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Comprehensive outlook on pharmacological implementation of Madagascar Periwinkle

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Abstract-*Periwinkle/ Madagascar periwinkle (Catharanthus roseus) commonly known as sadabahar, sadafuli, vinca is used as a lifesaving medicine since ages due to its alkaloids such as vincristine, vinblastine, vindoline. This plant has antibacterial properties which make it a potential medicine for combating infectious diseases, including those caused by multidrug-resistant pathogens. Alkaloids derived from C. roseus exhibit anti-inflammatory effects by modulating cytokine synthesis suggesting potential applications in treating inflammatory conditions and neuroprotective properties according to recent research. It is also used as medicine for several severe conditions like cancer, diabetes etc. due to their regulatory effect on cell division and free radical scavenging activity. Herbal use of the powder is carried out by decoction in warm water which is sometimes difficult to take or doesn't appear fascinating to take by different age groups. The study is about discussing the details of pharmaceutical qualities of Catharanthus roseus for the formulation of medicines other than cancer such as diabetes and infections which affect major populations taking the toxicity effects in consideration through crude intake by the people due to lack of awareness.*

Key Words: Catharanthus roseus, regulatory effect, free radical scavenging, antimicrobial, decoction, formulation

1. INTRODUCTION

Table No.1 Taxonomy of the plant

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Gentianales
Species	C. roseus
Family	Apocynaceae
Genus	Catharanthus
Species	C.roseus C. coriaceus Markgr. C. lanceus, C. longifolius, C. ovalis Markgr., C. pusillus, C. scitulus, C. trichophyllus (Bak) Pichon

The traditional use of pharmacologically active plants has gain tremendous importance due to their safety profile and side-lining the undesirable effects of chemically derived drugs (1) The therapeutic drugs used for cancer treatments by using cytotoxic and radiations therapy have harmful effects thus the medicinal plants may reduce the side effects and promote good health (2). The availability and low prices favour the uses of medicinal flora for treating clinical conditions reported by World Health Organization (WHO) (3,4).

The scientific name for sadaphool is Catharanthus roseus L. (G.) Don categorized under dicot vascular plant belongs to Apocynaceae family. The Indigenous medicinal Legacy of vinca rosea leaves, stem, roots in various parts of countries like Europe, West indies, India, China for treating high blood pressure metabolic disorders, blood loss, diuretic, wound infections (3). The Phytochemistry of Madagascar periwinkle includes broad range of flavonoids, phenolics compounds, alkaloids, organic acids antibacterial agents and amino carbohydrates (5). The Tryptamine formation via Tryptophan decarboxylase, anthranilate synthase using main substrate as tryptophan and geraniol leading alkaloids formations (6). In 950s Vinca alkaloids was reported by Charles Beer and Robert Noble (7). Various around 400 alkaloids, phenolics, flavonoids are found in periwinkle plants. The traditional uses of Madagascar periwinkle have turn pharmaceuticals companies outlook for treatment of antidiabetic (8), anticarcinogenic (9) antihypertensive activity (10), inhibition of fungal, bacterial and viral strains (11). It supresses fever, prevent damage from 2,2-diphenyl-picrylhydrazyl (DPPH) radical and skin infections and ulcers (12,13).

The Vinca rosea may be taken in form of powder, liquid or tablets. The necessity of dosage for administration to avoid toxicity must be studies. In 1960 vinblastin sulfate salt or vincaleukoblastin commercially available product was injected (5). The issue arises on unregulated bioprospecting on traditional uses and 2001 patent file by pharma companies on medicinal uses of this plant parts. The C. roseus may have some underlying adverse effects on organs like liver and kidney, allergic conditions like rashes, breathing problem, severe itchiness and also may interfere with other medicine (10). Thus, review threw major focus on C. roseus applications along with its toxicological studies.

2. PHYTOCHEMISTRY

The plant is found to contain about 400 alkaloids that are used in different ways such as food additives, pesticides, agricultural products, flavouring agents, perfume components and pharmaceuticals. The aerial parts contain alkaloids such as vinblastine, vincristine whereas roots

consist of catharanthine derivatives, reserpine and vinamine. It is discovered that its alkaloids are proved to have moderate antimicrobial activity with long lasting hypotensive effects (11, 14).

2.1. Leaf

Alkaloids: Apparicine, akuammicine, catharanthine, cavincine, cathariciné, cathovaline, catharanthamine, cathindine, cavincidine, ibogaine, N -oxide, sitsirikine, 4'-anhydro-, roseadine, 19- acetoxy-11- hydroxy, strictosidine, raubasine, leurosine, lochnerine, β-carboline, iochrovicine, fluorocarpamine, rosicine, rosamine, tabersonine, Iochneridine, perivine, serpentine, vincarodine, vincoline, deacetoxy, tabersonine, bannucine, vincathicine, catharine, carosine, vinamidine, neoleurocristine, leurosinone, neoleurosidine, N b-oxide, pericyclivine, perosine, rovindine, vindoline, vindolidine, vindolicine, vindolinine, vinaphamine, vinaspine, vincamicine, vinblastine, vincristine, yohimbine.

Phenols: Kaempferol-3-O-(2,6-di-Orhamnosyl galactoside)-7-Ohexoside, Kaempferol-3-O- (2,6-diO rhamnosyl-galactoside), Quercetin-3-O-(2,6-di-O- rhamnosyl galactoside), Chlorogenic acid, 3-Ocaffeoylquinic acid, 4-Ocaffeoylquinic acid 5-Ocaffeoylquinic acid, Quercetin trisaccharides, 3-O-caffeoylquinic acid, kaempferol-3-O-(2,6-di-O-rhamnosyl-galactoside) 7-O-hexoside,4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, Quercetin-3-O-(2,6-di-O rhamnosyl-galactoside), Kaempferol-3-O-(2,6-di-O-rhamnosyl-galactoside) (15).

Others: Carbohydrates, flavonoid, loganic acid, saponins, steroids, tannins and triterpenoids,

2.2. Stem

Alkaloids: Catharanthine, leurosine, lochnerine, vindoline

Phenols: 3-O-caffeoylquinic acid, 4-Ocaffeoylquinic acid 5-O-caffeoylquinic acid, Isorhamnetin-3-O-(2,6-di-Orhamnosyl galactoside), Syringetin glycosides, Quercetin3-O-(2,6-di-O-rhamnosyl galactoside), Quercetin trisaccharides, Kaempferol-3-O-(2,6- di-O-rhamnosyl-galactoside), Quercetin-3-O-(2,6-di-O-rhamnosyl-galactoside)
Others: Carbohydrates, steroids, tannin

2.3. Root

Alkaloids: carbohydrate, Saponins, triterpenoid, tannins, ajmalicine, steroids, ajmalicine, ammorosine, cathalanceine, cathindine, cavincidine, catharanthine, alstonine, Horhammericine, Leurosine, Lochnerine, Reserpine, Tabersonine, Lochnericine, ammocalline, akuammicine, cavincine, echitovenine, venalstonine, perivine, serpentine, tetrahydroalstonine, Vindoline, yohimbine, vinosidine, strictosidine, maandrosine, perosine

2.4. Flower

Alkaloids: Apparicine, catharanthine, coronaridine, vindoline, leurosine, Lochnerine, perivine, Tricin (Flavones), tetrahydroalstonine, tabersonine,11-methoxy, mitraphylline, catharicine, carosine, rosindine.

Phenols: 4-O-(2,6-di-O-rhamnosylgalactoside) malvidin 3-O-(6-O-pcoumaroyl), kaempferol-3-O (2,6-di-Orhamnosyl-galactoside) petunidin 3-O-(6-Op-coumaroyl), quercetin-3-O-(2,6-di O-rhamnosylgalactoside), malvidin 3- O-glucosides, kaempferol-3-O-(2,6- di-O-rhamnosyl glucoside), kaempferol-3-O-(6-orhamnosyl galactoside), isorhamnetin-3-O-(6-O-rhamnosylglucoside), hirsutidin 3-oglucosides, kaempferol3-O-(6-O-rhamnosyl-glucoside), hirsutidin 3-O-(6-Op-coumaroyl), isorhamnetin-3-O-(6-O-rhamnosyl-galactoside)

Others: Steroids, tannin, saponins, carbohydrate

2.5. Seeds

Alkaloids: Methylvingramine, tabersonine, strictosidine, vinsedicine, vingramine etc.

Phenols: Isorhamnetin-3-O-(2,6-di-Orhamnosyl-glucoside), isorhamnetin-3-O-(6- O-rhamnosyl glucoside), kaempferol-3-O-(2,6-di-orhamnosyl-galactoside)-7-ohexoside, quercetin-3-O-(2,6-di Orhamnosyl-galactoside), kaempferol-3-O-(2,6 di-O-rhamnosyl-glucoside), kaempferol-3-O-(6-O-rhamnosylgalactoside) kaempferol3 O-(2,6-di-O-rhamnosylgalactoside), etc.

Shoots have alkaloids such as Catharine, cyclolochnerine, 21-hydroxy, catharanthine, serpentine, strictosidine lactam, horhammericine, tetrahydroalstonine, sitsirikine, 11-methoxy, vinblastine,3',4'-anhydro- etc. (3).

2.6. Whole plant

Phenols: Gallic acid, Vanillic acid, ferulic acid, hydroxytyrosol.

Others: Catharanthine, vindoline, vincristine, flavonoids, glycoside, mono terpenoids, vinblastine etc. (16-19).

3. THERAPEUTIC APPLICATIONS AND POTENTIAL OF PLANT

3.1 Pharmaceutical applications

Kumar et al., 2022 documented 344 chemicals which were showing pharmacological activities such as cytotoxicity, antimicrobial activity, hypolipidemic, antiulcerative, memory-enhancing, hypotensive, hypoglycemic activities of Catharanthus roseus (15). The plant contains nearly 129 TIAs (terpenoid indole alkaloids) and diverse bioactive

compounds across all plant parts which have wide commercial and scientific applications (20).

3.1.1 Vincristine and Vinblastine

The anticancer bisindole alkaloids are derived from cantharathine and vindoline. Vinca alkaloids used to treat sarcomas, lymphomas, neuroblastomas. Vincristine and vinblastine are chemotherapeutic agent used to treat various type of cancers. It causes pulmonary toxicity when combined with other chemotherapy drugs. 30% of 27 patients experienced when vincristine was combined with bleomycin, doxorubicin, cyclophosphamide, procarbazine, prednisone, and gemcitabine. Major anticancer medication derived from C. roseus are named as Oncovin and veiban (21). One of the antineoplastic vinca alkaloids is vinblastine. Vindoline and catharanthine are the two multiringed units that make these alkaloids useful for medicinal purposes since 1959. Periwinkle extract was first investigated for its hypoglycemic properties but antileukemic effects were found later have and to induce marrow suppression in rats. Vinblastine suppresses the immune system. Intramuscular, subcutaneous or intrathecally (22).

Vinoblastine (VBL) marketed as the Welban, is chemotherapy drug used to treat Hodgkin's malformation (fig 3) (23). It inhibits endothelial cell functions, destabilizes the arrangement of microtubules and stimulate the process of apoptosis leading to block tumor blood vessels and contributing to its anticancer activity.

3.1.2 Other bioactive alkaloids and derivatives

Vincamine improves cerebral blood flow and cerebral utilization of oxygen and in drugs such as centracetam, aethroma and dipervin. Vinpocetine, a derivative of vincamine, has memory improving properties, which also exhibit blood thinning, vasodilatory and hypoglycaemic effects. Vohimbine, an indole alkaloid of C. roseus, exerts significant antiviral activity against Herpes Simplex Virus type 1 (HSV-1) even at nanomolar concentrations. It involves interference in viral entry, fusion and replication which highlight its potential as a natural antiviral scaffold (24).

Tabersonine is a monoterpenoid indole alkaloid which has cytotoxic and antineoplastic potential. The enzyme tabersonine 16 –hydroxylase (T16H) converts tabersonine to 16 hydroxytabersonine which is intermediate in the biosynthesis vinodoline precursor of vinblastine.4. Catharoseumine has cytotoxic effects and proved to be anticancerous when tested against HL-60 cell lines of human promyelocytic leukemia, by reducing cell proliferation (25). Vinflunine has antitumor properties which disrupt microtubule dynamics and forthcoming the growth of cells. It has potential for treatment of advanced urothelial carcinoma including metastatic bladder cancer (3). Vindesine has potent anticancer properties that bind tubulin and prevent the formation of microtubules, and cause cell cycle arrest and apoptosis. It is used to treat malignancies such as lymphoma, breast cancer, lung cancer and other malignancies (3,10,14).

3.1.3 Anthocyanins, Flavonoids and Phenolic Acid

The flower contains rosindin which is anthocyanin pigment (26). It also contains flavonoids mainly quercetin and kaempferol derivatives which are essential for its anti-inflammatory and antioxidant efficacy. These flavonols are capable of neutralizing (ROS and RNS) a reactive oxygen and nitrogen species by free radicals' stabilization and chelating redox-active metal ions, therefore, mitigate oxidative damage to cellular macromolecules (27). C. roseus synthesizes phenolic acids such as gallic acid and vanillic acid, which belong to the benzoic acid class of secondary metabolites. They enhance the plant's total antioxidant capacity through synergistic redox cycling and hydrogen atom donation mechanisms. Gallic acid exhibits a high degree of radical scavenging, while vanillic acid inhibits peroxidation of lipids, inhibit and modulate oxidative enzyme activity (28).

Anthocyanins, are responsible for the range of colors (red, purple, and blue) of flowers, which depends on the cultivar specific hydroxylation in viz. glycosylation/ acylation of anthocyanidins to delphinidin, cyanidin, and pelargonidin (29).

3.2 Drug delivery

Vinblastine, which is being carried through dextran folate coated FeO nanoparticles. Effective cellular internalization is shown in in-vitro experiments due to interaction between folate receptor and folic acid coated nano-carrier. It showed no severe cytotoxicity indications showing adequate safety. This has showed the effectiveness of cancer inhibitors by reducing cell survival. Several researchers have developed liposome mediated delivery of vincristine compounds to tumor cells effectively. These contain a hydrophobic material within their cell membranes and release vincristine when exposed to ultrasonic vibrations, enhancing the targeted drug delivery (30).

Jeswani and associates synthesized vincristine sulphate nanogel conjugated thermosensitive matrix. In vitro MCF-7 cell line studies show unconjugated drugs indicate that small carrier linkage did not reduce activity while having less haemolytic effects compared to vincristine sulphate. Which gives potential for successful breast cancer treatment (31). Huang et al. prepared a magnet triggered delivery method for vinblastine by using chitosan microparticles that included iron oxide nanoparticles. When the particles were magnetized, complete elimination of the drug was carried out in approx. 80-130 minutes which allows controlled drug release (21, 32).

3.2.1 PLGA (lactic-co-glycolic acid) nanoparticles

PLGA (poly lactic-co-glycolic acid) nanoparticles coated with polyethylene glycol PEG, provide benefit of prolonged systemic circulation and protection from reticuloendothelial system also known as mononuclear phagocyte system (RES)-mediated clearance (33). These formulations increase therapeutic payload by selective accumulation in carcinoma tissues via enhanced permeability and retention effects (EPR) which maximize therapeutic payload at the disease site with minimal collateral damage to healthy cells. Liposome mediated delivery increase stability and solubility in aqueous and hydrophobic medium which lead to reduction in infusion-related toxicity (28).

Multifunctional nanocarriers serve as theranostic agents, enabling real-time imaging and targeted therapy, fluorescent dyes or superparamagnetic iron oxide nanoparticles (SPIONs) to vinca alkaloid-loaded carriers, monitor biodistribution and tumour regression in vivo with high fidelity. Vindolicine has an antidiabetic effect (for Diabetes mellitus-2) and vinorelbine and vinflunine- have antiplastic effect (26).

Vinorelbine is a chemotherapeutic agent used for small cell lung cancer treatment. It can be synthesised by vindoline and catharanthine through anhydrovinblastine. Vincoline, the plant's insulin-stimulating compound, has been isolated from this plant (21). Vinpocetine is reported to reduce the frequency of seizures significantly. It enhances psychomotor function and helps reduce intracranial hypertension (13). According to some studies, it suppresses the hypertrophic growth of cardiomyocytes and in-vitro cardiac fibroblasts activation via phosphodiesterase-1-dependent mechanism.

3.3 Antidiabetic potential

Vinca rosea indole alkaloids aids in Insulin secretion and regain the functioning of pancreas cells by supressing glucose-6-phosphate dehydrogenase leading to reduction of cholesterol and enhanced hepatic glucose clearance in muscles and liver cells (6,14). The components from the extracts helps in regulate glycaemic control by upregulating glycogen production. These alkaloids promote the glucose metabolism by different modes such as downregulate the protein tyrosine phosphatase1B (PTP-1B) alleviates insulin restoration (28).

Table 2. Vinca alkaloids and their antidiabetic applications.

Compound	Standard drug	Part of C. roseus	Effect
Alkaloids	Tolbutamide	Crude leaf extract	Low blood sugar
Vindogentianine	Insulin	Leaf	Hypoglycemic activity in -TC6 and C2C12
Alkaloids	Sitagliptin	Ethanolic extract of leaf	Lower blood sugar
Alkaloids and flavonoids	alloxan	Methanol Leaf extract	Reproduce beta cells Lowers high blood sugar
Alkaloids	Glibenclamide	Ethanolic extract of leaves and flowers	Hypo glycemic effect
Vindolicine and vindolinine	Insulin	dichloromethane leaves extract	glucose in myoblast C2C12

3.4 Anticancer potential

The US government endorse anticarcinogenic agents like vinblastine, vincristine, vindesine and vinorelbine extracted from sadaphool (22). Cancer like myeloid, lymphocytic, Hodgkin lymphoma, lung, eyes and bladder defects, carcinoma are treated with commercially available anticancer drugs like Oncovin and Welban which contain the monoterpenoid alkaloids like vincristine (29) and vinblastine (23) as main ingredients. Cathachunine, a novel drug is useful for breast cancer (26). Healthy population remains unaffected by only targeting exacerbated growth by these alkaloids make great clinical significance in treating the hematologic neoplasms and tumours (28). Chemotherapeutic agents extracted from C. roseus works on underlying mechanism by inhibition of tubulin heterodimer which facilitate spindle formation during cell proliferation and multiplication (10).

3.5 Antioxidant Activity

Alkaloids, flavonoids and phenolic compounds such as vindolicine, exhibit oxidative stress protective activity and exhibiting inhibition of tumour cells (22). The methanol and hexane extracts of the plant have low IC50 value and higher IC50 value respectively (34) and ethanolic extracts of root and flowers had shown antioxidant activity (35). The studies reveal that ethanolic solvent based roots and dichloromethane and methanol-based leaves extract show free radical scavenging activity β-TC6 cells (36).

3.6 Anthelminthic and Anti-Parasitic Activity

The experimental demonstration of C. roseus ethanolic solvent plant-based extract on Pheretima posthuma and Bovicola bovis schrank, Hippobosca maculata leach against the standard drug Piperazine citrate 50 mg/ml and

synthesized titanium dioxide nanoparticles and obtained (37) significant IC50 values.

3.7 Suppression of central nervous system and analgesic activity

The Central neural network and movement response was slowed down when compared with Diazepam drug. The pentobarbitone shown analgesic effect. The extract interacts with opioid binding sites and alleviates pain and inflammation in nerve ending (14).

3.8 Neuroprotective and Memory Enhancement Activity

Another feasible alkaloid vinpocetine found to show significant effects for treating Alzheimer disease, cyclic GMP and cerebrovascular circulation by suppressing phosphodiesterase type 1 to preserve neural functions. The reduced blood supply or amyloid induced dysfunctions are ameliorated by these alkaloids by scavenging oxidative stress radicals and anti-inflammatory functions (14). Serpentine, a therapeutic characteristic alkaloid of C. roseus, attenuates cholinergic abnormalities of progressive neurological diseases like AD by mitigating breakdown of acetylcholine at junctions, down regulating acetylcholinesterase activity (38).

3.9 Antimicrobial and Anti-inflammatory Activity

Root extract against Salmonella boydii, S. typhimurium, flower extract against C. diphtheriae (39), chloroform extract against Bacillus subtilis, Staphylococcus aureus and Micrococcus luteus (5), Escherichia coli, and Candida albicans (40), Trypanosoma brucei, Herpes Simplex Virus were found effective. The tissue fluid accumulation, leukocyte recruitment and prominent decrease in volume using C. roseus ethanol extract (41) by downregulating lipoxygenase and cyclooxygenase pathways. Charge on alkaloids and cell wall leads to electrostatic interactions altering metabolic, protein production and modulating structural changes in microbial membrane (28).

3.10 Other Therapeutic Properties

The antiulcer activity has been shown by vincamine and vindoline. The experimental studies on wistar rats model induce imbalanced bowel movements by castor oil while the plant extract exhibiting antidiarrheal activity (14). The anti-hyperglycemic activity enhanced glucose utilization act on liver (42). In polluted land source rehabilitation and restoration of chromium, leaves also act against cadmium toxicity (25,26). Hypotensive property has been tested on lab animals by injecting Hydroalcoholic or Dichloromethane-methanol leaf extracts (5). The medicinal use of C. roseus for breathing related disease like cough in traditional Chinese medicine (43). The periwinkle extract used to treat numerous conditions like inflammation of larynx, mycobacterial infection, thoracic pain, asthma, pharyngitis, ascorbate deficiency, skin problems like acne, rashes, dermal inflammation, excessive menstrual flow (4), bowel cleansing, detoxification (5). Induce neovascularization near wound infection. Leaf powder with dark chocolate controls nitric oxide synthesis aids in regulation of Insulin (44).

Table 3. C. roseus alkaloids and there anticarcinogenic applications.

C. roseus Components	Binding site	Mode of action	Effect on Cancer cell
Vindesine	tubulin	Suppression, polymerization of tubulin	Disrupts cell cytokinesis
Vinblastine and vincristine	tubulin	Attenuation of microtubule polymerization	Downregulate apoptosis and cell division
vinblastine	β-adrenergic blockers and mitomycin C	Mitochondrial disruptions Altering drug efflux transporters	Apoptosis Alleviates multidrug resistance
vinflunine,	fluorinated microtubule inhibitor	Stops polymerization of tubulin Initiate B (NF-κB) and JNK apoptotic pathway	urothelial carcinoma leukemia, breast, lung, and Hodgkin's disease

4. TOXICOLOGICAL ASSESSMENT AND SAFETY EVALUATION

We already know the traditional usage of medicinal herbs for treating numerous diseases, but ignoring the side effects and toxicity might be dangerous (1). Extract may contain adulterants, toxins, interfering substances or residual products (44). Few side-effects of Vinca rosea addressed are hypotension, auditory dysfunction, gastric discomfort, obstipation, allergy, lethality, blood loss etc. (10). Under regulatory act Louisiana State Act 159, the problems related to cardiac, paralysis is caused due to consumption of toxic plant extract. (26). Evaluation of administered dose of these indole alkaloids are essential for safety concerns. The failure or altering actions of metabolic processing CYP3A enzyme which facilitate the systemic elimination of vinblastine and vincristine may lead to the detrimental effects. (45). Vincristine may have long lasting effect on neuropathic injury and vinblastine on hematopoietic activity. (46). The experimental studies on dosage and time of exposure of plant extract were studied on hepatic, cardiac and renal injury (300 mg dose) (44). C. roseus effect on sheep shown altered coagulation markers (42), Mohammed BM et al. in

2016 has illustrated that at 2000 mg cause fatality and after significant doses adverse effects were noted such as involuntary shaking and restlessness (47).

The terpenoid indole alkaloids (TIAs) synthesis mechanism by Madagascar periwinkle remains unclear though having enough data on gene transcription and genomic data. Alkaloids like vindoline, vinblastine, ajmaline, serpentine synthesized from endophytic microbes residing in C. roseus are investigated (48). The surveillance of metabolic pathway modification, introduction of foreign genes, stimulation will be useful tools for alkaloids production (6). For further research, the techniques of extraction, design and optimization on commercial scale for more efficacy and safety is required (22). The advanced delivery system like hydrogels, nanoparticle carriers, dendrimer conjugates will enhance efficiency of these products, nevertheless need of assessing phased clinical trials, therapeutic delivery, toxicological evaluation, safety surveillance to explore genetics to cure the diseases. (28)

5. CONCLUSIONS

The review is focussed on various pharmaceutical applications of Catharanthus roseus such as anti diabetic, anticarcinogenic, antimicrobial activity, neuroprotective and immunomodulatory activities as well as toxicity of plant components. It can be used as an excellent external agent and particular alkaloids can be used for drug manufacturing for particular diseases but it is to get into people's knowledge that regular intake can make a normal person loss its cell functioning and can cause major issues related to gastroenteric system, hearing, allergy as well as lethality to some extent. Emergence of assessment of safety profile is mandatory. For potential research directions for new design, formulation and development of medicine, additional awareness regarding toxicity, dose and administration is required.

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