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CATHARANTHUS ROSEUS: TRADITIONAL USES, PHYTOCHEMISTRY, AND MODERN PHARMACOLOGY

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Abstract

In Madagascar periwinkle or Catharanthus roseus is one of the well-liked medicinal plants found to be prestigiously valued owing to its high phytochemical content and broad spectrum of pharmacological activities. It has been utilized in traditional medicine to treat diseases such as diabetes,hypertension, and infections for centuries. The plant is a cache of bioactive compounds such as alkaloids, flavonoids, and terpenoids, with vincristine and vinblastine being its most valuable secondary metabolites. These alkaloids have also been well known to contain extremely strong anticancer activities and are most widely applied in chemotherapy of leukaemia and other cancers.Phytochemical research has confirmed that C. roseus possesses antioxidant, antimicrobial, anti-inflammatory, and hypoglycemic activities, which are accountable For its medicinal applications. Recent pharmacological investigations have also continued to support its potential use in drug development, particularly in the treatment of cancer and diabetes. Its bioactive components have been examined for its molecular targets, which include inducing apoptosis, inhibition of angiogenesis, and

	glycaemic control. Although it is of great medicinal importance, its large-scale pharmacological utilization is limited by issues such as poor yield of alkaloids and issues of sustainability. New developments in plant biotechnology, genetic engineering, and tissue culture methods have been investigated to increase its metabolite yield. This review emphasizes the traditional importance, phytochemical diversity, and recent pharmacological developments concerning Catharanthus roseus, pointing towards its value in herbal medicine and drug development.

[1] INTRODUCTION

Catharanthus roseus (L.), or Madagascar periwinkle, an important medicinal crop belonging to family Apocyanaceae [1]. It has been widely reported for its medicinal activity to treat many life-threatening diseases, especially cancer [2]. In addition to its anticancer activity, C. roseus contains high antioxidant activity, which renders it helpful in managing oxidative stress and related diseases [3].There are two common varieties of C. roseus that are found to be available commonly, and they can be distinguished based on their flower color too, the pink flowered one, 'Rosea,' and the white flowered one, 'Alba' [4]. The plants are being cultivated extensively in northern India to meet the growing business needs in traditional medicinal systems and pharmaceutical companies [5]. However, factors such as gypsiferous soil pose a significant hindrance to its cultivation, affecting grade and standards [6].Wild and native to Madagascar, Catharanthus roseus is also referred to by several other names, such as Vinca rosea, Ammo Callis rosea, and Lochner rosea. Cultivated upright as a herb or a subshrub, Catharanthus roseus reaches a height of approximately one meter. It occurs predominantly in tropical and subtropical regions. [7, 8]. Shiny green leaves are found in opposite pairs, typically ranging anywhere from about 2.5 to 9.0 cm in length and 1.0 to 3.5 cm in width, possessing a well-defined central vein [9]. Five well-delineated-lobed dainty flowers with clear white to crimson pink color ranging with deeper colors in the center are produced by the plant. Its fruits come in pairs, which become follicles that are 2.0 - 4.0 cm long [10].Catharanthus roseus contains bioactive compounds and exhibits a wide range of pharmacological activities. It has been reported to have antibacterial, antifungal, antioxidant, anticancer, antiviral, antidiabetic, and antihypertensive activities [11]. The plant yields over 70 indole alkaloids, with vincristine and vinblastine being the most important among them. [12]. These alkaloids have been utilized for centuries in chemotherapy to cure Hodgkin's lymphoma and leukaemia in children [13]. Vincristine and vinblastine interfere with tubulin binding, hence inhibiting the development of microtubules. As a result, the mitotic spindle cannot develop normally, and cell cycle is halted during the stage of mitosis [14].Aside from its widespread medicinal use, Catharanthus roseus is also cultivated for its ornamental use. Its lovely pink, purple, and white flowers make gardens and landscapes more beautiful [15]. In Malaysia, the plant is culturally valued, with its periwinkle flower being a symbol of hope for cancer victims, according to the National Cancer Council of Malaysia [16].Due to its sedentary habit, C. roseus has developed intricate mechanisms to cope with environmental stresses [17]. Secondary metabolite synthesis, one of the salient survival strategies, plays a crucial role in defense against herbivores, pathogens, and environmental stresses. The salient members of these secondary metabolites are monoterpene indole alkaloids (MIAs) like ajmalicine and serpentine, which have been thoroughly investigated for their strong antihypertensive activity, referring to their high pharmacological potential [18].Catharanthus roseus is a very significant herb in traditional and modern medicine due to its broad range of medicinal properties and pharma applications. However, difficulties like diminished production of alkaloids and environmental factors highlight the need for ongoing research on sustainable production processes and biotechnological advancements to improve metabolite formation. Combining traditional medicinal wisdom with current scientific expertise will help us optimize the therapeutic uses of this remarkable plant [19]

Figure 1: Cathranthus roseus leaf

Table 1: Pharmacognostical properties of cathranthus rosoeus

Plant organ	**Name of Alkaloids present**
Leaf	Catharanthine, Vindoline, Vindolidine, Vindolicine, Vindolinine, ibogaine, yohimbine, raubasine, Vinblastine, Vincristine, Leurosine, Lochnerine
Stem	Leurosine, Lochnerine, Catharanthine, Vindoline.
Root	Ajmalacine, Serpentine, Catharanthine, Vindoline, Leurosine, Lochnerine, Reserpine, Alstonine, Tabersonine, Horhammericine, Lochnericine, ethaverine.
Flower	Catharanthine, Vindoline, Leucosin, Loch nerine, Tricin (Flavones).
Seed	Vin gramine, Methylvingramine.

Benzoic acid: Two benzoic acid derivatives, gallic acid and vanillic acid, have been reported only in the leaves of Catharanthus roseus based on earlier research. These bioactive metabolites have not been detected in any other plant part [20]. Gallic acid occurs in much greater quantities, around 42 mg per 100 g of leaf material, whereas vanillic acid occurs in much lower levels, around 1.3 mg per 100 g [21]. Gallic acid is very well known for its potent antioxidant, anti-inflammatory, antimicrobial, and anticancer activity and has been considered a significant secondary metabolite compound in medicinal plants. [22]. It is significant in neutralizing free radicals, defending cells against oxidative stress, and demonstrating potential therapeutic activity against chronic diseases. [23]. Vanillic acid, a phenolic compound resembling vanillin in structure, has long been recognized for its antioxidant, anti-inflammatory, and neuroprotective properties. In addition, its potential in sustaining cardiovascular health and regulating metabolic pathways [24] has been studied by researchers. The presence of such phenolic acids in the leaves of Catharanthus roseus is an indicator of their role in the plant's defense mechanism, stress tolerance, and medicinal property. [25]. their presence in the leaves particularly

highlights the significance of this plant material in traditional medicine and pharmaceutical interest. Further work needs to be carried out to investigate their biosynthetic routes, refine the extraction methods, and test their full medicinal potential for future drug use. The skeletal structure of gallic acid is shown below. [26]:

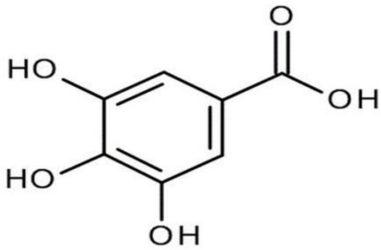

Figure 2: Gallic acid

Phenylpropanoids: Phenylpropanoids are C6–C3 phenolic compounds which are largely derived from the amino acid phenylalanine via the shikimate pathway [27]. These are essential compounds for defense in plants, structural purposes, and for numerous physiological processes. Numerous studies have been carried out to purify quinic acid and derivatives from Catharanthus roseus [28]. Four significant phenylpropanoids have thus far been discovered in this plant by scientists: 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, and ferulic acid [29]. Such compounds occur mostly in specific regions of the plant and usually in very minute quantities. Researchers have established that phenylpropanoids most commonly occur in the leaves and stems of C. roseus, but not at all in its seeds. [30]. The most abundant compound is 4-O-caffeoylquinic acid found in the petals at a concentration of around 1.12% of the total composition. Ferulic acid, on the other hand, occurs only in the leaves, with a measured concentration of about 0.25%. [31]. Phenylpropanoids have a broad spectrum of biological activities, such as antioxidant, anti-inflammatory, antimicrobial, and anticancer activities, which increase the medicinal potential ofplants. Phenylpropanoids play a critical role in protecting plants against environmental stresses like ultraviolet light, deleterious microbes, and herbivorous insects [32]. Moreover, these compounds are also directly involved in lignin formation, an essential structural cell wall component of plants. Because of their notable pharmacological activities, more studies on their biosynthetic pathways and potential biotechnological enhancements may provide useful information for medical intervention [32].

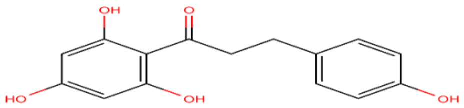

Figure 3: Phenylpropanoids

Flavonoids: Flavonoids are a diverse class of secondary metabolites characterized by their C6-C3-C6 structure. They are primarily produced by the shikimate and acetate pathways. Research conducted during the 1950s in Catharanthus roseus unveiled the occurrence of flavonoids such as kaempferol and quercetin, identified by paper chromatography techniques. [33]. These findings set the foundation for further research into the phytochemical content of the plant. In 1996, two flavonoids were extracted successfully from the leaves of Catharanthus roseus by scientists. These were characterized as Mauritianin and quercetin-3-O-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→6)-β-D-galactopyranoside [34]. The same flavonoid complexes were also isolated from the stems, together with a compound that was unique to this part, namely syringetin-3-O-robinobioside. These results further confirmed the extensive structural diversity of flavonoids found in C. roseus [33]. Later advancements in analytical techniques allowed for the implementation of high-performance liquid chromatography coupled with diode array detection and electrospray ionization mass spectrometry (HPLC-DAD-ESI-MS/MS), which facilitated more comprehensive analysis of phytochemical compounds [35]. This technique allowed for the identification of 15 kaempferol, quercetin, and isorhamnetin-derived glycosides, which provided a better understanding of the plant's flavonoid content [36]. Flavonoids in Catharanthus roseus have very impressive biological activities, including antioxidant, anti-inflammatory, and antimicrobial activities, as well as structural diversity [36]. The compounds are critical for human defence mechanisms, supporting resistance to environmental stresses such as pathogenic microorganisms and ultraviolet radiation [37]. Because of their strong pharmacological properties, research is continuously being done to study their potential use in drug formulation, particularly for the treatment of diseases associated with oxidative stress and cardiovascular disease. Further investigation into the biosynthesis and metabolic pathways of flavonoids in C. roseus can lead to improved medicinal uses and devising sustainable methods of extraction [38].

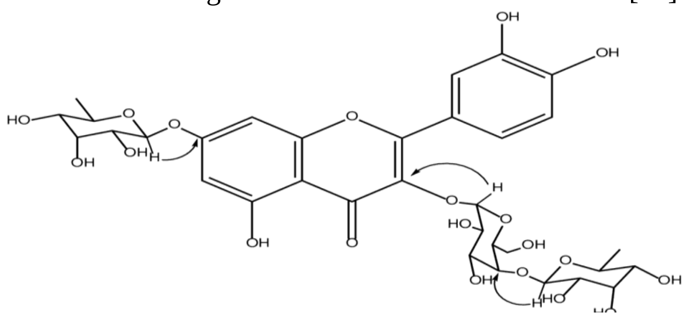

Figure 4: Quercetin-3-O-α-L-rhamnopyranosyl-(1→2)-α-Lrhamnopyranosyl-(1→6)-β-D-galactopyranoside

Anthocyanin: The occurrence of anthocyanins in Catharanthus roseus is highly dependent on the particular cultivar in question, since different cultivars exhibit a wide variation in petal color [39]. The difference in anthocyanin content influences pigmentation, with the range of colors varying from pale tints to deep intense colors. Six novel anthocyanins were isolated from the plant in studies conducted by Pereira et al. (2013). These included Petunidin-3-O-(6-O-p-coumaroyl) glucoside, Petunidin-3-O-glucoside, Hirsutidin-3-O-glucoside, Malvidin-3-O-(6-O-p-coumaroyl) glucoside, Malvidin-3-O-glucoside, and Hirsutidin-3-O-(6-O-p-coumaroyl) glucoside [40]. Interestingly, these anthocyanins were detected only in the leaves and not in the petals, indicating that their biosynthesis is through a different pathway in the foliage. Anthocyanins are essential in plants since they function as antioxidants and serve to protect the plant from several environmental stresses, such as ultraviolet radiation, pathogen infections, and oxidative stress. These pigments improve the aesthetic value of Catharanthus roseus and are also known to possess medicinal properties owing to their good capacity to quench toxic free radicals [41]. The existence and concentration of these substances can be affected by multiple elements, such as the composition of the soil, weather conditions, and farming methods [42]. More research is required to acquire a better insight into the regulation of anthocyanin biosynthesis in various cultivars of Catharanthus roseus and its possible use in the pharmaceutical and nutraceutical industries. Exploring their functions beyond coloration, specifically their role in plant defense mechanisms and medicinal uses, may provide valuable insights into further investigations [43].

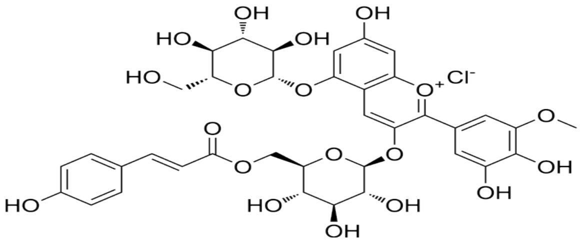

Figure 5: Petunidin-3-O-(6-O-p-coumaroyl) glucoside

Organic acid: The organic acids present in Catharanthus roseus have been extensively studied with High-Performance Liquid Chromatography with Ultraviolet Detection (HPLC-UV) [43]. A number of organic acids, including cis-aconitic acid, citric acid, pyruvic acid, malic acid, fumaric acid, and shikimic acid, have been effectively found in different plant parts, including its stems, leaves, seeds, and flowers [43]. The occurrence and quantity of these acids vary considerably depending on the part of the plant being tested [44].The stems contained the highest organic acids, followed by leaves, petals, and seeds. Organic acids contained a very variable concentration from a low of 0.96 g/kg in seeds to a high of 25.95 g/kg in stems [45]. Citric acid was the most dominant compound among the compounds identified, accounting for about 89% of the total organic acids in stems of C. roseus. Also, malic acid dominated the organic acids in the roots and accounted for approximately 72.1% of the overall content [46].Fumaric acid, cis-aconitic acid, and shikimic acid occurred in smaller amounts in the plant. Organic acids are required for a variety of metabolic processes involving energy production, protection against stress, and secondary metabolite formation. Besides, citric acid and malic acid are critical for physiological processes in the plant and help in its medicinal properties [47, 48].The variations of organic acid levels in different plant parts reflect the advanced metabolic control, which might be influenced by environmental conditions, developmental processes, and genetic attributes [49]. The knowledge on how these organic acids are present and accumulated will provide valuable insights into the biochemical nature of C. roseus, which may ultimately lead it to its pharmaceutical and industrial uses [50].

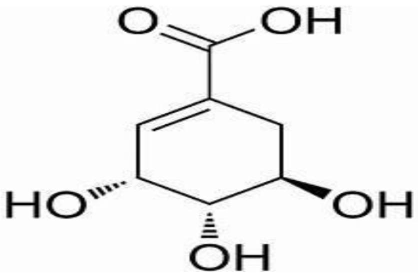

Figure 6: Shikimic acids

Amino acids: The presence of amino acids in the aqueous extract of Catharanthus roseus in different plant organs, including petals, stems, leaves, and seeds, has been established by researchers. Studies indicate that the leaf contains the highest arginine at 67.54 mg/g, followed by the stem at 6.38 mg/g, seeds at 6.17 mg/g, and petals at 5.63 mg/g. These results confirm that, among all the plant parts that were tested, the leaves contain the most arginine [51, 33]. A number of non-essential and essential amino acids, including arginine, have been identified in Catharanthus roseus, an indication of its medicinal and biochemical importance. Using the technique of high-performance liquid chromatography with ultraviolet detection (HPLC-UV), researchers have confirmed the presence of pivotal amino acids like glycine, arginine, histidine, threonine, and glutamic acid, predominantly found in the seeds and leaves of the plant. These amino acids are essential to plant metabolism and provide potential benefits to health, such as contributing to protein synthesis, enhancing immune function, and modulating neurotransmitters [52, 53]. The occurrence of these bioactive molecules further enhances the pharmacological importance of C. roseus. Amino acids have a vital role to play as basic building blocks in the process of synthesizing secondary metabolites such as the famous indole alkaloids, vincristine and vinblastine. These findings not only reinforce the medicinal importance of the plant but also open doors for exploring its future in nutritional and pharmaceutical areas [54].

Volatile components: Volatile components of the essential oil derived from leaves and flowers of Catharanthus roseus differ greatly depending on the geographical region, as evident from available researches [55]. Comparative data of different regions such as France, India, Portugal, and Africa indicate extreme variations in concentration and occurrence of basic chemical constituents. These differences are mainly shaped by agro-climatic conditions, genetic variations, and environmental influences [56]. Studies conducted in France revealed a significantly high presence of palmitic acid (64.9%), along with notable amounts of methyl palmitate (7.2%) and hexahydro farnesyl acetone (4.0%) in C. roseus. On the other hand, oil samples obtained from India showed a much lower concentration of palmitic acid (4.9%), with no traces of methyl palmitate or hexahydro farnesyl acetone. Instead, the Indian samples were abundant in compounds like nerol, citronellol, geraniol, and pentadecanal, which were found only in minimal quantities in the French samples. [57, 33]. The African oil exhibited a unique composition, with hexadecenoic acid, dotriacontane, dodecyl alcohol, stearic acid, and linoleic acid ethyl ester being the primary constituents. On the other hand, the oil samples from Portugal presented a distinct combination of benzaldehyde, β-ionone, 2,3-epoxy-α-ionone, dihydroactinidiolide, 2-nonen-1-ol, ethyl hexanoate, palmitic acid ethyl ester, 2-phenylethanol, trans-2-decen-1-ol, phenylacetaldehyde, and 1-phenyl ethanol. These notable differences emphasize the role of environmental conditions and genetic makeup in shaping the biosynthesis of essential oil compounds in Catharanthus roseus [58]. Another reason for these differences in composition is the method used to extract the oil and the condition of the plant material. In France and Africa, oil was prepared using dried leaves and flowers, whereas in India, fresh leaves were used. The use of fresh or dried plant material can greatly impact the volatile composition because of variations in enzymatic activity and degradation. Additionally, flower oils mainly contain fatty acid esters, which can also differ depending on the plant's growing environment and the way it is processed after harvest [58, 59].

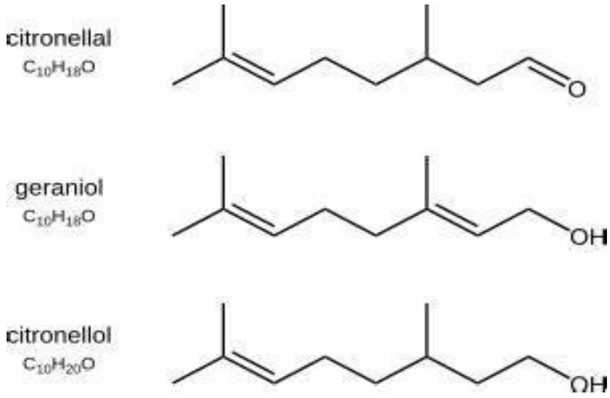

Figure 7: Citronellal, Geraniol, Citronellol

Alkaloids: Catharanthus roseus is a plant known for containing many different alkaloids, which are natural compounds with important medicinal properties. Since the 1990s, a lot of research has been done to find and study these helpful compounds [60]. With advancements in analytical techniques such as High-Resolution Electron Impact Mass Spectrometry (HR-EI-MS), several new alkaloids have been identified in recent years. Among these, two vinblastine-type N-oxide alkaloids—17-desacetoxyvinblastine N'b-oxide and 20'-deoxyvinblastine N'b-oxide—were recently isolated from the plant's leaves [61]. Additionally, catharoseumine was found in the entire plant, with a concentration of approximately 0.786 mg/kg. Another compound, catharoseumine, was found in the whole plant at about 0.786 mg per kg. Other new alkaloids, like 14', 15'-didehydrocyclovinblastine, 17-deacetoxyvinamidine, and 17-deacetoxycyclovinblastine, have shown they can help stop the growth of human cancer cells. [62]. Further studies led to the discovery of novel indole alkaloids such as Vindolicine, N-oxidenormacusine B, and N-oxidelochnerine [63]. Quantitative analysis of these alkaloids gives out that serpentine and its isomer were the amplest, constituting 64.7% of the total alkaloid content. Vindolinine and its isomer accounted for 23.9%, catharanthine made up 7.7%, and ajmalicine contributed 3.8%. Additionally, terpenoids were identified in the plant's leaves at a concentration of 6.28 µM. Three dimeric indole alkaloids—17-deacetoxyvinamidine, 17-deacetoxycyclovinblastine, and 14',15'-didehydrocyclovinblastine—were also successfully isolated. Furthermore, five previously known alkaloids, including lurasidone, cyclomerizing, catharine, leucosin, and viramidine, exhibited significant cell division inhibition against human breast cancer cell line MDA-MB-231, with an IC50 range of 0.73–10.67 µM [64, 65]. One promising compound from the plant, called Cathachunine, showed strong ability to fight leukaemia cells. It also had less harmful effects on normal healthy cells, suggesting it targets leukaemia cells while leaving healthy tissue mostly unharmed. In addition to Vinca alkaloids, different extracts from the plant, both organic and water-based, have shown anticancer effects. Research shows that extracts made with dichloromethane and methanol can kill cancer cells, such as those from HeLa (cervical cancer) and human breast cancer [66]. In 2010, Ahmad et al. reported that water extracts from C. roseus were effective against Jurkat T-cell leukaemia, as shown by an MTT assay. The plant's stem and root extracts also showed strong effects against several cancer cell lines. These anticancer activities result from the synergetic effect of numerous bioactive compounds and not a single active ingredient. The potential for the plant to be used as a medicine persists, with researchers seeking new methodologies to enhance its medicinal applications, such as with the use of biotechnology in enhancing the levels of alkaloids and optimizing methods of extraction. [67]. Due to its numerous favourable impacts, Catharanthus roseus remains a significant natural resource for the discovery of anticancer agents. This indicates its utility in traditional medicine as well as in contemporary drug research [68].

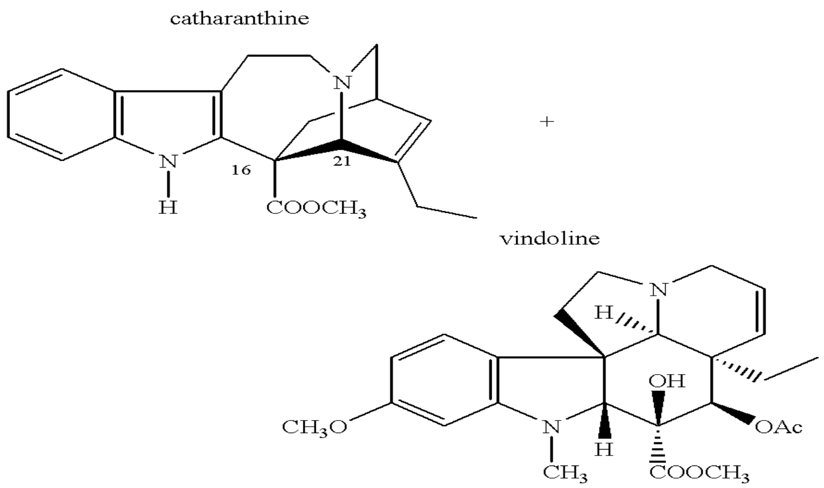

Figure 8: Catharanthine & Vindoline

Vincristine: which is also referred to as Lauro-Cristine and has the brand name Oncovin, is a commonly used chemotherapeutic agent that is well known for its efficacy in the treatment of several forms of cancers. It is an important agent in the treatment of hematologic and solid malignancies such as acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), Hodgkin's lymphoma, neuroblastoma, and small cell lung cancer. Vincristine, as a vinca alkaloid from Catharanthus roseus, exerts its effects by interfering with the formation of microtubules, and as a consequence, cancer cells cannot complete mitosis, culminating in cell death. Its beneficial therapeutic outcome comes with potential side effects that include peripheral neuropathy, constipation, and suppression of the bone marrow and therefore requires scrupulous dose adjustment to keep toxicity to a minimum [69, 70]. Vincristine, otherwise referred to as Lauro-Cristine and marketed under the brand Oncovin, is a widely utilized chemotherapy medication that is particularly effective in the treatment of various cancers. It is used effectively to treat cancers such as blood cancers, i.e., acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML), Hodgkin's lymphoma, neuroblastoma, and small cell lung cancer. Vincristine is synthesized from Catharanthus roseus and functions by preventing cancer cells from dividing normally, which causes them to die. Even though it’s effective, vincristine can cause side effects like nerve damage, constipation, and problems with the bone marrow, so doctors need to carefully monitor the dosage to avoid harmful effects. [71, 72]. Both vincristine and vinblastine remain crucial in oncology, significantly improving survival rates in cancer patients. Ongoing research continues to explore ways to enhance their efficacy, reduce side effects, and develop novel derivatives with improved therapeutic outcomes. As integral components of combination chemotherapy regimens, these drugs underscore the importance of plant-derived alkaloids in modern cancer treatment [73].

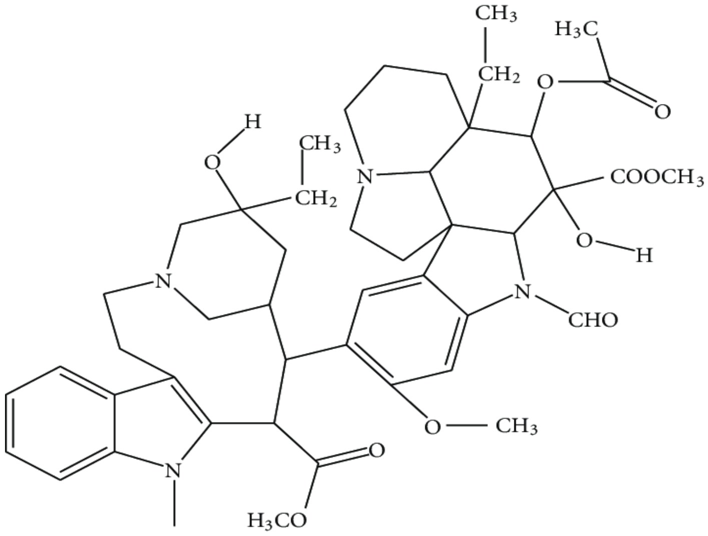

Figure 8: Vincristine

Vindesine: is a man-made version of vinblastine, a natural substance found in the Catharanthus roseus plant. Vindesine works by affecting tubulin, a protein that plays an important role in cell division. It attaches to tubulin and stops it from working properly, which blocks the process needed to form microtubules. As a result, the mitotic spindle, which helps separate chromosomes during cell division, doesn't develop correctly, preventing the cell from dividing properly. [74]. When cells are exposed to vindesine, they can't finish cell division and get stuck in the metaphase stage. This disruption leads to the cell dying naturally (apoptosis), which makes vindesine useful in chemotherapy. It has mainly been used to treat cancers like acute lymphoblastic leukemia, melanoma, and non-small cell lung cancer. Compared to vinblastine, its parent compound, vindesine is more effective at targeting fast-growing cancer cells and has a slightly different pattern of side effects. [75]. Vindesine has also been tested alongside other chemotherapy drugs to boost its cancer-fighting effects. However, like other vinca alkaloids, it can cause side effects like nerve damage, problems with the bone marrow, and issues with the digestive system. Ongoing research is working to make the drug more effective while reducing its side effects. Scientists are also looking into new ways to deliver the drug that could improve its ability to treat cancer. [76].

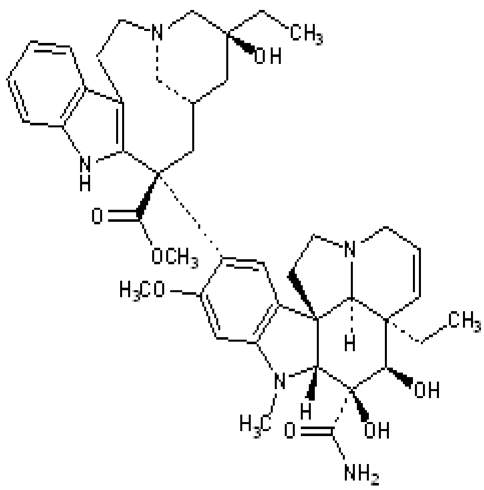

Figure 9: Vindesine

Tabersonine is a naturally occurring compound which possesses anti-cancer activity and is thus a candidate of choice for anticancer therapy. Tabersonine is a significant anti-cancer compound and an essential component of various biochemical reactions. Tabersonine is structurally an alkaloid ester and is also a monoterpenoid indole alkaloid. Tabersonine contains a methyl ester as well and is a complex molecule with five rings that are interrelated to each other [77]. This alkaloid is primarily present in the medicinal plant Catharanthus roseus and is a critical step in the production of vinblastine and vincristine—two popular chemotherapy drugs used to treat cancer. Due to its significance, tabersonine has been researched extensively for its anticancer potential, including its capacity to inhibit tumour growth and induce cell death in cancer cells. [78]. Aside from its anticancer activity, tabersonine is also explored for its nerve-protecting and heart-enabling effects. Researchers are presently looking into the betterment of how it can be extracted, synthesized, and even altered in order to use it as a medicine. As research on alkaloids from plants expands, tabersonine remains to be a valuable compound used in drug synthesis and pharmaceutical innovations. [79].

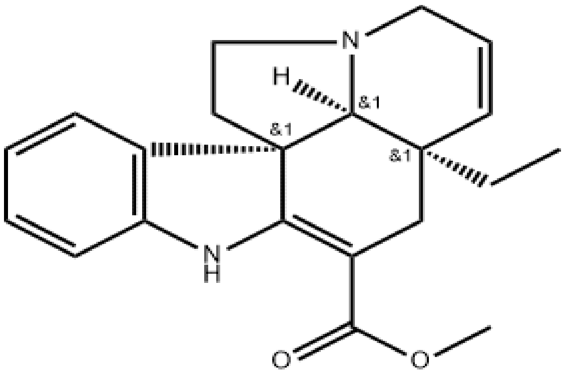

Figure 10: Tabersonine

Pharmacological properties of Catharanthus Roseus:

Anti-hyperlipidaemic Action

Catharanthus roseus has been found to possess significant properties that tend to decrease dangerous blood fats. Research indicates that plant extracts have the ability to decrease excessive levels of triglycerides, LDL (bad cholesterol), and total cholesterol in experimental models. These activities are more pronounced with higher concentrations, indicating its potential in treating excess blood fat content and lowering the risks of heart disease. The plant also possesses weak effects in reducing blood pressure, further contributing to its heart-protecting properties. Alkaloids, flavonoids, and terpenoids are thought to contribute to its blood fat-controlling effect. This makes C. roseus a hopeful natural therapy for cholesterol control and cardiac well-being. [80,81,82].

Antimicrobial Action

Catharanthus roseus also demonstrated very good capacity to resist bacteria, fungi, and parasites. Preparations from various parts of the plant, such as leaves, stems, flowers, and roots, were proven to inhibit the growth of pathogenic microorganisms. Flavonoids, phenolics, and alkaloids, such as catharoseumine, are thought to be responsible for its infection-fighting activity. [83]. Research has shown that C. roseus extracts are potent against bacterial pathogens like Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, and thus it is a useful natural antimicrobial agent. In addition, antifungal compounds in the plant, especially saponin-rich fractions from roots and stems, have strong activity against fungi like Aspergillus niger and Candida albicans. The antifungal activities of C. roseus make it a promising source of bioactive agents for the control of fungal infections, especially in immunocompromised patients [84]. In addition to its antibacterial and antifungal activities, C. roseus is also protective against parasites. One of the compounds in C. roseus, catharoseumine, has been found to attack Falcipain-2, a protein associated with malaria parasite Plasmodium falciparum. The plant's alkaloids can also inhibit the growth of Trypanosoma brucei, sleeping sickness parasite. [85]. Apart from the ability to combat bacteria and parasites, C. roseus is also found to combat viruses. Plant extracts are found to be able to halt the progression of the herpes simplex virus (HSV), proposing its potential to become a beneficial natural antiviral therapy. Amidst the ever-growing issue with drug resistance, C. roseus becomes one such prized plant with promise for infection treatment. bacterial and parasitic infections, C. roseus contains antiviral capability. [86]. Healing of a wound is a spontaneous process that enables repair of injured tissue and regaining its strength. It occurs in three principal phases: inflammation, proliferation, and maturation (or remodelling). During the initial phase, inflammation, the immune cells become activated to sterilize the wound and avoid infection. The next stage, proliferation, is when important processes like collagen production, new blood vessel growth, and skin cell regeneration happen to help rebuild the wound. In the final stage, maturation, the wound shrinks, the tissue is remodeled, and a scar forms, which helps restore the strength of the healed tissue. [87]. Natural plant-based remedies have become popular for helping wounds heal faster. One such remedy is the ethanolic extract of Vinca rosea, which has shown strong healing abilities, especially in the final stage of wound healing. Catharanthus roseus also exhibited excellent ability to resist parasites, fungi, and bacteria. Extracts of roots, stems, flowers, and leaves of the plant were found to be inhibiting the growth of disease-causing microorganisms. Alkaloids, phenolics, and flavonoids like catharoseumine are believed to account for its infection-fighting action. [83]. Studies have revealed that C. roseus extracts are effective against bacterial pathogens such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, and therefore it is an effective natural antimicrobial. Besides, fungal antifungal compounds in the plant, particularly saponin-containing fractions from roots and stems, exhibit significant activity against fungi such as Aspergillus Niger and Candida albicans. Antifungal activities of C. roseus renders it a potential source of bioactive compounds against fungal infection control, particularly in immunocompromised subjects [84]. Apart from its antifungal and antibacterial activities, C. roseus is also parasiticidal. One of the C. roseus compounds, catharoseumine, has been discovered to target Falcipain-2, a protein linked to malaria parasite Plasmodium falciparum. Alkaloids of the plant are also capable of suppressing the growth of Trypanosoma brucei, sleeping sickness parasite. [85]. In addition to the capacity to fight bacteria and parasites, C. roseus is also discovered to fight viruses.

Plant extracts are discovered to have the capacity to stop the advancement of the herpes simplex virus (HSV), suggesting its potential to be a useful natural antiviral therapy. In the midst of the ever-increasing problem with drug resistance, C. roseus becomes one such valuable plant with potential for infection treatment. bacterial and parasitic infections, C. roseus has antiviral potential. [86]. Wound healing is a spontaneous reaction that allows repairing damaged tissue and restoring its strength. It goes through three major phases: inflammation, proliferation, and maturation (or remodelling). In the first phase, inflammation, immune cells are activated to sterilize the wound to prevent infection.as shown by higher levels of hydroxyproline, an amino acid that helps measure tissue strength and health. [88, 89]. Apart from assisting with collagen synthesis, Vinca rosea also possesses strong antioxidant and anti-inflammatory activities that assist with wound healing. Through its stress and inflammation reduction in the body, it heals wounds quicker and avoids issues that may occur with slow healing, particularly in diabetic ulcers or chronic wounds. These encouraging results indicate that Vinca rosea may be a valuable natural remedy for wound healing and be investigated further in clinical practice. [90].

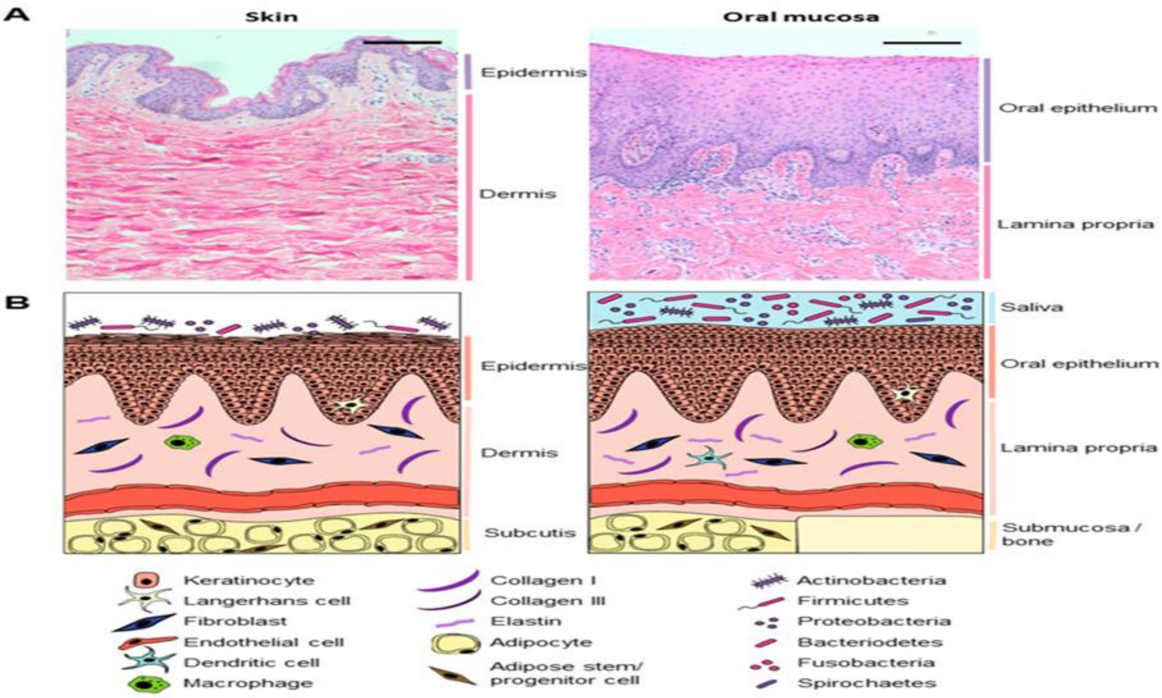

Figure 11: Internal parts of the skin to penetrate

Anti-diarrheal property: The ability of Catharanthus roseus to treat diarrhea was tested in Wistar rats using an ethanolic leaf extract. The rats were given the plant extract before being treated with castor oil to cause diarrhea. The findings indicated that the plant extract largely mitigated the episodes of diarrhea in a dose-dependent manner, confirming that it is effective in managing gastrointestinal disorders. [96]. At 200 mg/kg and 500 mg/kg doses, the extract effectively inhibited castor oil-induced diarrhea and reduced intestinal movement in the charcoal meal test significantly. The higher dose was more effective in regulating excessive bowel movement, indicating that the extract possesses potent anti-diarrheal activity. This is probably attributed to bioactive compounds such as flavonoids, alkaloids, and tannins that assist the intestines in the absorption of more substances, suppressing fluid secretion, and relaxing intestinal muscles [97]. Antioxidants are critical in protecting the body from free radical toxicity-induced damage, implicated in diseases including brain disorders and cancer. Catharanthus roseus (Vinca rosea) is well known for its strong antioxidant activity, which is due to its high content of useful compounds like vitamin C, alkaloids, flavonoids, tannins, and phenols. These compounds work synergistically to fight free radicals, preventing cellular damage. [91].

In contrast to most other medicinal plants, C. roseus has much higher levels of phenolic compounds and is therefore much more effective as a natural antioxidant. The leaf, stem, and root extracts have been shown in experiments to suppress the growth of cancer cells, which accounts for how it can be cell-protective and fight damage. The plant's antioxidant capability is particularly great at a concentration of approximately 800 µg, where it has been determined to be extremely effective in reducing free radicals. [92]. The bioactive substances of C. roseus, such as vindoline and vinblastine, assist in lowering oxidative stress by eliminating damaging molecules known as reactive oxygen species (ROS) and inhibiting damage to cellular fats. Studies indicate that C. roseus is a more potent antioxidant than C. alba, particularly when employing extracts of its roots. Furthermore, application of some plant growth regulators, i.e., triadimefon, can boost the yield of alkaloids and thus possibly render the plant still healthier for use by humans [93]. C. roseus flowers have a very high ability to uptake toxic oxygen molecules (ORAC), even more so than well-known antioxidants like vitamin C. The high ORAC value of the plant determines its possible application as a natural antioxidant source of pharmaceuticals and health supplements. Its many active compounds and high antioxidant activity make C. roseus remains one of the viable choices for production of herbal drugs for the therapy of disease conditions caused by oxidative stress. [94, 95]. The findings from this study validate the traditional application of Catharanthus roseus in the treatment of diarrhea. It is likely to act as a slow-down effect on intestinal motility and decreasing excessive secretion of fluid, promoting normal bowel function. Further research, such as analysis of the chemical constituents of the plant and clinical trials, may help better understand its possible use as a natural remedy for gastrointestinal disorders. The results also indicate that C. roseus has significant potential in herbal medicine for the treatment of gastrointestinal disorders. [98, 99].

Anti- ulcer activity: Vincamine and vindoline are two major compounds with the prospect of being used to cure ulcers. Vincamine, mainly from the leaves of Catharanthus roseus, has been studied for its role in brain protection and enhancing the flow of blood. It is likely to be helpful against diseases like dementia, memory loss, and stroke by improved oxygen and nutrient supply to the brain. [100, 101]. However, vincamine also bothers the stomach and harms the stomach lining in animal studies, specifically rats. High doses or extended use can result in ulcers, possibly through excess stomach acid or destroying the protective stomach lining. This suggests additional studies need to be conducted to make sure that it will be safe to take without causing stomach problems.[102]. Another active compound of C. roseus, vindoline, has been reported to be effective against ulcers as well because it has the ability to reduce oxidative stress and inflammation within the gastric lining. Vindoline is also crucial in synthesizing vinblastine and vincristine, two major cancer chemotherapy drugs that are used in the treatment of cancer. [103].

Memory enhancement: Vinpocetine is a Catharanthus roseus compound with remarkable ability to enhance brain function and memory. It is thus beneficial in the treatment of neurodegenerative disorders such as Alzheimer's. Research indicates that vinpocetine increases blood circulation to the brain, enhances the utilization of oxygen by the brain, and safeguards brain cells against damage from stress. These functions make vinpocetine beneficial in safeguarding the brain and enhancing cognitive functions. [104]. Clinical trials for vinpocetine in conditions like dementia and stroke have established that it is effective at a safe dose of up to 60 mg a day. There were fewer side effects, as well as enhanced thinking, mind clarity, and memory, with patients who applied this treatment. Vinpocetine also expands blood flow through the brain by blocking a specific enzyme (PDE1), which causes the blood vessels to dilate. This helps the brain function, especially in learning and memory consolidation [105]. Apart from helping in Alzheimer's disease, vinpocetine has also been used to treat age-related memory loss, vascular dementia, and stroke recovery. It has anti-inflammatory and antioxidant properties that help defend the brain by reducing free radical damage and inflammation. Some research also shows that vinpocetine can alleviate conditions like tinnitus (ringing in the ears) and vertigo (dizziness), which are caused by reduced blood supply to the inner ear and brain [106].Because of its many brain benefits and safety, vinpocetine remains a top research focus, with potential uses for both prevention and treatment of cognitive impairment. Apart from Alzheimer's disease, vinpocetine has potential for other conditions like age-related memory loss, vascular dementia, and stroke rehabilitation. Its antioxidant and anti-inflammatory properties can safeguard the brain through protection against free radical damage and inflammation. Vinpocetine is also claimed to treat conditions of tinnitus (ears ringing) and vertigo (dizziness) resulting from disturbed blood circulation in the inner ear and brain. [106]."}. Due to its numerous advantages for brain health and safety, vinpocetine remains a significant field of study. It can potentially be utilized to prevent as well as treat brain-related illnesses. [107]. Anti-cancer activity: Vinblastine and Vincristine are potent anti-cancer substances present in the leaves and stems of Vinca rosea (reclassified as Catharanthus roseus). These substances are useful in inhibiting the growth of some human tumours. They act by disturbing the microtubules present within cells, which are essential for cell division. This inhibition inhibits the division and growth of cells, rendering these compounds effective in combating cancers such as leukaemia, lymphoma, and solid tumours [108]. One of the things that is excellent about Vinblastine and Vincristine is that they can attack quite a variety of cancer cells. They are especially effective against tumors that are resistant to multiple drugs, which are harder to treat. These alkaloids work by attaching to tubulin proteins, stopping the formation of the mitotic spindle, which is needed for cell division. This causes cancer cells to get stuck in a stage of cell division (metaphase), leading to their death (apoptosis) [109]. Vinblastine is commonly used in chemotherapy to treat Hodgkin's lymphoma, testicular cancer, and breast cancer. Vincristine is especially effective for treating childhood leukemia, neuroblastoma, and non-Hodgkin's lymphoma. However, while these drugs are effective, they can cause side effects. Vincristine can cause nerve damage (neurotoxicity), and Vinblastine can affect the bone marrow (myelosuppression). Researchers are working to find ways to make these drugs more effective while reducing their side effects [110]. With ongoing advancements in biotechnology and genetic engineering, efforts are being made to improve the yield of these alkaloids from Catharanthus roseus through plant tissue culture and metabolic engineering techniques. These advances hold out hope for improving the access to these lifesaving medications and expanding their therapeutic applications in the treatment of cancer [111]. Hypoglycemic Activity Methanol leaf extract of Catharanthus roseus has been explored for its effect on the hypoglycemic action of commonly prescribed antidiabetic medication, metformin and glibenclamide. Phytochemical screening was conducted on the extract to ascertain its bioactive constituents, together with acute toxicity and lethality (LD_{50}) determinations. Median lethal dose (LD_{50}) of methanol leaf extract was established at 32 mg/kg, indicating its safety level at lower doses [112]. The study found that all treatment groups had a significant reduction in blood glucose level. However, the co-administration of metformin and C. roseus leaf extract had the highest hypoglycemic activity with the highest percentage reduction in blood glucose level at 64.86%. This suggests a good synergistic interaction between metformin and plant extract such that they have greater glucose-lowering effects than when each agent is administered alone [113, 114]. The potential mechanism of this enhanced activity may be attributed to the presence of bioactive compounds such as alkaloids, flavonoids, tannins, and saponins in C. roseus, which have been shown to exhibit antidiabetic activity. These compounds may increase insulin sensitivity, enhance peripheral tissue glucose uptake, or improve pancreatic beta-cell function. Moreover, the antioxidant activity of the plant extract may be responsible for its therapeutic effects by minimizing oxidative stress, a key cause of diabetes complications [115]. Anti-Parasitic Activity The blood-sucking fly Hippobosca maculata Leach (Diptera: Hippobosca) and the sheep-biting louse Bovicola ovis Schrank (Phthirapteran:

Trachodontidae) are major ectoparasites infesting livestock, resulting in economic losses and health complications. In this work, the adulticidal activity of titanium dioxide nanoparticles (Tio_2 NPs) biosynthesized by aqueous leaf extract of Catharanthus roseus against these parasites was tested. The evaluation encompassed crude aqueous C. roseus leaf extract, Tio_2 solution, and biosynthesized Tio_2 NPs at different concentrations for 24 hours exposure [116].

Among the treatments tested, the aqueous extract of C. roseus proved to have significant adulticidal activity against H. maculata and B. ovis, with LD_{50} values of 36.17 mg/L and 30.35 mg/L, respectively, and corresponding r^2 values of 0.948 and 0.908. Comparatively, the highest efficacy was in the 5 mM Tio_2 solution, where LD_{50} values for H. maculata and B. ovis were 33.40 mg/L and 34.74 mg/L, respectively, with r^2 values of 0.786 and 0.873. However, the highest adulticidal efficacy was demonstrated by the synthesized Tio_2 NPs, which produced the highest inhibition of parasite survival, recording LD_{50} values of 7.09 mg/L and 6.56 mg/L for H. maculata and B. ovis, respectively, and r^2 values of 0.88 [117]. These advances hold out hope for improving the access to these lifesaving medications and expanding their therapeutic applications in the treatment of cancer [111].

Hypoglycemic Activity Methanol leaf extract of Catharanthus roseus has been studied for its effect on the hypoglycemic activity of commonly used antidiabetic drugs, metformin and glibenclamide. Phytochemical analysis of the extract was also carried out to identify its bioactive compounds, along with acute toxicity and lethality (LD_{50}) tests. Median lethal dose (LD_{50}) of methanol leaf extract was determined as 32 mg/kg, which showed its safety at low doses [112].

The research revealed that there was a significant decrease in blood glucose across all treatment groups.However, the co-administration of metformin and C. roseus leaf extract exhibited the highest hypoglycemic activity, with the highest percentage reduction in blood glucose level at 64.86%. This suggests a good synergistic interaction between metformin and plant extract such that they exhibit enhanced glucose-lowering effects compared to each agent when administered alone [113, 114].

The probable mechanism of this enhanced activity may be attributed to the presence of bioactive molecules such as alkaloids, flavonoids, tannins, and saponins in C. roseus, which have been found to exhibit antidiabetic activity. These molecules may increase insulin sensitivity, raise peripheral tissue glucose uptake, or improve pancreatic beta-cell function. Additionally, the antioxidant activity of the plant extract may be attributed to its therapeutic action by reducing oxidative stress, a major etiology of diabetes complications [115]. Anti-Parasitic Activity Blood-sucking fly Hippobosca maculata Leach (Diptera: Hippobosca) and the sheep-biting louse Bovicola ovis Schrank (Phthirapteran: Trachodontidae) are serious ectoparasites that infest livestock, which lead to losses of money as well as pose health problems. The adulticidal efficacy of aqueous leaf extract of Catharanthus roseus biosynthesized titanium dioxide nanoparticles (Tio_2 NPs) were assayed for action against such parasites in the current research work. The bio-evaluation included crude aqueous C. roseus leaf extract, Tio_2 solution, and biosynthesized Tio_2 NPs at various concentrations for 24 hours exposure [116]. Among tested treatments, C. roseus aqueous extract was found to exhibit strong adulticidal activity against H. maculata and B. ovis with LD_{50} values of 36.17 mg/L and 30.35 mg/L, respectively, and corresponding r^2 values of 0.948 and 0.908. Compared to these, the most effective was the 5 mM Tio_2 solution, which exhibited LD_{50} values of 33.40 mg/L for H. maculata and 34.74 mg/L for B. ovis, respectively with r^2 values of 0.786 and 0.873. However, the strongest adulticidal activity was reported by the as-synthesized Tio_2 NPs that resulted in strong inhibition of the survival of the parasites with recorded LD_{50} values of 7.09 mg/L and 6.56 mg/L against H. maculata and B. ovis, respectively, and r^2 values of 0.88 [117]. scale applicability could help develop sustainable parasitic control strategies in animal health management [118, 119].

Nanoparticles have gained much popularity in recent years due to the fact that they can be utilized in a wide range of fields in medicine, particularly in the treatment of drug-resistant bacterial infections. Zinc oxide nanoparticles (ZnO NPs) were successfully synthesized in this research using an environmentally friendly, green chemistry method involving the leaf extract of Catharanthus roseus (Madagascar periwinkle). The biosynthesized ZnO NPs exhibited potent antibacterial activity against various Gram-positive and Gram-negative bacterial strains, including Staphylococcus aureus MTCC 9760, Streptococcus pyogenes MTCC 1926, Bacillus cereus MTCC 430, Pseudomonas aeruginosa MTCC 424, Proteus mirabilis MTCC 3310, and Escherichia coli (E. coli) [120]. The antimicrobial activity of ZnO NPs was further boosted when used in combination with streptomycin, as indicated by the increased zone of inhibition when used in combination compared to when used separately. This shows that ZnO NPs prepared from C. roseus leaf extract have a quick, cost-saving, and eco-friendly method of preparing new antibacterial agents against resistant microbial strains [121].

Besides the synthesis of zinc oxide nanoparticles (ZnO NPs), other researchers have also exploited the application of Catharanthus roseus leaf extract in silver nanoparticle synthesis (AgNPs). It is achieved via the utilization of the plant for the reduction of the silver ions (Ag^+) into solid silver (Ag^0). It is a green, safe, and effective method for synthesizing the nanoparticles. C. roseus natural products make the process rapid, demonstrating its potential for large-scale production of silver-based nanoparticles. Silver nanoparticles have high antibacterial activity and could be very useful in medicine, particularly in wound healing, drug delivery, and germ-killing coating. With the employment of C. roseus as a natural reducing agent to synthesize and stabilize the nanoparticles, the current work reports a promising method of producing antibacterial materials, which can combat the growing issue of antibiotic-resistant bacteria. [122, 123, 124, 125].

Antifungal Activity Catharanthus roseus has also been shown to possess intense antifungal activity,

which was found to be effective against the growth of most fungal pathogens such as Candida albicans, Aspergillus fumigatus, Aspergillus niger, and Fusarium moniliform. Antifungal activity was quantified using the paper disc diffusion method, a widely used technique for testing the resistance of a compound against microbes. Three liquids were used in this test—ethanol, acetone, and water—to determine how much C. roseus was resistant to fungi. [127]. What they found was that antifungal activity was variable according to what liquid had been used to isolate the plant components. The ones using organic solvents like ethanol and acetone were far better able to resist fungi than those that used water.Of the plant components that were tested, the leaves of C. roseus were most capable of antifungal activity, and most effective was the ethanol extract. Surprisingly, the ethanol extract was particularly effective at inhibiting Fusarium moniliform me growth, the first time that C. roseus has been found to resist this specific fungus [128]. MIC concentration of minimum extract to inhibit the fungi growth was 25-50 g/L, which shows that the plant is strongly antifungal. From the results, it can be concluded that C. roseus can be a critical natural source for the development of antifungal medicines. Additional research should be conducted to identify and study the actual compounds in the plant to achieve this antifungal activity and identify ways in which they can be used in medicine and agriculture [129].
HypotensiveProperty Catharanthus roseus leaf extract has demonstrated an excellent capacity for lowering blood pressure and is thereby potentially a suitable herbal treatment for hypertension. Its leaves contain about 150 active compounds, many of which contribute to the plant's various health benefits. Experiments have shown that alcohol-water mixture extracts or a mixture of dichloromethane and methanol extracts can reduce blood glucose and reduce blood pressure in animal models. [130, 131]. In addition to regulating blood pressure, these extracts are also studied to regulate blood sugar, which could be useful to manage diabetes. The alkaloids in the plant, including ajmalicine and serpentine, dilate blood vessels, enhance blood circulation, and lower blood pressure. The flavonoids and phenolic acids in the leaves also have antioxidant activities, which fight oxidative stress—something which is implicated in high blood pressure and diabetes complications. [132].Antimalarial Activity Aqueous extracts of Catharanthus roseus (L.) have been used in the green synthesis of silver nanoparticles with excellent antimalarial activity against Plasmodium falciparum, the malaria parasite.
Bio-reduction of silver ions using plant extracts provides a green, eco-friendly route for synthesizing nanoparticles, minimizing the use of toxic chemical reagents that are normally used in conventional routes. Phytochemicals from the leaves of C. roseus, including alkaloids, flavonoids, and terpenoids, are responsible for the reduction and stabilization of these nanoparticles [133].
Recent research showed that silver nanoparticles synthesized from the extracts of C. roseus exhibit potent antiplasmodial activity and inhibit the development and survival of P. falciparum at various life stages. This property opens new avenues for developing plant-based nanomedicines as an alternative strategy for malaria treatment. Given the rising drug resistance among Plasmodium species, the integration of nanotechnology with traditional herbal medicine could offer a novel therapeutic approach [134, 135].
Anthelminthic Activity Helminth infections are a significant health concern affecting both humans and livestock, often leading to chronic illnesses. Traditionally, Catharanthus roseus has been recognized for its medicinal properties, including its use as an anthelmintic agent. Historical records and ethnomedicinal practices suggest that this plant has been utilized to combat parasitic worm infestations for centuries [136].Recent experimental studies have evaluated the anthelmintic efficacy of C. roseus using Pheretima Posthuma (earthworms) as a model organism. Research has shown that preparations made from alcohol-water solutions or a mixture of dichloromethane and methanol were found to decrease blood sugar and blood pressure in model animals. [130, 131].

[2] CONCLUSION

In addition to managing blood pressure, the extracts of these compounds have also been studied to manage blood sugar, which could be useful in the management of diabetes. Plant alkaloids like ajmalicine and serpentine are utilized to dilate blood vessels, improve blood supply, and lower blood pressure. Flavonoids and phenolics of the leaf are also antioxidant in nature, which can combat oxidative stress—something which is a participant in high blood pressure and diabetes complications. [132].Antimalarial Activity Aqueous leaf extracts of Catharanthus roseus (L.) were utilized in the green synthesis of silver nanoparticles that have been demonstrated to have efficacy against the malaria-causing parasite Plasmodium falciparum. Plant extract-mediated bio-reduction of the silver ions represents a green protocol for nanoparticle synthesis, which avoids the extensive utilization of harmful chemical reagents involved in the conventional protocols. Phytochemicals present in C. roseus leaves such as alkaloids, flavonoids, and terpenoids are responsible for reduction and stabilization of the nanoparticles [133].Recent research has shown that silver nanoparticles synthesized from C. roseus extracts exhibit significant antiplasmodial activity, inhibiting the development and survival of P. falciparum at various stages of the parasite's life cycle.

[3] AUTHOR(S) CONTRIBUTION

Dr. Zealous Mary comprehended and conducted the study, as well as evaluated and interpreted the results. Dr. Vathana wrote and updated the main manuscript. All authors read and approved the final version of the manuscript.

[4] LIMITATIONS

The size of the sample was very small.
The study was completely conducted on senior citizens.

[5] RECOMMENDATIONS

Needs to conduct in Tai-chi exercise to assess the physical problems in old age people.
Comparison research may be done to discover changes in adults and old age
Recommend to do this study as qualitative research.

[6] ACKNOWLEDGEMENT

Individuals / resources participated in the work are acknowledged properly.

[7] SOURCES OF FUNDING

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[8] PLAGIARISM POLICY

The authors declare that any kind of violation of plagiarism, copyright, and ethical matters will be handled by all authors. Journalists and editors are not liable for the aforesaid matters.

[9] CONFLICT OF INTEREST

The authors declared that no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

[10] PROTECTION OF RESEARCH PARTICIPANTS

This study do not involve any such criteria or condition.

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