REVIEW ARICLE

Anticancer and anti-HIV activity of *Nerium oleander the* Kaner plant: A comprehensive review

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Abstract

This article provides a comprehensive review on the anticancer and anti-human immunodeficiency virus (HIV) activities of *Nerium oleander* (L.) from the *Apocynaceae* family. It highlights the presence of phytochemicals, namely, cardiac glycosides oleandrin and cardenolides, which have shown broad-spectrum cytotoxic effects against drug-resistant breast cancer and pancreatic cells. These compounds also exhibit potent antioxidant, antimicrobial, and anti-inflammatory properties, as well as inhibit the growth of human pancreatic cancer by targeting the PI3K/mTOR pathway. Oleandrin has been found to induce apoptosis and prevent cell proliferation, as well as inhibit tumor growth. It has also demonstrated effectiveness against SARS-CoV-2 and HIV, potentially reducing the spread of these viruses. The unique biological activity of Oleandrin is acknowledged, although its overall therapeutic benefits are still not fully understood. Therefore, it is crucial to thoroughly evaluate the toxicity profile of the plant's phytochemical components for drug development purposes.

Key words: Anti-cancer activity and drug development, Kanner, monoglycosidic cardenolides, *Nerium oleander*, oleandrin

INTRODUCTION

Nerium oleander (L.) is a species of the *Apocynaceae* family, also known as Kaner or yellow oleander [Figure 1]. It is native to various countries in Asia and the Mediterranean region and has been traditionally utilized for its medicinal properties. In addition, it is widely grown as a decorative plant. The oil from its seeds is used to create paint that is resistant to fungus, bacteria, and termites. This plant contains bioactive compounds that are of therapeutic interest, including cardiac glycosides (CGs), monoglycosidic cardenolides, α-tocopherol, digitoxigenin, urosolic acid, quercetin, adynerin, neritaloside, Odoroside A, odoroside H, adigoside, and oleandrin, and among others [Figure 2].[1] Oleandrin, in particular, is a saponin glycoside that is recognized as one of the most active and pharmacologically significant compounds in *N. oleander*.[2] The flowers of *N. oleander* L. are a potential source of natural antioxidants.[3] The ethanolic extract of its flowers has demonstrated strong antimicrobial and anti-inflammatory properties.[4] All parts of *N. oleander* L. are toxic to most animals, leading to accidental poisoning in humans due to the presence of CGs in its leaves. However, the toxins found in yellow oleander have been explored for their potential in biological pest control.[5]

N. oleander L. contains a variety of phytochemicals, each with a broad range of therapeutic and pharmacological benefits, including potential anticancer effects.[6] The extract from *N. oleander* L. leaves may contain bioactive compounds that can slow down the growth of HeLa cells, reduce their ability to move and halt their cell division at the G2/M phase in laboratory settings.[6] In addition, the leaf extract can significantly lower the levels of epidermal growth factor receptor and phosphorylated p-Rb (Ser 780) in cells. *N. oleander* leaves contain CGs oleandrin and Odoroside A, as well as polyphenolic monomers, which have shown anticancer properties against various types of cancer at low doses [Table 1].[7] Oleandrin, isolated from this

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plant, has been effective in treating gynecological cancers and is recognized for its superior pharmacological qualities. It is commonly used in traditional medicine for a variety of conditions, including heart failure. Recently, oleandrin has gained significant attention for its broad range of anticancer and unique antiviral properties.[8] The main challenge in cancer treatment is drug resistance, and it is possible that phytochemicals from *N. oleander* could help address this issue. This review article provides a detailed examination of the anticancer properties of *N. oleander* L. leaves.

Figure 1: Aerial vegetative parts of *Nerium Oleander* (L.) plant

SOURCE OF INFORMATION

For writing this comprehensive research review on *N. oleander* L: Kaner plant, various databases were searched. For the collection of relevant information, specific terms such as medical subject headings and keytext words, such as "Kaner (*N. oleander*) and its therapeutic uses" published till 2024 were used in Medline. Most specially for retrieving all articles pertaining to the traditional uses of *N. oleander* L for therapeutics, electronic bibliographic databases were searched, and abstracts of published studies with relevant information on the *N. oleander* L were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporation of recent knowledge, relevant research articles, books, conference proceedings', and public health organization survey reports were selected and collated based on the broader objective of the review. This was achieved by searching databases, including SCOPUS, Web of Science, EMBASE, PubMed, Swiss-Prot, and Google searches." From this common methodology, discoveries and findings were identified and summarized in this final review.

ANTICANCER POTENTIAL

N. oleander L possesses various phytochemicals which show strong antioxidant, anticancer, anti-human immunodeficiency virus (HIV), and wound healing activities.

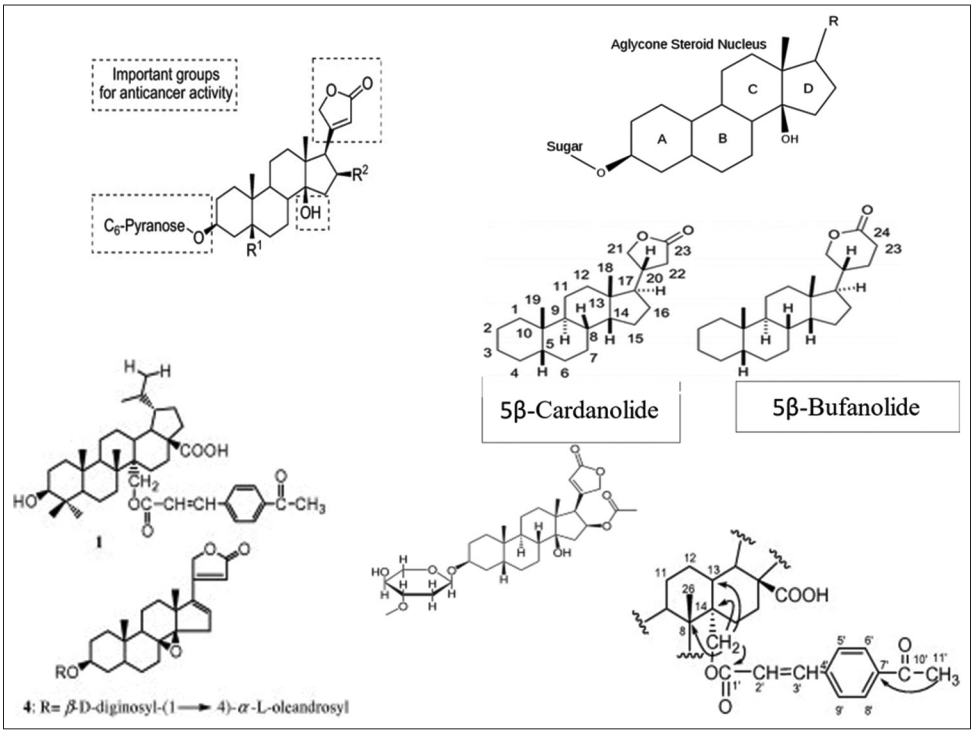

Figure 2: Important cardiac glycosides isolated from *Nerium Oleander* (L.)

Table 1: Anticancer properties of *Nerium Oleander* (L.) plant

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-κB, 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	Lin *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; Shailbala Singh *et al.*, 2013
Leaves	*Nerium Oleander*	Oleandrin	Inhibit replication of HIV-1 virus an reduces HIV-1 infectivity	Hutchison *et al.*, 2020
Leaves and flowers	*Nerium Oleander*	*N. oleander* extract	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	oleandrin also demonstrated broad antiviral activity against enveloped viruses	Farkhondeh *et al.*, 2020
Leaves and flowers	*Nerium Oleander*	Pentacyclic triterpene	Cytotoxicity in cancer cells	Siddiqui *et al.*, 2012
Leaves and flowers	*Nerium Oleander*	Cardenolides	Exhibited anticancer effects	Cao *et al.*, 2018
Leaves and flowers	*Nerium Oleander*	Oleandrin	It causes damage to cancer cells by suppressing the expression of Rad51	(Bao *et al.*, 2016)
Leaves and flowers	*Nerium Oleander*	Oleandrin, oleanderocioic acid	Decrease in the levels of OCT3/4 and β-catenin, as well as the reduction of MMP-9 (matrix metalloproteinase-9) activity	(Ko *et al.*, 2018)

Oleandrin

Oleandrin, a highly soluble cardiac glycoside present in the leaves and seeds of *N. oleander* (*Apocynaceae*)[9]. It can also cause nausea, abdominal pain, vomiting, increased salivation, and diarrhea. It has a severe impact on the gastrointestinal system, raises potassium levels in the blood, and can lead to respiratory paralysis.[2] Exposure to oleandrin affects the central nervous system, resulting in symptoms such as drowsiness, tremors, muscle shaking, seizures, collapse, and even coma, which can be fatal [Table 1].

Contact with oleander sap leads to severe eye inflammation and skin redness and causes allergic reactions including skin dermatitis.[10] The use of oleander and its components causes health effects in humans, such as a burning sensation in the eye's mucous membranes, and affects the digestive and respiratory systems, resulting in respiratory paralysis.[2] The use of *N. oleander* products is unsafe due to the poisonous chemicals present in its leaves. The estimated lethal amount for animals is approximately 0.5 mg per kilogram.[11] The highest safe level of oleandrin in the blood is 20 ng per milliliter, above which it becomes toxic [Table 1].[12]

Oleandrin, a key chemical in oleander, is linked to the harmful effects of oleander sap, similar to digoxin. In addition, oleandrin is transformed into oleandrigenin in human tissues.[13] Due to its water-loving nature, oleandrin readily enters the digestive system following ingestion Madden *et al*.[14] Its removal from the body, especially by the kidneys and primarily through urine, is slow.[14] It is excreted mostly in feces but also in urine. Given that the primary way it leaves the body is through the bile and ends up in feces, it primarily affects the liver.[14] There is also accumulation in the heart, which is why it can cause heart toxicity.[14] Specifically, oleandrin disrupts and inhibits the Na-K ATPase, which is a crucial process inside cells.[15] Oleandrin attaches to certain parts of the protein, rendering it non-functional[16,17] Oleandrigenin is a modified form of oleandrin. Oleandrin, structurally similar to glycosides and alkaloids, shows very high anti-cancer activity [Table 1].[15]

Oleandrin, a potent cytotoxic agent, exhibits significant antitumor properties that are proven to be highly effective against various forms of cancer.[18] It has been shown to significantly reduce the average size and volume of tumors and effectively halt the proliferation of cancer cells. In laboratory studies, it has been observed to induce apoptosis in cancer cells and inhibit their viability and cell cycle progression. Research has demonstrated its efficacy against numerous cancers including breast, lung, pancreatic, colon, prostate, ovarian, colorectal, oral, ovarian cancer, glioma, melanoma, glioblastoma, osteosarcoma, and histiocytic lymphoma.

Oleandrin was able to inhibit cell proliferation, decrease cell viability, and induce apoptosis and/or cell cycle arrest. Oleandrin targets several dysregulated signaling pathways in cancer, such as NF-κB, MAPK, and PI3K/Akt.[2] In addition, it inhibits the spread of metastatic MDA-MB-231 breast cancer cells. These cells show reduced invasion through pathways involving phospho-STAT-3, which is critical for the regulation of invasion-related molecules.[19] The action also leads to a decrease in the levels of OCT3/4 and β-catenin, as well as the reduction of MMP-9 matrix metalloproteinase-9 (MMP-9) activity, ultimately resulting in diminished cancer cell spread.[7] There is evidence suggesting that oleandrin can effectively slow down the growth of human cancer cells.[9] It causes damage to cancer cells by suppressing the expression of Rad51.[9] Oleandrin promotes apoptosis in human colorectal cancer cells through the mitochondrial pathway and modulates the levels of certain caspase proteins while downregulating BCL-2 proteins in response to its concentration.[19] Moreover, oleandrin increases the level of intracellular calcium and decreases the level of glutathione in cells. Given its toxic effects, the use of oleandrin in medical treatments is restricted.[8] This, in part, explains why oleandrin has not been approved as a prescription drug or dietary supplement by regulatory bodies. However, a combination of oleandrin with paclitaxel has shown promising results in inhibiting the growth of hematopoietic tumors and carcinomas [Table 1].[1]

Cytotoxic Effects

CGs may be utilized to treat cancer, according to recent research. *N. oleander*, an attractive shrub, has been used in traditional medicine to cure a variety of illnesses, including cancer. Leaf extracts from this plant are currently undergoing Phase I clinical studies. We generated a hydroalcoholic extract from *N. oleander* leaves (containing 4.75 ± 0.32 % of cardenolides) and evaluated its cytotoxic efficacy against MRC5 nonmalignant lung fibroblasts and A549 lung cancer cells in this communication. The outcomes demonstrated that the extract from *N. oleander* had cytotoxic effects on the cancer cell line that was much greater than those on the nonmalignant cell line. Its potency and selectivity were comparable to those of the anticancer medication cisplatin. DNA damage and cytotoxicity induced by *N. oleander* extract (gamma-H2AX focus formation). Reactive oxygen species are created during cytotoxicity, although they play a minor part. According to Calderón-Montaño *et al*.,[20] a hydroalcoholic extract derived from the leaves of *N. oleander* inhibits glycolysis and causes the selective death of lung cancer cells. In A549 cells, *N. oleander* extract significantly reduced glycolysis (the consumption of glucose and production of lactate), in a manner similar to that of the glycolysis inhibitor dichloroacetate, which is presently undergoing clinical development for the treatment of cancer. It was discovered that *N. oleander* L. flowers may be a good source of free radicals [Table 1].[3]

INHIBITION OF CANCER GROWTH

Using the PI3K/mTOR pathway as its target, PBI-05204, a supercritical CO_2 extract of *N. oleander*, inhibits the growth of human pancreatic cancer. Furthermore, it demonstrates strong antitumor activity.[21] Nuclear transcription factor-kappaB, activator protein-1 (AP-1), and c-Jun NH2-terminal kinase are all inhibited by oleandrin. Tumorigenesis and inflammation may be inhibited by substances that suppress the activation of AP-1 and nuclear factor-kappaB (NF-kappaB). Supercritical CO_2 extract of *N. oleander*, PBI-05204, inhibits human glioblastoma growth, lowers Akt/mTOR activities, and modifies the properties of GSC cell-renewal.[22] PBI-05204 inhibits the PI3k/mTOR pathways and induces apoptosis in tumor cells in addition to cancer stem cells.[23] Glioblastoma multiforme is the most prevalent and aggressive kind of brain cancer. Tumor necrosis factor (TNF) is blocked by oleandrin, which reduces inflammation and tumorigenesis.[24] Oleandrin inhibits lipopolysaccharide and phorbol ester-induced NF-kappaB activation. Oleandrin prevents NF-kappaB, AP-1, and the kinases linked to them from being activated. Oleandrin also inhibits TNF-induced NF-kappaB activation in concentration- and time-dependent manner.[24] It is carried out by blocking the phosphorylation and degradation of IkappaBalpha, an NF-kappaB inhibitor. CGs are steroid-like compounds derived from plants that selectively inhibit the Na+/K+-ATPase pump (NKA).[2] These compounds have

demonstrated radiosensitizing and antitumor properties.[25] Strong anticancer activity was demonstrated by AuNPs stable gold-conjugated nanoparticles from *N. oleander* stem bar [Table 1].[26]

Cardenolides

Furthermore, cold aqueous extract from *N. oleander* leaves affects tumor cells' ability to proliferate and stop their cell cycle at the S-phase or G2/M-phase, respectively.[1] Cardenolides isolated from *N. oleander* exhibited anti-proliferative activity, and Nerium leaves synthesize cardenolides glycosides. Monoglycosidic cardenolides with the structure of 3β,14β-dihydroxy-5β-card-20(22)-enolide, with or without an acetoxy group at C-16, are the most potent anticancer compounds. These substances, along with breast in, significantly inhibited the growth of cancer cells in culture (IC(50)-values ranging from 0.010 to 0.071 μg/mL).[1] From the dried aerial parts of *N. oleander* Linn, six new cardenolides-three 14-hydroxylated and three 14-carbonylated-have been identified. They exhibited anticancer properties in the majority.[27]

N. oleander leaves exhibited cytotoxic effects caused by inhibition of Na(+)/K(+)-ATPase bound to the plasma membrane.[1] *Nerium* leaves also include a pentacyclic triterpene that demonstrated cytotoxicity and flavonoids. Quercetin-5-O-[α-L-rhamnopyranosyl-(1→6)], oleanderocioic acid, two flavonoidal glycosides, and a pentacyclic triterpene. Both kaempferol-5-O-[α-L-rhamnopyranosyl-(1→6) and -β-D-glucopyranoside -oleandigoside, a cardenolide, and β-D-glucopyranoside. These demonstrated cytotoxic and growth-inhibitory effects on the human breast cancer cell MCF-7.[28] In a similar vein, *N. oleander* yielded cardenolides N-1 (1), N-2 (2), N-3 (3), and N-4 (4) in addition to two previously identified cardenolides, 5 and 12, and seven cardenolide monoglycosides, 6–11 and 13. According to Zhao *et al*.,[29] *N. oleander* derived bioactive components demonstrated cytotoxic effects on three human cell lines: Human liver tumor cells (HepG2), malignant tumor cells induced from WI-38 (VA-13), and normal human fibroblast cells (WI-38).[29] Similar to this, pregnanes isolated from *N. oleander* demonstrated significant inhibition of VA-13 and HepG2 cell growth, as did 21-hydroxypregna-4,6-diene-3,12,20-trione (1), 20R-hydroxypregna-4,6-diene-3,12-dione (2), and 16beta,17beta-epoxy-12beta-hydroxypregna-4,6-diene-3,20-dione (3) [Table 1].[30]

This is well known that *N. oleander* is toxic in nature but its poisonous nature can be managed to have anticancer therapeutic drugs.[31,32] Chewing of oleander green leaves by livestock is also poisonous.[33,34] Antitoxin can be generated to neutralize for plant poisoning.[35] Besides leaf extracts oleander smoke inhalation is also poisonous and harmful for human health.[36] Hence, self-medication is not safer for health.[37] Oleandrin shows wide-spectrum cytotoxicity and has been found highly effective in different types of cancers.[13,18,38] Oleandrin synergizes with cisplatin in human osteosarcoma cells by enhancing cell apoptosis through activation of the p38 MAPK signaling pathway.[39] It shows immunomodulatory activity of Nerium indicum through inhibition of nitric oxide and cyclooxygenase activity and modulation of TH1/TH2 cytokine balance in murine splenic lymphocytes.[40] Oleandrin has the mechanistic role in DNA damage response and repair signaling.[41] It also shows immunogenic which can be used to treat human cancer and tumors.[42,43] The glycoside oleandrin reduces glioma growth and shows direct and indirect effects on tumor cells [Table 1].[44]

ANTI-HIV ACTIVITY

Aqueous extract from *N. oleander* and Anvirzel™ demonstrated anti-HIV therapeutic action.[45] It has been demonstrated that the strong HIV replication inhibitor AZT dramatically lowers the amount of viruses produced.[45] Anvirzel™ treatment dramatically decreased the amount of virus generated overall but did not affect the infectivity of the virus generated from infected cells. It also increased the quantity of mononuclear cells in human peripheral blood. At 0.05 μg/mL concentration, oleandrin, the active principal ingredient in PBI-06150, demonstrated strong antiviral activity against SARS-CoV-2.[45,46] The amount of the gp120 envelope glycoprotein on HIV-type 1 particles is greatly decreased by it. The amount of the gp120 envelope glycoprotein on HIV-1 (human immunodeficiency virus type 1) particles is greatly decreased by it. *In vitro*, it reduces HIV-1 infectivity (Hutchison *et al*., 2020).[47] In co-culture experiments, *N. oleander* extract may prevent virus transfer from a GFP-expressing HTLV-1+ lymphoma T-cell line to huPBMCs. The botanical glycoside oleandrin inhibits human T-cell leukemia virus Type-1 infectivity and Env-Dependent virological synapse formation,[47] By lowering the incorporation of the envelope glycoprotein into mature particles – a stage of the infection cycle that is not targeted by contemporary HAART – oleandrin also demonstrated broad antiviral activity against enveloped viruses [Table 1].[48]

CONCLUSION

Potentially bioactive substances found in *N. oleander* L. may prevent cancer cells from proliferating, migrating, and stopping their cycle at the G2/M phase. Odoroside and oleandrin both exhibited broad-range cytotoxic effects. Treatment with oleandrin inhibits the phospho-signal transducer and activator of transcription (STAT)-3, which in turn significantly lowers the levels of OCT3/4, β-catenin, and MMP-9 activity. Treatment with oleandrin reduced cell viability in SW480, HCT116, and RKO cells as well as the *in vitro* transmission of HTLV-1. Broad antiviral activity against enveloped viruses, primarily SARS-CoV-2, is another

feature of oleandrin. This plant's phytoextracts have been shown to be effective against pancreatic, breast, and cervical cancer. Without a doubt, this plant's bioactive components can be used to create novel cancer-treating medications.

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