

## An insight on Potential benefits of *Nerium oleander*

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### Abstract

Medicinal plants have been widely employed to treat a variety of ailments since ancient times. *Nerium oleander* is a poisonous plant with a tropical and subtropical environment. Oleander included phenols, tannins, flavonoids, coumarins, sterols, triterpenes, alkaloids, Neridienone A, oleandrin, PBI-05204, and phlobatannins, according to qualitative phytochemical screening. Because cardiac glycosides are present in *Nerium oleander*, they impede the "Na<sup>+</sup>-K<sup>+</sup> ATPase pump" in cardiomyocyte membranes and cause toxicity. The antioxidant, anticancer, anti-inflammatory, antimicrobial, antibacterial, antioxidant activity, and cytotoxicity characteristics of *Nerium oleander* extract were reviewed in the current study.

**Keywords:** *Nerium oleander*, Medicinal plant, Activity of *Nerium oleander*, Toxicity

### 1. Introduction

As per World Health Organization, nearly 80% of the world's population belongs to developing or less developed countries, and ancient medicine meets almost all of their fundamental healthcare needs. Over 3.3 billion people in developing nations use herbal plants on a regular basis because they are the pillar of traditional medicine. Almost every one of the world's 2,000 native groups has its own specific ancient medical expertise and experiences (Ayouaz et al., 2023).

Medicinal plants are the foundation of India's traditional medical system. Pharmacological investigations have revealed the true significance of medicinal plants as a rich source of bioactive chemicals. The extraction and development of various medications from medical plants has led to the usage of medicinal plants in industrialized nations. Plant medications are typically non-toxic, harmless, and free of major adverse effects; yet, certain toxic plants contain life-threatening qualities. The screening of phytochemicals is mostly used for quality control in traditional medicine. Secondary plant metabolites with unknown pharmacological activity are currently being researched as a source of therapeutic medicines (Bhoyar, 2019). Traditional remedies primarily address the individual's general health rather than a specific symptom or disease. Herbal medications are more effective in disinfection, debridement, and the maintenance of a moist environment, and they aid in the natural healing of wounds with no adverse effects (Ramamoorthy et al., 2019).

### 2. Nomenclature

*Nerium oleander* is related to Apocynaceae family, a fast-growing evergreen shrub that blooms in the summer and grows in tropical, subtropical and mediterranean climates. It is frequently referred to as oleander. This plant species has been found to contain a variety of secondary metabolites, including phenols, alkaloids, flavonoids, and steroids. Several investigations have found that this plant has a variety of pharmacological qualities, including antioxidant, antibacterial and antifungal, anti-inflammatory, anthelmintic, insecticide, hepatoprotective, immunopotential, anticancer, and antipyretic action (Morsi et al., 2022). Although *Cascabela thevetia* (syn: *Thevetia peruviana*) classified to the same family as oleander and frequently known as yellow oleander but it has been treated as a different plant. The genus *Nerium* now contains only one species, oleander (Dey, 2020). Oleander is a poisonous flowering plant that is supposed to have originated in Southwest Asia, but no precise origin has been determined due to its widespread cultivation. This plant's natural range includes the Mediterranean region, subtropical Asia, and the India peninsula. It is found in the Himalaya ranges from Nepal to Kashmir, and has expanded to India, Baluchistan, and Afghanistan (Farkhondeh et al., 2020).

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### 3. Taxonomic classification of oleander

Kingdom: Plantae, Division: Tracheophyta, Class: Magnoliopsida, Order: Gentianales,

Family: Apocynaceae, Genus: Nerium, Species: Nerium oleander (Al-Snafi, 2020).

*Nerium oleander* has been used to cure a variety of ailments. A review of the literature indicated that numerous plant components of oleander, such as flowers, leaves, bark, seed, latex, and juice, have been used to treat various ailments. Throughout history, all plant components were employed as medicinal agents to treat a variety of illnesses. After boiling with water, the roots of this plant were used externally to treat haemorrhoids, ulcers, skin illnesses, herpes, and ringworm infections, while the roots powder was used to treat venereal diseases. Oleander bark was used as an emetic, diuretic, heart tonic, expectorant and diaphoretic. Tincture of leaves is use in homoeopathy to cure disorders such as hemiplegia, paralysis, and nervous system disease (Gaur et al., 2023).

**Table I** Physical observation of parts of Nerium oleander

Sl. No.	Parameter	Leave Observation	Flower observation	Fruit Observation
1	Shape and Structure	linear-lanceolate, smooth, thick and leathery, midrib prominent	Showy, terminal, 5-petaled, tips rounded	Pod like small narrow capsule
2	Colour	glossy dark green	white, pink or dark red	Green Colour
3	Size	10-15 X 1-2 cm	1.8 cm long	12-20 cm x 7 mm long
4	Taste	Pleasant Bitter	Sweetish	Highly poisonous
5	Odour	Sweet Scent	Pleasant Smell	Unpleasant

(Bhojar, 2019; Al-Snafi, 2020; Farooqui & Tyagi, 2018)

### 4. Phytoconstituents present in Nerium oleander

*Nerium oleander* was identified with 38 chemical components, the majority of which are terpenoid and fatty acid groups (oleic, stearic, linolenic, palmitic, and linolenic). Steroidal glycosides were extracted from its roots and cardenolides, triterpenes, phytosterols, pregnanes, and flavonoids were separated from the plant's leaves (Ali, 2020). D-limonene, durenebeta-myrcene, phytol, p-cresol, gamma-sitosterol, dl-isopulegol, phenyl ethyl alcohol, guaiol, and 8-quinolinol are the most common molecules accompanied by oxygenated derivatives and also 4-methyl, 2(4H)-benzofuranone, verbenone, squalene, and caryophyllene oxide are other examples (Zaid et al., 2022). Two known cardenolides, 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-5 beta-card-20 (22)-enolide and 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-16 beta-acetoxy-5 beta-card-20 (22)-enolide and two new cardenolides, 3 beta-hydroxy-8,14-epoxy-5 beta-Carda-16,20 (22)-dienolide and 3 beta-O-(D-2-O-methyl-digitalosyl)-14 beta-hydroxy-5 beta-Carda-16,20 (22)-dienolide have been isolated from leaves (Farooqui & Tyagi, 2018). A novel steroid from the lanostane class was obtained and identified as 3-acetoxy-5, 25 (26) diene, 24 hydroxy lanostane after characterisation and structure elucidation (Nawaz et al., 2023).

**Table II** Phytochemical Screening of Oleander Leaves, Flowers and seeds

Compounds	Oleander Leaves	Oleander flowers	Oleander Seeds
Flavonoids	No	Yes	Yes
Phenols & Tannins	Yes	Yes	No
Coumarins	Yes	Yes	No
Saponins	Yes	Yes	Yes
Alkaloids	Yes	Yes	Yes
Monoterpenes, sesquiterpenes and triterpenes	Yes	Yes	Yes
Phlobatannins	Yes	Yes	No
Coumarins	Yes	Yes	Yes
Carbohydrates	Yes	Yes	Yes
ketones	Yes	Yes	Yes

(Bhojar, 2019; Zaid et al., 2022; Saranya et al., 2017)

### 5. Potential benefits of Nerium oleander

- **Antioxidant Activity** *Nerium oleander* flower extract was investigated for DPPH free radical scavenging test and the reducing power assay which were used to assess antioxidant activity. Antioxidant experiment using DPPH

revealed that, ethanolic extract possessed significant scavenging and lowering power action (Gaur et al., 2023). The DPPH test was used to assess antioxidant activity of leaf extracts in terms of their ability to scavenge free radicals (Mozibullah et al., 2023). Nerium oleander's antioxidant properties is enhanced by the presence of wide range of phenolic chemicals. Rutin, catechin, epicatechin, quercetin, and quercetin acid are the primary phenolic chemicals found in *Nerium oleander* leaves and flowers (Mouhcine et al., 2019). The antioxidant activity of *Nerium oleander* leaves extract (72.8%) was higher than that of flower extract (68%) while the superoxide radical scavenging activity of crude flower extract (66%) was higher than that of leaves 25% (Farooqui & Tyagi, 2018). The flower extract had a stronger antioxidant effect and antiproliferative capacity in preventing HT29 cell proliferation. The values of DPPH and ABTS, as well as DPPH and HT29C5, are extremely modest, indicating that these variables are positively associated (Ayouaz et al., 2023; Balkan et al., 2018). The antioxidant potential of phenolic compounds allows them to avoid the oxidation induced by radicals in the body by oxidising themselves and allowing the radicals to be reduced by their electrons (Farkhondeh et al., 2020).

- **Anticancer** Oleander, which contains the cardiac glycoside oleandrin, was investigated in phase I and II clinical trials for cancer patients as a valid radio-sensitizing drug for the treatment of Rhabdomyosarcoma, particularly the inherently radio-resistant fusion positive rhabdomyosarcoma (Vaccaro et al., 2022). A supercritical CO<sub>2</sub> cardiac glycoside extract from Oleander, PBI-05204 which inhibited the expression of pAkt, pS6, and p4EPB1 in Panc-1 tumour tissues as well as cancer cell lines of human pancreas in a concentration-dependent manner, suggesting that this new botanical drug has significant anticancer activity (Pan et al., 2015). PBI-05204's active components can easily pass the blood-brain barrier and suppresses stemness of Glioblastoma multiforme not dependent of the highly resistant EGFR or EGFR VIII mark (Colapietro et al., 2020). Breastin is a water extract of oleander leaves that inhibits cancer cell lines (myeloma, leukaemia) and epidermal cell (different carcinoma) in vitro and in vivo. Monoglycosidic cardenolides adynerin, oleandrin, neritaloside, odoroside A, odoroside H, and vanderoside were discovered by phytochemical profiling as breastin's key bioactive secondary metabolite (Rashan et al., 2023).

Neridienone A (pregnane from oleander) significantly inhibited cell proliferation in HepG2 and VA-13 cells. To test the MDR-reversal activity of the separated compounds, the amount of calcein accumulated in MDR human ovarian cancer 2780AD cells in the presence of each component was measured. Three substances [20S,21-dihydroxypregna-4,6-diene-3,12-dione (neridienone B), 20R-hydroxypregna-4,6-diene-3,12-dione; and 21-hydroxypregna-4,6-diene-3,12,20-trione] inhibited calcein build-up significantly (Bai et al., 2007). Oleandrin, a specified extract (PBI-05204) and cardiac glycoside isolated from *Nerium oleander*, and containing chemical that suppress human glioblastoma growth and modify glioma patient-derived stem cell renewal (Colapietro et al., 2022). The ability of oleander extracts to suppress the growth of prostate cancer cell line was investigated in order to determine the plant's antiproliferative efficacy (Ahmed et al., 2023). Purified cardiac glycoside oleandrin inhibited cell proliferation, decreased cell viability, and induced apoptosis and/or cell cycle arrest in lung cancer, glioma, breast cancer, glioblastoma, melanoma, pancreatic and colon tumour cells, colorectal cancer, prostate cancer, histiocytic lymphoma, human oral cancer, ovarian cancer and osteosarcoma (Dias Francischini et al., 2022; Ko et al., 2018).

- **Anti-inflammatory effect** In vitro, oleander flower extract was discovered to have potent anti-inflammatory properties. This extract's active ingredients were identified as kaempferol-3-O-D-glucoside, kaempferol, and chlorogenic acid. Although these chemicals had previously been documented to be anti-inflammatory components in a variety of other plant treatments, their presence in oleander flowers was reported, contributing to chemical profile of the flowers (Balkan et al., 2018). Plant extract's anti-inflammatory activity was established by a decrease in the mRNA expression and levels of different pro-inflammatory mediators. Oleander extract dramatically lowered total leukocyte count and CRP levels. This decrease in CRP and leukocyte levels appears to have provided strong evidence that oleander extract with comprehensive in vivo safety in ethanolic floral extract has a significant potential to develop anti-inflammatory activity (Shafiq et al., 2021). Murine peritoneal macrophages inhibited cell adhesion significantly after stimulation with *Nerium oleander* extracts. Because TNF is a prominent inducer of cell-adhesion activity in phagocytes, the cell-adhesion inhibitory effect of oleander extracts could be related to its TNF inhibitory activity (Dey & Chaudhuri, 2016).

- **Antibacterial and Antifungal activity** Because of the existence of several active chemicals in oleander, which function as natural antibiotics that can be used instead of antibiotics, extracts of the oleander plant suppress the growth of bacteria against the bacterium under study (Chetwani et al., 2017). Ethanolic extracts of all coloured oleander flowers inhibited *S. aureus*, with white flower extract having the highest antifungal activity, followed by red flowers and then pink flowers (Dardona & Shahabuddin, 2022). The most susceptible bacteria to *Nerium oleander* extracts were found to be *P. aeruginosa*. *Nerium oleander* extracts were more effective against Gram-negative bacteria (Abderrahim et al., 2017). The zone of inhibition was demonstrated by the antibacterial activity of oleander against *S. aureus* and antifungal activity of Copper Nanoparticles produced using oleander plant leaf extract against *Candida albicans* (Srivastava & Dwivedi, 2018). Aqueous extract of oleander suppressed the growth of two bacterial strains, *E. faecalis* and *L. monocytogenes*, more effectively than the ethanol extract. Only certain Gram-positive bacteria were active against aqueous and ethanolic extracts. This could be due to the presence of a cell membrane, which could render the plant extracts under investigation impermeable and limit their access into the bacteria (Mouhcine et al., 2019).

Bio-synthesized copper nanoparticles have been shown to exhibit significant anti-microbial efficacy against bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhi*, and *Klebsiella pneumoniae* (Chassagne et al., 2021). *Nerium oleander* silver nanoparticles have antibacterial properties against *Bacillus pumilus* and *Micrococcus luteus*. *Micrococcus luteus* and *Staphylococcus aureus* (Shinde & Kote, 2022). This extract's GC-MS study revealed the presence of 15 chemicals, including maltol, octadecanoic acid, and cis-vaccenic acid, which is responsible for its antibacterial activity against *L. monocytogenes*, *S. carpa*, *S. dysenteriae*, and *Salmonella* sp (Saeed et al., 2023). Herbal extracts were discovered to have antibacterial action against the bacterial species *S. typhimurium*, *E. coli*, *S. aureus*, and *S. agalactia*. Secondary metabolites responsible for antibacterial action must be identified through phytochemical screening of the studied plants (Abdi et al., 2022).

- **Insecticides and larvicides** It is possible to investigate using this locally available plant material as a potential source of pesticide. Oleander aqueous leaf extract displayed larvicidal and ovicidal capabilities, as well as ovicidal and adulticidal activities against *Anopheles stephensi* (Raveen et al., 2014). In vivo, a *Nerium oleander* defatted methanolic extract and several fractions derived from it displayed antischistosomal activity by lowering worm load and egg count. HPLC-ESI-MS research revealed polyphenolic compounds as the principal constituents of this plant's defatted methanolic extract (Morsi et al., 2022). Mortality rate of cabbage butterfly larvae rose considerably with increasing leaf and bark extract concentrations and exposure time (Rafiq et al., 2022).

With different doses as chemical insecticides, oleanders biological control appears to be an alternative way to control severe pests in citrus orchards, including the Citrus Leaf Miner (CLM) *Phyllocnistis citrella* and the Mediterranean fruit fly (Medfly) *Ceratitis capitata* (Elimem et al., 2022). According to the insecticide, some plant species used as food sources may weaken mosquitos, making them more vulnerable to the pesticide in terms of caused 24-hour mortality. The phenotypic manifestation of pyrethroid resistance in *Anopheles* mosquitos can be altered by natural plant diet (Paré et al., 2022). The defatted methanolic extract of oleander discovered polyphenolic components, and a fraction produced from it demonstrated antischistosomal activity in vivo by lowering worm load and egg count (Morsi et al., 2022).

**Table III Experimental outcomes of *Nerium oleander***

Sl. no	Research activity	Experimental outcome	Reference
1.	Three spectrophotometric tests (DPPH, ABTS and FC) to evaluate the antioxidant capacity in vitro and HT29 cancer cells	Oleander extract inhibits HT29 cancer cell proliferation, which contributes significantly to antioxidant capacity	Ayouaz et al., 2023
2.	<i>Bacillus subtilis</i> , <i>E. coli</i> , <i>Staphylococcus aureus</i> and <i>Pseudomonas anuginosa</i>	By using an agar well diffusion test, determined the antimicrobial potential	Gaur et al., 2023
3.	a. 0.1mM DPPH b. <i>Klebsiella pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Vibrio cholerae</i> C6706	a. Exhibited scavenging activity b. Active against the three tested bacteria	Mozibullah et al., 2023
4.	a. DPPH scavenging and $\beta$ -	a. Oleander extracts provide scavenging	Mouhcine et al., 2019

	<p>carotene bleaching tests</p> <p>b. Agar disc diffusion method for bacteria</p> <p>c. HT-29 colon adenocarcinoma cell line and human breast cancer cell line MDA-MB-231</p>	<p>activity and prevent the oxidation of <math>\beta</math>-carotene by peroxide radicals.</p> <p>b. Effect on Gram-positive bacteria</p> <p>c. Cytotoxic activities against tumor cell lines</p>	
5.	FN- and FP-RMS cancer models <i>in vitro</i> and <i>in vivo</i>	PBI-05204 exhibited antitumor and radio-sensitizing properties <i>in vivo</i> , as well as enhanced sensitivity of FP-RMS <i>in vitro</i> and <i>in vivo</i>	Vaccaro et al., 2022
6.	Panc-1 orthotopic human pancreatic cancer model	In a concentration-dependent manner, PBI-05204 suppressed Panc-1 cancer cell proliferation and decreased pS6, pAkt, 7., and p4EPB1 expression	Pan et al., 2015
7.	<i>In vitro</i> and <i>in vivo</i> cancer models to study glioblastoma	PBI-05204 inhibited glioblastoma multiform cell lines U87MG, U251, and T98G in a concentration dependent manner	Colapietro et al., 2020
8.	LPS induced Raw 264.7 macrophages	Inhibited multiple signalling molecules (TNF, PGE2, COX-2, iNOS, NF-B) and diminish LPS-induced NO generation in J774A.1 cell	Balkan et al., 2018
9.	<p>a. Granuloma induced by cotton-pellet (rat paw edema induced by carrageenan)</p> <p>b. MRSA, <i>S. aureus</i>, <i>S. epidermidis</i> and <i>S. enterica</i></p>	<p>a. Carrageenan treatment reduced the generation of PGE2, NO, IL-1, and TNF in the rat paw</p> <p>b. Highly sensitive to plant extract</p>	Shafiq et al., 2021
10.	Four bacterial species, <i>S. carpa</i> , <i>L. monocytogenes</i> , <i>S. dysenteriae</i> and Salmonella sp. were tested	Showed moderate antibacterial activity against all the four tested bacterial species	Saeed et al., 2023

## 6. Oleander toxicity

The plant is hazardous in all parts and contains a number of cardiac glycosides, including oleandrin. Nausea, vomiting, stomach pain, diarrhoea, dysrhythmias, and hyperkalaemia result from accidental intake (Bandara et al., 2010). The "Na<sup>+</sup>/K<sup>+</sup> ATPase pump" can be inhibited by glycoside component of *Nerium oleander* in cardiomyocyte membranes, resulting in increase of intracellular sodium concentration. Oleander disrupted electromechanical function in the heart by inhibiting sodium (Na<sup>+</sup>) and potassium (K<sup>+</sup>) pumps, causing mitochondrial edema, and impairing sarcoplasmic Ca<sup>2+</sup>-ATPase. In acute cardiac glycoside poisoning, hyperkalaemia demonstrates the severity of toxicity. Oleander leaves (110 mg/kg body weight) caused different degrees of haemorrhage, hepatocyte degeneration and localised necrosis, fatty degeneration, hepatocyte necrosis, and mononuclear inflammatory cell infiltration in liver (Mokri et al., 2018).

Flower or leaf of oleander cause detrimental effect on exposed animals' lung tissue, including blood vessel congestion, bronchus mucosal rupture, neutrophils in the bronchoalveolar and produced inflammatory cells, and caused congestion or haemorrhage in lung tissue (Abbasi et al., 2018). After treatment of 14 days, oral administration of ethanolic oleander extract caused diffuse mild interfascicular edema with occluded arteries and many myofibrils fragmentations in degraded myocytes in heart muscles (Abdou et al., 2019; Botelho et al., 2017). The seeds of oleander are the most harmful parts of the plant, and lethal dose varies greatly depending on the amount of seeds consumed. Seeds of oleander contain extremely active glycosides such as oleandrin, thevetin, nerin, thevetin, digitoxigenin, and thevetin, and most toxic is oleandrin. They are capable of causing deadly brady and tachyarrhythmias such as asystole and ventricular fibrillation (Giridharan et al., 2023). At greater doses, the aqueous extract of *Nerium oleander* is not safe as an oral medication, and should be used with caution for treating specific disorders (Maarouf et al., 2022). At high concentrations, the alcoholic extract of oleander is exceedingly dangerous because of numerous chemical

components presence such as alkaloids, particularly N-hexadecanoic acid, which has cytotoxic potential (Jaddoa & Mohammed, 2021).

It has been established that oleander is rapidly absorbed in the gastrointestinal tract and causes acute harmful effects following oral ingestion. Stomach contents from patients or the deceased may be useful in determining oleander toxicity. To present, clinical investigations of oleander toxicity have primarily focused on the detection of oleandrin in blood, serum, liver, and heart tissues (Bai et al., 2022). Oleander poisoning causes polymorphous symptoms that vary in onset and intensity based on the number of active components consumed. Indeed, there was a rapid start of symptoms upon plant consumption, followed by the death of the first animal (Ceci et al., 2020). Poisoning with *Nerium oleander* extract caused behavioural changes such as myorelaxation and lack of postural reflex, which were consistent with the tracing patterns obtained in the EEG and EMG recordings. Using phenytoin, phenobarbital, diazepam, and scopolamine, the likelihood of seizure reversal was investigated (De Melo et al., 2020).

## 7. Future prospects

There are several primary and secondary metabolites in the plant *Nerium oleander* that are responsible for treating a variety of acute and chronic illnesses; hence, there are several pharmacological actions that have yet to be characterised. It may be straightforward for new researchers to understand those activities for the greatest plant exploration. Numerous phytochemicals have been discovered in various sections of *Nerium oleander*; they may one day be used to treat illnesses and create new research opportunities. These findings spur future exploration into the incorporation of oleandrin into antineoplastic therapy protocols in both human and animal medicine, as well as further examination of antimetastatic capabilities and the possible increase in patient survival and decrease in tumor indicators. Patients' dose and/or toxicity profiles must be closely monitored.

## 8. Discussion

Since ancient times, humans have long employed medicinal plants for therapeutic purposes, most notably the widespread usage of raw extracts of diverse medicinal plant components to treat human ailments. The purpose of current study is to evaluate the numerous actions of oleander. The human population today relies on herbal medicines to treat illnesses, and they pick herbal medications for their principal effects simply because they have fewer side effects, are more easily accessible, and are less expensive. Despite having a high level of pharmacological activity and being a beautiful decorative plant, *Nerium oleander* has been found to be safe at various levels of inquiry. The purpose of this review is to investigate the pharmacological potential of phytochemicals found in *Nerium oleander* for treating a number of maladies, including antibacterial, anticancer, antioxidant, and inflammatory diseases. Many studies are available that detail the work of many researchers in demonstrating the important features and applications of active compounds derived from plant extracts. Antibacterial activity is one of the important features of various plant active components. Furthermore, the presence of antibacterial and antifungal substance helps to improve health. There is a greater opportunity to produce medications from natural sources to combat antibiotic resistance and bacterial infections. The antioxidant capacity of phenolic compounds, such as DPPH, permits them to escape oxidation caused by free radicals in the body. In several cancers, neridienone A, cardiac glycoside oleandrin, and PBI-05204 of *Nerium oleander* reduced cell growth and triggered apoptosis and cell cycle arrest. Anti-inflammatory components included active substances such as kaempferol-3-O-D-glucoside, kaempferol, and chlorogenic acid.

Additional phytochemical investigation should be carried out to discover the chemicals that exhibit the aforementioned therapeutic qualities

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## References

1. Abbasi, M.H., Fatima, S., & Khawar, M.B. (2018). An in vivo study on intoxicating effects of Nerium oleander water-based extract on multiorgans of Wistar rat, *Can J Gastroenterol Hepatol*, 4739637, doi: [10.1155/2018/4739637](https://doi.org/10.1155/2018/4739637)
2. Abderrahim, L.A., Taibi, K., Alomery, A.M., & Abderrahim, N.A. (2017). Antibacterial activity of medicinal plants extracts; Rosmarinus officinalis and Nerium oleander, *AGJSR*, 35 (1,2,3,4): 46-53, DOI:[10.51758/AGJSR-1/2/3/4-2017-0005](https://doi.org/10.51758/AGJSR-1/2/3/4-2017-0005)
3. Abdi, M. I., Hassan, A. A., Abdirahman, F. A., & Weldegebriel, S. (2022). In-Vitro Evaluation of Antibacterial Activity of Nerium oleander, Solanum linnaeanum, and Nicotiana glauca against Escherichia coli, Salmonella typhimurium, Staphylococcus aureus, and Streptococcus agalactiae in Mekelle, Ethiopia. *OIRT Journal of Scientific Research*, 2(5), 50–59. <https://doi.org/10.53944/ojsr-2221>
4. Abdou, R.H., Basha, W.A., & Khalil, W.F. (2019). Subacute toxicity of Nerium oleander ethanolic extract in mice, *Toxicol Res*, 35(3): 233, doi: [10.5487/TR.2019.35.3.233](https://doi.org/10.5487/TR.2019.35.3.233)
5. Ahmed, O.H., Ezghayer, M.A., Jabir, M.S., & Tawfeeq, M.F. (2023). Cytotoxic activity of methanolic extract of Nerium Oleander Naturally Grown in Iraq, *Journal of Survey in Fisheries Sciences*, 10(3S) 2517-2524, DOI: <https://doi.org/10.17762/sfs.v10i3S.926>
6. Ali, R. (2020). Phytochemical Investigations of Nerium Oleander L. Leaves and Flowers, *International Journal of Scientific Research*, 7(4),1-04, <https://www.researchgate.net/publication/348151744>
7. Al-Snafi, A.E. (2020). Bioactive ingredients and pharmacological effects of Nerium oleander, *IOSR Journal of Pharmacy*, 10(9) Series. I, 19-32
8. Ayouaz, S., Koss-Mikołajczyk, I., Adjeroud-Abdellatif, N., Bartoszek, A., Arab, R., Aji Muhammad, D.R., Nur, D.L., & Madani, K. (2023). Anticarcinogenic and antioxidant activities of leaves and flowers hydroalcoholic extracts of Nerium oleander L.: PCA analysis and phytochemical content by FTIR analysis, *The North African Journal of Food and Nutrition Research*, (15): 1-8. <https://doi.org/10.51745/naifnr.7.15.1-8>
9. Bai, L., Wang, L., Zhao, M., Toki, A., Hasegawa, T., Ogura, H., Kataoka, T., Hirose, K., Sakai, J., Bai, J., & Ando, M. (2007). Bioactive Pregnanes from Nerium oleander", *Journal of Natural Products*, 70 (1), 14-18, DOI: 10.1021/np068030o
10. Bai, X., Wang, G., Ren, Y., & Han, J. (2022). Detection of Highly Poisonous Nerium oleander Using Quantitative Real-Time PCR with Specific Primers, *Toxins*, 14, 776. <https://doi.org/10.3390/toxins14110776>
11. Balkan, I.A., Doğan, H.T., Zengin, G., Çolak, N., Ayaz, F.A., Gören, A.C., Kırmızıbekmez, H., & Yeşilada, E. (2018). Enzyme inhibitory and antioxidant activities of Nerium oleander L. flower extracts and activity guided isolation of the active components, *Industrial Crops and Products*, 112, 24-31. <https://dx.doi.org/10.1016/j.indcrop.2017.10.058>
12. Balkan, I.A., Gören, A.C., Kırmızıbekmez, H., & Yeşilada, E. (2018). Evaluation of the in vitro Anti-inflammatory Activity of Nerium oleander L. Flower Extracts and Activity-Guided Isolation of the Active Constituents, *Rec. Nat. Prod.*, 12:2, 128-141, DOI: <http://doi.org/10.25135/rnp.15.17.05.100>
13. Bandara, V., Weinstein, S.A., White, J., & Eddleston, M. (2010). A review of the natural history, toxinology, diagnosis and clinical management of Nerium oleander (common oleander) and Thevetia peruviana (yellow oleander) poisoning, *Toxicol*, 1;56(3):273-81. doi: 10.1016/j.toxicol.2010.03.026
14. Bhojar, S. (2021). Physicochemical analysis and antibacterial activity of cascabela thevetia (l) lippold seeds, *World Journal of Pharmaceutical Research*, 10(6), DOI: 10.20959/wjpr20216-20399
15. Botelho, A.F.M., Santos-Miranda, A., & Joca, H.C. (2017). Hydroalcoholic extract from Nerium oleander L. (Apocynaceae) elicits arrhythmogenic activity, *J Ethnopharmacol*, 206: 170–177, DOI: [10.1016/j.jep.2017.05.031](https://doi.org/10.1016/j.jep.2017.05.031)
16. Ceci, L., Girolami, F., Capucchio, M.T., Colombino, E., Nebbia, C., Gosetti, F., Marengo, E., Iarussi, F., & Carelli, G. (2020). Outbreak of Oleander (Nerium oleander) Poisoning in Dairy Cattle: Clinical and Food Safety Implications, *Toxins*, 12, 471; doi:10.3390/toxins12080471
17. Chassagne, F., Samarakoon, T., Porras, G., Lyles, J.T., Dettweiler, M., Marquez, L., Salam, A.M., Shabih, S., Farrokhi, D.R., & Quave, C.L. (2021). A Systematic Review of Plants with Antibacterial Activities: A Taxonomic and Phylogenetic Perspective, *Frontiers in Pharmacology*, 11, DOI=10.3389/fphar.2020.586548
18. Chetwani, K., Agnihotri, R.K., & Chaturvedi, P. (2017). Aqueous, Acetone and Ethanolic extract of Nerium indicum L. as potential antibacterial agent against Pseudomonosa aeruginosa", *International Journal of Applied Environmental Sciences*, 12(9), 1721-1732
19. Colapietro, A., Yang, P., Rossetti, A., Mancini, A., Vitale, F., Martellucci, S., Conway, T.L., Chakraborty, S., Marampon, F., Mattei, V., Gravina, G.L., Biordi, A.L., Wei, D., Newman, R.A., & Festuccia, C. (2020). The Botanical Drug PBI-05204, a Supercritical CO<sub>2</sub> Extract of Nerium Oleander, Inhibits Growth of Human Glioblastoma, Reduces Akt/mTOR Activities, and Modulates GSC Cell-Renewal Properties, *Front Pharmacol*, 11; 11:552428. doi: 10.3389/fphar.2020.552428
20. Colapietro, A., Yang, P., Rossetti, A., Mancini, A., Vitale, F., Chakraborty, S., Martellucci, S., Marampon, F., Mattei, V., Gravina, G.L., Iorio, R., Newman, R.A., & Festuccia, C. (2022). The Botanical Drug PBI-05204, a Supercritical CO<sub>2</sub> Extract of Nerium Oleander, Is Synergistic with Radiotherapy in Models of Human Glioblastoma, *Front. Pharmacol*, 13:852941. doi: 10.3389/fphar.2022.852941
21. Dardona, A.W.Y., & Shahabuddin, D. (2022). Evaluation of Antimicrobial Activity of Methanolic and Ethanolic Extracts of Three Varieties of Nerium Oleander, *Journal of Pharmaceutical Negative Results*, 13(7), 1821-1829, DOI: <https://doi.org/10.47750/pnr.2022.13.S07.248>
22. De Melo, B.S., De Moraes, B.P., De Souza, Ferreira Sa, V.S., Lourinho, F.D., Pinheiro Toda, I.P.S., Do Nascimento, J.L.M., Marques, D.N., da Silva, M.C.F., Cardoso, G.T.M., Barbas, L.A.L., Torres, M.F., Muto, N.A., de Mello, V.J., & Hamoy, M. (2020) Behavioural, electrocorticographic, and electromyographic alterations induced by Nerium oleander ethanolic

extract: Anticonvulsant therapeutics assessment, *Neurotoxicology*, 78, 21-28, doi:

<https://doi.org/10.1016/j.neuro.2020.02.001>

23. Dey, P. (2020). The pharmaco-toxicological conundrum of oleander: Potential role of gut microbiome, *Biomedicine & Pharmacotherapy* 129, 110422, <https://doi.org/10.1016/j.biopha.2020.110422>
24. Dey, P., & Chaudhuri, T.K. (2016). Comparative Phytochemical Profiling and Effects of Nerium Oleander Extracts on the Activities of Murine Peritoneal Macrophages”, *Arch Biol Sci.*, 68(3):515-531, DOI:10.2298/ABS150816042D
25. Dias Francischini, C.R., Mendonça, C.R., Barcelos, K.A., Silva, M.A.M., & Botelho, A.F.M. (2022). Antitumor effects of oleandrin in different types of cancers: Systematic review”, *Toxicon*, 216, 15–27, <https://doi.org/10.1016/j.toxicon.2022.06.010>
26. Elimem, M., Jaouadi, R., Kalboussi, M., Lahfef, C., Rouz, S., Kharroubi, H., Boulila, A., Kouki, S., Ragnoni, G., Pizzuti, G., Primavera, F., Riccini, A., & Cari, A. (2022). Management of Ceratitis Capitata and Phyllocnistis citrella with Basalt powder “Farina di Basalto® compared to two botanical extracts (Citrus aurantium and Nerium oleander) in citrus orchard, *International Journal of Zoological and Entomological Letters*, 2(1): 71-80, DOI: <https://doi.org/10.22271/letters.2022.v2.i1b.37>
27. Farkhondeh, T., Kianmehr, M., Kazemi, T., Samarghandian, S., & Khazdair, M.R. (2020). Toxicity effects of Nerium oleander, basic and clinical evidence: A comprehensive review, *Hum. Exp. Toxicol*, 39, 773–784, DOI: [10.1177/0960327120901571](https://doi.org/10.1177/0960327120901571)
28. Farooqui, S., & Tyagi, T. (2018). Nerium Oleander: It’s Application in Basic and Applied Science: A Review, *Int J Pharm Pharm Sci*, 10(3), 1-4, DOI: <http://dx.doi.org/10.22159/ijpps.2018v10i3.22505>
29. Gaur, R., Rathore, A., Sharma, A.K., Pathak, D., & Kulshreshtha, M. (2023). Scientific Update on the Pharmacognostic, Pharmacological and Phytochemical Properties of Thevetia peruviana, *Pharmacognosy Communications*, 13(1):2-8, DOI: 10.5530/pc.2023.1.2
30. Giridharan, V., Daranendran, C., Rajendran, A.S., & Shafeek, S. (2023). Clinical Outcomes of Oleander Seed Poisoning Based on Biochemical and Cardiac Parameters, *Journal of Pharmaceutical Negative Results*, 14(1), DOI:10.47750/pnr.2023.14.S01.127
31. Jaddoa, N.T.M., & Mohammed, R.K. (2021). Evaluating the anti- Pseudomonas Aeruginosa Efficacy and Potential Cytotoxicity of Nerium Oleander Alcoholic Extract, *Indian Journal of Forensic Medicine & Toxicology*, 15(2), 3026-3033, <https://doi.org/10.37506/ijfmt.v15i2.14836>
32. Ko, Y.S., Rugira, T., Jin, H., Park, S.W., & Kim, H.J. (2018). Oleandrin and its derivative odoroside A, both cardiac glycosides, exhibit anticancer effects by inhibiting invasion via suppressing the STAT-3 signaling pathway, *Int. J., Mol. Sci.* 19, 3350, <https://doi.org/10.3390/ijms19113350>
33. Maarouf, T., Otmani, I., Talbi, A., Hamamdia, Z., Bendali-Saoudi, F., & Abdenmour, C. (2022). Toxicopathological Assessment of Nerium Oleander Roots and Leaves on Wistar Rat, *UPJOZ*, 43(21): 40-50, DOI: 10.56557/UPJOZ/2022/v43i213210
34. Mokri, F., Assmar, M., Zarrabi, I.S., & Messiah, A. (2018). The evaluation of Antibacterial effect of Aquatic and alcohol, *NCMBJ*, 8(31): 75-85, <http://dorl.net/dor/20.1001.1.22285458.1397.8.31.5.2>
35. Morsi, E.A., Abdel-Hameed, E.S., ElSayed, M.M., & Rabia, I.A. (2022). HPLC-ESI-MS Characterization of Certain Compounds of Methanolic Extract of Nerium Oleander and Its Fractions as well as Evaluation of their Potential against Schistosomiasis mansoni, *Egypt. J. Chem*, 65(2) 133-143, DOI: 10.21608/EJCHEM.2021.81939.4054
36. Mouhcine, M., Amin, L., Saaïd, A., Khalil, H., Laila, B., & El Mzibri, M. (2019). Cytotoxic, antioxidant and antimicrobial activities of Nerium oleander collected in Morocco, *Asian Pac. J. Trop. Med.*, 12(1): 32-37, doi:10.4103/1995-7645.250342
37. Mozibullah, M., Ahammad, H., Tarin, T., Islam, M.J., Khatun, M., Islam, M.J., & Sikder, M.A. (2023). Evaluation of anti-oxidant and antibacterial activities of Ixora chinensis and Cascabela thevetia leaf extracts: An in vitro study, *J. pharmacogn. phytochem.*, 12(1):35-40, DOI:<https://doi.org/10.22271/phyto.2023.v12.i1a.14545>
38. Nawaz, Z., Khalid, H.N., Sajid, A., Arshed, F., Ahmed, E., Sharif, A., Khan, I.H., Javaid, A., & Sajid, A. (2023). A New Bioactive Steroid Isolated from Nerium Oleander L., *Int. J. Biol. Biotech.*, 20 (1): 31-36
39. Pan, Y., Rhea, P., Tan, L., Cartwright, C., Lee, H.J., Ravoori, M.K., Addington, C., Gagea, M., Kundra, V., Kim, S.J., Newman, R.A., & Yang, P. (2015). PBI-05204, a supercritical CO<sub>2</sub> extract of Nerium oleander, inhibits growth of human pancreatic cancer via targeting the PI3K/mTOR pathway, *Invest New Drugs*, 33(2):271-9. doi: 10.1007/s10637-014-0190-6.
40. Paré, P.S.L., Hien, D.F.D.S., Bayili, K., Yerbanga, R.S., Cohuet, A., Carrasco, D., Guissou, E., Louis-Clément, G., Yaméogo, K.B., Diabaté, A., Ignell, R., Dabiré, R.K., Thierry Lefèvre, T., & Gnankiné, O. (2022). Natural plant diet impacts phenotypic expression of pyrethroid resistance in Anopheles mosquitoes, *Scientific Reports*, 12:21431, <https://doi.org/10.1038/s41598-022-25681-6>
41. Rafiq, S., Bandral, R.S., Ganai, S.A., Akbar, R., Rashid, S., & Jan, R. (2022). Study on the Evaluation of Toxicity of Nerium indicum (M.) Against Cabbage Butterfly, Pieris brassicae (L.) (Lepidoptera: Pieridae)”, *Biological Forum – An International Journal*, 14(1): 356-361
42. Ramamoorthy, R., Muthalag, M., Andra, S., Ravichandran, B., & Narayanasamy, M. (2019). Investigation on antimicrobial, antioxidant and cytotoxicity properties of triple bark extract formulated using traditional medicinal plants, *SN Applied Sciences*, 1:772, <https://doi.org/10.1007/s42452-019-0791-y>
43. Rshan, L.J., Özenver, N., Boulos, J.C., Dawood, M., Roos, W.P., Franke, K., Papisotiriou, I., Wessjohann, L.A., Fiebig, H.H., & Efferth, T. (2023). Molecular Modes of Action of an Aqueous Nerium oleander Extract in Cancer Cells In Vitro and In Vivo”, *Molecules*, 28, 1871. <https://doi.org/10.3390/molecules28041871>
44. Raveen, R., Kamakshi, K.T., Deepa, M., Arivoli, S., & Tennyson, S. (2014). Larvicidal activity of Nerium oleander L. (Apocynaceae) flower extracts against Culex quinquefasciatus Say (Diptera: Culicidae), *Int J Mosquito Res*, 1:38–42

45. Saeed, H.M., Ferdosi, M.F.H., Khan, I.H., Javaid, A., & Sultan, M.W. (2023). Antibacterial Activity and GC-MS Analysis of White Flowers Extract of Nerium Oleander L.”, *International Journal of Biology and Biotechnology*, 20 (1): 163-168.
46. Saranya, S., Archana, D., & Santhy, K.S. (2017). Antimicrobial and Antioxidant Effects of Nerium oleander Flower Extracts, *Int.J.Curr.Microbiol.App.Sci*, 6(5): 1630-1637, <https://doi.org/10.20546/ijcmas.2017.605.178>
47. Shafiq, Y., Naqvi, S.B.S., Rizwani, G.H., Bushra, R., Ghayas, S., Rehman, A.A., & Asghar, M.A. (2021). A mechanistic study on the inhibition of bacterial growth and infammation by Nerium oleander extract with comprehensive in vivo safety profile, *BMC complement. med.*, 21:135 <https://doi.org/10.1186/s12906-021-03308-z>
48. Shinde S.A., Kote J.R., “Green Synthesis of Silver Nanoparticles from Nerium Oleander L. Extract for Enhanced Antimicrobial Efficacy”, *Ecology Research* 2022; Volume IV, 45-49, <https://www.bhumipublishing.com/books/>
49. Srivastava, A.K., & Dwivedi, K.N. (2018). Formulation and Characterization of Copper Nanoparticles Using Nerium odorum Soland Leaf Extract and Its Antimicrobial Activity, *Int J Drug Dev & Res*, 10(3): 29-34, ISSN: 0975-9344
50. Vaccaro, S., Rossetti, A., Porrazzo, A., Camero, S., Cassandri, M., Pomella, S., Tomaciello, M., Macioce, G., Pedini, F., Barillari, G., Marchese, C., Rota, R., Cenci, G., Tombolini, M., Newman, R.A., Yang, P., Codenotti, S., Fanzani, A., Megiorni, F., Festuccia, C., Minniti, G., Gravina, G.L., Vulcano, F., Milazzo, L., & Marampon, F. (2022). The botanical drug PBI-05204, a supercritical CO2 extract of Nerium oleander, sensitizes alveolar and embryonal rhabdomyosarcoma to radiotherapy in vitro and in vivo, *Front. Pharmacol.*, 13:1071176. doi: 10.3389/fphar.2022.1071176
51. Zaid, R., Canela-Garayoa, R., Ortega-Chacón, N.M., & Mouhouche, F. (2022). Phytochemical analyses and toxicity of Nerium oleander (Apocynaceae) leaf extracts against Chaitophorus leucomelas Koch, 1854 (Homoptera: Aphididae), *J. Saudi Soc. Agric. Sci.*, 21, 310–317, <https://doi.org/10.1016/j.jssas.2021.10.011>

