UP-TO-DATE REVIEW ON THERAPEUTIC INTERIOR OF CATHARANTHUS ROSEUS; FOR ANTICANCER AND ANTIDIABETIC ACTIVITIES

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ABSTRACT

Catharanthus roseus comprise a group of alkaloids mainly vincristine, vinblastine, resperine, ajmalicine. Here we review the recent advances in the biosynthetic pathway of terpenoid indole alkaloids (TIAs) in C. roseus, and the identification and characterization of the corresponding enzymes involved in this pathway. Vincristine and vinblastine are used for treatment of various type of cancer such as Hodgkin’s disease, breast cancer, leukemia etc. Madagascar periwinkle is poisonous if ingested or smoked. The pharmacognostical aspects of catharanthus roseus alkaloid cover botanical, phytochemical and analytical data. It has high medicinal value which needs to be explored extensively.

KEYWORD: Catharanthus roseus, Vinblastine, Vincristine, Anticancer, Antidiabetic.

INTRODUCTION

India is a country known for ancient scripts the number system and invention of zero and Vedas. Medicines in India are used by about 60 percent of world’s population. With the scripts in the Atharva Veda, we have evidence of a traditional use of medicinal plants that is more than 3000 years old. It is estimated that about 80,000 species plants are utilized in some forms other by the different system of India medicine. The corroborative and tonic plant generally known as the rasayana drugs in ayurveda are known to prevent ageing, increase longevity and offer resistance to disease by augmenting the immune system.[1] World health organization (WHO) have been prepared a list of 21000 medicinal important plant one such plant is Catharanthus roseus (L) It belongs to family Apocynaceae and a rich source of alkaloid. These are used for various purposes such as pharmaceuticals, food additives and dyes.

CATHARNTHUS is a genus of flowering plants in the dogbane family, Apocynaceae like genus vinca, they are commonly known as periwinkles [2] there are eight known species, and seven are endemic to Madagascar [3] Though one, CATHARANTHUS ROSEUS is widely naturalized around the world.[4] Name CATHARANTHUS comes from the Greek word “Pure flower”[5]

Botanical Description

i. Height: It is an herbaceous plant growing 1m long[6]
ii. Leaves: The leaves are oval to oblong 2.5 -9cm. broad, glossy green hairless with a pale midrib and a short petiols 1-1.8cm long [7]
iii. Flower: The flowers are white to dark pink with a darker red centre[8]
iv. Fruit: The fruit is a pair of follicles 2-4cm. longand 2mm. broad [9]

Plant Introduction
Plant Use - There are following use of c. roses:

i. Used as medicine: In Ayurveda the extracts of its roots and shoots, is used against several disease including Diabetis, Malaria etc.[7]

ii. Used as anticancer: The substance vinblastine and vincristine extracted from the plant are used in treatment of leukemia, Hodgkin’s lymphoma.[9]

iii. In plant pathology: C. roseus is used in plant pathology as an experimental host for phytoplasmas.[11] 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 significant reduced leaf size[12]

Table 1: Different Alkaloid Produced By C.roseu

<table>
<thead>
<tr>
<th>PRODUCED BY</th>
<th>ALKALOID</th>
<th>PROPERTIES</th>
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<tbody>
<tr>
<td>ROOT</td>
<td>Ajmalicine</td>
<td>Cardio-vascular disease and high blood pressure</td>
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<td></td>
<td>Catharanthine</td>
<td>Anti-Diabetic properties</td>
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<td></td>
<td>Raubasin</td>
<td>Pain relieving properties</td>
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<td>Reserpine</td>
<td>Tranquilizers</td>
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<td>Serpentine</td>
<td>Cardio-vascular disease and high blood pressure</td>
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<td>AERIAL PART LIKE LEAVES</td>
<td>Vinblastine</td>
<td>Anti-Tumour properties</td>
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<td></td>
<td>Vincristine</td>
<td>Anti-Tumour properties</td>
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<td></td>
<td>Vindoline</td>
<td>Anti-Tumour properties</td>
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Figure 3: General properties of C. Roseus
CULTIVATION

Culture
Madagascar periwinkle does best in poor, well-drained soils. Flowering will suffer if soils are too fertile. Pinch back early in the season to encourage branching and a fuller plant. Madagascar periwinkle doesn’t need deadheading - the flowers drop off when they finish blooming.

Light Full sun or partial shade

Moisture Madagascar periwinkle should be watered moderately during the growing season, but it is relatively drought resistant once established. In fact, it is unusually drought resistant for an annual. Madagascar periwinkle is not at all tolerant of overwatering

Hardiness USDA Zones 9-11. Non-stop summertime flowers and heat resistance make this rugged plant a good choice to grow as an annual in cooler Zones.

Propagation Madagascar periwinkle is usually grown from seed, but also can be rooted from cuttings taken in spring or summer. It will reseed itself if the soil is loose.[13]

WARNING
Madagascar periwinkle is poisonous if ingested or smoked. It has caused poisoning in grazing animals. Even under a doctor's supervision for cancer treatment, products from Madagascar periwinkle produce undesirable side effects.[13]

Phytochemical and Biochemical Properties

Catharanthus roseus is one of the most extensively investigated medicinal plants, which can produce more than 130 alkaloids, including the powerful antitumor drugs vinblastine and vincristine. Here we review the recent advances in the biosynthetic pathway of terpenoid indole alkaloids (TIAs) in C. roseus, and the identification and characterization of the corresponding enzymes involved in this pathway. Strictosidine is the central intermediate in the biosynthesis of different TIAs, which is formed by the condensation of secologanin and tryptamine. Secologanin is derived from terpenoid (isoprenoid) biosynthetic pathway, while tryptamine is derived from indole biosynthetic pathway. Then various specific end products are produced by different routes during downstream process. Although many genes and corresponding enzymes have been characterized in this pathway, our knowledge on the whole TIA biosynthetic pathway still remains largely unknown up to date. Full elucidation of TIA biosynthetic pathway is an important prerequisite to understand the regulation of the TIA biosynthesis in the medicinal plant and to produce valuable TIAs by synthetic biological technology [14]

The Madagascar periwinkle produces a large palette of Monoterpenoid Indole Alkaloids (MIAs), a class of complex alkaloids including some of the most valuable plant natural products with precious therapeutically values. Evolutionary pressure on one of the hotspots of biodiversity has obviously turned this endemic Malagasy plant into an innovative alkaloid engine. Catharanthus is a unique taxon producing vinblastine and vincristine, heterodimeric MIAs with complex stereochemistry, and also manufactures more than 100 different MIAs, some shared with the Apocynaceae, Loganiaceae and Rubiaceae members. For over 60 years, the quest for these powerful anticancer drugs has inspired biologists, chemists, and pharmacists to unravel the chemistry, biochemistry, therapeutic activity, cell and molecular biology of Catharanthus roseus. Recently, the "omics" technologies have fuelled rapid progress in deciphering the last secret of
strictosidine biosynthesis, the central precursor opening biosynthetic routes to several thousand MIA compounds. Dedicated *C. roseus* transcriptome, proteome and metabolome databases, comprising organ-, tissue- and cell-specific libraries, and other phylogenetomics resources, were developed for instance by PhytoMetaSyn, Medicinal Plant Genomic Resources and SmartCell consortium. Tissue specific library screening, orthology comparison in species with or without MIA-biochemical engines, clustering of gene expression profiles together with various functional validation strategies, largely contributed to enrich the toolbox for plant synthetic biology and metabolic engineering of MIA biosynthesis.[15]

Environmental pressures forced plants to diversify specialized metabolisms to accumulate noxious molecules such as alkaloids constituting one of the largest classes of defense metabolites. *Catharanthus roseus* produces monoterpenoid indole alkaloids via a highly elaborated biosynthetic pathway whose characterization greatly progressed with the recent expansion of transcriptomic resources. The complex architecture of this pathway, sequentially distributed in at least four cell types and further compartmentalized into several organelles, involves partially identified inter-cellular and intra-cellular translocation events acting as potential key-regulators of metabolic fluxes. The description of this spatial organization and the inherent secretion and sequestration of metabolites not only provide new insight into alkaloid cell biology and its involvement in plant defense processes but also present new biotechnological challenges for synthetic biology [16]. Monoterpenoid indole alkaloids (MIAs) encompass plant natural products with important pharmacological relevance. They include the anti-tumoral MIAs found in *Catharanthus roseus* and *Camptotheca acuminata*. The often low yields of bioactive alkaloids in plants has prompted research to identify the factors regulating MIA production. Oxidative stress is a general response associated with biotic and abiotic stresses leading to several secondary responses, including elicitation of MIA production. These changes in secondary metabolism may take place directly or via second messengers, such as Ca(2+) and reactive oxygen species (ROS). H2O2 is the main ROS that participates in MIA biosynthesis. This review analyzes the links between oxidative stress, elicitation of bioactive MIA production and their potential roles in antioxidative defense, as well as exploring the implications to developing biotechnological strategies relevant for alkaloid supply.[17] This review looks back on the terpenoid indole alkaloid pathway and the regulatory factors in *Catharanthus roseus* were identified and characterized, and how metabolic engineering, including genetic engineering and metabolite profiling, was conducted based on the gained knowledge. In addition, further examination of the terpenoid indole alkaloid pathway is proposed.[18]

*Catharanthus roseus* (The Madagaskar Periwinkle) plant is commercially valued for harbouring more than 130 bioactive terpenoid indole alkaloids (TIAs). Amongst these, two of the leaf-derived bisindole indolaloaloids-vinblastine and vincristine-are widely used in several anticancer chemotherapies. The great pharmacological values, low in planta occurrence, unavailability of synthetic substitutes and exorbitant market cost of these alkaloids have prompted scientists to understand the basic architecture and regulation of biosynthesis of these MIAs in *C. roseus* plant and its cultured tissues. The knowledge gathered over a period of 30 years suggests that the TIA biosynthesis is highly regulated by developmental and environmental factors and operates through a complex multi-step enzymatic network. Extensive spatial and temporal cross talking also occurs at inter- and intracellular levels in different plant organs during TIA biogenesis. A close association of indole, methylyethyrythiol phosphate and secoiridoid monoterpenoid pathways and involvement of at least four cell types (epidermis, internal phloem-associated parenchyma, laticifers and idioblasts) and five intracellular compartments (chloroplast, vacuole, nucleus, endoplasm reticulum and cytosol) have prompted scienists to understand the basic biosynthesis of TIA. Accordingly, the research in this area is primarily advancing today to address six major issues namely: precise localization and expression of pathway enzymes using modified in situ RNA hybridization tools, mechanisms of intra- and intercellular trafficking of pathway intermediates, cloning and functional validation of genes coding for known or hitherto unknown pathway enzymes, mechanism of global regulation of the pathway by transcription factors, control of relative diversion of metabolite flux at crucial branch points and finally, strategising the metabolic engineering approaches to improve the productivity of the desired MIAs in plant or corresponding cultured tissues. The present literature update has been compiled to provide a brief overview of some of the emerging developments in our current understanding of TIA metabolism in *C. roseus* [19].

In plants, organ formation and cell elongation require the constant adjustment of the dynamic and adaptable cell wall in response to environmental cues as well as internal regulators, such as light, mechanical stresses, pathogen attacks, phytohormones, and other signaling molecules. The molecular mechanisms that perceive these cues and translate them into cellular responses to maintain integrity and remodelling of the carbohydrate-rich cell wall for the coordination of cell growth are still poorly understood. In the last 3 years, the function of six membrane-localized receptor-like kinases (RLKs) belonging to the CrRLK1L family has been linked to the control of cell elongation in vegetative and reproductive development. Moreover, the presence of putative carbohydrate-binding domains in the extracellular domains of these CrRLK1Ls makes this receptor family an excellent candidate for coordinating cell growth, cell-cell communication, and constant cell wall remodeling during the plant life cycle [20]. The roll of receptor like kinases in regulating cell wall function.[21]

The Madagascar periwinkle is a plant species known for its production of TIAs (terpenoid indole alkaloids), many of which are pharmacologically important. Ajmalicine and serpentine are prescribed for the treatment of hypertension, whereas the bisindoles vinblastine, vincristine and 3',4'-anhydrovinblastine are used for their antineoplastic activity in the treatment of many cancers. However, TIAs are produced in small yields in *C. roseus*, which makes them expensive. Cell and metabolic engineering has focused on increasing flux through the TIA pathway by various means, including optimization of medium composition, elicitation, construction of model culture systems and introduction of genes encoding specific metabolic enzymes into the *C. roseus* genome. The present review will attempt to present the state-of-the-art of research in this area and provide an
Brassinosteroids represent a class of plant hormones. More than 70 compounds have been isolated from plants. Currently 42 brassinosteroid metabolites and their conjugates are known. This review describes the miscellaneous metabolic pathways of brassinosteroids in plants. There are some types of metabolic processes involving brassinosteroids in plants: dehydrogenation, demethylation, epimerization, esterification, glycosylation, hydroxylation, side-chain cleavage and sulfonation. Metabolism of brassinosteroids can be divided into two categories: i) structural changes to the steroidal skeleton; and ii) structural changes to the side-chain.[23]

Monoterpenic indole alkaloids (MIAs) are a large class of plant alkaloids with significant pharmacological interest. The sustained production of MIAs at high yields is an important goal in biotechnology. Intensive effort has been expended toward the isolation, cloning, characterization and transgenic modulation of genes involved in MIA biosynthesis and in the control of the expression of these biosynthesis-related genes. At the same time, considerable progress has been made in the detailed description of the subcellular-, cellular-, tissue- and organ-specific expressions of portions of the biosynthetic pathways leading to the production of MIAs, revealing a complex picture of the transport of biosynthetic intermediates among membrane compartments, cells and tissues. The identification of the particular environmental and ontogenetic requirements for maximum alkaloid yield in MIA-producing plants has been useful in improving the supply of bioactive molecules. The search for new bioactive MIAs, particularly in tropical and subtropical regions, is continuously increasing the arsenal for therapeutic, industrially and agriculturally useful molecules. In this review we focus on recent progress in the production of MIAs in transgenic cell cultures and organs (with emphasis on Catharanthus roseus and Rauvolfia serpentina alkaloids), advances in the understanding of in planta spatial-temporal expression of MIA metabolic pathways, and on the identification of factors capable of modulating bioactive alkaloid accumulation in nontransgenic differentiated cultures and plants (with emphasis on new MIAs from Psychotria species). The combined use of metabolic engineering and physiological modulation in transgenic and wild-type plants, although not fully exploited to date, is likely to provide the sustainable and rational supply of bioactive MIAs needed or human wellbeing [24]. Advances in the study on critical steps in the biosynthesis pathway of Catharanthus alkaloids and the regulation of their metabolism [25] studies on the biosynthesis of sterol side chain in higher plants. Campesterol [3] and dihydrobrassicasterol [4] typical C28-sterols in higher plants, are biosynthesized from a steroidal 24-ene precursor (desmosterol 1) via 24-methylenecholesterol [2] and 24-methyldesmosterol [5] A typical plant C29-sterol, sitosterol [6] is produced from 24-methylenecholesterol via isofucosterol [7] and 24-ethyl desmosterol [8]. The biosynthetic mechanism, focusing stereochemical features of these side-chain transformations has been studied in detail by feeding region and stereoselectively 13C- or 2H-labeled steroidal substrates to cell cultures of higher plants such as Oryza sativa, Catharanthus roseus and Morus alba. These studies allowed correlating the metabolic origin of C-26 and C-27 of the intermediate sterols. It has been established that the 1st methylation leading to 24-methylenecholesterol from desmosterol involves a Re-face hydrogen migration from C-24 to C-25 based on unambiguous assignment of the isopropyl pro-R-Me and pro-S-Me of 24-methylenecholesterol. The 2nd methylation leading to isofucosterol was revealed to proceed in a trans-mechanism in which addition of the methyl group and elimination of the C-28 hydrogen occur on opposite faces of the original delta 24(28) plane. The double bond isomerization from delta 24(28) to delta 24(25) was found to proceed in a syn-SE2' mechanism with the pro-S-methyl group of isofucosterol becoming the (E)-methyl of 24-ethyl desmosterol. Finally, feeding studies of [E-Me-13C]- and [Z-Me-13C]-24-methyl des mosterols established that an anti-mode of hydrogen addition is operating in the conversion of 24-methyl desmosterol to campesterol and dihydrobrassicasterol. Similar studies established that 24-ethyl desmosterol is converted to sitosterol in an anti-mode of hydrogen addition. In addition, the mechanism of sterol side-chain formation in hairy root cultures of Ajuga reptans var. atropurpurea is briefly described [26]. Alkaloid accumulation in Catharanthus roseus suspension cultures [27]

A significant amount of research has contributed to characterization of several individual steps in the biosynthetic pathway of medicinally valuable alkaloids. However, knowledge of the regulation of these pathways is still sparse. Using hairy root cultures, we studied the responses of alkaloid metabolism to environmental stimulation such as light and elicitation. Through precursor feeding studies, the putative rate-limiting steps of the terpenoid pathway in hairy root cultures also have been examined. Relating this knowledge to specific events at the molecular level, and the cloning of corresponding genes are the next key steps in metabolic engineering of the C. roseus alkaloids. [28] Biosynthesis of steroidal plant hormones, brassinosteroids, was studied using the cell culture system of Catharanthus roseus. Feeding labeled compounds of possible intermediates to the cultured cells, followed by analyzing the metabolites by gas chromatography-mass spectrometry disclosed the pathways from a plant sterol, campesterol, to brassinolide. There are two pathways, named the early C6-oxidation pathway and late C6-oxidation pathway, both of which would be operating in a wide variety of plants. Recent findings of brassinosteroid-deficient mutants of Arabidopsis and the garden pea by several groups, and the possible blocked steps of the mutants in the biosynthetic pathways are also introduced [29].

Indole alkaloids in Catharanthus roseus have been in focus because of their medicinal value. These alkaloids consist of an indole moiety provided by tryptamine and a terpenoid portion provided by the secoaglanin. The most important catharanthus alkaloids are vinblastine (VLB), vincristine (VCR) and ajmalicine. VLB and VCR are clinically useful anticancer agents whereas ajmalicine is used for the
treatment of circulatory diseases. VCR and VLB are the most expensive because of their low abundance in the plant, and are formed by the coupling of monomeric indole alkaloids vindoline and catharanthine, catalysed by peroxidases. The pathway that lead to monomeric indole alkaloids involves more than 20 enzymes of which 16 enzymes have been isolated and characterized biochemically, and only three at the molecular level. The present state of knowledge on enzymes and genes involved in indole alkaloid biosynthesis and various aspects of their regulation has been discussed.[30] Alkaloids of *Catharanthus roseus* G. Don. new group of biologically active compound [31]

**Clinical and Pharmacological Properties**

*Catharanthus roseus* is a medicinal plant belonging to the family Apocynaceae which produces terpenoid indole alkaloids (TIA)s of high medicinal importance. Indeed, a number of activities like antidiabetic, bactericide and antihypertensive are linked to *C. roseus*. Nevertheless, the high added value of this plant is based on its enormous pharmaceutical interest, producing more than 130 TIA,s some of which exhibit strong pharmacological activities. The most striking biological activity investigated has been the antitumour effect of dimeric alkaloids such as anhydrovinblastine, vinblastine and vincristine which are already in pre-, clinical or in use. The great pharmacological importance of these indole alkaloids, contrasts with the small amounts of them found in this plant, making their extraction a very expensive process. To overcome this problem, researches have looked for alternative sources and strategies to produce them in higher amounts. In this sense, intensive research on the biosynthesis of TIA,s and the regulation of their pathways has been developed with the aim to increase by biotechnological approaches, the production of these high added value compounds. This review is focused on the different strategies which improve TIA production, and in the analysis of the beneficial effects that these compounds exert on human health.[32]

*Catharanthus roseus* (L.) known as Madagascar periwinkle (MP) is a legendary medicinal plant mostly because of possessing two invaluable antitumor terpenoid indole alkaloids (TIA)s, vincristine and vinblastine. The plant has also high aesthetic value as an evergreen ornamental that yields prolific blooms of splendid colors. The plant possesses yet another unique characteristic as an amiable experimental host for the maintenance of the smallest bacteria found on earth, the phytoplasmas and spirioplasmas, and serves as a model for their study. Botanical information with respect to synonyms, vernacular names, cultivars, floral morphology, and reproduction adds to understanding of the plant while the geography and ecology of periwinkle illustrate the organism's ubiquity. Good agronomic practices ensure generous propagation of healthy plants that serve as a source of bioactive compounds and multitidinous horticultural applications. The correlation between genetic diversity, variants, and TIA production exists. MP is afflicted with a whole range of diseases that have to be properly managed. The ethnobotanical significance of MP is exemplified by its international usage as a traditional remedy for abundant ailments and not only for cancer. TIA,s 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 [33]

Vinca alkaloids Vinca alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant. They are naturally extracted from the pink periwinkle plant, *Catharanthus roseus* G. Don and have a hypoglycemic as well as cytotoxic effects. They have been used to treat diabetes, high blood pressure and have been used as disinfectants. The vinca alkaloids are also important for being cancer fighters. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VCR, VBL and VRL have been approved for use in the United States. Vinflunine is also a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium being developed for other malignancies. Vinca alkaloids are the second-most-used class of cancer drugs and will stay among the original cancer therapies. Different researches and studies for new vinca alkaloid applications will be carried out in this regard [34]

An exploration of the potential mechanisms and translational potential of five medicinal plants for applications in Alzheimer's disease (AD) is the most common type of dementia, and represents a vast worldwide socio-economic burden, and in the absence of a current cure, effective therapeutic strategies are still needed. Cholinergic and cerebral blood flow deficits, excessive levels of oxidative stress, neuroinflammation and glutamate excitatory mechanisms are all believed to contribute to the development and progression of the disease. *Scoparia dulcis, Catharanthus roseus, Sesamum indicum, Erythrina senegalensis* and *Vigna unguiculata* represent five plants that have been used as traditional medicines for the treatment of AD in certain cultures. Review of the scientific literature was conducted to explore the properties of these plants that might be beneficial and explain what would be perceived by many to be largely anecdotal evidence of their benefit. All plants were found to possess varying levels of anti-oxidant capability. Scoparia dulcis was also found to potentiate nerve growth factor-like effects upon cell lines. *Catharanthus roseus* appears to inhibit acetylcholinesterase with relatively high potency, while *Sesamum indicum* demonstrated the strongest antioxidant ability. Comparisons with currently used plant derived therapeutics illustrate how these plants may be likely to have some therapeutic benefits in AD. The evidence presented also highlights how appropriate dietary supplementation with some of these plants in various cultural settings might have effects analogous or complementary to the so-called protective Mediterranean diet. However, prior to embarking on making any formal recommendations to this end, further rigorous evaluation is needed to better elucidate the breadth and potential toxicological aspects of medicinal properties harbored by these plants. This would be vital to ensuring a more informed and safe delivery of preparations of these plants if they were to be considered as a form of dietary supplementation and where appropriate, how these might interact with more formally established therapies in relation to AD[35]

The antimicrobial activities of four medicinal plants *Argemona mexicana, Achyranthes aspera, Catharanthus*
Micropropagation: a tool for the production of high quality plant-based medicines. Medicinal plants are the most important source of life saving drugs for the majority of the world's population. The biotechnological tools are important to select, multiply and conserve the critical genotypes of medicinal plants. Plant tissue culture techniques offer an integrated approach for the production of standardized quality phytopharmaceutical through mass-production of consistent plant material for physiological characterization and analysis of active ingredients. Micropropagation protocols for cloning of some medicinal plants such as Catharanthus roseus (Apocynaceae), Chlorophytum borivilianum (Liliaceae), Datura metel (Solanaceae), and Bacopa monnieri (Scrophulariaceae) have been developed. Regeneration occurred via organogenesis and embryogenesis in response to auxins and cytokinins. The integrated approaches of our culture systems will provide the basis for the future development of novel, safe, effective, and high-quality products for consumers [38].

The Catharanthus (or Vinca) alkaloids comprise a group of about 130 terpenoid indole alkaloids. Vinblastine is now marketed for more than 40 years as an anticancer drug and became a true lead compound for drug development. Due to the pharmaceutical importance and the low content in the plant of vinblastine and the related alkaloid vincristine, Catharanthus roseus became one of the best-studied medicinal plants. Consequently it developed as a model system for biotechnological studies on plant secondary metabolism. The aim of this review is to acquaint a broader audience with the recent progress in this research and with its exciting perspectives. The pharmacognostical aspects of the Catharanthus alkaloids cover botanical (including some historical), phytochemical and analytical data. An up-to-date view on the biosynthesis of the alkaloids is given. The pharmacological aspects of these alkaloids and their semisynthetic derivatives are only discussed briefly. The biotechnological part focuses on alternative production systems for these alkaloids, for example by in vitro culture of C. roseus cells. Subsequently it will be discussed to what extent the alkaloid biosynthetic pathway can be manipulated genetically ("metabolic engineering"), aiming at higher production levels of the alkaloids. Another approach is to produce the alkaloids (or their precursors) in other organisms such as yeast. Despite the availability of only a limited number of biosynthetic genes, the research on C. roseus has already led to a broad scientific spin-off. It is clear that many interesting results can be expected when more genes become available.[39]

Neurological syndromes linked with the intake of plants and fungi containing a toxic component (I). Neurotoxic syndromes caused by the ingestion of plants, seeds and fruits. A wide range of plants, seeds and fruits used for nutritional and medicinal purposes can give rise to neurotoxic symptoms. We review the neurological pathology associated with the acute or chronic consumption of plants, seeds and fruits in human beings and in animals. Of the plants that can trigger acute neurotoxic syndromes in humans, some of the most notable include Mandragora officinalis, Datura stramonium, Conium maculatum (hemlock), Coriaria myrtifolia (redouli), Ricius communis, Gloriosa superba, Catharanthus roseus, Karwinskaie humboldtiana and Podophyllum pelatum. We also survey different neurological syndromes linked with the ingestion of vegetable foodstuffs that are rich in cyanogenic glycosides, Jamaican vomiting sickness caused by Blighia sapida, Parkinson dementia ALS of Guam island and exposition to Cynas cirsialis, Guadeloupean parkinsonism and exposition to Annaceous, konzo caused by ingestion of wild manioc and neuralthrysm from ingestion of Lathyrus sativus, the last two being models of motor neurone disease. Locoism is a chronic disease that develops in livestock feeding on plants belonging to Astragalus and Oxytrops sp., Sida carpinifolia and Ipomea carnea, which are rich in swainsonine, a toxin that inhibits the enzyme alpha mannosidase and induces a cerebellar syndrome. The ingestion of neurotoxic seeds, fruits and plants included in the diet and acute poisoning by certain plants can give rise to different neurological syndromes, some of which are irreversible.[40]
Aryltetralin lignans: chemistry, pharmacology and biotransformations. Podophyllotoxin derivatives like etoposide 7a, etophos 7b, and teniposide 7c are used clinically as potent chemotherapeutic agents for a variety of tumors including small cell lung carcinoma, testicular cancer, and malignant lymphoma. These compounds derived from a series of modifications which converted podophyllotoxin 1a from an entity that interacted with tubulin and blocks mitosis to one that induced a block in late S or early G2 by interacting with topoisomerase II. Synthetic studies on podophyllotoxin derivatives can be divided in four general approaches (the oxo-ester route, the digydroxy acid route, the tandem conjugate addition route and the Diels-Alder route). Albeit a number of synthetic sequences afforded products with excellent enantiopurities, the low overall yields still disqualify synthesis as an alternative for naturally produced materials. An alternative route based on the enzyme-catalyzed cyclization of synthetic intermediates to analogues of the podophyllotoxin family is being explored. Synthetic dibenzylbutanolides, which were revealed by biosynthetic studies to be the precursors of aryltetralin lignans, have been treated with enzymes derived from cell cultures of *Podophyllum peltatum*, *Catharanthus roseus*, *Nicotiana sylvestris* and *Cassia didymobotrya*. The cyclization process afforded however compounds with a different stereochemistry in the C ring. The obtainment of a novel compound with a benzylidenebenzylbutiolactone structure still leaves considerable scope for exploring biotransformations in order to obtain podophyllotoxin analogues via a combination of synthetic chemistry and biotechnological methods.[41]

Clinical pharmacokinetics of vinorelbine. Vinorelbine (5'-noranhydrovinblastine) is a recently developed semisynthetic anticancer drug which belongs to the *Catharanthus* alkaloid family. Its mechanism of action is only partially known but it is assumed that it acts, like vinblastine and vincristine, as an antineoplastic agent arresting cell division in mitosis. Clinica lly, vinorelbine has mainly shown activity in the treatment of advanced non-small-cell lung cancer and the treatment of metastatic breast cancer. Early pharmacokinetic data were obtained with radioactive assays (radio-immunoassay or 3H-labelled vinorelbine), then with more selective high performance liquid chromatographic techniques. Vinorelbine is usually administered intravenously but there has also been some experimentation with an oral formulation. The bioavailability of a liquid filled gelatin capsule ranges between 12 and 59% with a mean value of 27% [standard deviation (SD) 12%]. Vinorelbine is rapidly absorbed with peak serum concentration reached within 2 hours. In vitro, vinorelbine is mainly distributed into the blood cells, especially platelets (78%) and lymphocytes (4.8%). The unbound blood fraction is around 2%. In lung tissue vinorelbine concentrations are much higher than in serum, by up to 300-fold 3 hours after administration. Little is known about the biotransformation of vinorelbine. Desacetylvinorelbine is considered to be a minor metabolite and is only found in urine fractions, representing 0.25% of the injected dose. Urinary excretion of vinorelbine is low, accounting for less than 20% of the dose. Faecal elimination has been demonstrated in 2 patients who were administered 3H-labelled vinorelbine; the amount of radioactivity recovered in the faeces was 33.9 and 58.4% for the 2 patients, respectively. The pharmacokinetic profile of vinorelbine is often described as a 3-compartment model characterized by a long terminal half-life (t1/2) that varies between 20 and 40 hours and a large apparent volume of distribution (Vd) of around 70 L/kg. Systemic clearance ranges between 72.54 and 89.46 L/h (1209 and 1491 ml/min) when determined by high performance liquid chromatography and is higher than that reported by radioimmunoassay [46.2 L/h (770 ml/min)]. This could be due to the greater specificity of the chromatographic method. Vinorelbine has been administered by continuous intravenous infusion over 4 days. Steady-state was reached and the concentrations obtained were above the in vitro IC50 (concentration of drug causing 50% inhibition). The effect of liver disease on vinorelbine pharmacokinetics has been studied in patients with breast cancer. Patients with massive secondary liver disease had a lower systemic clearance than those who have no liver disease or a lesser invasion. In children, vinorelbine seems to display a shorter t1/2 (14.7 hours) than that found in adults. In addition, the systemic clearance is highly variable [from 12 to 93.96 L/h/m2 (200 to 1566 ml/min/m2)]. Vinorelbine is often co-administered with cisplatin in the treatment of advanced non-small-cell lung cancer. The disposition of the alkaloid is not altered by concurrent administration of cisplatin.[42]

Pharmacology of *Catharanthus* alkaloids. *Catharanthus* alkaloids are antitumoral drugs widely used in the treatment of malignant diseases. This review summarizes different aspects of their pharmacology (mechanism of action, resistance, clinical pharmacokinetics) as well as information on their uses in the clinical setting.[43] Cytchrome P-450 in plant/insect interactions: geraniol 10-hydroxylase and the biosynthesis of iridoid monoterpenoids. The interactions between plant secondary metabolites (particularly monoterpenes) and insects are discussed. Such metabolites are likely to have influenced the evolution of cyt P450-linked detoxification systems in animals, through animal/plant coevolution. The biosynthesis of many classes of plant secondary metabolites involves cyt P450 enzymes. Of these, one of the best characterised is the geraniol/nerol 10-hydroxylase which catalyses a key step in the biosynthesis of the iridoid class of plant terpenes. It would appear that these monoterprenoids are synthesised (via cyt P450 hydroxylation) from different precursors in different plant species, namely geraniol, its isomer nerol, or the related monoterpenoid, citronellol. We show that cyt P450 from the plants *Catharanthus roseus* and *Nepeta racemosa* are capable of hydroxylating geraniol, nerol and citronellol, and thus do not impose precursor specificity on iridoid biosynthesis in plants.[44]

The pharmacology of extinction. It is impossible to predict what compounds of pharmacological interest may be present in an unexamined species. The extinction of such species may result, therefore, in the loss of therapeutically significant compounds. The fact that science will never know what has been lost does not lessen the significance of the loss. A number of species are discussed to exemplify the potential loss. *Ginkgo biloba* is an ancient plant, apparently saved from a natural extinction by human intervention. From this tree, the ginkgolides have been isolated. These are potent inhibitors of platelet activating factor and hold promise in the treatment of cerebral ischemia and brain edema. Two species, the tree *Taxus*
brevifolia and the leech Hirudo medicinalis, are threatened as a result of human activity. Both have recently yielded complex compounds of therapeutic importance. The antitumor agent, taxol, is obtained from T. brevifolia and the thrombin inhibitor, hirudin, is found in H. medicinalis. Catharanthus roseus, source of the anticancer agents vincristine and vinblastine, although not threatened, derives from a largely unexamined but severely stressed ecosystem of some 5000 plant species. In other examples, ethnobotanical knowledge of certain plants may be lost while the species survive, as exemplified by the suppression of the Aztec ethnobotany of Mesoamerica by the invading Spanish. Finally, the fallacy of the 'snail darter syndrome', where species may be viewed as too insignificant to worry about, is exposed by consideration of the pharmacological activities of a sea hare (ashell-less marine mollusc) and various leeches.[45]

The dimeric Vinca alkaloids represent a group of important anti-tumor compounds whose intracellular target is tubulin, the protein monomer of microtubules. In this review data on the binding of these drugs to tubulin and microtubules in vitro are examined. The simplest model which fits the binding data is one in which there is one intrinsie site which is linked to the self-association process. Effects of solution variables on the binding and self-association explain the wide variation of reported apparent binding constants for Vinca alkaloids to tubulin. The Vinca drugs also bind to microtubules via a low number of sites at the ends of microtubules with apparent high affinity and which are involved in the inhibition of tubulin dimer addition to the microtubule ends, and to sites along the microtubule wall with apparent low affinity which are involved in the disruption of the microtubules into spiraled protofilaments. This review also compares available binding data for different natural and semi-synthetic Vinca alkaloids.[46]

**Anticancer Properties**

Many anticancer drugs are obtained from natural sources. Nature produces a variety of toxic compounds, which are often used as anticancer drugs. Up to now, there are at least 120 species of poisonous botanicals, animals and minerals, of which more than half have been found to possess significant anticancer properties. In spite of their clinical toxicity, they exhibit pharmacological effects and have been used as important traditional Chinese medicines for the different stages of cancer. The article reviews many structures such as alkaloids of Camptotheca acuminata, Catharanthus roseus and Cephalotaxus fortunei, lignans of Dyosoma versipellis and Podophyllum emodi, ketones of Garcinia hanburyi, terpenoids of Mylabris and Ginkgo biloba, diterpenoids of Tripterygium wilfordii, Euphorbia fischeriana, Euphorbia lathyris, Euphorbia kansui, Daphne genkwa, Pseudolarix kaempferi and Brucea javanica, triterpenoids of Melia toosendan, steroids of Periploca sepium, Paris polyphylla and Venenum Bufoxis, and arsenic compounds including Arsenicum and Realgar. By comparing their related phytochemistry, toxic effects and the recent advances in understanding the mechanisms of action, this review puts forward some ideals and examples about how to increase antitumour activity and/or reduce the side effects experienced with Chinese medicine.[47]

Vincristine is a dimer-indo-alkaloid which is extracted from the leaves of Catharanthus roseus. It is effective to treat acute lymphocytic cell leukemia, Hodgkin disease and non-Hodgkin disease clinically. But the severe side effects, such as neurotoxic and tissue damage, limit its application. In this paper, we summarize physical, chemical, pharmacological and pharmacokinetical properties of VCR and advances in decreasing its side effects. In clinic, association with other medication is adopted. In pharmacotherapy, people adopt some new methods and technology such as conjugation with the antibody, encapsulation in liposomes or controlled release films. [48] The IBOGA alkaloids and their role as precursors of antineoplastic bisindole Catharanthus alkaloids.[49]

Interactions of antimitotic peptides and depsipeptides with tubulin. Tubulin is the target for an ever increasing number of structurally unusual peptides and depsipeptides isolated from a wide range of organisms. Since tubulin is the subunit protein of microtubules, the compounds are usually potently toxic to mammalian cells. Without exception, these (depsi) peptides disrupt or prevent microtubule dynamics at low concentrations. Most of the (depsi) peptides inhibit the binding of Catharanthus alkaloids to tubulin in a noncompetitive manner, GTP hydrolysis by tubulin, and nucleotide turnover at the exchangeable GTP site on beta-tubulin. In general, the (depsi) peptides induce the formation of tubulin oligomers of aberrant morphology. In all cases tubulin rings appear to be formed, but these rings differ in diameter, depending on the (depsi) peptide present during their formation.[50]

Natural products of plant origin as anticancer agents. Natural products have been used as effective remedies for the treatment of various ailments. Numerous plant products in the form of decoction, tincture, tablets and capsules have been clinically used for the treatment of different kinds of cancer. This review covers some of the important plants with clinically proven anticancer activity, including Catharanthus roseus, Podophyllum peltatum, Taxus brevifolia, Camptothecin acuminata, Cephalotaxus harringtoniana, Viscum album, Onchorhiza elliptica, Annona bullata, Asmina triloba and Rhizoma zedoariae. Synthetic analogues in some cases have also been prepared to improve the efficacy and decrease the side effects of parent compounds. The modes of action of clinically used drugs are also delineated.[51]

In folklore medicine, extracts of the leaves of the subtropical plant Catharanthus roseus (L.) G. Don (sometimes known as Madagascar periwinkle) were reputed to be useful in the treatment of diabetes. This review describes how attempts to verify the anti-diabetic properties of the extracts led instead to the discovery and isolation of two complex indole alkaloids, vinblastine and vincristine, which are used in the clinical treatment of a variety of cancers. The two alkaloids, although structurally almost identical, nevertheless differ markedly in the type of tumors that they affect and in their toxic properties. These and related alkaloids have been the subject of many
pharmacological and biochemical investigations both in vivo and in vitro in the search for improved cancer treatments. A model system used in these studies, a transplantable lymphoma in Noble strain rats designated Nb2 node, has serendipitously led to the development of a highly sensitive and specific bioassay for lactogenic hormones[52]

**Genetic and Molecular Analysis**

In plants, receptor-like kinases regulate many processes during reproductive and vegetative development. The Arabidopsis subfamily of *Catharanthus roseus* RLK1-like kinases (CrRLK1Ls) comprises 17 members with a putative extracellular carbohydrate-binding macletin-like domain. Only little is known about the functions of these proteins, although mutant analyses revealed a role during cell elongation, polarized growth, and fertilization. However, the molecular nature of the underlying signal transduction cascades remains largely unknown. CrRLK1L proteins are also involved in biotic and abiotic stress responses. It is likely that carbohydrate-rich ligands transmit a signal, which could originate from cell wall components, an arriving pollen tube, or a pathogen attack. Thus, post-translational modifications could be crucial for CrRLK1L signal transduction and ligand binding [53]

This review focuses on the published data regarding the molecular determinants (enzymes, transporters, orphan nuclear receptors) of *Catharanthus* (vinca) alkaloids pharmacokinetics in humans. The clinical impact of these determinants (drug disposition, drug-drug interactions) is also discussed [54]

Transcription factors: tools to engineer the production of pharmacologically active plant metabolites. Plants produce a variety of secondary metabolites, some of which are used as pharmaceuticals or are health promoting as food components. Recent genetic studies on the flavonoid biosynthetic pathway show that transcription factors are efficient new molecular tools for plant metabolic engineering to increase the production of valuable compounds. The use of specific transcription factors would avoid the time-consuming step of acquiring knowledge about all enzymatic steps of a poorly characterized biosynthetic pathway. Although genetic approaches are difficult for most plant species, promoter studies of single-pathway genes and T-DNA activation tagging are feasible alternative approaches for isolating transcription factors, as illustrated for terpenoid indole alkaloid biosynthesis in *Catharanthus roseus* [55]

Metabolism of the *Catharanthus* alkaloids from Streptomyces griseus to monoamine oxidase B. More than three decades after their discovery and implementation in medicine, essentially nothing is known about the metabolism or the implications of metabolism in mechanism of action or toxicity of the *Catharanthus* alkaloids. The frustrating paucity of information about pathways of metabolism has limited a major source of structure-activity relationship information and has blocked a critical avenue necessary for the logical development of new and more useful *Catharanthus* alkaloids. Microbial transformations, peroxidases, copper oxidases, mouse and rat cytochrome P-450 systems, and mouse brain and bovine liver monoamine oxidase (MAO) preparations have been explored in the study of *Catharanthus* alkaloid metabolism. In this report, we present results which have clarified the involvement of enzymatic and chemically catalyzed one-electron oxidations that yield nitrogen-centered cation radicals, iminium, and carbinolamine intermediates, all of which explain how new carbon-carbon and carbon-oxygen bonds form, or break and rearrange. The dimeric *Catharanthus* alkaloids are recalcitrant to oxidations catalyzed by monoamine oxidases and to both normal and induced P-450 rat microsomal preparations. However, the *Catharanthus* alkaloids appear to be selective reversible inhibitors of MAO-B. Chemical and biochemical aspects of the metabolic transformations of dimeric *Catharanthus* alkaloids are reviewed together with the implications of our findings[56]

Strategies for the genetic manipulation of alkaloid producing pathways in plants. Increasingly as a result of recent biochemical work, there exists a realistic possibility of taking a molecular genetic approach to the manipulation of alkaloid-producing pathways in plant tissue cultures. In the pathways forming indole alkaloids in *C. roseus*, tropane alkaloids in Datura and Hyoscyamus species, and nicotine in Nicotiana species, recent studies have identified a number of key enzymes and at least some of the factors that regulate their levels of activity. Such knowledge contributes the basis upon which it has become feasible to design a strategy by which the flux in these pathways may be enhanced at the genomic level. This review presents a summary of the state-of-the-art pertaining to these pathways and discusses the strategy to be adopted for a molecular approach to their manipulation, together with some of the pitfalls that may arise when trying to alter their natural regulation.[57]

**Antidiabetic Properties**

Useful ethnophytomedicinal recipes of angiosperms used against diabetes in South East Asian Countries (India, Pakistan & Sri Lanka). This paper is based on data recorded from various literatures pertaining to ethnophytomedicinal recipes used against diabetes in South East Asia (India, Pakistan and Sri Lanka). Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus. In total 419 useful phytorecipes of 270 plant species belonging to 74 Angiospermic families were collected. From the review it was revealed that plants showing hypoglycemic potential mainly belong to the families, Cucurbitaceae (16 spp.), Euphorbiaceae (15 spp.), Caesalpinaceae and Papilionaceae (13 spp. each), Moraceae (11 spp.), Euphorbiaceae (10 spp.), Mimosaceae (09 spp.), Asteraceae, Malvaceae and Poaceae (08 spp. each), Hippocrateaceae, Rutaceae and Zingiberaceae (07 spp. each), Apocynaceae, Asclepiadaceae and Verbenaceae (06 spp. each), Apiaceae, Convolvulaceae, Lamiaceae, Myrtaceae, Solanaceae (05 spp. each). The most active plants are *Syzigium cumini* (14 recipes), *Phyllanthus emblica* (09 recipes), *Centella asiatica* and *Momordica charantia* (08 recipes each), *Azadirachta indica* (07 recipes), *Aegle marmelos*, *Catharanthus roseus*, *Ficus benghalensis*, *Ficus racemosa*, *Gymnema sylvestre* (06 recipes each), *Allium cepa*, *A. sativum*, *Andrographis paniculata*, *Curcuma longa* (05 recipes each), *Citrus luculcyth, Justicia adhatoda, Nelumbo nucifera*, *Tinospora cordifolia*, *Trigonella foenum-graecum*, *Ziziphus mauritiana* and *Wattakaka...*
Medicinal plants used for treatment of diabetes by the Marakh sect of the Garo tribe living in Mymensingh district, Bangladesh. Diabetes mellitus is an endocrinological disorder arising from insulin deficiency or due to ineffectiveness of the insulin produced by the body. This results in high blood glucose and with time, to neurological, cardiovascular, retinal and renal complications. It is a debilitating disease and affects the population of every country of the world. Around 200 million people of the world suffer from this disease and this figure is projected to rise to 300 million in the coming years. The disease cannot be cured with allopathic medicine as the drugs used do not restore normal glucose homeostasis and moreover have side-effects. On the other hand, traditional medicinal practitioners of various countries claim to cure diabetes or at least alleviate the major symptoms and progression of this disease through administration of medicinal plants. The Garos are an indigenous community of Bangladesh, who still follow their traditional medicinal practices. Their traditional medicinal formulations contain a number of plants, which they claim to be active antidiabetic agents. Since observation of indigenous practices have led to discovery of many modern drugs, it was the objective of the present study to conduct a survey among the Marakh sect of the Garos residing in Mymensingh district of Bangladesh to find out the medicinal plants that they use for treatment of diabetes. It was found that the tribal practitioners of the Marakh sect of the Garos use twelve medicinal plants for treatment of diabetes. These plants were Lannea coromandelica, Alstonia scholaris, Enhydra fluctuans, Terminalia chebula, Coccinia grandis, Momordica charantia, Cuscuta reflexa, Phyllanthus emblica, Syzygium aqueum, Drynaria quercifolia, and Clerodendrum viscosum. A review of the scientific literature demonstrated that almost all the plants used by the Garo tribal practitioners have reported antidiabetic and/or antioxidant properties and have enormous potential for possible development of new and efficacious antidiabetic drugs.[59]

CONCLUSION

Catharanthus roseus is one of the best studied medicinal plants. Most recently, extract from periwinkle have been shown to be effective in treatment of diabetes, high blood pressure, asthma, constipation, skin cancer, hodgkin’s disease. Catharanthus roseus in the mid 20th century after learning of its use as diabetes treatment in the Caribbean and Asia. Further Study need to be exploring its anti-tumor and anti-diabetic effects. In this article have assembled almost all information related to different research activity of plant. Same types of reviews have been published on Tribulus terrestris [60] Oxalis corniculata [61] Solanum nigrum [62] Cuscuta reflexa [63], Acorus calamus [64] and Simarouba Glauca-An oil Yielding Plan [65]This became popular articles for further investigations on particular medicinal herbs.

This review will help to researchers & scholars to go deep in this area as plant indicate vast range of phytochemical related to origin so it can be suggested the further work can be done on Catharanthus roseus which is collected from different season and agro climatic zone. Definitely it is assumed that research will be able to find out more suitable and specific drug plants having particular activity in specific season. Some scientist needs this data and concepts to re-research on the present scientific plant. It can really contribute to medical and pharmaceutical practices. There are still many more activities waiting for screening the drug from Catharanthus roseus.

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