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A review on phytochemical constituents and pharmacological properties of *Catharanthus roseus* (L.) G. Don

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Abstract
Ethnopharmacological relevance: *Catharanthus roseus* (also called Sadabahar in India), is utilized as a common traditional medicine in India, England, Thailand, Japan and Australia. It was traditionally used to treat wasp string, gonorrhoea, hypertension and menstrual cycle. Various compounds obtained from this plant are utilizeds for medicinal purposes. It is even commercially formulated for its anticancer properties.
Aims: This review aims to provide a systematic summary of *Catharanthus roseus* and to reveal the correlation between the traditional uses and pharmacological activities so as to offer inspiration for future research.
Materials and methods: All corresponding information about *Catharanthus roseus* was collected using Google Scholar and from various scientific databases including Springer, Science Direct, Wiley, and PubMed. Local dissertations and books were searched as well.
Results: According to classical ayurvedic text, *Catharanthus roseus* dominantly displays antidiabetic effect in diabetes mellitus person and its hypertension properties which were verified in modern medicine for their use. In modern research, more than 200 compounds were identified from *Catharanthus roseus.* Leaves contain large number of alkaloids along with flavonoids, sterols, saponins, amino acid, polyphenols and anthocyanins. Alkaloids such as vindoline, vincristine, vinblastine, and catharanthine, are considered as the characteristic and active constituents of this plant. They exhibited anticancer, antidiabetic, antivirus, antibacterial effects, etc. Vinblastine and vincristine acts on the cancer cells by disrupting the mitotic spindle fibres thereby inhibiting cell division. Currently, there is no lethal effect of *Catharanthus roseus* at lower dosage on human i.e., less than 5000 mg/kg.
Conclusions: Due to pantropical distribution of *C. roseus*, it has wide range of traditional uses in different countries. Among these uses antitumor, anticancer and antidiabetic potentialswere further supported by scientific research and clinical trials to develop commercial medicine. For future research, still other traditional uses are yet to be authenticated so more *in vivo* experiments and clinical studies are encouraged to further clarify the relation between these traditional uses and their modern applications.

Keywords: *Catharanthus roseus*, traditional uses, phytochemistry, pharmacological activities, pharmacokinetics

Introduction
The utilization of natural products as medicinal herbs in the form of extracts or specific formulations as a cure for various disorders is an age-old concept. These remedial properties are used in a different type of medicinal systems like Homeopathic, Ayurvedic, Unani, Modern medicine, etc. due to the efforts of great pioneer scientists. Today, various studies have been conducted on the medicinal herbs for their traditional utilization, phytoconstituents, clinical applications and toxicity. Drugs like morphine, vinblastine, vincristine, quinine, aspirin, digitoxin are the example of the medicine derived from traditional herbs. Around over 25% of present-day prescriptions are directly or indirectly obtained from natural sources. The therapeutic vegetation of South Asia is a significant wellspring of various pharmacologically significant mixtures that are generally consumed as home cures in restoring or treating different sorts of illnesses from normal cold to malignant growth (Patel, 2011) [135].
One such important plant with multiple pharmacological applications is *Catharanthus roseus*. Itis one of the most commercially explored flowering plants due to its wide range of medicinal properties. C. roseus belongs to the family Apocynaceae and it is possibly one of the most significant medicinal plants in history.

It is mentioned in different historical and religious textbooks. The leaves and stems of this plant are used in ancient medicine for several ailments including back pain, diabetes, asthma, fever, bronchitis, cough, chest congestion, dizziness, chronic headache, inflammation, infertility, and other gastrointestinal disorders like diarrhea, and dysentery (Yang *et al*., 1987; Perry 1980; Swanston-Flatt *et al*., 1989) [214, 185, 143].

Methodology

The scientific literature used for the preparation of this paper was collected from PubMed, Springer, Scopus, Google Scholar, Science Direct, ACS, Wiley and Taylor & Francis. Various offline and online resources were referred for writing this paper. The search was made using keywords *C. roseus* and traditional uses, *C. roseus* and phytochemistry, *C. roseus* and pharmacological properties; *C. roseus* and clinical trials, etc. An attempt was made to document the relevant literature between 1944-2020.A distinct search was conducted on *C. roseus* which was not confined to specific dates. Along with this, the references of selected papers were also screened manually for supplementary information.

Plant description

C. roseus is an evergreen plant with 80-100 cm of height, sub-woody at the base and profusely branched (Hogan, 2003) [73] (Fig 1). Two basic cultivars of *C. roseus* are named based on their bloom shading, one creating pink blossom called "Rosea" (Lata, 2007) [101] and the other, white blossoms "Alba". Flowers are pedicellate, bracteate, hermaphrodite, actinomorphic, complete, hypogynous, pentamerous and are borne in pairs in axils (Hogan, 2003) [73]. Stem color differs from yellowish-green to light pink or dark purple. Leaves are 3- 9 cm long, 1-4 cm broad with glossy green in color. These are oblong, opposite, short-petiole with smooth or pubescent along the entire margin (Gajalakshmi *et al*., 2013) [61]. Corolla is 5 lobed, salver-shaped, cylindrical tube and can be purple or white in color (Pandey *et al*., 2020) [131]. Stamen is positioned 0.4-0.6 cm below the corolla mouth. It consists of white-colored fibers, filiform and anthers (Das *et al*., 2020; Mishra and Verma, 2017) [47, 111]. Stem diameter ranges from 1- 8.8 cm and the separation between the internodes varies from 0.4-6.7 cm. Calyx lobes are pubescent, linear to subulate, 5 in number and 0.09- 0.70 cm in size (Das *et al*., 2020) [47]. Anthers are merged to the fibers and vary from sagittate to thin lanceolate in shape. The style is reduced in thickness with its size ranging from 0.5–3.0 cm in length (Das *et al*., 2020) [47]. In *C. roseus*, two carpels are present which are partially fused, in each carpel 10–30 ovules are arranged in two sequences. The fruit consists of two follicles which are 0.6- 3.5 cm in length. Each follicle is piercing, elongated and cylindrical in shape with numerous blackish seeds. The seeds are present in cylindrical or oblong shapes and their size varies from 0.06-0.70 cm (Mishra and Verma, 2017) [11] (Fig. 1).

Scientific name and classification

It belongs to the genus Apocynaceae. *Catharanthus* comprises of eight species all derived from Madagascar *viz C. trichophyllus* (Baker) Pichon, *C. scitulus* (Pichon) Pichon, *C. coriaceus* Markgraf, *C. lanceus* (Bojerex) Pichon, *C. roseus* (L.) G. Don*C. ovalis* Markgraf, *C. longifolius* (Pichon) Pichon original to Madagascar and one *C. pusillus* (Murray) G. Don resident to India (Stearn 1975) [172]. In this review, we will be discussing the *Catharanthus roseus* variety. In the beginning, there was uncertainty regarding the logical writing in regards to the exact arrangement of the class of the plant. In 1753, Carolus Linnaeus perceived the class *Vinca* and recognized it into species *V. major* and *V. minor* in his Species Plantarum. Later in 1759, Linnaeus published *C. roseus* as *Vinca rosea* in his book "Systema Naturae". Ludwig Reichenbach in 1828 proposed the name *Lochnera* in his "Conspectus Regni Vegetabilis" without giving the reference or description for it. Saint George Don in 1835 apportioned the name *Catharanthus* in "General System of Gardening and Botany" (Wijnands 1983) [9].

Domain: Eukaryota
Kingdom: Plantae
Phylum: Tracheophytes
Subphylum: Angiosperms
Class: Magnoliopsida
Order: Gentianales
Family: Apocynaceae
Genus: *Catharanthus*
Species: *roseus*

Distribution

It has pantropical distribution as it is naturally found in Asia, North America, Southern America, Europe, Australia and Africa (Van Bergen, 1996) [97]. The dispersal might be due to the sailors who took the plant on board during their travels. The sailors used the leaves of plants to decrease the sensations of fatigue and hunger by chewing them (Markgraf, 1976) [110]. The earliest reports of *C. roseus* goes back to 1648-1655 when botanist Flacourt in Madagascar studied it. Its cultivation started in Europe when the seeds of *C. roseus* were sent to the Royal Gardens in Paris from Madagascar. In 1757, the seed was raised by Philip Miller at Chelsea Physic Garden in London who incorporated its description in his "Figures of the Most Beautiful, Useful and Uncommon Plants". The species type available at British Museum was collected by Miller in 1758 and was studied again by Stearn (Stearn, 1975) [172]. During the same period, David van Royen (Director of Hortus Botanicus in Leiden) received seeds from a French diplomat. These seeds were most likely from the same French source as the seeds, which were cultivated in Chelsea. In 1758, Van Royen showed Linnaeus this plant which led to its scientific classification (Snoeijer, 1998) [171]. In the second half of the 19th century, the seeds of the *Catharanthus* became commercially available (Snoeijer, 1998) [171]. The distribution of *C. roseus* is represented in Fig 2.

Synonym

Due to its distribution, *C. roseus* is known around the globe with various vernacular names. In India, it is commonly known as Nayantara, Periwinkle, Rattanjot, Sadabahar, Sadaphul, Billaganneru, Ainskati, Nityakalyani and Ushamanjairi. In Guyana, Jamaica, the USA, Philippines, West Indies and Madagascar it is popularly known as Periwinkle. In China, it is known as Changchun hua and Zhangchunhua. In West Indies, it is known as White tulip, Sailor's flower, red rose, Ram goat rose, Pink Flower, Periwinkle, Old maid, Consumption bush and Brown man's fancy. Various synonym name and their countries are listed in Table 1.

Traditional significance

In the ayurvedic, *C. roseus*is mentioned as Nithyakalyani and documented as a useful plant for the treatment of various diseases like diabetes, wasp bites, nasal bleeding, etc. Seeds

of this plant are considered as diuretic and tonic in the various places of Punjab (Kirtikar and Basu 1999) [85]. A fine paste of the leaves of *C. roseus*along with the turmeric is applied to the wounds (Don 1999) [51]. Root powder (250-500 mg) along with little honey is used for the treatment of type II diabetes. The whole plant powdered material is mixed with cow's milk for the treatment of diabetes in the Kancheepuram district of Tamil Nadu, India (Muthu *et al*., 2006) [119]. It is also used for the treatment of borderline hypertension by consuming 2-3 ml of fresh leaves juice in the early morning or the late night and thus controlling blood pressure (El-Sayed and Cordell 1981) [57]. Around 6 to 8 leaves of *C. roseus* boiled in water are consumed for three consecutive menstrual cycles to control heavy menstrual flow and regularizes scanty flow as well. Thereis evidence of its use as folk practices in Bhatkal, Sirsi, Ellapur, and Bhatkal places of Karnataka. Fresh juice or fine paste of leaves applied to the bite area of the insects and wasps helps in reducing irritation and swelling (Kirtikar and Basu 1999) [85].

In northern Europe, it was used by traditional healers for the treatment of diabetes mellitus. In the Philippines, root decoction was used as an emmenagogue and leaves decoction was prescribed for diabetes. In Unani medicine, cold maceration of the leaves of this plant is utilized for the treatment of gonorrhea. In South Africa, it is practiced for the treatment of menorrhagia, diabetes and gonorrhea, especially in Limpopo Province. *C. roseus* was widely used for the treatment of diabetes in ancient times by various countries like England, Japan, Thailand, Europe, and Australia (Yang *et al*., 1987; Perry 1980; Swanston-Flatt *et al*., 1989; Webb 1984) [214, 143, 185, 208]. In Madagascar Islands, the aqueous extract of stems and leaves of this plant was utilized as a cure for nausea and as a laxative (Don 1999) [51]. *C. roseus* was even utilized as a remedy for digestive disorders like gastritis, loss of appetite, diarrhea, enteritis, and even utilized for asthma, depression, cystitis, muscular pain, gum, and nose bleeding in different countries (Table 2). Though, most of the traditional uses mentioned for the *C. roseus* have not yet been explored.

Chemical constituents

Scientist all over the globe has carried out extensive research work on the phytochemical constituents of *C. roseus.* Till now two benzoic acids, four phenylpropanoids, eighteen flavonoids, six anthocyanins, six organic acids and nineteen amino acids are reported. According to the reported literature, volatile compounds in this plant can vary according to location. More than 130 terpenoid indole alkaloids are reported in this plant out of which 70 of them are pharmacologically active. The study of *C. roseus* has expanded in the view of its ability to generate secondary metabolites for instance terpenoid indole alkaloids such as, vinorelbine which is preferred for its use in the treatment of breast cancer and lung cancer (Favali *et al*., 2004) [58]. An elaborated account of the phytoconstituents isolated from different parts of the *C. roseus* plantis summarized below.

Benzoic acid

From the literature reported to date, two benzoic acids namely gallic acid and vanillic acid have been reported only from the leaves of the *C. roseus* (Table 3). These compounds were found to be absent in other parts of the plant. The quantity of gallic acid (42 mg/100 g) was higher as compared to vanillic acid (1.3 mg/100 g) (Pereira *et al*., 2013; Proestos *et al*., 2005) [141, 152].

Phenylpropanoids

Phenylpropanoids are the class of C6–C3 phenolics which are generally derived from phenylalanine (Ferreres *et al*., 2008) [59]. Numerous investigations have been done for the isolation of quinic acid from this plant. Four phenylpropanoids are reported till date *i.e.*, 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid and Ferulic acid (Mustafa and Verpoorte 2007, Pereira *et al*. 2013) [118, 141] (Table 3). They are usually found in small quantities in the stem and leaf of the plant (Ferreres *et al*. 2008, Pereira *et al*. 2009(a)) [139, 59]. Phenylpropanoids are completely absent in the seeds while 4-O-caffeoylquinic acid (1.12%) is reported in the petals of *C. roseus*. Ferulic acid (0.25%) is reported only in the leaves of the plant (Ferreres *et al*. 2008) [59].

Flavonoids

Flavonoids are the class of C6-C3-C6 skeleton generally derived from shikimate and acetate pathways. Investigation in the 1950s on the plant of *C. roseus* has depicted the existence of flavonoids like kaempferol and quercetin through paper chromatography. In 1996, two flavonoids were separated from the leaves of the plant namely mauritianin and quercetin-3-O-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→6)-β-D-galactopyranoside by Nishibe *et al*., 1996 [127] The same complexes were also separated from the stems of the plant along with syringetin-3-O-robinobioside (Brun *et al*., 1999) [38]. High-performance liquid chromatography-diode array detection-electrospray ionization-mass spectrometry (HPLC-DAD-ESI-MS/MS) was performed on this plant to isolate 15 glycosides of kaempferol, quercetin and isorhamnetin (Mustafa and Verpoorte 2007; Pereira *et al*., 2013) [118, 141] (Table 3).

Anthocyanin

These anthocyanins are extremely reliant on the cultivar that is under study, as it can result in diverse petal colors (Mustafa and Verpoorte 2007, Piovan *et al*., 1998) [118]. In 2013, Pereira *et al*., [141] described the isolation of 6 anthocyanins i.e.,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 and these were found only in the leaves of the plant(Table 3).

Organic acid

Organic acid present in *C. roseus* was investigated using High-performance liquid chromatography-ultraviolet detection (HPLC-UV) (Pereira *et al*., 2009(b)) [140]. Cis-aconitic, citric, pyruvic, malic, fumaric and shikimic compounds have been found in different parts of the plant (stems, leaves, seeds, and petals) (Pereira *et al*., 2009(a); Pereira *et al*., 2009(b)) [139-140] (Table 3). According to the quantitative perspective, stems displayed a larger quantity of organic acids preceded by leaves, petals, and seeds. The quantity of organic acids in the plant differs largely from seeds (0.96 g/kg) to stems (25.95 g/kg). Citric acid was one of the significant compounds covering 89% in stems and malic acid covers 72.1% in roots. Fumaric, cis-aconitic, and shikimic acids were the minor compounds reported in this species (Jones 1998; Ma *et al*., 2001) [79, 101].

Amino acids

Amino acids were also identified in the aqueous extract of *C. roseus* petals, stems, seeds, and leaves using HPLC-UV (Pereira *et al*., 2009(a); Aziz *et al*., 2015) [139, 29]. Around 19

amino acids were reported in the leaves, seed, stem, and petals of the plant (Yang and Gao 2007; Aziz *et al*., 2015) [213, 29] (Table 3). According to the literature, leaves were found to have the highest arginine content 67.54 g/mg preceded by stem 6.38 mg/g, seed 6.17 mg/g, and petals 5.63 mg/g. Glycine, arginine, histidine, threonine, and glutamic acid were found to be the most dominating amino acids of *C. roseus* leaves (Pereira *et al*., 2009(a) [139].

Volatile compounds

According to the reported literature, volatile compounds present in the leaves and flower oil showed the difference in their composition according to their geographical areas. The data obtained from France, India, Portugal and Africa showed great variation in their results. The oil obtained from France was reported to have a high concentration of palmitic acid (64.9%), methyl palmitate (7.2%) and hexahydrofarnesyl acetone (4.0%) (Brun *et al*., 2001) [37] whereas Indian data showed a low concentration of palmitic acid (4.9%) and absence of other compounds like hexahydrofarnesyl acetone and methyl palmitate. In the Indian sample neral, citronellol, geraniol and Pentadecanal were found to have higher concentrations in comparison to French oil in which these were present as minor components (Pandey *et al*., 2006) [132]. In African oil, the major constituents were hexadecanoic acid, dotriacontane, dodecyl alcohol, stearic acid and linoleic acid ethyl ester (Lawal *et al*. 2015) [102]. Benzaldehyde, β-ionone, 2, 3-epoxy-αionone, dihydroactinidiolide, 2-none-1-ol, ethyl hexanoate, palmitic acid ethyl ester, 2-phenylethanol, trans-2-decen-1ol, phenyl-acetadelhyde and 1- phenylethanol were the major compounds obtained from the Portugal sample. The difference in these results could be due to agro-climatic conditions in which they are grown, differential genotype, or environment interactions. The dried leaves and flowers were used for France and African oil preparation whereas fresh leaves were taken for Indian oil preparation. The oil of flowers mainly constitutes fatty acid esters (Aziz *et al*., 2015; Pandey *et al*., 2006) [132, 29] and in the leaves are terpenoids (Brun *et al*., 2001) [37].

Alkaloids

A large range of dominant alkaloids is found in *C. roseus*. Most of the studies on the isolation of the alkaloids from this plant have been done since the 90s. Most of the alkaloids isolated in the previous years from this plant were reported by Heijden *et al*., (2004) [194]. With the introduction of the HR-EI-MS technique, a greater number of new alkaloids have been reported in the past few years (Wang *et al*., 2011; Zhang *et al*., 2013) [206, 116]. Recently, Zhang *et al*., (2013) [116] isolated two vinblastine-type N-oxide alkaloids *viz* 17-desacetoxyvinblastine N'b-oxide and 20'-deoxyvinblastine N'$_b$-oxide from the leaves of *C. roseus*. Wang *et al*. (2012(a)) [204] isolated Catharoseumine from the whole plant at the concentration of 0.786 mg/kg.14', 15'-didehydrocyclovinblastine, 17-deacetoxyvinamidine and 17-deacetoxycyclovinblastine was also isolated by Wang *et al*. (2012(b)) [205] and these alkaloids were proved to be effective in controlling human cancer cell lines. Wang *et al*., in 2011 [206] were also able to isolate new indole alkaloids from this plant i.e., Vindolicine, N-oxidenormacusine B, and N-oxidelochnerine. Quantification of the reported alkaloids showed that serpentine and its isomer (64.7%) were present in maximum quantity as compared to the other alkaloids, of which vindolinine and its isomer covers 23.9%, 7.7% is occupied by catharanthine and 3.8% by ajmalicine (Kutney *et al*., 1980) [97].

Pharmacological Potential

Biological activities of the extracts and bioactive compounds of *C. roseus* species have been investigated by several research groups. Among these researches, anticancer activity is the most studied to date and attributed to the higher anticancer potential of *Vinca* alkaloids. Two of the compounds are available on market as registered drugs. Anti-diabetic, anti-inflammatory, antimicrobial (antibacterial, antifungal, and antiviral), and other pharmacological activities of *C. roseus* have also been assessed but most of the studies are conducted *in vitro* and further *in vivo* studies are required (Fig. 3).

Anticancer Potential

C. roseus has a wide range of alkaloids that are effective against anticancer activity including vindoline, vincristine, vinblastine, vindolicine, vindolidineand vindolinine (Tiong *et al*., 2015; Tiong *et al*., 2013; Crag and Newman 2003) [192, 45, 193]. All these alkaloidswork by inhibiting the cell proliferation by changing its microtubular dynamics causing apoptosis (Cragg and Newman, 2005) [45].

Vinblastine is the first chemotherapy drug that was commercialized under the brand name Velban obtained from *C. roseus* used for the treatment of various cancers including Kaposi's sarcoma, testicular, breast, bladder and lymphomas cancer (Hodgkin's disease) (Han *et al*., 2008) [70]. The immunosuppressive activity was exerted by vinblastine alkaloid. Glutamic acid was reported to be effective in reducing neurotoxicity. Although it did not show effectiveness in the case of childhood cancer of endothelial cells (Bradfield *et al*., 2015) [35]. Vinblastine in combination with β-blockersis used to treat angiosarcoma. It works by binding with β-tubulin which causes disruption in mitotic spindle resulting in cell division inhibition (Pasquier *et al*., 2016; Schläger and Dräger, 2016) [134, 151]. Vinblastine is also administered in combination with mitomycin C and cisplatin to treat breast cancer patients. Mitoxantrone, vinblastine and lomustine mixture was effective against breast cancer but mild toxicity was observed in the patients (Urruticoechea *et al*., 2005) [195].

The main mode of action of vincristine and vinblastine is that they bind with tubulin which in turn prevents making spindles, thus showing effective anticancer activity by inhibiting cell division (Sertel *et al*., 2011) [165]. In 2013, Kumar *et al*. 2013 [95] reported that vincristine in combination with other chemotherapy drugs was used to treat certain types of leukaemia including acute lymphoblastic and acute myeloid leukaemia. Vincristine alkaloid together with cytostatic drugs like anthracyclines, dexamethasone and irradiation help in decreasing cell death rate up to 86% (Ehrhardt *et al*., 2013) [54]. Isono *et al*., (2016) [78] reported that vincristine is a lifesaver drug as it even shows its effectiveness at the advanced stage of cancer like that of in rhabdomyosarcoma. It was also concluded from different studies that vincristine was used for the treatment of diffused large B-cells cardiotoxicity and lymphoma when applied in combination with prednisolone along with monoclonal antibody rituximab, doxorubicin and cyclophosphamide (Su *et al*., 2011; Pfreundschuh *et al*., 2011) [145]. Vincristine alkaloid was also used for the treatment of neuroblastoma.

In 2012a, Wang *et al*. [204] found that Catharoseumine another alkaloid from *C. roseus* possesses an inhibitory effect on the human promyelocytic leukaemia HL-60 cell line with an IC_{50}

of 6.28 µM. Along with these three dimeric indole alkaloids were also isolatedi. e., 17-deacetoxyvinamidine, 17-deacetoxycyclovinblastine, 14',15'-didehydrocyclovinblastine and five known isolated alkaloids (Leurosidine, cycloleurosine, catharine, leurosine and vinamidine) possessed *in vitro* cell division inhibition against human breast cancer cell line MDA-MB-231 (IC_{50} range 0.73–10.67 µM) (Wang *et al*. 2012b) [205]. Cathachunine alkaloid isolated from this plantshowed antitumour effect against human leukaemia cells, but at much lesser cytotoxicity against normal endothelial cells of human, indicating that selectively inhibits leukaemia cells (Wang *et al*. 2012b) [205].

Apart from *Vinca* alkaloids, the organic and water extracts of *C. roseus* are also effective as anticancer agents. Wong*et al*., in 2011 reported that the dichloromethane and methanol extract of *C. roseus* was beneficial in the treatment of both HeLa and human breast carcinoma cancer cell lines. In 2010, Ahmad *et al*., 2010 [4] reported that the *C. roseus* water extract was functional against the Jurkat cancer T-cells which was shown by MTS assay. Its stem and root extract possessed *invitro* cytotoxic activity against various cancer cell lines (Pham *et al*., 2019; Pham *et al*., 2018; Fernández-Pérez *et al*., 2013) [146, 147, 60]. The extracts were effective against cancer cells due to the synergistic effect of bioactive compounds present in the extract (Bhuyan *et al*., 2018; Barth *et al*., 2007) [34, 31].

Antidiabetic Potential

C. roseus has been traditionally exploited for the treatment of diabetes in many regions of the world (Table 2). Its juice was recommended for the treatment of diabetic patients as an adjuvant and also for urinary disorder treatment (Lans, 2006; Nammi *et al*., 2003) [100, 120]. Ethanolic extract of the plant has higher antidiabetic activity as compared to its aqueous extract. The recommended dosage is between 100 and 200 mg/kg body weight in the animal model (Al-Shaqha 2015) [11]. *C. roseus* ethanolic extract was prepared in combination with glibenclamide and metformin and was given to alloxan-induced rats. For a period of 7 days, different concentration dosage was given to rats which were divided into 6 different groups, each group consisting of five rats (Swanston-Flatt *et al*., 1989; Ohadoma and Michael, 2011) [128, 185]. The first group was labeled as control, the second group of rats was given 250 mg/kgbw of *C. roseus* extract, the third group of rats was treated by using 100 mg/kgbw of metformin, the fourth group with 1 mg/kgbw of glibenclamide, fifth group consumed 250 mg/kgbw of plant extract in combination with 100 mg/kgbw of metformin and sixth group with 250 mg/kgbw of plant extract along with 1mg/kgbw of glibenclamide (Ohadoma and Michael, 2011) [128]. After the experiment, it was concluded that *C. roseus* plant extract in combination with metformin showed the highest antidiabetic activity in comparison to other groups (Benjamin *et al*., 1994; Ohadoma and Michael, 2011) [128, 33].

To prove the above study, methanolic extract of whole plant parts was used which showed effective antihyperglycemic activity in combination with enhancement in the regeneration of β-cells, lipid profile and bodyweight of pancreatic diabetic mice (Ahmed *et al*., 2010a) [5]. In 2013, Tiong *et al*., [193] examined the antidiabetic potential of four alkaloids i.e., vindolinine, vindolicine, vindolidine and vindoline isolated from the leaf using the assays of 2-NBDG glucose uptake and inhibition of PTP-1B. It was concluded from the study that the four alkaloids increased the uptake of glucose in mice myoblast C2C12 and β-TC6 pancreatic cells, along with the inhibition of their PTP-1B cells. Among the four alkaloids, vindolicine showed the maximum activity. The results obtained were supported by the traditional utilization of the *C. roseus* for the treatment of diabetes, highlighting that it could be used as a potent source for further exploring as antidiabetic agents for clinical usage.

Anti-Alzheimer's Potential

Alzheimer's disease is associated with memory loss and other mental functions. The acetylcholinesterase inhibitors ease out some impairments associated with Alzheimer's disease. The aqueous extracts of leaves, roots and stem of *C. roseus* showed effectiveness in inhibiting acetylcholinesterase in an *in vitro* microassay (Pereira *et al*., 2009b) [140]. Serpentine present in this plantshowed strong activity against acetylcholinesterase with a low IC_{50} value i.e., 0.775 µM (Pereira *et al*., 2010) [142]. Vinpocetine is the alkaloid of *C. roseus* has the potential to increase cerebral blood flow and neuroprotective effect (Szilágyi *et al*., 2005; Dézsi *et al*., 2002) [187, 50]. In 1959, Chopra *et al*., 1959 [43] reported the benefits of Vinpocetine for Alzheimer's disease but there was insufficient evidence to support its clinical uses. Vinpocetine has been used at a dosage of 60 mg/d for clinical trials for strokes and dementia (Balaji, 2014) [30]. A clinical trial of Vinpocetine was conducted on 728 patients suffering from Alzheimer's disease which produces a significant improvement in these patients. Along with this, a double-blind placebo-controlled trial of 16-week was conducted on 203 patients with mild to moderate dementia symptoms using Vinpocetine which showed significant results in the treated group (Szatmari and Whitehouse 2003) [186]. Still, there is a need for further trials to prove its effectiveness for commercial use.

Anti-Hypertension Potential

It was reported that Resistant hypertension could be treated using vincristine by the method of chemical sympathetic denervation. To prove this study vincristine was injected in Landrace swine animal models using catheters. Following twenty-eight days, the histopathological sample report revealed that the injured nerve was lower in the vincristine treated group as compared to the placebo group (Stefanadis *et al*., 2013) [173]. *C. roseus* leaf extract along with atenolol showed hypertensive and lipid-lowering effects in adrenaline-induced hypertensive rats. The dosage of Atenolol was taken according to its pharmacokinetic parameters. (Ara *et al*., 2009) [15]. Ajmalicine has been used as an α-adrenergic receptor antagonist due to which it is considered as a hypotensive agent (Wink *et al*., 1998) [211].

Anti-Psoriasis Activity

It is a skin disorder where the skin cell builds up and forms itchy, scaly and dry patches. The research was conducted on the effectiveness of *C. roseus* leaves extract for the treatment of psoriasis at the molecular level (Pattarachotanant *et al*., 2014) [137]. The ethanolic extracts of the plant were testified for psoriatic marker and Keratin 17 (K17) in human keratinocytes. From the experiment, it was concluded that *C. roseus* shows effectiveness against K17 expression when treated at different concentrations with IFN-γ (Pattarachotanant *et al*., 2014) [137]. *C. roseus* showed a reduction in the expression of K17 in a dose-dependence manner throughout the JAK-STAT signaling pathway and was compared with the expression of K17 in IFN-γ-treated HaCaT cells with piceatannol for 48 hours. It was also used as a paste in combination with aloe vera gel to apply at psoriasis affected area (Shawahna and Jaradat, 2017) [168].

Wound Healing Potential

The ethanolic extract obtained from the flowers of *C. roseus* showed wound healing property in the Sprague Dawley rat models using dead space model and incision. The daily dose of 100 mg/kg flower extract was given to all the rodents each day. Extract of *C. roseus* flower displayed a significant decrease in time for the wound healing in comparison to control. (Nayak and Pinto Pereira, 2006) [121]. The same experiment was also conducted using ethanolic extract of leaves of *C. roseus* which also showed significant wound healing activity in comparison to control (Nayak *et al*., 2007) [122]. Ethanolic extract of flowers showed better-wound healing activity as compared to leaves extract. Different concentration of methanolic extract of leaves and metformin were given to the Streptozotocin-induced diabetic rats (60 mg/kgbw in 200 µl double distilled water (dd) H_2O, 30 mg/kgbw Metformin in 100 µl ddH_2O + 100 mg/kgbw extract in 100 µl ddH_2O, 200 mg/kgbw extract in 200µl ddH_2O, 400 mg/kgbw extract in 200µl ddH_2O) to study wound healing property. Methanolic leaf extract showed a 15% topically increase in wound healing epithelization in Wister rats and provide strength to collagen tissues (Singh *et al*., 2014) [170]. Although the extracts showed promising results to cure wounds of diabetic rats. Still, studies are needed to find its usage in humans as well as to decide its dosage.

Antiviral and Antimicrobial Activity

Researchers demonstrated the antiviral impact of the yohimbine compound of *C. roseus* against the herpes simplex virus or type I virus which showed an impact of cytopathogenicity at the dose of 0.8 µg/ml (Özçelik *et al*., 2011; Cordell *et al*., 2001; Almagro *et al*., 2015) [130, 44, 10]. Monoterpene alkaloid catharoseumine extracted from the parts of the whole plant has one peroxy molecule and is recognized as an inhibitor against the falciparum-2 protozoan parasite that causes malaria, demonstrating an IC_{50} estimation of 4.06 µM (Wang *et al*., 2012; Manigandan *et al*., 2014) [204, 109]. *Trypanosoma cruzi* which causes trypanosomiasis in humans was inhibited by the antiparasitic activity of vinblastine and vincristine. It prevents mitosis and affects the shape of the cell in a dose-dependent mode (Abraham and Farnsworth, 1969; Grellier *et al*., 1999) [1, 64]. 50 µM of vincristine and 15 µM vinblastine was utilized to suppress nuclear division along with the cytokinesis whereas 10 µM vincristine and 3 µM vinblastine together inhibits cytokinesis without causing any change in cell cycle progression (Grellier *et al*., 1999; Abraham and Farnsworth, 1969) [64, 1]. In comparison to other extracts, Petroleum ether extract showed greater inhibition in the activity of malarial larvae of *Anopheles Stephens.* The extracts of *C. roseus* showed better results in combination with standard drugs for vector control programs (Panneerselvam *et al*., 2013) [133].

Many studies have been directed on the antimicrobial activity of the *C. roseus* extract against various microorganisms. *C. roseus* crude extract was assessed for antimicrobial activity against *Fusarium moniliform*, *Escherichia coli, Aspergillus fumigatus, Candida albicans* and *Bacillus fusiformis.* Ethanolic extract of the stems, flowers, roots and leaves was evaluated as an antibacterial agent against various bacteria. The leaves extracts showed significantly higher activity as compared to other parts (Nayak and Pereira 2006) [121]. Flower extract (200 µg/mL) obtained from the *C. roseus* showed antimicrobial activity against *Staphylococcus aureus*, *Enterobacter agglomerans, Beta-hemolytic streptococci* and *Pseudomonas aeruginosa* (Patil and Ghosh, 2010) [136]. Silver (Kotakadi *et al*., 2013) [91] and zinc oxide (Gupta *et al*., 2018) [66] nanoparticles of *C. roseus* leaves were proved to be an effective antimicrobial agent against activity against Gram-positive bacteria like *Pseudomonas fluorescens* and *Escherichia coli*.

Miscellaneous Uses

Antispermatogenic action was observed when the hot aqueous extract was induced in the male mice at the dosage of 10 mg/kg (Murugavel *et al*., 1989; Joshi and Ambaye, 1968) [117, 80]. It showed changes by degenerating all germinal elements, increasing cholesterol in testes, seminiferous tubules and Leydig cells. Petroleum ether extract of the leaves of *C. roseus* displayed antiestrogenic activity in female albino mice by showing a decline in the uterine weights of the experimental mice. It also showed antiestrogenic activity when observed in combination with estradiol-17-â (Gupta, 2009) [67]. Vinblastine and vincristine affected spermatogenic cell lines other than spermatogonia in male rats (Morgenfeld *et al*., 1975; Chinoy and Ranga, 1983; Akbarsha *et al*., 1995; Gupta and Sharma, 2006) [112, 42, 8, 68]. In 1996 Averal *et al*., 1996 [28] reported the pathological changes in the principal and apical cells of caput and nuclear cells of cauda causing impairment of epididymal function supporting antiandrogenic properties of vincristine.

Antidiarrheal *in vivo* action was tested on the Wister rats by using castor oil and ethanolic leaves extract as an instigating agent for experimental diarrhoea. For comparative studies, atropine and loperamide were utilized as standard drugs. The antidiarrheal impact brought about by the ethanolic extract displayed a dose-dependent suppression of castor oil, preventing diarrhoea at the dosage of 500 and 200 mg/kg (Hassan *et al*., 2011; Rajput *et al*., 2011) [71, 154].

Vindoline, Vinpocetine and *Vinca*mine alkaloids of *C. roseus* displayed antiulcer activity. *Vinca*mine and vindoline helped in protecting gastric mucosa of gastric ulcers in rats (Lakshmi *et al*., 2013) [99]. Sain and Sharma (2013) [160] reported the antiulcer activity of 96% of the ethanolic extract obtained from the leaves of *C. roseus* against experimentally induced gastric damage in rats. Methanolic extract of the plant at the dosage of 500 mg/kg displayed a substantial decrease in the incidence of ulcers in forced swim-induced rats implementing antiulcerogenic activity (Mahathi *et al*., 2013) [108]. Methanolic and ethanolic extract of the plant showed antiulcer activity on pylorus ligation-induced ulcers in rodents. The methanolic extract at a dosage of 500 mg/kg showed maximum inhibition by preventing oxidative stress (Rambhai *et al*., 2019) [155].

C. roseus leaf extract helped in reducing the total triglycerides, total cholesterols, LDL and VLDL cholesterols (Antia and Okokon, 2005) [14]. The hypolipemic activity was evaluated using a UV spectrophotometer in Albino Wister rats (Patel *et al*., 2011) [135]. Ethanolic extract of *C. roseus* leaves (150 mg/g) given to the normal or the induced diabetic rats displayed inhibition in their serum glycerides level (Akhtar *et al*., 2007) [9] and the ethyl acetate leaves extract (150 mg/kg) showed inhibition in their serum triglyceride level in streptozotocin-induced diabetic rats (Islam *et al*., 2009) [77]. Hot aqueous leaves extract given orally to rabbits displayed a reduction in the level of cholesterol exhibiting anti hyper cholesterolemic activity (Asthana and Misra, 1979) [19]. Ara *et al*., in 2009 [15] reported the hypolipemic of *C. roseus* on adrenaline-induced rats in combination with atenolol.

Aqueous and ethanolic extract of *C. roseus* leaves showed *in vivo* anti-inflammatory activity against carrageenan-induced albino rats. It showed a reduction in paw edema at the dosage of 250 and 300 mg/kg (Gupta *et al*., 2014; Chattopadhyay *et*

al., 1992) [69, 40]. *C. roseus* showed antidiuretic action in the rats when alkaloid fraction extract was given subcutaneously to male rats at a dose of 50.0 mg/kg (Neagi and Bhatia, 1956) [123].

70% of ethanolic extract of leaves of this species displayed antimitotic activity in female rats. The extract was given for four days after tumour cell inoculation ascetic samples were removed. It was injected after 2, 4, 6 and 24-hours post-treatment (El-Merzabani *et al*., 1979) [55]. In 1982, Sharma *et al*. reported an antimutagenic effect when a hot aqueous extract of leaves was given to the rats. It showed a decrease in the micro-nucleated polychromatic RBCs brought about by different mutagens which displayed antimutagenic action. Vincristine mutagenic effect was evaluated using a sex-linked recessive lethal test system in *Drosophila melanogaster*. It produced various chromosomal effects including cell arrest in metaphase and inhibition of tubulin polymerization (Ahmed *et al*., 2010b) [6].

Commercialized medicine

In 1963 and 1960 two significant alkaloids namely, vincristine and vinblastine were introduced in the market under the trademark Vincovin/Oncovin and Velban respectively (Das *et al*., 2020; Sharma *et al*., 2016) [47]. They were used for the treatment of Hodgkin's disease and leukemia. The artificially designed alkaloids from vinblastine and vincristine are also available on the market. Fildesine and Eldisine are the trade name commonly used for vindesine alkaloids. It is utilized for the treatment of refractory lymphoma and acute lymphoblastic leukemia (Das *et al*., 2020, Kulkarni *et al*., 2016) [47, 94]. Vinorelbine is available with the trade name Navelbine and is utilized for the treatment of lung and breast cancer (Das *et al*., 2020; Kulkarni *et al*., 2016) [47, 94]. Hydrosepan and Lamuran are the trade names for the ajmalicine alkaloid which is utilized as a cure for hypertension (Das *et al*., 2020, Van der Heijden *et al*., 2004) [194, 47]. It was introduced in the market in 1957. It is noteworthy to mention that *C. roseus* holds great importance for the treatment of cancer in modern medicines.

Toxicity

No acute toxicity of water and ethanol extract of the leaves of *Catharanthus roseus* in mice. The toxicity of *C. roseus* was evaluated by using an aqueous extract of the plant in male Wister rats. It was observed that none of the rats died during the trial and the median lethal dose of the aqueous extract was estimated to be ≤ 5000 mg/kg/body. The rats which were fed with 500 mg showed limited morbidity during the initial 6 hrs but afterward got normalized (Kabubii *et al*., 2015) [82]. The acute oral toxicity of ethanolic leaf extract was evaluated in the Albino Wister rats by Vutukuri *et al*., in 2017. It was also reported that SGOT, SGPT, Creatinine phosphokinase, LDH, urea and creatinine showed elevation at the dosage of 300 mg and 2000 mg. They reported that the ethanolic extract did not display any mortality at these dosages. Ajuru *et al*., in 2019 [7] reported that ethanolic extract did not show any mortality at 5000 mg dosage. It was even concluded that the LD50 of the plant extract is slightly higher than 5000 mg which can lead to mortality. Sub-acute oral toxic effects of methanol leaves extract were evaluated on liver and kidney functions. 24 female rats were divided into 4 groups. The first group was used as a control by treating it with distilled water, the other three groups were treated orally by giving a single dosage of 0.1, 0.5, and 1 g/kg of methanol extract respectively for a period of 14 days. Food consumption and body weight were recorded daily. Blood was collected on the 15th day and the serum level of alanine aminotransferase, aspartate aminotransferase, urea, creatinine and alkaline phosphate was determined. Continuous administration of 1 and 0.5 g/kg of extract causes mortality and diarrhea in female rats after few days of the treatment. No significant change was observed in food intake, body weight and biochemical markers in rats treated with 0.1 g/kg of methanolic extract as compared to the control (Kevin *et al*., 2012) [84]. The dose-dependent toxic effect of vincristine is neurotoxicity, whereas vinblastine is myelosuppression. *Vinca* alkaloids bind with tubulin and inhibit microtubular formation, therefore arresting cell division at metaphase by disrupting the formation of the mitotic spindle (Plumlee 2004) [150].

Pharmacokinetics

Vinblastine sulfate and vincristine sulfate pharmacokinetics studies in cancer patients displayed a triphasic serum decay pattern followed by rapid intravenous injection. The half-lives of vinblastine sulfate observed are 3.7 min, 1.6 h, 24.8 h respectively. The volume of the central compartment is 70% of the bodyweight reflecting rapid tissue binding to form elements of the blood. The body stores it for 48 and 72 h after injection. Most of the excretion occurs through the biliary system. Toxicity for this drug increase when there is hepatic excretory insufficiency. *Vinca* alkaloids metabolism is reported to be mediated by the action of hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily. The metabolic pathway can be decreased in the patient suffering from hepatic dysfunction. An increased amount of toxicity is reported in the patient's using erythromycin. After vinblastine is injected in cancer patients, 14% radioactivity was reported in urine, 10% in faces and the remaining activity was not reported. Similarly, in dogs, after a period of 9 days, 30 to 36% radioactivity was found in the bile and 12-17% I urine. Likewise, in rat's highest radioactivity was demonstrated in the liver, spleen, kidney and lungs after 2 hours of injection (Levêque and Jehl 2004) [104]. Vincristine sulfate pharmacokinetics is often described as a two-compartment system. Its initial, middle and terminal half-lives are 5 min, 2.3 h, and 85 h respectively. However terminal half-life can vary from 19-155 h. Most of the excretion of the drug occurs through the liver. Within 15-30 min, over 90% of the injected dose distributes from blood to tissues where it remains tightly. Around 80% of the vincristine sulfate injected dosage is found in the faces and 10-20% in urine (Leveque and Jehl 1997, Levêque and Jehl 2004) [104-105]. Vinorelbine behaves as a three-compartment system with a long terminal half-life (t1/2) that varies between 20 and 40 hours. It distributes mainly in the blood cells i.e., 78% in platelets and 4.8% in lymphocytes. Vinorelbine contraction sin lungs are much higher as compared to the serum by up to 300-fold 3 hours after injection. 20% of the injected dose is excreted via urine. 33.9-58.4% of the vinorelbine was recovered in the fecal excretion (Nelson 1982, Owellen *et al*., 1977) [124, 129]. Navelbine pharmacokinetics are similar in their action to IV bolus injection. It has a high oral clearance 0.43-1.45 1/h/kg, long terminal half-life i.e., 24.2-56.5 h and a large volume of distribution. The liver plays an important role in the metabolism of navelbine (Zhou *et al*., 1991) [219].

Nano formulations of Vincristine

The VCR therapy is used for the treatment of acute lymphoblastic leukaemia (ALL) but the treatment also results in P-glycoprotein (P-gp) overexpression which develop

multidrug resistance. To resolve this issue, nano drug delivery system is used which optimise targeted delivery, enhance circulation time, improve aqueous solubility and permit controlled release. This is because the small particle size and surface modification property helps to deliver the anticancer drugs to cancer cells. The clinical interventions showed that the dose of vincristine above 1–1.4 mg/m^2 every 3 weeks shows a significant neurotoxic effect and inter-patient variability (Vinsant *et al*., 2013) [201]. There are a number of drug delivery systems based on vincristine successfully employed in the recent times to combat the multidrug resistance issues. Such as Lipid based nanoparticles-Liposomes DSPEG-Transferrin, Liposomes Egg sphingomyelin (ESM), Solid lipid NPs (SLNs) of Stearic acid, Hydrid lipid NPs Cetyl palmitate–Dextran sulphate; Polymeric nanoparticles- Polymeric NPs PLGA-PEG-folic acid, Polymeric NPs Chitosan-folic acid, Polymeric NPs PLGA-Dextran Sulphate, Polymeric NPs Accurin polymeric nanoparticle; and Inorganic nanoparticles-Inorganic NPs Chitosan-Silver or Gold.

The novel polymeric NP, VCR polylactide polyethylene glycol (Accurin) was developed and was attached with prostate specific membrane targeting antigen (PSMA) for site-specific delivery of VCR. A significant decrease in tumour size was observed when treated with this nano-carrier compared to free VCR injectable formulation in athymic mice (Cadzow *et al*., 2015) [39]. In 2019 a folic acid and R7 peptide anchored pegylated PLGA NPs was developed for the delivery of VCR sulphate to tumour site and overcome multidrug resistance (Wang *et al*., 2014) [207]. Recently a smart Nano formulation of Vincristine Drug with Polymeric Magnetic Nanoparticles was developed which displayed ten times higher cytotoxicity than the comparable free drug concentration (Al-Musawi *et al*., 2021) [2].

Anticancer drug gemcitabine can encapsulate in lipid based nano-carriers. The formulation SLNs of VCR has been made using cetyl palmitate and dextran sulphate *via* microemulsion technique. It has been found that SLNs enhanced the VCR sulphate cytotoxic activity on MDA-MB-231 cell lines, revealed improved pharmacokinetics with prolonged residence time compared with free VCR-treated groups (Kobarfard *et al*., 2014) [86]. Lipid polymer hybrid nanocarriers were developed for co-delivery of VCR and quercetin which enhanced the anti-tumour efficacy, showed synergistic cytotoxicity and also found that lipid nanocarriers can be used for the treatment of chemo resistant lymphoma (Zhu *et al*., 2017) [220]

The inorganic nanocarriers are mostly used for their diagnostic applications as they form chemical bond with fluorescent dyes and functions as efficient theranostic (Kolovskaya *et al*., 2020) [90]. In a report, gold-VCR complex NPs were encapsulated into the liposomes and treatment with the prepared liposomes coupled with UV light exposure produced greater antitumour effects in nude mice and reduced side effects, as compared with free VCR sulphate (Liu *et al*., 2015) [106]. In one more study, chitosan-encapsulated silver NPs were used to deliver VCR to tumour cells. The nanocarrier showed triggered release under tumour microenvironment condition and was able to deliver VCR in A459 cells efficiently (Varadharajan *et al*., 2017) [199].

Fig 1: Leaves and flowers of *C. roseus*

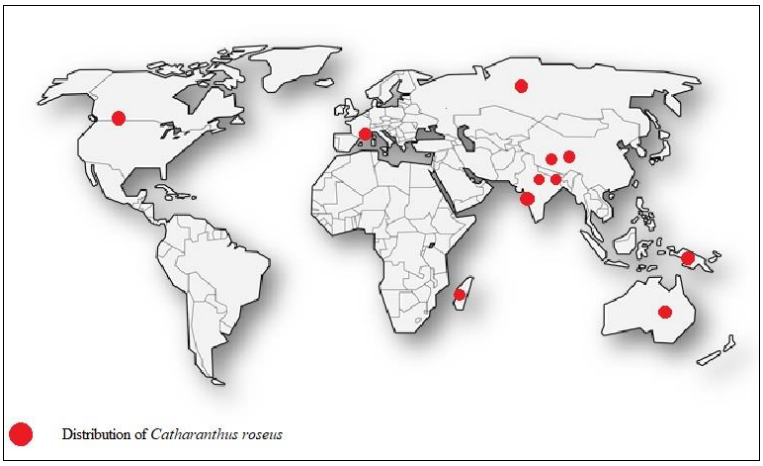


Fig 2: Distribution area of *Catharanthus roseus*

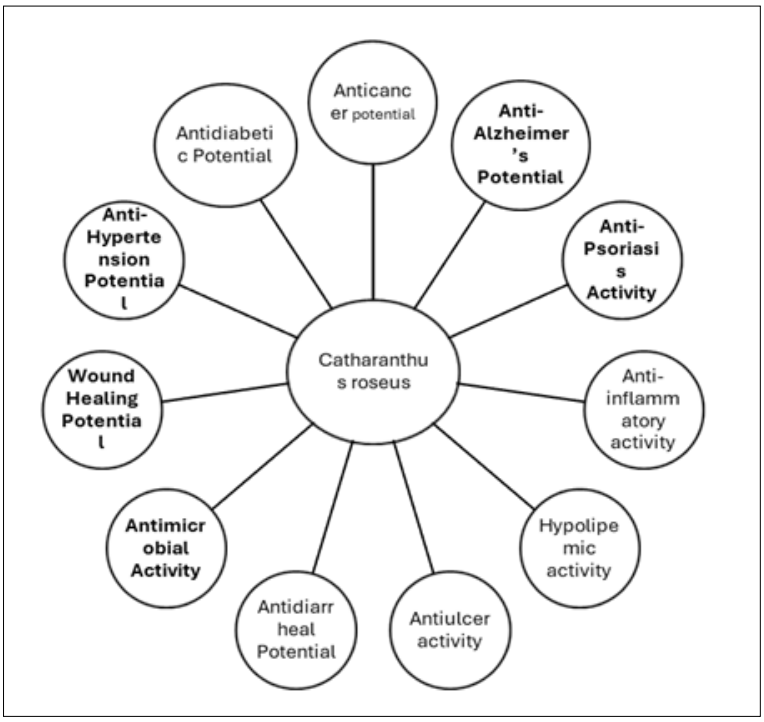


Fig 3: Schematic diagram of Pharmacological applications of *Catharanthus roseus*

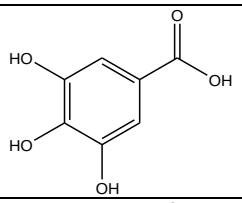
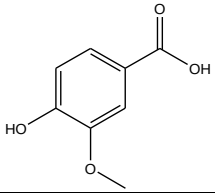
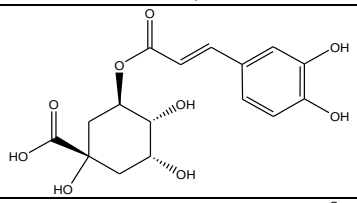
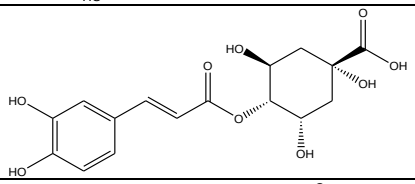
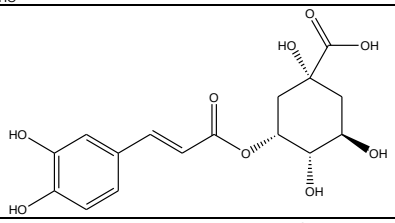
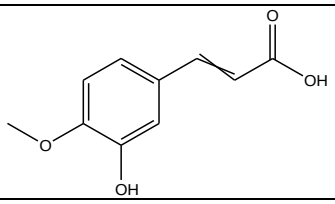
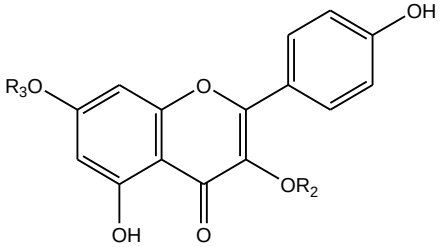
Table 1: Vernacular names of *C. roseus*in different countries

Country	Vernacular Name	Country	Vernacular Name
India	Nayantara, Periwinkle, Rattanjot, Sadabahar, Sadaphul, Billaganneru, Ainskati, Nityakalyani, Ushamanjairi	West Indies	White tulip, Sailor's flower, Red rose, Ram goat rose, Pink Flower, Periwinkle, Old maid,Consumption bush, Brown man's fancy
Philippines	Atay-biya, Chichirica, Kantotan, Periwinkle, Tsitsirika	Bangladesh	Nayantara
Brazil	Boa-noite, Congorca	Japan	Nichinich-so, Nichinichi-so
Sri Lanka	Patti-poo, Mini-mal	Mexico	Ninfa
Dominica	Caca poule	Guyana	Periwinkle
Guatemala	Chatilla	Jamaica	Periwinkle
Peru	Chavelita	USA	Periwinkle
Vietnam	Dua can	Guiana	Pervenchede
Venda	Liluvha	Thailand	Phaengphoifarang, Phang-puai-fa-rang
Madagascar	Madagascar periwinkle	Pakistan	Sada-bahar
Kenya	Maua	Cook Island	Tiare-tupapaku-kimo
China	Changchunhua, Zhangchunhua	France	Catharanthe rose, Pervenche de Madagascar

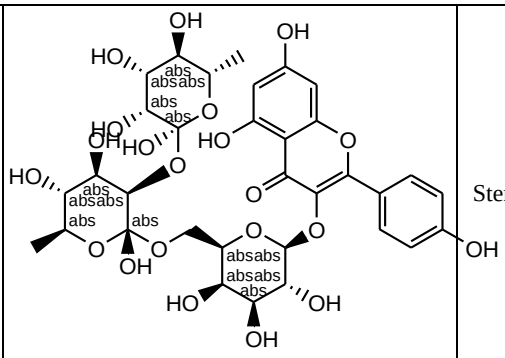
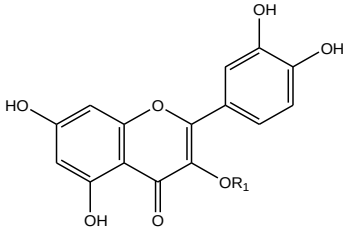
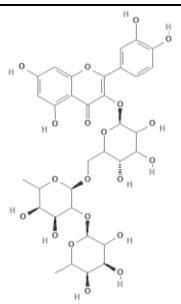
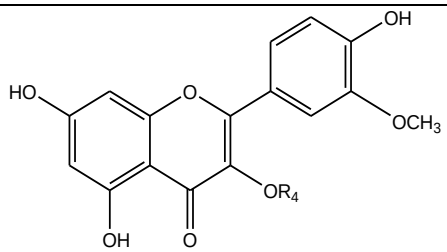
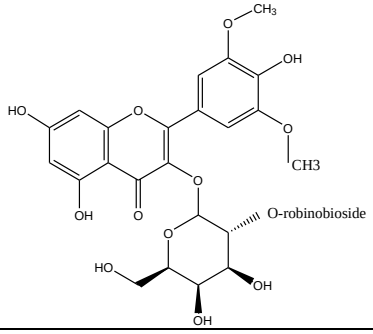
Table 2: Tradition uses of *C. roseus* in various continents

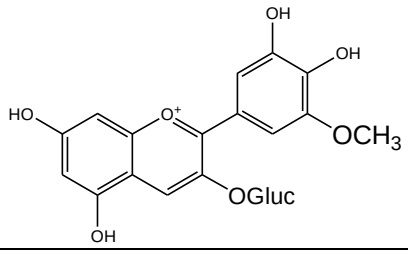
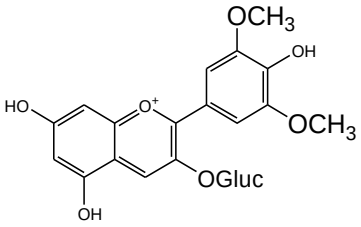
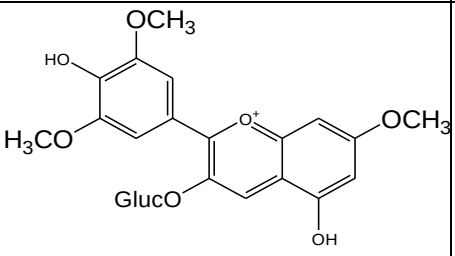
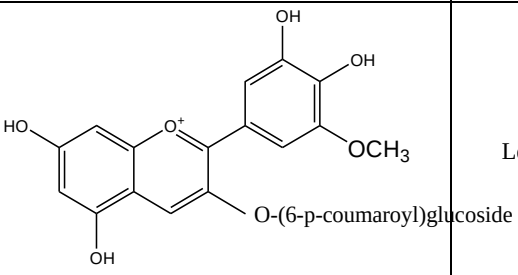
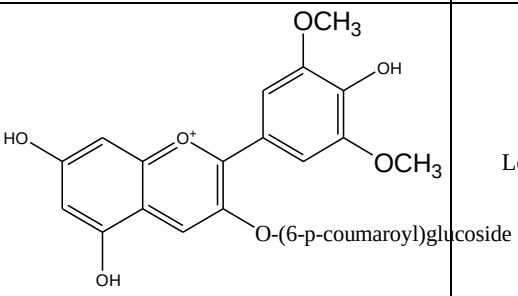
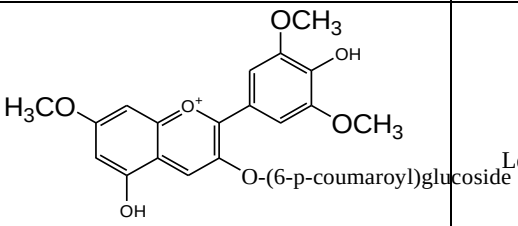
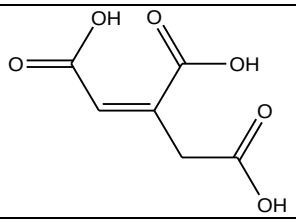
Continent	Country	Plant Part	Extract Type	Mode of Administration	Diseases	Reference
Africa	Mozambique	Leaves	Aqueous via Decoction	Oral intake	Rheumatism, febrifuge, hypertension	Amico (1977) [12]
	Rodriguez Islands	Flower	Aqueous	Applied topically	Eyewash for the infants	Duke (1985) [53]
	Kenya	Leaves	Hot Aqueous	Oral intake	Diabetes	Morrison and West (1982) [113]
		Roots	Hot Aqueous	Oral intake	Stomach problems	
	Venda	Leaves	Aqueous extract	Oral intake	High blood pressure and venereal diseases.	Arnold and Gulumian (1984) [16]
	South Africa	Leaves	Aqueous extract	Oral intake	Diabetes and menorrhagia	Duke (1985) [53]
Australia/ Oceania	Cook Islands	Leaves	Aqueous extract via Decoction	Oral intake	Cancer, hypertension and diabetes	Holdsworth (1990) [74]
	Marshall Islands	Leaves	Aqueous extract	Oral intake	Diabetes, arthritis and kidney problems	Taafari *et al*., (2006) [188]
	Australia	Roots and leaves	Hot aqueous extract	Oral intake	Febrifuge, menorrhagia and diabetes in adults.	Webb (1984) [208]
Asia	India	Whole plant	Aqueous extract	Oral intake	Wasp stings, hypertension, muscle pain, nose and gum bleeding. It is even utilized as a cure for cancer, Hodgkin's disease, sore throats and mouth ulcer.	Don (1999) [51], El-Sayed and Cordell (1981) [57], Tiong *et al*., (2013) [193]
	Pakistan	Ovules	Hot aqueous extract	Oral intake	Diabetes	Rahman (1982)
	China	Aerial parts	Hot aqueous extract	Oral intake	Malaria, as a menstrual regulator, cough and diuretic remedy.	Aslam *et al*., (2013) [17]
	Malaysia	Leaves	Aqueous extract	Oral intake	Diabetes	Kevin *et al*., (2012) [84]
	Taiwan	Plant	Aqueous extract	Oral intake	Liver diseases and diabetes mellitus.	Hsu and Cheng (1992) [75]
	Thailand	Plant	Aqueous extract	Oral intake	Diabetes	Yang *et al*., (1987) [214]
	Japan	Whole plant	Aqueous extract	Oral intake	cancer and stomach ulcer	Perry (1980) [143]
	Vietnam	Aerial parts	Aqueous extract via Decoction	Oral intake	menstrual regulations and galactagogue.	Virmani *et al*., (1978) [202]
	Philippines	Roots	Aqueous extract	Oral intake	Produce abortion and for irregular menstrual cycles	Zaguirre (1944) [215]
	Sri Lanka	Aerial parts	Aqueous extract via Decoction	Oral intake	High blood pressure, blood sugar and soothing toothaches and insect bites.	Samara (2015) [161]
	Indonesia	Leaves, stalks	Aqueous extract	Oral intake	Dysmenorrhea	Taafari *et al*., (2006) [188]
Europe	England	Entire plant	Hot aqueous extract	Oral intake	Galactagogue and diabetes	Don (1999) [51], Thompson (1976) [191]
	Dutch	Leaves	Aqueous extract	Oral intake	High blood pressure	Posthouwer *et al*., (2016) [151]
	Kew	Whole plant	Aqueous extract	Oral intake	Cancer and diabetes	Hussey (1964) [76]
	France	Roots	Aqueous extract	Oral intake	Hemostatic, vermifuge, toothache remedy and purgative	Brun *et al*., (2001) [37]
	Spain	Leaves	Aqueous extract	Oral intake	Diabetes	Seaforth (2006) [164]
South America	Brazil	Roots	Hot aqueous extract	Oral intake	Malaria, diabetes and fevers	Brandao *et al*., (1985) [36]
	Peru	Entire Plant	Aqueous extract via Decoction	Oral intake	Cancer, leishmaniasis and heart diseases	Ramirez *et al*., (1988) [156]
North America	West Indies	Leaves	Aqueous extract via Decoction	Oral intake	Diabetes	Nguywen (1977) [126]
	Mexico	Roots	Aqueous extract via Decoction	Oral intake	Diabetes	Andrade-Cetto and Heinrich (2005) [13]
	Guatemala	Leaves	Aqueous extract via Decoction	Oral intake	Diabetes	Duke (1985) [53]
	Dominica	Leaves	Aqueous extract via Decoction	Oral intake	Diabetes and to combat primary inertia in childbirth during pregnancy	Hodge and Taylor (1956) [72]
	Cuba	Leaves	Aqueous extract via Decoction	Oral intake	Diabetes	Seaforth (2006) [164]
	Jamaica	Flower	Aqueous extract	Oral intake	Eyewash in the infants.	Duke (1985) [53]
	USA	Whole plant	Aqueous extract	Oral intake	Chest pain, sore throat and laryngitis	Morton (1976) [114]
	Caribbean	Flower	Aqueous extract	Applied topically and oral intake	Eyewash to treat eye infections and diabetes.	Seaforth (2006) [164]

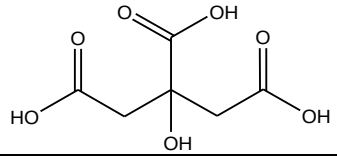
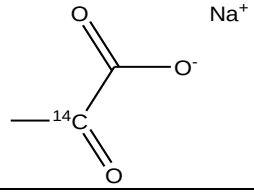
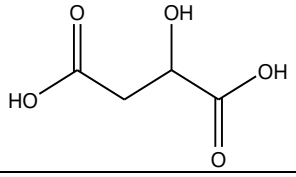
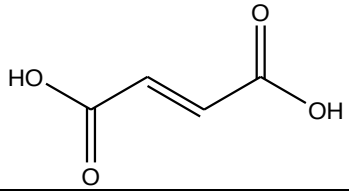
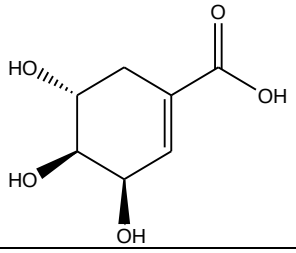
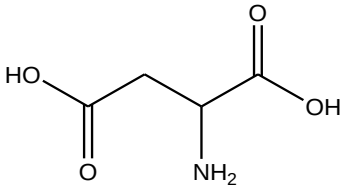
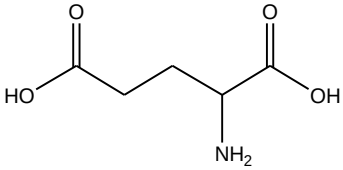
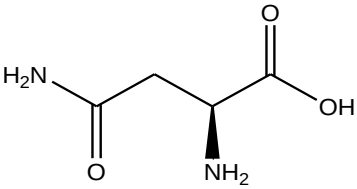
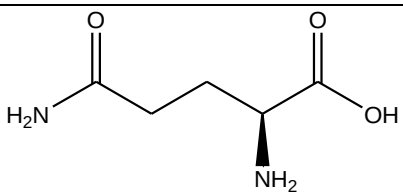
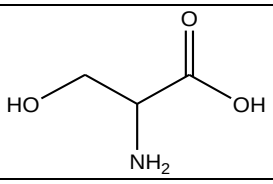
Table 3: Phytoconstituents from different parts of the plant *C. rosea*.

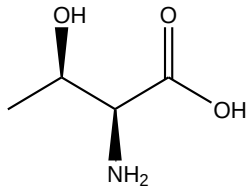
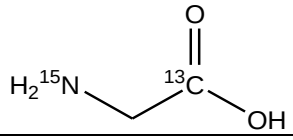
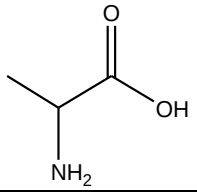
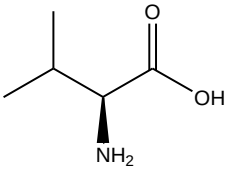
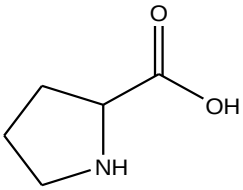
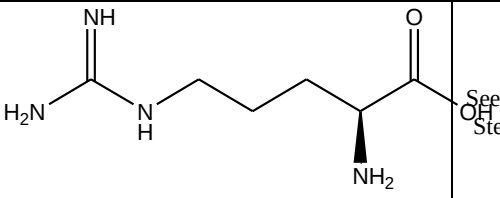
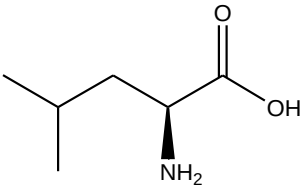
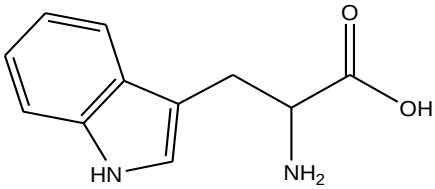
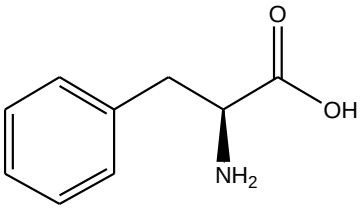
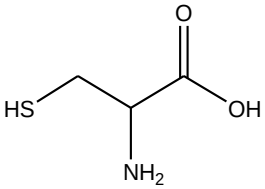
S. No	Active Constituent	Structure	Part	Group	Reference
1.	Gallic acid		Leaves	Benzoic acid	Pereira *et al*., 2013 [141]; Proestos *et al*., 2005 [152]
2.	Vanillic acid		Leaves	Benzoic acid	
3.	3-O-Caffeoylquinic acid		Stem, Leaves	Phenylpropanoids	Mustafa and Verpoorte 2007 [118]; Ferreres *et al*., 2008 [59]; Pereira *et al*., 2009(a) [139]
4.	4-O-Caffeoylquinic acid		Stem, Leaves, Petals	Phenylpropanoids	
5.	5-O-Caffeoylquinic acid		Stem, Leaves	Phenylpropanoids	
6.	Ferulic acid		Leaves	Phenylpropanoids	
7.	Kaempferol-3-O-(2,6-di-O-rhamnosyl-galactoside)-7-O-hexoside		Seeds, Leaves	Flavonoids (Kaempferol derivatives)	Mustafa and Verpoorte 2007 [118]; Ferrers *et al*., 2008 [59]; Pereira *et al*., 2009(a) [139]; Pereira *et al*., 2013 [141]; Nishibe *et al*., 1996 [127]
8.	Kaempferol-3-O-(6-O-rhamnosyl-galactoside)-7-O-galactoside		Seeds, Petals	Flavonoids (Kaempferol derivatives)	
9.	Kaempferol-3-O-(6-O-rhamnosyl-galactoside)-7-O-glucoside		Petals	Flavonoids (Kaempferol derivatives)	
10.	Kaempferol-3-O-(2,6-di-O-rhamnosyl-galactoside)		Seeds, Stems, Leaves, Petals	Flavonoids (Kaempferol derivatives)	
11.	Kaempferol-3-O-(2,6-di-O-rhamnosyl-glucoside)		Seeds, Petals	Flavonoids (Kaempferol derivatives)	
12.	Kaempferol-3-O-(6-O-rhamnosyl-galactoside)		Seeds, Petals	Flavonoids (Kaempferol derivatives)	
13.	Kaempferol-3-O-(6-O-rhamnosyl-glucoside)		Seeds, Petals	Flavonoids (Kaempferol derivatives)	

7. . R2=2,6-di-O-rhamnosyl-galactoside R3 = hexoside
8. R2=6-O-rhamnosyl-galactoside R3 = galactoside
9. R2=6-O-rhamnosyl-galactoside R3 = glucoside
10. R2=2,6-di-O-rhamnosyl-galactoside R3 = H
11. R2=2,6-di-O-rhamnosyl-glucoside R3 = H
12..R2=6-O-rhamnosyl-galactoside R3 = H
13. R2=6-O-rhamnosyl-glucoside R3 = H

14.	Mauritianin		Stems, Leaves	Flavonoids (Kaempferol derivatives)	
15.	Quercetin-3-O-(2,6-di-O-rhamnosyl-galactoside)	 15. R1=2,6-di-O-rhamnosyl-galactoside 16. R1=2,6-di-O-rhamnosyl-glucoside 17. R1=6-O-rhamnosyl-galactoside 18. R1=6-O-rhamnosyl-glucoside	Seeds, Stems, Petals, Leaves	Flavonoids (Quercetin derivatives)	Mustafa and Verpoorte 2007 [118]; Ferreres *et al*., 2008 [59]; Pereira *et al*., 2009(a) [139]; Pereira *et al*., 2013 [141]; Nishibe *et al*., 1996 [127]
16.	Quercetin-3-O-(2,6-di-O-rhamnosyl-glucoside)		Petals	Flavonoids (Quercetin derivatives)	
17.	Quercetin-3-O-(6-O-rhamnosyl-galactoside)		Petals	Flavonoids (Quercetin derivatives)	
18.	Quercetin-3-O-(6-O-rhamnosyl-glucoside)		Petals	Flavonoids (Quercetin derivatives)	
19.	Quercetin-3-O-α-L-rhamnosyl-(1→2)-α-L-rhamnosyl-(1→6)-β-D-galactoside		Stems, Leaves	Flavonoids (Quercetin derivatives)	
20.	Isorhamnetin-3-O-(2, 6-di-O-rhamnosyl-galactoside)	 20. R4=2,6-di-O-rhamnosyl-galactoside 21. R4=2,6-di-O-rhamnosyl-glucoside 22. R4=6-O-rhamnosyl-galactoside 23. R4=6-O-rhamnosyl-glucoside	Stems	Flavonoids (Isorhamnetin derivatives)	Mustafa and Verpoorte 2007 [118]; Ferreres *et al*., 2008 [59]; Pereira *et al*., 2009(a) [139]; Pereira *et al*., 2013 [141]
21.	Isorhamnetin-3-O-(2, 6-di-O-rhamnosyl-glucoside)		Seeds	Flavonoids (Isorhamnetin derivatives)	
22.	Isorhamnetin-3-O-(6-O-rhamnosyl-galactoside)		Petals	Flavonoids (Isorhamnetin derivatives)	
23.	Isorhamnetin-3-O-(6-O-rhamnosyl-glucoside)		Seeds, Petals	Flavonoids (Isorhamnetin derivatives)	
24.	Syringetin-3-O-robinobioside		Stems, Leaves	Flavonoids	Brun *et al*., 1999 [38]

25.	Petunidin-3-O-glucoside		Leaves	Anthocyanins	Mustafa and Verpoorte 2007 [118], Piovan *et al*., 1998, Pereira *et al*., 2013 [141]
26.	Malvidin-3-O-glucoside		Leaves	Anthocyanins	
27.	Hirsutidin-3-O-glucoside		Leaves	Anthocyanins	
28.	Petunidin-3-O-(6-O-p-coumaroyl) glucoside		Leaves	Anthocyanins	
29.	Malvidin-3-O-(6-O-p-coumaroyl) glucoside		Leaves	Anthocyanins	
30.	Hirsutidin-3-O-(6-O-p-coumaroyl) glucoside	 (30)	Leaves	Anthocyanins	
31.	Cis-aconitic acid		Seeds, Leaves, Stems, Petals	Organic acids	Pereira *et al*., 2009(a) [139]; Pereira *et al*., 2009(b) [140]

32.	Citric acid		Seeds, Leaves, Stems, Petals	Organic acids	
33.	Pyruvic acid		Seeds, Leaves, Stems, Petals	Organic acids	
34.	Malic acid		Seeds, Leaves, Stems, Petals	Organic acids	
35.	Fumaric acid		Seeds, Leaves, Stems, Petals	Organic acids	
36.	Shikimic acid		Seeds, Leaves, Stems, Petals	Organic acids	
37.	Aspartic acid		Seeds, Leaves, Stems, Petals	Amino acids	Aziz *et al*., 2015 [29]; Pereira *et al*., 2009(a) [139]
38.	Glutamic acid		Seeds, Leaves, Stems, Petals	Amino acids	
39.	Asparagine		Seeds, Leaves, Stems, Petals	Amino acids	
40.	Glutamine		Seeds, Leaves, Stems, Petals	Amino acids	
41.	Serine		Seeds, Leaves, Stems, Petals	Amino acids	

42.	Threonine		Seeds, Leaves, Stems, Petals	Amino acids	
43	Glycine		Seeds, Leaves, Stems, Petals	Amino acids	
44.	Alanine		Seeds, Leaves, Stems, Petals	Amino acids	
45.	Valine		Seeds, Leaves, Stems, Petals	Amino acids	
46.	Proline		Seeds, Leaves, Stems, Petals	Amino acids	
47.	Arginine		Seeds, Leaves, Stems, Petals	Amino acids	
18.	Leucine		Seeds, Leaves, Stems, Petals	Amino acids	
49.	Tryptophan		Seeds, Leaves, Stems, Petals	Amino acids	
50.	Phenylalanine		Seeds, Leaves, Stems, Petals	Amino acids	
51.	Cysteine		Seeds, Leaves, Stems, Petals	Amino acids	Aziz *et al.*, 2015 [29]; Pereira *et al.*, 2009(a) [139]

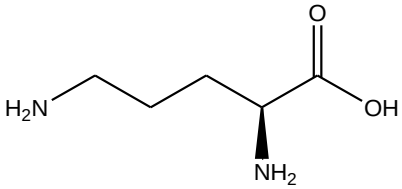
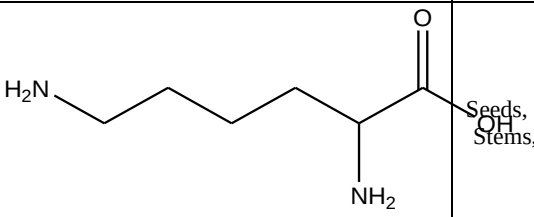
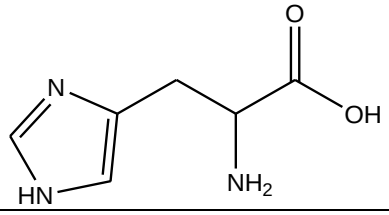
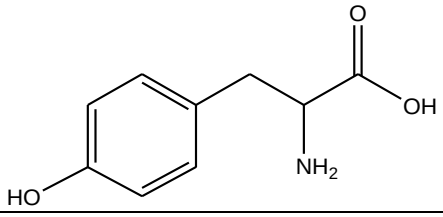
52.	Ornithine		Seeds, Leaves, Stems, Petals	Amino acids	
53.	Lysine		Seeds, Leaves, Stems, Petals	Amino acids	
54.	Histidine		Seeds, Leaves, Stems, Petals	Amino acids	
55.	Tyrosine		Seeds, Leaves, Stems, Petals	Amino acids	

Table 4: List of the major identified alkaloid in the *Catharanthus roseus*

Alkaloid	Plant part	MW (g mol^{-1})	Alkaloid	Plant part	MW (g mol^{-1})
Class - Corynanthean					
Tetrahydroalstonine (Lee *et al*.1988) [103]	P, F, R, C, CS, ST, HR	352.4	Alstonine (Lee *et al*.1988) [103]	R, C	348.4
Akuammine (Stolle and Groeger 1967) [176]	P	382.4	Sitsirikine (Lee *et al*.1988) [103]	P, CS, C, L, ST	354.4
19,20-*cis*-16-(*R*)-isositsirikine (Kohl *et al*. 1984) [89]	CS, P	354.4	Yohimbine (Kutney *et al*. 1980) [97]	HR, CS, C, SD, R, P	354.4
19,20-*trans*-16-(*R*)-isositsirikine (Kohl *et al*. 1984) [89]	CS, P	354.4	Dihydrositsirikine (Kohl *et al*. 1982) [88]	CS, C, R, L, P	356.4
19,20-*trans*-16-(*S*)-isositsirikine (Kohl *et al*. 1984) [89]	CS, P, L	354.4	Perimivine (Svoboda *et al*. 1964) [183]	R, P	366.4
Akuammiline (Adams and Smith 2016) [3]	CS, P	394.4	Serpentine (Lee *et al*.1988) [103]	CS, C, HR, ST, R, L, SD	348.4
7-Hydroxyindolenineajmalicine (Gueritte *et al*. 1983) [65]	C	368.4	Cathenamine (Stöckigt *et al*. 1977) [175]	P	350.4
Pseudoindoxylajmalicine (Gueritte *et al*. 1983) [65]	C	368.4	Ajmalicine (Kutney *et al*. 1980) [97]	C, CS, F, L, P, SD, ST	352.4
10-hydroxyldeacetylakuammiline (Gueritte *et al*. 1983) [65]	C	368.4	19-epiajmalicine (Kohl *et al*. 1982) [88]	CS, C, P	352.4
Mitraphylline (Gorman and Neuss 1964) [63]	C, F	368.4	3-epiajmalicine (Gueritte *et al*. 1983) [65]	CS, C, P	352.4
Anthirine (Kohl *et al*. 1982) [88]	CS, P	296.4	Akuammigine (Lee *et al*.1988) [103]	CS	352.4
Pericyclivine (Mukhopadhyay and Cordell 1981a) [115]	L,P	322.4	O-deacetylakuammiline (Atta *et al*. 1984c) [25]	C, L	352.4
Pleiocarpamine (Kohl *et al*. 1982) [88]	CS	322.4	Perivine (Gorman and Neuss 1964) [63]	CS, C, R, F, L, P	338.4
Cavincine (Willamanand Li 1970) [210]	HR, C, R, P, L	324.4	21-hydroxycyclolochnerine (Kohl *et al*. 1984) [89]	HR, ST, CS, C	340.4
Lochnerine (Nguyen *et al*. 1984) [125]	CS	324.4	Cavincidine (Svoboda and Barnes 1964) [183]	CS, C, R, L, P	*
Cathindine (Svoboda and Barnes 1964) [183]	CS, L, R	*	Perosine (Svoboda and Barnes 1964) [183]	C, R, L, P	*
Class - Bisindole					
3',4'-anhydrovinblastine (Roepke *et al*.	ST, L	792.9	Rovindine (Aslam *et al*. 2010) [18]	L, P	*

2010)					
Vingramine (Jossang *et al*. 1998) [81]	S	792.9	Vinaphamine (Svoboda and Barnes 1964) [183]	L, P	*
4'-deoxyvinblastine (Van der Heijden *et al*. 2004) [194]	L, P	794.9	Vinaspine (Svoboda and Barnes 1964) [183]	L, P	*
Vinosidine (Svoboda *et al*. 1963) [184]	P, R	796.9	*Vinca*micine (Svoboda *et al*. 1961) [182]	L, P	*
N-desmethyl-vinblastine (Tafur *et al*. 1975) [190]	P	796.9	Leurosivine (Svoboda *et al*. 1963) [184]	L	732.8
Methylvingramine (Jossang *et al*. 1998) [81]	S	806.9	N_b-oxideneoleurosidine (Van der Heijden *et al*. 2004) [194]	L, P	*
Catharanthamine (El-Sayed and Cordell 1981) [57]	L, P	808.9	17-deacetoxyleurosine (De Bruyn *et al*. 1982) [48]	P	750.9
Leurosine (Abraham and Farnsworth 1969) [1]	ST, L, P	808.9	4-deacetoxyvinblastine (De Bruyn *et al*. 1982) [48]	L, P	752.9
Roseadine (El-Sayed *et al*. 1981) [57]	L, P	808.9	Deacetylvinblastine (Tafur *et al*. 1975) [190]	P	768.9
*Vinca*thicine (Tafur *et al*. 1975) [190]	L, P	808.9	Vinsedine (Svoboda 1969) [179]	S	778
Roseamine (El-Sayed *et al*. 1981) [57]	P	810.9	Leurosinine (Aslam *et al*. 2010) [18]	P	778.8
Vinblastine (Gorman and Neuss 1964) [63]	C, F, L, P, SD	810.9	Vindorosine (Chen *et al*., 2017) [41]	S	780
20'-epi-vinblastine (Kuehna *et al*., 1991) [93]	L, P	810.9	N_b'-oxide-Leurosine (El-Sayed *et al*. 1981) [57]	L	824.9
Catharicine (Svoboda *et al*. 1962) [181]	F, L, P	820.9	Vinamidine (Tafur *et al*. 1975) [190]	L, P	824.9
5'-oxoleurosine (El-Sayed *et al*. 1980) [56]	L	822.9	Vincristine (Siddiqui *et al*. 2011) [169]	L, P	824.9
Carosine (Willamanand Li, 1970) [210]	F, L, P	824.9	N_b-oxide-leurosidine (Mukhopadhyay and Cordell, 1981b) [116]	P	826.9
Vindolicine (Pyuskyulev *et al*. 1995) [153]	P, L	925.0	14'-hydroxyvinblastine (Tafur *et al*. 1975) [190]	P	826.9
Leurosinone (Atta *et al*. 1988) [20]	L	865.0	15'-hydroxyvinblastine (Dorman and Paschal 1976) [52]	L	826.9
Neoleurosidine (Willamanand Li 1970) [210]	L, P	871.0	Neoleurocristine (Svoboda 1969) [179]	L, P	856.9
Catharine (Pyuskyulev *et al*. 1995) [153]	ST, L, P	822.9			
Class - Plumeran					
Tabersonine (Lee *et al*.1988) [103]	CS, SD, L, P	336.4	Bannucine (Atta *et al*. 1986) [23]	L,P	539.6
Venalstonine (Cuellar and O'Farrill, 1976) [46]	R	336.4	Vindoline (Gorman and Neuss 1964) [63]	ST, SD, F, L, P	456.5
Cathovaline (Atta *et al*. 1985a) [24]	L	426.5	19-Acetoxy-11-hydroxytabersonine (Kurz *et al*.1980) [96]	CS	424.4
Vindolidine (Svoboda, 1969) [179]	F, P	426.5	19-hydroxytabersonine (Atta *et al*. 1984c) [25]	CS	352.4
Lochnericine (Kutney *et al*. 1980) [97]	CS, L, P	352.4	Deacetylvindoline (Pyuskyulev *et al*. 1995) [153]	L, P	414.5
Minovincine (Varga *et al*. 2020) [200]	P	352.4	Rosicine (Atta *et al*. 1984d) [26]	L	324.3
Vincoline (Svoboda *et al*.1964) [183]	L, P	368.4	19-(S)-epimisiline (Peraza-Sanchez *et al*.1998) [138]	HR	368.4
Vindolinine (Kutney *et al*. 1980) [97]	ST, CS, L, P	368.4	Hörhammericine (Rijhwani and Shanks 1998) [157]	ST, CS	368.4
Deacetoxyvindoline (Kutney *et al*. 1980) [97]	SD, L, P	398.5	11-methoxytabersonine (Sun *et al*.2018) [118]	F,P	366.4
16-Hydroxytabersonine (Sun *et al*.2018) [118]	CS, L, P	352.4	11-methoxyhörhammericine (Rijhwani and Shanks 1998) [157]	ST,CS	398.4
O-deacetylvindolidine (Van der Heijden *et al*. 2004) [194]	SD	384.4	Minovincinine (Laflamme *et al*. 2001) [98]	CS	354.4
19-hydroxy-11methoxytabersonine (Kurz *et al*.1980) [96]	P	382.4	N_b-oxidevindolinine (Kohl *et al*. 1981) [87]	CS, P	352.4
19-epivindolinine (Zhou *et al*. 2005) [218]	CS, P, L	368.4	19-epi-N-oxidevindolinine (Kohl *et al*. 1981) [87]	CS	352.4
Class - Strychnan					
Lochneridine (Svoboda *et al*. 1961) [182]	HR, L, C, CS	340.4	Lochnerinine (Kai *et al*. 2012) [83]	CS, L, P	382.4
Preakuammicine (Scott and Qureshi 1969) [162]	SD	352.4	Xylosyloxyakuammicine (Aslam *et al*. 2010) [18]	CS	470.2
Akuammicine	L, R, C, CS, R	322.4	12-hydroxyakuammicine	CS	338.4

(Mukhopadhyay and Cordell 1981b) [116]			(Vachnadze *et al*. 1973) [196]		
Vinervine (Kuchenkova *et al*. 1965) [92]	CS	338.4			
Class - Aspidospermatan					
Apparicine (Stöckigt and Soll 1980) [174]	F, L	264.3	Tubotaiwine (Petiard *et al*. 1982) [144]	CS, C	324.4
Class - Vallesiachotaman					
Strictosidine lactam (Kutney *et al*. 1980) [97]	HR,CS, ST	498.5	Vallesiachotamine (Kutney *et al*. 1980) [97]	CS, C	350.4
Isovallesiachotamine (Petiard *et al*. 1982) [144]	CS,C	350.4			
Class - Ibogan					
Coronaridine (Zhong *et al*. 2010) [217]	F	338.4	Catharanthine (Lee *et al*.1988) [103]	ST, CS, C, SD, F, L, P	336.4
*Vinca*difformine (Atta *et al*. 1984a) [21]	R	338.4			
Class - Eburnan			**Class - Vincosan**		
*Vinca*rodine (Pyuskyulev *et al*.1995) [153]	L,P	398.4	Strictosidine (De Waal *et al*.1995) [49]	CS, C, S, R, L, P	530.5
Unknown Structure					
Ammorosine (Svoboda *et al*. 1963) [184]	R	*	Lochnerivine (Svoboda *et al*. 1963) [184]	R, L	424.4
Cathalanceine (Aslam *et al*. 2010) [18]	R	*	Lochrovicine (Svoboda *et al*. 1964) [183]	L	322.4
Ammocalline (Svoboda *et al*. 1963) [184]	R, P	278.3	Vincolidine (Svoboda *et al*. 1964) [183]	L, P	378.4
Rosamine (Atta *et al*. 1984b) [22]	L	352.4	Lochrovidine (Svoboda *et al*. 1964) [183]	P	382.4
Lochrovidine (Svoboda 1969) [179]	R, L	*	Perividine (Svoboda *et al*. 1963) [184]	P	354.4
Maandrosine (Glasby 1975) [62]	R, P	*	Lochrovine (Svoboda *et al*. 1964) [183]	P	382.5
Vinsedicine (Svoboda 1969) [179]	R	780.0			
Miscellaneous					
N-oxidefluorocarpamine (Bashir 1983) [32]	L, P	354.4	β-carboline (Atta *et al*. 1985b) [27]	L	168.1
N_b-acetyltryptamine (Lee *et al*.1988) [103]	CS	202.2	N, N-dimethyltryptamine (Kutney *et al*. 1980) [97]	CS	188.2

P = plant extract, C = callus culture, HR = hairy root, L = leaf, F = flower, SD = seedling, R= root, S = seed, CS= cell suspension culture, ST = shoot, * = data not available

Conclusion and Future Perspective

Taking into consideration the reported literature, the morphology, traditional uses, pharmacological uses and phytochemistry of *C. roseus* have been stated in this review. In today's era of research, *C. roseus* utilization for the treatment of cancer and diabetes has been widely accepted. Apart from this, the chemical components of *C. roseus* and its pharmaceutical uses have been intensively studied. However, there is an increase in the number of researches of finding new chemical compounds from *C. roseus*, so these researches give way for finding the new biological roles and their mechanisms along with their toxicity studies. Keeping in mind that there are still various critical issues to be dealt with in future studies. First of all is that *C. roseus* was conventionally used for the treatment of various disorders like ulcers, memory loss, malaria, stomach problems, menorrhagia and tooth problems but very few modern kinds of researches are available to support these uses. There is further need to investigate these topics as the increase in the number of evidence confirms that natural medicines possess great potential for the treatment of various disorders with low toxicity values. The research on the effect of *C. roseus* extract on the central nervous system is very limited to support its clinical trials. Though *C. roseus* is still in use as a cure for various disorders in some parts of the world so to verifies its effect there is a need for further investigation. Most of the research related to *C. roseus* is limited to its leaves and flowers part of the plant. Seeds, stems, fruits and roots are still not been explored completely. Research conducted using leaves and flowers should also be conducted using other parts of the plant to find its effectiveness as they have different chemical compositions. This provides us with a vast area of research for exploration in the *C. roseus* plant as it helps in laying a good foundation for further development of *C. roseus* and helps effectively in guiding the clinical medication. To summarize, further chemical and pharmacological studies on *C. roseus* will help clarify its toxicity, clinical efficiency and quality control based on the bioactive compounds present in it. Besides, this review might be useful for future researchers to get a hand on the current status of the study of *C. roseus* and would give a direction for future research.

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Ethics approval and consent to participate

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Availability of data and materials

The research work has been carried out by us, and we assure

you that it can be provided to you whenever required.

Author's Contribution

Parul Sharma: Searched and selected articles, extracted the data, Wrote original draft, given final approval of the version to be published.

Ramandeep Kaur: Drafting and revising the manuscript, given final approval of the version to be published.
Urvashi Bhardwaj: Conceptualization and final approval of the version to be published.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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