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Review Article

Nerium oleander L.: A review of diversity, toxicity, chemical compositions and biological activities

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Abstract:

The Apocynaceae family includes the evergreen ornamental shrub known as oleander (*Nerium oleander*). Numerous cultivars were listed in this species, and these differ essentially by the color of the flower. The level of diversity within this species is linked to several factors, such as the geographical region where it grows naturally, environmental conditions, and genetic diversity. Numerous studies of this plant have highlighted bioactive ingredients and several pharmacological effects. *Nerium oleander* is an extremely toxic and even fatal plant because cardiac glycosides such as oleandrin and neriin are constituents present in different parts of the plant. However, a few common oleander pests occasionally feed on the bush. Despite the danger, oleander is of great medicinal importance. Compounds such as terpenes, steroids, polyphenols, and flavonoids have been identified in extracts of different plant parts. The essential oil also includes compounds such as digitoxigenin. Its compounds are involved in several biological activities such as anti-inflammatory, antioxidant, anticancer, hepatoprotective, antimicrobial, larvicidal, and antidiabetic activities which can be used to produce natural drugs.

Key words:
Nerium oleander, biological activities, chemical composition, diversity, toxicity

Apstrakt:

***Nerium oleander* L.: Pregled diverziteta, toksičnosti, hemijskog sastava i bioloških aktivnosti**

Porodica Apocynaceae obuhvata zimzeleni ukrasni žbun poznat kao oleander (*Nerium oleander*). Ova vrsta obuhvata brojne kultivare koji se uglavnom razlikuju po boji cveta. Nivo diverziteta unutar vrste zavisi od više faktora, uključujući geografsko područje prirodnog rasprostranjenja, ekološke uslove i genetičku raznovrsnost. Brojna istraživanja ove biljke istakla su prisustvo bioaktivnih sastojaka i različite farmakološke efekte. *Nerium oleander* je izrazito toksična, pa čak i smrtonosna biljka, jer različiti delovi sadrže srčane glikozide, poput oleandrina i neriina. Ipak, pojedine štetočine povremeno se hrane ovom biljkom. Uprkos svojoj toksičnosti, oleander ima značajnu medicinsku primenu. U ekstraktima različitih delova biljke identifikovana su jedinjenja poput terpena, steroida, polifenola i flavonoida. Etarsko ulje sadrži i jedinjenja kao što je digitoksigenin. Njegovi bioaktivni sastojci učestvuju u brojnim biološkim aktivnostima, uključujući antiinflamatorno, antioksidativno, antikancerogeno, hepatoprotektivno, antimikrobno, larvicidno i antidijabetičko dejstvo, te se mogu koristiti u proizvodnji prirodnih lekova.

Ključne reči:
Nerium oleander, biološke aktivnosti, hemijski sastav, diverzitet, toksičnost

Introduction

Nerium oleander L. or oleander is a Mediterranean species grown worldwide as an ornamental plant. It is a 2–5 m tall evergreen shrub with 5–20 cm long leaves. Flowers display a range of hues, including pink, red, white, peach, and yellow (Dey et al., 2015). It has been introduced to several regions of Africa, such as Tunisia and Algeria. This plant is widely distributed in the Mediterranean region and subtropical Asia (Bandara et al., 2010), but it has now expanded worldwide, including the United States, Australia, China, and Middle Eastern countries. The presence of oleanders around the

Mediterranean basin has been referenced since the Miocene (Palamarev, 1989). Oleander has the potential to be lethal for people, animals, and even insects (Langford & Boor, 1996) due to the presence of cardenolides, which include oleandrin, neriin, and digitoxigenin. Although it is toxic in all its parts, this species is widely cultivated, making it one of the most toxic cultivated plants (Saadaoui et al., 2023). Despite the fact that it is the only species of the genus *Nerium*, it presents various forms of variability (color, leaf shape, seed shape, etc.) (Pagen, 1987). This diversity is linked to genetic factors, mainly the mode of reproduction. Oleander is a hermaphrodite, but new genotypes might arise because of its highly heterozygous and allogamous nature.

Several chemical screening applied to medicinal plants confirmed that *N. oleander* produces many bioactive metabolites grouped as pregnanes (Bai et al., 2007), cardenolides (Bai et al., 2010), phenolics, cardiac glycosides (Aiazzi-Mancini, 1962; Bauer et al., 1984), alkaloids, tannins, flavonoids and terpenoids (Siddiqui et al., 1995) that are integrated and assembled in all parts or specific parts of the plant, and that some of them have significant pharmacological interest. *Nerium oleander* has proved its efficiency in medicine by treating different pathologies. Identifying the metabolites present in the plant is based on various approaches, some of which could be enzymatic, ultrasonic, or fluid methods, giving different content of chemical compounds (Zaid et al., 2022).

The richness of *N. oleander* with diverse chemical compounds, mainly secondary metabolites, gives it various biological activities such as hepatoprotective (Singhal, 2012), anticancer (Montano, 2013), antidiarrheal, larvicidal (Raveen, 2014), antihelmintic (Native, 2014), anti-ulcer (Sabira, 1998) and cytotoxic (Hassan, 2011). Different improvements are reported in common cancer treatments by finding secondary compounds of natural products and medicinal herbs (Ayouaz et al., 2023). Not only extracts, but also *N. oleander* essential oil have been the object of numerous studies. It was analyzed and reported to possess high antimicrobial (Derwich et al., 2010), antioxidant, and antitumor activities (Ali et al., 2010). This study's purpose is to compile information concerning *N. oleander* in terms of genetic diversity, toxicity, and the responsible causative agents. This review is also designed to highlight this plant's phytochemical composition and different biological activities.

Description and distribution of N. oleander

Nerium oleander is an evergreen shrub regularly grown as an attractive plant in gardens and public city areas. At present, it is the only species listed in the genus *Nerium*. It has linear and leathery leaves in various colors, from dark green to grey-green, with separate light yellowish veins. The flowers of *N. oleander* are funnel-shaped and fragrant, with single or double flowers, white, yellow, pink, or red. Its fruit is a narrow sheath holding many silky-haired seeds. Oleander has flexible branches with smooth pale green to light gray bark that releases a milky juice when cut. Each stem node has two or three narrow elliptical leaves with entire margins on short petioles (Garima & Amla, 2010). The plant has extensive root systems and is often used to stabilize soil in warmer areas (Garima & Amla, 2010; Sinha & Biswas, 2016). *Nerium oleander* is a species with hermaphrodite flowers, theoretically fully self-compatible, although the spatial separation of pollen and stigma prevents self-fertilization, leading to high heterozygosity when the plants are reproduced by seeds (Lazzaro et al., 2018), and it shows great variability in seedling populations (Garima & Amla, 2010; Sinha & Biswas, 2016). *Nerium oleander* is introduced to many parts of the world with Mediterranean or subtropical climates (California, Australia, and others) (Bañon et al., 2006).

Taxonomic ambiguity

Morphological traits were utilized in the early stages of taxonomic categorization and systematic classification to classify forms. However, their weaknesses and disadvantages were increasingly evident as they were used. The environment can strongly influence them, and they are therefore not directly heritable, which explains the great confusion regarding *N. oleander* and its different varieties. For a long time, *Nerium oleander* has been assigned to the Apocynaceae family (Ramade, 2008). Oleander variants are still difficult to name and identify, mostly because of materials sold under dubious labels. Many cultivars have been selected within this species, but they differ only in certain morphological characteristics. Pages (1987) listed more than 400 cultivars based mainly on morphological characters (**Fig. 1**) such as shape, flower color, and leaves (often variegated). Several studies (Pagen, 1987; Ebrahimi et al., 2018; Al-Snafi, 2020) confirmed that *N. oleander* is the only species of the genus *Nerium*, and they listed the rest of the varieties as *N. oleander* synonyms. However, other studies revealed that *N. indicum*, originally from Asia, is a second species in the genus *Nerium* (Bi et al., 2016). This taxonomic ambiguity confirms that the classification of this species is only based on the morphological aspect; thus, it remains a subject of research and discussion in the scientific community. According to the The Plant List (Page, 2025), synonyms include: *Nerium indicum, Nerium indicum subsp. kotschyi, Nerium indicum var. leu-*

Fig. 1. Six *N. oleander* cultivars: **a**) *N. oleander* with double dark pink flowers and variegated leaves; **b**) *N. oleander* with red flowers; **c**) *N. oleander* with simple light pink flowers; **d**) *N. oleander* with double white flowers; **e**) *N. oleander* with pink flowers; **f**) *N. oleander* with double pink flowers and simple leaves

canthum, Nerion oleandrum, Nerium carneum, Nerium flavescens, Nerium floridum, Nerium grandiflorum, Nerium indicum f.leucanthum, Nerium indicum var. lutescens, Nerium odoratissimum, Nerium odoratum, Nerium odorum, Nerium oleander var. indicum, Nerium indicum f. lutescens, Nerium indicum var. plenum, Nerium japonicum, Nerium kotschyi, Nerium latifolium, Nerium lauriforme, Nerium luteum, Nerium mascatense, , Nerium oleander subsp. kurdicum, Nerium splendens, Nerium thyrsiflorum, Nerium verecundum, Oleander indica, and Oleander vulgaris (http://www.theplantlist.org/tpl/record/kew-135196).

Nerium oleander pests

Oleander blooms profusely in the summer and fall with large, fragrant blossoms. Oleander is a resilient evergreen plant that blooms in intense heat and drought. Despite its defensive and toxic secondary metabolites, *N. oleander* is attacked by many phytophagous pests, essentially aphids such as *Aphis nerii* (Homoptera: Aphididae) and the striped mealybug, *Ferrisia virgata* (Homoptera: Pseudococcidae) (El-Shazly, 2002). Aphids can be found throughout the growing season, although they are often most prevalent in the spring. Several pests, including oleander caterpillars like *Syntomeida epilais*, can harm any plant part. The *Xylella fastidiosa* strain causes oleander leaf scorch, and *Aspidiotus nerii,* whitish insects found on leaves' top or bottom surfaces, causes malformation, shriveling, and plant death. These pests have a distinct appearance at every stage of development, and eggs colonize the undersides of leaves (Popenoe et al., 2019).

Genetic diversity of Nerium oleander

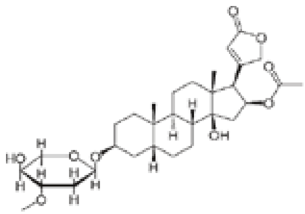
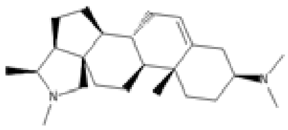
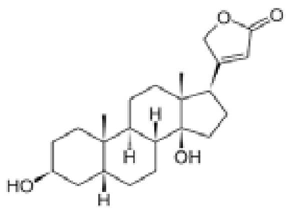
Genetic diversity of *N. oleander* can be investigated by using agro-morphological (Alizadeh et al., 2017; Roughani et al., 2018), biochemical (Keshavarzi et al., 2015), cytogenetic (Salmasi et al., n.d.); and molecular markers (Portis et al., 2004; Ibrahim et al., 2014). Morphological analysis of oleander grown spontaneously or cultivated in Tunisia and belonging to different bioclimates, has shown high intra-specific diversity (Saadaoui et al., 2023). SDS-PAGE (Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis) is one of numerous biochemical procedures that have been effectively utilized to address taxonomy and evolutionary issues with several plants (Khan, 1992; Rabbani et al., 2001). In this context, De Britto & Sebastian (n.d.) analysed the protein variability among five varieties of *N. oleander* with flowers in various colors through SDS PAGE electrophoresis, and the results clearly showed that there was a high degree of diversity among these varieties of plant species. Portis et al. (2004) reported genetic relatedness among 71 accessions of *N. oleander* using an amplified fragment length polymorphism (AFLP) marker. Their results demonstrated that, compared to the few morphological features typically employed for variety differentiation, the AFLP technique provides far more information about the genetic relationships and origins of accessions. Also, they highlighted a high variability related to the fact that oleander is substantially allogamous and highly heterozygous. Furthermore, Ibrahim et al. (2014) studied the cytogenetic diversity of several Apocynaceae species populations, such as *N. oleander*. They found that all populations are diploid and that there is variation in karyotypic traits within and between species.

Oleander grows in the mild, temperate climate of the Mediterranean basin in gullies, rivers, and streambanks. There is a dearth of information on the phylogeography of Mediterranean riparian tree and shrub species. A study by Mateu-Andrés et al. (2015) performed on Mediterranean natural populations of oleander which used plastid DNA showed a high homogeneity at both intra- and inter-population levels in this species. A low mutation rate and/or recent recolonization of the Mediterranean basin could explain the absence of plastid variability in oleander. According to Fussi et al. (2010; 2012), the latest post-glacial period's quick and recent recolonization may cause this low variability. Lorenzo et al. (2018) tried to comprehend the origin of oleander populations in Montecristo and Pistoia (Italy) using ISSR (Inter-Simple Sequence Repeat) molecular markers. Because of the accuracy and repeatability of the results, plant population genetics uses this genome-scanning technology extensively (Rakoczy-Trojanowska & Bolibok, 2004). The results highlight medium levels of genetic diversity, hardly higher than those reported by Hamrick & Godt (1996) for long-lived outcrossing taxa (0.180) with a widespread distribution (0.183), which seems to support an anthropic origin of such population. This hypothesis is also suggested by the general relativeness between Montecristo and Pistoia, which may arise from a possible common anthropic origin of these two populations (Lazzaro et al., 2018). Actually, no recent study has focused on the genetic diversity of *N. oleander* and the origin of different cultivars. Thus, an accurate method for their identification and characterization is necessary, mainly to confirm the presence of a single species and determine the genetic relationship between different varieties and cultivars.

Toxicity

Nerium oleander is indeed a highly toxic plant, recognized for its dangerous cardiac glycosides (Turan et al., 2006). These toxins include compounds like oleandrin, neriin, and digitoxigenin, all of which impact the heart by inhibiting Na^+/K^+-ATPase pump activity, leading to a toxic buildup of intracellular Na^+ and Ca^{2+}. This effect, which resembles the cardiac impact of digitoxin (from *Digitalis* or foxglove) (Bandara et al., 2010), can lead to severe cardiovascular effects, including increased contraction force and potential heart failure (Blum & Rieders, 1987). Oleander's toxicity varies by plant part and flower color, with red-flowered plants typically producing higher glycoside concentrations than white-flowered ones (Karawya et al., 1973). Roots and seeds contain the highest glycoside levels (Bandara et al., 2010). The main cardiac glycoside of *N. oleander* is oleandrin (Hameed et al., 2015). Oleandrin ($C_{32}H_{48}O_9$) is a white crystalline powder with a melting point of 250 °C and a molecular weight of 576.727 Da, and it is insoluble in water and soluble in methanol, ethanol, and chloroform (Zhai et al., 2022). The roots contain the highest concentration of oleandrin, followed by the leaves, stems, and flowers. The concentrations of oleandrin in the various plant sections were as follows: 0.18 to 0.31 mg/g dry weight in the leaves, 0.12 to 0.23 mg/g dry weight in the stem, and 0.34 to 0.64 mg/g dry weight in the roots (Tayoub et al., 2014). Several other cardenolides are added to oleandrin: nerizoside, neritaloside, odoroside, and nerioside (Rashan et al., 2011). Neriin is also known as a potent cardiac glycoside, present in all parts of the plant (**Tab. 1**). Digitoxigenin, with a molecular formula of $C_{23}H_{34}O_4$ inhibits the heart's functioning by hindering the action of Na^+/K^+-ATPases. The two cardiac glycosides, oleandrin and neriin, are the most noteworthy of these toxins. These poisons may be found in many plant sections, but they are more prevalent in the sap. The bark of oleanders contains rosagenin, which is recognized for having effects similar to those of strychnine, along with many other unidentified chemicals that may have potentially harmful effects (Dardona & Shahabuddin, 2022). *Nerium oleander* is highly toxic to humans, animals, and certain insects, with all parts of the plant (fresh, dried, or boiled) capable of causing fatal poisoning. Even minimal ingestion can be deadly due to its cardiac effects (Al-Snafi, 2020). Clinical and toxicological studies report that in humans, *N. oleander* ingestion causes severe gastrointestinal symptoms like nausea, vomiting, colic, and bloody diarrhea, as well as cardiac issues such as decreased pulse rate, irregular heartbeat, and respiratory paralysis, which can lead to death. Secondary neurological symptoms like tremors, drowsiness, ataxia, and hypotension have also been noted, with some cases including seizures (Gopalakrishnan et al., 2017). In animals, oleander poisoning has been documented across species (Barbosa et al., 2008). Horses, for instance, often die within 8 to 10 hours after ingesting lethal amounts, displaying symptoms like cold extremities, ataxia, colic, and convulsions (Turner & Torres, 2017). Cattle show signs such as polydipsia, bloody diarrhea, muscle tremors, fever, dehydration, tachypnea, and tachycardia, with post-mortem examinations revealing extensive hemorrhaging in the lungs and heart (Souza, 2018). Accidental and/or experimental cases of oleander poisoning have been described in several other species, including monkeys (Schwartz et al., 1974), rabbits (Al-Farwachi et al., 2008), and goats (Barbosa et al., 2008). Animals' lungs, liver, and heart are affected negatively by the toxicity of *N. oleander* leaves or flowers. *Nerium oleander* leaf extract causes mononuclear infiltration in the lung, especially around the blood vessels (Abbasi et al.,

Table 1. Molecular formula, structure, and molecular weight of *N. oleander* cardiac glycosides (oleandrin, neriin, digitoxigenin)

Component	Molecular formula	Structure	Molecular weight (g/mol)
Oleandrin	$C_{32}H_{48}O_9$		576.72
Neriin	$C_{24}H_{40}N_2$		356.6
Digitoxigenin	$C_{23}H_{34}O_4$		374.5

2018), histopathological changes in the lung tissue (Abbasi et al., 2014), as well as interstitial hemorrhage in the lung one hour after receiving the oleander, resulting in congestion and edema (Aslani et al., 2004; Aslani et al., 2007). Majeed (2012) demonstrated that *N. oleander* flower extract caused severe blood vessel congestion and edema around the esophagus, particularly at high doses. The liver can also be affected by the toxicity of *N. oleander* components, particularly from the leaves, which can cause different levels of bleeding, hepatocyte degeneration and localized necrosis, hepatocyte necrosis, fatty degeneration, and infiltration of mononuclear inflammatory cells (Ozmaie et al., 2013). Depending on the extract dose, the administration of *N. oleander* revealed various characteristics of cardiac toxicity. In cardiac cells, *N. oleander* leaf extract causes pathomorphological alterations and intrasarcoplasmic vacuole myocytolysis (Taheri et al., 2013). An earlier study conducted by Aslani et al. (2004) on the cardiotoxicity impact of *N. oleander* (110 mg/kg, orally, single dose) in male sheep indicated that sinus bradycardia was seen as the first symptom in electrocardiogram (ECG) 0.5 h after receiving this plant (Aslani et al., 2004). *Nerium oleander* toxicity can also affect insects. The presence of lipophilic components explains the insecticidal effect of *N. oleander* extracts. Zaid et al. (2022) assessed *N. oleander*'s insecticidal efficacy against *Chaitophorus leucomelas* viviparous females. Four days following the treatment, at a concentration of 5.15 g/m^2, a 100% mortality rate was noted.

Phytochemical screening

Nerium oleander contain a high number of chemical compounds, the bulk of which are listed below, according to the results of the phytochemical screening: adenerine, neriin, digitoxigenin, cardenolides, bufadienolides, ouabain, proscillaridin, kanersoide, neriumoside, *cis* and *trans* karenin, oleandrin, folinrin, 4-oxooctyl-2-hydroxy-undecanoate, heptacosane-3-enyl-5-hydroxyhexanoate, betulin, betulinic acid, stigmasterol, quercetin-5-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside and kaempferol-5-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside (Hase et al., 2016). The plant's leaves contain a variety of physiologically significant metabolites, including proteins, carbohydrates, alkaloids, flavonoids, terpenoids, cardiac glycosides, tannins, and saponins (Suganya, 2012). Nawaz et al. (2023) recently isolated a new bioactive steroid 3β-acetoxy-5, 25(26) diene, 24β-hydroxy lanostane from this plant.

Extract composition

Many approaches are employed to extract the chemical components of *N. oleander*, with varying outcomes. Plant sections displayed a variety of phytochemical substances. Essential oils were extracted using polar and non-polar solvents, including ethanol, diethyl ether, hexane, cyclohexane, and ethyl acetate. Certain metabolites are only synthesized under specific environments, or their contents significantly increase under these conditions (Ebrahimi et al., 2018). Every part of *N. oleander* revealed a specific compound. The preliminary phytochemical screening showed that the leaves of this plant contain carbohydrates, flavonoids, alkaloids, steroids, cardiac glycosides, and tannins (Sinha & Biswas, 2016). Oleandrin, neriin, cardenolides, gentiobiosyl, and odoroside are the primary glycosides (Farooqui & Tyagi, 2018). The seeds possess glucosides (oleandrine, odorosidesandadigoside). The bark also contains glucosides (rosaginoside, nerioside, and corteneroside), and the roots contain steroids (Garima & Amla, 2010). Fifteen chemicals were detected in the *N. oleander* alkaloid leaf extract, and eight alkaloid components were found in the methanolic extract (Hameed et al., 2015) and are presented in **Tab. 2**. The maximum concentration of phenolic compounds, which are found in both leaves and flowers of *N. oleander*, such as rutin, epicatechin, quercetin, and quenonic acid, were found in the methanolic extract of the plant *in vitro* (Saranya et al., 2017). The ethyl acetate extract of *N. oleander* leaves yielded the taraxasterane-type triterpenes (20 *β*,28-epoxy-28*α*-methoxytaraxasteran-3*β*-ol and 20*β*,28-epoxytaraxaster-21-en-3*β*-ol) and ursane-type triterpenes (28-nor-urs-12-ene-3*β*,17β-diol and 3*β*-hydroxyurs-12-en-28-aldehyde) (Zhao et al., 2006). A 2.3% crude polysaccharide was obtained from a water extract of crushed *N. oleander* leaves. A pectic polysaccharide made up primarily of galacturonic acid, in addition to rhamnose, arabinose, and galactose, made up the majority of the fraction (67%). The hydro-ethanolic extract of the *N. oleander* plant collected in Morocco underwent phytochemical screening, which identified the presence of coumarins, terpenes, triterpenes, flavonoids, and sterols. However, no mucilage, tannins, or leucoanthocyanins were found (El-Akhal et al., 2015). This result is consistent with previous research demonstrating that flavonoids, coumarins, and triterpenes are produced by Apocynaceae family plants, including *Nerium* (Sedaghat et al., 2011; Roni et al., 2013). According to the study of Zaid et al. (2022), 38 chemical components, mostly made up of the terpenoid and fatty acid group (oleic, linolenic, palmitic, and stearic), were identified in the methanolic extract. The majority of terpene compounds that are associated with oxygenated derivatives include

Table 2. Chemical composition of *N. oleander* extracts

Plant part	Extract type	Composition	References
Leaves	Ethanol extraxt	Siloxane compounds: cycloheptasiloxane, tetradecamethyl, cyclooctasiloxane, hexadecamethyl, cyclononasiloxane, octadecamethyl, cyclodecasiloxane, eicosamethyl	Hameed et al., 2015
	Methanolic extraxt	Cyclopentenes: 2-cyclopenten-1-one, 2-cyclohexen-1-one, 5-Hydroxy-methylfurfural, *β*-D-allopyranoside Fatty acids: 9,12,15-octadecatrienoic acid, octadecane Phenolic compounds: rutin, catechin, epicatechin, quercetin, quenonic acid Flavonoids: isoquercetin, luteolin-7-O-glucoside Triterpenoids: betulinic acid, oleanolic acid, hederagenin Cardenolides: oleandrin, neriin, digitoxigenin	Hameed et al., 2015; Saranya et al., 2017; Ling et al., 2025
	Ethyl acetate extract	Triterpenes: taraxasterin-type (e.g., 20*β*,28-epoxy-28*α*-methoxy-taraxasteran-3*β*-ol) and ursane-type (e.g., 3*β*-hydroxyurs-12-en-28-aldehyde)	Zhao et al., 2006
	Aqueous extract	Pectic polysaccharides: primarily galacturonic acid, with rhamnose, arabinose, and galactose	Sinha & Biswas, 2016
Flowers	Methanolic extract	Phenolic compounds: rutin, catechin, epicatechin, quercetin and quenonic acid; Other compounds: Maltol, oleic acid, cis-vaccenic acid, benzene, 4H-pyran-4-one	Saranya et al., 2017; Saeed et al., 2023
	Ethanol extraxt	Flavonoids: kaempferol 3-O-β-glucopyranoside and chlorogenic acid	Atay Balkan et al., 2018
Roots	Methanolic extract	Phenolic compounds	Gunes et al., 2017
Twigs		Phenolic derivatives: caffeic acid, ferulic acid, p-coumaric acid	Ling et al., 2025

p-cresol, isopulegol, guaiol, phenylethyl alcohol, durene, beta-myrcene, phytol, gamma-sitosterol, and 8-quinolinol. Verbenone, squalene, 2-(4H)-benzofuranone, 4-methyl, and caryophyllene oxide. Apart from these findings, additional compounds were extracted from the ethyl acetate sub-extract of the ethanolic extract of *N. oleander* flowers (Atay Balkan et al., 2018). The recent study by Ling et al. (2025) identified 50 compounds in the leaves of N. oleander and 25 compounds in the twigs, including cardenolides, flavonoids, phenolic derivatives, and triterpenoids, with a greater diversity of compounds found in the leaves compared to the twigs.

Essential oil of N. oleander

The essential oils of *N. oleander* flowers from China, Morocco, and Saudi Arabia exhibit distinct chemical profiles, reflecting the influence of geographic origin on their composition and properties. Morocco stands out with a higher essential oil yield (1.76%) (Derwich et al., 2010), as well as the presence of bioactive compounds such as neriin (22.56%) and digitoxigenin (11.25%). While neriin remains poorly studied, it may possess interesting biological properties, whereas digitoxigenin is a well-known cardiotonic compound used to treat heart conditions (Patel, 2016). Limonene (5.01%), known for its aromatic properties and applications in the perfume and food flavoring industries, is also present in oleander essential oil (Sun, 2007). In oil from Saudi Arabia, camphor (12.76%), a compound widely studied for its analgesic, anti-inflammatory, and decongestant properties (Dos Santos et al., 2021) dominates in the chemical profile (Ali et al., 2010). Moreover, the presence of thymol (8.43%) in Saudi oil is notable, as this compound is recognized for its antiseptic, antifungal, and antioxidant properties (Marchese et al., 2016). In China, Bi et al. (2016) identified twenty-nine components from *N. indicum* flowers, corresponding to 83.1% of the total composition. The data show the presence of compounds such as tricosane (7.4%) and pentanal (4.4%), although no major compound clearly dominates the chemical profile (Bi et al., 2016). Other minor compounds have been identified in this study with a percentage higher than 1% and are detailed in **Tab. 3**. Several studies (Derwich et al., 2010; Ali et al., 2010; Bi et al., 2016) confirmed that geographic origin is a key factor contributing to the chemical composition of essential oils (Szakiel et al., 2011). However, further research is needed to explore the impact of extraction methods, cultivation conditions, and seasonal variations.

Table 3. Essential oil yields in *N. oleander* in flowers of China, Marocco and Saudi Arabia and the main compounds with a percentage higher than 1%

Origin	China	Morocco	Saudi Arabia
Plant part		Flowers	
Chemical compounds (%)	Tricosane (7.4)	Isocaryophyllene (1.1)	Myristicin (1.04)
	1-Nonanal (2.7)	Terpinene-4-ol (3.98)	Cuparene (1.76)
	Phenylacetaldehyde (2.9)	Myrtenal (1.25)	*β*-Bisabolene (1.01)
	Docosane (3.2)	Neriin (22.56)	*β*-cubenene (1.87)
	Hexyl alcohol (2.4)	Digitoxigenin (11.25)	Camphene (2.75)
	2,3,7 Trimethyldecane (1.2)	*α*-Terpinene (1.52)	*β*-Elemene (1.08)
	Pentalan (4.4)	Amorphane (8.11)	*β*-funebrene (2.77)
	Butyl isobutyl phtalate (1.3)	1,8-cineole (6.58)	*α*-phellandrene (1.43)
	Hexanal (1.2)	*α*-pinene (5.54)	*β*-ocimene (1.05)
	Furfural (1.6)	Clarence (5.12)	*β*-sesquiphellandrene (1.98)
	Heneicosane (8.7)	Limonene (5.01)	Ocimene (1.79)
	2-Hexenal (3.2)	*β*-Phellandrene (4.84)	Caryophyllene (3.43)
	Linoleic acid (1.8)	Sabinene (3.22)	Guaiol (1.88)
	Leaf alcohol (5.9)	Globulol (1.1)	*α*-cubebene (3.43)
	Linolenic acid (3.4)	3-Carene (2.56)	*α*-Humulene (2.43)

Chemical compounds (%)	Heptacosane (4.4)	Isoledene (2.94)	*β*-charnigrene (1.08)
	2,6-Di-tert-butyl-p-cresol (2.7)	Verbenol (1.24); Humulene (2.29)	*Trans*-calarnenene (0.82); Germacrene D (2.76)
	Pentacosane (4.5)	*β*-Pinene (2.01)	*β*-selinene (1.98)
	Lauric acid (1.6)	Seychellene (1.09)	*γ*-curcumene (1.09)
	Hexacosane (1.4)	Cymen-8-ol (1.67)	Camphore (12.76)
	Tetradecanal (1.7)	Ylangene (1.2)	Myrcene (1.31)
	1-Heptacosanol (1.7)	Germacrene-D (1.01)	Thymol (8.43)
	Myristic acid (1.8); Diisobutylphtalate (1.4); 4-Octadecanolide (2.1); 1,19-Eicosadiene (1.6); 1,6-Cyclodecadiene (2.3); 6,10,14-Trimethyl-2-pentadecanone (2.7)	Patchoulene (1.02)	*α*-campholenal (5.05); Eugenol (10.45); *α*-copaene (1.5); *δ*-cadinene (1.27)
Essential oils yield (%)	0.11	1.76	0.1
Total oil (%)	83.1	93.21	94.69
References	Bi et al., 2016	Derwich et al., 2010	Ali et al., 2010

Biological activities of Nerium oleander

Nerium oleander components are becoming more and more interesting because of their significance, widespread consumer acceptance, and potential for multipurpose functional use despite their toxicity (Sawamura, 2000; Ormancey, 2001; Sacchetti et al., 2005). In prior pharmacological investigations, this plant has exhibited anti-inflammatory, analgesic, hypolipidemic, anticancer, antibacterial, antiparasitic, anti-inflammatory, dermatological, and cardiovascular properties (Al-Snafi, 2020). Other studies revealed antifungal, molluscicidal, cytotoxic, larvicidal, and insecticidal activities (Hussain & Gorsi, 2004; Hadizadeh et al., 2009; El-Akhal et al., 2015).

Antimicrobial activities of Nerium oleander

According to several studies (Cao et al., 2009; Havlik et al., 2009), oleander essential oil has considerable antibacterial properties due to various components, including phenolic and terpene compounds (**Tab. 4**). In Saudi Arabia, essential oil extracted from oleander flowers was used to evaluate antimicrobial activity, and excellent results were obtained (Ali et al., 2010). In this same study, two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), two Gram-negative bacteria (*Escherichia coli* and *Salmonella typhimurium*), and three fungal species (*Fusarium oxysporum, Rhizoctonia solani,* and *Macrophoma mangiferiae*) were tested. On the other hand, the antibacterial activity of the *N. oleander* essential oil extracted by hydro-distillation inhibited the *Pseudomonas aeruginosa* biofilm at very low concentration (Almanaa et al., 2021). The antibacterial properties of essential oils derived from *N. oleander* were investigated in Morocco by applying minimum inhibitory concentration (MIC) and disk diffusion testing methods. As test bacterial strains, *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus* were employed. According to the results, the strain of *E. coli* that showed the highest susceptibility to this oil had an inhibition zone of 28.89 mm. With an inhibition zone of 18.22 mm, *P. aeruginosa* was more sensitive than the other microorganisms, while inhibitory zones of 6.32 mm were found against *S. aureus*, indicating modest activity (Derwich et al., 2010).

Mouhcine et al. (2019) also investigated the

Table 4. Antimicrobial activity of *N. oleander* essential oil

Activity	Plant part	Microorganism	Result	Reference
Antibacterial	**Flowers**	***G+:*** *Bacillus subtilis and Staphyllococcus aureus;* ***G-****: Escherichia coli, Salmonella typhimirium, Pseudomonas aeruginosa*	+	Ali et al., 2010; Derwich et al., 2010; Almanaa et al., 2021
	Leaves	***G-:*** *Escherichia coli and Salmonella typhimirium*	+	Almanaa et al., 2021
Antifugal	**Flowers**	*Fusarium oxysporum, Rhizoctonia solani, Macrophoma mangiferae*	+	Ali et al., 2010

*(+): effect / (-): no effect; *G+: gram positive bacteria/G-: gram negative bacteria

antibacterial activity of *N. oleander* extracts. Six bacterial strains were used, including 3 Gram-positive bacteria: *Enterococcus faecalis*, *Listeria monocytogenes,* and *Staphylococcus aureus*, and three Gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*. The outcomes showed that the *E. faecalis* strain was susceptible to the effects of both ethanolic and aqueous extracts, with the inhibition zone diameter reaching 5.3 mm and 10 mm, respectively. In contrast, *L. monocytogenes* was not sensitive to the action of the aqueous extract. The other organisms that were tested, including *P. aeruginosa, S. aureus* CECT 476, *E. coli*, and *S. typhimurium*, were resistant to both extracts. Numerous other studies have focused on the organs of *N. oleander* (flowers, leaves, roots, roots bark) to study the antibacterial activity against a high number and types of bacteria. The antibacterial activity of the leaf and flower extracts was investigated against *B.cereus, B. pumilus*, *Bacillus epidermidis,* and *Erwinia carotovora.* Strong antibacterial action against both Gram-negative and Gram-positive bacteria was demonstrated by dichloromethane and methanol extracts of leaves and flowers (excluding *Staphylococcus epidermidis*) (Namian et al., 2013). Jeyachandran et al. (2010) observed that the methanolic extract of *N. oleander* showed maximum zone of inhibition (28 mm) against *S. typhi*. Hussain & Gorsi (2004) focused on the antibacterial activity of *N. oleander* root, bark, and leaf extracts against *Aspergillus niger*, *Bacillus pumilus*, *Staphylococcus aureus*, and *Escherichia coli*. After an incubation period of 24 hours, the chloroform, ethanol, and methanol extracts of *N. oleander* exhibited strong action against every tested bacterium (growth inhibition zone: 20–23 mm). None of the crude extracts - chloroform, ethanol, or methanol exhibited any antifungal action against *A. niger*. On the other hand, studies of antifungal and antiviral activities of *N. oleander* remain rare compared to other activities; very few studies focused on this plant species. Siddiqui et al. (2016) examined the antifungal activities of *N. oleander* using aqueous, methanol, ethanol, chloroform, and acetone extracts from its leaves, stem, and root against three fungal species: *Macrophomina phaseolina, Sclerotium rolfsii,* and *Fusarium oxysporum*. Similarly, El Sawi et al. (2010) investigated the antifungal activity of *N. oleander* extracts against six fungal species*: Aspergillus flavus, A. fumigatus, A. niger, Fusarium moniliforme, Penicillium expansum,* and *Rhizopus oryzae*. The crude extract exhibited the highest antifungal activity against *A. flavus*, with inhibitory zones of 15 mm and 20 mm. Among the tested species, *A. flavus* had the lowest minimum inhibitory concentration (MIC) of the active crude extract (25 µg/ml), while the MIC values for the remaining strains were as follows: *R. oryzae* >100 µg/ml, *P. expansum* 50 µg/ml, *F. moniliforme* >100 µg/ml, and *A. fumigat*us >100 µg/ml. The primary studies focusing on antibacterial activity are summarized in **Tab. 5**.

Cytotoxic activity of N. oleander

Essential oils and their components are used in medicine as constituents of different medical products and have stronger biological activities, such as cytotoxic activity. *Nerium oleander* oil was tested against several carcinoma cell lines, revealing a gradual increase in antitumor activity. Ali et al. (2010) tested *N. oleander* oil against the growth of Ehrlich Ascites Carcinoma cell line. The results demonstrated that oleander essential oil significantly improves anti-tumor activity, which reaches 100% with 8 µl/ml of oleander essential oil. Several researchers have studied the cytotoxic effect of extracts and components isolated from *N. oleander*. Mouhcine et al. (2019) have investigated the cytotoxic capabilities using the WST-1 bioassay on two human cancer cell lines: MDA-MB-231 for breast cancer and HT-29 for colon adenocarcinoma.

Table 5. Antimicrobial activities of *N. oleander* extracts (antiviral, antibacterial and antifungal)

Activity	Extract	Plant part	Strains tested	Result	References
Antibacterial	Ethanolic and aqueous crude extracts	Leaves	*G+: Listeria monocytogenes* and *Enterococcus faecalis*	+	Mouhcine et al., 2019
			G+: Staphylococcus aureus; G-: Escherichia coli, Pseudomonas aeruginosa and *Salmonella typhimurium*	-	
	Dichloromethane and methanol extracts	Flowers and leaves	*G-: Escherichia coli, Erwinia carotovora; G+ : Staphylococcus aureus, Bacillus cereus, Bacillus pumilus*	+	Namian et al., 2013
			G+: Staphylococcus epidermidis	-	
	Chloroform, ethanol and methanol extracts	Root, bark and leaves	*G+: Bacillus pumilus, Bacillus subtilis, Staphylococcus aureus; G- : Escherichia coli*	+	Hussain & Gorsi, 2004
	Aqueous and ethanol extracts	Leaves	*Shigella dysenteriae, Aeromonas hydrophila, Escherichia coli, Enterobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa* and *Staphylococcus aureus*	+	Aboud, 2015
	Aqueous extract	Leaves	*G+: Bacillus subtilis, Staphylococcus aureus; G- : Pseudomonasaeruginosa, Escherichia coli* and *Proteus mirabilis*	+	Minnat, 2016
	Ethanolic, aqueous and chloroform extracts	Flowers	*G+: Bacillus subtilis, Staphylococcus aureus; G- : Escherichia coli, Salmonella typhi* and *Pseudomonas aeruginosa*	+	Saranya et al., 2017
	Ethanolic extract	Leaves	*G+: Staphylococcus aureus; G-: Escherichia coli* and *Pseudomonas aeruginosa*	+	Malik et al., 2015
	Crude and pure extracts	Flowers	*G-: Escherichia coli, Pseudomonas aeruginosa* and *Salmonella enteritidis; G+: Bacillus subtilis, Listeria monocytogenes* and *Staphylococcus aureus*	+	El Sawi et al., 2010
	Methanolic extract	White flowers	G+: *Listeria monocytogenes, Staphylococcus caprae; G-: Shigella dysenteriae* and *Salmonella sp.*	+	Saeed et al., 2023
	Methanolic extract	White, red and pink flowers	G-: *Escherichia coli*; G+: *Streptococcus* group A	-	Cardona & Shahabuddin, 2022

Antibacterial	Ethanolic extract	White, red and pink flowers	*G+: Staphylococcus aureus*	+ (except white)	
			G-: Escherichia coli	-	
			G+: Streptococcus group A	- (except red)	
			G+: Staphylococcus aureus	+	
Antifungal	Chloroform, ethanol, and methanol extracts	Roots, bark, and leaves	*Aspergillus niger*	-	Hussain & Gorsi, 2004
	Ethanolic, aqueous and chloroform extracts	Flowers	*Aspergillus niger, A. flavus, A. fumigatus, Rhizopus* spp.	+	Saranya et al., 2017
	Crude and pure extracts		*Aspergillus flavus, A. fumigatus, A. niger, Fusarium moniliforme, Penicilium expansum, Rhizopus oryzae*	+	El Sawi et al., 2010
	Aqueous, methanol, ethanol, chloroform, and acetone extracts	Roots, leaves, stems	*Macrophomina phaseolina, Slerotium rolfsii, Fusarium oxysporum*	+	Siddiqui et al., 2016
Antiviral	Aqueous extract	N/A	*HIV*	+	Singh et al., 2013
	Cold extract, hot extract	N/A	*poliovirus type 1 (Sb-1)*	+	Sanna et al., 2021
			herpes simplex virus type 1 (HSV-1), vesicular stomatitis virus (VSV), reovirus type-1 (Reo-1), human immunodeficiency virus type-1 (HIV-1), yellow fever virus (YFV)	-	

*(+): effect / (-): no effect; *G+: gram positive bacteria/G-: gram negative bacteria

Based on cell viability indicators, the WST-1 test showed that both ethanolic and aqueous extracts decreased cell viability in both cell lines. According to their findings, the aqueous extract exhibited higher activity than the ethanolic extract. For MDA-MB-231 cells, the IC_{50} values were 1.67 µg/mL and 2.36 µg/mL, respectively, while for HT29 cells, they were 2.89 µg/mL and 5.09 µg/mL. Barai et al. (2018) used the phytochemicals included in *N. oleander*'s stem bark extract to synthesize stable, gold-conjugated nanoparticles that preferentially induce the apoptosis of cancer cells, particularly the MCF-7 breast cancer cell line. At 74 µg/ml, it is destroying the cancer cells.

According to other studies, such as those conducted by Calderón-Montaño et al. (2013), *N. oleander* extract exhibited a strong effect on the A549 lung cancer cell line. Its cytotoxicity was found to be significantly higher than that of non-malignant cell lines, and its potency and selectivity were comparable to those of the anticancer drug cisplatin. Furthermore, using an orthotopic human pancreatic cancer model, researchers investigated the anticancer effectiveness of PBI-05204, a supercritical CO_2 extract of *N. oleander* containing oleandrin. The results showed that PBI-05204 inhibited the proliferation of Panc-1 tumor cells. Additionally, PBI-05204 reduced the expression of pAkt, pS6, and p4EBP1 in Panc-1 tumor tissues and human pancreatic cancer cell lines in a concentration-dependent manner (Pan et al., 2015; Newman & Yang, 2015). The primary cause of the intriguing cytotoxicity of *N. oleander* extracts on cell lines is the presence of cardiac glycosides, which have been extensively studied for their anticancer properties. In human pancreatic tumor cells (PANC-1), the main glycoside extracted from *N. oleander* inhibited cell proliferation and arrested cells at the G2/M stage of the cell cycle (Newman et al., 2007). Oleandrin, the main compound with cytotoxic activity, has been extensively studied without overlooking the effects of other glycosides such as odorside, neritaloside, and the aglycone oleandrigenin (Wang et al., 2000). Using various cancer cell lines, the Anvirzel™ supplement, derived from *N. oleander* and containing oleandrin, odorside, neritaloside, and the aglycone oleandrigenin, has demonstrated notable anticancer activity. Additionally, fractions containing cardenolides from the cold aqueous extract of *N. oleander* leaves exhibited anticancer properties against 36 human tumor cell lines, with an IC_{50} value of 0.85 µg/ml (Rashan et al., 2011).

Insecticidal activity of N. oleander

Certain plant extracts are employed as phytopesticides or bioinsecticides to counteract the overuse of pesticides. These substitute methods have less of an adverse effect on the environment and are more considerate of the health of people and animals (Regnault-Roger et al., 1993; Kellouche, 2005). In this context, *N. oleander* has been the subject of several studies on its toxicity against some insects. This plant is toxic to larvae of *Culex pipiens* (Barbouche et al., 2001), Rhizotrogini and *Lymantra dispar* (Madaci et al., 2008; Kerris et al., 2008) and to *Schistocerca gregaria* in Morocco (Bagari et al., 2013). Harizia and Doumandji (2014) reported that the insecticidal efficacy of *N. oleander* essential oil resulted in total mortality of *Schistocerca gregaria* larvae (5th larval stage) by the 7th day after treatment. The essential oil exhibited insecticidal effects by reducing body weight and deterring consumption. Similarly, Bagari et al. (2013) observed complete mortality after 12 days when larvae were fed exclusively on fresh leaves of the same plant during the fourth stage of development. Oleander extracts have demonstrated larvicidal effects against various insect species. According to Rao et al. (2012), the aqueous leaf extract exhibited insecticidal activity against *Culex tritaeniorhynchus* and *C. gelidus*. Several studies have also reported that ethanol extracts from *N. oleander* leaves possess larvicidal effects against *Aedes aegypti* mosquitoes (Komalamisra et al., 2005), the third and fourth larval stages of *Culex pipiens* (El-Akhal et al., 2015), as well as the second instar larvae of the medically important false stable fly, *Muscina stabulans* (El-Shazly et al., 1996). In another study, *C. pipiens* was used as a test subject to evaluate the larvicidal properties of water, chloroform, acetone, and diethyl ether extracts of *N. oleander* leaves. Based on LC_{50} values, the toxicity of these four extracts was higher at 10 °C than at 35 °C (El-Sayed & El-Bassiony, 2016). Using enzymatic, ultrasonography, and supercritical fluid extraction techniques, researchers identified 38 bioactive compounds, including D-limonene. This compound exhibited insecticidal activity by reducing certain reproductive parameters in viviparous female *Chaitophorus leucomelas* (Zaid et al., 2022). Furthermore, natural populations of *C. leucomelas* exposed to a 5.15 g/m² methanol leaf extract under semi-controlled field conditions exhibited 100% adjusted mortality after four days. Moreover, a recent study by Al-Ansi et al. (2024) suggested that *N. oleander* leaf extracts could serve as a natural alternative to synthetic insecticides against *Pachycondyla sennaarensis* ants, while emphasizing the need for strict precautions in their application. The phytochemical components, including flavonoids, sterols, terpenes, triterpenes, and coumarins, may contribute to the larvicidal activity observed in *N. oleander* extracts (El-Akhal et al., 2015). The larvicidal activity of *N. oleander* flowers against *Culex quinquefasciatus*, the filarial vector, was studied. Mortality was observed during both 24 and 48 hours. The larvicidal activity of hexane flower extract was maximal after 24 and 48 hours, with LC_{50} values of 102.54 ppm and 61.11 ppm, respectively (Raveen et al., 2014). Therefore, the effect of the plant (toxic, repellent, or antifeedant) and the type of extract utilized (aqueous extract, essential oil, fresh leaves), as stated by these authors, are mostly responsible for the variability of larval mortality (Harizia & Doumandji, 2014).

Antioxidant activity

Nerium oleander has strong antioxidant properties; extracts from its leaves, stems, and roots effectively scavenge free radicals and can be utilized as a natural source of powerful antioxidants (Farooqui & Tyagi, 2018). The compounds extracted from the leaves demonstrated excellent hydroxyl radical, peroxynitrite, hypochlorous acid scavenging, and iron chelation activity. The stem had the most potent capacity to scavenge DPPH radicals and nitric oxide, whereas the root demonstrated lipid peroxidation, superoxide anion, hydrogen peroxide, and singlet oxygen scavenging activities (Dey & Chaudhuri, 2014). It has also been found that *N. oleander* flowers can serve as an excellent source of natural antioxidants (Mohadjerani, 2012). Both leaves and flowers have been shown to contain phenolic compounds, such as rutin, catechine, epicatechin, quercitin, and quenonique acid (Saranya et al., 2017), that display the highest levels of antioxidant activity (Garima, 2011).

Table 6. Pharmacological effect of *N. oleander* extracts

Effect	Plant Extract	Experimental model	Result	References
Anti-inflammatory	Flower ethanolic extract	Mice	inhibition ERK phosphorylation (by 20.53% at 200 µg/ml); concentration-dependent inhibition of protein (albumin) denaturation at concentrations ranging from 100 to 500 µg/ml; significant antinociceptive activity against p-benzoquinone-induced abdominal contractions	Erdemoglu et al., 2003; Mary et al., 2017; Atay Balkan et al., 2018
Dermatological	Aqueous leaf extract	Rabbit	complete healing at 6-7 days	Minnat, 2016
Anti-hyperlipidemic	Hydroethanolic extracts of *N. oleander* flowers	Rats	a dose-dependent, considerable ameliorative effect on increased lipids and lipoproteins in comparison to standard (test conducted in hyperlipidemic rats); beneficial effects on cholesterol metabolism-related gene	Gayathri et al., 2013; Demirel Kars et al., 2014
Nervous effects	Hydroalcoholic, methanol, chloroform flowers extracts	Mice	significant reduction in spontaneous locomotor activity, anxiolytic activity	Singhal & Gupta, 2011; Shashikala et al., 2018
Antidiabetic	Hydromethanolic leaf extract	Mice	antihyperlipidemic activity, percentage decrease in different livel marker enzymes, decrease in triglyceride and cholesterol levels (test applied in diabetic mice induced by alloxan)	Dey et al., 2015
Cardiovascular	Methanolic leaf extracts	Rats	The elevation of marker enzymes in plasma, including lactate dehydrogenase, γ-glutamyl transferase, creatine kinase (CK-MB and creatine phosphokinase), aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, was prevented in rats by pretreatment with the extract (10, 30, and 100 mg/kg) and propranolol for two weeks after isoproterenol challenge (test against isoproterenol-induced myocardial toxicity in rats compared to propranolol)	Gayathri et al., 2011

Hepato-protective	Methanolic flower extracts	Rats	Maximal hepatoprotection at 400 mg/kg dose level, with a dose-dependent substantial normalizatin by the extract (rat hepatotoxicity caused by CCI_4)	Singhal & Gupta, 2012

Nerium oleander essential oil possessed significant antioxidant activity, which was studied by three methods (DPPH assay, β-carotene/linoleic acid bleaching assay, and ferric reducing power assay)(Al-Snafi, 2020). When compared to synthetic antioxidants such as Trolox and BHT, oleander essential oil exhibited much higher antioxidant activity (Ali et al., 2010). Additional research, such as that conducted by Bi et al. (2016), found that the essential oil of *N. indicum* (also known as *N. oleander* syn) exhibited notable scavenging properties against free radicals such as DPPH, ATBS, and superoxide anion, with IC_{50} values of 45.29, 32.47, and 67.31 g/ml. The antioxidant properties of the leaves and flower extract were assessed by Namian et al. (2013) using DPPH at doses of 0.5, 0.25, 0.125, 0.0625, 0.0312, 0.0156, 0.0078, 0.0039 and 0.0019 mg/ml. The leaves and flowers methanol extracts demonstrated strong antioxidant activity, with IC_{50} values of 0.27 and 0.2 mg/ml, respectively. The antioxidant activity of water, methanol, water: methanol and acetone extracts of *N. oleander* grown in the north of Iran was studied by employing various *in-vitro* assays (DPPH free radical scavenging, reducing power and total antioxidant capacity). The extracts with the highest antioxidant potency were the methanolic and aqueous methanolic extracts. Four extracts of *N. oleander* leaves (water, methanol, water: methanol and acetone) showed total antioxidant activity of 1.280, 1.246, 0.982, and 0.912, while for flowers, there are 2.330, 1.386, 1.596, 2.930 mg ascorbic acid equivalents/mg extract (Al-Snai et al., 2019). Oleander flower extract's antioxidant capacity was assessed utilizing the DPPH free radical scavenging assay and the reducing power assay. According to the results of applied assays, the ethanolic extract demonstrated a significant scavenging capacity and reducing power activity (Saranya et al., 2017).

Ethanol and aqueous extracts of *N. oleander* were also investigated for their antioxidant activities with DPPH scavenging assay and the β-carotene bleaching test. Mouhcine et al. (2019) reported the high antioxidant capacity of *N. oleander* extracts. While all the tested concentrations of the aqueous extract had comparable results to BHT, with an impact above 50%, the ethanol extract's IC_{50} was 2.2 mg/L. Furthermore, the β-carotene bleaching assay demonstrated that both *N. oleander* extracts significantly reduced the oxidation of β-carotene. Oleander various extracts were investigated for pharmacological activities and were found to possess anti-inflammatory, skin-healing, anti-hyperlipidemic, anxiolytic, positive cardiovascular and hepatoprotective effects (**Tab. 6**).

Conclusion

Nerium oleander is a unique species characterized by high intraspecific diversity, many varieties, and significant toxicity. Extracts from this species contain various chemical compounds, the most important of which include carbohydrates, proteins, alkaloids, flavonoids, terpenoids, cardiac glycosides, tannins, and saponins. Neriin, oleandrin, cardenolides, gentiobiosyl, and odoroside are the primary toxic compounds of this plant. These toxic chemicals have been utilized as effective pharmaceutical agents for treating various infectious and chronic diseases. Additionally, *N. oleander* extracts are known for their diverse biological activities, including antimicrobial, antioxidant, and insecticidal properties. Furthermore, *N. oleander* exhibits potent cytotoxic activity, making it a promising candidate for future cancer treatments due to the presence of active glycosides such as oleandrin and is also being explored as a potential new treatment for HIV.

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