ABSTRACT

Sri Lanka. All parts of the plant are toxic and contain a variety of cardiac glycosides which includes nerine, oleandrin, cardenolides, gentiobiosyl and odoroside. This plant species also produce secondary metabolites such as alkaloids, flavonoids and steroids which have pharmacological applications. The important pharmacological activities are antibacterial, anthelmintic, anti-inflammatory, hepatoprotective, immunopotential, anti-pyretic, antioxidant, antifungal, anticancer and anti-HIV activity. This review describes the evidence-based information regarding pharmacological applications. The important pharmacological activities are antibacterial, anthelmintic, anti-inflammatory, hepatoprotective, immunopotential, anti-pyretic, antioxidant, antifungal, anticancer and anti-HIV activity. This review describes the evidence-based information regarding pharmacological activity as well as phytochemicals of this plant.

Keywords: Nerium oleander, Antibacterial, Pharmacological, Anthelmintic, Antioxidant

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INTRODUCTION

Nerium oleander is an evergreen shrub in the dogbane family Apocynaceae (fig. 1). It is the only species currently classified in the genus Nerium. It is commonly known as oleander, from its superficial resemblance to the unrelated olive Olea. It is widely cultivated and though to be originated from Southwest Asia. Oleander grows well in warm subtropical regions, where it is extensively used as an ornamental plant in landscapes, in parks, and along road sides. The oleander is most prevalent, and its alluring flowers make it a particular hazard for accidental ingestion [1]. The plant also has shown the toxicologic importance for accidents when used in folk medicines, in homicides or suicides [2]. All parts of the oleander plant contain cardiac glycosides, including the roots and the smoke produced from burning, as heat does not inactivate the glycosides. This plant is known by many names throughout the world which includes Adelfa, Baladre, Cascabela thevetia, Cerbera thevetia, Common Oleander, Exile Tree, Huang Hua Jia, Jia Zhu Tao, Kaner, Karvir, Karvira, Laurel Rosa, Laurier-Rose, Laurier Rose, Laurose, Nérier à Feuilles de Laurier, Néron, Nierium indicum, Nerium Oleander, Nerium odorum, Oleander blatter, Oleandrea, Oleandri folium, Rose Bay, Rose Laurel, Sweet Scented Oleander, Thevetia nerifolia, Thevetia peruviana, Yellow Oleander.

Fig. 1: Nerium oleander L. plant in a flowering condition

Nerium oleander has historically been considered a poisonous plant because some of its compounds exhibit toxic effect, especially to animals, when consumed in high amounts. Ingestion of this plant can affect the gastrointestinal system, the heart, and the central nervous system. Some invertebrates are known to be unaffected by oleander toxins and feed on the plants. Caterpillars of the polka-dot wasp moth (Symptema epilais) feed specifically on oleanders and survive by eating only the pulp surrounding the leaf-veins, avoiding the fibres. Larvae of the common crow butterfly (Euploea core) also feed on oleanders, and they retain or modify toxins, making them unpalatable to would-be predators such as birds, but not to other invertebrates such as spiders and wasps. Despite the danger, oleander is of great medicinal importance and used for heart conditions, asthma, epilepsy, cancer, painful menstrual periods, leprosy, malaria, ringworm, indigestion, and venereal disease; and to cause abortions, as well as drugs derived from this plant, is used in treatment of cancer and the research is ongoing for its future implementation.

Chemical constituents

The plant contains a number of related cardiac glycosides similar in activity to digitalis [3]. The main glycosides are oleandrin, nerine, Cardenolides, gentiobiosyl, oleandrin and odoroside are also present [4]. In addition, a variety of other pharmacologically active compounds, including folinierin, rosagmin, rutin and oleandmycin, have been identified in the plant.

In leaves, two new cardenolides, 3 beta-O-(D-2-O-methyl-digitalosyl)-14 beta-hydroxy-5 beta-Carda-16,20 (22)-dienolide (1) and 3 beta-hydroxy-8,14-epoxy-5 beta-Carda-16,20 (22)-dienolide (2), and two known cardenolides, 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-16 beta-acetoxy-5 beta-carda-20 (22)-enolide (3) and 3 beta-O-(D-digitalosyl)-14 beta-hydroxy-5 beta-carda-20 (22)-enolide (4), have been isolated [5].

Four CNS depressant cardenolides including a new cardenolide, neridiginoside and three known constituents, nerizoside, neritaloside and odoroside-H, have been isolated which showed CNS depressant activity. The structure of neridiginoside was elucidated as 3 beta-O-(D-diginnosyl)-5 beta, 14 beta-dihydroxy-carda-20 (22)-enolide [6]. A polysaccharide fraction, NIB-2, was obtained from the 3% aqueous sodium carbonate extract which was composed of rhamnose, arabinose, galactose, in the ratios of 1.0:10.4:4.4, along with 4% of galacturonic acid. 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 arabinofuranosyl residues, and a small proportion of galactosyl...
residues at the termini. 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), 3beta,27-dihydroxy-12-ursen-28-oic acid, 3beta,13beta-dihydroxysurs-11-en-28-oic acid, 3beta,28-norurs-12-en-3beta-ol, 3beta,28-norurs-12-en-3beta-ol, urs-12-ene-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) [7].

Two new taxasterane-type triterpenes, 20beta,28-epoxy-28 alpha-methoxytaxasteran-3beta-ol and 20 beta, 28-epoxytaxaster-21-en-3beta-ol, were isolated from an ethyl acetate extract of the leaves of *Nerium oleander*, together with ursane-type triterpenes, 28-norurs-2-ENE-3beta-17beta-diol and 3beta-hydroxysurs-12-en-28-aldehyde [8]. Hot-water extract of *N. Indicum* leaves yielded 3-O-cafeoylquinic acid (chlorogenic acid) and its structural isomer, 5-O-cafeoylquinic acid. Both compounds were shown to inhibit alpha-glucosidases in a non-competitive manner and thus were anti-hyperglycemicas [9].

Three nematocidal cardenolides were obtained from the AcOEt extract of *Nerium indicum* Mill. By bioassay-guided fractionation. They include a new compound, 3 beta-O-[(beta-D-diginosyl)-14, 15 alpha-monoglycerides, cardenolides B-1 and B-2 were isolated from *Nerium oleander*, together with oleanogenin which is the first isolated compound from natural sources. The structure of compounds were established on the basis of their spectroscopic data [11].

**Ethnomedicinal value**

A decoction of the leaves has been applied externally in the treatment of scabies and to reduce swellings. Bark is bitter and is used as cathartic, febrifuge and intermittant poison. Oil prepared from the root bark is used in the treatment of leprosy and skin diseases of a scaly nature. Seeds are used as a purgative in dropsy and the root bark is used in the treatment of leprosy and skin diseases, especially to animals, when consumed in high amounts. The entire plant contains toxic cardiac glycosides. The highest levels of these compounds are oleandrin and oleandrigenin, known as "cardiac glycosides" which are known to have a narrow therapeutic index and are toxic when ingested. Symptoms of oleander toxicity include pain in the oral cavity, nausea, emesis, abdominal pain, cramping, and diarrhoea.

**Toxicity**

*Nerium oleander* has historically been considered a poisonous plant based on a number of its compounds that may exhibit toxicity, especially to animals, when consumed in high amounts. The entire oleander plant contains toxic cardiac glycosides. The highest levels are found in the roots and seeds. Even smoke from the plant and water in which the plant has been immersed can be toxic. Among these compounds are oleandrin and oleandrigenin, known as "cardiac glycosides" which are known to have a narrow therapeutic index and are toxic when ingested. Symptoms of oleander toxicity include pain in the oral cavity, nausea, emesis, abdominal pain, cramping, and diarrhoea.

Birds, there is a little 0.12 to 0.7 g of the plant has caused death [21]. Toxicity studies conducted [22] on animals concluded that the rodents were observed to be relatively insensitive to oleander "cardioactive glycosides" whereas other mammals, such as dogs and humans, are relatively sensitive to the effects of cardiac glycosides [23, 24]. The death of a woman who self-administered "an undefined oleander extract" both orally and rectally and her oleandrin tissue levels were in the high range of reported levels at autopsy [25]. The death of a woman who ingested oleander "tea" [26]. The cardiac glycosides may induce conduction defects among which most common were defects affecting the sinus or AV nodes with PR.
interval prolongation and progression to atrioventricular dissociation and systemic hyperkalemia induced by the plant may worsen cardiac function [27].

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 [28]. 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 for usual digoxin toxicity.

*Nerium oleander* in applied science
*Nerium oleander* (containing oleandrín and other cardiac glycosides) was administered orally to 46 cancer patients where doses explored included those from 0.2 mg to 10.2 mg extract/day. These doses were administered daily in cycles consisting of 21 out of every 28 d. The researchers concluded that PBI-05204 was “well tolerated up to the 10.2 mg extract/day dosage” with few significant side effects and with evidence of tumor response. There does not appear to be any toxicity associated with exposure of a *Nerium oleander* extract to the skin. Both animals [29] and human [30] studies suggest that dermal application of *Nerium oleander* extract is safe indicating that these compounds are not readily absorbed through the skin. This clearly indicates that the extracts of this plant can be safely used not only for controlling pests but also can improve the immunity system of the insects of interest at a lower dose.

The unique properties of *Nerium oleander* also provide a remarkable age-defying result when applied to the skin. This finding led to the formation of *Nerium* International and the creation of the *Nerium* AD skin care line. *Nerium* scientists developed a breakthrough process, NBio-PL2, to derive an extract from the *Nerium oleander* plant in a way that preserves its unique and beneficial properties. This patented extraction process yields the NAE-8 extract, with powerful antioxidant properties, used to formulate the first-of-its-kind, age-defying *Nerium* product line.

The National Cancer Institute has defined oleandrín, one of the principal glycosides in *Nerium oleander* as “A lipid-soluble cardiac glycoside with potential antineoplastic activity”. Cancer research at The University of Texas has demonstrated that components of Anvirzel™ are active on dual pathways at the cellular level to promote apoptosis and/or autophagy (cell death) in human tumors, but not normal cells and blocks activation of a potent signal (NF-kb) that leads to tumor cell proliferation and metastases.

Future application of *Nerium oleander*
Utilizing biotechnology research and new breakthrough extraction technology, *Nerium* is continuing to develop a complete line of products that harnesses *Nerium 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 of such products. According to the American Cancer Society, “even a small amount of oleander can cause death”, and “the effectiveness of oleander has not been proven”. *Nerium* is also effective in increasing the CD4 counts of HIV-positive individuals with initial CD4 counts of less than 400 in a meaningful way over a 60-day period. *Nerium oleander* aqueous extract as a novel anti-HIV therapeutic. This oleander is useful in future cancer and AIDS treatment [31]. *Nerium* as environmentally safer and greener approach for mosquito control and other pest control measure in the future [17].

CONCLUSION
From the review of the existing work it was concluded that *N. oleander* has been used in the treatment of various diseases and shows antancer and antitumor properties as well as acts as a novel anti-HIV therapeutic. In recent years, ethnobotanical 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 the best classical approach in the search of new molecules for management of various diseases. Various bioactive compounds isolated from different parts of this plant. So, it is an utmost of importance to explore its potential in the field of medicinal and pharmaceutical sciences for novel application. As *N. oleander* is a popular remedy among the various ethnic groups, this plant is used in Ayurvedic and traditional medicine. So further or more work is needed to investigate the therapeutic potential of this plant.

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AUTHOR CONTRIBUTION
Both the authors contributed equally to the review work.

CONFLICTS OF INTERESTS
All authors have none to declare.

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