REVIEW ARICLE

# Phytochemistry, therapeutic and pharmacological potential of *Nerium oleander* L.

**Ravi Kant Upadhyay**

*Department of Zoology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India*

**Abstract**

This study explains the phytochemistry, therapeutic, and pharmacological potential of *Nerium oleander* L, commonly known as Kaneir or Kaner. Kaner is a most common small ornamental plant grown in gardens and parks in temperate and semi-arid climates. The present paper outlines the antifungal, antibacterial, cardioprotective, hepatoprotective, neuroprotective, anti-inflammatory, anti-cancer, cardiotonic, diuretic antimicrobial, and insecticidal properties of this plant. *N. oleander* leaves are highly toxic to livestock and humans. *N. oleander* L. stem extract has antihyperglycemic potential, showed protective effect against injuries and wounds without side effects. *N. oleander* flower components showed anti-convulsant activity, while root powder has anti-venom activity along with anti-myotoxic and anti-hemorrhagic properties. This study explains the antitumor, anticancer, and anti-HIV activity of *Nerium* and its associated species with active ingredients. The active ingredients of *N. oleander* inhibit the replication of viruses and successfully prohibit the infection cycle inside host cells. These active ingredients exhibit cytotoxic and anti-proliferation and anti-tumor activity. They are also effective in regulating fertility and the breakdown of pregnancy. This article states that the arial parts of the *Nerium* plant are toxic and self-harmonic drugs must be prohibited. It is therefore necessary to investigate the long-term effects of plant natural products of *Nerium* plant on body metabolism to prevent unnecessary toxicity to other organs. After a thorough screening, these could be used for therapeutic purposes.

**Key words:** Kaner, *Nerium oleander*, phytochemistry, therapeutic and pharmacological potential

## INTRODUCTION

*Nerium oleander* L. *Nerium indicum* Mill, *Nerium odorum* Aiton belongs to the *Apocynaceae* family. This plant is often called Kaneir or Kaner in Hindi. In English, it is called yellow *oleander*. In Spanish, it is called "Cascabel," "Cascavel" or "Cascabela."[1] The plant is a small tree or shrub and has sparkling green leaves, yellow flowers and green fruits. This is cultivated along the borders of gardens and houses for decorative and ornamental purposes. The plant has dazzling green glossy leaves, in a linear-lanceolate form. These are covered with a wax coating to reduce water loss (typical for *oleander*s). Its stem is green, which turns into silver/grey, as *Thevetia peruviana*[2] blooms from summer to autumn. Long funnel-shaped yellow flowers (less common apricots, sometimes white are in a few flowers in terminal clusters.[2] *Nerium* is a rain-resistant plant found in India's semi-arid climate zones. Plants are grown mainly for decoration and ornamental purpose sin Andhra Pradesh, Delhi, Gujarat, Madhya Pradesh, West Bengal, Rajasthan, Tamil Nadu, Uttar Pradesh, Orissa, and Assam. It is also planted as a large flowering shrub or as a small ornamental tree intemperate climate gardens and parks. The plant is also used by ethnic groups for the treatment of insect and snake bites and for religious purposes. This plant is an ever green shrub, also found in many parts of the world as a small tree [Figure 1].

*N. oleander* leaves are highly toxic to livestock and human beings. These contain cardiac glycosides. Every year, cases of intentional and accidental poisoning of humans are reported from many parts of the world.[3] The main toxicity is due to presence of the vetin A and B. Plant also contains

**Address for correspondence:**
Ravi Kant Upadhyay, Department of Zoology, Deen Dayal Upadhyaya Gorakhpur University, Gorakhpur, Uttar Pradesh, India.
E-mail: rkupadhya@yahoo.com

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**Figure 1:** Floral and vegetative parts of various *Nerium* species

other bioorganic components such as peruoside, nerifolin, thetoxin, and ruvoside.[4,5] Both leaf and flowe rextract of this showed in secticidal and antimicrobial activities. *T. peruviana* seed oil is used for making a paint that possesses antifungal, antibacterial, and anti-termite properties.[6] However, toxic effects of *N. oleander* poisoning can be neutralized by digoxin-specific Fab-antibody fragments.[7]

*Oleander* is traditionally used in the treatment of cardiac disease, asthma, diabetes, corn, scabies, cancer, and epilepsy, and in wound healing as an antimicrobial/antimicrobial. Cardenolides cause heart and digestive problems. Antibodies such as activated charcoal and atropine and digoxin immune fabs (antibodies) are only a solution.[8-10] Its synonym biotype is *T. peruviana*, which is found in the India and Sri Lanka. The main metabolites of this species are triterpenoids, iridoids, alkaloids, and cardenolides, which have extensive biological and pharmacological effects such as cardiovascular, hepatic, neuroprotective, anti-inflammatory, anti-cancer, and antimalarial properties.[11] It is reported that *Cascabela thevetia* has anti-sperm activity in rats.[12]

### Ethnomedicinal Value

*N. oleander* L. is an ethnopharmacologically important plant. Conventionally, the plant is used by tribes for medicinal purposes. Plants are used to treat diabetes and are used for diabetes in most African and Asian countries. The leaves and flowers of *Nerium* are cardiotonic, diaphoretic, diuretic, anti-cancer, and antibacterial. Kaner is also mentioned in Ayurveda and is prescribed for the treatment of scabies and enlargement. Plant leaves are used to treat diabetes *Nerium* thin flower petals, leaves, leaf juice or latex, bark and roots have been used against corn, warts, cancer ulcers, carcinoma, ulcers, or hard tumors.[13] The bark of the stem is used as a fever, cathartic, and intermittent fever. Root bark oil is used in the treatment of leprosy and skin diseases. The root powder is used in plaster and is used externally for tumors. Other therapeutic uses of *N. oleander* include the treatment of ulcers, hemorrhoids, leprosy, ringworm, herpes, and abscesses. Leaf components are used to treat bladder, colorectal, breast, pancreatic, appendix, and malignant tumors.[14,15] *Oleander* flower extracts have shown anti-inflammatory activity by inhibiting the production of nitrogen oxides, probably due to the contents of kaempferol.[16] The whole *oleander* plant contains toxins, including steroidal glycoside cardenolides and pentacyclic terpenoids. This is why *Oleander* flowers and flowers are highly toxic.[17,18] This comprehensive research review provides a detailed study of the *N. oleander* L: Kaner plant and its phytochemistry, therapeutic and pharmacological potential [Figure 1].

## SOURCE OF INFORMATION

For the writing of this extensive research review, various databases were searched for *N. oleander* L: Kaner plant. To collect relevant information, specific terms such as MeSH and key text words such as "Kaner (*N. oleander*) and its therapeutic uses" published until 2024 were used in Medline. The most specifically targeted research, aimed at retrieving all articles related to the traditional uses of *N. oleander* L for therapeutics, was conducted in electronic bibliography databases and abstracts of published studies with relevant information on *N. oleander* L were collected. In addition, additional references were included by searching for references cited in the studies on the present topic. The relevant terms were used individually and in combination to ensure extensive literature search. To update information on a subject and incorporate recent knowledge, relevant research articles, books, conferences, and surveys of public health organizations were selected and compiled based on the broader objectives of the review. This was done by searching databases such as SCOPUS, Web of Science, EMBASE, Pub Med, Swiss-Prot, and Google. Based on this common methodology, the results and results were identified and summarized in this final review.

### Phytochemistry

The *Nerium* species has numerous phytochemicals that exhibit various therapeutic and pharmacological activities. The leaves of the *N. oleander* contain ursane-typetriterpenes1, oleane-type triterpene 2, and dammarane-type triterpenes, 3beta-hydroxy-12-ursen-28-oic acid (ursolic acid, 3), 3beta-27-dihydroxy-12-ursen-28-oic acid (4), 3beta-13beta-dihydroxyurs-12-en-3beta-ol(8), urs-12-hydroxy-20-lupen-28-oleanoic acid, and (20S,24R)-epoxydammarane-3beta,25-diol The leaves also contain 3beta, 20alpha-dihydroxyurs-21-en-28-oic acid,3beta,12alpha-dihydroxyoleanan-28,13beta-olideand (20S,24S)-epoxydammarane-3beta,25-diol, respectively. Among these compounds, a few exhibit anti-inflammatory activities, while the methylesters of ursolic acid and oleanic

acid cell growth inhibit the induction of intercellular adhesion molecule-1 (ICAM-1) intercellular attachment molecules in human cell lines.[19] Oleandrinis acardiac glycoside, an important chemical in *oleander*, Oleandrin is a highly soluble cardiac glycoside present in the leaves and seeds of *N. oleander* (Apocynaceae).[20] Cardiac glycosides are used to treat congestive heart failure and arrhythmias [Figure 2].

Oleandrin also shows strong inhibition of growth of hematopoietic tumors and carcinomas.[21] Some compounds, such as 5-hydroxy-8-methoxy-4-phenylisoquinolin-1(2H)-one (3), quinolinone alkaloids 3-O-methylviridicatin (1) and viridicatol (2), have been isolated from the fermentation of the endophytic fungus *Penicillium* spp. R22 in *Nerium indicum*.[22] Mono glycosidic cardenolides with the structure of 3,14-dihydroxy-5-card-20(22)-enolides with or without an acetoxy group atC-16are the strongest anticancer compounds isolated from the *oleander* of *Nerium*. The leavesof *T. peruviana* contain quercetin and kaempferol. *Nerium* leaves synthesize cardenolide glycosides that exhibit anti-apoptotic and anti-proliferative activity. Six new cardenolides – three 14-hydroxylated and three 14-carbonylated – have been

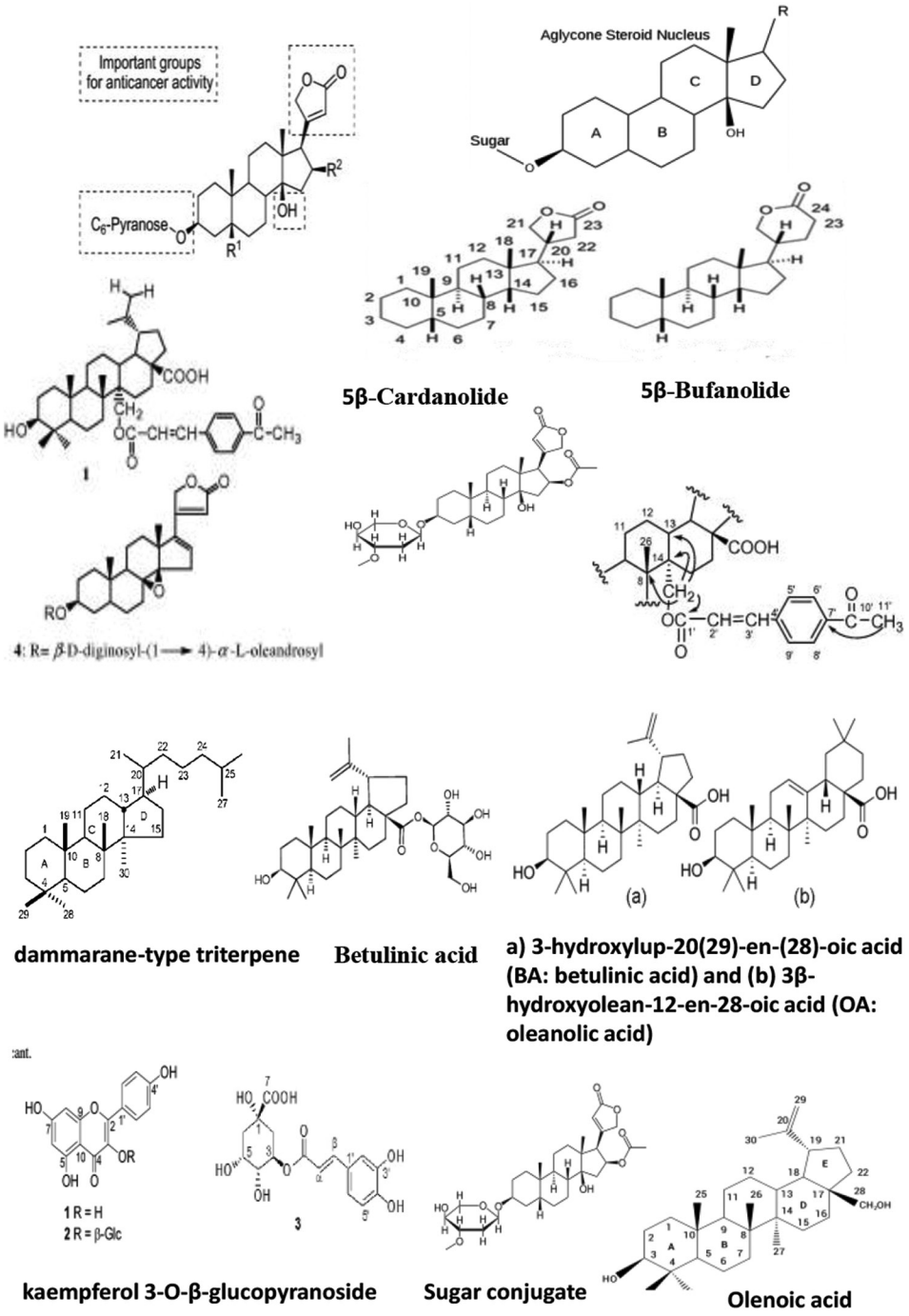


**Figure 2:** Various bio-organic compounds isolated from *Nerium oleander* "Kaner"

identified from dried parts of *N. oleander* Linn [Figure 2]. They showed anti-cancer properties in most cases.[23]

*Nerium* leaves synthesize pentacyclic triterpene flavonoids, that is, Quercetin-5-O-[-L-rhamnopyranosyl-(16)], *oleander*ocioic acid and flavonoids glycosides. Both kaempferol-5-O-[-L-rhamnopyranosyl-(16) and--D-glucopyranoside-oleandigoside, acardenoideand-D-glucopyranoside. These showed the cytotoxic and growth inhibitory effects on human breast cancer cell MCF-7.[24] *N. oleander* leaves cardenolides and cardenolides monoglycosides. Furthermore, pregnant women isolated from *N. oleander* showed a significant inhibition of VA-13 and HepG2 cell growth.[25] *N. oleander* also contains 21-hydroxypregna-4,6-diene-3,12,20-trione (1), 20R-hydroxypregna-4,6-diene-3,12-dione (2), and 16-epoxy-12-beta-hydroxypregna-4,6-diene-3,20-dione (3)[26] [Figure 2 and Table 1].

## Biological Effects/Treatment

This plant possesses enormous therapeutic and pharmacological potential. Plant extracts and its natural products showed anti-diabetic, anti-inflammatory, antioxidant, anticancer, antimicrobial, and anti-apoptotic and wound healing activities.

## Antioxidant and Anti-Hyperglycemic

The stem extract of *N. oleander* L. has antihyperglycemic potentials.[27] It also showed an inhibitory potential on porcine pancreatic alpha-amylase.[28] The extract of *N. oleander* L. hydromethanolichas anti-diabetic properties in mice with alloxan-induced diabetes.[29] Plant stem and root extracts restore glucose levels and inhibit the activity of liver aminotransferase, alanine aminotransferase, and alkaline phosphatase enzymes in streptozotocin-induced diabetic rats.[30] *Oleander* stem and root extracts show an increase in the systemic antioxidant activity and are responsible for improved glycemic control.[26] *N. oleander* ethanolic flower extract (NFE) decreased glucose and HbA1c and increased insulin and C peptide. In addition, NFE has improved the parameters of liver damage biomarkers and lipid profile in serum.[31] *Oleander* poisoning generally leads to cardiac arrhythmias, hyperkalemia, and gastrointestinal irritation.[32] *N. oleander* controls blood sugar levels in hypoglycemia dogs.[32] Hydroalcoholic extract of *N. oleander* leaves on the pituitary-gonadal axis, sperm mobility and number, antioxidant system, changes in the structure of testicles, and sperm formation in healthy and diabetic rats.[33] At doses of 50 and 100 mg/kg of *Nerium* extract, testicular morphology, sperm parameters, and reproductive organs in diabetic rats have significantly increased to various degrees. In treated animals, levels of glutathione peroxidase and catalase (CAT) in testicular tissues were found [Table 1].

## Genotoxic Effects

Similarly, leaf and flower extracts of *N. oleander* L. phytochemical content show potential cytotoxicity and genotoxicity because they alter the mitotic index, micronucleus and chromosome abnormality.[34] They also altered levels of malondialdehyde, glutathione, superoxide dismutase, and CAT as indicators of oxidative stress.[34]

## Skin Burns

The components of the *N. oleander* L. showed a protective effect against injuries and wounds without any side effects.[35] In contrast to this, *N. oleander* L. constituents show bradycardia with sinus nodal arrest and junction escape consistent with a cardiac glycoside effect.[36]

## Ameliorative Effects

NFE of *N. oleander* L showed an improvement effect on STZ-induced diabetic rats.[37] *Nerium* seeds and their associated species contain heart glycosides that cause intoxication and have harmful biological effects in animals.[5,37] *T. peruviana* synthesizes cardioactive glycosides such astervetin A, tervetin B, nipiglin, peruvosa, teritoxinand ruvosa. *T. peruviana* seeds cause heart, brain, and mental damage and manifest themselves as tachycardia, heart attack, paralysis, ataxia, and confusion.[5] The pure water extract of the leaves, leaves, and seeds of *T. peruviana* causes cardiac, neuromotor, and mental damage and is manifested as tachycardia, arrhythmia, paralysis, ataxia, and disorientation problems in experimental animals.[37]

## Anti-Fertility Activity

The methanol extract of the stem of *T. peruviana* inhibits sperm genesisin mice.[38] It has a serious effect on spermatocytes, secondary sperm, round sperm and mature sperm and can be used for the development of herbal contraceptives formen.[38] It significantly reduced the total protein and sialic acid content of the testes, epididymis, seminalveins, and ventral prostate, as well as the glucose content of the testicularcells.[38] These anti-fertility effects in experimental animals are due to the presence of heart glycosides.[39] The methanol extract from *T. peruviana* leaves can induce uterine contraction, prolong the estruscycle, and inhibit implantation by reducing levels of progesterone.[40] The leaves of *T. peruviana* are in nature abortive.[41]

## Antioxidant, Anti-Inflammatory, and Anti-Apoptotic

*Oleander* extract (NAE-8®) demonstrates antioxidant and anti-inflammatory effects in laboratory and animal studies. It exhibits antioxidant properties without triggering immune

**Table 1:** Chemical constituents found in various plant parts of *Nerium oleander* and its biological activities

| Plant part | Name of plant species | Bio-organic constituent/s | Biological activities | References |
|---|---|---|---|---|
| Leaves | *Nerium Oleander* | Oleandrin, a saponin glycoside | Broad spectrum cytotoxic activities | Rashan *et al*., 2023 |
| Leaves | *Nerium Oleander* | Oleandrin | Inhibit cancer cell proliferation, decrease cell viability, and induce apoptosis and/or cell cycle arrest. | Kanwal *et al*., 2020 |
| Leaves | *Nerium Oleander* | Oleandrin | Dysregulated signaling pathways in cancer, such as NF-□B, MAPK, and PI3K/Akt | Kanwal *et al*., 2020 |
| flowers | *Nerium oleander* L. | Oleandrin | Anticancer activity | Mohadjerani *et al*. |
| Leaves | *Nerium Oleander* | Odoroside, adigoside | Inhibition of phospho-signal transducer and activator of transcription | Manna *et al*., 2000 |
| Leaves and flowers | *Nerium Oleander* | Pregnanes | Significant inhibition of VA-13 and HepG2 cell growth | Bai *et al*., 2007 |
| Leaves and flowers | *Nerium Oleander* | Oleandrin | Promotes apoptosis in human colorectal cancer cells and downregulating BCL-2 proteins in response to its concentration | Pan *et al*., 2017 |
| Leaves and flowers | *Nerium Oleander* | Oleandrin and PBI-06150 | Display strong antiviral activity against SARS-CoV-2 | Plante *et al*., 2021; Singh *et al*., 2013 |
| Leaves | *Nerium Oleander* | Oleandrin | Inhibit replication of HIV-1 virus and reduces infectivity | Hutchison *et al*., 2020 |
| Leaves and flowers | *Nerium Oleander* | Oleandrin and terpenes | Prevent virus transfer from a GFP-expressing HTLV-1+ lymphoma T-cell line to huPBMCs | Hutchison *et al*., 2020 |
| Leaves and flowers | *Nerium Oleander* | Cardenolide monoglycosides | Antiviral activity against enveloped viruses | Farkhondeh *et al*., 2020 |
| Leaves and flowers | *Nerium Oleander* | Pentacyclic triterpene | Cytotoxicity | Siddiqui *et al*., 2012 |
| Leaves and flowers | *Nerium Oleander* | Cardenolides | Exhibited anticancer activity | Cao *et al*., 2018 |
| Leaves and flowers | *Nerium Oleander* | Oleandrin, | Destroy cancer cells by suppressing the expression of Rad51 | Zhengqiang *et al*., 2016 |
| Leaves and flowers | *Nerium Oleander* | Oleandrin, *oleander*ocioic acid | Decrease in the levels of OCT3/4 and β-catenin, as well as the reduction matrix metalloproteinase-9 activity, | Ko *et al*., 2018 |
| Dried aerial parts | *Nerium oleander* Linn, | Six new cardenolides 14-hydroxylated 14-carbonylated— | Anticancer activity | Cao *et al*., 2018 |
| Leaf extract | *Nerium oleander* Linn, | cardenolides | Anti-hyperglycemic potential | Dey *et al*., 2019 |
| Leaves and flowers | *Nerium oleander* Linn, | Cardiac glycosides and cardenolides | Cardiac arrhythmias, hyperkalemia, and gastrointestinal irritation | Page and Murtaugh, 2015 |
| Leaves and flowers | *Nerium oleander* Linn, | Cardenolides, terpenes | Sperm motility and number, antioxidant system, changes in testicular tissue structure, and spermatogenesis | Karimi *et al*., 2024 |
| Leaves and flowers | *Nerium oleander* Linn, | Cardiac glycosides and cardenolides | Exhibit potential cytotoxic and genotoxic effects | Bakir Çilesizoğlu *et al*., 2022 |
| Flower extract | *Nerium oleander* Linn, | Cardiac glycosides and terpenes | Ameliorative effects in STZ-induced diabetic rats | Battal *et al*., 2020 |
| Methanol extract of the stem bark | *Thevetia peruviana* | Cardiac glycosides and terpenes | Inhibits spermatogenesis in mice | Gupta *et al*. |

*(Contd...)*

**Table 1: *(Continued)***

| Plant part | Name of plant species | Bio-organic constituent/s | Biological activities | References |
|---|---|---|---|---|
| The methanol extract of leaves | *Thevetia peruviana* | Oleandrin, and terpenes | Prolong the estrus cycle and is anti-implantation by lowering progesterone levels | Samanta *et al*., 2016 |
| Flower and leaf extracts | *Nerium oleander* Linn | Oleandrin, and terpenes | Protect against electroshock-induced convulsions | Singhal and Gupta, 2014 |
| Flower and leaf extracts | *Nerium oleander* Linn, | Oleandrin, and terpenes | Behavioral and electrophysiological alterations in Wistar rats | Silva de Melo *et al*., 2020) |
| Flower and leaf extracts | *Nerium oleander* Linn | Oleandrin, and terpenes | Antivenom, anti-myotoxic, anti-hemorrhagic | Liaqat *et al*., 2022 |
| Flowers chloroform and ethyl acetate extract | *Nerium oleander* Linn | Oleandrin, and terpenes | Anti-anxiety effects | Singhal and Gupta, 2014 |
| Leaf extract | *Nerium oleander* Linn | Oleandrin, and terpenes | Wound healing | Sajon *et al*. |
| Ethanolic extract of flowers | *Nerium oleander* | Bioorganic components | Hypolipidemic potential in high fat diet-fed Sprague Dawley rats | Gayathri *et al*. |
| Ethanolic extract of flowers | *Nerium oleander* | Monoglycosidic cardenolides | Improves beta cell function and increase HDL concentration | Gayathri *et al*. |
| extract of leaves | *Nerium oleander* | Monoglycosidic cardenolides | Anti-urolithiatic activity | Suman *et al*., 2017 |
| Leaf extract | *Nerium oleander* | Methyl esters of ursolic acid and oleanoic acid | Cell growth inhibitory activity | Fu *et al*., 2005 |
| Leaf extract of *Nerium* | *Nerium oleander* | Betulinic acid | Antibacterial activity against *Staphylococcus aureus* | Ma *et al*., 2017 |
| Leaf extract of | *Nerium oleander* | betulin | Antifungal activity against *Fusarium*oxysporum and *Fusarium solani* | Hadizadeh *et al*., 2009 |
| Leaf extract | *Nerium oleander* | betulinic acid | Antimycotic activity against *Mucor circinelloides* | Begum, 2022 |
| Leaf extract | *Nerium oleander* | Oleandrin, and terpenes | Cardenolides from *Nerium* species showed antiplasmodialactivity | Chan *et al*., 2016 |
| Green leaves | *Nerium oleander* | Uzarigenin (2) and cardenolide N-1 (3) | Nematicidal activity against *Caenorhabditis elegans* | Wang *et al*., 2009 |
| Green leaves | *Nerium oleander* | Oleandrin, and terpenes | Larvicidal activity highly effective against stages 3 and 4 of *Culex pipiens* | El-Akhal *et al*., 2015 |
| Green leaves | *Nerium oleander* | synthesized silver nanoparticles AgNPs | Larvicidal activity *Culex quinquefasciatus* and *Anopheles stephensi* | Pushpalatha and Muthukrishnan, 1995 |
| Solvent extracts leaves | *Nerium oleander* | Oleandrin, and terpenes | Kill first to fourth instar larvae and pupae of malaria vector, Anopheles stephensi | Roni *et al*., 2013 |
| Solvent extracts leaves | *Nerium oleander* | Oleandrin, and terpenes | significant dominant lethality in both male and female adults | El-Sayed *et al*., 2015 |
| Solvent extracts leaves | *Nerium oleander* | Oleandrin, and terpenes | Larvicidal activity against mosquito larvae, particularly *Culex pipiens* | El-Akhal *et al*., 2015 |
| Solvent extracts leaves | *Nerium oleander* | Oleandrin, and terpenes | Insecticidal activity against German Cockroaches (*Blattella germanica*) | El-Akhal *et al*., 2105 |

*(Contd...)*

**Table 1: *(Continued)***

| Plant part | Name of plant species | Bio-organic constituent/s | Biological activities | References |
|---|---|---|---|---|
| *Leaf powder* | *Nerium oleander* | Oleandrin, and terpenes | Kill adults of *Tribolium castaneum* | Zohra *et al*., 2014 |

cell activation or inflammatory cytokine release.[41] It has a distinct biological efficacy.[42] Both leaf and flower extracts of *N. oleander* L. lead to a decrease in GSH levels due to the presence of glycosides and alkaloids.[34] The anti-inflammatory activity of *N. indicum* inhibits prostaglandin E2 in murine splenic lymphocytes.[29] The bioactive fraction of *N. indicum* leaf (NILE) up-regulates interleukin-2 (IL-2), IL-10, interferon-gamma, and down-regulates IL-4, tumor necrosis factor-alpha (TNF-α), nitric oxide, cyclooxygenase-1 (COX-1), and COX-2 activities.[29]

The ethanolic extract from *N. oleander* flowers demonstrated a highly significant ($P < 0.005$) anti-inflammatory effect in models involving cotton pellets and carrageenan, indicating its potential as a therapeutic agent for inflammation.[43] Furthermore, it reduced the expression of genes responsible for producing nitric oxide synthase (iNOS), TNF-α, Interleukin-1 beta, and cyclooxygenase-2 (COX-2) mRNA. In addition, it led to a notable decrease in the number of leukocytes (73.09%) and levels of C-reactive protein (54.60%), while also blocking the activity of COX-1, COX-2, 5-LO, and 12-LO enzymes in a significant way. However, at higher doses (2000 mg/kg), it was found to have hepatotoxic effects. The leaves of *N. oleander* also contain triterpenes, specifically ursane-type triterpene 1, oleanane-type triterpene 2, and dammarane-type triterpene, which have shown the ability to inhibit the production of ICAM-1.[44]

## Anticonvulsive Activity

In an animal model under experimentation, an ethanol extract of *N. oleander* flowers shown anticonvulsant properties. At dosages of 100 and 200 mg/kg, the extract potentiated pentobarbital-induced sleep and significantly decreased ($P < 0.01$) spontaneous locomotor activity. The extract demonstrated 66% protection against convulsions caused by electroshock at the higher dose of 200 mg/kg, whereas at the lower dose of 100 mg/kg, there was a substantial reduction ($P < 0.01$) in convulsions caused by pentylenetetrazol.[45] Wistar rats (200–250 g) treated with ethanolic extract of *N. oleander* Linn experience behavioral and electrophysiological changes.[46] At a dose level of 400 mg/kg, *N. oleander* petroleum (PE) ether, methanolic, and aqueous extracts demonstrated anticonvulsant effectiveness in Pentylene Tetrazole Induced Seizures test mice.[47]

## Anti-Venom Activity

*N. oleander* flower and leaf extracts demonstrated anti-inflammatory, anti-myotoxic, and anti-hemorrhagic effects in addition to anti-venom activity.[48] These also counteract the nephrotoxicity, necrosis, and bleeding caused by venom's systemic effects.[48] However, this behavior has been shown to harm some snake species. In addition, this plant includes secondary metabolites that are pharmacologically active, primarily flavonoids, which have been shown to inhibit metalloproteases, lipoxygenases, and phospholipases.[48] Extracts from the flowers and leaves of *N. oleander* shown anti-venom properties and were utilized as a snakebite remedy.[49]

## Anti-Anxiety Effects

Chloroform and ethyl acetate extract from *N. oleander* flowers had anti-anxiety properties.[45] This herb is frequently used for anxiety and traditional medicine.[50]

## Anti-Obese Activity

In Sprague Dawley rats fed a high-fat diet, the ethanolic extract of *N. oleander* has hypolipidemic potential.[51] *N. oleander* raises HDL levels and enhances beta cell function. In Type 2 diabetes, the distillate portion of *N. oleander* affects the metabolism of both fat and glucose.[52] It reduced insulin resistance, low density lipoprotein, atherogenic index, triglyceride-HDL ratio, fasting blood glucose, HbA1c, insulin resistance, total cholesterol, and leptin levels.[52]

## Anti-Urolithiatic Activity

At 500 mg/kg body weight, *N. oleander* extract demonstrated notable anti-urolithiaticaction.[53] *N. oleander* extract lowers the solubility product of crystallizing salts such calcium and phosphate as well as the components in the kidney that cause stone formation.[53]

## Antibacterial

The ethanolic floral extract (NOEE) of *N. oleander* demonstrated significant bacterial kills by inhibiting bacterial growth and inflammation. Two quinolinone alkaloids, 3-O-methylviridicatin (1) and viridicatol (2), and an isoquinolone alkaloid, 5-hydroxy-8-methoxy-4-phenylisoquinolin-1(2H)-one (3), were identified from the fermentation of an endophytic fungus, *Penicillium* spp. R22, in *N. indicum*, exhibiting potent antifungal activity. Compound 2 was found to have strong antibacterial properties against Staphylococcus aureus, with a minimum inhibitory concentration of 15.6 μg/mL.[54].

### Antifungal Activity

An antifungal extract from *N. oleander* L. demonstrated efficacy against *Fusarium oxysporum* and *Fusarium solani*. For the prevention of fungal infections in plants, these could be effective substitutes for chemical additions.[55] *In vitro* culture of *N. indicum* leaf extract exhibits antimycotic action against *Mucor circinelloides*.[56]

### Antiparasitic Activity

Cardenolides found in *Nerium* species have demonstrated possible anti-plasmodial action.[56] Similarly, 3-beta-O-(beta-D-diginosyl)-14,15 alpha-dihydroxy-5alpha-card-20(22)-enolide (1) and two recognized chemicals, uzarigenin (2) and cardenolide N-1 (3), are presented in *N. indicum* AcOEt extract. Nematicidal activity was demonstrated by these components against *Caenorhabditis elegans*.[57]

### Anti-HIV Activity

The antiviral activity of hot and cold extracts from *N. oleander* was found effective against six distinct viruses including herpes simplex virus type 1 (HSV-1), polio virus type 1(Sb-1), vesicular stomatitis virus, reovirus type-1(Reo-1), human immunodeficiency virus type-1 (HIV-1), and yellow fever virus (YFV).[58] Aquatic extract derived from Anvirzel TM or *N. oleander*, cause its therapeutic activity as anti-HIV.[59] It has been proved that AZT is a potent inhibitor of HIV replication, which drastically reduces the quantity of virions produced.[59] While AnvirzelTM treatment significantly reduced the total number of viruses generated, it did not change the infectivity of the virus produced by infected cells. It also raised a lot more mononuclear cells in human peripheral blood. At a concentration of 0.05 µg/mL, oleandrin, PBI-06150's active lead compound showed a potent antiviral activity against SARS-CoV-2).[60] *N. oleander* extract (PBI-06150) could be used to reduce the severity of disease caused by SARS-CoV-2 as well as associated COVID-19 and potentially for reducing person-to-person transmission by those diagnosed early after infection.[59,60] These numbers are highly down-regulated on particles containing gp120 envelope glycoprotein and HIV-1.

It significantly reduces the amount of the gp120 envelope glycoprotein on HIV-1 particles. It significantly reduces the amount of the gp120 envelope glycoprotein on HIV-1 particles. It lowers HIV-1 infectivity *in vitro*.[61] A GFP-expressing HTLV-1+ lymphoma T-cell line and huPBMCs (Human T-cell Leukemia Virus Type-1) are not infected by *N. oleander* extract.[61] Oleandrin also showed broad antiviral activity against enveloped viruses by reducing the incorporation of the envelope glycoprotein into mature particles, a stage of the infection cycle that is not targeted by modern HAART.[62]

### Cytotoxic Effects

A cardiac glycoside with strong cytotoxicity is oleandrin. Oleandrin causes programmed cell death in PC3 cell line culture and inhibits the activity of nuclear factor kappa-light-chain-enhancer of activated B chain (NF-κB) in a variety of cultured cell lines, including U937, CaOV3, human epithelial cells, and T cells.[63] Oleandrin enhances fibroblast growth factor-2 cellular export, induces tumor cell autophagy, produces superoxide radicals that damage tumor cells by disrupting mitochondria, inhibits interleukin-8, a mediator of tumorigenesis, and induces apoptosis through Fas gene expression in tumor cells. Triterpenoid *N. oleander* Uvaol is a hazardous and carcinogenic chemical.[64]

### Inhibition of Cancer Growth

*N. oleander* supercritical $CO_2$ extract (PBI-05204) prevents human pancreatic cancer from growing. It has potent antitumor activity and targets the PI3K/mTOR pathway.[65] Oleandrin suppresses the activation of nuclear factor-kappaB (NF-kappaB) and activator protein-1 (AP-1), which lowers tumrogenesis and inflammation. It also inhibits nuclear transcription factor-kappaB, AP-1, and c-Jun NH2-terminal kinase. *N. oleander* supercritical $CO_2$ extract, PBI-05204, inhibits the growth of human glioblastoma, decreases Akt/mTOR activity, and alters the characteristics of GSC cell-renewal.[66] In addition to cancer stem cells, PBI-05204 causes apoptosis in tumor cells by blocking the PI3k/mTOR pathways.[66] Among brain cancers, glioblastoma multiforme is the most common and aggressive type. Oleandrin inhibits TNF, which lowers inflammation and tumorigenesis.[67] It is accomplished by preventing the phosphorylation and degradation of the NF-kappaB inhibitor IkappaBalpha. These substances have shown antitumor and radiosensitizing qualities.[68] AuNPs stable gold-conjugated nanoparticles from *N. oleander* stem bark showed strong anticancer activity.[69]

### Anti-Tumor Activity

*N. oleander* is known to be poisonous, but its toxicity can be controlled to produce anticancer therapeutic drugs.[70,71] Livestock can also be poisoned by chewing on green *oleander* leaves.[72,73] To counteract the plant posions, antitoxins are employed.[74] In addition to leaf extracts, inhaling *oleander* smoke is toxic and bad for human health.[75] Therefore, self-medication is not more health-wise for people.[76] Oleandrin exhibits broad spectrum cytotoxicity and has proven to be very successful in treating a variety of cancers.[77-79] In human osteosarcoma cells, oleandrin and cisplatin work in concert by promoting cell apoptosis through activation of the p38 MAPK signaling pathway.[80] Through the suppression of COX and nitric oxide production as well as the modification of the TH1/TH2 cytokine balance in murine splenic lymphocytes, it exhibits immunomodulatory activity.[81] Oleandrin plays

a mechanistic role in the response to and repair of DNA damage.[82] Furthermore, it exhibits immunogenicity, which means that human cancer and tumors may be treated with it.[83,84] Through both direct and indirect effects on tumor cells, oleandrin inhibits the growth of gliomas.[85]

### Insecticidal Activity

At a dose of 57.57 mg/mL, extracts from the leaves of *N. oleander* demonstrated larvicidal activity against Culex pipiens mosquito larvae in stages 3 and 4.[86] In addition, a leaf extract demonstrated larvicidal activity against *Culex quinquefasciatus* and *Anopheles stephensi* larvae in their I and II instars.[87] In a similar vein, it was discovered that silver nanoparticles (AgNPs) made from *N. oleander* (*Apocynaceae*) leaf extract were effective against *A. stephensi (Diptera: Culicidae)*, the malaria vector, in its first through fourth instar larvae and pupae.[88] The synthesized AgNPs against A. stephensi larvae and pupae in their first to fourth instars showed the highest larval mortality, ranging from 20 to 33.99 ppm.[88] When compared to untreated insects, the diethyl ether extract's LC50 significantly reduced the duration of the larvae, pupae, percentage of pupation, percentage of adult emergence, longevity of the females, fecundity, and oviposition activity index. However, it significantly increased the growth index and the percentage of development per day of the larvae and pupae.

Furthermore, administration of this extract resulted in notable dominant lethality in adult males and females.[89] *N. oleander* leaf extract in diethyl ether may be used as a *C. pipiens* control agent. Ether of PE: The larvicidal activity of *N. oleander* leaf extracts (1:1) was observed in *C. quinquefasciatus* and A. stephensi instars I and II. *N. oleander*'s ethanolic extract exhibits massive killing of *C. pipiens* larvae, as evidenced by LC50 and LC90 values that range from 57.57 mg/mL to 166.35 mg/mL, respectively. *N. oleander* may prove to be a viable and efficient natural biocide with larvicidal properties for mosquito larvae, specifically targeting *C. pipiens*[90] and German cockroaches *(Blattella germanica)*.[91] In comparison to synthetic pesticides like cypermethrin (0.1%), *N. oleander* extracts also reduced the ability of cockroaches to lay eggs, hatch them, and undergo metamorphosis.[91] Similarly, adult *Tribolium castaneum* (red flour beetle) was successfully controlled with *oleander* leaf extracts. In the insecticidal bioassay, it demonstrates 100% mortality at a dose of 0.5 g following 7 days of exposure).[92] The methanolic extract exhibited exceptional effectiveness in suppressing the larvae of adult *Tribolium confusum* and *T. castaneum*.[92]

## CONCLUSION

The plant known as Kaner *N. oleander* (L.) possesses a variety of phytochemical groups that exhibit a range of biological activities. Despite being toxic to humans, the plant's bioactive ingredients have been shown to have anti-inflammatory, anti-diabetic, anti-carcinogenic, anti-tumor, anti-microbial, cytotoxic, analgesic, ameliorative, anti-parasitic, nematicidal, and insecticidal properties. Plant extracts demonstrated exceptional effectiveness against the larvae and pupae of insect pests that are significant to medicine, including *B. germanica, A. stephensi, C. quinquefasciatus*, and *C. pipiens.* Fruits and plant seeds work well as anti-fertility remedies. Oleandrin exhibits broad spectrum cytotoxicity and has proven to be very successful in treating a variety of cancers. It can be cytotoxic to microbiological cells. Several viruses have been found to respond well to *N. oleander*. The structure-activity relationship of the bio-organic components is crucial for obtaining its pharmacological and therapeutic potential. Furthermore, it is necessary to test their mode of action as well as the physiological and biochemical effects in animal models.

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