

Therapeutic and Anticancer Properties of *Nerium oleander*- A Poison as Medicine

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ABSTRACT

Cancer is a heterogeneous disease and ranks among the most pressing health concerns faced by humans and requires a proactive treatment approach. Plants are a rich source of compounds and offer a promising avenue for cancer research. Chemotherapy has so far been effective, but it comes with some very unpleasant side effects. *Nerium oleander*, an evergreen plant cultivated throughout the world, has many metabolites, including cardiac glycosides, phenols, saponins and terpenoids. The plant and its derivatives have been an essential component of traditional medicine for treating several ailments from the beginning of time, notably cancer, diabetes mellitus, asthma, and cardiac disease. However, the scientific community has not gone much further into the information. This review aims to understand the therapeutic applications of *N. oleander*, focusing on cancer. The leaf extract, anvizel and PBI-05204 has entered clinical trials and other derivatives like oleandrin and breast in are still under *in-vitro* and *in-vivo* studies. In order to combat cancer, the plant operates on several cancer-related signaling pathways, including the Akt mTOR downstream pathway.

Keywords: Cancer, Plants, *Nerium oleander*, Chemotherapy, Leaf extract.

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INTRODUCTION

Nerium oleander, commonly acknowledged as oleander is a small evergreen plant with a height of 2 to 6 meters and is cultivated throughout temperate and subtropical areas.¹ The origin is debatable due to its extended cultivation but is proposed to be from the Mediterranean and Indo-Pakistan subcontinent.² The leaves are thick, leathery, and pointy and arranged in pairs or a group of three whorls around the stem. A eudicot with typical minute reticulate venation covers the entire lanceolate which is 5 to 21 cm long and 1 to 3.5 cm wide. The inflorescence is terminal panicles of cymes with flowers that are showy and fragrant. The petals are majorly observed in pink, red and white with corolla campanulate, 5 petals, rounded and overlapping. Bracts are small calyx divided to the base with 5 linear and acute lobes. In 5 stamens with short filaments and 2 carpels are also observed. The plant produces many comose seeds (Figure 1).³⁻⁶

The plant is a member of the Apocynaceae family and the systematic position is as follows (USDA):

Kingdom: Plantae
 Division: Angiosperms
 Class: Magnoliopsida
 Subclass: Asteridae
 Order: Gentianales
 Family: Apocynaceae

Genus: *Nerium* L.

Species: *oleander* L.

In spite of the poisonous components, the plant has been used since time immemorial in various aspects. The *oleander* flowers are showy, profuse, and fragrant, making them suitable as ornamental plants along roadsides and gardens.⁷ *Oleander* traditionally played a major role in treating cardiac illness, corns, scabies, asthma, diabetes, cancer, and epilepsy. The plant exhibits antimicrobial activities aiding in wound healing.⁸ But most of the activities are yet to be proven scientifically. But the plant and different parts exhibit many medicinal properties and is mentioned in Figure 2.

Toxicity

Due to its poisonous properties primarily as an outcome of the presence of cardiac glycosides, the plant is used as an animal poison, especially as rat poison.⁹ Studies on goats showed signs of *oleander* toxicosis began one hour after taking the plant. Goats die within 4 to 48 hours due to varying degree of hemorrhages.¹⁰ A fatal case of self-poisoning as an attempt to commit suicide using *N. oleander* extract has been reported. A 71-year-old lab technician consumed an extract consisting of cardiac glycosides and ended his life. Toxicological screening for oleandrin and other cardiac glycosides were performed on all biological samples.¹¹



Figure 1: Flowers, leaves and seeds of *N. oleander*

Natural Products and Cancer

Cancer is a heterogeneous disease leading to uncontrollable cell division, accounting for nearly 10 million mortalities in 2020. With 12.5 and 12.2% of all cases, respectively, breast and lung cancers were the most prevalent worldwide in 2020.¹² Currently used synthetic chemotherapeutic drugs result in various fatal side effects and thus, the scientific community are focusing on developing plant and nature-based drugs with minimum side effects. Various phytochemicals present in plants like carotenoids, flavanoids, polyphenols, indoles and glucosinolates, can lower the risk of developing cancer. Some phytochemicals prevent tumor progression.^{13,14} Most phytochemicals have antioxidant properties. Antioxidant aims to eradicate the body's free radicals and prevent mutation which might lead to cancer.¹⁵ Taxol, the well-known chemotherapeutic agent against breast, ovarian and lung cancer, is taken from the bark of *Taxus brevifolia*.¹⁶ Curcumin, a phytochemical from *Curcuma longa* has been reported against breast, colorectal, pancreatic, lung, and head and neck cancer.¹⁷⁻²¹

N. oleander: A Potential Anticancer Agent

Various studies have reported anticancer properties of different parts of *N. oleander* consisting of the leaves, bark, stem, flowers, seeds and roots. The extracts and phytochemicals act on different downstream pathways of cancer and prevent multiplication of cells.

Oleander in Clinical Trails

Like various herbal medicines, crude *N. oleander* exhibits anticancer activities in different cancer subtypes.

Crude extract of *N. oleander* leaves

N. oleander crude extract were administered on 46 cancer patients at doses ranging from 0.2 to 10.2 mg per day. These dosages were given out daily in rotations that lasted 21 in every 28 days. The extract was well acceptable with minimal side effects.²² Extracts from the leaves of the plant has proved to inhibit cancer growth in many, including breast and lung cancers and have already entered clinical trials phase 1. The extract inhibit glycolysis, downregulates EGFR expression and pRb expression, arrest the cycle at G2/M phase in cervical cancer, inhibit cellular spread and migration and induce cell death in cancer cells.²⁷

Anvirzel

Another drug anvirzel isolated from *N. oleander* entered the phase 1 clinical trials for treating refractory solid tumors

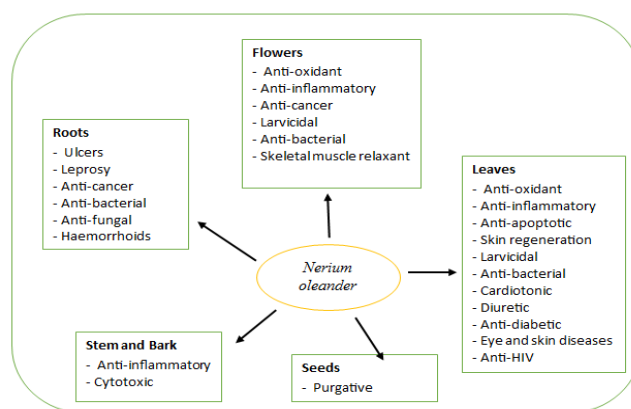


Figure 2: Therapeutic uses of *N. oleander*^{7,22-26}

and non-small cell lung cancer. But the promising study was withdrawn early without proper trials.^{28,29} Anvirzel majorly consists of oleandrin and oleandrigenin and demonstrated anticancer properties in various human cell lines, including breast, lung, prostate, colon, pancreatic cancer and melanoma.³⁰ The phytochemical activates capase cascade and inhibits bFGF transportation and blocks the Na⁺/K⁺ channel, thus preventing the activation of NF-κB, leading to proliferation and metastases of the cancer cells.³¹

PBI-05204

Similarly, PBI-05204, a supercritical CO₂ fluid (SCF) extract of *N. oleander* leaves, was found to exhibit anticancer properties against pancreatic cancer and glioblastoma.^{32,33} The drug was administered on 58 advanced cancer patients in phase I clinical trials and was found that a dose of 0.0083 mg/kg/day by mouth with 3 weeks per cycle would eliminate cancer.³⁴ The drug entered phase II clinical trails by treating candidates with metastatic pancreatic cancer.³⁵ The drug activates the innate immune system, NK cells and increases the IFN-γ levels, making the immune system work more specifically against the cancer cells.³⁶ PBI-05240 reduced the protein expressions in Akt and mTOR pathway.³³

Active Phytochemicals with Anticancer Properties

There are many active phytochemicals in *N. oleander* that possess anticancer properties. Some have been studied positively in *in-vitro* and *in-vivo* studies shown in Table 1. Further studies are required to rule out the chances of toxicity.

Oleandrin

Oleandrin is a monomeric substance attained from seeds and leaves of *N. oleander*.⁴² Numerous researches have reported the competence of oleandrin as an anticancer agent. The phytochemical induces cell death by actuating endoplasmic reticulum stress against breast cancer.⁴¹ Rad51, a DNA damage repair protein, was discovered to be downregulated by oleandrin.⁴² Reports have found the efficiency of phytochemicals in stimulating cell cycle arrest and death, inhibiting the growth of the tumor in mice and sensitizing cancer to chemotherapy and radiotherapy in humans.⁴³

Table 1: Active phytochemicals with anticancer properties

Extract/ phytochemical	Extract used	Therapeutic use	Dose/concentration IC ₅₀ (µg/mL)	Reference
Whole plant extract	Methanolic extract	PC3 Prostrate cancer	50.33	37
Leaf extract	Dichloromethane	T47d Breast cancer	57.77	38
		HepG-2 Hepatocellular carcinoma	233.42	38
		K562 myeloid carcinoma	55.90	38
	Aqueous	HT-29 Colon cancer	2.89	39
		MDA-MB-231 Breast cancer	1.67	39
	Ethanolic extract	HT-29 - Colon cancer	5.09	39
MDA-MB-231 - Breast cancer		2.36	39	
Flower extract	Dichloromethane	T47d Breast cancer	108.31	38
		HepG-2 Hepatocellular carcinoma	70.03	38
		K562 myeloid carcinoma	102.31	38
Phenolic compounds	Ethanolic extract	HT29 Colorectal cancer	2.432	8
		Oleandrin	0.02 µM	40
		MCF-7 - breast cancer	0.0145 µM	41
		SK-BR-3	0.00613 µM	41
MDA-MB-231 - breast cancer	0.24 µM	41	41	

Oleandrin and its cardiac glycoside derivatives suppress the STAT-3 signaling pathway and thus inhibit invasion.⁴⁴

Breastin

Breastin is a cold-water extract of the leaves of *N. oleander* and consists mainly of phenolic compounds chlorogenic acid and rutin. Studies have reported the anticancer activity in solid tumor cell lines, leukemia, hematopoietic cell lines, and multiple myeloma (Rashan *et al.*, 2023). Breastin has higher potential as an anticancer agent than currently used drugs, namely cisplatin, fluorouracil and cyclophosphamide. When combined with current drugs, the efficiency of the drugs increases. Breastin can inhibit the membrane Na⁺/K⁺ ATPase. They arrest the cycle at G2/M or at S-phase.⁴⁵

Cardiac glycosides

Cardiac glycosides have been proven as potent anticancer agents in *in-vitro* and *in-vivo* studies. *N. oleander* consists of many cardiac glycosides namely oleandrin, neritaloside, odoroside H, oleandrigensarmentoside and odoroside A.⁴⁶ The cardiac glycosides induce autophagy in tumor cells and have been reported in human glioblastoma in pancreatic cancer cells.⁴⁷

CONCLUSION

Cancer is a deadly disease affecting millions every year. Currently used synthetic drugs and treatment methods adversely affect the well-being of the patient by affecting various organs and causing the recurrence of cancer. Plant extract and derivatives are the safer alternatives to overcome this issue. *N. oleander* is a small evergreen plant with various medicinal properties and has been used in traditional medicine systems since immemorial. The scientific world has positively explored *N. oleander* as an anticancer agent despite being a

poison and targeting multiple signaling pathways directly and indirectly to inhibit cancer progression and migration.

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