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REVIEW ARTICLE

Nerium oleander Lin: A Review of Chemical, Pharmacological and Traditional uses

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ABSTRACT

Nerium oleander Lin, which is the only species listed in the genus *Nerium* and a member of the Apocynaceae family, was frequently employed in traditional medicine to address various pathologies. *N. oleander* has demonstrated its efficacy in various disease models at a time when pharmaceutical firms are focusing more on plant-based traditional medicines to prevent side-effects and resistance against synthetic drugs. Neriin, oleandrin, cardenolides, gentiobiosyl, and odoroside are just a few of the cardiac glycosides that are present in this plant and are toxic in all sections. Additionally, this plant species creates secondary metabolites with pharmacological value, such as alkaloids, flavonoids, and steroids.

Introduction

Many developing countries around the world are endowed with significant resources of natural products. This prestigious heritage, which includes medicinal plants, has been used by indigenous people for centuries as medicines to relieve disease, health care products, perfumes, aromas, sweeteners and pest control materials [1]. Today, a growing number of studies have examined the various health benefits and protective effects of natural substances found in plants. The scientific evaluation of medicinal plants used in the preparation of folk remedies has provided modern medicine with effective pharmaceutical drugs for the treatment of many infectious and chronic diseases. The rate of increase in the incidence of cancer and the lack of anti-cancer drugs has forced scientists to conduct pharmacological and chemical research in the field of medicinal plants to find anti-cancer agents [1]. Today, it is estimated that about half of today's pharmaceutical drugs are derived, directly or indirectly, from natural sources; in particular, more than 60% of anti-cancer compounds useful for cancer patients are obtained from plant, marine and microorganism sources [2]. Roughly speaking, the great medicinal benefits of these plants are attributable, on the one hand to some phenolic compounds with antioxidant properties, while on the other, to several non-phenolic compounds, including essential oils, terpenoids, or saponins with anti-inflammatory properties [3]. Current strategies are directing investigations towards prevention and the development of new

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therapeutic approaches, targeted at the biological and molecular characteristics of these cancers. Nowadays, numerous studies have been carried out and have obtained satisfactory results. Important scientific work carried out on plant extracts has demonstrated a remarkable antiproliferative effect [1]. Medicinal plants have a long history in both traditional and modern cancer treatments, and have been used to treat human diseases for centuries. Thus, it is possible that traditional medicinal plants can serve as potential sources for developing new drugs more effective anti- cancer agents for future therapy [4]. Plants produce a wide range of chemical compounds, these compounds are called secondary metabolite. Polyphenols, Alkaloids, terpenoids, flavonoids, pigments, and tannins are important constituents of these compounds. Secondary metabolites have biologic effects such as anti-inflammatory, anticancer, contraceptive, and different effects on hematopoietic cells [5], lipids [4] and cardiovascular systems [4]. Different improvements are reported in common treatments of cancer by finding secondary compounds of natural products and medicinal herbs. Many chemopreventive anti-cancer drugs have antioxidant potential to protect against certain forms of human cancer [6]. The strong association between *in vitro* and *in vivo* studies. The antioxidant property as well as the protective effects and anticancer activity of these molecules have been demonstrated [7,8]. *In vitro* studies have provided evidence that chemotherapeutic agents such as extracts can induce the death of apoptotic tumor cells *in vivo* [9]. Also, different researches and studies have proved the positive effect of plants in curing diabetes, fertility and sterility [4] thyroid disorders and psychological disorder etc [10,11]. For these reasons, the search for antioxidants as chemopreventive agents and the phytochemical study of plant-based products is a continuous process, thus, finding plants that replace chemotherapy and cumbersome cures of cancer with cytotoxic effects is necessary [12].

Nerium oleander Lin belongs to the family Apocynaceae and is the only species classified in the genus *Nerium*, was widely used in traditional medicine to treat certain pathologies. In the present time, when the pharmaceutical companies are concentrating more toward the plant based traditional medicines to avoid the side-effects and resistance against synthetic drugs, *N. oleander* has proved its efficiency in different disease models. All parts of the plant are toxic and contain a variety of cardiac glycosides which includes neriin, oleandrin, cardenolides, gentiobiosyl and odoroside. This plant species also produces secondary metabolites such as alkaloids, flavonoids and steroids which have pharmacological interests [13].

Botanical Aspect

The Apocynaceae are a family of trees, shrubs and lianas, and more rarely cactiform species or perennial or annual herbs like the few species found in temperate regions. The Apocynaceae family comprises more than 2000 species that are distributed mostly in tropical regions and have been recorded in 63 volumes of the Flora of China. This family has great importance due to its use in food, its economic implications related to medicinal and ornamental applications, and its toxicological aspects [14]. The plants of the Apocynaceae family are rich in alkaloids, terpenoids, steroids, flavonoids, glycosides, simple phenols, lactones, and hydrocarbons [15,16]. Some members of the Apocynaceae family are widely used ethnomedicines around the world. It has been reported that crude extracts and single compound(s) isolated from various members of the Apocynaceae family possess a wide range of bioactivities, including antioxidant activity, anti-inflammatory/analgesic activity, anticancer/cytotoxic activity, antimicrobial activity, and cardioprotective activity [17-20].

Many species in the Apocynaceae family are known in different parts of the world as toxic and medicinal. The poisonous plant database from the U.S. Food and Drug Administration (FDA, www.accessdata.fda.gov/scripts/) classifies certain species of the family as toxic if ingested, including *Strophanthus hispidus*, *Cerbera manghas*, *Thevetia peruviana*, and *Nerium oleander*. *Nerium oleander* contains a mixture of very toxic cardiac glycosides that cause poisoning *via* the inactivation of Na^+ and K^+ ATPases in the plasma membraneof cardiac myocytes [21]. The toxic effects of oleander have been reported in horses, cattle, sheep, goats, dogs, cats, birds, humans, donkeys, camels, monkeys, budgerigars, geese, ducks, turkeys, toed sloths and bears [22].

Nerium genus

Nerium, is a genus comprising a single species, *Nerium oleander* L [23], found in North Africa, the eastern Mediterranean basin, and Southeast Asia, and dry river beds. It belongs to the Apocynaceae family.

Nerium oleander

Nerium oleander or *oleander* (locally called Defla) is the only species classified in the genus *Nerium* [24], is a shrub belonging to the family Apocynaceae. The Latin name *Nerium* comes from the Greek nerion meaning "wet", indicating the predilection of this plant for wetlands. The specific name *oleander* comes from the Italian "oleandro" which comes from the Latin "olea" which refers to the olive tree, referring to the resemblance of the foliage of the olive tree to that of the olive tree [25]. It is extensively used as an ornamental plant in landscapes, in parks, and alongroadsides due to its profuse flowering which are long lasting along with their moderate hardiness. In Northern regions it may be grown as an indoor or patio plant. The *oleander* is most prevalent, and itsalluring flowers make it a particular hazard for accidental ingestion [26].

Synonyms common names

Nerion oleandrum, Nerium carneum, Nerium flavescens, Nerium floridum, Nerium grandiflorum, Nerium indicum, Nerium indicum subsp. kotschyi, Nerium indicum var. leucanthum, Nerium indicum f. leucanthum, Nerium indicum var. lutescens, Nerium indicum f. lutescens, Nerium indicum var. plenum, Nerium japonicum, Nerium kotschyi, Nerium latifolium, Nerium lauriforme, Nerium luteum, Nerium mascatense, Nerium odoratissimum, Nerium odoratum, Nerium odorum, Nerium oleander var. indicum, 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 is known under different common names according to the countries and regions considered:

Afrikaans: selonsroos; Arabic: Difla, Ward Al-Hemar, Sim Al-Hemar; English: oleander, rose bay, rose-laurel; French: oleander; German: Oleander; Japanese: kyōchiku-tō; Portuguese: espirradeira, oleandro; Spanish: Adelfa, balandre, laurel rosa, Pascua (https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?id=25229).

Botanical description

Nerium oleander L. is a small evergreen shrub or densely branched tree with 2-5 m in height [25,26]. *Oleander* has flexible branches with a smoothpale-green to light-gray bark that exudes milky juice when cut. Each stem node has two or three narrow, elliptic leaves with entire margins on short petioles [27]. Plants have an extensive root system and are often used to stabilize soil in warmerareas [25,27].

The leaves are opposite or whorled, measure 5 to 20 cm long, tough, with pinnate secondary veins, very numerous, tightly packed, dark green above and lighter green below, and turn yellow before falling. The flowers grow in clusters at the end of each branch; about 5 cm in diameter with five petals and different colors vary from lilac, red, salmon, carmine, deep to pale pink, purple, copper, apricot, orange, white, yellow or bicolored. They are often, but not always, scented; they bloom from June to September. The fruit consists of a narrow follicle 5-23 cm (2.0-9.1 in) long, which splits open at maturity to release numerous downy seeds. The Seed fluffy, is surmounted by a sessile egret which facilitates its diffusion [25,28].

Geographical distribution

It was distributed in Africa (Algeria, Libya, Morocco, Tunisia, Mauritania and Niger), Asia (United Arab Emirates, Afghanistan, Cyprus, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, China, India, Nepal, Pakistan), Europe (Albania, Croatia, Greece, Italy, Malta, France, Portugal, Spain) and cultivated in wide areas [26].

In North Africa, *Nerium oleander* is quite common in the steppe zone. In Algeria its presence is quite common, especially on alluvial and rocky ground. It advances along the wadis in the Northern Sahara and is found in the Tassili and Hoggar mountains.

Nerium oleander is now distributed in many regions of the world (California, Australia ...) and in different ecological places (Mediterranean or subtropical climate) [26].

Traditional use

Since antiquity, mankind has used various plants found in its environment to treat and cure all kinds of diseases. *N.oleander* is used in traditional medicine despite its established toxicity, for the treatment of many diseases and is also part of several local pharmacopoeias [29]. The traditional uses of the different organs of *N. oleander* in different countries are described in the table 1. All plant parts were used medicinally.

Table 1: Main uses of *Nerium oleander* in traditional medicine according to countries.

Parts Used	Country	Indications/References	Instructions for use
Fresh or dried leaves	South Africa	Abortifacient [29]	*
	Algéria	Cleaning and softening of the feet (skin), against cavities and dental rages [30]	Decoction
	Iran	Cardiotonic and diuretic [29]	Infusion
	*	-Chronic and obstinate skin diseases of serious nature including leprosy [31]. Juice of young leaves is effective in the cure of eye diseases, The leaves used as expectorant, heart tonic, diuretic, emetic and diaphoretic [32] used in snake and other venomous bites [26] -Used as a snuff for treating epilepsy [31] - Treat diabetes and syphilis [30]	Decoction powder
	Marocco	Antidiabetic, abortifacient, itching, head male [33], antigale, against hair loss and eczema [30]	Decoction, infusion, maceration
	Tanzania and Turkey	antibacterial [29,34]	Decoction
Flowers	*	Are emetic, cardiotonic, diaphoretic, cardiotonic, expectorant, sternutatory, diuretic, anticancer, antibacterial and anti-fungal [26,32,35]	*
Root	*	Treatment of gynaecological disorders, adjunctive treatment, rheumatic and joint pain, in the form of fire spikes, haemorrhoids and ulcers. relieve venereal diseases.Oil of rootbark gave good results in leprosy [30,31] is used in the form of plasters and is applied to tumours because of its poisonous nature it is only used externally [26]	Fumigations Stickers Decoction powder
Bark	*	Are used as expectorant, heart tonic, diuretic, emetic and diaphoretic [32] used also as cathartic, febrifuge and intermittent fever. Oil prepared from the root bark is used in the treatment of leprosy and skin diseases of a scaly nature [26]	Maceration Decoction,
Seeds	*	Are used as a purgative in dropsy and rheumatism [26]	*
Different parts	Cuba	Folklore medicine [29]	*
	India and Bangladesh	*Nerium* is beaten into a paste with water and applied to lesion and ulcers on the penis, antibacterial [29,32]	*

*Not precise

Chemical aspect

Nerium genus

Considerable amount of work has been carried out and Isolation of a number of secondary metabolites has been reported from the genus *Nerium*. Though triterpenoids [36] are major constituents of this genus, other secondary metabolites, such as pregnanes, cardenolides [1,14] cardiac glycosides [14] etc. were also frequently isolated and characterized (Figure 1).

Species *Nerium oleander*

The preliminary phytochemical screening showed that the plant contained alkaloids, flavonoids, carbohydrates, tannins, phenolics, saponins, cardenolides, cardiac glycosides, pregnanes, triterpenoids, triterpenes and steroids [37,38], About thirty cardenolides were separated or characterized, mostly represented by oleandrin and odorosides.

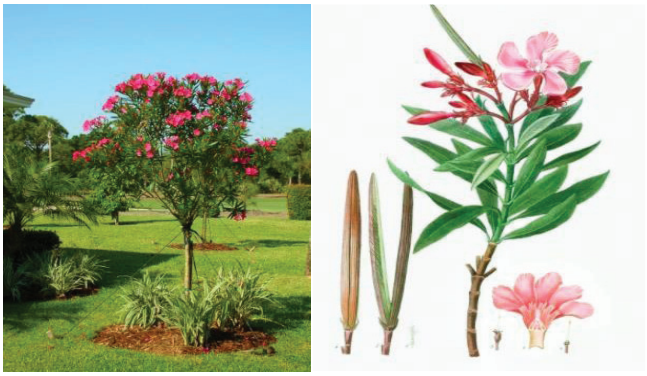

Figure 1 *Nerium oleander* (https://www.toxiplante.fr; consulted on January 4, 2021).

The plant accumulates cardenolide heterosides in all the organs of the plant. The main glycosides in leaves are oleandrin, neriin, cardenolides, gentiobiosyl and odoroside are also present. The leaves contain approximately 1.5% cardenolides, of which 0.1% is oleandrin or 3-o-α-Loleadrosyl-

16-acetylgitoxigenin [26]. The seeds contain glucosides (oleandrine, odorosides, adigoside). The bark alsocontains glucosides (rosaginoside, nerioside, corteneroside) and the roots contain steroids [27]. In addition, a variety of other pharmacologically active compounds, including folinerin, rosagenin, rutin and oleandomycin have been identified in the plant [26]. The maximum amount of oleandrin was in the roots, followed leaves, stems then flowers. Oleandrin concentrations in plant parts ranged from 0.18 to 0.31 mg/g dry weight (10-18%) in leaves, and from 0.12-0.23 mg/g dry weight (9-20%) in stem, and from 0.34 to 0.64 mg/g dry weight (10-18%) in roots [39]. These concentrations vary according to genetic and environmental considerations. Oleandrin is accompanied by steroid analogues such as: gitoxigenin, adynerigenin, uzarigenin. Seeds contain oleandrin and related compounds: odorosides, adigoside, gluco-strospeptide, etc [13].

The different groups of subsantnces and/or substances isolated in the different parts of the plant are summarized as follows:

Leaves

Siddiqui et al, reported a pentacyclic triterpene, oleander ocinoic acid, flavonoid glycosides, quercetin-5-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside and kaempferol-5-O-[α-L-rhamnopyranosyl-(1→6)]-β-D-glucopyranoside and a cardenolide, oleandigoside [40] screened the ethanolic extract of the leaves of *N. oleander* and found to contain carbohydrates, proteins, amino acids, alkaloids and cardiac glycosides. Flavonoids and terpenpoids were absent. The preliminary studies of Patel S[1], et al. reported the presence of alkaloids, glycosides, tannins and phenolic compounds for methanolic extract of *N. indicum.* Almahy H[2], et al. reported two aristolochic acid derivatives and 3-aristolactam derivatives in addition to one methylparaben from the *N. oleander* leaves aqueous and methanolic extract. Siddiqui BS[3], et al. reported two novel cytotoxic pentacyclic triterpenoids cis-karenin (3-β-hydroxyphenoxy-28-Z-p-coumaroyloxy-urs-12-en-27-oic acid) and trans-karenin (3-β-hydroxy-28-E-p-coumaroyloxy-urs-12-en-27-oic acid). Siddiqui S[4], et al. reported two new cardiac glycosides kaneroside and neriumoside from the fresh undried, winter leaves of *N. oleander* and their structures established as 3β-O-(D-diginosyl)-2α-hydroxy-8,14β-epoxy-5β-carda-16:17,20:22-dienolide and 3β-O-(D-diginosyl)-2α,14β-dihydroxy-5β-carda-16:17,20:22-dienolide respectively through chemical and structural studies. A new cardenolide, neridiginoside and three knownconstituents, nerizoside, neritaloside and odoroside-H, have been isolated which showed CNS antidepressant activity. The structure of neridiginoside was elucidated as 3 beta-O-(D-diginosyl)-5 beta, 14 beta-dihydroxy-card-20 (22)-enolide [26].

Gas Chromatography-Mass Specroscopy (GC-MS) analysis of *N. oleander* alkaloid leaf ethanol extract revealed the existence of the 5-hydrooxy methyl-furfural, β-d-allopyranoside, methyle 6-dioxy-2-o methyl, cycloheptasiloxane, tetradecamethyle, cyclooctasiloxane, hexadecamethyl, cyclononasiloxane, octadecamethyl, cyclodecasiloxane,eicosamethyl, 2-cyclopenten-1-one, 2-hydroxy-3-methyl, 9.12.15- octadecatrienoic acid, 2,3bis [trimethyl-silyl]oxy] propyl ester, octadecane, 3-ethyl-5-(2-ethylbutyl), 1- monolinoleoylglycerol trimethylsilyl ether, 1.1.3.3.5.5.7.7.9.9-decamethyl-9-(2-methyl propoxy) pentasiloxane, 2-cyclohexen-1-one, 4-(hydroxybutyle)-3.5.5-trimethyl, octasiloxane, 1.1.3.3.5.5.7.7.9. 9.11.11.13.13.15.15-hexadecamethyl and 3-eicosene [41]. The aqueous extract of leaves of *N. oleander* yielded 2.3% of crude polysaccharide. Major of the fractions was pectic polysaccharide which is composed of arabinose, galacturonic acid, galactose, and rhamnose [25]. Further analysis showed that it mainly contained arabinogalactan having a backbone of 1,6-linked beta-Galp, with branches at O-3, consisting of a terminal, 1,5-, and 1,3,5- linked arabino furanosyl residues, and a small proportion of galactosyl residues at the termini [26].

Flowers

The flowers yielded 1.76% total oil, 34 compounds were identified in the oil, the major components were nériine (22.56%), digitoxigénine (11.25%), amorphane (8.11%), 1.8-cineole (6.58%), α-pinene (5.54%),

Endnote

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calarene (5.12%), limonene (5.01%), β-phellandrene (4.84%), terpinene-4-ol (3.98%), sabinene (3.22%), isoledene (2.94%), 3-carene (2.56%), humulene (2.29%), β-pinene (2.01 %) and cymen-8-ol (1.67%) (56). A water extract of crushed leaves of *N. oleander* yielded 2.3% crude polysaccharide. The main fraction (67%) was a pectic polysaccharide, which mainly mainly composed of galacturonic acid besides rhamnose, arabinose and galactose. Kaempferol, kaempferol 3-O-β-glucopyranoside and chlorogenic acid were isolated from the ethyl acetate sub-extract of the *N. oleander* flower ethanolic extract [42]. Polysaccharide fraction was isolated from the hot water extract of flowers ofthis plant using ethanol precipitation, cetyltrimethyl ammonium bromide (CTAB) complexing, gelpermeation chromatography and anion exchange chromatography [25] (Figure 2).

Seed, bark and steem

The seeds contain glucosides (oleandrine, odorosides, adigoside). The bark alsocontains glucosides (rosaginoside, nerioside, corteneroside) and the roots contain steroids [27] reported two new compounds heptacosane-3-enyl-5-hydroxyhexanoate and 4-oxooctyl-2-hydroxyundecanoate were isolated from the stems of *N. oleander.*

Polyphenols in Nerium oleander

Few studies have focused on the phenolic fraction of *N. oleander*. It has been revealed that a high quantity of polyphenols is present in the leaves of *N. oleander* and the cinnamic acid was the major component and other components were epicatechine, catechin and chlorogenic acid. The total phenolics of *N. oleander* flower was 136.54 ± 3.32 mg gallic acid equivalent/g essential oil. The total phenolic content of water, methanol, water: methanol and acetone extracts of *N. oleander* leaves were 4.54 ± 0.23, 4.25 ± 0.23, 2.08 ± 0.38 and 4.21 ± 0.29 and of flowers were 7.52 ± 0.93, 7.15 ± 0.43, 6.24 ± 0.57 and 7.13 ± 0.49 µg gallic acid equivalent per 100 µg extract respectively (60). Kaempferol, kaempferol 3-O-β-glucopyranoside and chlorogenic acid were isolated from the ethyl acetate sub-extract of the *N. oleander* flower ethanolic extract [42].

Pharmacological properties

According to the literature, various parts of *N. oleander* have exhibited a range of biological and pharmacological activities *in-vitro* and *in-vivo* (Table 2).

Preventive measures

Poisoning and reactions to oleander plants are evident quickly, requiring immediate medical care in suspected or known poisonings of both humans and animals. The activated charcoal may be administered orally and the conduction defects can usually be managed with atropine and isoproterenol [65]. Anti-digoxin Fab fragments have been shown to be a safe and effective treatment for serious cardiac arrhythmias induced by yellow oleander. Administration of anti-digoxin antibodies can restore sinus rhythm and rapidly correct bradycardia and hyperkalemia. However, the lower affinity of digoxin-specific Fab for nondigoxin cardiac glycosides in oleander results in a larger dose requirement than forusual digoxin toxicity.

Figure 2 A). *Nerium oleander* leaves, **B).** Fruit **C).** Flowers, (https://www.toxiplante.fr, consulted on January 4, 2021).

Table 2: Pharmacological properties and biologicals activities of *Nerium oleander*.

Parts Used	Pharmacological Properties and Biologicals Activities/References
Leaves	Cardiotonic [43] CNS depressant effect, anticancér [44,45] antimicrobial [46], antifungal [47], Larvicidal activity [32], antihyperglycaemic [32], antioxydant, anti-inflammatory activities [26,48], antiviral activity [49], immunomodulating activity [35] antiproliferative activity [50,51], antidiabetic activity [52]
Flowers	Cardiotonic, root CNS-active and spasmolytic activity [31] antifungal [53] antimicrobial, Larvicidal activity [32,54], Antioxidant activity [55,56], anti-inflammatory activity, [35,57], anticancer activity [58,59] hepatoprotective activity [60]
Roots	Anticancer [61], anti-leprosy, anti-ulcer, antibactériens, cardiotonic, antioxydant, larvicidal [26,32] antifungal activities [47]
Barks	antimicrobial, antifungal, larvicidal activities [32,43]
stems	Antioxdant, larvicidal [26,32] antifungal [47] anticacer activities [61]
Different parts	The whole plant exhibited potent cardiotonic activity, digitalis like effect on EKG and heart lung preparation, antimalaria, antiviral [32,62] antimicrobial [10] anti-ulcer, antidote [31,63] antioxidant [59] insecticide [29] and as an antiparasitic [63] The whole plant has anticancer properties and its use in the treatment of cancer and found that they have been used against corns, warts, cancerous ulcers, carcinoma, ulcerating or hard tumours, diuretic effect [26,35,64] Nerium in Cosmetics: Nerium AD Age defying treatment- skin care range is known for its antioxidant properties. Two products are in range Nerium AD night cream and Nerium AD day cream. Primary ingredient is Nerium oleander in these preparations.These preparations are used for ageing and skin damage, hyperpigmentation, fine lines and wrinkles and uneven skin texture [31]. Abortive, as an abortifacient, antispasmodic and in the treatment of angina pectoris [32]

Conclusion and Future Application

Utilizing biotechnology research and new breakthrough extraction technology, *Nerium* is continuing to develop a complete line of products that harnesses *N. oleander's* unique and effective properties. Anti-aging skin creams are abundant in today's cosmetic marketplace. Future product development includes *nerium* AD Eye Cream Spot Cream, Skin Repair Cream, Blemish Cream and lots ofsuch products. According to the American Cancer Society, "even asmall amount of oleander can cause death", and "the effectiveness ofoleander has not been proven". *Nerium* is also effective in increasingthe CD4 counts of HIV-positive individuals with initial CD4 counts ofless than 400 in a meaningful way over a 60-day period. *N. oleander* aqueous extract as a novel anti-HIV therapeutic. This oleander is useful in future cancer and AIDS treatment. *Nerium*as environmentally safer and greener approach for mosquito controland other pest control measure in the future [66].

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