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PHARMACOLOGICAL ACTIVITIES OF CATHARANTHUS ROSEUS: A PERSPECTIVE REVIEW

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ABSTRACT

India possess a rich biodiversity of the medicinal plants that were still not explored completely. The need for the novel pharmaceutical products out from the plant has attained a great interest in the present research world due to the cost and the higher side effects that are associated with the chemically manufactured drugs. *Catharanthus roseus,*which is a potent medicinal plant many of the pharmacological actions such as antimicrobial, antioxidant, anthelmintic, antifeedant, antisterility, antidiarrheal, antidiabetic effect etc. That is used to treat many of the fatal diseases. Alkaloids were the major phytochemical constituent of the above medicinal plant and have different types possessing various medicinal uses. The pharmacology of the plant was found to be associated mostly especially with the alkaloids that occupies almost most of the parts of the plant. In this review, an attempt has been made to summarize the pharmacological effect of the above plant against various disease starting from the antimicrobial to that of the antineoplastic diseases in a precise way to help the scientist and learners to understand the basis medicinal value of the plant.

KEYWORDS: ***Catharanthus roseus,*** **Apocynaceae, Monoterpenoid, Catharanthine, Antineoplastic.**

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INTRODUCTION

Catharanthus roseus (L.) which is an important medicinal plant of the family Apocynaceae is used to treat many of the fatal diseases. *C. roseus* also possess good antioxidant potential. There are about two common cultivars of *C. roseus* which is named on the basis of their flower color that is the pink flowered 'Rosea' and the white flowered 'Alba'[1]. *C. roseus* is extensively cultivated in northern India in order to meet their commercial and the ever increasing demand in the indigenous systems of the medicine also their need to the pharmaceutical industry. However, certain factors like the soil salinity hampers the cultivation of this plant very severely[1, 2].*Catharanthus roseus* which is pridely known as the Madagascar periwinkle is found to be a species of *Catharanthus* native and also endemic to Madagascar. The synonyms of the plant name include *Vinca rosea*, *Ammocallis rosea* and *Lochnera rosea.*Other English names occasionally used for the plant include Cape Periwinkle, Rose Periwinkle, Rosy Periwinkle and "Old maid"[3]. A traditionally used medicinal plant *Catharanthus roseus* is an erected procumbent herb or under the shrub containing latex. It grows widely to about 1m tall at the subtropical area. The leaves are found to be of oval to oblong, 2.5 – 9.0cm 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 and they are arranged in the opposite pairs. The flowers looks white to dark pink with a darker red centre and a basal tube of 2.5 – 3.0 cm long with a corolla of about 2.0 – 5.0 cm diameter with five petals like lobes. The fruits are found to be a pair of follicles of about 2.0- 4.0 cm long and 3 mm broad[4]. This plant is found to be rich in their pharmacological actions that includes antibacterial, antifungal, antioxidant, anticancer and antiviral activates[5].

PLANT DISTRIBUTION

In the wild, it is found to be an endangered plant and the main cause of their decline is the habitat destruction by the slash and burn agriculture. However, it is also widely cultivated and naturalized in the subtropical and tropical areas of the world[3]. It is found to be an evergreen sub-shrub or the herbaceous plant that grows to about 1 m tall with white to dark pink flowers[4].

PHYTOCHEMICAL COMPONENTS AND THEIR MEDICINAL USES

Alkaloids that are isolated from *C. roseus* are found to be hypotensive, sedative and possess tranquilising and anti cancerous properties. Traditionally, the plant has been used for relieving muscle pain, depression of the central nervous system and wasps stings. It is used in the cases of nose bleed, bleeding gums, mouth ulcers and sore throats. It has also been used internally for the treatment of the loss of memory, hypertension, cystitis, gastritis ,enteritis, diarrhoea and the raised blood sugar levels[6]. Its application ranges widely from the prevention of cancer, cancer treatment, anti-diabetic, stomachic etc[7]. *Catharanthus roseus* was the highly exploited and studied medicinal plants as it was found to produce more than 100 monoterpenoid indole alkaloids (MIAs) that includes the two major commercially important cytotoxic dimeric alkaloids that are used in the cancer chemotherapy[8]. *C. roseus* was also found to be a good source of the non-enzymatic and enzymatic antioxidants[9,10]. From the Traditional period itself, the plant has been used to cure diabetes and high blood pressure as it was believed to promote the insulin production or to increase the body's usage of the sugars from the food in case of diabetes[11]. During the period of 1950s, *C. roseus* was found to possess a large number of chemicals in the alkaloid class. Alkaloids are the bitter-tasting plant compounds that contains mostly of nitrogen many of them was found to possess pain relieving or the anticancer properties. Especially two major alkaloids in *C. roseus* such as vinblastine and vincristine was developed into the prescriptions for the anticancer drugs[12]. These injectable drugs and its derivatives such as vinflunine acts in several pathways and was found to interfere with the division of the cancer

cells. Recently, it was also found that certain chemicals in *C. roseus* involves in the prevention of the growth of the new blood vessels that is supporting the tumour growth[13].Vincristine was found to be produced by *Fusarium oxysporum* which is an endophyte of this host[14], while another group has isolated the vinblastine from an endophytic fungus[15]. *Catharanthus roseus* L. is found to be an important source of the indole alkaloids that are present in all plant parts. The plant has been used for the treatment of diabetes, fever, malaria, throat infections, chest complaints, regulation of menstrual cycles and as a euphoriant[16]. The physiologically important antineoplastic alkaloids such as vincristine and vinblastine are present in the leaves and the antihypertensive alkaloids are found in the roots such as ajmalicine, serpentine, and reserpine[17]. Vincristine and vinblastine alkaloids are found to be useful in the treatment of various types of lymphoma and leukemia[18,19]. These *Catharanthus* alkaloids are found to be used for the treatment of both malignant and non-malignant diseases and in the platelet and platelet associated disorders[16].

A US government screening program has discovered incidentally that the *Catharanthus* extracts were antineoplastic in vitro that leads ultimately to the licensing of the alkaloids such as vinblastine and vincristine, as well as some of the synthetic analogs today, as the highly toxic chemotherapy drugs. The absolute levels of vinblastine and vincristine are considered to be far too low in order to explain the activity of crude extracts of *Catharanthus*[20, 21]. Other pharmacological uses of *C. roseus* include wound healing, analgesic, vasodilatory and hypoglycaemic[22]. Hence, *Catharanthus roseus* (L.) G. Don is found to be the most extensively investigated medicinal plant that is known mainly for its pharmacologically important alkaloids [23].present, the *Catharanthus* alkaloids was found to comprise a group of about 130 terpenoid indole alkaloids (TIAs)[24]. No other single plant species was reported to produce such a wide array of the complex alkaloids[25]. Wide differences has been noted in the compositions of the alkaloids that are isolated from the underground and aerial tissues of the plant[26,27]. The roots of the plant was found to accumulate ajmalicine and serpentine, which are the important components of medicines that are used for controlling the high blood pressure and other types of the cardio-vascular maladies. However, the plant has been particularly known for its economically significant leaf-specific bisindole alkaloids, vinblastine and vincristine, which are found to be the potent antineoplastic agents[28,29] and the indispensable constituents of the most cancer chemotherapies. Vindoline that is found specifically in the green parts of the plant and not in the roots or cell suspension cultures was found to be biosynthesized from the branch-point intermediate tabersonine[30] .Catharanthine was reported to be present in the root tissue and in the aerial part of the plant[31]. Alkaloids that are present in the plants was found to be effective in leukaemia treatment, diabetes, hypertension and menorrhagia etc[32]. But, only little work has been done on the anti-insect properties of the root extract of *C. roseus* when compared with that of the aerial portion[33]. Vindoline and catharanthine are found to be the major monomer alkaloids.Vinblastine and vincristine are the two well known anticancer drugs that are used in the treatment of acute leukemia and Hodgkin's disease[34]. Low "dimeric" alkaloid contents in the plants has encouraged the intense research for the alternative production methods by involving the usage of cell cultures [35,36], metabolic engineering[37], semi-synthesis[38,39] or even the total chemical synthesis[40]. Total synthesis was found to be difficult due to the structural complexity of the molecules and also the complicated reaction steps that involves the stereochemical constraints. Various semi-synthetic procedures was developed for these alkaloids on the basis of their chemical[38,39] or enzymatic[41] coupling of the commercially available catharanthine and vindoline. A photochemical one pot synthesis has been proposed as a means of the simpler and economically feasible semi-synthesis of the vinblastine and vincristine[42].

PHARMACOLOGICAL ACTIVITIES

ANTIOXIDANT ENZYME ACTIVITIES

An experiment was carried out in order to determine the changes in the antioxidant enzyme activities with respect to different concentrations of sodium chloride (NaCl) in *alba* and *rosea* varieties of *Catharanthus roseus* (L.) G. Don. in pot culture at various stages of growth. Especially, Superoxide dismutase (SOD), peroxidase (POX), catalase (CAT) enzymes antioxidant potentials were analysed. The result revealed the fact that the SOD activity was found to be increased at the level of 50 mM NaCl, but was reduced at further higher treatment levels. There were no significant changes obtained on the POX activity at the range of 25 mM NaCl level but showed significant increases of this activity at the next, higher levels of NaCl. From the above experiment,it was proved that *C. roseus* is an ideal plant for the cultivation in salt affected areas and we can obtain plants with the higher antioxidant and medicinal values[43].

ANTHELMINTHIC ACTIVITY

Helminthes infections are the chronic illnesses affecting human beings and cattle. *Catharanthus roseus* was found to be used from the traditional period as an anthelminthic agent. The anthelminthic property of *Catharanthus roseus* has been evaluated by using *Pherithema posthuma* as an experimental model and with Piperazine citrate as the standard reference. The ethanolic extract of the concentration of 250 mg/ml was found to show the significant anthelminthic activity with death time of 46.33 min whereas the standard drug at 50 mg/ml was found to show the death time of 40.67 min This investigation supported the ethnomedical claims of *Catharanthus roseus* as an anthelminthic plant[44].

ANTI HYPERGLYCEMIC EFFECT

The effect of the daily oral administration of *Catharanthus roseus* (CR) leaf dichloromethane: methanol (1:1) extracts (500 mg/ body weight) for 20 days was tested on the blood glucose and hepatic enzymes in the normal and Alloxan induced diabetic rats. The extract showed a significant increase in the body weight and decrease in the blood glucose, urea, cholesterol levels of the test animals. The activity of the hepatic enzymes such as hexokinase was increased whereas glucose 6-phosphatase and fructose 1, 6-bisphosphatase were found to be decreased significantly[45].

ANTINEOPLASTIC AND ANTIDIABETIC EFFECT

Different percentage of the methanolic crude extracts of *Catharanthus* was found to show the significant anticancer activity against numerous cell types in the *in vitro* condition[46] and especially greatest activity was found against the multidrug resistant tumor types[47].Several animal studies have proved that the ethanolic extracts of the leaves and flowers of *Catharanthus* has lowered the blood glucose levels[48,49]. The aqueous extract was found to lower the blood glucose of about 20% in diabetic rats when compared to that of the dichloromethane and methanol extracts which lowered the blood glucose level to 49-58%[50]. The hypoglycemic effects has appeared due to the result of the increased glucose utilization in the liver[51].

IN VIVO ANTIDIARRHEAL ACTIVITY

The *in vivo* antidiarrheal activity of *C. roseus* ethanolic leaf extract was tested in the Wistar rats with castor oil as a experimental diarrhea inducing agent in addition to the pretreatment of the extract. Loperamide and atropine sulphate was used as the standard drugs . The antidiarrheal effect of ethanolic extract of *C. roseus* showed the dose dependant inhibition of the castor oil induced diarrhea at the doses of 200 and 500 mg/kg[52].

ANTIMICROBIAL ACTIVITY OF CATHARANTHUS ROSEUS

Catharanthus roseus is found to be an important medicinal plant for the production of the novel pharmaceuticals as most of the bacterial pathogens were developing resistance against many of the available anti microbial drugs. Plants have been proved to be a

significant natural resources for the effective chemotherapeutic agents and offers a broad spectrum of activity with the greater emphasis on the preventive action. This study aims to investigate some of the anti microbial properties of this plant. The antimicrobial activity of the leaf extracts of the plant was checked against the microorganisms like *Pseudomonas aeruginosa* NCIM 2036, *Salmonella typhimurium* NCIM 2501, *Staphylococcus aureus* NCIM 5021 and was found that the extract coud be used as the prophylactic agent in the treatment of many of the diseases[53].

TRANSCRIPTOME ANALYSIS

In *Catharanthus roseus* (L.) G. Don each plant tissue was known to produce a distinct spectrum of terpenoid indole alkaloids. But, the invaluable antineoplastic bisindole alkaloids was found to be restricted to the aerial parts of the plant and not in its underground tissues.Hence,the identification of the structural and regulatory factors that are operating distinctly in the shoot/leaf of the plant would be of a common necessity for the modulation of bisindole alkaloid biosynthesis. The elucidation of the differential gene expression in the two main tissues (leaf and root) of the plant which is well known for their distinct terpenoid indole alkaloid profiles was done indirectly through the construction and characterization of the separate cDNA libraries and directly through a strategically designed suppression subtractive hybridization by using the leaf and root cDNA populations as the tester and driver, respectively. Out of the total of 155 ESTs subjected to the homology-based classification, direct approach has yielded an EST for sgd (strictosidine *b*-D-glucosidase) and 16 novel ESTs[54].

EFFECT OF PERIWINKLE ON LEPIDOPTEROUS INSECT

Five fractions that were obtained from the root of the common periwinkle was evaluated for their antifeedant activity, growth regulatory potential and its effect on the fecundity and fertility against various stages of a lepidopterous insect, *Spilarctia obliqua*. The chloroform and ethyl acetate fractions was found to be highly effective as the antifeedants, growth inhibitors and was found to cause sterility in the treated male adults. Initial instars of the test insect was found to be quite susceptible to the chloroform fraction at the concentration of 5%, whereas the late instar arvae was found to be unaffected[55].

STUDY ON THE POLYAMINES AND THE CELL CYCLE OF CATHARANTHUS ROSEUS CELLS IN CULTURE

The effect of partial depletion of polyamines (PAs) which is induced by the treatment with inhibitors of the biosynthesis of PAs, on the cell distribution at each phase of the cell cycle in Catharanthus roseus (L.) G. Don. cells in the suspension cultures was studied by means of using flow cytometry. Inhibitors of arginine decarboxylase (ADC) and omithine decarboxylase (ODC) was found to accumulate more cells in the G, phase whereas the inhibitor of spermidine (SPD) synthase was found to show no effect on the distribution of cells. Two peaks of the endogenous level of PAs, in particular, of PUT and SPD was observed during the cell cycle. Levels of PAs was found to increase markedly prior to the synthesis of DNA in the S phase and prior to the cytokinesis.Activities of ADC was found to be much higher than that of ODC throughout the cell cycle, but both ODC and ADC changed in concert with the changes in levels of Pas[56].

ANTIOXIDANT PROPERTIES

Free radicals are found to be the fundamental of any biochemical process and hence represents an essential part of the aerobic life and metabolism and could show a dual role in our body as both the deleterious and beneficial species. The antioxidant potential of the ethanolic extracts of the roots of the two varieties of Catharanthus roseus L. namely ‘rosea’(pink flowers) and ‘alba’(white flowers) was obtained by using different systems of assay such as Hydroxyl radical-scavenging activity, superoxide radical-scavenging activity, DPPH radical- scavenging activity and nitric oxide radical inhibition method. The results obtained proved that the ethanolic extracts of

the roots of Periwinkle varieties extracts has exhibited the satisfactory scavenging effect in all the radical scavenging assays in a concentration dependent manner but *Catharanthus rosea* was found to possess more antioxidant activity than that of *Catharanthus alba*[57].

EFFECT OF AN ANTIDIABETIC EXTRACT OF CATHARANTHUS ROSEUS ON ENZYMIC ACTIVITIES

Hypoglycemic activity was detected by using the dichloromethane:methanol extract (1:1) of the leaves and twigs of *Catharanthus roseus* medicinal plant in streptozotocin (STZ) induced diabetic rat model at the dose of 500 mg/kg that was given orally for 7 and 15 days.The extract showed 48.6 and 57.6% hypoglycemic activity and further treatment for 30 days has provided complete protection against STZ challenge (75 mg/kg/i.p.×1). Enzymic activities of glycogen synthase, glucose 6-phosphate-dehydrogenase, succinate dehydrogenase and malate dehydrogenase was found to be decreased in the liver of diabetic animals which would be significantly improved after treatment with extract at dose 500 mg/kg p.o. for 7 days. Results indicated the increased metabolization of glucose in treated rats with the increased levels of lipid peroxidation [58].

CONCLUSION

Medicinal plants were the potent source of various novel pharmaceutical products that shows ect causing potent pharmacological effect on the human beings. Instead of using the side effects causing chemical drugs, the ancient medicine could be explored to identify the novel drug formulations that are more effective with lesser side effects and also cheaper cost. Though, many of the traditional drugs were used without understanding the basic mechanism,their effect could be proved further with the help of the present technology and tools. The active compound that is responsible for the pharmacological effect could be found very easily and also commercialized as a drug product itself with proper approval from the respective organizations.The above plant was investigated from the ancient time for their phytochemical components and their pharmacological effect.The plant contains enormous phytochemical constituents of various medicinal application.The plant alsopossesvarious activitiessuchasantimicrobial, antioxidant,anthelmintic,antifeedant,antisterility, antidiarrheal,antidiabetic activities, etc. Hence, more work could be done on the above plant to reveal the unknown mysteries which would help the need of the present pharmaceutical world.

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