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MEDICINAL AND THERAPEUTIC BENEFITS OF *CATHARANTHUS ROSEUS* LINN (*APOCYANACEAE*): AN UPDATED REVIEW

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ABSTRACT
Ayurveda is the Indian traditional system of medicine which focuses on the potentiality of medical plants which are a rich source of compounds for the development of clinically useful therapeutic agents. *Catharanthus roseus*, a well recognized evergreen plant in Ayurveda, found in many tropical and subtropical regions around the World, is cultivated as an ornamental plant almost throughout the tropical world. It is abundantly naturalised in many regions, particularly in arid coastal locations. The flowers of this plant may vary in colour from pink to purple and leaves are arranged in opposite pairs. It produces nearly 130 alkaloids mainly ajmalcine, vinceine, resperine, vincristine, vinblastine and raubasin. Vincristine and vinblastine are used for the treatment of various types of cancer such as Hodgkin's disease, breast cancer, skin cancer and lymphoblastic leukemia. It has many pharmacological properties such as anti-oxidant, anti-microbial, anti-diabetic, wound healing, anti-ulcer, hypotensive, antidiarrhoeal, hypolipidemic and memory enhancement. Alkaloids are one of major phytochemicals responsible for its anti-cancer properties followed by phenolic compounds such as flavonoids. It is an endangered species and need to be conserved using techniques like micropropagation. It has high medicinal values which need to be explored extensively. The purpose of the current study was to document updated data about traditional uses, isolated bioactive compounds and pharmacological activities of *C. roseus*.

KEYWORDS: Medicinal plants, *Catharanthus roseus*, phytochemicals, vinblastine, pharmacological activities.

1. INTRODUCTION
Medicinal plants have a long history of usage in traditional medicine as these are high rich source of many potent and powerful drugs (Srivastava et al., 1996). Since pre-historic era, medicinal plants are being used to treat human diseases. In recent times, 80% of the world population especially in developing countries uses medicinal plants as a source of medicines from one generation to another (Hashim et al., 2010). Ethno-botanical information and the uses of medicinal plants are useful in the conservation of traditional cultures, biodiversity, community health care and drug development (Ajaib et al., 2010). The whole medicinal plant, or its different parts such as leaf, stem, bark, root, flower, seed, etc, or their secondary product such as gum, resins, and latex are used as folk recipes (Khan et al., 2011). Medicinal plants interacts with the human body directly or indirectly by its active chemical constituents which are absorbed into the blood; circulate through blood stream; and influence the blood stream to derive the required benefits (Kolasani et al., 2011). Now-a-days, the development of drug resistant human pathogens to commonly and traditionally used drugs has highlighted the searching of a new drug; and medicinal plant research has been focussed to achieve this aim. Screening of medicinal plants for active phytochemicals is important for finding potential new drugs for therapeutic uses (Retna and Ethalsha, 2013).

Catharanthus roseus Linn. (Madagascar periwinkle), a medicinal plant, also known as *Vinca rosea*, *Ammocallis rosea* and *Lochnera rosea* belongs to the family of Apocynaceae. Cape Periwinkle, Rose Periwinkle, Rosy Periwinkle and Old Maid are other English names which are occasionally used for this plant (Jaleel et al., 2006). *Catharanthus roseus* (*C. roseus*) exhibits various pharmacological activities due to presence of abundant useful alkaloids and active phytoconstituents. It has been used as traditional medicine for the treatment of a wide range of ailments worldwide such as diabetes, blood pressure, asthma, constipation, cancer and menstrual problems (Singh et al., 2001). Vinblastine and vincristine, two powerful anticancer molecules, belonging to the group of terpenoid-indole alkaloids (TIAs) are isolated from *C. roseus*. Due to their unique mode of action and effectiveness, these compounds have been extensively used for the treatment and cure of thousands of patients since last 40 years (Kulkarni et al.,

1999). *C. roseus* also use in Ayurvedic medicine and traditional Chinese medicine. All parts of this plant have been used in regional herbal medicine. In 20th century, the Western medical science started the research on this plant, and find out several useful anti-cancer compounds (Pillai et al., 1959).

As a potential source of important bioactive secondary metabolites, *C. roseus* has been taken into consideration for an extensive study. The purpose of the current study is to document updated data about its traditional uses, isolated bioactive compounds and pharmacological activities reported.

2. Botany

2.1 Taxonomic Classification

Changes in plant taxonomic classification with continuous research makes inconsistency of nomenclature in the literature. In the appellation of *Catharanthus roseus* (L.); *Catharanthus* means clean or pure flower in Greek, *roseus* signifies being rose-colored in Latin, and L. is the standard abbreviation for Linnaeus, who first published the plant's description, and G. Don refers to George Don, who named the flower as such in 1837 (Kohlmuzer, 1968). The classification of the *C. roseus* species are described below (Erdogrul, 2002).

Botanical Name(s): *Vinca Rosea*. (*Catharanthus roseus*)
Family Name: Apocynaceae.
Kingdom: Plantae.
Division: Magnoliophyta. (Flowering plants)
Class: Magnoliopsida. (Dicotyledons)
Order: Gentianales.
Family: Apocynaceae.
Genus: Catharanthus.
Species: *C. roseus.*

2.2 Vernacular Names

Vernacular names of *C. roseus* in different languages are summarized below (Plaizier, 1981). Nayantara (Bengali); Chang Chun Hua (Chinese); Roze maagdenpalm (Dutch); Bright-eyes, Cape periwinkle, graveyard plant, Madagascar periwinkle, old-maid, old-maid-flower, rose periwinkle, rosy periwinkle (English); Phlox (Ethiopia); Kaka poule, Bigalo (Creole); Pervenche de Madagascar, rose amere, sorcerer's violet (French); Zimmerimmergrun (German); Sadabahar, Baramassi, Ainskati, Ushamanjairi (Hindi); Tapak dara, kembang sari cina (Indonesian); Sadapushpa (Konkani); Nithyakalyani, Savakkottappacha, Ushamalari (Malayalam); Kemunting cina (Malay); Sada-phul/Sadaphuli (Marathi); Thin-Baw-MA-Hnyo (Myanmarese); Gul-e-farang Boa-noite, Boa-tarde, Lavadeira, Pervinca-rosa (Persian); Vinca-de-gato, Vinca-de-madagascar, Vina-rosea (Portuguese); Rattanjot (Punjabi); Nityakalyani (Sanskrit); Ngyange (Krio); Kanniedood (Afrikaans); Chatas, Chula, Pervinca de Madagascar, Vinca pervinca, Hierba doncella (Spanish); Rosenskona (Swedish); Sudukattu mallikai (Tamil); Billaganneru (Telugu).

2.3 Morphological Characteristics

C. roseus, an annual evergreen subherb or herbaceous plant, growing to 1 m. tall and secretes milky latex. Its roots extend to 70 cm. in depth and stems are cylindrical, longitudinally ridged or narrowly winged, green or dark red. The leaves are oval to oblong, 2.5-9.0 cm. long and 1-3.5 cm. broad. They are arranged in the opposite pairs. The flowers are pentamerous, actinomorphic with five petal like lobes; white to dark pink or red center with a basal tube about 2.5- 3 cm. long and a corolla about 2-5 cm. diameter. The fruit is a pair of follicles about 2-4 cm. long and 3 mm broad (Tolambiya and Mathur, 2016).

3. Geographical Distribution and Cultivation

C. roseus is native to the Indian Ocean Island of Madagascar. It is now common in many tropical and subtropical regions worldwide including the Southern United states and has been utilized for decoration and as a popular ornamental plant. In Spain, United States, China, Africa, Australia, India and Southern Europe it is cultivated commercially for its medicinal uses. The medicine derived from this plant makes a huge market in USA, Hungary, West Germany, Italy, The Netherlands and UK. In recent times this plant is found to be an endangered plant due to the habitat destruction by the slash and burn agriculture (Lata, 2007).

C. roseus, an annual bedding plant, best grown in drained sandy loams with full sunlight to partly shade. Cultivaters select the variaties of flower colour (white, mauve, peach, scarlet and reddish orange). Its cultivation required regular moisture; but overhead watering is restricted. Soil drainage is the key factor for growing this plant. This plant may be cultivated in hot and humid summer weather (Sain and Sharma, 2013).

4. Genetics

4.1 Cytology

All the species of *Catharanthus* genus bears the chromosome number of $2n$=16 with a 1500Mbp genome size. Treatment of colchicines causes the doubling of chromosome number and tetraploidy that boost the TIAs, larger stomata, branches, and leaves; but reduces the pollen fertility with poor seed set compared with diploid plants (Dnyansagar and Sudhakaran, 1970).

4.2 Reproduction

Self-compatibility makes this species unique among the other species in the family. Due to physical separation between stigma and anthers, intra-flower self-pollination does not happen in periwinkle; but this is achieved by a phenomenon known as reverse herkogamy. Some periwinkles that contain elongated ovaries or styles allow the intra-flower self-pollination. The environmental conditions and presence of seasonal pollinators like butterflies and moths are controlling factors of degree of out-crossing, whereby the floral structure is adapted to

pollination by these long-tongued insects. Self-incompatible strains are engage in natural inter-specific hybridization which is found to be common locally in Madagascar (Sreevalli et al., 2000).

4.3 Genetic Diversity

In spite of investigation of many aspects of alkaloid biosynthesis, the genetic variation between accessions in relation to alkaloid content and the effects of breeding for flower color or growth habit on the levels of vinblastine (VBL) and vincristine (VCR) are still poorly understood. Divergent cultivars accumulate TIAs in various parts of the plant. Hence, efforts need to be taken to identify accessions out of the vast resources of naturally occurring germplasm for their chemotherapeutic potential, for determining the active compounds accumulating plant tissues, and administering genetic improvements for yielding higher alkaloids (Zarate and Verpoorte, 2007).

5. Phytochemistry

Various Research teams investigate the medicinal properties *C. roseus* and discovered that it contains a group of extremely toxic alkaloids that had impending uses in cancer treatment. Plants have the ability to synthesize a wide variety of chemical compounds that are mainly used to perform important biological functions, and to defend themselves from attack of predators such as insects, fungi and herbivorous mammals. *C. roseus* contains carbohydrate, flavinoid, alkaloids, glycosides, flavonoids, tannin, saponin, proteins, amino acids, fats and oils (Prajapati et al., 2003). Alkaloids, the most potentially active chemical constituents of *C.* roseus, are used as pharmaceuticals, agrochemicals, flavor and fragrance, ingredients, food additives and pesticides. The alkaloids like actineo plastidemeric, Vinblastine, Vincristine, Vindesine, Vindeline Tabersonine etc. are mainly present in aerial parts of *C.* roseus; whereas ajmalicine, vinceine, vineamine, raubasin, reserpine, catharanthine etc. are present in roots and basal stem of *C.* roseus. Rosindin, an anthocyanin pigment is present in the flower of *C. roseus* (Bennouna et al., 2008).

5.1 Alkaloids

C. roseus, a potent source of about 150 active alkaloids; out of which vincristine, vinblastine and vindiscline are use in the treatment of Cancer (Negi, 2011), and other alkaloids such as vincristine is being used for Hodgkin and non-Hodgkin lymphomas and vinblastine is being used as a major component in chemotherapy for germ cell, breast, bladder and some types of brain malignancies (Mann, 2002). Vinblastine and Vincristine (Figure 1) are anti-tubulin drugs which act by suppressing the spindle microtubule dynamicity in the cells during mitosis and thereby arresting cell division and causes cell death (Jordan et al., 1991).

Vinblastine and vincristine, the dimmers, found abundantly in the aerial parts of the plant are formed by the coupling of Monoindole alkaloids such as catharanthine and vindoline (Renault et al., 1999). Vinblastine and vincristine have been isolated by chromatographic techniques like vacuum liquid chromatographic column on silica gel: aluminium oxide (1:1) mixed bed vacuum liquid chromatography (VLC), charcoal column, and finally purified by centrifugally accelerated radial chromatography (Chromatotrone) (Shams et al., 2009). Several other methods like high performance liquid chromatography (Siddiqui et al., 2011) and supercritical fluid extraction (Sang et al., 1992) have also been devised to efficiently quantify these alkaloids in the plant. The biosynthetic pathway of these alkaloids has been found to be under strict developmental regulation in the plant (Chandra and Chandra, 2011). Various studies on the regulation of the biosynthetic pathways revealed that TIA biosynthesis is subjected to different enzymatic and genetic regulation in the plant system.

5.2 Polyphenolics

Study of non-coloured phenolics from seeds, stems, leaves and petals of *C. roseus* and evaluation of their antioxidant activity led to the characterization of three caffeoylquinic acids and some flavonol glycosides (Figure 1). The scavenging ability of different plant matrices was assessed and a concentration-dependent protective effect was found for seeds and tissues, with petals found to be most active followed by seeds and leaves, indicating their potential for use in food, pharmaceutical and cosmetic industries (Ferreres et al., 2008).

5.3 Anthocyanins

The *in vivo* and *in vitro* production of anthocyanins from *C. roseus* has been established. The 3-O-glucosides and 3-O-(6-O-p-coumaroyl) glucosides of hirsutidin, malvidin and petunidin have been identified as major anthocyanins through *in vivo* and *in vitro* plant cell cultures (Figure 1) (Piovan and Filippini, 2007). Apart from these, the presence of tricin, a flavone, was reported in the mature *C. roseus* petals (Vimala and Jain, 2001).

5.4 Steroids

Studies have shown that crown gall cells of octopine and nopaline-types derived from *C. roseus* (L.) produce brassinosteroids with the main components identified as brassinolide and catasterone. Brassinosteroids is a steroidal growth-promoting plant hormones which is useful in agricultural industry for increasing crop production, and improving stress resistance of crops against drought, chilling and pesticides (Sakurai and Fujioka, 1997).

5.5 Flavonoid glucosides

New flavonoid glucosides such as 3',4'-di-O-methylquercetin-7-O-[(4"→13"')-2"',6"',10"',14"'-tetramethylhexadec-13"'-ol-14"'enyl]-β-D-glucopyranoside, 4'-O-methyl kaempferol-3-O-[(4''→13"')-2"',6"',10"',14"'-tetramethylhexadecane-

13”’-olyl]-β-D-gluco pyranoside,3’,4’-di-O-methylbutin-7-O-[(6”→1”’)-3”’,11”’,-dimethyl-7”’-methylenedodeca 3”’, 10”’ dienyl]-β-D-glucopyranoside and 4’-O-methylbutin-7-O-[(6”→1”’)-3”’,11”’,-dimethyl-7”’-hydroxymethylenedodecanyl]-β-D-glucopyranoside were isolated from the methanol extract of *C. roseus* hairy roots for the first time. These new flavonoids were shown to inhibit MMP-9 activity and TNF-α production in THP-1 cells implying to their use as potential anti-inflammatory medication (Chung et al., 2009).

5.6 Iridoid glucosides

C. roseus is known to accumulate monoterpene indole alkaloids that are derived from the coupling of tryptamine and iridoids like loganin and secologanin (Figure 1). The distribution of these iridoids at sub-cellular levels was studied in secologanin accumulating *C. roseus* cells and secologanin was found to be stored exclusively in the vacuoles (Oudin et al., 2007; Contin et al., 1999).

5.7 Novel metabolites from cell cultures of *Catharanthus roseus*

C. roseus is not only an important source of the metabolites discussed earlier but also it has been studied as the source of some novel active metabolites. Some of the novel metabolites obtained from the cell cultures of *C. roseus* and the approaches used to produce them are discussed here a little bit. Plasma membranes of suspension cultured *C. roseus* cells produces Phosphatidate kinase metabolites which is the key enzyme for phospholipid metabolism (Wissing et al., 1994). Dual culture of *Trichoderma harzianum* and *C. roseus* callus produces trichosetin that has been used as antibiotics (Marfori et al., 2002). Suspension cultured cells of *Catharanthus* produces phytic acid that is responsible for storage of phosphorus, mRNA export and chromatin remodelling (Mitsuhashi et al., 2005).

6. Traditional use of *Catharanthus roseus*

C. roseus has historically been used to treat a wide assortment of diseases. There are many traditional and folkloric uses of periwinkle which are time-tested and confirmed with peoples’ belief. The paste of *C. roseus* leaves is an excellent wound healer and also relieves the wasp sting pain. It can stop bleeding, thereby quickening the healing process. Many also say that periwinkle is useful in bringing relief from depression, headaches and fatigue. The traditional uses of the *C. roseus* in different-countries are summarized below:

In Australia, hot water extract of dried leaves of *C. roseus* is taken orally for the treatment of menorrhagia and diabetes, and extract of root bark is taken orally as afebrifuge (Bhandari and Mukerji, 1959). The hot water extract of dried whole plant of *C. roseus* is taken orally in Brazil, Dominica, England, Europe, Jamaica, Kenya, Malaysia, Pakistan, South Africa, Thailand, Venda, West Indies for the treatment of diabetes mellitus (Brandao et al., 1985; Thompson, 1976; Morrison and West, 1982; Ong et al., 2011; Siegel, 1976). In China and North Vietnam, the hot water extract of the aerial parts of *C. roseus* is taken orally as a menstrual regulator. In South Vietnam, the hot water extract of the entire plant is used orally by human adults as an antigalactagogue. In France, the hot water extract of entire plant is taken as an antigalactagogue (Virmani et al., 1978). In Cook-Island and Tiwan, decoction of dried leaves of *C. roseus* is used orally to treat diabetes, hypertension, Cancer and liver disease (Holdsworth, 1990). In French, the guina hot water extract of the entire plant of *C. roseus* is taken orally as a cholagogue (Luu, 1975).

In India, the hot water extract of dried entire plant of *C. roseus* is taken orally by human for the treatment of cancer; hot water extract of dried leaves of *C. roseus* are use orally to Hodgkin’s disease; the root extract of *C. roseus* is taken orally for menorrhagia (Virmani et al., 1978). In Mozambique, the hot water extract of leaves of *C. roseus* is taken orally for the treatment of diabetes and rheumatism and the root extract of *C. roseus* is use orally as hypotensive and febrifuge (Amico, 1977). In Peru, the hot water extract of dried whole plant of *C. roseus* is used orally by human adults for the treatment of cancers, heart disease and leishmaniasis (Ramirez et al., 1988). In Philippines, the hot water extract of the root of *C. roseus* is taken orally by pregnant women to produce abortion (Virmani et al., 1978). In USA, the hot water extract of leaves of *C. roseus* is smoked as a euphoriant and in Venda, the water extract of dried root of *C. roseus* is taken orally for venereal disease (Siegel, 1976).

7. Cytotoxic Activity of *Catharanthus roseus*

C. roseus is well known for being rich in alkaloids. The cytotoxic activity of *C. roseus* was investigated by MTT assay against Human Colorectal Carcinoma Cell Line (HCT 116). The preliminary study showed dose independent cytotoxic activity of the methanol extract of *C. roseus* against HCT-116 colorectal carcinoma cell line (Siddiqui et al., 2010). Simple method has been developed for the isolation of bioactive compounds like catharanthine and vindoline from *C. roseus*. The n-hexane, chloroform and methanol fractions of *C. roseus* also showed dose independent cytotoxic activity. The chloroform fraction of *C. roseus* showed the highest activity. Water fraction of *C. roseus* showed a minor cytotoxic activity. Vindoline showed a little cytotoxic activity at 200µg/ml. Catharanthine showed the most promising cytotoxic activity with dose dependent and its IC_{50} value was found at 60µg/ml (Retna and Ethalsha, 2013). The aqueous extract of *C. roseus* leaves standardised to Vinblastine was found to inhibit the proliferation of Jurkat cell line. This indicates the efficacy of aqueous extract for modulating normal and transformed immune cells in leukemia patients (Ahmad et al., 2010). Three new dimeric indole alkaloids were isolated from the *C. roseus* and their potential cytotoxic activities have been evaluated against human breast cancer cell line MDA-MB-231 (Wang et al., 2012).

8. Pharmacological activities of *Catharanthus roseus*

8.1 Anti-tumor activity

An U.S. government screening program discovered that *C. roseus* alkaloids especially vinblastine and vincristine; and as well as some synthetic analogs have high toxic chemotherapeutic activity like potent available drugs (Sharma et al., 2011). Semi synthetic analogs, vinorelbine (VRLB) and vindesine (VDS), obtained from the active bioactive compounds of *C. roseus* showed potential activity in combination with other chemotherapeutic drugs against leukemias, lymphomas, advanced testicular cancer, breast cancer, lung cancer and Kaposi's sarcoma (Cragg and Newman, 2005). Vinflunine, a bifluorinated derivative of vinorelbine showss a greater anti-tumor activity than other vinca alkaloids e.g. vinorelbine and vinblastine. The mechanism of mitotic block is still not clear but hypothetically it may be stated that this anti-tumor activity may be due to the decrease in microtubule dynamicity during mitosis and may be due to the increase in time centromere spends in the resting state during cell cycle. This novel vinca alkaloid is currently under Phase II clinical trials (Okouneva et al., 2003).

8.2 Anti-cancer activity

The anticancer alkaloids Vinblastine and Vincristine are derived from stem and leaf of *C. roseus*. (Banskota et al., 2002). These alkaloids have growth inhibitory effect to some human tumors. Vinblastine is used experimentally for treatment of neoplasmas and is recommended for Hodgkins disease, chorio carcinoma; whereas Vincristine is used for leukemia in children. Different percentage of the methanolic crude extracts of *C. roseus* exhibits significant *in vitro* anticancer activity against numerous cell types (Ueda et al., 2002) and especially enormous activity was found against multidrug resistant tumor types (Wang *et al.*, 2004). These are also used for the treatment of leukemias, lymphomas, and testicular cancer (Retna and Ethalsa, 2013). The methanol extracts of aerial and roots of *C. roseus* reduced the proliferation of the human ductal breast epithelial tumour cell lines (T47D) with a mean IC_{50} of 2.8% by apoptosis (Widowati et al., 2013). Aqueous extract of *C. roseus* leaves induces cell death of human leukemic T-cells (Jurkat) in a dose and duration dependent manner with mean IC_{50} value of 2.38µg/ml by DNA fragmentation (Ahmad et al., 2010). Preliminary cytotoxicity study has revealed a dose independnet activity of methanol extracts of *C. roseus* against HCT-116 colorectal carcinoma cell lines at 200µg/ml (Siddiqui et al., 2010).

8.3 Anti-mutagenic and Anti-mitotic activity

Female mice were administrated with ethanol (70 %) extract of dried *C. roseus* leaves to examine the the anti-mitotic activity, that showed the positive results on CA-Fhrlich ascites vs. induction of metaphase arrest in ascites cells (El Merzabani., 1979). When the red blood cells (RBCs) were subjected to hot water extract of dried leaves the number of micro-nucleated polychromatic RBCs decreased, that proved the anti- mutagenic effect of *C. roseus* (Sharma et al., 1982). The mutagenic effect of vincristine, an alkaloid secreted by *C. roseus* was studied using sex linked recessive lethal (SLRL) test system in *Drosophilla melanogaster*. The results showed that vincristine produced many chromosomal effects, arrest cells at metaphase with highly contracted chromosomes and inhibition of tubulin polymerization (Aahmed et al., 2010). When the root tips of *C. roseus* were treated with ethylmetahne sulphonate (EMS) then a number of chromosomal anomalies were observed such as persistent nucleolus, condensation, fragmentation, laggered, bridge, cleft and binucleolated cells (Verma et al., 2012).

8.4 Anti-diabetic activity

The ethanolic extracts of the leaves and flower of *C. roseus* showed a dose dependent lowering of blood glucose level in comparable to the standard drug glibenclamide. The aqueous extract of *C. roseus* was found to lower the blood glucose level in diabetic rats by 20% in compared with dichloromethane and methanol extracts which lowered the same by 49-58%.This hypoglycemic effect may appeared due to the increase utilization of glucose in liver (Chattopadhyay, 1994).

Maximum of the reported work about anti-diabetic potential of this plant is being conducted using the crude extract rather than the pure bioactive compounds (Ohadoma and Michael, 2011; Ganga et al., 2012). In streptozotocin induced diabetic rat this plant induces hypoglycemic effect (Gacche and Dhole, 2011). All four isolated alkaloids e.g. vindoline, vindolidine, vindolicine and vindolinine from *C. roseus* leaves induces relatively high glucose uptake in pancreatic β-TC6 or myoblast C2C12 cells, with vindolicine showing the highest activity. In addition, compounds vindolidine, vindolicine and vindolinine demonstrated good protein tyrosine phosphatase-1B (PTP-1B) inhibition activity, implying their therapeutic potential against type 2 diabetes (Tiong et al., 2013). The hypoglycemic activity of isolated alkaloids from *C. roseus* has been studied pharmacologically and an antidote derived from this plant has been marketed under the propritery name Vinculin as a treatment for diabetes (Singh et al., 2001; Chattopadhyay, 1994).

8.5 Anti-microbial activity

Crude extracts from different parts like leaves, stem, root and flowers of *C. roseus* were tested for antibacterial activity. The leaf extract of *C. roseus* exhibited significantly higher activity suggesting that bioactive compounds of *C. roseus* can be a potentially exploited as antibacterial agents. Gram negative strains were found to be more sensitive than the Gram positive (Ramya et al., 2008). The ethanolic extracts were more active against almost all the test microbes and Gram-positive bacteria were found to be more sensitive than the Gram-negatives (Goyal et al., 2008). Crude extracts of *C. roseus* leaves exhibits significantly higher anti-microbial efficacy against *Pseudomonas aeruginosa* NCIM2036,

Salmonella typhimuruim NCIM2501, *Staphylococcus aureus* NCIM5021 than the extracts from different parts of the plant; indicating its use as prophylactic agent in the treatment of various diseases (Prajakta and Ghosh, 2010). Ethanol extract of the *C. roseus* flowers has properties to rendering its capability for promoting accelerated wound healing activity, increased wound contraction and tensile strength, increased hydroxyproline content and antimicrobial activity supported the topical use of *C. roseus* in wound treatment and management (Nayak and Pereira, 2006).

The leaf extract of *C. roseus* has also been shown to have significant fungitoxic activity against *Macrophomina phaseolina* and *Sclerotium rolfsii* the causative agents of the root rot disease in chickpea (*Cicer arietium* L.). The extracts strongly inhibited the mycelial growth in both the fungi at 50, 75 and 100% concentration when compared with the control (Wadikar and Nimbalkar, 2010). In a study to explore the antiplasmodial potential of *C. roseus* L, *Coccinea grandis*, *Thevetia peruviana*, *Prosopis juliflora*, *Acacia nilotica*, *Azadirachta indica* (Abr. Juss) and *Morinda pubescens*, the bark extract of *A. indica* (Abr. Juss) was found to have excellent antiplasmodial activity followed by leaf extract of A. *indica* (Abr. Juss) and leaf extract of *C. roseus* L (Sundaram et al., 2012).

8.6 Anti-oxidant activity

In the last few years, oxidative stress related diseases/disorders like metabolic, neurodegenerative, cardiovascular, mitochondrial diseases and even cancer have gained a special attention. Various studies were focussed on investigating the underlying triggering factors, in order to understand the mechanisms of action of free radicals, as well as to discover effective substances towards preventing and even reversing the occurrence of oxidative damages (Halliwell, 2012). Accumulation of free radicals can causes several pathological consequences like ischemia, asthma, arthritis, inflammation, neuro-degeneration, Parkinson's diseases, mongolism, aging process and perhaps dementia (Kaur and Mondal, 2014). Antioxidants, both from natural and synthetic sources, have proved to be highly effective to control the magnitude of free radicals production, to prevent its undesirable effects, as well as to support the organism's antioxidant and detoxifying mechanisms (Holst and Williamson, 2008). Phenolic compounds have shown promising antioxidant properties, and hence the study of the antioxidant potential of phenolic extracts derived from plant species is one of the hot topics among the scientific community; however, in vitro studies are the most common (Dai and Mumper, 2010).

C. roseus contains significant amounts of volatile and phenolic compounds including caffeoylquinic acids and flavonol glycosides which are known to possess antioxidant activity. It has an important role in the body's defense system that acts as antioxidants against reactive oxygen species (ROS), which are harmful by forming such products through normal cell aerobic respiration (Salah et al., 1995). The flower petals, seeds and other parts of *C. roseus* exhibit antioxidant properties. Thus, phenolic compounds have redox properties that act as reducing agents, hydrogen donors, singlet oxygen quenchers or metal chelators. It has multiple applications in foods, cosmetics, and pharmaceutical industries. Besides antioxidant activity, these compounds exhibit anti-allergic, anti-inflammatory, antimicrobial, anti-thrombotic, cardio protective and vasodilatory effects (Garg et al., 2012).
The anti-oxidant potential of ethanolic extract of the roots of two varieties of *C. roseus* namely rosea (pink flower) and alba (white flower) was obtained by using different system of assay such as radical-scavenging and inhibition method. The result showed that the ethanolic extract of the roots of Periwinkle varieties has exhibited the satisfactory scavenging effect in a concentration dependent manner but *C. roseus* was found to possess more antioxidant activity than that of *C. alba* (Alba Bhutkar and Bhise, 2011). Vindolicine, present in the plant showed the highest antioxidant potential and it also alleviated H_2O_2-induced oxidative damage in β-TC6 cells at 12.5μg/mL and 25.0μg/mL (Tiong et al., 2013).

8.7 Anti-helminthic activity

Helminthes infections are the chronic illness which affecting the human beings and cattle. *C. roseus* was found to be used from the traditional period as an anti-helminthic agent. The anti-helminthic property of *C. roseus* has been evaluated by using *Pheretima posthuma* as an experimental model and with Piperazine citrate as the standard reference. 250mg/ml ethanolic extract was found to show the significant anti-helminthic activity with death time of 46.33 min; whereas the standard drug at a concentration of 50mg/ml showed the death time of 40.67 min. In the study, the control drug Piperazine citrate showed more potent anthelmintic activity compared to the methanol, aqueous, ethanol and ethylacetate extract of *C. roseus*. The investigation thus revealed that ethanol extract of *C. roseus* showed significant anti-helmintic activity against *Pheretima posthuma*; and supported the ethnomedical claims of *C. roseus* as an anti-helminthic plant (Agarwal et al., 2011).

8.8 Anti-ulcer activity

Vincamine and Vindoline alkaloids of *C. roseus* showed anti-ulcer property. The plant leaves proved their anti-ulcer activity against experimentally induced gastric damage in rats (Babulova et al., 2003). Vincamine, the alkaloid present in the plant leaves shows cerebro-vasodilatory and neuroprotective activity (Sain and Sharma, 2013).

8.9 Anti-diarrhea property

The anti-diarrheal activity of the ethanolic leaf extracts of *C. roseus* was tested in the wistar rats with castor oil as a experimental diarrhea inducing agent in addition to the pretreatment of the extract. The anti-diarrheal effect

of ethanolic extracts *C. roseus* showed the dose dependant inhibition of the castor oil induced diarrhea **(**Rajput et al., 2011).

8.10 Anti-hypotensive property

Isolated alkaloids from *C. roseus* are found to be hypotensive, sedative and possess tranquilising and anti-cancerous properties. The leaves have been known to contain 150 useful alkaloids among other pharmacologically active compounds. Significant anti-hyperglycemic and hypotensive activity of the leaf extracts (hydroalcoholic or dichloromethane-methanol) have been reported in laboratory animals (Pillay et al., 1959).

The leaves extract of *C. roseus* was investigated for hypotensive effects in adrenaline-induced hypertensive rats (AIHR) and compared with Atenolol in a crossover design. *C. roseus* leaves extract treated animals have shown the hypotensive effects. Hypotensive effects were also shown by Atenolol. The pharmacologically Active components of *C. roseus* which is responsible for hypotensive activities were isolated from plant using bioassay guided purification approach and the structure of the compounds was proposed by spectroscopic methods. The *C. roseus* leaves extract made significant changes in each cardiovascular parameter after investigation (Ara et al., 2009).

8.11 Wound healing property

Rats treated with 100mg/kg b.w/day of ethanol extract of *C. roseus* had a high rate of wound
contraction and significantly decreased epithelisation period, and showed significant increase in dry weight and hydroxyproline content of the granulation tissue when compared with the controls. Wound contraction together with increased tensile strength and hydroxyproline content support the use of *C. roseus* in the management of wound healing (Nayak et al., 2007).

8.12 Hypolipidimic effect

Anti-atherosclerotic activity of the leaf juice of *C. roseus* was observed as suggested by significant reduction in the serum levels of total cholesterol, triglycerides, LDL-c, VLDLc and histology of aorta, liver and kidney. These effects could have resulted from the antioxidant effect of flavonoid, and probably, vinpocetine like compound present in leaf juice of *C. roseus* (Patel, 2011).

8.13 Memory enhancement activity

Vinpocetine has been reported to have a variety of actions that would hypothetically be beneficial in Alzheimer's disease (AD). The only study investigating this agent in a well defined cohort of AD patients found no benefit. Meta-analysis of older studies of vinpocetine in poorly defined dementia populations concluded that there is insufficient evidence to support its clinical use at this time. Vinpocetine has been well tolerated at doses up to 60mg/day in clinical trials of dementia and stroke, and no significant adverse events were observed (Mishra and Verma, 2017).

8.14 Neuroprotective activity

The possible neuroprotective effect of *C. roseus* leaf extract was investigated against streptozotocin induced hyperglycaemia in the rat brain; that reveals that *C. roseus* leaf extract is an effective neuroprotective agent against diabetic oxidative damage because treatment of *C. roseus* reduced lipid peroxidation and Sorbitol DH production and increased glutathione levels significantly in compared to the streptozotocin induced diabetic-untreated rats (Jyothi and Kumara, 2012).

8.15 Anti-fertility activity

Oral administration of leaf extract of *C. roseus* Linn leads to widespread testicular necrosis, hyalinization of tubules and sertoli cell, notable reduction in glycogen and fructose levels in reproductive tissues that confirmed the antifertility properties of *C. roseus* extract (Mathur and Chaudan, 1985). The petroleum ether extract of *C. roseus* leaves inhibited the estrogen induced gain in the uterine weight when administered along with estradiol into the female albino mice thus proving to be highly effective in suppressing pregnancy (Gupta, 2009).

8.16 Biopesticidal property

Biological activity of solvent extracts of *C. roseus* were evaluated against larvae of gram pod borer *Helicoverpa armigera* (Lepidoptera: Noctuidae). Ethyl acetate fractions of *C. roseus* leaf extract was found to be a potent biopesticide. Insecticidal properties of *C. roseus* have also been reported (Deshmukhe et al., 2010). The pupicidal action was evaluated by treating the pre-pupal stage of Spodoptera litura with *C. roseus* leaf extract by topical application method. 73.33%, 49.33%, 33.33%, 28.00% and 17.33% mortality was observed when pre-pupae were treated with 2.0%, 1.5%, 1.0%, 0.5% and 0.1% of *C. roseus* leaf extract, respectively (Sandey and Summarwar, 2016).

8.17 Phytoremediation property

Phytoremediation is used to remove pollutants from environment components. during germination the toxic effects of cadmium and lead with respect to *C. roseus* are the maximum and the plant gradually becomes more resistant to these heavy metals as it attains maturity (Pandey et al., 2007). The phytoremediation potential of *C. roseus* with respect to chromium has been analyzed by Ahmad et al. (Ahmad et al., 2014). *C. roseus* was shown to absorb up to about 38% of the amount of Cr present in primary and secondary sludge amended soil through roots and accumulate it to about 22% in leaves, thereby, proved useful in the reclamation and remediation of chromium contaminated soil and land. *C. roseus* has been used for lead and nickel phytoremediation (Subhashini and Swamy, 2013). *C. roseus* is used in plant pathology as experiment host for phytoplasmas. This is because it is easy to infect with a large majority of phytoplasmas and also often has very

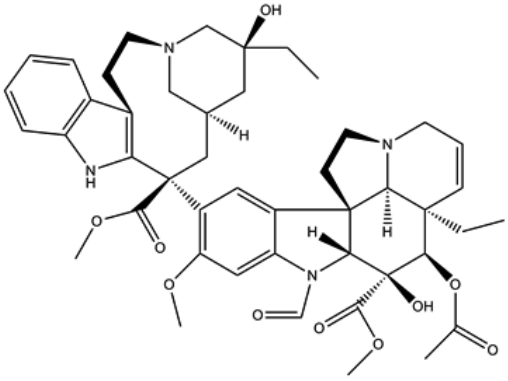
distinctive symptoms such as phyllody and significantly reduced leaf size (Das and Sharangi, 2017).

9. Toxicity and Side effects of *Catharanthus roseus*

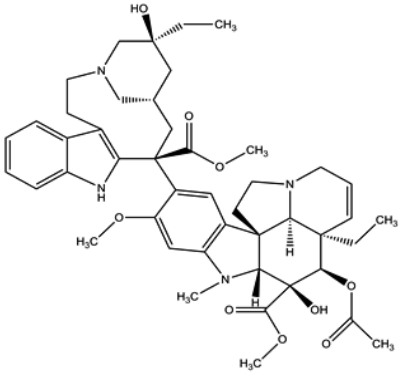
C. roseus is not recommended for oral administration because it may worsen the side effects including psychological influences. The advised route for *C. roseus* and its derivatives are intravenous. Vinca alkaloids have been applied clinically since the end of the 1950s as major drugs in the treatment of Hodgkins disease, testicular germ cell cancer, lymphomas, solid tumors, lung cancer and acute lymphocytic leukemia etc. (Leveque D. and Jehl, 2007). In spite of their extraordinary benefits, all of the *C. roseus* alkaloids have neurotoxic activity, particularly vincristine, affecting neurotransmission (Nobili et al., 2009). Vincristine and vinblastine are highly toxic antimitotic that blocks mitosis in metaphase after binding to the microtubules (Jordan and Wilson, 2004). Moreover, many side effects have been reported for these drugs comprising abdominal pains, constipation, nausea/vomiting, ulcerations of the mouth, cell destruction, kidney damage, pulmonary fibrosis, urinary retention, amenorrhea, hypotension and hypertension. Hence the dosage and administration must be cautiously measured to reduce side-effects (James et al., 2007).

10. Possible pathways and mode of action of *Catharanthus roseus*

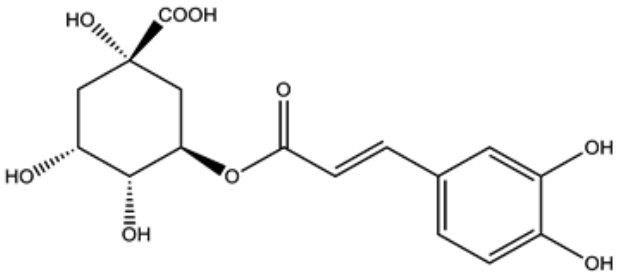
Vinca alkaloids are cell cycle specific agents and they block cells in mitosis. The vinca alkaloids bind specifically to β-tubulin and block its ability to polymerize with α-tubulin into microtubules. In the absence of an intact mitotic spindle, duplicated chromosomes cannot align along the division plate and cell division is arrested in metaphase. Cells are blocked in mitosis undergoes to apoptosis. They are also used for treatment of leukemias, lymphomas, and testicular cancer (Das and Sharangi, 2017).



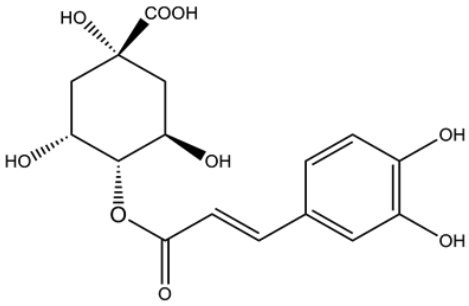
Vincristine



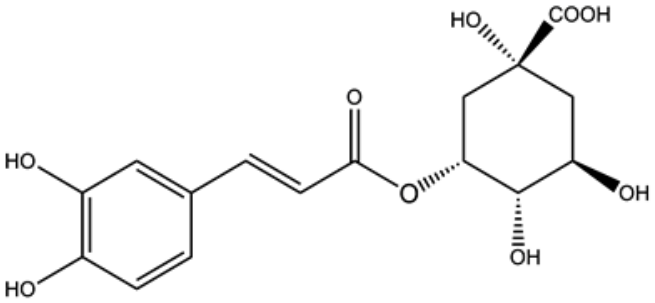
Vinblastine



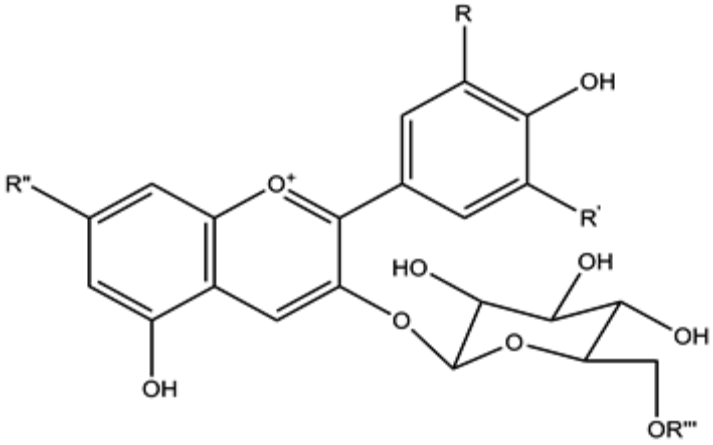
3-O-Caffeoylquinic Acid



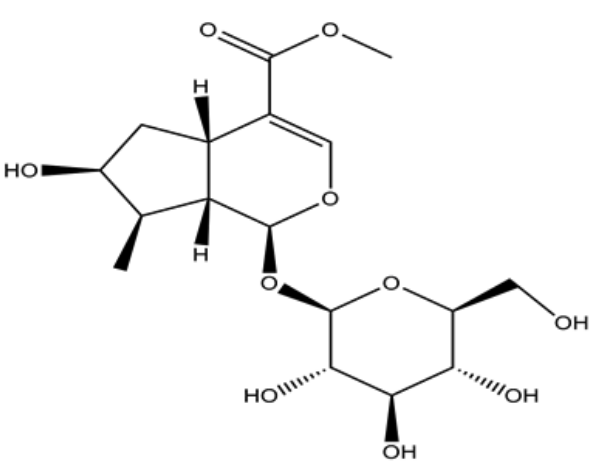
4-O-Caffeoylquinic Acid



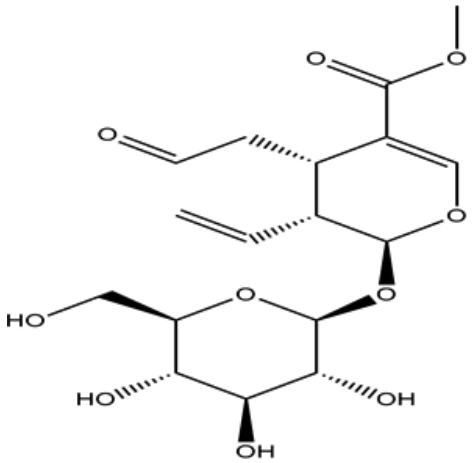
5-O-Caffeoylquinic Acid



Anthocyanins



Loganin



Secologanin

Fig. 1: List of important bioactive compounds of Catharanthus roseus.

11. CONCLUSION

Medicinal plants are the potent source of various novel pharmaceutical products that shows potent pharmacological effects on the human beings. Instead of using the side effects causing chemical drugs, the ancient medicine could be explored to identify the novel drug formulations that are more effective with lesser side effects and also cheaper cost. Though, many of the traditional drugs were used without understanding the basic mechanism, their effect could be proved further with the help of the present technology and tools. The active compound that is responsible for the pharmacological effect could be found very easily and also commercialized as a drug product itself with proper approval from the respective organizations. *Catharanthus roseus* was investigated from the ancient time for their phytochemical components and their therapeutic effect. The plant contains enormous phytochemical constituents of various medicinal applications. The plant also possesses various properties such as anti-cancerous, anti-diabetic, anti-helminthic, anti-diarrheal, anti-microbial etc. Hence there is ample scope of research work to be done on the above plant to

reveal the unknown mysteries which would help the need of the present pharmaceutical world.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ABBREVIATIOS

AD	Alzheimer's disease
AIHR	Aadrenaline-induced hypertensive rats
C. roseus	*Catharanthus roseus*
EMS	Eethylmetahne sulphonate
HCT	Human Colorectal Carcinoma Cell Line
IC	Inhibitory concentration
MMP	Mitochondrial membrane potential
MTT	3-(4,5-dimethylthiazol-2-YI)-2,5-diphenyltetrazolium bromide
PTP-1B	Protein tyrosine phosphatase-1B
ROS	Reactive oxygen species
SLRL	Sex linked recessive lethal ()
TIAs	Terpenoid-indole alkaloids
TNF-α	Tumor necrosis factor
VBL	Vinblastine
VCR	Vincristine
VDS	Vindesine
VLC	Vacuumliquid chromatography
VRLB	Vinorelbine

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