Review Article

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# *CATHARANTHUS ROSEUS* (TAPAK DARA):"A CONTROVERSIAL" MEDICINAL PLANT IN INDONESIA

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**ABSTRACT**

Herbal medicine industry in Indonesia was shaken when Indonesian National Agency of Drugs and Food control prohibits the development of herbal medicines made from *Catharanthus roseus*. The reason given is that *Catharanthus roseus* contains alkaloids causing bone marrow depression. The purpose of this article to explore the effects of both preclinical and clinical pharmacological of *Catharanthus roseus*. The result of the research shows *Catharanthus roseus* have many pharmacological effects include: antidiabetic, hypolipidemic, antihypertension, anticancer, antiangiognesis, antispermatogenic, antifungal, antibacteria, antioxidant, wound healing and even hepatoprotective activity.

**Keywords**: *Catharanthus roseus*, Herbal medicine, Pharmacological, Alkaloid, Bone suppression

## INTRODUCTION

Indonesian National Agency of Drugs and Food Control released regulation no. 10 of 2014 that prohibit the development (manufacture & distribute) of herbal medicines / supplements made from *Catharanthus roseus*. This raises questions and allegations as to be *Catharanthus roseus* is a dangerous plant.[1] The regulation stated that the alkaloids in *Catharanthus roseus* may cause bone marrow depression. Interestingly, many studies suggest a variety of pharmacological effects of *Catharanthus roseus*. Most studies are still in the preclinical stage study, but some others already in early stages of clinical trials. Vincristine and Vinblastin of *Catharanthus roseus* even been marketed. The prohibition should not be necessary if the development of herbal medicines made from *Catharanthus roseus* can eliminate the presence of alkaloids. This review tries to investigate pharmacological effects of *Catharanthus roseus*.

### Description

*Catharantus roseus* is tropical/subtropics plant that is spread throughout the world.[2] This plant belongs to the family of Apocynaceae. This plant is herbaceous/ sub herbaceous with a high CMM 40-80. The flower color are purple and pink white.[3] It has different names in several countries, among others: *Tapak dara* (Indonesia), *Kemuning china* (Malaysia), *Periwinkle* (Madagascar), *Nayantara* (Bangladesh), *Ainskati, Nityakalyani, Rattanjot, Sadaphul, Ushamanjairi* (India), *Kantotan* (Filipina), *Nichinich-so* (Jepang), *Chatilla* (Guatemala), *Phaeng phoi farang* (Thailand), etc.

### Traditional Uses

Leaves of *Catharanthus roseus* is commonly used as antidiabetic in Northern Europe (Swanston-Flatt) and India.[4] In Brazil, Dominica, England, Cook Islands, Jamaica, Mozambique, Pakistan, Taiwan, Thailand and West Indies, decoction of *Catharanthus roseus* leaves are also used as antidiabetic.[5] In India this plant was used to treat depression, muscle pain, bleeding gums, mouth, ulcers and sore throats.[6] This plant was also used to treat cystitis, gastritis, hypertension, enteritis, diarrhea.[7] In South Africa, people use *Catharanthus roseus* as urogenital infection,[8] diabetes mellitus (Zulu people),[9] menorrhagia[10] and rheumatism.[11] In Southern and Eastern Africa, this plant was used to treat unspecified venereal diseases.[12] The people of Mutirikwi, Zimbabwe, used *Catharanthus roseus* to treat stomach ache.[13] The decoction of leaves of *Catharanthus roseus* were used to treat diabetes mellitus (In the Kancheepuram, a District of Tamil Nadu, India).[14]

### Preclinical studies of pharmacological properties

#### Antidiabetic

The ethanolic extract of *Catharanthus roseus* leaves & flower reduced blood glucose level in diabetic rats.[15,16] The combination of dichloromethane : methanol extract with ratio 1:1 dosage 500mg/kg bw orally for 7 days and 15 days reduced blood glucose level with hypoglycemic activity 48.6 and 57.6% in streptozotocin induced diabetic rats.[17] *Catharanthus roseus* leaf powder suspension in 2 ml distilled water (100 mg/kg body weight/day/60 days) orally can reduced plasma glucose and increase plasma insulin in diabetic rat induced by streptozotocin.[18] The aqueous extract of *Catharanthus roseus* leaves dose 1g/kgbw can reduced blood glucose level significantly as compared to control (28.20±0.34 vs 32.99±0.89 m mol/L).[19] The aqueous extract of *Catharanthus roseus* leaves, roots, flower and stem at doses 250mg/kgbw intra peritoneal for 14 days can reduced blood glucose level and the reduction percentage is 52,90%.[20] The combination of

dichloromethane : methanol (1:1) extract doses 500mg/kgbw orally 20 days can decrease blood glucose level in male wistar albino rats compared to control diabetic (110.08± 8.6 vs 241.62 ± 2.3 mg/dL).[21] The juice of *Catharanthus roseus* leaf dose 0,5; 0,75 and 1,0ml/kgbw orally can decrease blood glucose level after 6, 8, 10, 12, 16, 18, 20 & 24 h drug administration with reduction percentage of 16.7% (6 h, $p < 0.05$), 28.6% (18 h, $p < 0.05$), and 31.9% (20 h, $p < 0.01$).[22] The combination of dichloromethane: methanol (1:1) extract of whole plant of *Catharanthus roseus* (500mg/kg body weight) daily orally for 14 days can reduced blood glucose level on diabetic female albino rats wistar strain induced by alloxan 80 mg/kgbw.[23] The aqueous extract of *Catharanthus roseus* can decreased blood glucose on diabetic rats significantly.[24] Research by Islam *et al*., found that the ethyl acetate fraction of ethanolic extract of *Catharanthus roseus* leaves dose of 150 mg/kgbw intra peritoneal can reduce fasting blood glucose on 24 h with 40.6 percent of reduction on diabetic rats induced by streptozotocin (45 mg/kg).[25] The chemical compound of this fraction that hypoglicemic effect are alkaloid like as catharanthin, leurosine, lochnerine, tetrahydroalstonin, vindoline and vindolinine ($p<0.01$).[26]

**Hypolipidemic**

The *C. Roseus* leaf powder suspension in 2 ml distilled water (100 mg/kgbw/day) for 60 days orally can decrease total cholesterol, triglyceride, LDL, VLDL, atherogenic index but it increases HDL.[18] The aqueous extract of *Catharanthus roseus* of dose of 250 mg, 350 mg, and 450 mg/kg body weight for 30 days can reduce lipid profile (TC, TG, LDL & VLDL) significantly in diabetic rats.[24] The fraction of petroleum ether, ethyl acetate and chloroform of ethanolic extract of *Catharanthus roseus* leaves at dose of 150 mg/kgbw intraperitoneally can decrease total cholesterol, triglyceride after 24 h.[25]

**Antispermatogenic**

The aqueous extract of *Catharanthus roseus* has antispermatogenic on the male Swiss albino mice. The mice were treated by this extract had a sperm count and percentage of motile sperm less than control. The dead sperm of treated mice was more than control. [27]

**Antihypertensive**

Research by Ara *et al*., 2009 found that the leaves extract of *Catharanthus roseus* at dose of 30 mg/155±15 g body weight by intra peritoneal injection for one week reduced blood pressure on hypertensive rats induced by adrenalin. This effect was equivalent with atenolol at dose of 0,1mg/ 155±15 g body weight.[28]

**Antifungal**

The ethanolic extract of *Catharanthus roseus* leaf has antifungal activity toward *Aspergillus niger, Aspergillus flavus, Aspergillus fumigates, Candida albicans* and *Penicillium chrysogenum* by disc diffusion method. The width of zone of inhibition 4.2 mm; 3mm; 1.8mm; 1.6mm and 3.3mm respectively. Secondary metabolites such as alkaloids in *Catharanthus roseus* were suspected causing antifungal effect.[29]

**Anticancer and cytotoxic**

The chloroform extracts of crude of *Catharanthus roseus* has cytotoxic activity to human colorectal carcinoma cell line (HCT 116). Vindolin and catharantine are two isolated compound from *Catharanthus roseus* which has cytotoxic activity to HCT 116. The cytotoxic activity of catharantine was greater than vindolin. Catharantine has cytotoxic activity to HCT 116 with $IC_{50}$ 60µg/mL.[30]

Vincaleukoblastine derivative from alkaloid vinea has antineoplastic activity in mice, was transplanted by leukemia L1210, P1534 and Ehrlich ascites tumor cells,[31] while vincristine has antineoplastic effect on patients with Hodgkin's disease. 39% patients with Hodgkin's disease treated by vincristine have temporary remission more than one month.[32] The mechanism involved were binding of this agent to tubulin. This binding could block the mitosis cell that causes metaphase capture.[33,34]

**Antibacterial**

The 10, 25, 50, 75 and 100 mg of the dried whole plant extracts with dichloromethane: methanol (1:1) have antibacterial activity to *K. pneumoniae, P. aeruginosa, E. coli, B. cereus, B. subtilis,* and *S. aureus*.[23] Research by Balaabirami *et al*., 2012 found that the ethanolic extract of *Catharanthus roseus* leaves has antibacterial effect to *Escherichia coli, Klebsiella oxytoca, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhimurium, Salmonella paratyphi* and *Staphylococcus aureus*.[29]

**Hepatoprotective**

The ethanolic extract of *Catharanthus roseus* leaves at dose of 500 mg/kgbw reduced blood SGOT and SGPT level in rats. This effect may be due to by antioxidant property of phenolic compound from this extract.[35]

**Antioxidant**

The methanolic extract of *Catharanthus roseus* val. Alba leaves at doses of 200 &400 mg/kgbw have antioxidant effect. This extract reduced plasma superoxide dismutase, catalase and glutathione levels significantly of diabetic rats as compared to controls.[36]

**Wound healing activity**

The ethanolic extract of *Catharanthus roseus* flower 100mg/kgbw/day orally for 10 days showed wound healing activity in wound model rats SD strain. This extract increased the wound breaking strength in the incision wound and decreased wound area and epithelization period in excision wound compared with controls ($P < 0.001$).[37] Research by Dewi et al., 2013 found that the methanol leaf extract of *Catharanthus roseus* 15% topically increases wound healing/epithelization in wistar rats.[38]

**Antiangiogenesis**

Several plants of traditional Chinese medicinal herb have anti-angiogenesis effect on chick embryo chorioallantoic membrane model. The aqueous extract of *Catharanthus roseus* leaves at dose of 1g herb/mL has anti-angiogenesis activity with percentage of inhibition is (33.65 ± 1.62%).[39]

**Clinical studies of pharmacological properties**

**Anticancer**

Vincristine sulfate is indicated to treat lymphoblastic leukemia acute and lymphoma. This agent was approved by US FDA in 1963 with brand name Oncovin®. Vinblastine is indicated to treat lymphomas inclusive of Hodgkin's disease, bladder and breast cancers. In 1965, Vinblastine sulfate was approved by FDA. This agent was marketed with brand name (Velban®).[34,40]

Vindesine and Vinorelbine, a semisynthetic derivate of vinblastine have potency to treat hematologic malignancy. Vindesine (Eldisine®) is used in France, the UK, and other countries to treat drug-resistant acute of lymphoid leukemia, [41] while vinorelbine shows potency to treat Hodgkin's disease.[42,43] Vinorelbine tartrate (Navelbine®) is used to treat non-small cell lung carcinoma or advanced breast cancer.[40]

**Antidiabetic**

In a clinical study involved 60 people suffered from diabetic mellitus, the administration of the aqueous extract of *Catharanthus roseus* at dose of 75mg/day for 30 days can reduce blood glucose level 2 h post prandial, glycated Hb, Total Cholesterol, Total Triglyceride, LDL-C, VLDL-C, HDL-C significantly as compared to control (placebo).[44]

**Circulatory disorder**

Ajmalicine, alkaloid from *Catharantus roseus*, is used for treatment circulatory disease.[45]The monomeric alkaloids ajmalcine and serpentine are used in the treatment of circulatory diseases.[46-53]

**Chemical compounds**

*Catharanthus roseus* contains about 130 different alkaloids.[54] The several alkaloid among others: reserpine, ajmalcine, vinceine, raubasin,[54] catharantine and vindoline.[30] Anticancer drugs are vincristine & vinblastine,[30] cartharathine, lochnenine, vindoline, vindolinenine, tetrahydroalstronine, reserpinne, serpentine.[26] Vincristine is indicated to treat Hodgkin's Lymphoma, while vinblastine revealed to treat leukemia on child, [55] yohimbin, [56] and flavonoid hirsutidin.[57]

The Phytoconstituents of *Catharanthus roseus* are carbohydrate, alkaloid, glycoside, flavonoids, tannin, saponins, protein, amino acid, fats and oils.[23] Fraction of petroleum ether of ethanolic of *C. roseus* leaves contains tannin, alkaloid, flavonoid, while fraction of chloroform & ethyl acetate contains alkaloid and flavonoid.[25]

## THE PROFILE OF HERBAL MEDICINE INDUSTRY IN INDONESIA

Indonesia is a tropical country and known as having second largest biodiversity after Brazil. It is estimated that there are around 25000-30000 plants found in Indonesia. This quantity is about 80% of the total populations plants in the world and 90% of the population of plants in Asia.[58,59] It is estimated that 7000 species of plants are utilized by Indonesian people as a traditional medicine and about 283 species of medicinal herbs are used by industry and registered to Indonesia National Agency of Drugs and Food Control.[59]

The development of herbal medicine industry in Indonesia continues to increase. In 2002 recorded only 29 small traditional medicine industry. This number increased to 172 in 2006. The complete list can be seen in Table 1

**Table 1: Herbal Medicine industry profile in Indonesia.** [60]

| Year | Small industry of Traditional medicine | Industry of Traditional medicine | Pharmacy industry | Total |
|---|---|---|---|---|
| 2002 | 29 | 10 | 16 | 55 |
| 2003 | 164 | 58 | 82 | 304 |
| 2004 | 217 | 54 | 85 | 356 |
| 2005 | 197 | 47 | 87 | 331 |
| 2006 | 172 | 40 | 79 | 291 |

Research by the Agency for Health Research and Development of Ministry of Health in 2007 on the use of herbal medicine by the people of Indonesia showed that 35.7% of people use herbs and more than 85% of them admitted the beneficial herbs for health.[61] In 2010 research was repeated and the result were 59.12% and 95.6% people admitted the beneficial herbs for health.[62]

Only 32 herbal medicine industries in Indonesia have been following good manufacturing practices for herbal medicine.[63] The majority of herbal medicine in Indonesia are not concerned with the alkaloids content of *Catharantus roseus* that might cause bone marrow depression. This possibly underlies the prohibition of this herb production by Indonesia National agency of Food and Drugs Control.

## CONCLUSION

*Catharantus roseus* has many pharmacological effects. The prohibition of the development of herbal medicines made from *Catharanthus roseus* due to its alkaloids contents could be avoided if the industry can eliminate these alkaloids. Within certain limits this rule can be understood as the practical level. Most Indonesian herbal medicine industries are small and medium industries which are sometimes less concern with the risk of alkaloids resulted from the *Catharanthus roseus*.

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