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An Overview of the Toxic Effects of Oleander in Humans

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ABSTRACT

Nerium oleander, commonly known as oleander, is an important medicinal plant in Indian traditional medicine. It is one of the best pharmacognostic available in now-a-days. The modern as well as traditional uses make this plant much more valuable. Oleander is produced recently in pots and hence, large scale propagation of plant material for commercial uses has great importance. This plant species also produce secondary metabolites such as alkaloids, flavonoids and steroids which have pharmacological uses. The important pharmacological activities are antibacterial, larvicidal, anticancer, antidiabetic activities.

Keywords: *Olender, poisoning, human.*

INTRODUCTION

Plant poisoning is one of the most important issues in clinical toxicology. Plant toxicity is common, especially in children under the age of 5 years and is considered as one of the causes of poisoning at this age (1). In terms of prevalence, according to data published in the United States, about 5 to 10 percent of all reported cases of toxicogenic control centers in the country constitute plant poisoning (2).

Between 1990 and 1998, more than 17695714 cases of contact and consumption with toxic plants were reported to poison control centers in the United States. In terms of classification, the factors causing poisoning of plants in terms of prevalence in the fourth row after detergents, analgesics and substances artificial cosmetics (1). Yahan is considered as the main agent of illness and seduction, including the causes of plant toxicity in adults. The statistics of drug information centers and poisons in Iran inform that poisoning with plants and herbal medicines is wide spread among common people (3).

During many years, natural medicines, especially medicinal plants, were the base and, in some cases, the only treatment, while the raw materials used in the pharmaceutical industry were used. In the beginning of the century, the advancements in chemistry and the discovery of complex systems of organic synthesis led to the development of the pharmaceutical industry and the replacement of chemotherapy. In this way, modern medicine managed to treat many undefined and dangerous diseases, for example infectious diseases treated with sulfanamides, antibiotics and other chemical compounds.

However, the herbal medicines and their medical effects are never completely abandoned. Effective raw materials stored in plants are used continuously as non-replaceable materials. Also, human medicine and perfumery never stopped using these materials and have always passed traditional medicine in the form they inherited from their ancestors and forefathers.

Over time, the number of known medicinal plants was increased and the scope of their applications became wider. The discovery of new plants from far lands, the achievement of new applications as auxiliary drugs in chemical treatments or antibiotics, the discovery of new medical products such as vitamins, hormones, anti-infectious substances Microbial, antiviral, antitumor us among known plants or recently discovered plants have once again helped in the advancement of herbal medicine.

In the new era of pharmaceutical industry, physicians and research groups in many countries re-focused their attention to natural resources and medicinal plants, so today we see

extensive experimental farms. We are producing them; the cultivation of medical plants is now regarded as an important branch of agriculture to extract and produce the raw materials used for treatment. Considering the above mentioned cases, it is observed that even nowadays our attention to medicinal plants and effects of application and their uses are not completely discontinued.

Toxic Effects of Plants on the Organs of the Body

It should be considered that most of the plant poisoning has a wide range of symptoms, and most often, especially in poisoning with plants that contain specific toxins, several organs of the body are involved. Therefore, during treatment, attention should be paid to all symptoms of poisoning and measures should be taken to eliminate them.

Cardiovascular System

There are many types of plants that, if consumed in toxic quantities, have effects on the cardiovascular system along with other symptoms in the body.

Oleander

Pearl is an effective herbal medication in Chinese, Egyptian and Greek treatment regimens. Today, the pharmacological activities of this plant are determined by scientists, the main active ingredients of the plant include: Triterpenoids, a and Glycosides, Cardenolides (4). The extracted compounds of this plant have different levels of analgesia in mice, as well as ethanolic compounds extracted from the flowers of this plant have strong anti-inflammatory activity in mice (5). The main venom of this plant which more studies are carried out is a combination of Neuvalendr in.It is present in all parts of the plant and oleander in that is colorless, odorless and very bitter with the molecular formula C42H48O9, and is insoluble in water and alcohol, it is completely resistant to heat, but against the light is very sensitive.

The Importance of This Plant Includes Anti-Activity

Different chemical compounds are used to make drugs for the treatment of various diseases. One of these drugs is Anvirzel which is a blue compound extracted from the herb, containing two polar and nonpolar compositions. Anvirzel contains Oleandrine as a major cytotoxic agent. It has pharmacologic activity against human cancer cells, in addition to its activity in inhibiting the activity of Na K ATP ase, it induces apoptosis in cancer cells (6).

Chemical Constituents

The most well-known effects of oleander are due to two glycosides, neriin and, and an alkaloid, oleandrin which have a cardio stimulatory action (7) and to the glycosides gentiobiosyloleandrin, gentiobiosyl-nerigoside and gentiobiosyl-beaumontoside extracted from the leaves (8). Oleander is also diuretic and lenitive on dermatosis and contusion (9). In addition, its lymph is rich of minerals (10) and α-tocopherol, an important antioxidant (11).

Adyregenin is a compound with no cardiac effect. There are also weakly active cardenolides (heterosides of uzarigenine) and inactive cardenolides (heterosides of adynergenine, of digitalose), triterpenoids,a resin, tannins, glucose, a paraffin, ursolic acid, vitamin C and an essential oil. The seeds contain glucosides (oleandrine, odorosides, adigoside). The bark also contains glucosides(rosaginoside, nerioside, corteneroside).The roots contain steroids.

Anti –Bacteria Activity

The study of Mali showed that the ethanolic extract of Nerium oleander leaves has highest antibacterial action against Pseudomonas aeruginosa at 900mg/ml concentration, whereas, Nicoti anatabacum showed maximum zones of inhibition against Staphylococcus aureus at 900mg/ml concentration.

The results showed that the leaves extracts of these plants have great power as anti-microbial agents against these common bacterial isolates (12).In a study by Namian et al., The results showed that the minimum inhibitory concentration methanolic extract of E. coli, E. carotovora, S. epidermidis, S. aureus, B. cereus, B. pumillus was 0.025, 0.0015, 0.025, 0.025, 0.025, and 0.025 mg / ml Respectively (13). In the study of McRae et al., The antimicrobial effect of Nerium oleander on Salmonella typhi and Listeria monocytogenes was investigated. The results showed that in the agar diffusion method, all of the concentrations of ethanolic extract of Herbosa wort had an inhibitory effect on Salmonella typhi. However, the inhibitory effects of its ethanolic extract were higher than of the aqueous extract. The minimum inhibitory concentration of ethanol extract was 128 mg / ml and the minimum drainage concentration was 256 mg / ml; both the aqueous and ethanolic extracts of this plant did not affect the standard strain of Listeria monocytogenes (14).

The study of Hussain, the invitro antimicrobial activity of Nerium oleander roots bark and leaf extracts were studied against Bacillus pumilus, Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Aspergillus niger. The chloroform, ethanol and methanol extracts of Nerium oleander showed high activity against all the tested bacteria. None of the crude extracts of the selected plant showed activity against Aspergillus Niger. These results were compared with the Zones of inhibition produced by commercially available standard antibiotics. The inhibitory effects of extracts are very close and identical in magnitude and are comparable with the standard antibiotics used (15).

The study of Bhuvaneshwari, analyse its phyto chemical constituents in solvents like Benene, Chloroform and Alcohol and to screen its antibacterial activity. The dried leaf sample is extracted with solvents by cold maceration. The phytochemical analysis showed the presence of Alkaloids, Terpenoids, Cardiac glycosides, Saponins, Tannins & Carbohydrates in all the solvents. All the extracts were screened for antibacterial activity by Disc Diffusion Method. Out of the cultures used Staphylococcus aureus, Pseudomonas aeruginosa and Salmonella typhimurium showed better zone of inhibition which is 10mm, 9mm & 7 mm respectively (16).

In most of the cases the leaves of the plants have reported to contain more phyto constituents than any other part of the plant. The presence of metabolites in these plants is more concentrated that's why this indicated that they contain more active metabolites. So it was the best reason to choose the leaves of these plants (17). While at the concentration of (900, 500mg/ml) N. oleander showed different zones of inhibition which were 22mm and 13mmrespectively against Staphylococcus aureus as also observed by Wong et al. (2013).According to the report of Jeyachandran et al. (2010) the methanolic extract of Nerium oleander had maximum zone of inhibition (28mm) against S. typhi(18).

Anti-Fungal Activity

The study of Hadizadeh showed antifungal activity against all the tested fungi. Among the plants, Nettle and Colocynth were the most effective against A. alternate and R. solani while Oleander shows the best inhibition effect on F. oxysporum and F. solani. Konar was the most effective extract by reducing the growth of Rizoctoniasolani than other fungi. These results showed that extracts could be considered suitable alternatives to chemical additives to control the fungal diseases in plants (19). Siddiqui screened for antifungal activity against three economically important fungi Macrophomina phaseolina, Sclerotium rolfsii and Fusarium oxysporum. Chloroform root extract has reduced the growth of the fungi to its maximum, 2.03 followed by acetone root extract respectively.

Leaves chloroform extract displayed the best antifungal activity thus giving a colony diameter of 1.43 in S.rolfsii followed by methanol, acetone, and ethanol leaves extracts. In F. oxysporum trend has entirely changed, shoot induced the maximum effect as the diameter of the fungal colony was 0.37 in acetone; this trend was followed by chloroform and ethanol shoot extracts respectively (20).

Anti-Virus Activity

Ethno pharmacology provides an alternative path in the present antiviral therapy to fight against various virus borne diseases. Various polyherbal formulations and bioactive compounds isolated from the plants have demonstrated potent antiviral activity. Singh *et al*. (21) studied the effect of an aqueous extract (Anvirzel™) of the plant on HIV infectivity in human peripheral blood mononuclear cells. They have demonstrated that without any alteration in the total number of virus particles, Anvirzel™ reduced the HIV ability to infect new cells.

Oleanderin, which is a cardiac glycoside isolated from the leaves, down-regulated HIV coat protein g120 expression, which is the primary mediator of HIV infection. Low concentration of Anvirzel™ (10 µg/ml) was enough to inhibit the HIV infection abilities. Rajbhandari *et al*., (22) demonstrated that the methanolic extract of *N. indicum* shows potential effects against influenza virus and herpes simplex virus. The extract showed inhibitory concentration 50 (IC50) values of 10 µg/ml against the influenza virus.

Malaria Activity

Sharma *et al*., have studied the larvicidal activity of ethanol and acetone extracts of the plant by investigating efficiency of these extracts on the 3rd in star larvae of two malaria causing vectors *Anopheles stephensi* and *Culex quinquefasciatus* (23). The ethanolic extract was proved to be more potent than the acetone extract against *A. stephensi* and vice versa against *C. quinquefasciatus* after 24 and 48 h. Lethal concentration 50 value of the ethanolic

extract on *A. stephensi* was 185.99 ppm (24 h) and 184.05 ppm (48 h), whereas on *C. quinquefasciatus* was 494.07 ppm (24 h) and 194.49 ppm (48 h). In case of acetone extract, the lethal dose 50 (LD50) value was 229.28 (24 h) and 149.43 (48 h) for *A. stephensi* and 209.00 ppm (24 h) and 155.97 ppm (48 h) for *C. quinquefasciatus*.

Anti- Cancer Activity

The study of Pathak examined 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 microg/ml) or Oleandrin (0.01 ng/ml to 50 microg/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; the cell-killing potency of Oleandrin was greater than that of Anvirzel. Canine oral cancer cells treated with Anvirzel showed intermediate levels of response, with some abnormal metaphases and cell death resulting from the treatment. 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 (24).

The study of Mekhail reports a phase 1 trial to determine the maximum tolerated dose (MTD) and safety of Anvirzel in patients with advanced, refractory solid tumors. Patients were randomized to receive this agent by intramuscular injection at doses of 0.1, 0.2, 0.4 ml/m2/day with subsequent patients receiving 0.8 or 1.2 ml/m2/day sequentially. Eighteen patients were enrolled and completed at least one treatment cycle of three weeks. Most patients reported mild injection site pain (78%) (25) Antitumor activity of this novel plant extract, the relative abilities of oleandrin and oleandrigenin to inhibit FGF-2 export from two human prostate cancer cell lines, DU145 and PC3, were examined (26).Anvirzel and Oleandrin are extracts of oleander induce cell death in human cancer cells (27). Toxicity of Nerium oleander (28). The aqueous extract of Nerium oleander L. has been undergoing clinical investigations as an anticancerous agent. Oleandrin and its aglycone oleandrigenin are the active compounds that are isolated from this plant which shown to have anticancerous properties. Anvirzel has also revealed cytotoxicity in human tumor cell lines with evidence of apoptosis as a principal mode of cell death (29).

Ali and co-workers were able to extract essential oil from the flowers of the oleander. It showed antitumor activity on the cell lines, Ehrlich Ascites Carcinoma (EAC). Pathak et al. used different amount of Anvirzel (1.0 ng.ml-1 to 500 microgram.ml-1) or Oleandrin (0.01 ng.ml-1 to 50 microgram.ml-1) in both continuously treated and pulse-treated/recovery Cell cultures. Both Oleandrin and Anvirzel were able to induce cell killing in human cancer cells, but not in murine cancer cells (32).

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