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Natural Bioactive Products from an Ornamental- Medicinal Flower (*Catharanthus roseus* (L.) G. Don) forms Promising Therapeutics: A Critical Review of Natural Product-Based Drug Development

Somashekara Rajashekara* and Utpal Baro

Centre for Applied Genetics, Department of Studies in Zoology, Bangalore University, Jnana Bharathi Campus, Off Mysuru Road, Bengaluru 560 056, India

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*Corresponding author's email: rajachandra3908@yahoo.co.in
*ORCID: http://orcid.org/0000-0002-2512-6617

Abstract

Catharanthus roseus (L.) G. Don (Apocynaceae) commonly called as "flower of immortality", "the flower of death", "violet of the sorcerers" and "an emblem of friendship". It is a well-known weed to employed for treating various disorders. The study aims at far-reaching review on phytochemistry, pharmacological activities, ethnopharmacology, characterization, chemical composition, and biological applications of *C. roseus* plants which aids to provide scientific evidence for the ethnobotanical claims and to identify gaps required to be conducted as a future research requirement. Most of the traditional and systematic uses obtained from the extraction of *C. roseus* plants were validated by the scientific studies such as antimicrobial activity, anticancer activity, antidiabetic activity, antileukemia activity, antioxidant activity, chemotherapeutic drugs and therapy, wound healing, production of nanoparticles and nanoproducts, etc. Isolated compounds, mainly terpenoid indole alkaloids (TIA) such as ajmalicine, anhydrovinblastine, catharanthine, serpentine, vindoline, vinblastine, vincristine, and vindolinine were confirmed and showed potent activity. This review article explores the phytochemistry, ethnopharmacological, pharmacological and biological activities of *C. roseus* plants which gives the evidence of a potent and commercial drug which up on further research leads to the most viable drug for variety of treatments.

Keywords: Anticancer activity, Antidiabetic activity, Antileukemia activity, Antimicrobial activity, Antioxidant activity, Chemotherapeutic drugs.

1. INTRODUCTION

1.1. *Catharanthus roseus* (L.) G. Don synonyms and taxonomy

Catharanthus roseus (L.) G. Don (Apocynaceae) is an ornamental plant, an evergreen sub herb or herbaceous plant. A native to Madagascar, this herbaceous plant grows to 80 cm to 1 m high and blooms continuously year-round with pink, purple, or white flowers. The leaves are oval to oblong, 2.5- 9.0 cm long and 1- 3.5 cm broad glossy green hairless with a pale midrib and a short petiole about 1- 1.8 cm long and they are arranged in the opposite pairs. There are two common cultivars of *C. roseus* named on the basis of their flower color, one producing pink flower "*rosea*" and the other, white flowers "*alba*". The flowers are white to dark pink with a dark red centre, with a basal tube about 2.5- 3 cm long and a corolla about 2-5 cm diameter with five petal like lobes (Fig. 1).

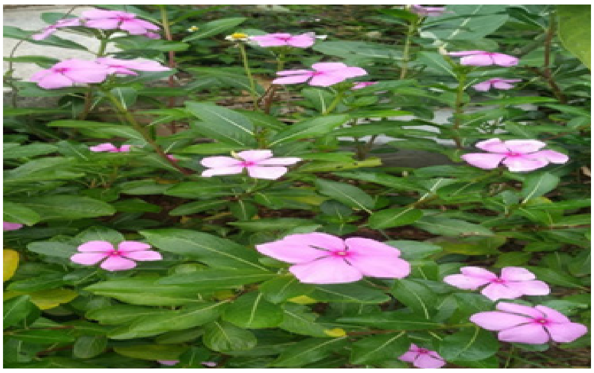

Fig. 1. *Catharanthus roseus*. (Photograph taken at Garden Department, Bangalore University Campus, Bengaluru, India).

The fruit is a pair of follicles about 2-4 cm long and 3 mm broad. The plant grows widely to about 1 m tall at subtropical areas. Its leaves are found to be of oval to oblong, 2.5 – 9.0 cm long and 1.0-3.5 cm broad, glossy green, hairless, with a pale midrib and a short petiole of about 1.0-1.8 cm long (Fig. 2) and hence they are arranged in the opposite pairs (Das and Sharangi, 2017).

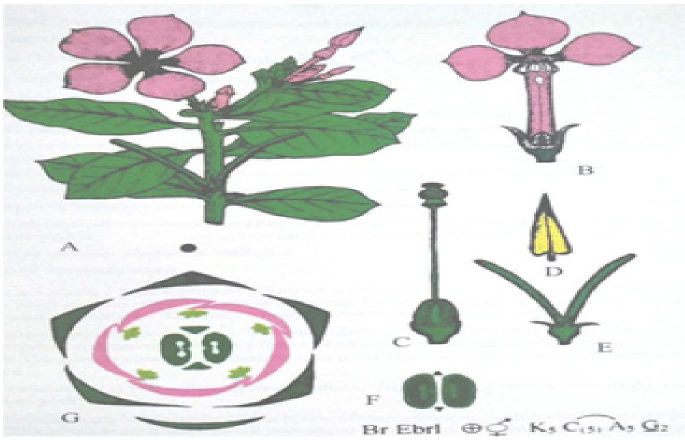

Fig. 2. Distinctive representation of the *Catharanthus roseus*. A) Flowering twig; B) Longitudinal section of flower; C) Gynoecium; D) Sagittate anther; E) Pair of follicles; F) Transverse section of apocarpous ovary.

Traditionally, different parts of *C. roseus* plants are used for the treatments of various diseases in many countries such as Australia, Brazil, China, Cook Island, Dominica, England, Europe, France, French Guiana, India, Jamaica, Kenya, Mexico, Mozambique, North Vietnam, Pakistan, Peru, Philippines, South Africa, South Vietnam, Taiwan, Thailand, USA, Venda, Vietnam, West Indies, etc. (Aslam *et al.,* 2010). The plant tissues of *C. roseus* are composed of various cell types with unique sizes, shapes, and biological functions that play different roles in normal plant growth, development, and reproduction (Murata *et al.,* 2008). The synonyms of the plant and authors were confirmed as per www.theplantslist.org which is listed as below.

Synonyms of *Catharanthus roseus* (L.) G. Don
Ammocallis rosea (L.) Small
Catharanthus roseus var. *albus* G. Don
Catharanthus roseus var. *roseus*
Hottonia littoralis Lour.
Lachnea rosea (L.) Rchb.
Lochnera rosea (L.) Rchb. ex Endl.
Lochnera rosea var. *alba* (G. Don) Hubbard
Lochnera rosea var. *flava* Tsiang
Pervinca rosea (L.) Gaterau
Pervinca rosea (L.) Moench
Vinca gulielmi-waldemarii Klotzsch
Vinca rosea L.
Vinca rosea var. *alba* (G. Don) Sweet
Vinca rosea var. *albiflora* Bertol.
Vinca speciosa Salisb. [Illegitimate]

Das *et al.* (2020) reported that genus *Catharanthus* includes eight species, out of which seven (*C. longifolius, C. coriaceus, C. roseus, C. lanceus, C. trichophyllus, C. ovalis* and *C. scitulus*) are prevalent in Madagascar and only one, *C. pusillus* is from India. As the name "Madagascar periwinkle" indicates *C. roseus* is native and endemic to Madagascar, located in the Indian Ocean. *Catharanthus roseus* is localized in America, continental Africa, Asia, Southern Europe, Australia, and in quite a few islands of the Pacific Ocean. It is cultivated as an ornamental plant in most of the tropical and sub-tropical areas. In India, *C. roseus* is distributed along the Northwestern and Northeastern Himalayas, Western Ghats, Eastern Ghats, West Coast, East Coast, Central Deccan Plateau, and Indo-Gangetic Plain. It grows well in the temperate regions as an annual plant and thrives through frost as well also can survive in extreme abiotic stress due to its wide adaptability.

Catharanthus roseus is an apparent that various external agents and environmental conditions affect growth and secondary metabolites production. Most importantly, weather fluctuation, water availability and scarcity, salt and drought stress including several adverse soil conditions directly or indirectly influence the yield of alkaloids (Idrees *et al.,* 2017). This plant is a traditionally used medicinal plant in former days and is commonly known as different vernacular names in different parts of India (Fig. 3). Also, it is commonly recognized as bright eyes, cape periwinkle, graveyard plant, madagascar periwinkle, old maid, pink periwinkle, rose periwinkle, etc.

1.2. Traditional use

Pandey *et al.* (2020) reported that the *Catharanthus roseus* is famous as the plant of Ayurveda and these medicinal plants are used in the traditional medicine of India from many years. *Catharanthus roseus* also has a reputation as magic plant, the Germans called it the "flower of immortality", the Italians called it "the flower of death" and the French referred to it as "violet of the sorcerers" and "an emblem of friendship". European thought it could ward off evil spirits, it was also used to garland those awaiting execution, and laid on the biers of dead children (Senbagalakshmi *et al.,* 2017).

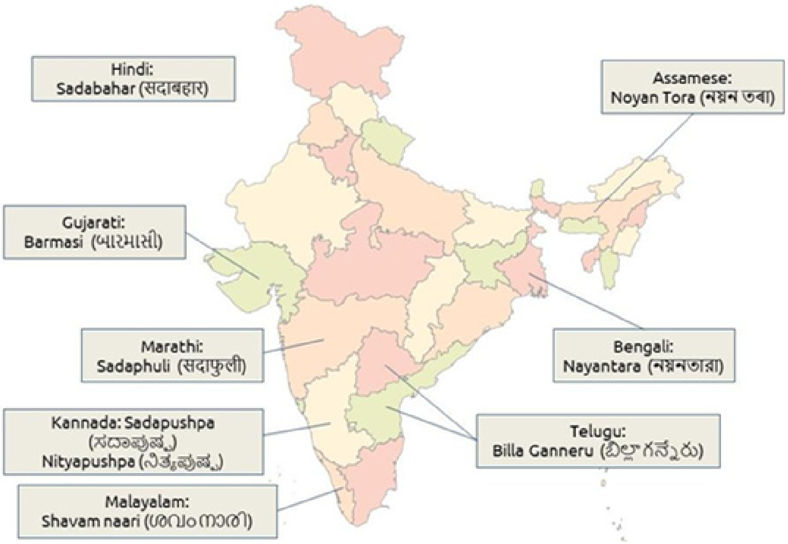

Fig. 3. Different names of *Catharanthus roseus* in India.

Rajesh *et al.* (1963) stated that *Catharanthus* alkaloids have been used in traditional medicine since ages for treating a variety of ailments. The unexpected discovery of antineoplastic property of *Catharanthus* alkaloids in the 1950s has had far reaching effects in clinical oncology and has paved the path for the discovery of a number of plant-derived anticancer drugs. Henceforth, *C. roseus* are the most popular plants such as long rhizomes and fibrous roots possessing of traditional healing properties (Taher *et al.,* 2019).

2. Phytochemistry

Aziz *et al.* (2016) explored the elemental composition of the leaves and flowers of *C. roseus* due to the plant's wide application in the indigenous medicinal system and importance of its chemical constituents. The presence of 13 important elements such as Na, K, Ca, Mg, Cr, Fe, Zn, Al, Cu, Ni, Pb, Cd and Mn was quantitative analyzed in both leaves and flowers of *C. roseus* employing the atomic absorption spectrophotometer. The leaves of *C. roseus* showed high concentration of all elements except K and Zn, while flowers of *C. roseus* showed higher concentration of K and Zn. The elemental composition in both leaves and flowers of *C. roseus* were found to be different. Consequently, different parts of this medicinal plant are enriched in some micro and macro nutrients such as Fe, Ca, Na, K and Zn that forms a very important for biological metabolic system as well as human health.

In roots of *C. roseus* plants, the catharanthine contents increased with the age in control and growth regulator treatments. The serpentine contents of the plant increased with plant growth regulators (PGR) treatments, but the increase was more prominent in paclobutrazol (PBZ) treatments when compared to other treatments (Jaleel *et al.,* 2009). *Catharanthus roseus* cell suspension cultures converted exogenously supplied curcumin to a series of glucosides. The glucoside yield was 2.5 mmol/g fresh weight of the cells at an optimal culture condition (Kaminagaa *et al.,* 2003).

Leaf biomass showed its highest proportion with high N, under elevated CO_2. Elevated CO_2 rather significantly increased starch, organic carbon, while it decreased soluble sugar in higher N supply. Therefore, plants grown with low level of N showed significant reduction in total foliar nitrogen due to CO_2 enrichment (Singh *et al.,* 2015).

Catharanthus roseus produces different alkaloids in different organs and tissues. Plants were maintained for two days at root-zone temperatures of 12 ºC, 25 ºC (control temperature), and 30 ºC; the alkaloid content of the roots and shoots of the plants was then analyzed, and the expression level of genes involved in alkaloid biosynthesis pathways was determined. In *C. roseus*, the lowest vinblastine content was detected in the leaves of plants with a root-zone temperature of 30 ºC. Incubation at a root-zone temperature of 12 ºC greatly enhanced the root ajmalicine content. In general, the expression of genes involved in alkaloid biosynthesis was highest in *C. roseus* plants with a root-zone temperature at 12 ºC. Genes involved in the nicotine pathway were more highly expressed in plants with a root-zone temperature of 12 ºC. Therefore, the root-zone temperature potentially was altered the biosynthesis and accumulation of alkaloids in plant tissues (Malik *et al.,* 2013).

Agrobacterium rhizogenes-mediated transformation of *C. roseus*, an important ornamental-medicinal plant that produces the powerful anticancer drug vincristine, was achieved by infecting stem and leaf explants with strain K599 harboring p35SGFPGUS^{+} plasmid. Leaf explants induced hairy roots at a higher frequency than stem explants when infected with the *Agrobacterium* strain. The molecular evidence of hygromycin phosphotransferase (HPTII), β-glucuronidase (GUS) and green fluorescent protein (GFP) genes integration was confirmed by PCR amplification. Consequently, the accumulation of alkaloids (i.e., vinblastine, vincristine and catharanthine) in the transgenic hairy root and also secreted in the liquid culture medium (Hanafy *et al.,* 2016).

The drought with $CaCl_2$-treated *C. roseus* plants showed an increase in total indole alkaloid content in shoots and roots when compared to drought stressed and well-watered plants (Jaleel *et al.,* 2007c). A huge local accumulation of strictosidine was scrutinized in attacked leaves that could repel caterpillars through its protein reticulation properties, newly developed leaves displayed an increased biosynthesis of the toxic strictosidine-derived MIAs, vindoline and catharanthine, produced by up-regulation of monoterpene indole alkaloids (MIAs) biosynthetic genes. Therefore, the leaf consumption caused in a rapid death of *Manduca sexta* caterpillars that could be linked to the MIA dimerization observed in intestinal tracts (Bernonville *et al.,* 2017).

Vázquez-Flota *et al.* (2004) analyzed the mechanical wounding on alkaloid metabolism in *C. roseus* seedlings. Wounding induced an increase in ajmalicine accumulation without affecting catharanthine. It could be helpful in mediating the wound-induced increase activities in alkaloid synthesis. Cell culture systems that are derived from CMCs may also provide a cost-effective and eco-friendly basis for the sustainable production of a number of important plant natural products such as superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), and lipoxygenase (LOX) (Elkahouia *et al.,* 2005; Moon *et al.,* 2015).

A dynamic metabolic model was investigated to understand the relationship between the potentials for the production of primary and secondary metabolites in the *C. roseus* (Fig. 4). Also, the carbohydrates accumulation is an important factor for the production potential (Cloutier *et al.*, 2007). The malate and alginate combining treatment stimulates defense responses in all *C. roseus* culture processes and this might mediate the indole alkaloid production via jasmonate pathway (Zhao *et al.*, 2001a, 2001b).

Fig. 4. Phytochemicals of *Catharanthus roseus* plants.

3. Characterization

Parthasarathy *et al.* (2019) isolated the endophytic fungi (*Curvularia verruculosa*) producing high yields of indole alkaloids such as vinblastine analogous to their host *C. roseus*. The extract was examined for vinblastine by TLC techniques showing the purple color spot co-migrated with authentic vinblastine and Rf was calculated by HPTLC (Vin 1 vinblastine – 0.75; authentic vinblastine-0.78), and these results confirmed vinblastine presence in the Vin1 extract. The extrac analyzed by HPLC revealed 182 µg/L vinblastine. Therefore, TLC purified fungal vinblastine was analyzed for the cytotoxicity effect on HeLa cell line and depicted a higher activity with IC50-8.5 µg/mL and forms the apoptotic morphological changes.

The HPLC method was used to detect the separation of 11 compounds consisting of eight TIAs (ajmalicine, serpentine, catharanthine, vindoline, vindolinine, vincristine, vinblastine, and anhydrovinblastine) and three related precursors i.e., tryptophan, tryptamine and loganin in different types of *C. roseus* samples to facilitate study of the TIA pathway and its regulation (Pan *et al.,* 2016). Lin *et al.*(2014) determined the main five alkaloids of *C. roseus* for trace samples using a high-performance liquid chromatography–electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS) analysis method.

Musetti and Favalib (2003) analyzed the potassium pyroantimonate (KPA) Ca2þ precipitation technique, X-ray microanalysis and Electron Energy Loss Spectroscopy carried out by transmission electron microscopy to check the Ca2þ distribution in *C. roseus* leaves infected with phytoplasmas belonging to different taxonomic groups, and in phytoplasma cells. The essential oils of essential oils of *C. roseus* obtained from the leaves and flowers was characterized by utilizing the gas chromatography-flame ionization detector (GC-FID) and GC-MS techniques (Lawal *et al.,* 2014).

Koel *et al.* (2020) extracted and identified the major constituents, namely, the indole alkaloids from the medicinal plant species*, C. roseus* when using different solvents in ultrasound-assisted processes by liquid chromatography in liquid separation methods. In *C. roseus*, the concentrations ranged from 60.2 – 329.9 and 114.8 – 659.7 $\mu g\ g^{-1}$ for catharanthine and vindoline respectively. Jeong *et al.* (2018) established an ultraperformance liquid chromatography-quadrupole time-of-flight (UPLC-Q-TOF) mass spectrometry method that allows sensitive, rapid, and reliable detection and identification of six representative indole alkaloids (vincristine, vinblastine, ajmalicine, catharanthine, serpentine, and vindoline) that exhibit physiological activity in *C. roseus*. The contents of bis-indole alkaloids (vincristine and vinblastine) were high in the aerial parts, while the contents of mono-indole alkaloids (ajmalicine, catharanthine, serpentine, and vindoline) were high in the roots. Hence, the UPLC-Q-TOF method could be useful for the investigation of phytochemical constituents of medicinal plants.

4. Chemical composition

Catharanthus roseus are the most popular plants such as long rhizomes and fibrous roots possessing of traditional healing properties. Chemical solvents are used for the extraction of bioactive compounds that might lead to environmental pollution. Long term exposure to the hazardous solvent waste from many industrial processes can lead to the harmful effect on respiratory, hematological and thyroid functioning. The water extraction method required a long time in order to complete the extraction process *C. roseus* produce several indole alkaloids known as *Vinca* alkaloids. This is widely used as antimitotic drugs in the treatment of cancer. This includes natural products such as vincristine and vinblastine are used as the anticancer agents clinically and their semisynthetic derivatives such as vindesine and vinorelbine (Taher *et al.,* 2019).

Catharanthus roseus plants produces many pharmaceutically important indole alkaloids, of which the bisindole alkaloids - vinblastine and vincristine are antineoplastic medicines and the monoindole alkaloids - ajmalicine and serpentine are antihypertension drugs. *Catharanthus roseus* cell cultures had studied for producing these medicines or precursors - catharanthine and vindoline without a commercially successful process due to biological and technological limitations (Zhao and Verpoorte, 2006).

Catharanthus roseus is an herbaceous subshrub producing the numerous indole alkaloids and phenolic compounds with an important therapeutic activity. So, two avonols trisaccharides of kaempferol and quercetin along with the syringetin was identified from the leaves of *C. roseus* (Bruna *et al.,* 1999). Two molecularly imprinted polymers (MIP) for catharanthine and vindoline was synthesized in order to specifically extract these natural indole alkaloids from *C. roseus* by solid-phase extraction (SPE) method (Lopez *et al.,* 2011).

The cultured cells of *C. roseus* were able to convert 2-, 3-, and 4-hydroxybenzyl alcohols into their corresponding hydroxybenzyl-d-glucopyranosides or -d-glucopyranosylbenzyl alcohols, and then convert 2- and 3-hydroxybenzyl-dglucopyranosides into primeverosides and vicianosides. Further, the *C. roseus* cells were capable of hydroxylation of 2-hydroxybenzoic acid to afford 2,5-dihydroxybenzoic acid and then glucosylation of the phenolic hydroxyl group (Shimoda *et al.,* 2002). Takemoto *et al.* (1995) synthesized the optically active α-phenylpyridyl methanols by reduction or hydrolysis with calcium alginate immobilized cells of *C. roseus*.

Cloning, characterization, and subcellular localization of an enzyme with a hydro vinblastine synthase activity identified as the major class III peroxidase present in *C. roseus* leaves and named CrPrx1 (Costa *et al.,* 2008). The deduced amino acid sequence corresponds to a polypeptide of 363 amino acids including an N-terminal signal peptide showed the secretory nature of CrPrx1. CrPrx1 has a two-intron structure and is present as a single gene copy.

Terpenoid indole alkaloids (TIA), graciously characterized in *C. roseus*, are a large group of about 2,000 naturally occurring compounds which are widely distributed amongst the members of the family Apocynaceae (van der Heijden *et al*., 2004). Molecules such as CNS suppressant reserpine, antihypertensive serpentine, vasodilatory yohimbine, antimalarial quinine, antiarrythmic ajmalicine and most importantly the anticancer vinblastine and vincristine that are being widely used as prescription drugs in the pharma sector belong to this group of plant alkaloids. Subsequently, TIA synthesis in *C. roseus* is strictly regulated at the level of pathway genes and enzymes that are differentially expressed at discrete inter- and intracellular locations under the influence of several developmental and ecophysiological and environmental signals (Verma *et al.,* 2011).

The occurrence of indole alkaloids in the chloroform leaf surface extracts was present in the cuticle at the leaf surface of *C. roseus* (Abouzeida *et al.,* 2019). The biosynthesis of vinblastine in *C. roseus* plants begins with the amino acid tryptophan and the monoterpenoid geraniol, and requires the involvement of at least 35 intermediates, 30 enzymes, 30 biosynthetic and 2 regulatory genes, as well as 7 intra and intercellular compartments (Zarate and Verpoorte, 2007).

Goodbody *et al.* (1987) evaluated that immobilized plant cells could potentially be used for the continuous production of certain commercially valuable secondary metabolites such as indole alkaloids - ajmalicine and serpentine. Addition of various concentrations (0.5-20 raM) of acetyl salicylic acid (ASA) to tumour lines of *C. roseus* cultivated *in vitro* and requiring corn starch as carbon source, produced remarkable effects on secondary metabolite production (Hernndez and Vargas, 1997).

Pereira *et al.* (2009) worked on the different parts of this species (leaves, stems, seeds and petals) was achieved, namely phenolics by HPLC-DAD and organic acids and amino acids by HPLC-UV. Also, the biological potentials are expressed as acetylcholinesterase inhibitory activity. In some parts, an acetylcholinesterase inhibitory capacity higher than 85% was found (IC_{50} at 422, 442 and 2683 lg/mL in leaves, stems and petals, respectively). *C. roseus* aqueous extract forms a rich source of phenolics, namely caffeoylquinic acids and flavonoids derivatives (up to 4127 mg/kg in stems, 4484 mg/kg in seeds, 8688 mg/kg in leaves and 41125 mg/kg in petals), organic acids (962, 6678, 25972 and 12463 mg/kg in seeds, petals, stems and leaves, respectively), such as citric acid (over 85% in some plant parts), and amino acids (31557, 39327, 50540 and 159697 mg/kg in stems, petals, seeds and leaves, respectively), of which arginine was a major compound.

Variations in alkaloid pattern during drying of leaves of *C. roseus* showed that treatment with methyl jasmonate can induce formation of bisindole alkaloids as a result of catabolism of the monomeric alkaloids catharanthine and vindoline (El-Sayeda and Verpoorte, 2005). Esyanti and Muspiah (2006) optimized the rate of aeration and initial weight of cell aggregates in the production of ajmalicine in *C. roseus* cell culture in airlift bioreactor.

Catharanthus roseus was used as a model medicinal plant to produce TIAs by suspension culture of the leaves in the phytohormone-free MS liquid medium (Iwase *et al.,* 2005). They developed the system for producing ajmalicine and serpentine using direct culture of leaves in *C. roseus* intact plant.

A 41 kDa glucosyltransferase was isolated from the cultured cells of *C. roseus*. The enzyme glucosylates regioselective 5-hydroxyl group of 2,5-dihydroxybenzoic acid (gentisic acid) by the transfer of glucose from UDP-glucose (UDPG) (Yamane *et al.,* 2002). The biotransformation of cinobufagin (1), into desacetylcinobufotalin (2), 3-epi-desacetylcinobufagin (3), 1-hydroxyl desacetylcinobufagin (4) and 3-epi-desacetylcinobufotalin (5) an animal-originated bufadienolide, by cell suspension cultures of *C. roseus* and *Platycodon grandiflorum* were examined (Ye *et al.,* 2003).

Geraniol 10-hydroxylase (G10H) is a P450 containing enzyme involved as first step in the biosynthesis of monoterpene indole alkaloids (MIAs), including the *C. roseus*-anticancer drugs vinblastine and vincristine (Canche *et al.,* 2005). *Catharanthus roseus* consists of both heteromeric and homomeric GPPS enzymes, that are the main contribution of only heteromeric GPPS with CrGPPS.SSU regulating the GPP flux for the biosynthesis of MIA (Raia *et al.,* 2013).

Strictosidine-D-glucosidase activity (SGD) activity was associated with a protein aggregate of a size of 650 kDa in *C. roseus* cells (Zárates *et al.,* 2001). In addition, 6-deoxocathasterone, a presumed biosynthetic intermediate in the late C6-oxidation pathway, was identified as an endogenous brassinosteroid in cultured cells of *C. roseus* (Fujiokaa *et al.,* 2000). Also, Tonk *et al.,* (2017) biosynthesized the secondary metabolites by starting with the plant metabolites with the end products of a complex process comprising the involvement of several enzymes, genes, regulatory genes and (transport through) intra- and intercellular compartments.

A connecting relationship was established between elicitor-induced oxidative burst and phenylalanine ammonia-lyase (PAL) activation in *C. roseus* suspension cells and suggested a sequence of signaling events from reactive oxygen intermediates (ROI) production to PAL activation and catharanthine synthesis (Xu *et al.,* 2005).

A *C. roseus* cell line was characterized for the accumulation of secologanin, tryptophan, tryptamine, strictosidine and ajmalicine that forms the pivotal activities of the enzymes such as geraniol 10-hydroxylase, tryptophan decarboxylase and strictosidine synthase (Contin *et al.,* 1998a, 1998b).

For the establishment of a secologanin transport mechanism, the biochemical and molecular pathways are involved in their biosynthesis that mobilizes this iridoid between different plant organs in *C. roseus* plants and also, that secologanin transport to the mutant across the graft union permits the formation of MIAs in leaves of the mutant (Kidd *et al.,* 2019). In addition to this, the foliar extracts of *C. roseus* are the unique source of vindoline and catharanthine, both are monomeric precursors of the commercial production of terpenoid indole alkaloid (Curenoa *et al.,* 2021).

The anticancerous alkaloids, viz. vinblastine and vincristine are mainly present in the leaves of *C. roseus* plants. High demand and low yield of these alkaloids in the plant has led to explore the alternative means for their production. Gamma irradiated sodium alginate (ISA) has proved as a plant growth promoting substance for various medicinal and agricultural crops. The application of ISA at 80 mg L^{-1} resulted in the maximum swell in the content and yield of vindoline, increasing them by 18.9 and 20.8% and by 81.8 and 87.2% at 120 and 150 days after planting (DAP) respectively (Naeem *et al.,* 2015). Furthermore, the cellular localization of tryptophan decarboxylase (TDC) and desacetoxyvindoline 4-hydroxylase (D4H) catalyzes the penultimate reactions of vindoline biosynthesis in developing seedlings. Thus, regulatory factors might respond to light to activate localized expression of the late stages of vindoline biosynthesis (Vaazquez-Flota *et al.,* 2000).

5-Phosphomevalonate kinase activity was partially purified from suspension cultured cells of *C. roseus*. The enzyme had an estimated Mr of 128,000 as determined by size-exclusion chromatography (Schulte *et al.,* 1999). Kinetic studies indicated that the mechanism of action was sequential with true Km values of 0.35 and 0.22 mM for 5-phosphomevalonate and ATP respectively. In addition to this, the enzyme was strongly inhibited by Hg^{+2} and Teepol. The reaction product analysis suggested the endo-nature of the purified enzyme. Consequently, the most conspicuous feature of *C. cellulase* is its ability to hydrolyze suspensions of crystalline and partially swollen cellulose, although at rates lower than CM-cellulose (Smriti and Sanwal, 1999).

The cytochrome P450 enzyme geraniol IO-hydroxylase plays an important role in the biosynthesis of TIAs in suspension cultures of *C. roseus*. Accordingly, the alkaloid accumulation increased after phenobarbital treatment whereas it decreased after ketoconazole treatment (Contin *et al.,* 1999). The activities of antioxidant enzymes viz. glutathione reductase (GR), superoxide dismutase (SOD), peroxidase (POD), catalase (CAT) and glutathione-S-transferase (GST) and alkaloid accumulation were investigated in leaf pairs (apical, middle, basal) and in roots of *C. roseus* seedlings under the conditions of different nitrogen sources (20 mM KNO_3 and 2 mM NH_4Cl) and salinity, in the absence (non-saline control) and in the presence of 100 mM NaCl in the nutrient solution. Higher peroxidase activity concomitant with the increased accumulation of alkaloid was found in all leaf pairs, as well as in roots of *C. roseus* of NO_3^- fed plants as compared to NH_4^+ fed plants (Misraa and Gupta, 2006).

Methyl jasmonate, a chemical inducer of secondary metabolism was established to promote the tabersonine biosynthesis in hairy root cultures of *C. roseus*. Tabersonine 6,7-epoxidase enzyme converts tabersonine to lochnericine by selective epoxidation at positions 6 and 7 via a reaction dependent on NADPH and molecular oxygen. This enzyme activity was found in microsomes indicating that tabersonine 6,7-epoxidase, a cytochrome P-450-dependent monooxygenase (Rodrigueza *et al.,* 2003). Henceforth, the development of a comprehensive flux analysis tool for the *C. roseus* plant hairy root system was projected to be valuable in evaluating the metabolic impact of genetic or environmental changes (Sriram *et al.,* 2007).

Geraniol 10-hydroxylase (G10H) is an important enzyme in the biosynthetic pathway of monoterpenoid alkaloids found in diverse plant species. The *C. roseus* G10H controls the first committed step in biosynthesis of TIAs. Hence, the G10H promoter contains unique binding sites for several transcription factors suggested that the G10H promoter may be regulated by a different transcriptional cascade (Suttipanta *et al.,* 2007).

NaCl-stressed plants showed increased TBARS, H_2O_2, glycine betaine (GB) and PRO contents, decreased proline oxidase (PROX) activity, and increased γ-glutamyl kinase (γ-GK) activity when compared to control. The antioxidant enzymes superoxide dismutase (SOD), peroxidase (POX) and catalase (CAT) were increased under salinity and further enhanced due to $CaCl_2$ treatment. Consequently, the NaCl-with-$CaCl_2$-treated *C. roseus* plants showed an increase in total indole alkaloid content in shoots and roots when compared to NaCl-treated and untreated plants (Jaleel *et al.,* 2007a, 2007b, 2007c, 2007d).

5. Phytochemistry

The phytoconstituents of *C. roseus* was used as antimicrobial, antioxidant, antifeedant, antisterilty and anticancer agents. It consists of 70 types of alkaloid contents where monoterpene indole alkaloids, vinblastine and vincristine were used for the treatment of leukemia in children, breast and lung cancer (Baskar *et al.,* 2016).

Mustafa and Verpoorte (2006) assessed the alkaloids from the *C. roseus* plants with producing a wide spectrum of phenolic compounds. This includes C6C1 compounds such as 2,3-dihydoxybenzoic acid, as well as phenylpropanoids such as cinnamic acid derivatives, flavonoids and anthocyanins. Therefore, the elucidation of the pathways and considering their regulation are imperative for metabolic engineering to expand the manufacture of desired metabolites.

The isolation and characterization of the 55-kDa hydroxylase enzyme from the cultured cells of *C. roseus* which played a key role in gentisate formation have become of interest that forms the ecofriendly with reference to a pollution control (Shimoda *et al.,* 2004). Also, the identification of an active site residue that impacts substrate selectivity produces a primary sequence identifier that might be helped to differentiate the indolic and phenolic substrate specificities of individual *C. roseus* plant aromatic amino acid decarboxylases (AAADs) (Spence *et al.,* 2014). Further, the biotransformation of cinobufagin by cell suspension cultures of *C. roseus* was investigated to obtain the four glycosylated derivatives such as desacetylcinobufagin 16-O--D-glucoside, 3-epi-desacetylcinobufagin 16-O--D-glucoside, 3-oxo-desacetylcinobufagin 16-O--D-glucoside, and cinobufagin 3-O--D-glucoside (Ye *et al.,* 2002).

Catharanthus roseus accumulates the high levels of the pentacyclic triterpene, ursolic acid, as a component of its wax exudate on the leaf surface (Yu *et al.,* 2013). Cloning and functional expression in yeast of a triterpene synthase derived from this tissue showed predominantly an a-amyrin synthase (CrAS). Furthermore, the studies revealed that the mesophyll, idioblasts, laticifers and vasculature of leaves using laser capture microdissection to harvest RNA from epidermis which showed the leaf epidermis to be the preferred sites of CrAS expression and provided decisive evidence for the involvement in the biosynthesis of ursolic acid in *C. roseus* (Yu *et al.,* 2013).

Catharanthus roseus was found to be a good accumulator of lead, nickel, zinc, cadmium and chromium. From the consolidation of the results obtained, the *C. roseus* species can be endorsed for the phytoextraction of lead, nickel, zinc, cadmium, and chromium contaminated soils. Henceforth, the phytoremediation is an environmental-friendly technology in which a plant's ability to remove contaminants for pollution prevention, control, and remediation from the environment (Subhashini and Swamy, 2017).

6. Biological applications

Apart from the fact that *C. roseus* was a weed, numerous studies have been carried out to identify the active molecules and possible biological activities. Different biomedical and pharmacological activities (Fig. 5) were tested for various extracts, fractions and isolated compounds from different parts of the *C. roseus* plants for analgesia, anthelmintics, asthma, arthritis, bacterial infections, cancer, convulsions, diabetes, diarrhoea, histamine allergy, inflammation, anti-pyretic, anti- oxidant, ulcer, cardio-protectivity, cytotoxicity, hepatoprotectivity, high fructose insulin resistance, hypoglycaemia, fibrinolysis, mosquitocidal, nerve, skeletal muscles activity, vasodilation and wound healing which were described below and also listed in table 1.

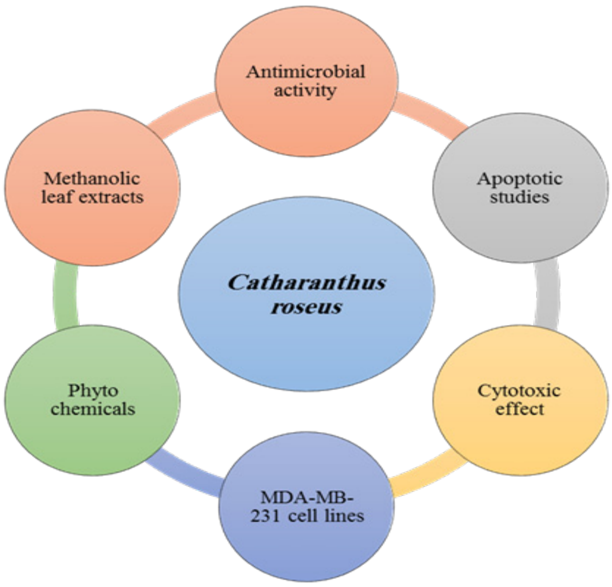

Fig. 5. Concepts of biological synthesis and characterization using the *Catharanthus roseus* methanolic leaf extracts.

Table 1. Several parts of *Catharanthus roseus* are used as plant extracts for the determination of biomedical and pharmacological activities.

Sl. No.	Pharmacological activities	Parts of the Calotropis gigantea plants
1	Analgesic activity	Latex
2	Anti-arthritic activity	Leaves
3	Anti-asthmatic activity	Flowers, Roots, Root barks
4	Anti-bacterial activity	Latex, Root, Stem, Root bark, Leaves and Flowers
5	Anti-cancer activity	Root barks and Flowers
6	Anti-convulsant activity	Stem barks
7	Anti-diabetic activity	Leaves, Flowers
8	Anti-diarrheal activity	Aerial parts, Powdered plant mixtures
9	Anti-fungal activity	Root barks and Latex
10	Anti-helminthic activity	Flowers, Flower infusion
11	Anti-histamine activity	Roots
12	Anti-histamine activity	Roots
13	Anti-inflammatory activity	Flowers and Aerial parts
14	Anti-oxidant activity	Leaves, Roots, Stems, Flowers and Whole plant
15	Anti-pyretic activity	Aerial parts
16	Anti-tumor activity	Flowers and Root barks
17	Anti-ulcer activity	Flowers and decoction
18	Cardioprotective studies	Roots
19	CNS activity	Peeled roots
20	Contraceptive activity	Fruit pulp and latex of the plant
21	Cytotoxic activity	Roots and Root barks
22	Hepatoprotective activity	Leaves, Flowers and Stems
23	Fibrinolytic activity	Latex
24	Mosquitocidal activity	Leaves
25	Nerve muscle activity	Latex
26	Skeletal muscle activity	Latex
27	Vasodilation activity	Latex
28	Wound healing activity	Latex, Latex ointment, Root barks

Karimi and Raofie (2019) explained the wide applications of plant products in the biomedical and pharmacological industries and their improvements in the properties of active pharmaceutical ingredients. The different parts of this medicinal plant are enriched in some micro and macro nutrients such as iron (Fe), calcium (Ca), sodium (Na), potassium (K) and zinc (Zn) that forms a very important for biological metabolic system as well as human health (Aziz *et al.,* 2016).

6.1. Antimicrobial activity

Catharanthus roseus is an important medicinal plant for pharmaceuticals since most of the bacterial pathogens are developing resistance against the currently existing antimicrobial drugs. The extracts from the leaves of these plants could be used as prophylactic agent in many of the epidemic diseases (Patil and Ghosh, 2010). The n-butanol fraction obtained from the *C. roseus* stem forms a rich source of bioactive compounds. This can be used for their potential applications as antimicrobial drugs or antitumor therapeutic agents (Pham *et al.,* 2018). Furthermore, the antimicrobial activity from ethanol leaf extract of *C. roseus* against some human pathogenic microorganisms (*S. aureus* and *E. coli*) along with pathogenic fungi (*Candida albicans*) (Khalil, 2012).

Good antibacterial action was scrutinized against three different organisms (*E. coli, B. subtilis* and *S. aureus*) of aqueous infusion of *C. roseus* (Syeda and Riazunnisa, 2020). Govindasamy and Srinivasan (2012) standardized the antibacterial activity and phytochemical analysis of *C. roseus* and made the screening of leaf, stem, flower and root extracts of the plants. Hence, the ethanolic extract of *C. roseus* can be used as potential antibacterial sources.

6.2. Antidiabetic activity

Nayak and Pereira (2006) used the *C. roseus* plants to treat a wide assortment of diseases including diabetes. *Catharanthus roseus* is an important evergreen medicinal herb used mainly for treatment of cancer and diabetics (Lahare *et al.,* 2020). Even then, it is a traditional antidiabetic herb widely used in many countries, and the alkaloids are considered to possess hypoglycaemic ability (Yao *et al.,* 2013; Goboza *et al.,* 2020). Aruna *et al.* (2015) used the infusion of the leaves to control haemorrhage and scurvy, as a mouthwash for toothache, and for the healing and cleaning of chronic wounds, to treat diabetic ulcer and oral hypoglycemic agent. Furthermore, Singh *et al.,* (2001) perceived the hypoglycemic activity in dichloromethane: Methanol extract (1:1) of leaves and twigs of *C. roseus* using streptozotocin (STZ) induced diabetic rat model.

6.3. Antioxidant activity

Peroxidase (POD) enzymes acted on guaiacol, 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), o-dianisidine, o-phenylenediamine (o-PD) and pyrogallol (Limam *et al.,* 1997). Jaleel *et al.,* (2006a, 2006b) considered the effects of triadimefon, a triazole compound on the antioxidant potentials and root alkaloid ajmalicine content in the two varieties, *rosea* and *alba* of *Catharanthus* genus.

6.4. Wound healing

Scientists evaluated the wound healing activity of the flower extract of *C. roseus* in rats. An increased wound contraction and tensile strength, improved hydroxyproline content along with antimicrobial activity reinforced the utilization of *C. roseus* in the topical management of wound healing (Nayak and Pereira, 2006).

6.5. Pharmacological activity

The roots, shoots and leaves of *C. roseus* plant extracts are being used against several diseases such as diarrhoea, alzheimer's disease, asthma, coughs, throat ailments, sore throat, prevention of dementia, water retention (edema), dysentery, rheumatism, flatulence, tuberculosis, dyspepsia, tonsillitis, chest pain, intestinal pain, toothache, insect's sting, for external use to tr eat skin problems like dermatitis, eczema and acne, swelling (anti- inflammatory), brain stimulatory actions, cardio tonic, CNS depressant, anti-angiogenesis effects, anti-feedant, anti-sterility, anti- malarial, also potent anti-microbial, anti-oxidant activity, possess anti-cancer, anti-diabetic, cytotoxic, high blood pressure, hypolipidemic activity, etc. (Senbagalakshmi *et al.,* 2017). Consequently, *C. roseus* is a potent medicinal plant known for its pharmacological actions such as antimicrobial, antioxidant, anthelmintic, antifeedant, antisterility, antidiarrheal, antidiabetic activities etc., used for the treatment of several fatal diseases (Gajalakshmi *et al.,* 2013; Rajashekara *et al.,* 2021).

Barrales-Cureño *et al.* (2017) exploited the diverse methods of *in vitro* cultures of the medicinal plant *C. roseus* and thus, primary and secondary plant metabolites are obtained from the suspension cell cultures of *C. roseus*, along with major pharmacological studies. *Catharanthus roseus* roots majorly constitute a promising source of compounds with pharmaceutical interest (Pereira *et al.,* 2010). In addition to this, the leaves of *C. roseus* constitute the only source of the well-known indolomonoterpenic alkaloids - vincristine and vinblastine.

6.6. Anticancer activity

Catharanthus roseus is an important medicinal plant that produces indole alkaloids used in cancer chemotherapy. The anticancerous alkaloids, viz. vinblastine and vincristine are mainly present in the leaves of *C. roseus*. High demand and low yield of these alkaloids in the plant has led to explore the alternative means for their production (Naeem *et al.,* 2015).

Cancer is a major disease around the world with high mortality rate and this may be due to internal and external factors. The presently available treatment methods for different cancers are chemotherapy, radiotherapy and surgery. The current treatment methods cause severe side effects to the patient, and more over the treatment cost is highly expensive. Medicinal plants could be the better alternative to cut down these barriers. The potent anticancer compounds are synthesized in shikimate, mevalonate and methyl-erythritol phosphate (MEP) pathways (Prabhu and Rajeswari, 2017).

A rapid, sensitive and reproducible method using ultra-high-performance liquid chromatography was corroborated for simultaneous quantitation of anticancer (vincristine, vinblastine, vindesine), antihypertensive (ajmaline, ajmalicine, reserpine), aphrodisiac (yohimbine), sedative (serpentine) agents, dietary supplement (vinpocetine, yohimbine) and precursor of vinblastine (vindoline) from the crude extracts of *C. roseus* (Kumar *et al.,* 2018).

Catharanthus roseus is a therapeutic plant producing indole alkaloids that mainly used in the cancer chemotherapy. It was the most commonly used model plant for the study of the biosynthetic pathways regarding indole alkaloids. The most important anticancer alkaloids of *C. roseus* are vincristine and vinblastine which are extracted commercially from large amount of leaf-biomass of *C. roseus* plants. Hence, there is a huge demand for enhancing the production of these medicinally important alkaloids taking into consideration their massive need global (Naeem *et al.,* 2017). Furthermore, the biosynthesis of the essential anticancer dimeric alkaloids, vincristine that was scarcely detected in the wild plant and vinblastine which exhibited a 3.39-fold increase compared to the wild plant (Mekky *et al.,* 2018).

Catharanthus roseus produces a variety of anticancerous compounds including the important antioxidant enzymes such as superoxide dismutase, catalase, ascorbate peroxidase and glutathione reductase and their activities had enriched level of alkaloids (Maqsood and Mujib, 2017).

Catharanthus roseus is an important dicotyledonous medicinal plant that produces anticancer compounds. The active alkaloids ajmalicine, catharanthine, vinblastine, vindoline and vinleurosine were recognized by direct-injection ion trap-mass spectrometry (IT-MS) (Chen *et al.,* 2013).

The genetic engineering and expression of the terminal step of vindoline biosynthesis was obtained in the presence of deacetylvindoline-4-O-acetyltransferase (DAT) in *C. roseus* hairy root cultures. *Catharanthus roseus* is a pantropical plant of horticultural value that produces the powerful anticancer drugs - vinblastine and vincristine that are derived from the dimerization of the monoterpene indole alkaloids (MIAs), vindoline and catharanthine (Magnotta *et al.,* 2007; Barrales-Cureño, 2015; Barkat *et al.,* 2017; Kaur *et al.,* 2017).

Catharanthus roseus is an important medicinal plant with rich sources of remarkable health benefits consisting more than 100 alkaloids and significant amounts of bioactive compounds. These compounds have been widely used as a folk medicine for treatment of several pathologies (Moon *et al.,* 2018).

6.7. Antileukemia activity

Catharanthus alkaloids were cytotoxic toward human leukemia cells to a greater extent than toward normal human endothelial cells, and the anti-proliferation and pro-apoptosis abilities of cathachunine were much more effective than other previously reported alkaloids. Thus, the induction of apoptosis by cathachunine occurred through an ROS-dependent mitochondria-mediated intrinsic pathway rather than an extrinsic pathway, and was regulated by the Bcl-2 protein family (Wanga *et al.,* 2016). This plant is valued for harboring more than 130 bioactive TIAs including the two of its leaf derived bisindole alkaloids - vinblastine and vincristine which are indispensable constituents of antineoplastic drugs used in metastatic malignancy associated with acute lymphoblastic leukaemia’s and Hodgkin’s/Non-Hodgkin’s lymphomas (Verma *et al.,* 2017). Hence, the study on plant metabolic engineering is gaining a lot of attention these days.

Catharanthus roseus is one of the renowned plants used in folk medicine for the treatment and management of many forms of diseases and infections (Ukoha *et al.,* 2017). The administration of the aqueous extract of *C. roseus* could trigger off hepatocellular damage and haematological disorder if taken in large doses. Therefore, the effects of the extract in the activities of hepatocellular enzymes and haematological indexes were found to be concentration dependent (Ukoha *et al.,* 2017).

The plant is a source of important primary and secondary metabolites that forms the biochemical and pharmacological compounds widely used in pharmacology. Vinblastine and vincristine are the important alkaloids as plant products employed in the treatment of leukemia. The techniques mostly used in the field of modern biotechnology such as the *in vitro* culture of callus and suspension cells, as well as those related to organs, roots, and seedlings (Barrales-Cureno *et al.,* 2017).

6.8. Antimitotic activity

Nowadays, some drugs were approved for the clinical use of target microtubules with the toxins and *Vinca* alkaloids showing much success against a variety of cancers. Drugs are the disturb mitotic progression are normally referred to as 'antimitotic' and are used extensively for the treatment of cancer (Alam *et al.,* 2017). *Catharanthus roseus* are the most popular plants such as long rhizomes and fibrous roots possessing of traditional healing properties. These plants produce several indole alkaloids known as Vinka alkaloids, and widely used as antimitotic drugs in the treatment of cancer. This includes natural products such as vincristine and vinblastine are used as the anticancer agents clinically and their semisynthetic derivatives (Taher *et al.,* 2019).

Catharanthus roseus consists of a range of dimeric indole alkaloids with significant antitumor activities (Wanga *et al.,* 2016). *Catharanthus* alkaloids were cytotoxic toward human leukemia cells to a greater extent than the normal human endothelial cells, and the anti- proliferation and pro-apoptosis abilities of cathachunine were much more potent than other alkaloids. Thus, the induction of apoptosis by cathachunine occurred through an ROS-dependent mitochondria-mediated intrinsic pathway rather than an extrinsic pathway, and was regulated by the Bcl-2 protein family.

Even though *C. roseus* is highly valued for its diversity of more than 130 MIAs, the only source for the low-abundance antitumor agents is vinblastine and vincristine and they form an extensively as a model for medicinal plants improvement (Tang and Pan, 2017). Nejat *et al.* (2015) described that *C. roseus* is a fabulous medicinal plant mostly because of possessing two invaluable antitumor TIAs, vincristine and vinblastine. Also, the plant has high aesthetic value as an evergreen that yields prolific blooms of splendid colors. TIAs are present only in micro quantities in the plant and are highly poisonous *per se* rendering a challenge for researchers to increase yield and reduce toxicity.

Vinca alkaloids (VAs) obtained from the *C. roseus* and employed in clinical purposes owing to their antitumor effects. Analysis of structure-toxicity relationships indicated that acylamide at C3 position and hydroxyl at C4 position contributed to their more toxicity. A long conjugation effect appearing in VAs could increase the toxicity when the N1 position was substituted with formyl group (Wang *et al.,* 2016).

6.9. Analgesic activity

Cytochrome P450 enzyme was induced by the treatment of cells with phenobarbital, and inhibited by treatment with ketoconazole. The activity of this enzyme was induced by the treatment of cells with phenobarbital and inhibited by the treatment with ketoconazole. Thus, the alkaloid accumulation increased after phenobarbital treatment whereas it decreased after ketoconazole treatment (Contin *et al.,* 1999).

6.10. Circulatory disorder

Catharanthus roseus hairy roots showed that the biomass growth of 5.12 ± 0.46 g/l and ajmalicine content of 24.9 ± 1.2 mg/l on 30th day. A 60% increase in ajmalicine overall productivity and a 2.5 fold increase in volumetric yield was obtained by the "increasing feed rate strategy". The alkaloid accumulation a combination of statistically optimized mixture of elicitor was added that resulted in a significantly high ajmalicine concentration of 123.2 ± 8.63 mg/l (Thakore *et al.,* 2015). Hence, *C. roseus* shown to produce the ajmalicine and mainly used for the treatment of circulatory disorders (Thakore *et al.,* 2016).

6.11. Chemotherapeutic drugs and therapy

Catharanthus roseus is a major source of the monoterpene indole alkaloids (MIAs) and are of significant interest due to their therapeutic value (Krithika *et al.,* 2014). These molecules are formed through an intermediate, cis-trans-nepetalactol, a cyclized product of 10-oxogeranial. One of the key enzymes involved in the biosynthesis of MIAs is an NAD(P)1 dependent oxidoreductase system, 10-hydroxygeraniol dehydrogenase (Cr10HGO) that catalyzed the formation of 10-oxogeranial from 10-hydroxygeraniol via 10-oxogeraniol or 10-hydroxygeranial.

Rosy periwinkle is an important medicinal plant and forms the major source of several widely marketed chemotherapeutic drugs. It is also commonly grown for its ornamental values and, due to ease of infection and distinctiveness of symptoms. It is often used as the host for studies on phytoplasmas, an important group of uncultivated plant pathogens (Chua *et al.,* 2013). Blom *et al.,* (1991) isolated the vacuoles from ajmalicine-producing cell suspensions of *C. roseus* accumulated the alkaloid ajmalicine. Overindulgence of the trans tonoplast pH gradient with nigericin abolished ajmalicine accumulation, whereas indulgence of the trans tonoplast potential with valinomycin had no effect.

Madagascar periwinkle is highly specialized for the biosynthesis of many different MIAs with powerful biological activities. Such MIAs include the commercially important chemotherapy drugs vinblastine, vincristine and other synthetic derivatives that are derived from the coupling of catharanthine and vindoline (Yu and Luca, 2013). Hence, the phylogenetic analysis showed that CrTPT2 was closely related to a key transporter involved in cuticle assembly in plants and was MIA-producing plant species, where it mediated the secretion of alkaloids to the plant surface.

"The periwinkle is a great binder" said an old herbalist, and thus, it was considered a good remedy for cramp (Senbagalakshmi *et al.,* 2017). *Catharantus roseus* consists of many pharmacological effects. Hence, the plant (roots, shoots and leaves) extracts are being used against several diseases such as diarrhoea, alzheimer's disease, asthma, coughs, throat ailments, sore throat, prevention of dementia, water retention (edema), dysentery, rheumatism, flatulence, tuberculosis, dyspepsia, tonsillitis, chest pain, intestinal pain, toothache, insect's sting, for external use to treat skin problems like dermatitis, eczema and acne, swelling (anti- inflammatory), brain stimulatory actions, cardio tonic, CNS depressant, anti-angiogenesis effects, anti-feedant, anti-sterility, anti-malarial, also potent anti-microbial, anti-oxidant activity, possess anti-cancer, anti-diabetic, cytotoxic, high blood pressure, hypolipidemic activity etc. (Senbagalakshmi *et al.,* 2017). Accordingly, *C. roseus* also had a reputation as magic plant, the Germans called it the "flower of immortality", the Italians called it "the flower of death" and the French referred to it as "violet of the sorcerers" and "an emblem of friendship".

6.12. Production of nanoparticles and nanoproducts for therapeutical uses

Nanotechnology is one of the best tools of this decisive period where antibiotics lose their credibility against several bacterial and fungal species (Ahmad *et al.,* 2019; Rajashekara *et al.,* 2020).

Gupta *et al.* (2018) synthesized the zinc oxide nanoparticles (ZnO NPs) using leaf extract of *C. roseus* under different physical parameters. An elucidation of results demonstrated that it is a rapid, cost-effective, environmentally friendly and convenient method for ZnO NPs synthesis, that could be used as a potential antimicrobial agent against drug resistant microbes.

Ponarulselvam *et al.* (2012) developed a method for the green synthesis of silver nanoparticles using aqueous leaves extracts of *C. roseus* and found active against malaria parasite *Plasmodium falciparum*. Also, several plant extracts were synthesizing the metal nanoparticles to eradicate the substances from toxic to insect pests and vectors. Prabhu and Rajeswari (2017) explained that cancer is a major disease around the world with high mortality rate. This could be opening doors to a new era in the development of nanotechnology-based drugs from the *C. roseus* plants. The green carbon quantum dot (CQD) derived from *C. roseus* plant leaves exhibited great promise as sensing probe for the cancer diagnosis and treatment and also multi-ions in the field of environmental water analysis (Arumugham *et al.,* 2020).

CONCLUSIONS

The cavernous literature review reflects the gap in profiling of pure compounds obtained from the *C. roseus* plants in authentication with the traditional information. The factors such as geographical variation play a significant role in the validation of the chemical ingredients responsible for the activity which also can be an area of interest. Some of the studies inter-relate with other studies which can give a clear picture in relating the mechanical pathways useful for defining a disease in-specific. However, the review may have the draw back in regard of methodical data verification collected from journals other than English.

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