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PHYTOCHEMICAL AND PHARMACOLOGICAL POTENTIAL OF *NERIUM OLEANDER*: A REVIEW

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ABSTRACT

Nerium oleander L. is an important medicinal material in Chinese folk medicine. In early times it is assumed that all parts of the oleander plant are poisonous to humans, animals and certain insects but now a day's numbers of pharmacological activities are determined by different scientists. Its main active constituents are polysaccharides, cardenolides, glycosides, and triterpenoids. The important pharmacological activities are antinociceptive, anti-inflammatory, antibacterial, anticancer and CNS depressant activity. This paper explains the evidence-based information regarding the phytochemistry and pharmacological activity of this plant.

INTRODUCTION: *Nerium oleander* L. is a small evergreen tree of 2–5 m in height with a wide geographical and ecological distribution[1], and its certain parts are used as medicinal materials in Chinese folk medicine [2]. Oleanders are drought-tolerant evergreen plants of the Family *Apocynaceae* that originated from Mediterranean countries [3]. Two common oleanders are *Nerium oleander* and *Thevetia peruviana* (yellow oleander). All parts of the oleander plant are poisonous to humans, animals and certain insects [4]. *Nerium oleander* L shows terminal flower clusters that are available in different colors.

This species also produces secondary metabolites[5], some of which are of pharmacological interest. It is widely grown as an ornamental plant in warm temperate and subtropical regions, due to its abundant and long lasting flowering and moderate hardiness [6-7]. It is used for screens, hedging along highways, planting along beaches and in urban areas by removing suckers and leaving just a few stems, it can also be formed into very attractive small trees. In Northern regions it may be grown as an indoor or patio plant. Oleander has flexible branches with green, smooth bark eventually turning to dark grey.

Cut or broken branches exude a thick, white sap [8-11]. The leaves are 5 to 20 cm long, narrow, acuminated or acute in the apex, shortly petiolate, with a coriaceus dark-green blade. Some cultivars have white or yellow variegated leaves. Flowers are produced in terminal heads and their colors vary from deep to pale pink, lilac, carmine, purple, salmon, apricot, copper, orange, yellow and white [12]. Each flower is about 5 cm in diameter with five petals, although some cultivators have double flowers. The fruit consists of a narrow follicle 7.5 to 17.5 cm long which opens to disperse fluffy seeds. Oleander can be propagated by seed [13] but, being allogamous and highly heterozygous, it shows great variability in seedling populations.

Chemical Constituents: A water extraction of crushed leaves of *Nerium oleander* yielded 2.3% of a crude polysaccharide. The main fraction (67%) represents a pectic polysaccharide mainly composed of galacturonic acid besides rhamnose, arabinose and galactose [14]. Four new cardenolide monoglycosides, cardenolides N-1, N-2, N-3, and N-4, were isolated from *Nerium oleander*, together with two known cardenolides, and seven cardenolide monoglycosides [15]. Three new pregnanes, 21- hydroxypregna- 4, 6-diene- 3, 12, 20- trione, 20R-hydroxypregna-4,6-diene- 3, 12- dione , and 16beta, 17beta-epoxy- 12beta-hydroxypregna- 4, 6-diene- 3, 20- dione , were also found in *Nerium oleander*, together with two known compounds, 12beta- hydroxypregna- 4, 6, 16- triene-3,20-dione (neridienone A) and 20S, 21-dihydroxypregna- 4, 6- diene-3, 12- dione (neridienone B) [16].

Two new coumaryloxy triterpenoids, neriucoumaric and isoneriucoumaric acids have been isolated from fresh, undried and uncrushed leaves of *Nerium oleander* [17]. A new labdane diterpene, oleanderoic acid and a new triterpene, oleanderen have been isolated from the fresh, undried and uncrushed leaves of *Nerium oleander*. Their

structures have been established as 8alpha-methoxylabdan-18-oic acid, and 12-ursene, respectively, through chemical and spectral studies, including 2D-NMR (COSY-45, NOESY and 2D- J resolved) and (13) C-NMR data [18]. Two new cardiac glycosides, kaneroside and neriumoside, have been isolated from the fresh, undried, winter leaves of *Nerium 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 spectral studies [19]. Two new triterpenoids have been isolated from the fresh, uncrushed leaves of *Nerium oleander* and their structures elucidated as 3β, 27-dihydroxy- urs- 18- en- 13, 28- olide and 3β, 22α, 28-trihydroxy-25-nor-lup-1 (10), 20 (29)-dien-2- one[20]. The isolation and structure elucidation of two novel cytotoxic pentacyclic triterpenoids *cis*-karenin (3β-hydroxy-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) from the leaves of *Nerium oleander* is isolated[21].

Two new cardenolides, 3 beta-hydroxy- 5alpha- carda- 14 (15), 20 (22)-dienolide (beta- anhydroepidigitoxigenin) and 3 beta-O- (D- digitalosyl)- 21-hydroxy-5 beta- carda- 8, 14, 16, 20 (22)-tetraenolide (neriumogenin- A- 3 beta- D-digitaloside), and two known compounds, proceragenin and neridienone A, have been isolated from the roots of *Nerium oleander* [22]. New ursane-type triterpene 1, oleanane-type triterpene 2, and dammarane-type triterpene 15 were isolated from the leaves of *Nerium oleander* together with 12 known triterpenes, 3beta- hydroxy- 12- ursen-28- oic acid (ursolic acid, 3), 3beta, 27-dihydroxy- 12- ursen- 28-oic acid, 3beta, 13beta- dihydroxyurs- 11- en- 28- oic acid, 3beta- hydroxyurs- 12- en- 28- aldehyde, 28- norurs- 12- en- 3beta- ol, urs-12- en-3beta- ol , urs- 12- ene- 3beta,28-diol , 3beta- hydroxy- 12- oleanen- 28- oic acid (oleanolic acid), 3beta, 27- dihydroxy- 12-oleanen- 28- oic acid, 3beta- hydroxy-20 (29)- lupen- 28- oic acid (betulinic acid), 20 (29)- lupene- 3beta, 28- diol (betulin), and (20S, 24R)- epoxydammarane-3beta, 25- diol [1]. Two new taraxasterane- type triterpenes, 20 beta, 28- epoxy- 28alpha-methoxytaraxasteran- 3beta- ol and 20beta, 28- epoxytaraxaster- 21- en-3beta- ol, were isolated from an ethyl acetate extract of the leaves of *Nerium oleander*, together with ursane- type triterpenes, 28- nor- urs- 12- ene- 3 beta, 17 beta- diol and 3 beta-hydroxyurs- 12-en- 28- aldehyde [23].

Two new triterpenoid isomers alpha-neriursate and beta-neriursate have been isolated from the fresh, uncrushed leaves of *Nerium oleander* and their structures elucidated as 3alpha-acetophenoxy- urs- 12- en- 28- oic acid and 3beta-acetophenoxy- urs- 12- en- 28-oic acid, respectively [24]. Two new triterpenes, oleanderolic acid and kanerodione, have been isolated from the fresh, undried and uncrushed leaves of *Nerium oleander* and their structures established as 3β- *p*-hydroxyphenoxy-11α- methoxy- 12α- hydroxy- 20- ursen-28- oic acid and 28- hydroxy-20 (29)-lupen-3, 7-dione, respectively [25]. From the fresh, undried, and uncrushed leaves of

Nerium oleander a new triterpenoid, kanerocin, has been isolated along with known ursolic and oleanolic acids and its structure established through chemical and spectroscopic methods as 3 alpha-hydroxy- urs- 18, 20-dien- 28- oic acid [26]. From the leaves of *Nerium oleander* nucleotide bound D-sarmentose and D-diginose were isolated [27].

Four CNS depressant cardenolides including a new cardenolide, neridiginoside and three known constituents, nerizoside, neritaloside and odoroside- H, have been isolated from the leaves of *Nerium oleander* [28].The seed oil in *Nerium oleander* contains about 12% isoricinoleic acid (Δ9- hydroxy-18: $1^{\Delta 12}$) [29]. Polar glycosides from the air-dried leaves were re-examined, and gentiobiosyl-nerigoside and gentiobiosylbeaumontoside isolated along with the major trioside, gentiobiosyl-oleandrin. Minor triosides also include glycosides of 8β- hydroxy- and Δ^{16}- 8β-hydroxy- digitoxigenin, and Δ^{16}-neriagenin, along with glycosides of known cardenolides, oleandrigenin, digitoxigenin, adynerigenin, neriagenin and their Δ^{16}-derivatives [30].

The leaves and husk of *Nerium oleander* L. contains Heterosides: biosides and triosides [31-32]. *Nerium oleander* is a source of folinerin also [33]. The cardiac aglycones and glycosides of were separated from *Nerium oleander* flowers by thin-layer chromatography [34]. The leaves of *Nerium oleander* also contain ursolic acid [35]. The roots of *Nerium oleander* yielded a new cardenolide, 12β-hydroxy- 5β- carda- 8, 14, 16, 20 (22)-tetraenolide [36].

Pharmacological activity:

Antinociceptive activity: Ethanolic and aqueous extracts from *Nerium oleander* L. dried and fresh flowers and leaves, were shown to possess significant antinociceptive activity in varying degrees against p-benzoquinone-induced abdominal contractions in mice [37].

Anti-inflammatory activity: The ethanolic extracts of *Nerium oleander* dried and fresh flowers exhibited potent anti-inflammatory activity against carrageenan-induced hind paw edema model in mice without inducing any gastric damage [37].

Antifungal activity: Anti-mycotic activity of the ethanol extracts from Oleander (*Nerium oleander* L.) floral parts were screened in vitro against four important plant pathogenic fungi viz.; Alternaria alternate, Fusarium oxysporum, Fusarium solani and Rizoctonia solani using agar dilution bioassay. Extracts showed antifungal activity against all the tested fungi. Oleander possesses the best inhibition on F. oxysporum and F. solani [38].

Antibacterial activity: The roots of *Nerium oleander* yielded a new cardenolide, 12β- hydroxy- 5β- carda-8, 14, 16, 20 (22) - tetraenolide (**2**). Biological screening of the compound revealed antibacterial and digoxin-like cardiac activities [36].

Locomotor activity: Fresh, undried and uncrushed leaves of *Nerium oleander* were subjected to methanol extraction and bioassay directed fractionation. This

led to the isolation of two purified fractions namely, B-1 and B-3. Fractions B-1 and B-3 were studied with respect to their actions on the central nervous system and behavior pattern in mice. Both fractions were found to produce reduction in locomotor activity, rota rod performance and potentiation of hexobarbital sleeping time [39].

CNS depressant activity: A bioactivity directed isolation of the methanolic extract of the fresh, uncrushed leaves of *Nerium oleander* showing a central nervous system (CNS) depressant effect in mice has been undertaken. As a result, four CNS depressant cardenolides including a new cardenolide, neridiginoside and three known constituents, nerizoside, neritaloside and odoroside-H, have been isolated which exhibited CNS depressant activity in mice at a dose of 25 mg/kg [40].

Diuretic effect: Potable extract of *Nerium oleander* has significant diuretic activity [41].

Antileukemic effects: Concentrations of 1000, 500 and 50 microgram/ml from each extract possess marked antileukemic effects [42].

Immunomodulating activity: A water extraction of crushed leaves of *Nerium oleander* yielded 2.3% of a crude polysaccharide. The main fraction (67%) represents a pectic polysaccharide mainly composed of galacturonic acid besides rhamnose, arabinose and galactose. Investigation of immunomodulating activity brought some indications for mitogenic activity and a weak macrophage-mediated cytotoxicity [14].

Anticancer activity: The purpose of this study was to examine the mechanism(s) and differential cell-killing effects of Anvirzel, an extract of oleander (*Nerium oleander*; family- Apocynaceae), and its derivative compound Oleandrin on human, canine and murine tumor cells. Cells received different concentrations of Anvirzel (1. 0 ng/ml to 500 microgram/ml) or Oleandrin (0.01 ng/ml to 50 microgram/ml) in both continuously treated and pulse-treated/recovery cultures. The cytotoxicity of these compounds was then determined. Both Anvirzel and Oleandrin were able to induce cell killing in human cancer cells, but not in murine cancer cells; From these results we conclude that Anvirzel and Oleandrin act in a species-specific manner, and while testing the effectiveness of a new compound for cancer treatment, one must use not only murine but a variety of cancer cells, including those of human origin [43].

CONCLUSION: Major thrust by whole of the pharmaceutical industry is focused towards design and development of new innovative/indigenous plant based drugs through investigation of leads from traditional system of medicine[44]. In recent years, ethno-botanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. It is best classical approach in the search of new molecules for management of various diseases. Thorough screening of

literature available on *Nerium oleander* depicted the fact that it is a popular remedy among the various ethnic groups, Ayurvedic and traditional practitioners for treatment of ailments. Researchers are exploring the therapeutic potential of this plant as it has more therapeutic properties which are not known.

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