced nations. Surprisingly, the plant-derived anticancer agent vinblastine as well as vincristine were the first phytoconstituents to be utilised for drug development. In vitro suppression of human breast cancer cell lines was successfully demonstrated by new isolated biologically active compounds from this plant, such as catharoseumine, 17-deacetoxy-cyclovinblastine etc. Furthermore, vindoline, vindolicine, vindolinine and vindolidine extracted from *Catharanthus roseus* plant displayed anti-diabetic or anti-hyperglycaemic activity in vitro. Such findings strongly suggest how this plant has become a viable source of biologically active compounds and needs to be analysed further. This article highlights the function and sources of bioactive compounds derived from *Catharanthus roseus*, as well as the traditional uses and characteristics of phytoconstituents of this plant. Furthermore, the potential advantages of bioactive components found in *Catharanthus roseus* were reviewed in order to promote their potential as therapeutics.

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Introduction:

India obtains a priceless herbal heritage (Bhattacharjee, 2021; Sarkar et al., 2016; Sarkar, 2017). In India, the traditional medical system continues to be crucial to the country's overall healthcare system, along with homoeopathy and folk medicine (Sanyal et al., 2018; Kundu, 2022). Since the beginning of time, humans have used medicinal plants as necessary ingredients in foods, drinks, and treatments. The nutritional, pharmacological, biological, and toxicological properties of medicinal plants have extensive industrial applications (Erfani, 2021; Kar et al., 2022).

Diabetes and cancer are two diseases that are diversified, multi-factorial, serious, and chronic. Due to their recurrence, reciprocal influence, sometimes minor ones, can have a massive effect (Onitilo et al., 2012). Diabetes mellitus is a serious and rising health issue throughout the world. It is associated with significant acute and persistent health problems that have a detrimental effect on the lifestyle quality and the survival of those who have it. Diabetes affects 537 million individuals worldwide, which is expected to rise to 783 million in the next twenty years. It is a chronic metabolic disorder that develops when the pancreatic beta cells stop producing sufficient insulin or when cells continue to fail to use the insulin produced effectively. Several genetic, environmental, and other variables also contribute to it (WHO, 2022). It is categorized mainly into two types such as T1DM & T2DM.

Over the next twenty years, the global cancer burden is predicted to rise at a rate of 22 million cases per year, requiring rapid advances in chemo-, targeted-, and immune-therapy investigations to encounter this increasing epidemic head-on (Thun et al., 2009). Cancer is currently the world's second most common cause of death, and several research works over the last decade have concentrated on finding therapeutic approaches to decrease the side consequences of existing treatments (Wang et al., 2019). Cancer is a broad term for a group of disorders characterised by the unregulated proliferation of malignant cells with the capability to invade and destroy normal human tissue. It has the potential to spread all throughout the body (Mathur et al., 2015). Genetic alterations inside cells trigger cancer. Within a cell, DNA is organized into many specific genes, each of which consists a set of commands informing the cell what activities to perform and how it should grow and split. Mistakes in the commands could really lead the cell to cease to function normally and even end up causing it to develop into cancer cells. Tumours become extremely heterogeneous as they advance, resulting in a mixed group of cells with specific biochemical characteristics and widely different responsiveness to therapies. Notwithstanding, studies have discovered that cancer treatment is far more complicated than previously thought, with a confounded system of biochemical abnormalities and a rigorous tumour microenvironment (TME) making a contribution to the issue (Hassanpour & Dehghani, 2017). Most cancer therapeutic strategies currently rely on a specific target and genotoxic agents explored using one gene, one target, and one disease strategy. Whereas this framework has contributed to many developments in cancer pharmacognosy, specific target drug discovery, and a greater understanding of cancer pathogenesis and progression, it has significant attrition rates as well as slow clinical translation, denoting that it is unsatisfactory to meet the increasing requirements

for cancer therapies and prevention (Pucci et al., 2019). Recent reports and studies indicate that traditional phytomedicines or their separated bioactive constituents are increasingly being used as adjuvants or supplementary chemotherapeutics agents in cancer sufferers to ameliorate disease manifestations or promote healthy lifestyles (Yin et al., 2013). Whilst also circumstantial evidence is used to support years of ethnobotanical use of phytomedicines, evidence-based information obtained from omics technology platforms, such as genomics, proteomics, and metabolomics, assists scientists and clinicians in evaluating the worth of biochemical pharmacodynamic systems targeted by bioactive substances or pharmacological medicinal herbs that might be advantageous in treating cancer (Choudhari et al., 2020). Furthermore, these methods ensure quality and assess systemic side effects such as carcinogenicity and safety.

Epidemiological research shows that individuals with diabetes have an elevated incidence of many kinds of cancers (such as pancreatic, hepatic, ovarian, colorectal and urogenital). Morbidity is also slightly higher. As a result, if hyperglycaemia is linked to even a minor increase in the chance of cancer, the population-wide implications could be significant (Onitilo et al., 2012). Numerous general and site-specific predisposing variables start making appropriately analysing the chance of developing cancer in diabetic individuals challenging. Diabetes timeframe, widely different levels of glycaemic control, types of drugs used for treatment, and long-term side effects are among these variables (Shahid et al., 2021). Hyperinsulinemia most probably promotes cancer in individuals with diabetes because insulin is indeed a growth factor both with metabolic as well as oncogenic impacts, and thus its activity in tumour tissues is aided by processes that act both at the receptor as well as post-receptor levels. Overweight, hyperglycaemia, and enhanced reactive oxygen species may all play a role in diabetes-related cancer incidence (Wang et al., 2020). Whereas anti-hyperglycaemic pharmaceuticals have a slight effect on cancer threat, chemotherapeutic pharmaceuticals might very well lead to diabetes or aggravate pre-existing metabolic syndrome (Gristina et al., 2014). Aside from the well-studied hyperglycaemic effects of steroid hormones and anti-androgens, an overwhelming amount of directed anti-cancer compounds may interact with glucose homeostasis by intervening at differing stages on the signalling substances shared by IGF-I and insulin receptors (Novosyadlyy & LeRoith, 2012). As a result, diabetes mellitus and cancer have a complicated relationship that necessitates too much immediate medical attention and effective studies.

Natural resources, such as medicinal herbs, that consist of a wide range of phyto-constituents appealing as traditional medication to cure prolonged and potentially life-threatening diseases, are thought to really be safer and more efficient than chemically synthesized agents (Ekor, 2014). Among some of the various medicinal herbs discovered, *Catharanthus roseus* has indeed been extensively utilized in different regions throughout the globe for treating different diseases (Kumar et al., 2022).

Vinca alkaloids are a form of organic compound which are frequently extracted from different plants. Even though the term suggests alkali, a few do not have alkaline characteristics. Several more alkaloids that really are toxic also have pharmacological effects that render them helpful as medications. The vinca alkaloids are the ancient group of plant-derived metabolites used to fight

testicular and breast and lung cancers. The *Catharanthus roseus* plant yields vinca alkaloids. These vinca alkaloids may be naturally occurring or semi-synthetic also (Moudi et al., 2013). Too many factual studies have shown that specific phyto-constituents derived from this plant may well have therapeutic effects. Pharmacological uses of this kind of plant necessitate the assessment of these substances for antidiabetic activity, which would be minor in comparison to their cytotoxic characteristics. They are being used to treat diabetes, hypertension, and also being used as antibacterial agents (Al-Shaqha et al., 2015). Nonetheless, the vinca alkaloids are critical cancer fighters. Four main pharmacologically active vinca alkaloids are vinblastine, vincristine, vindesine and vinorelbine (Dhyani et al., 2022).

This review focuses on various antidiabetic and anti-cancer alkaloid bioactive compounds, including vincristine, vindesine, vinorelbine and vinblastine within diverse aspects of existing knowledge on all these compounds, including such their clinical applications (modern/traditional), method of antineoplastic activity, and prospective scale-up biopharmaceutical research on in-vitro experiments. This review will be a useful factor contributing to the growth of plant-based anticancer agents containing various secondary metabolites.

Taxonomic description & Traditional Uses of *Catharanthus roseus*:

Catharanthus roseus belongs to the Order: Gentianales, Family: Apocynaceae and Genus: *Catharanthus*. It is currently being grown in several countries and has become a popular decorative, easy-to-grow, and spreading evergreen herb. *C. roseus* grows to be 0.5-1.0 m in height, with young pubescent branches (Marles & Farnsworth, 1995). It has oval or oblong leaves that are membranous, greenish, glossy, hairless, obtuse, narrow petioles about 1-1.8 cm, and are organised in opposing pairs. The inflorescence is axillary, and the colour of flowers range from whitish to dark pink according to variety. The corolla tube is about 2-5 cm in diameter, pubescent above, and hairy beneath the stamens, however the calyx is small. The ovary is long and has pentagonal stigmata. It has two follicles and fruits (Mishra & Verma, 2017; Swanston-Flatt et al., 1989).

This herb is used as an ethnomedicine throughout many countries around the world. In North-east India, Australia, England, Philippines, Europe, and Taiwan, the dried plant parts are boiled in water and extract are taken as a drink to alleviate hyperglycaemia (Holdsworth, 1990; Khan, 2010). Vietnamese people use the extract of plant parts or entire plants as an alternative and complementary medicine for different kinds of cancer, including mouth, abdomen, and gastrointestinal cancers (Ochwang'I et al., 2014). Powder of the entire plant is mixed with regular milk in the Kancheepuram District of Tamilnadu, India, and taken as a drink to control hyperglycaemia (Muthu et al., 2006). Dehydrated root is crushed and mixed with water for treatment of urinogenital infections in South Africa, and abdominal swelling in Zimbabwe (Fernandes et al., 2008; Semenya & Potgieter, 2013; Chigora et al., 2007).

Table 1. Traditional utilization of *Catharanthus roseus* throughout the world.

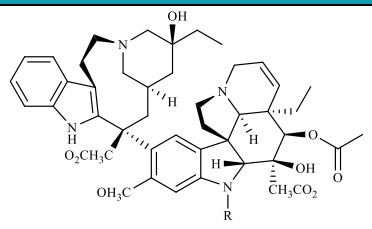
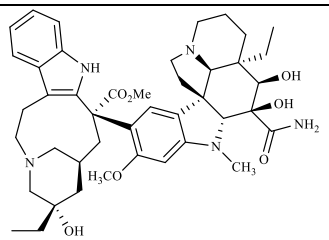
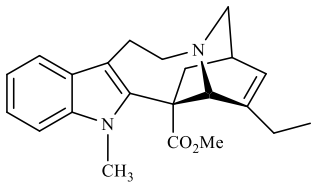
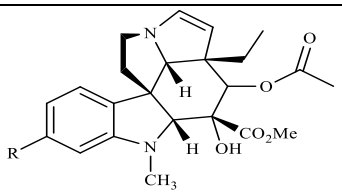
Plant Components	Preparation	Diseases	Country	Ref.
Whole plant	Soaked and steamed in water	Diabetes, Hypertension, Dysentry	Vietnam	Pham et al., 2020
		Diabetes Mellitus (DM)	Pakistan	Nisar et al., 2016
		Cancer	India	Kumar et al., 2022
		Throat, stomach, oesophageal cancer	Kenya	Vo, 2012
	Dried, soaked and steamed in water	DM	England	Kumar et al., 2022
	Dried, ground into a fine powder and diluted in regular cow milk	DM	Tamilnadu, India	Muthu et al., 2006
	Dried and prepared an extract by decoction	DM	Taiwan	Hsu & Cheng, 1992
Leaf	Dried and prepared an extract by decoction	DM	Northern European countries	Swanston-Flatt et al., 1989
	Soaked and steamed in water	DM, Menorrhagia	Australia	Webb, 1948
Roots	Crushed and added with water	Stomach pain	Zimbabwe	Chigora et al., 2007
	Dried and crushed	Urogenital infection	South Africa	Pham et al., 2020
	Boiled in water	Gonorrhoea	South Africa	Semenya & Potgieter, 2013
Upper part	Boiled in water	Menstrual regulation	China	Virmani et al., 1978
Stem	Boiled in water	DM	North America	Aslam et al., 2010

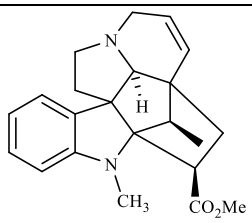
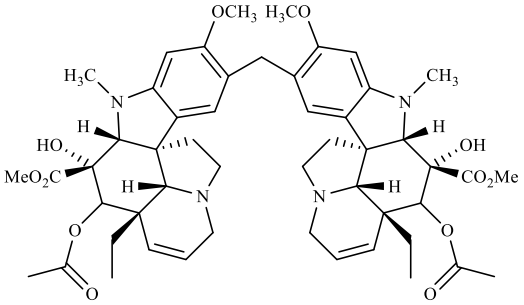
Some major bioactive compounds obtained from Catharanthus roseus:

Catharanthus roseus contains a variety of metabolites (nitrogen-containing organic substances apart from amino acid residues, peptides, pyrimidines and derivative products, and antimicrobials). Based on their chemical structure, alkaloids are categorised as either

heterocyclic or non-heterocyclic. Heterocyclic alkaloids have a nitrogen atom inside the ring structure, and based on their size, they are classified as pyridine, quinoline, piperidine, pyrrole, pyrrolizidine, isoquinoline, or indole alkaloids. Non-heterocyclic alkaloids are less prevalent in nature. Such molecules contain a nitrogen atom that does not belong to any ring structure, unlike colchicine (Wansi et al., 2013). This plant contains a numerous pharmacological bioactive compounds that contribute significantly to the ethnomedicinal sector; even so, the quantities observed there in the plant seem to be frequently lesser. It is worth noting that both biotic and abiotic variables influence the metabolic pathways of phytoconstituents. Due to plant's protective role, environmental constraints have indeed been discovered to enhance the yield of biologically active compounds, including alkaloids. As a result, more experiments are being initiated to increase the quantities of these substances by altering environmental factors such as illumination, alkalinity, soil composition and microelements, drought, and metal stress (Pham et al., 2020).

Table 2. Some important bioactive compounds derived from *Catharanthus roseus.*

Bioactive Compound	Plant Part	Chemical Structure	Ref
Vincristine	Leaf, Stem, Root	 Vincristine: R = CHO Vinblastine: R = CH_3	Alam et al., 2017
Vinblastine	Leaf, Stem, Root		
Vindesine	Leaf, Stem, Root		Arora et al., 2010
Catharanthine	Leaf		Jair Barrales-Cureño et al., 2019
Vindolidine	Leaf	 Vindolidine: R = H Vindoline: R = OCH_3	Jair Barrales-Cureño et al., 2019
Vindoline	Leaf, Stem, Root		

Vindolinine	Leaf		Eng et al., 2022
Vindolicine	Leaf		Jair Barrales-Cureño et al., 2019

Mode of synthesis of Terpenoid Indole Alkaloids (TIA) in Madagascar Periwinkle: *Catharanthus roseus*:

Alkaloids are types of naturally occurring plant-derived products containing nitrogen. Amongst various terpenoids, Terpenoid indole alkaloids are the major ones with nearly 3000 diversities. *Catharanthus roseus* which belongs to Apocynaceae family, is a widely studied plant from which more than 130 alkaloids are found and characterized (Heijden et al., 2004). *Catharanthus roseus* became the potential model system to study the biosynthesis of TIA which include more than 50 complicated biosynthetic pathway involving various kinds of genes, enzymes, transcription factors etc. (Zhao et al., 2013). These TIAs have strong pharmacological activities and are considered to treat various diseases (Heijden et al., 2004). The principal vinca alkaloids found in *Catharanthus roseus* are vincristine, anhydrovinblastine, vinblastine, vinorelbine, ajmalicine, vindolicine, vindolinine etc. Among all these, the vinblastine and vincristine are the most potent naturally derived anti cancerous drug and ajmalicine and serpentine are the naturally synthesized strong antihypertensive drug and the two are very much useful in treating various cardiac diseases (Jair Barrales-Cureño et al., 2019).

Three steps involved in achieving the synthesis of bisindole alkaloids are – **1)** Very first step involved in the biosynthetic pathway includes the genesis of tryptamine from L-tryptophane amino acid, which was catalysed by tryptophan decarboxylase (TDC) enzyme in the shikimate pathway and formation of secologanin, last product of the iridoid biosynthesis in the terpenoid pathway catalysed by Strictosidine synthase (STR) enzyme. **2)** Formation of strictosidine, the precursor of all monomeric alkaloids, by tryptamine and secologanin pairing takes place under catalysis of the enzyme STR. **3)** Metabolism of strictosidine takes place through various enzymes including D4H and DAT with the formation of two monomeric alkaloid vindoline along with catharanthine, two monoterpene precursors of vinblastine and vincristine (Goddijn et al., 1995; Yu et al., 2015; De Luca et al., 1988).

Shikimate Pathway of TIA:

Initiation of the TIA's shikimate pathway involves the production of anthranilate from chorismite by the activity of the enzyme anthranilate synthase (AS). Then the anthranilate is converted to tryptophan, which is turned into tryptamine with the enzyme tryptophan decarboxylase (TDC) (Li & Last, 1996; Noé et al., 1984).

Mevalonate (MVA) Pathway and Methyl Erythritol Phosphate (MEP) Pathway:

The MVA and MEP pathway leads to the formation of Isopentenyl pyrophosphate. The MVA pathway involves the production of triterpenes and sesquiterpenes. At the beginning, under the catalysis of hydroxymethyglutaryl synthase (HMGS) one molecule of acetyl-coA binds with one molecule of acetoacyl-coA to form 3-hydroxy-3-methyglutaryl-coA (HMG-coA). Then mevalonate is formed by the effort of the enzyme HMG-coA reductase (HMGR). Thereafter, mevalonate is phosphorylated to form mevalonate 5-diphosphate (MVAPP)by mevalonate kinase followed by the synthesis of isopentenyl pyrophosphate (IPP) by the function of the enzyme mevalonate 5-diphosphate decarboxylase. Then IPP is converted into dimethylallyl diphosphate(DMAPP) by the catalysis of the enzyme IPP isomerase(IDI) (Lange & Croteau, 1999).

Formation of geranyl diphosphate (GPP), the predecessor of secologanin, has occurred in the iridoid pathway by the fusion of DMAPP and IPP under the catalysis of geranyl diphosphate synthase. The iridoid pathway comprises nine steps by which geraniol is constructed via conversion of GPP by an enzyme geraniol synthase. At last secologanin is formed through the modification of geraniol to 10-hydrxygenaniol, iridodial, 7-deoxylaganic acid, loganic acid, loganin (Collu et al., 2001; Geu-Flores et al., 2012; Asada et al., 2013).

Formation of Strictosidine:

Synthesis of Strictosidine occurs via the conjugation of tryptamine and iridoid glycoside secologanin under the activity of the enzyme strictosidine synthase (STR). It is a predecessor in the TIA biosynthesis pathway (Treimer & Zenk, 1979).

Formation of Catharanthine and Vindoline:

Strictosidine-β-D-glucosidase (SGD) plays a major role in converting strictosidine into a highly reactive 4,21-dehydrogeissoschizine by removing a glucose moiety from strictosidine. This step is followed by the formation of cathenamine by cathenamine synthase and then cathenamine to tabersonine to vindoline. Many enzymes play crucial role in the formation of vindoline from taberosine, includes- tabersonine16- hydroxylase (T16H), N-methyltransferase (NMT), O-methyl transferase (OMT), deacetylvindoline-4-O-acetyltransferase (DAT) and deacetoxyvindoline-4-hydroxylase (D4H) by various modifications like – hydroxylation of aromatic residues, hydration of 2,3-double bonds, O-methylation, 4-O-acetylation, N(1)-methylation (El-Sayed & Verpoorte, 2007).

There is very limited information regarding catharanthine biosynthesis. Somehow catharanthine is synthesized by 4,21-dehydrogeissoschizine (El-Sayed & Verpoorte, 2007).

Construction of Vinblastine and Vincristine in the TIA biosynthesis pathway:

Synthesis of two naturally synthesized anticancer drug vinblastine and vincristine, is essential and possesses great importance. The pairing of vindoline and catharanthine forms these two. At first, α-3′-4′-anhydrovinblastine is formed thereafter, it is turned to vinblastine and then to vincristine by the activity of the enzyme anhydrovinblastine synthase (AVLBS) (Costa et al., 2007).

Anticancer Activity of Vinca Alkaloids:

Catharanthus roseus is regarded as an ornamental as well as the most medically important plant throughout the world. This plant contains near about 130 various types of Terpenoid indole alkaloids (TIA), which have potential pharmacological significance. These alkaloids have been used for years after years against various diseases like cancer, diabetes, heart related problems etc. Vinblastine and Vincristine, two dimeric alkaloids, are famous for their anticancer properties and they are the first naturally synthesized anticancer drugs. Some semi-synthetic drugs like vinorelbine, vinflunine also contain antitumor properties (Noble, 1990). These TIAs are now used progressively in medicine and serve as immunosuppressive or antitumor agents. All these vinca alkaloids can be employed singly or in association with other natural substances or synthetic medication. After administering intravenously, these alkaloids are readily metabolized by the liver and excreted quickly (Bennouna et al., 2006; Almagro et al., 2015).

Vinblastine (VLB):

The official name of vinblastine is vincaleukoblastine. It is a sulphur derivative and mostly a colourless crystalline compound produced from the shoot of the plant. The construction of vinblastine can be established by X-ray crystallography. This dimeric alkaloid is soluble in water as well as in methanol. Plants produce more amount of vinblastine than vincristine. Sometimes vinblastine can be converted to vincristine chemicallyor by using microbes. Vindoline occupies fifty percent constituents of vinblastine. Vinblastine serves as a panacea for various kinds of cancer like- non-small cell lung cancer, cancer of head and neck, testicular cancer, Hodgkin's lymphoma, and breast cancer (Silvestri, 2013).

Mode of Action:

Vinblastine is widely regarded as the first naturally synthesized anticancer drug worldwide. It was first discovered in Madagascar periwinkle plant and its' utility came into force when it was crushed into tea, leading to a decrease in the amount of white blood cells. Since it was postulated that vinblastine bears anticancer properties in opposition to white blood cells. Vinblastine is an antimitotic agent and it prevents cell cycle by binding with tubulin protein leading to the disassembly of the microtubules at the cell cycle M-phase. It also evokes programmed cell death by changing dynamics of the microtubules, components of cytoskeleton. The microtubules are

the mitotic spindles' core components, which induces separation of chromosomes and properly maintains cellular structure during meiosis and mitosis. Microtubules are constructed with α-tubulin and β-tubulin by creating polymerisation and depolymerisation dynamics at their terminal. This assembly and disassembly are regarded as "treadmilling" and "dynamic instability" sequentially. Interruption in the dynamics of these microtubules leads to halt of the cell cycle and induces apoptosis that is programmed cell death. This phenomenon is used in tumour cells to arrest them during the mitosis phase when these vinca alkaloids bind at the surface between tubulin heterodimers and GTP- binding sites (Wilson et al., 1999). Vinblastine binds slowly or rapidly to the two existing alkaloid binding sites of each tubulin dimer. Binding of vinblastine prevents the assembly of microtubules leading to stop the process of metaphase. Vinblastine do not interfere the action of any drugs that alkylate DNA. Recent study displays that these alkaloids can also bind with calmodulin and many microtubules associated protein and inhibit the metabolism of amino acids (Jordan et al., 1991; Gigant et al., 2005).

Side Effects:

Vinblastine is a mutagenic agent and also toxic for embryos, so it is not prescribed during pregnancy. Vinblastine also induces bone marrow suppression, causes gastrointestinal toxicity, extravasation injury. When patients are infected with viruses this drug is not prescribed. It also causes laryngeal paralysis. Thrombocytopenia, anaemia can be seen by using vinblastine. It also gives rise to acute cardiac ischemia, chest pain, fever etc. (Arora et al., 2010b).

Vincristine (VCR):

It is also known as leurocristine. Vincristine is a colourless fluid and act as mitotic inhibitor thus used in chemotherapy. It is a dimeric alkaloid made by paring of vindoline and catharanthine. Vincristine is widely adopted for the prevention of various diseases like- acute leukaemia, neuroblastoma, Wilm's tumor, Hodgkin's lymphoma etc. (Arora et al., 2010b).

Mechanism of Action:

Vincristine prevents polymerization of microtubules by binding with tubulin dimer. Thus, mitosis is arrested at the metaphase stage and cell cycle can't proceed further. This phenomenon is used in cancer cells and makes the growing cancer cells stop at metaphase. This drug binds at the end of these microtubules forming 'end-capping' or 'poisoning' effect. Vincristine performs its' function under micromolar concentration ranging from 10nM to 1μM. At higher concentrations (>10μM), vincristine forms tubulin paracrystals causing tubulin polymerization (Arora et al., 2010b).

Side Effects and Toxicity:

Major side effects regarding the use of vincristine is – hyponatremia, loss of hair, constipation, peripheral neuropathy. If vincristine is used along with other anticancer drugs secondary cancer will form as then vincristine will act as a carcinogen. Besides vincristine also causes leukopenia, weakness of motor neurons, neuromyopathy, psychoses, depression, nausea,

vomiting, peripheral neuritis etc. In some patients, breathing problem also occurs (Arora et al., 2010b).

Vindesine (VDS):

The marketed name of vindesine is Eldisine and Fildesin. The commercial availability of vindesine is in a powdered form and when it is dissolved into water it seems to be a colourless fluid. Vindesine is an antimitotic inhibitor and are popularly used in the treatment of several kinds of cancer such as -leukaemia, breast cancer, melanoma, lymphoma lung cancer etc. The side effects of vindesine is same as vinblastine (González-Burgos & Gómez-Serranillos, 2021).

Vinorelbine (VNLB, VRL):

This drug is created semi-synthetically from the monomeric alkaloid vindoline and catharanthine. It is regarded as the earliest and foremost 5′-NOR semi-synthetic alkaloid of *Catharanthus roseus*. It has a very wide range of antitumor activity in relation to other vinca alkaloids. It being an antimitotic agent also used as the remedy of various types of cancers. Neurotoxicity of vinorelbine is less compared to other alkaloids. Vinorelbine displays antitumor activity against MX-1 breast cancer and LC-6 non-small cell lung cancer. Vinorelbine accompanied with Cisplatin (CDDP) shows greater effect in chemotherapy (Okouneva et al., 2003).

Side Effects:

Vinorelbine shows potential side effects like- constipation, bleeding, nausea, anaemia, vomiting, diarrhoea, inflammation of the vein in which vinorelbine is injected (Arora et al., 2010b; Ngan et al., 2000; Nazir et al., 2016).

Vinflunine (VFL):

Vinflunine is made synthetically from vinorelbine with the addition of two fluorine molecules through chemistry in association with super acid in a tiny exploited region of catharanthine moiety. It became known as the fluorinated mitotic inhibitor amongst vinca alkaloids. It is extensively regarded as a remedy for breast cancer, translational cell carcinoma, non-small cell lung cancer. It performs by declining the metaphase to anaphase transition thereby obstructing cancer cells at metaphase-inducing apoptosis. Vinflunine is currently under phase three trials. Phase one trial of vinflunine activity shows prolonged inhibitory effect on the growth of tumour. Vinflunine has unique 3-16 folds weaker binding activity with tubulin. Vinflunine imparts differences in the inhibitory effects on microtubule dynamics. Vinflunine produces a much stronger effect in combination with compounds like Cisplatin, doxorubicin, or 5-fluorouracil. Vinflunine also expresses antiangiogenic and anti-vascular activity when administered in non-toxic concentration (Kruczynski & Hill, 2001).

Antidiabetic Activity of Vinca Alkaloids:

Catharanthus roseus has historically been utilized to control diabetes throughout many countries all over the world. Extract from the leaf of *Catharanthus roseus* has been shown to increase glycemic control both in diabetic and healthy rabbits (Nammi et al., 2003). In diabetic mice, *Catharanthus roseus* methanol extracts demonstrated excellent antidiabetic activity, which was associated with improved body mass, serum lipids, and pancreatic cell regeneration (Ahmed et al., 2010). Scientists investigated the in vitro anti-diabetic effects of four different bioactive compounds separated from *Catharanthus roseus* leaves, which include vindolidine, vindolinine, vindolicine and vindoline using 2-NBDG glucose uptake as well as downregulation of PTP-1B which inhibit the insulin signalling pathway (Tiong et al., 2013). Boosting glucose absorption in pancreatic cells can improve glycemic control in T2DM individuals. Four alkaloids were reported to boost glucose absorption in mouse -TC6 pancreatic and myoblast C2C12 cells while inhibiting PTP-1B. Vindolicine was the most active among the four alkaloids (Muhammad et al., 2021). The results demonstrated the conventional use of *Catharanthus roseus* for therapeutic applications in diabetic patients, emphasising *Catharanthus roseus* as a promising source for further research into anti-diabetic agents (Pham et al., 2020; Tandon et al., 2022).

Conclusion:

Since ancient, *Catharanthus roseus* has been serving as a cure-all for various types of diseases far and wide. It has come to light as one of the most potent plants worldwide. This study shows that the vinca alkaloids found in the plant have strong anticancer, and anti-proliferative qualities. In no time, the vinca alkaloids became so popular over various synthetic anticancer drugs as they can cure the disease naturally. But surprisingly the vinca alkaloids are produced in very low quantity. So, keeping in mind about the vast process of synthesis of these vinca alkaloids they should be produced synthetically in vitro. Besides the anticancer properties of vinblastine, vincristine, vinorelbine, vindoline, vindolinine, vindolicine exerts antidiabetic activity. Till now little is known about their role in immunology, so there is hope that we will get important updates on this matter in the impending future. Besides all these good qualities, it should not forget that these phytomedicines also cause various significant side effects such as it is found that vincristine can cause male infertility, however, the exact mechanism is not known. So, precautions must be taken before using these phytomedicines. Furthermore, characterization and separation of novel phytoconstituents from this plant should go on. The bioactive components obtained from this plant must be examined further before using in the pharmaceutical and biomedical industries.

Conflicts of Interest:

None

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