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HERBAL POTENTIAL OF *NERIUM OLEANDER*: PHYTOCHEMICAL PROFILE AND PHARMACOLOGICAL SIGNIFICANCE

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Abstract:
Nerium oleander L. (Apocynaceae), commonly known as oleander, is a widely distributed ornamental shrub recognized both for its remarkable therapeutic potential and its pronounced toxicity. Traditionally used in several healing systems, the plant contains a diverse reservoir of bioactive phytochemicals, especially cardenolides, triterpenoids, flavonoids, alkaloids, and phenolic compounds, which collectively contribute to its pharmacological actions. Over the past decades, extensive scientific interest has focused on its antioxidant, antimicrobial, anti-inflammatory, anticancer, cardiotonic, insecticidal, and wound-healing properties. However, the plant's potent cardiac glycosides, such as oleandrin and neriifolin, impart narrow therapeutic windows and raise safety concerns. This review comprehensively examines the botanical identity, phytochemical profile, ethnomedicinal relevance, and pharmacological significance of N. oleander, while also addressing its toxicological implications. Understanding both the beneficial and hazardous aspects of this plant is essential for advancing safe therapeutic applications, guiding future research, and developing novel formulations that optimize efficacy while mitigating risks.

Keywords: *Nerium oleander, Phytochemistry, Pharmacological significance, Herbal toxicity, Cardiac glycosides etc.*

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INTRODUCTION:

Nerium oleander L. is a perennial evergreen shrub belonging to the family Apocynaceae and is widely cultivated across tropical, subtropical, and Mediterranean regions. Renowned for its striking flowers and adaptability to harsh climates, the plant holds significant medicinal relevance in several ancient healthcare systems, including Ayurveda, Unani, and various folk medicinal traditions.[1-5] Historically, preparations derived from its leaves, flowers, and roots have been used to treat skin diseases, inflammation, ulcers, parasitic infestations, and cardiac conditions. Despite its therapeutic reputation, *N. oleander* is equally recognized for its potent toxicity due to the presence of cardenolide-type cardiac glycosides capable of influencing cardiac muscle contractility.[6-8]

The increasing scientific interest in *N. oleander* stems from its rich and diverse phytochemical composition. Bioactive molecules such as oleandrin have shown considerable pharmacological promise, particularly as anticancer agents through mechanisms involving apoptosis induction, NF-κB pathway modulation, and inhibition of cellular proliferation. Additionally, extracts of the plant demonstrate strong antioxidant, antimicrobial, anti-inflammatory, and insecticidal properties, highlighting its broad therapeutic potential. A critical rationale for reviewing *N. oleander* lies in balancing its medicinal value with its toxicological risks.[8-12] While several studies have presented compelling evidence supporting the pharmacological applications of its constituents, safer delivery systems, dose standardization, and mechanistic understanding are essential for its responsible clinical translation.

Globally, *N. oleander* thrives in dry, warm climates and is commonly found in roadsides, gardens, and riverbanks, making it easily accessible in many countries. Its widespread availability and documented traditional uses justify a comprehensive evaluation of its phytochemical and pharmacological significance. This review synthesizes existing knowledge to support future research directions and encourage the development of controlled, safe, and effective herbal therapies based on this plant.[13-15]

BOTANICAL DESCRIPTION OF *NERIUM OLEANDER*

Nerium oleander is the sole species widely recognized under the genus *Nerium*, although closely related genera exist within Apocynaceae. Its taxonomical identity is well-established due to its distinct botanical features and chemical characteristics.

Table 1: Taxonomical Classification[16-18]

Rank	Classification
Kingdom	Plantae
Division	Angiosperms
Class	Eudicots
Order	Gentianales
Family	Apocynaceae
Genus	*Nerium*
Species	*Nerium oleander* L.

Morphological Features

Nerium oleander is an evergreen, erect shrub ranging from 2–6 meters in height. The plant bears long, narrow, lanceolate leaves arranged oppositely or in whorls of three. The leaves possess thick, leathery textures with prominent midribs, contributing to drought resistance. Flowers are typically funnel-shaped and available in diverse colors such as white, pink, red, and yellow, depending on the cultivar. They produce a characteristic fragrance and appear in clusters at branch tips. Fruits are slender capsules containing numerous silky-haired seeds that enable wind dispersal. The entire plant exudes a milky latex when injured, indicative of its high content of cardiac glycosides and other bioactive metabolites.[19-21]

Fig. 1: *Nerium oleander L.* Plant

Plant Anatomy (Leaf, Flower, Stem, Root)[22-25]

Microscopically, the leaves show a thick cuticle with multilayered palisade tissue, aiding in water conservation and heat tolerance. Secretory ducts and laticifers, typical of Apocynaceae, are distributed throughout the mesophyll and vascular bundles. Flowers exhibit a tubular corolla with fused petals and specialized nectaries at the corolla base. The stem is characterized by a woody periderm, abundant laticifers, and well-developed vascular tissues containing secretory canals. Roots exhibit typical dicot features with xylem and phloem arranged radially, but also contain specialized tubules storing glycosides and resins.

Anatomical adaptations of *N. oleander* not only allow survival in harsh environments but also contribute to the accumulation of secondary metabolites with medicinal value.

Fig. 2: Leafs of *Nerium oleander L.*

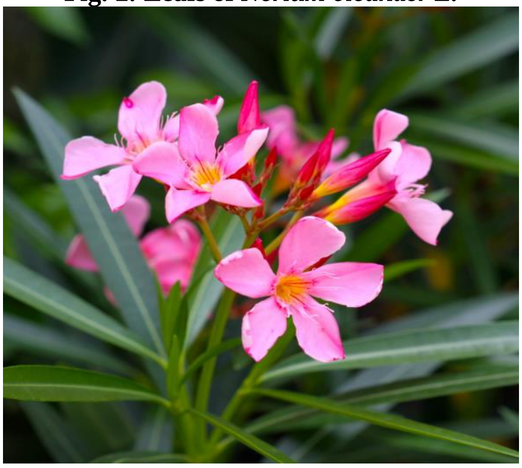

Fig. 3: Flowers of *Nerium oleander L.*

Fig. 4: Roots of *Nerium oleander L.*

Habitat and Cultivation Requirements

Nerium oleander thrives primarily in warm, arid to semi-arid climates and is native to the Mediterranean basin, Middle East, and parts of South Asia. It tolerates poor soils, salinity, and prolonged periods of drought, making it a hardy ornamental plant. Optimal growth occurs in full sunlight with well-drained soil. The plant's resilience has facilitated its global cultivation, particularly in landscaping and roadside plantations. However, its cultivation for medicinal use requires controlled conditions, as phytochemical content varies with soil, climate, stress factors,[26-29] and plant part. Sustainable cultivation practices are needed to ensure standardized phytochemical profiles for pharmaceutical research and production.

TRADITIONAL AND ETHNOMEDICINAL USES OF *NERIUM OLEANDER*

Nerium oleander has a long-standing presence in several traditional healing systems across Asia, the Middle East, and Mediterranean regions. Despite its recognized toxicity, controlled and carefully prepared formulations have been used historically for managing various ailments. Ancient medical practices document numerous therapeutic applications of its leaves, flowers, and roots, highlighting the plant's complex dual nature as both a potent remedy and a poisonous species.[30-36]

Mentions in Ayurveda, Unani, and Siddha Systems

In Ayurveda, *N. oleander* is referred to as Karavira, categorized under plants with strong biological action. Classical Ayurvedic texts describe its processed (detoxified) leaf and root preparations for managing skin diseases, ulcers, leprosy, parasites, and inflammatory conditions. Specific formulations were prepared using purification (Shodhana) techniques to reduce toxicity while retaining therapeutic potency.[37-39]

Similarly, in Unani medicine, oleander extracts have been employed topically for joint pain, ulcers, eczema, and dermatitis, owing to their warming and resolvent properties. Siddha medicine attributes its use to correcting derangements in bodily energies, applying it externally for wound healing, ringworm, and inflammation. Across these traditional systems, ingestion is rarely recommended due to severe cardiac toxicity; instead, external applications dominate therapeutic practices.[40]

Traditional Therapeutic Uses

Historically, diverse plant parts have been used in folk practices:

- **Leaves**: Employed in poultices for skin infections, abscesses, and painful swellings.
- **Flowers**: Used in balms for headache relief and soothing inflamed tissues.
- **Roots**: Traditionally utilized in controlled doses for cardiotonic properties, although this practice is rare today due to safety concerns.
- **Latex**: Applied externally in diluted form for scabies, fungal infections, and warts.

Traditional healers recognized oleander as a potent herbal drug, emphasizing careful dosing, detoxification, and external usage.[41-45]

Regional Folk Medicinal Claims

Across India, North Africa, and the Mediterranean, oleander preparations appear in village-level ethnomedicinal practices:

- Decoctions used for fever, malaria, and intestinal worms.
- Poultices applied for joint inflammation, sprains, and snake bites.
- Crushed leaves used as antimicrobial dressings for chronic wounds.
- Flower paste applied for dermatological conditions, including psoriasis.

In rural Middle Eastern communities, oleander extracts mixed with oils are used to treat scalp infections**,** lice, and eczema, demonstrating broad traditional acceptance despite toxic risks.[46-51]

Historical Documentation

Historical references to oleander date back to ancient Greek, Roman, and Persian texts. Dioscorides and Pliny the Elder described its poisonous nature but acknowledged medicinal potential when prepared cautiously. Medieval Arabic manuscripts mention oleander as a potent plant requiring purification for topical use. Over centuries, the plant has retained its reputation as a dangerous yet medicinally valuable herb, which laid the foundation for modern phytopharmacological investigations.[52-54]

Major Phytochemical Classes[55-66]

Cardiac Glycosides

Among all phytochemicals present in N. oleander, cardiac glycosides are the most pharmacologically potent and scientifically studied. Compounds such as oleandrin, neriifolin, and digitoxigenin derivatives exhibit strong biological activity by interacting with the Na^+/K^+-ATPase enzyme, thereby influencing cardiac muscle contraction. While this mechanism contributes to cardiotonic effects, it also explains the severe cardiotoxicity seen in cases of plant ingestion. Interestingly, these glycosides have also demonstrated promising activities in experimental oncology, including induction of apoptosis, suppression of NF-κB signaling, and inhibition of tumor cell proliferation. Some cardenolide molecules additionally exhibit antiviral and anti-inflammatory attributes, expanding their therapeutic relevance beyond cardiovascular modulation.

Cardenolides

Cardenolides represent a broader subclass of steroidal glycosides characterized by a distinct lactone ring attached to their aglycone backbone. *N. oleander* produces several structurally unique cardenolides, particularly in its stems and roots. These compounds have displayed noteworthy cytotoxicity toward cancer cell lines and potent insecticidal effects, underlining their ecological and pharmacological significance. Their structural diversity accounts for varied biological interactions, making them an important group for phytochemical and medicinal studies.

Flavonoids

Flavonoids such as quercetin, kaempferol, and their glycosides are abundant in the leaves and flowers of the plant. These polyphenolic compounds are best known for their antioxidant capacity, which enables them to neutralize harmful free radicals and reduce oxidative stress. Furthermore, flavonoids contribute to the plant's anti-inflammatory and hepatoprotective actions, supporting several traditional herbal applications. Their presence enhances both the medicinal value and safety profile of oleander extracts, particularly when fractions low in cardenolides are used.

Alkaloids

Although present in relatively small quantities, indole-type and steroidal alkaloids add to the plant's pharmacological complexity. These nitrogen-containing compounds have been associated with mild analgesic, neuroactive, and antimicrobial properties. Their low concentration may not contribute significantly to toxicity, but they play an important role in the overall bioactivity of plant extracts.

Terpenoids

Terpenoids, including various triterpenes and sesquiterpenes, are another prominent class of constituents identified in *N. oleander*. These molecules possess a broad range of biological activities, including anti-inflammatory, anticancer, and antimicrobial effects. Recent discoveries of novel triterpenes from oleander extracts have shown strong cytotoxic potential, making terpenoids an emerging area of medicinal interest.

Phenolic Compounds

Phenolic constituents most notably phenolic acids**,** chlorogenic acid derivatives, and tannins are present in both leaves and flowers. These compounds are powerful antioxidants, capable of scavenging reactive oxygen species and enhancing cellular defense mechanisms. They are also linked to hepatoprotective and anti-inflammatory actions, which may complement the therapeutic roles of other metabolite classes.

Table 2: Major Phytochemical Classes in *Nerium oleander*

Class	Representative Compounds	Key Biological Roles
Cardiac glycosides	Oleandrin, Neriifolin, Digitoxigenin derivatives	Anticancer, antiviral, cardiotonic, cardiotoxic
Cardenolides	Thevetin-like cardenolides	Cytotoxic, cardiotonic
Flavonoids	Quercetin, Kaempferol	Antioxidant, anti-inflammatory
Alkaloids	Indole-type alkaloids	Neuroactive, antimicrobial
Terpenoids	Triterpenes, Sesquiterpenes	Anti-inflammatory, anticancer
Phenolics	Chlorogenic acid derivatives, Tannins	Antioxidant, hepatoprotective

Extraction Techniques[67-69]
The efficiency of extracting bioactive constituents from *N. oleander* depends heavily on the solvent used, extraction method, and the specific plant part chosen. Various extraction approaches have been adopted in phytochemical investigations to maximize yield and preserve compound integrity.

Solvent Extraction
Solvent extraction remains the most widely used technique due to its simplicity and adaptability.

- **Methanol** is particularly effective for isolating cardiac glycosides, flavonoids, and phenolic compounds.
- **Ethanol** is commonly used in herbal pharmacognosy and yields a broad spectrum of compounds, including terpenoids and tannins.
- **Aqueous extracts** mainly contain polar compounds such as simple phenolics and sugars, and although less potent, they are considered safer for traditional use.

Soxhlet Extraction
Soxhlet extraction enables continuous hot extraction, making it ideal for isolating thermally stable constituents such as cardenolides, non-polar flavonoids, and lipophilic terpenoids. This method ensures high extraction efficiency and is frequently used in analytical research.

Maceration
Maceration involves soaking plant materials in solvent at ambient temperature, which preserves thermolabile compounds like certain phenolics and volatile components. This cold extraction method is particularly useful in traditional herbal preparations and research involving delicate phytochemicals.

Ultrasonic-Assisted Extraction (UAE)
UAE enhances extraction efficiency through acoustic cavitation, which promotes solvent penetration into plant tissues. Benefits include:

- Improved yield of metabolites
- Reduced processing time and solvent consumption
- Better preservation of glycosides and other sensitive compounds
- This method has gained popularity for preparing analytical-grade extracts.

Analytical Techniques[70-75]
Modern analytical methods are essential for the accurate identification, characterization, and quantification of *N. oleander* phytochemicals. Due to the plant's toxic profile, precise chemical profiling is crucial for safety and therapeutic standardization.

High-Performance Liquid Chromatography (HPLC)
HPLC is extensively used to detect and quantify oleandrin, neriifolin, and various phenolic compounds. Coupling with UV or photodiode array detectors enhances sensitivity and specificity.

LC–MS/MS
Liquid chromatography–tandem mass spectrometry provides highly sensitive and selective detection of low-abundance metabolites. It is indispensable for:

- Cardiac glycoside quantification
- Pharmacokinetic profiling
- Toxicological analyses

Fourier Transform Infrared Spectroscopy (FTIR)
FTIR offers rapid functional-group identification, enabling preliminary screening of glycosides, terpenoids, and phenolic compounds without extensive sample preparation.

UV–Visible Spectroscopy
This method is commonly applied to measure total phenolic content, flavonoid concentration, and antioxidant activity in extracts using colorimetric assays.

Gas Chromatography–Mass Spectrometry (GC-MS)
GC-MS is suitable for analyzing volatile and semi-volatile constituents, particularly terpenoids, fatty acids, and floral aroma components. It provides detailed fragmentation patterns valuable for compound identification.

Quantification of Major Bioactives
Quantification of key bioactive compounds is essential not only for research reproducibility but also for safety assessment due to the plant's narrow therapeutic window. Various quantitative methods are applied:

- **HPLC-based oleandrin estimation** relies on calibration curves and retention times for precise quantification.
- **Total phenolic content (TPC)** is commonly determined using the Folin–Ciocalteu method, with results expressed in gallic acid equivalents.
- **Total flavonoid content (TFC)** is measured using aluminum chloride colorimetry.
- **LC–MS/MS** allows accurate quantification of structurally similar cardenolides through specific mass transitions.
- **DPPH and ABTS assays** evaluate the antioxidant potential of phenolic-rich extracts by measuring radical-scavenging activity.

PHARMACOLOGICAL ACTIVITIES[76-92]
Nerium oleander exhibits a broad spectrum of pharmacological actions attributed to its rich phytochemical composition, particularly cardiac glycosides, flavonoids, terpenoids, tannins, and phenolic acids. Although its therapeutic potential has been explored across various traditional systems, modern scientific investigations have provided deeper insight into its biological activities. These pharmacological effects, however, must be evaluated with caution due to the plant's narrow safety margin and well-documented toxicity.

Anticancer / Antitumor Activity
The anticancer potential of *N. oleander* has attracted significant research interest, largely due to the activity of oleandrin and other cardenolides. These compounds exert cytotoxic effects by inhibiting the Na^+/K^+-ATPase pump, leading to disruption of cellular ion homeostasis and induction of programmed cell death. Oleandrin has been shown to suppress multiple molecular pathways implicated in cancer progression, including NF-κB, Akt/mTOR, and MAPK signaling. Experimental studies demonstrate its ability to induce apoptosis, inhibit angiogenesis, and reduce proliferation in various cancer cell lines such as breast, lung, pancreatic, leukemia, and melanoma. Moreover, semi-synthetic formulations like PBI-05204 have progressed to preclinical and early clinical evaluations, highlighting the translational potential of oleander-derived compounds. Despite these promising findings, the therapeutic application of oleander cardenolides must be balanced against their cardiotoxic risks, necessitating careful dosage control and targeted delivery approaches.

Table 3: Anticancer / Antitumor Activity of *Nerium oleander*

Phytochemicals / Extracts	Mechanism of Action	Experimental Evidence	Therapeutic Implication
Oleandrin, Cardenolides	Inhibition of Na^+/K^+-ATPase; apoptosis induction; NF-κB suppression	Effective against breast, lung, pancreatic, leukemia, melanoma cell lines	Potential anticancer agent; basis for formulations like PBI-05204
Leaf/flower extracts	Anti-proliferative, anti-angiogenic effects	Reduction in tumor volume in animal models	Support role in integrative cancer therapy
Nano-oleander formulations	Targeted toxicity to cancer cells	Enhanced cytotoxicity vs. crude extracts	Promising for drug-delivery research

Antioxidant Activity
The antioxidant activity of *N. oleander* is primarily attributed to its phenolic constituents, including chlorogenic acid derivatives and flavonoids like quercetin and kaempferol. These compounds effectively scavenge reactive oxygen species (ROS) and help stabilize cellular redox balance. In vitro assays, such as DPPH and ABTS radical-scavenging tests, have demonstrated significant antioxidant capacity in leaf and flower extracts. This antioxidant potential suggests a protective role against oxidative stress-associated disorders,

including inflammation, aging, and degenerative diseases. The synergistic interaction between phenolics and flavonoids enhances the plant's overall antioxidant profile, making oleander extracts an interesting candidate for antioxidant-based therapeutic research.

Antimicrobial Activity

Oleander extracts possess noteworthy antimicrobial properties against a wide range of pathogenic microorganisms. Methanolic and ethanolic extracts of the leaves and flowers have shown inhibitory effects on Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Antifungal activity has been documented against species such as *Fusarium oxysporum* and *Candida albicans*, attributed to the combined action of cardiac glycosides, terpenoids, and phenolic compounds. Some studies also highlight antiviral potential, particularly oleandrin's ability to reduce viral replication in models including HIV and vaccinia virus. These results suggest that *N. oleander* holds potential as a source of natural antimicrobial agents, although toxicity must be carefully managed for practical applications.

Anti-inflammatory Activity

The anti-inflammatory activity of *N. oleander* is linked to its diverse bioactive constituents, which modulate inflammatory pathways through multiple mechanisms. Flavonoids and terpenoids inhibit key enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX), thereby reducing the production of pro-inflammatory mediators. Oleandrin and related glycosides also suppress cytokine expression by interfering with transcription factors like NF-κB. In vitro and in vivo studies have demonstrated reduced edema, decreased inflammatory cell infiltration, and lowered oxidative markers following treatment with oleander extracts. These findings support the plant's traditional use for managing swellings, joint pain, and inflammatory skin conditions.

Antidiabetic Activity

Preliminary investigations indicate that certain fractions of *N. oleander*, particularly polar leaf extracts, may possess antidiabetic properties. Experimental models of chemically induced diabetes have shown improved glucose tolerance, reduced fasting blood glucose levels, and increased antioxidant enzyme activity following extract administration. These effects are possibly mediated by enhanced insulin secretion, improved peripheral glucose uptake, and protection of pancreatic β-cells from oxidative damage. Although promising, this area of research remains underdeveloped and requires more detailed molecular and clinical evaluation due to the potential risk of toxicity with internal use.

Insecticidal and Larvicidal Activity

Nerium oleander has been traditionally used as a botanical insecticide, and modern studies confirm its strong insecticidal and larvicidal efficacy. Extracts from the leaves and flowers have shown lethal effects against mosquito larvae, including *Anopheles stephensi* and *Culex quinquefasciatus*. These bioactivities are primarily attributed to cardenolides and terpenoids, which interfere with insect neurological and metabolic processes. Plant-mediated nanoparticles synthesized from *N. oleander* extracts further enhance larvicidal potency and offer eco-friendly vector control alternatives. Such insecticidal properties position oleander as a valuable natural resource in integrated pest management strategies.

Hepatoprotective Activity

Although cardiac glycosides dominate discussions on oleander, certain extracts—particularly those low in toxic fractions—have shown hepatoprotective effects in experimental models. Administration of flower or leaf extracts in carbon tetrachloride (CCl_4)-induced hepatotoxicity models has resulted in reduced serum markers of liver damage, improved antioxidant enzyme levels, and restoration of normal histological architecture. These protective effects are primarily linked to the antioxidant activity of flavonoids and phenolic compounds rather than cardenolides. This dual nature of *N. oleander*, where specific fractions exhibit therapeutic potential despite overall toxicity concerns, highlights the need for careful fractionation and standardization.

Central Nervous System (CNS) Activity

Several traditional systems have employed oleander extracts externally for neurological complaints such as headaches or seizures. Modern studies in rodents suggest that certain solvent extracts may exhibit sedative, anxiolytic, and CNS depressant effects, likely due to interactions with neurotransmitter pathways influenced by alkaloids and flavonoids. These extracts have demonstrated reduced locomotor activity, prolonged sleep duration, and dampened anxiety-like behaviors in experimental models. However, due to the overlap between therapeutic effects and potential toxicity, CNS-related pharmacological use requires significant caution and rigorous safety evaluation.

Wound-Healing Activity

The wound-healing potential of *N. oleander* has been validated through its antimicrobial, antioxidant, and anti-inflammatory mechanisms. Topical application of leaf or flower extracts has been shown to accelerate wound contraction, enhance collagen synthesis, and promote reepithelialization. The combined presence of phenolics, flavonoids, and low-toxicity phytoconstituents contributes to improved cellular regeneration and reduced infection risk. These findings align with traditional uses where oleander paste or leaf extracts were applied externally for ulcers, cuts, and chronic wounds.

TOXICITY PROFILE OF *NERIUM OLEANDER*[93-110]

Despite its long history of medicinal use, *Nerium oleander* is widely recognized as one of the most toxic botanical species. All parts of the plant—including leaves, flowers, stems, latex, and roots—contain potent cardiac glycosides that exert significant effects on the cardiovascular and gastrointestinal systems. The toxicity of oleander is closely linked to its primary constituents, such as oleandrin, neriifolin, and related cardenolides, which share structural similarity with digoxin and other digitalis-type compounds. These molecules have a powerful ability to inhibit the Na^+/K^+-ATPase pump in cardiac muscle cells, leading to disturbances in intracellular ion balance, increased vagal tone, and potential life-threatening arrhythmias.

Acute and Chronic Toxicity

Acute poisoning generally results from ingestion of plant parts, consumption of herbal preparations, or accidental exposure. Symptoms often develop rapidly and may include nausea, vomiting, abdominal pain, bradycardia, dizziness, confusion, and visual disturbances. In severe cases, cardiac arrhythmias, conduction defects, and cardiovascular collapse may occur. Chronic exposure, though less common, can result from repeated intake of sub-toxic doses, leading to cumulative glycoside accumulation. Such cases may present with progressive cardiac dysfunction, neurological symptoms, and electrolyte imbalances, particularly hyperkalemia.

Cardiotoxicity and Mechanism of Action

Cardiotoxicity represents the most critical risk associated with *N. oleander*. By inhibiting Na^+/K^+-ATPase, cardiac glycosides increase intracellular calcium through secondary effects on the Na^+/Ca^{2+} exchanger, resulting in enhanced contractility but also predisposing cardiac cells to arrhythmogenic activity. This mechanism explains both the plant's historical cardiotonic use and its potential lethality. Even small doses—such as a few leaves—can be toxic to humans, children, and domestic animals. Case reports from various regions document fatalities linked to oleander ingestion, highlighting the narrow therapeutic window and need for extreme caution in any medicinal application.

Gastrointestinal and Neurological Toxicity

Beyond cardiovascular effects, oleander ingestion commonly induces gastrointestinal distress as an early warning sign. Nausea, persistent vomiting, abdominal cramping, and diarrhea may develop shortly after exposure. Neurological manifestations—including dizziness, confusion, lethargy, and seizures—can occur in advanced toxicity, especially when electrolyte impairments amplify CNS disturbances. In animals, oleander toxicity often presents with ataxia, tremors, and behavioral changes, underscoring the plant's multisystem impact.

Toxicity in Animals

Oleander poisoning is frequently reported in livestock, particularly grazing animals such as cattle, sheep, goats, and horses, which may accidentally ingest fallen leaves or contaminated forage. The glycosides remain active even in dried plant material, making hay contamination a significant hazard. In veterinary cases, clinical signs mirror those observed in humans, including cardiac irregularities, colic, weakness, and sudden death. Analytical detection of oleandrin in tissues has aided veterinary diagnostics and toxicological investigations.

Dose-Dependence and Toxicity Threshold

The severity of oleander toxicity is dose-dependent, and even minute quantities can be dangerous. Approximately 0.005% of body weight as fresh leaf material may be sufficient to induce clinical toxicity in humans. Variability in glycoside concentration across plant parts, seasonal changes, and differing extraction methods further complicate prediction of toxic doses. For this reason, modern therapeutic research efforts focus on isolating safer analogues, modifying glycoside structures, or developing targeted delivery systems that minimize systemic exposure.

Management of Poisoning

Management of oleander poisoning requires urgent medical attention. Supportive care, correction of electrolyte disturbances, and continuous cardiac monitoring are essential. Digoxin-specific antibody fragments (Digibind or DigiFab) have been successfully used to treat severe oleander intoxication by binding circulating cardiac glycosides and reducing their physiological effects. Gastric decontamination with activated charcoal may be useful in early stages depending on time of ingestion. Nevertheless, prevention through public awareness remains the most reliable strategy for reducing oleander-related morbidity and mortality.

Table 4: Comprehensive Toxicity Profile of *Nerium oleander*

Toxic Component / Factor	Primary Source in Plant	Mechanism of Toxicity	Clinical Manifestations	Affected Species	Notes / Risk Level
Oleandrin	Leaves, latex	Inhibits Na^+/K^+-ATPase → disrupts cardiac conduction	Arrhythmias, bradycardia, dizziness, hyperkalemia	Humans, livestock, pets	Highly toxic even in small doses
Neriifolin & related cardenolides	Leaves, stems, roots	Alters calcium influx → cardiac contractility changes	Nausea, vomiting, abdominal pain, ECG changes	Humans, cattle, goats, horses	Toxicity persists in dried leaves
Thevetin-like glycosides	Roots, bark	Severe GI irritation + cardiotoxicity	Diarrhea, confusion, seizures, cardiac arrest	Humans, animals	Extremely narrow therapeutic window
Whole plant ingestion	All plant parts	Systemic toxicity due to multiple glycosides	Multisystem failure, coma, death	Humans, grazing animals	One of the most toxic ornamental plants
Sub-acute / chronic exposure	Repeated low-dose intake	Accumulation of glycosides in tissues	Fatigue, persistent GI upset, arrhythmias	Humans, animals	Cumulative toxicity documented
Management considerations	—	Binding of cardiac glycosides	Use of Digoxin-Fab, electrolyte correction	—	Requires emergency care

NANOFORMULATIONS AND NOVEL DRUG-DELIVERY APPLICATIONS[111-120]

Recent advances in nanotechnology have opened new opportunities for enhancing the therapeutic potential of *Nerium oleander* while minimizing its inherent toxicity. Several studies have demonstrated that nano-delivery systems can improve the solubility, stability, and bioavailability of plant-derived compounds, including oleandrin and other bioactives. Nanocarriers also offer the advantage of targeted delivery, where toxic constituents can be directed specifically toward diseased tissues—such as tumors—thereby reducing systemic exposure.

Nanoparticle Synthesis Using *Nerium oleander*

Extracts from *N. oleander* have been employed as natural reducing and stabilizing agents for the green synthesis of metallic nanoparticles, including silver nanoparticles (AgNPs) and iron nanoparticles (FeNPs). These plant-mediated nanoparticles exhibit notable antimicrobial, larvicidal, and anticancer properties, often with greater potency than crude extracts. The presence of flavonoids, terpenoids, and phenolics in oleander helps cap and stabilize nanoparticles, contributing to their enhanced biological performance.

Nanoemulsions, Phytosomes, and Niosomes

Nanoemulsion systems incorporating oleander extracts have shown improved cellular uptake and sustained release profiles. Phytosomes®, which complex phytochemicals with phospholipids, significantly enhance the bioavailability of compounds like phenolics and triterpenoids. Niosomes—vesicular carriers formed from non-ionic surfactants—serve as biocompatible delivery vehicles that can encapsulate oleander fractions with reduced toxicity. These systems provide controlled release and improved pharmacokinetic behavior, supporting further development for therapeutic use.

Gold Nanoparticle and Polymer-Based Delivery

Oleander extract-loaded gold nanoparticles have demonstrated strong cytotoxic effects against cancer cells, attributed to both the intrinsic activity of oleander compounds and the photothermal properties of gold nanostructures. Polymer-based micelles and nanovesicles have also been utilized to encapsulate cardiac glycosides, enabling targeted delivery to tumor cells while decreasing off-target toxicity. Such systems exemplify how nanotechnology can transform dangerous phytochemicals into safer, more effective therapeutic candidates.

Future Prospects of Nano-Enhanced Oleander Therapies

The integration of oleander bioactives with nanotechnology represents a promising frontier in herbal drug development. Targeted delivery, improved solubility, and controlled release mechanisms significantly enhance therapeutic indices. However, rigorous safety evaluation, long-term toxicity studies, and clinical validation remain essential steps before nano-oleander formulations can transition into mainstream clinical practice.

Table 5: Nanoformulations and Drug-Delivery Applications of *Nerium oleander*

Nanoformulation Type	Plant Component Used	Enhanced Biological Activity	Mechanism / Advantage	Potential Applications
Silver nanoparticles (AgNPs)	Leaf extract	Strong antibacterial, antifungal, larvicidal effect	Phytochemicals act as reducing & stabilizing agents	Mosquito control, antimicrobial coatings
Gold nanoparticles (AuNPs)	Leaf/flower extract	Enhanced anticancer activity	Photothermal + phytochemical synergy	Cancer therapy (targeted)
Nanoemulsions	Oleander extract/oil	Improved solubility & permeability	Nanoscale droplets increase surface area	Topical anti-inflammatory & wound care
Phytosomes®	Phenolics & flavonoids	Higher absorption & stability	Phospholipid complexation improves bioavailability	Antioxidant & anti-inflammatory formulations
Niosomes	Oleandrin-rich fractions	Controlled release, reduced systemic toxicity	Vesicular system enables targeted delivery	Cancer drug delivery research
Polymeric micelles / nanovesicles	Purified glycosides	Enhanced tumor targeting	Encapsulation reduces cardiotoxicity	Investigational anticancer therapies
Green-synthesized FeNPs	Flower/leaf extract	Potent larvicidal and antimicrobial effects	Eco-friendly synthesis with plant metabolites	Vector control & environmental applications

CLINICAL AND PRECLINICAL EVIDENCE[102-120]

Although *N. oleander* has been traditionally used for centuries, modern clinical and preclinical research has provided both supportive and cautionary evidence regarding its therapeutic use. Experimental studies using cell culture, animal models, and early-phase clinical trials have evaluated the pharmacological potential of oleander extracts—especially in oncology and inflammatory disorders.

Preclinical Findings

Preclinical studies consistently demonstrate that oleander-based compounds exert potent biological effects. In cancer research, oleandrin induces apoptosis, suppresses tumor growth, and enhances the cytotoxic effects of chemotherapeutic drugs. Animal models have shown reductions in tumor volume, inhibition of angiogenesis, and improvement in oxidative stress markers following treatment with oleander extracts or nanoformulations. Additionally, antimicrobial, hepatoprotective, and anti-inflammatory actions have been documented across several in vivo studies.

Clinical Investigations

Clinical evaluation of oleander compounds is still in its early stages due to toxicity challenges. One of the most studied formulations, PBI-05204, a supercritical CO_2 extract of *N. oleander*, has undergone Phase I and II clinical investigations for advanced cancers. Early trials reported tolerability at low doses, biological activity against tumor pathways, and manageable adverse effects when carefully monitored. However, cardiotoxicity and gastrointestinal disturbances remain major concerns, restricting broader applications.

Challenges in Clinical Translation

The transition from traditional use and preclinical promise to clinical acceptance is limited by safety concerns, lack of standardized dosing, and variability in phytochemical composition. Future clinical research must emphasize purified compounds, targeted delivery strategies, and strict pharmacovigilance to fully harness oleander's therapeutic potential.

CONCLUSION:

Nerium oleander remains a plant of significant medicinal intrigue, possessing a large repertoire of bioactive compounds that demonstrate meaningful pharmacological actions. Its antioxidant, anticancer, anti-inflammatory, and antimicrobial activities are extensively supported by preclinical data. However, its substantial cardiotoxic potential necessitates caution in therapeutic development. Modern approaches such as nanotechnology, structural modification of glycosides, and advanced analytical methods offer promising paths to safely harness its medicinal potential. A balanced understanding of both its therapeutic efficacy and toxicological risks is essential to guide future research and innovative drug-development initiatives.

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