

REVIEW ARTICLE

A Review on Pharmacological Properties, Therapeutic Applications of *Nerium oleander*



Sangeetha S^{*1}, Saravanakumar A², Parthiban P³, Pavithra R⁴

¹ Associate Professor, Department of Pharmaceutical Chemistry, Vellalar College of Pharmacy, Chennai, Tamil Nadu, India

² Professor & Principal, Department of Pharmaceutical Biotechnology, Vellalar College of Pharmacy, Chennai, Tamil Nadu, India

³ Professor & Head, Department of Pharmaceutical Chemistry, Vellalar College of Pharmacy, Chennai, Tamil Nadu, India

⁴ UG Scholar, Department of Pharmaceutical Chemistry, Vellalar College of Pharmacy, Chennai, Tamil Nadu, India

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Abstract: *Nerium oleander* (Apocynaceae) is a valuable medicinal plant with several pharmacological properties. It has gained a lot of attention for its extensive traditional uses and potential therapeutic applications. Phytochemical analysis shows the presence of bioactive compounds including cardiac glycosides, terpenoids, flavonoids, and phenolic compounds. The plant exhibits pharmacological activities such as antimicrobial, antidiabetic, anticancer, and anti-inflammatory properties. Traditional medicine systems across various regions have utilized different parts of *N. oleander* for treating conditions ranging from cardiac disorders to skin ailments. However, the plant's therapeutic potential is counterbalanced by significant toxicity concerns due to the presence of cardiac glycosides, particularly oleandrin and nerine. These compounds can cause severe cardiovascular complications and gastrointestinal disturbances. Recent research has revealed the molecular mechanisms underlying both therapeutic effects and toxicity profiles. The effects of *Nerium oleander* on various organ systems, including cardiac, hepatic, and renal tissues, have been documented through experimental studies. Modern analytical techniques have identified specific bioactive compounds responsible for both beneficial and adverse effects. The growing scientific evidence supports traditional therapeutic applications while emphasizing the critical need for careful consideration of safety parameters in medicinal use.

Keywords: *Nerium oleander*; Cardiac glycosides; Oleandrin; Pharmacological activities; Toxicology

1. Introduction

Nerium oleander L., belongs to the Apocynaceae family, has established its significance in traditional medicine systems worldwide [1]. The genus *Nerium*, established by Tournefort in 1700 and later renamed from "Nerion" to "Nerium" by Linnaeus in 1737, comprises a single species. The etymology traces back to Dioscorides' use of "nerion" for oleander, highlighting its historical significance in medicine [2]. Morphologically, *N. oleander* manifests as an evergreen shrub characterized by glabrous branches and distinctive linear-lanceolate leaves. The leaves, measuring 10-15 x 1-2 cm, exhibit a prominent midrib and possess a thick, coriaceous texture. The flowers, appearing either solitary or in pairs, display a range of colors from white to dark red, with dimensions of 3-4 cm across. The floral structure includes silky peduncles and pedicels, accompanied by small bracts measuring 5-7.5 mm [3]. The plant has acquired various vernacular names across different cultural and linguistic contexts. In English-speaking regions, it is commonly known as Oleander or Rose Bay. Indian languages refer to it as Kaner (Hindi) and Karavira (Sanskrit). Arabic-speaking regions use the term Difla, while Chinese traditional texts reference it as Jia Zhu Tao [4].

It belongs to the order of Gentianales, division Magnoliophyta and the class Magnoliopsida. The plant's systematic classification reflects its evolutionary relationships and morphological characteristics that distinguish it from related taxa [4]. The anatomical features, particularly the leaf structure, demonstrate adaptive modifications suitable for its ecological niche. The presence of specialized structures such as stomatal crypts and distinctive epidermal characteristics contribute to its xerophytic adaptations [5]. Geographical distribution extends across diverse regions, with primary natural occurrences in the Mediterranean basin, North Africa, and parts of Asia. The plant has successfully naturalized in various climatic zones, demonstrating remarkable adaptability to different environmental conditions [6]. This widespread distribution has contributed to its incorporation into multiple traditional medical systems and the development of diverse ethnomedicinal applications [7].

The historical usage of *N. oleander* spans centuries, with documented applications in Chinese, Indian, and Mediterranean traditional medicine. These traditional systems have utilized various plant parts for treating conditions ranging from dermatological disorders to cardiac ailments [8]. However, the therapeutic potential of *N. oleander* is complexly intertwined with its toxicological properties, necessitating careful scientific investigation and standardization of its medicinal applications [9]. Modern scientific research has

* Corresponding author: Sangeetha S

focused on elucidating the chemical composition, pharmacological activities, and safety parameters of *N. oleander*. The identification of bioactive compounds, particularly cardiac glycosides and other secondary metabolites, has provided molecular insights into both therapeutic and toxic effects [10]. This scientific understanding has become crucial for developing standardized approaches to utilize the medicinal potential while mitigating safety risks. The current state of research emphasizes the need for a balanced approach in studying *N. oleander*, considering both its therapeutic potential and associated risks. This necessitates detailed investigation of its chemical constituents, pharmacological activities, and toxicological profiles, supported by modern analytical techniques and experimental methodologies [11].



Figure 1. Leaves and flowers of *Nerium oleander*

2. Macroscopical and Microscopical Characteristics

2.1. Macroscopic Characteristics

N. oleander presents distinctive morphological features characteristic of its adaptation to diverse environmental conditions. The plant typically grows as a robust evergreen shrub, reaching heights of 2-6 meters. The stem shows multiple branches with smooth, grayish-brown bark that becomes fissured with age [12].

2.1.1. Leaf

The leaves of *N. oleander* display a characteristic linear-lanceolate shape with dimensions ranging from 10-15 cm in length and 1-2 cm in width. They maintain a whorled or opposite arrangement, typically with 3-4 leaves emerging from each node. The leaf texture is notably thick and leathery (coriaceous), featuring a prominent midrib. The adaxial surface presents a dark green, glossy appearance, contrasting with the lighter abaxial surface. The venation pattern is distinctly pinnate, with parallel secondary veins extending from the central midrib [13].

2.1.2. Flowers

The floral structure of *N. oleander* manifests in terminal cymes, with individual flowers measuring 3-4 cm in diameter. The flowers exhibit color variations ranging from white to pink and dark red. Each flower comprises five twisted petals arranged around a distinctive corona. The reproductive structures include five stamens with characteristic hairy appendages. The flowering period extends from spring through autumn, allowing for prolonged blooming phases [14].

2.1.3. Fruits and Seeds

The reproductive structures develop into follicles measuring 12-20 cm in length. These fruits contain numerous brown seeds equipped with silky hairs, facilitating wind-based dispersal mechanisms. The seed structure demonstrates specific adaptations for anemochorous distribution [15].

2.2. Microscopic Characteristics

2.2.1. Leaf

The microscopic examination of leaf shows specialized anatomical adaptations. The epidermal layer exhibits a thick cuticle with specialized stomatal crypts distributed across the surface. The multi-layered epidermis incorporates various trichomes and protective

structures. The internal organization shows well-developed palisade tissue with compact mesophyll arrangement. Vascular bundles appear with distinct bundle sheaths, and latex cells are present throughout the tissue [16, 17].

2.2.2. Stem

The stem anatomy reveals a complex organization with multi-layered periderm tissue. The cortical region contains prominent collenchyma cells, while the vascular cylinder exhibits well-developed phloem fibers. A distinct pith region occupies the central portion of the stem [18-20].

3. Geographical Distribution and Cultivation

3.1. Distribution

N. oleander exhibits a widespread natural distribution pattern, primarily centered in the Mediterranean basin. The plant's native range extends across Southern Europe, encompassing countries like Spain, France, Italy, Greece, and Portugal. Its distribution continues through North Africa, including Morocco, Algeria, Tunisia, and Libya, extending into Western Asia through Turkey, Israel, and Jordan [22].

3.2. Habitat

The species demonstrates remarkable adaptability to various ecological conditions, particularly thriving in Mediterranean-type climates. It naturally occurs along watercourses, dry river beds, and coastal areas, showing preference for well-drained soils and full sun exposure. The plant's natural habitat typically includes areas with annual rainfall between 200-800 mm and temperatures ranging from 10°C to 36°C [23]. Through human intervention, *N. oleander* has been successfully introduced to numerous regions globally. In North America, it has naturalized in states like California, Florida, and Texas. The plant has also established populations in South America, particularly in Argentina, Brazil, and Chile. Its presence extends to various parts of Asia, including India, China, and Japan, where it has both ornamental and medicinal significance [24].

Table 1. Geographical Distribution and Environmental Factors

Region	Climate Type	Annual Rainfall (mm)	Temperature Range (°C)	Soil pH
Mediterranean	Semi-arid	200-500	10-35	6.5-8.0
North Africa	Arid	100-300	15-40	7.0-8.5
South Asia	Tropical	500-1500	20-35	6.0-7.5
North America	Subtropical	400-1200	5-35	6.5-7.5
South America	Temperate	600-1000	15-30	6.0-7.0

3.3. Cultivation

3.3.1. Environmental Factors

Successful cultivation of *N. oleander* requires specific environmental parameters. The plant thrives in full sunlight, requiring minimum exposure of 6-8 hours daily for optimal growth and flowering. While adaptable to various soil types, it performs best in well-drained, slightly acidic to neutral soils with pH ranging from 6.0 to 8.0 [25].

3.3.2. Growth Parameters

The cultivation process necessitates careful attention to spacing and positioning. Plants require 4-12 feet spacing depending on intended use and variety. Growth rates vary with environmental conditions, with plants typically achieving mature size within 3-5 years under optimal conditions [26].

3.4. Cultivation Methods

3.4.1. Propagation

Propagation occurs through both sexual and vegetative means. Seed propagation, while possible, is less common due to variable germination rates. Vegetative propagation through stem cuttings represents the preferred method, offering greater consistency in plant characteristics and faster establishment [27]. Initial establishment demands regular irrigation, gradually reducing frequency as plants develop drought tolerance. Fertilization requirements remain moderate, with applications of balanced nutrients during the growing season supporting optimal development [28].

3.4.2. Seasonal Care

Spring marks the primary growth period, necessitating increased attention to cultural practices. Pruning activities focus on removing winter-damaged tissue and shaping plants to promote robust growth. Fertilization programs typically commence during this period to support new growth [29]. While drought tolerant, plants benefit from deep watering during extended dry periods. Deadheading spent blooms promotes continuous flowering throughout the season [30]. In regions experiencing cold winters, protection measures become crucial. Container-grown plants require relocation to protected areas when temperatures approach freezing. In-ground specimens may need mulching around root zones to prevent frost damage [31].

3.5. Harvesting Methods

Collection of plant material for medicinal purposes follows specific protocols regarding timing and technique. Leaf collection typically occurs during morning hours when chemical constituent concentrations reach optimal levels. Proper identification and collection of specific plant parts ensure material quality for medicinal applications [32].

4. Phytochemistry

N. oleander contains various phytochemical compounds distributed throughout various plant parts. Primary chemical groups include cardiac glycosides, terpenoids, flavonoids, and phenolic compounds. The plant's chemical profile varies significantly based on geographical location, growth conditions, and harvesting period [33].

4.1. Cardiac Glycosides

4.1.1. Cardenolides

Oleandrin represents the principal cardiac glycoside, accompanied by related compounds including neriin and digitoxigenin. These compounds share a characteristic steroid nucleus with an unsaturated lactone ring at C-17 and sugar moieties attached at C-3. The concentration of oleandrin ranges from 0.08% to 0.15% in dried leaves, with higher concentrations observed in warm climate specimens [34].

4.1.2. Other Cardiac Glycosides

Additional cardiac glycosides identified include adynerin, neriumoside, and kaneroside. These compounds exhibit structural variations in their sugar components and oxidation patterns. Odoroside A and B demonstrate significant biological activity, particularly in cardiovascular effects [35].

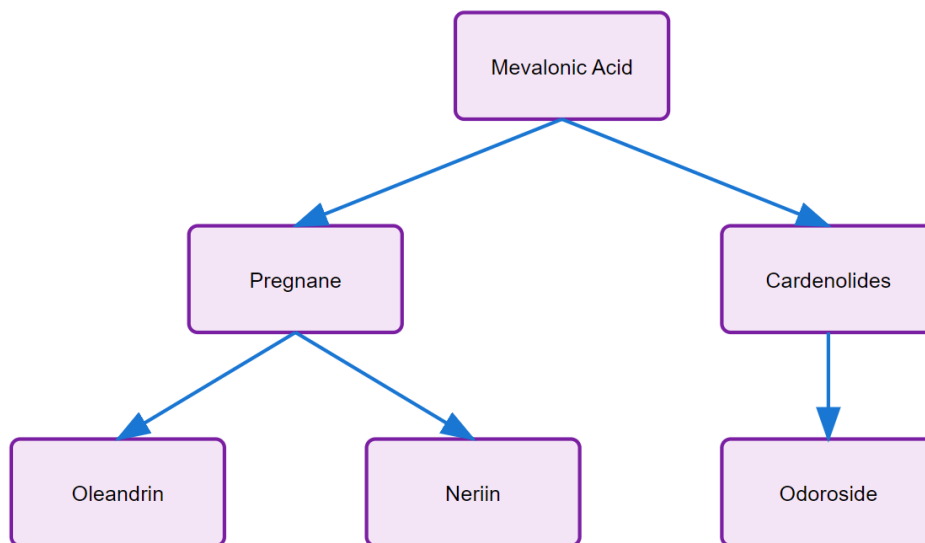
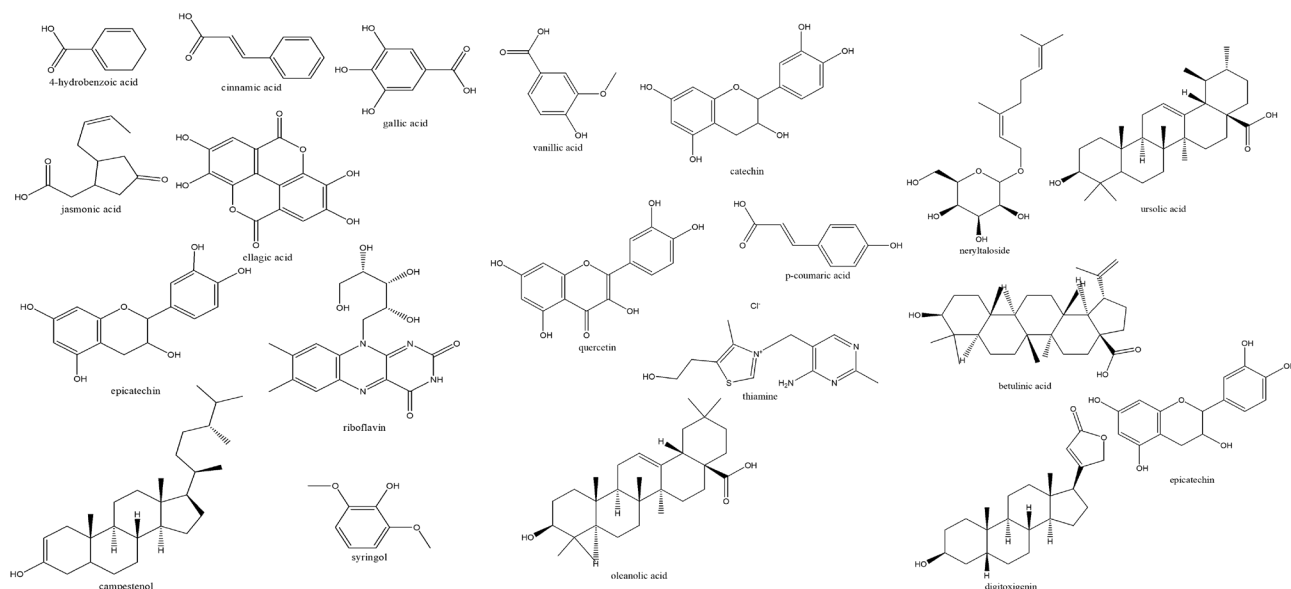


Figure 2. Major Metabolic Pathways of Cardiac Glycosides in *N. oleander*

Figure 3. Major Phytochemicals in *N. oleander*

4.2. Terpenoids

4.2.1. Triterpenes

The plant synthesizes several triterpenic compounds including ursolic acid, oleanolic acid, and betulinic acid. Three novel triterpenes isolated from leaves demonstrate significant anti-inflammatory properties. The concentration of triterpenes shows seasonal variation, with peak levels during summer months [36].

Table 2. Major Phytochemical Constituents of *Nerium oleander*

Chemical Class	Compound Name	Plant Part	Concentration (%)
Cardiac Glycosides	Oleandrin	Leaves	0.08-0.15
	Neriin	Leaves, Bark	0.05-0.12
	Odoroside A	Root	0.03-0.08
Terpenoids	Ursolic acid	Leaves	0.12-0.20
	Oleanolic acid	Bark	0.08-0.15
Flavonoids	Rutin	Leaves	0.25-0.35
	Quercetin	Flowers	0.15-0.22
Phenolic Acids	Gallic acid	Leaves	0.18-0.25
	Vanillic acid	Stem	0.10-0.16

4.2.2. Other Terpenoids

Additional terpenoid compounds include phytol derivatives and sesquiterpenes. These compounds contribute to the plant's aromatic properties and exhibit various biological activities including antimicrobial effects [37].

4.3. Phenolic Compounds

4.3.1. Flavonoids

Flavonoid constituents include rutin, quercetin, and kaempferol derivatives. The leaves contain particularly high concentrations of flavonoids, measuring approximately 93.06 ± 0.03 mg/mL quercetin equivalent per 100 mg plant extract [38].

4.3.2. Phenolic Acids

Major phenolic acids identified include p-coumaric acid, gallic acid, vanillic acid, and 4-hydroxybenzoic acid. Total phenolic content reaches 87.38 ± 0.16 mg/mL gallic acid equivalent per 100 mg plant extract [39].

4.4. Distribution of Phytochemicals

4.4.1. Leaves

Leaves contain the highest concentration of cardiac glycosides and flavonoids. The distribution pattern shows variation between young and mature leaves, with mature leaves generally containing higher concentrations of active compounds [40].

4.4.2. Root and Bark

Root tissue demonstrates unique chemical profiles with specific cardiac glycosides and triterpenes. Bark contains distinctive compounds including pregnane derivatives and novel cardenolides [41].

4.5. Analysis of Bioactive Compound

4.5.1. Analytical Methods

Modern analytical techniques including HPLC, GC-MS, and NMR spectroscopy enable precise identification and quantification of bioactive compounds. These methods have revealed complex chemical profiles and helped establish structure-activity relationships [42].

4.5.2. Chemical Markers

Specific compounds serve as chemical markers for standardization and quality control. Oleandrin and related cardiac glycosides function as primary markers for authentication and potency assessment [43].

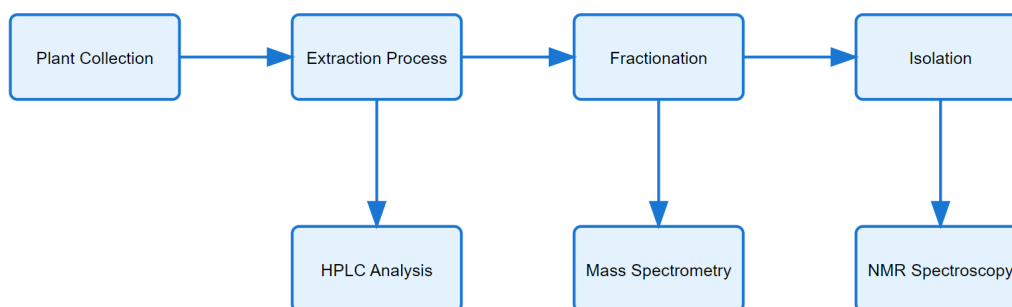


Figure 4. Bioactive Compound Isolation and Characterization Process

4.6. Influence of Environmental Factors on Phytochemicals

4.6.1. Growth Conditions

Environmental factors significantly influence phytochemical composition. Stress conditions often lead to increased production of secondary metabolites, particularly cardiac glycosides and phenolic compounds [44].

4.6.2. Seasonal Variation

Seasonal changes affect both the quantity and quality of bioactive compounds. Maximum concentrations of most active compounds occur during summer months, correlating with peak metabolic activity [45].

5. Pharmacological Activities

5.1. Cardiovascular Effects

The cardiac glycosides in *N. oleander* demonstrate significant cardiovascular activity through Na⁺/K⁺-ATPase inhibition. This mechanism increases intracellular calcium concentration, resulting in enhanced myocardial contractility. Clinical investigations reveal positive inotropic effects at therapeutic doses, though the therapeutic window remains narrow [46].

5.2. Antineoplastic Activity

Research demonstrates significant anticancer properties across multiple cell lines. Oleandrin specifically shows cytotoxic activity against various cancer types through multiple mechanisms including:

The compound induces apoptosis via activation of caspase-dependent pathways and modulates cellular signal transduction. Studies indicate selective cytotoxicity toward malignant cells while showing reduced effects on normal cells [47].

5.3. Anti-inflammatory Properties

N. oleander extracts exhibit considerable anti-inflammatory activity through multiple pathways. The mechanism involves inhibition of pro-inflammatory mediators including TNF- α , IL-1 β , and COX-2. Clinical studies demonstrate reduction in inflammatory markers and symptomatic improvement in various inflammatory conditions [48].

Table 3. Pharmacological Activities and Their Mechanisms of Action

Activity	Mechanism of Action	Active Compounds	Clinical Effects
Cardiovascular	Na ⁺ /K ⁺ -ATPase inhibition	Oleandrin, Neriin	Positive inotropic effect
Antineoplastic	Apoptosis induction	Oleandrin	Cancer cell death
Anti-inflammatory	COX-2 inhibition	Ursolic acid	Reduced inflammation
Antimicrobial	Cell membrane disruption	Terpenoids	Bacterial growth inhibition
Neuroprotective	Antioxidant activity	Flavonoids	Reduced oxidative stress

5.4. Antimicrobial Activity

5.4.1. Antibacterial Effects

Extracts show broad-spectrum antibacterial activity against both gram-positive and gram-negative organisms. The mechanism involves disruption of bacterial cell membrane integrity and interference with protein synthesis. Minimum inhibitory concentrations vary depending on bacterial strain and extract preparation method [49].

5.4.2. Antifungal Properties

Studies demonstrate significant antifungal activity against various pathogenic fungi. The activity appears related to both cardiac glycosides and terpenoid compounds, with synergistic effects observed between different constituent classes [50].

5.4.3. Neuroprotective Effects

Recent research reveals neuroprotective properties through multiple mechanisms. These include reduction of oxidative stress, modulation of neurotransmitter systems, and prevention of neuronal apoptosis. Studies indicate potential applications in neurodegenerative disorders [51].

5.4.4. Immunomodulatory Activity

The plant exhibits significant effects on immune system function. Compounds modulate both cellular and humoral immune responses, affecting cytokine production and lymphocyte proliferation. These effects demonstrate therapeutic potential in immune-related disorders [52].

5.4.5. Antidiabetic Properties

Research indicates potential antidiabetic activity through multiple mechanisms:

- Enhancement of insulin secretion
- Improvement in glucose uptake
- Reduction of hepatic glucose production
- Studies show promising results in both in vitro and in vivo models [53].

5.4.6. Hepatoprotective Activity

Extracts demonstrate liver-protective effects against various hepatotoxic agents. The mechanism involves antioxidant activity and modulation of hepatic enzyme systems. Clinical studies show improvement in liver function parameters [54].

5.4.7. Effects on Skin

Topical preparations show efficacy in various skin conditions. The activity involves anti-inflammatory, antimicrobial, and wound-healing properties. Clinical studies demonstrate improved healing rates and reduced inflammation in dermatological conditions [55].

5.5. Molecular Mechanisms

5.5.1. Signal Transduction

Active compounds influence multiple cellular signaling pathways including MAPK, NF- κ B, and PI3K/Akt pathways. These interactions result in diverse biological responses affecting cell growth, differentiation, and survival [56].

5.5.2. Gene Expression

Studies reveal significant effects on gene expression patterns, particularly those involved in cell cycle regulation and apoptosis. Molecular analysis demonstrates selective modulation of specific gene families [57].

5.5.3. Structure-Activity Relationship

Research has established correlations between chemical structure and biological activity, particularly for cardiac glycosides. These relationships guide the development of semi-synthetic derivatives with improved therapeutic profiles [58]

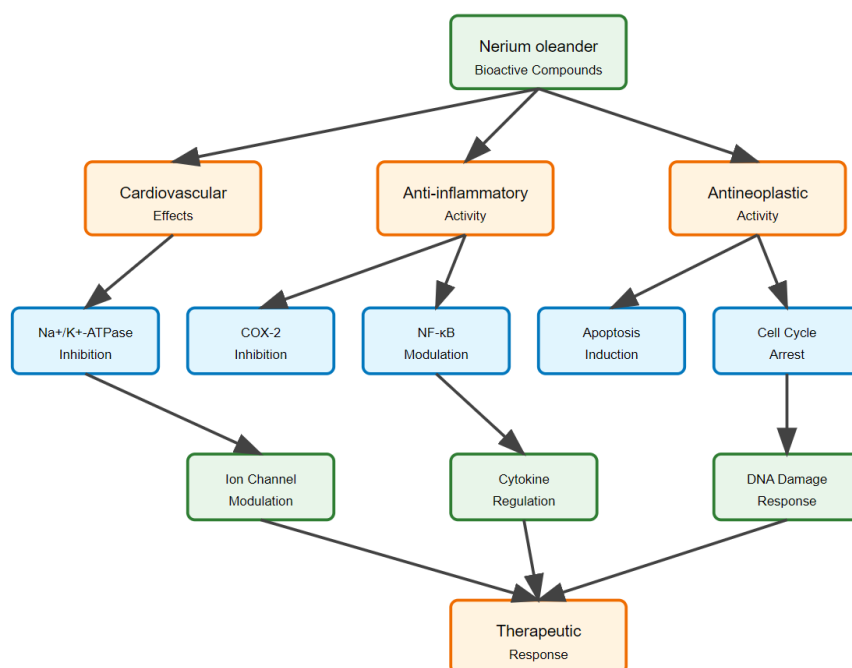


Figure 5. Pharmacological Activities and Mechanism of Action

6. Toxicity

N. oleander exhibits significant toxicity across multiple biological systems. The toxic effects primarily stem from cardiac glycosides, with oleandrin being the most potent compound. The median lethal dose (LD50) varies among different plant parts and preparation methods, with leaves containing particularly high concentrations of toxic compounds [59].

Table 4. Toxicity and Clinical Manifestations

System Affected	Clinical Symptoms	Onset Time	Severity Grade
Cardiovascular	Arrhythmias, Heart block	2-4 hours	Severe
Gastrointestinal	Nausea, Vomiting	4-12 hours	Moderate
Neurological	Confusion, Seizures	6-24 hours	Moderate-Severe
Respiratory	Dyspnea, Tachypnea	4-8 hours	Moderate
Renal	Electrolyte imbalance	12-48 hours	Mild-Moderate

6.1. Mechanisms of Toxicity

The primary mechanism involves inhibition of Na⁺/K⁺-ATPase, leading to disruption of cellular ion gradients. This disruption causes increased intracellular calcium, resulting in enhanced cardiac contractility and potential arrhythmias. Secondary mechanisms include interference with cellular energy metabolism and membrane transport systems [60].

6.2. Clinical Manifestations

6.2.1. Cardiovascular Effects

Initial cardiac manifestations include bradycardia or tachycardia, followed by various arrhythmias. Severe cases may present with ventricular fibrillation and cardiovascular collapse. ECG changes typically show characteristic alterations in ST segments and T waves, along with various degrees of heart block [61].

6.2.2. Gastrointestinal Symptoms

Early symptoms include nausea, vomiting, and abdominal pain, typically occurring within 4-12 hours of exposure. Severe cases may present with hemorrhagic gastroenteritis and electrolyte imbalances [62].

6.2.3. Neurological Manifestations

Central nervous system effects include dizziness, drowsiness, and confusion, potentially progressing to seizures in severe cases. Peripheral nervous system involvement may manifest as paresthesias and muscle weakness [63].

6.3. Risk Factors

6.3.1. Route of Exposure

Toxicity varies significantly with exposure route. Ingestion represents the most common form, though dermal exposure and inhalation of smoke from burning plant material also present risks. Parenteral exposure through traditional medicine preparations poses particular dangers [64].

6.3.2. Population Susceptibility

Certain populations show increased susceptibility to oleander toxicity. Children, elderly individuals, and patients with pre-existing cardiac conditions demonstrate heightened risk. Genetic variations in Na⁺/K⁺-ATPase may influence individual susceptibility [65].

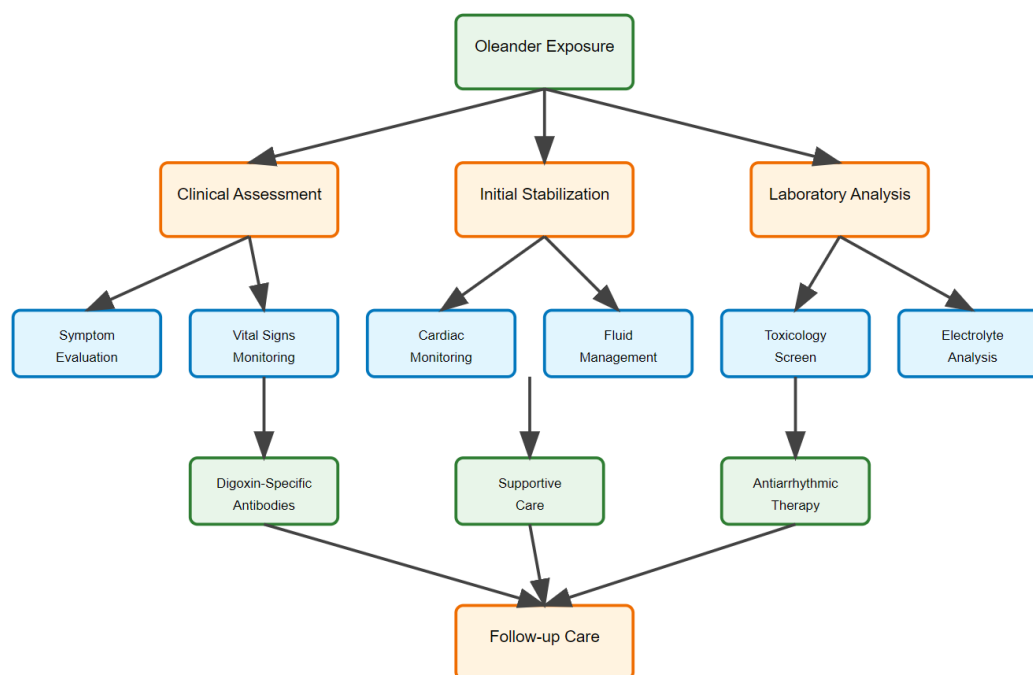


Figure 6. Treatment for *N. oleander* Toxicology

7. Conclusion

The extensive phytochemical profile and diverse pharmacological activities of *N. oleander* shows its importance in both traditional medicine and modern pharmaceutical research. The current understanding of *N. oleander* has evolved significantly through advanced analytical techniques and molecular studies. Research has shown the exact mechanisms of action for various bioactive compounds, particularly cardiac glycosides and their derivatives. The development of standardized extraction methods and quality control parameters remains crucial for therapeutic applications. Modern pharmaceutical technology offers opportunities to enhance safety profiles through novel drug delivery systems and modified molecular structures. The integration of traditional knowledge with modern scientific methods offers promising directions for future research. This approach may reveal new therapeutic applications while validating traditional uses through evidence-based investigation.

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