OLEANDER: AS PROTAGONIST AND ANTAGONIST

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ABSTRACT

Herbal products have been utilized by populations to cure and prevent diseases throughout history; however, the quality and safety of these herbal products has now become a serious issue because several cases of intentional self-harm and accidental ingestion have been reported from across the world. Due to scarcity of well documented case reports, cardiac toxicity is a statistically uncommon phenomenon. Oleander plant is draught tolerant ornamental plant. It contains polysaccharides, glycosides and titerpenoids. The parts of plant are used as traditional remedy in various diseases. This species also produces secondary metabolites some of which are of pharmacological interests. This review paper is evidence based information regarding the toxicity and pharmacological activity of this plant.

KEY WORDS: Herbal products; poison; cardiac glycosides; oleander; cardiac toxicity.

INTRODUCTION

From the past few decades there has been a dramatic increase in use of plant product in preparations throughout the industrialized world. According to World Health Organization 70-80\% of the populations rely on non-conventional medicinal sources such as herbal in their primary health care, there has increased growth of popularity of medicinal products or other natural sources.\textsuperscript{[1]} Medicinal plants have been used by human beings from time immemorial for healing different ailments. This practice still continues, even after the advent of modern allopathic medicine.\textsuperscript{[2]} It is essential to take cognizance of the fact that overuse or abuse of medicinal constituents of plants can cause danger.\textsuperscript{[3]} Plants containing glucosides, acids or alkaloids are used as medicines, and the latex white or colored sap found in families of
Apocynaceae, Asclepiadaceae, Sapolaceae, Euphorbiaceae and Papaveraceae, if used in excess always act as poison.\textsuperscript{[4-10]}

A poison is a substance which, when administered, inhaled or ingested, is capable of acting deleteriously on human body. Thus, there is a very thin limit, for a medicine in a large dose is a poison and a poison in a small dose may be a medicine means, it depends on dose/quantity only. In law, real difference between a medicine and a poison is the intent with which it is given. If the substance is given with the intention for betterment of life, it is a medicine but if it is given with the intention to cause bodily harm, it is a poison.\textsuperscript{[11]} It is fact that almost any substances can be harmful at high concentration- as Paracelsus (1493-1541), the father of toxicology, “Everything is a poison and there is poison in everything, only dose makes a thing not a poison.”\textsuperscript{[12]}

Throughout the human history, intentional application of poison has been used as a method of assassination, murder, suicide and execution. Poison includes both naturally produced compounds and chemicals manufactured by humans. Natural poisons are produced by species of bacteria, fungi, protists, plants and animals. Poisonous plants are those which cause serious problems, even death occur, if a small quantity of its stem, leaves, seeds, fruits and roots are ingested.\textsuperscript{[13]} Other plants are normally harmless but they may become toxic if preparative from them are taken in excess in strong doses or for a long period of time.\textsuperscript{[14]} Poisonous plants have played so large part, in romance as well as crime, that the subject is one which claims the attention of even student of human nature.\textsuperscript{[15]}

Ancient Egyptians and Romans first used plants containing cardiac glycosides medicinally as emetics for heart ailments. Therapeutic use of herbal cardiac glycosides continues to be a source of toxicity today. It has been also found in Chinese and Asian herbal products being a source of human toxicity. But the growing series of case reports indicate that cardiotoxicity is an important factor in morbidity and mortality associated with the products.\textsuperscript{[16]}

An analysis of Johannesburg forensic database over the years 1991-1995 revealed 206 cases where traditional remedy was either stated to be the cause of death or was found to be present in a case of poisoning with an unknown substance. The range of toxins detected was wide, with herbal materials being found in 43\% of cases, half of these cases involved the use of herbal cardiac glycoside.\textsuperscript{[17]}
While the clinical recognition, even quantity appraisal of congestive heart failure is a matter of routine in practice of medicine, no precise definition of this state has been formulated which is equally satisfactory to clinicians, physiologists and pathologists. When the circulation is affected, it is not necessary that there is some major or primary defect is present in cardiac function. But there may be change in cardiac output, blood volume, sodium retention, and diastolic heart volume, mechanical efficiency of the heart, peripheral venous pressure, intra-cardiac pressures and peripheral vasomotor reactions.[18]

Cardiac glycosides primarily affect cardiovascular, neurologic and gastrointestinal systems. Glycosides are sugar derivatives and aglycones or genins, the nonsugar complement, are generated when the sugar moiety is detached; in cardiac glycosides, or cardenolides, which bear a structural resemblance to steroid saponins, the aglycones are distinguished from other steroids by structural features that impart cardiotoxic properties.[19]

Cardenolides are composed of an aglycone that stems from plants terpenoid metabolism and may or may not be glycosidically bound to one or more sugars. The aglycone has a typical steroid structure comprising a four membered ring system while the sugars may often be idiosyncratic for specific cardenolides.[20]

Cardenolides are members of a larger group, the cardiac glycosides, that comprises two classes of compounds which differ in the structure of their aglycone: cardenolides have a five membered lactone group in β position at c17,[21] cardenolides occur in total of 12 families.[22] They are most prominent in the Apocynaceae (now including the Asclepiadaceae,[23] yet the occurrence in the genus Digitalis among the Scrophulariaceae is for medical reason very renowned.[22,24] Being mostly polar compounds, cardenolides are predominantly stored in the cell vacuole[25] and may occur in all plant tissues.[22] Given the widespread yet erratic distribution in just some genera per plant family (with exception of the Apocynaceae) cardiac glycosides are a convergent evolution.[20]

Although mostly recognized as a typical plant compounds cardenolides may also be produced via the cholesterol pathway in animal tissues.[21,26,27] Over the last 3 decades, evidence has accumulated that cardiac glycosides are actually mammalian hormones found in blood plasma, the adrenal cortex and the hypothalamus. They regulate blood pressure, cardiac, kidney function, salt mechanism, also cell proliferation and cell half-life. Structurally these endogenous cardiac glycosides comprise two cardenolides, ouabin and digoxin, that are
identical to plant produced compounds. \[^{28}\] This suggests that plant producing cardenolides are actually synthesizing hormone analogs.\[^{20}\]

To humans cardenolides are bitter tasting compounds depending on their polarity and structure. In mammals, a chemoreceptor trigger zone in medulla is responsible for induction of vomiting at concentrations below toxic doses. Other effects including headache, altered vision, psychosis and hormonal effects have also been described in humans.\[^{24}\] While the mechanisms leading to these symptoms are still hard to trace, the immediate toxic effect of ingested cardenolides is simple and well understood. The primary mode of action of cardenolides is the inhibition of Na\(^+\)/K\(^+\) - ATPase, or sodium pump. This transmembrane ion-motive ATPase is responsible for the maintenance of membrane potentials that drive secondary transport mechanisms and enable the generation of action potentials in nerve cells. During each cycle of Na\(^+\)/K\(^+\) - ATPase one molecule of ATP is hydrolysed and the energy is used to translocate three Na\(^+\) ions to extracellular side in exchange for two K\(^+\) - ions that are shuffled into the cystol.\[^{29-31}\]

The structure of heterodimeric Na\(^+\)/K\(^+\) - ATPase is highly conserved in animal kingdom: a catalytic α-subunit with ten transmembrane domains forming five extracellular loops interacts with a small heavily glycosylated β-subunit that crosses the membrane only once. In addition a regulatory γ-subunit may or may not be present. Cardenolides reversibly bind to the α-subunit from extracellular side and lock it in its phosphorylated E2-P conformation, thereby disrupting ion translocation.\[^{29}\] The pharmacological effect of cardenolides in humans used in the treatment of heart insufficiencies is an increased level of intracellular Na\(^+\) that secondarily leads to elevated intracellular Ca\(^{2+}\) levels by Na\(^+\)/Ca\(^{2+}\) exchange. This increased intracellular Ca\(^{2+}\) concentration triggers the release of excess Ca\(^{2+}\) from the sarcoplasmic reticulum by a cascade presumably involving the inositol-triphosphate receptor the Ca\(^{2+}\) - ATPase and finally results in an increased strength of heart contraction.\[^{28}\] Even before the existence of endogenous cardiac glycosides in mammals could be proven it had been speculated that this kind of regulation of blood pressure and heart contraction may be the true reason for the highly conserved cardenolide binding site and that endogenous cardenolide like substances await discovery.\[^{32}\] By now the existence of endogenous cardiac glycosides is firmly established\[^{33-35}\] and evidence for additional signaling cascades triggered by the docking of endogenous cardiac glycosides to the Na\(^+\)/K\(^+\) - ATPase have emerged.\[^{28}\]
Exposure of humans and different domestic animals to oleander cardenolides are common in plant growing regions. Oleander poisoning is clinically well-documented, and has been profusely used in suicide, homicide as well as abortifacient. This plant is highly toxic since all parts contain several potent glycosides with digoxin-like activity.

Most of the cases reported in past few decades have history of poisoning through; seeds, leaf extract and flower poisoning were observed to be fatal, in few cases patients were saved by activated charcoal, Digitoxin specific Fab antibody fragments and atropine sulphate.

Nerium oleander is small evergreen tree of 2-5m in height. Two common species-Nerium oleander Linn. and Thevetia peruviana belongs to the Dogbane family, Apocynaceae are drought tolerant evergreen plants. Nerium oleander L. is distributed in Mediterranean region, subtropical Asia, South western United States, is indigenous to Indo-Pakistan subcontinent. This species is often grown in gardens as ornamental plants due to its abundant and long-lasting flowering and moderate hardiness and its certain parts are used as medicinal materials in Chinese folk medicine. Whole plant is poisonous to humans, animals and certain insects and in some parts of the world they are considered noxious weeds. Oleander is an evergreen shrub or small tree; with diffusely branched and dense-crown, it has flexible branches with green, smooth bark eventually turning grey. The leaves are 5-20 cm long narrow, acuminated or acute in the apex, shortly petiolate, with coriaceous dark-green and shining above, midrib stout, nerves numerous, spreading horizontally. Leaves are linear-lanceolate, leathery and dark green to grey green, with distinct yellowish veins. Some cultivators have white or yellow variegated leaves. Oleander shows terminal flower clusters that are available in different colors and their color vary from deep to pale pink, lilac, carmine, purple, salmon, apricot, copper, orange, yellow and white. Flower is about 5 cm in diameter with 5 petals, although some cultivators have double flowers. The fruit consists of narrow follicle 7.5 to 17.5 cm long, rigid at length separating fleshy, triangular drupe, green turning yellow and then black which opens to disperse fluffy silky haired seeds. Calyx-lobes lanceolate, corolla-3.8 cm diameter, filaments hairy, appendages of anthers twice as long as cells. The sap is thick, gummy and milky white. Oleander can be propagated by seed but, being allogamous and highly heterozygous, it shows great variability in seedling populations. Variety identification is mainly based on flower color and shape, but other discriminating characters are presence of...
foliage variegation and growth habit. The plant is commonly known as ‘kaner’ and its various parts are reputed as therapeutic agents in treatment of swellings, leprosy, eye and skin diseases.\textsuperscript{[44,73-75]} Although dismissed from modern pharmacopoeias, preparations of oleander have been used for centuries as rodenticides and insecticides, as well as folk remedies for indigestion, malaria, leprosy, mental or venereal diseases, or as abortifacients.\textsuperscript{[76]}

**Table 1: Studies performed on different animals.**

<table>
<thead>
<tr>
<th>Author Subject (animal)</th>
<th>Dose and died in duration</th>
<th>Symptoms</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz\textsuperscript{[77]} Monkey</td>
<td>0.30g/kg Died in 2-4hr</td>
<td>Vomiting, salivation, polyuria, bradycardia, vaginal hemorrhage, abortion, anorexia, constipation, narcosis, restlessness, weakness, shallow and rapid respirations</td>
<td>Haemorrhages, degeneration or necrosis were observed in heart, gastrointestinal tract, skeletal muscles, ovaries, adrenal glands, liver, kidneys, pancreas. The organ weight of pancreas were reduced. Significant increase in weight of adrenal glands was probably manifestation of compensatory hyperplasia.</td>
</tr>
<tr>
<td>Reid Hanson\textsuperscript{[78]} Horse</td>
<td>10 grams of leaves Died in 1-48hr</td>
<td>Cholic, diarrhea, weakness and heart failure</td>
<td>Determined minimum toxic amount, developed tests for determining exposure to oleanderin, provided diagnostic tool to identify previously undiagnosed oleander poisoning in horses, before and after death</td>
</tr>
<tr>
<td>Adam\textsuperscript{[79]} Sheep</td>
<td>0.25g/kg Died in 18-24hr</td>
<td>Uneasiness, anorexia, grinding of the teeth, salivation, moaning, frequent urination, dyspnoea, ruminal bloat, ataxia and recumbency</td>
<td>In single dose of 0.25g/kg of oleander leaves, congestion or haemorrhage particularly observed on the heart, kungs, liver, intestines, abomasums and spleen, pulmonary emphysema and cyanosis, hepatorenal fatty change and necrosis were observed. No lesions were observed in the brain or peripheral nerves.</td>
</tr>
<tr>
<td>Aslani\textsuperscript{[36]} Sheep</td>
<td>1.10g/kg Died in 4-12hr</td>
<td>Tachyarrhythmias, ruminal atony, tympany, abdominal pain, polyuria, polakiuria, bradycardia, atrioventricular blocks, depression of S-T segments, tachycardia and ventricular fibrillation.</td>
<td>Clinical signs of toxicosis in sheep began to appear about 30 min after receiving the oleander, Decrease in heart rate followed by cardiac pauses. Histopathological examination revealed myocardial degeneration and necrosis, degeneration and focal necrosis of hepatocytes, necrosis of tubular epithilium in kidneys, odedema in lungs and ischemic changes in cerebrum.</td>
</tr>
<tr>
<td>Source</td>
<td>Dose</td>
<td>Symptoms</td>
<td>Findings</td>
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<tr>
<td>Blanco [37]</td>
<td>0.005% of bodyweight</td>
<td>Prostration, recumbence, inappetence, haemorrhagic diarrhea, dehydration, ataxia, staggering gait, stretched neck, salivation, tachycardia, panting, rapid breathing, paralysis.</td>
<td>All reported cases occurred during dry season. Total 92 cattels were poisoned by oleander in 7 different heards, 57 animals died. Pharmacokinetic studies showed that oleandrin is rapidly absorbed after oral administration with bioavailability of about 30% and biotransformed to oleandrigenin, probably through an enzymatic process.</td>
</tr>
<tr>
<td>Barbosa [80]</td>
<td>1.10g/kg</td>
<td>Apathy, colic vocalizations, hyperpnea, polyuria and moderate rumen distention</td>
<td>Bradycardia was first clinical sign noted, 30 min after administration. Necrosis was found convoluted as well as in collecting tubules. Renal tubule necrosis is responsible for renal failure and is due to impairment of k+/Na+ - ATPase pump</td>
</tr>
<tr>
<td>Anna [81]</td>
<td>-</td>
<td>Cardiac dysfunction</td>
<td>30 equids were reported having medical records with detectable concentrations of oleandrin in serum, plasma, urine, gastrointestinal fluids samples. Oleander toxicosis lead to gastrointestinal tract, cardiac and renal problems</td>
</tr>
<tr>
<td>Mizanur [82]</td>
<td>0.039g/ml</td>
<td>Paralysis, death</td>
<td>Anthelmintic activity of yellow oleander bark extract was determined.</td>
</tr>
</tbody>
</table>

Table 1 shows the reported work of studies performed on different animals their doses, symptoms and main findings due to oleander poisoning. These reports gave diagnostic symptoms and the postmortem findings after providing different doses of oleander extract to the subject animals. These studies confirmed that oleander possess the cardio toxicity Schwartz et al suggested lesions of the heart, gastrointestinal tract and liver were consistently found in monkeys that died from effects of oleander. Reid Hanson gave presumptive and postmortem findings for diagnostic tools for detection of oleander poisoning. Adam et al studied the rapid death attributed to respiratory and cardiovascular failure. Aslani et al studied that sheep are as susceptible as cattle to oleander toxicosis. Sheep may be used as a model to study the different aspects of intoxication with cardiac glycosides in ruminants. Blanco et al studied oleandrin is readily absorbed and arrives at the heart causing immediate damage to cardiomyocytes, also can cross the blood-brain barrier and accumulate in CNS. Barbosa et al suggested that brain in goats are not affected by oleander poisoning which could be due differences in susceptibility to intoxication of different species, also kidney and heart failure was similar to other species. Anna et al suggested that oleander intoxication
should be a differential diagnosis for equids with colic in geographic areas where oleander is found, especially when azotemia or cardiac arrythmias are detected concurrently. Mizanur et al proved the methanolic extracts of oleander possess cytotoxic properties.

In the cardiac toxicity study, various instrumentation techniques have been used. Chromatographic procedures have more seldomly employed. The autopsy samples of oral and rectal administration of oleander poisoning was done by thin-layer chromatography(TLC) while its quantification were performed in fluorescence spectrophotometry on dry extracts reconstituted in water/methanol. Thermolability and nonvolatility of cardiac glycosides were performed by using GC/MS, HPLC/MS, which proved to be the method of choice for unequivocal identification of therapeutic compounds such as digoxin or digitoxin. Fluorescence polarization immunoassay is been used in the diagnosis of plant induced cardiac glycoside poisoning on livestock in southern Africa. The diagnosis is based on circumstantial evidence of presence of plant cardiac glycosides in animal specimens, like plasma levels in humans and dogs as well as in the rumen and organs of dosed sheep. The positive FPIA values were obtained with bufadienolide containing plants and negative results indicated diagnosis of cardiac glycosides. Electrospray ionization (ESI) in combination with mass spectrometry is an efficient method to analyze the polar and non-volatile cardiac glycosides, because gentle ionization can be achieved under atmospheric pressure conditions. C_{18} reversed-phase high-performance liquid chromatography, using bi or ternary solvent mixtures, is a convenient method to separate cardiac glycosides. Typical mobile phases are water, methanol and acetonitrile, buffered with formic acid and ammonium formate respectively. The preferred detection technique is (tandem) mass spectrometry. The use of triple-quadruple analyzer in the MRM (multiple reaction monitoring) mode enables the analysis of cardiac glycosides even in complex human matrixes. The hybrid system, namely a quadruple time of flight (Q-TOF) mass spectrometer was used to characterize the six thevetia glycosides.

The multiple body fluid samples were analysed by Liquid chromatography- mass spectrophotometry (LC-MS/MS) and concentration of oleandrin was detected. Serum samples were assayed immunochemically for digitoxin related compounds by electro-chemiluminsicent immunoassay, using HPLC-MS/MS analysis for oleandrin.
Medicinal importance

The main constituents of oleander are polysaccharides, cardenolides, glycosides and titerpenoids. Various parts of Nerium oleander have been used medicinally, chiefly as a heart tonic, diuretic, in treatment of swelling, leprosy and eye and skin diseases and are reported to possess a wide range of biological activities including antinociceptive, anti-inflammatory, cardiotonic, antibacterial, anti-cancer, cytotoxic, antiplatelet aggregation, and central nervous system depressant activities.

The important pharmacological activities are anti-inflammatory, anti-bacterial, anti-cancer, antinociceptive and CNS depressant activity. The leaves and flowers are cardio tonic, diaphoretic, diuretic, anticancer, antibacterial, antifungal and expectorant. A decoction of the leaves has been applied externally in the treatment of scabies and to reduce swellings. This is a very poisonous plant, containing a powerful cardiac toxin and should only be used with extreme caution. The root is powerfully resolvant is used in the form of plasters and is applied to tumors because of its poisonous nature it is only used externally. It is beaten into a paste with water and applied to lesion and ulcers on penis.

The bark is bitter and is used as cathartic, febrifuge and intermittent fever. Plants have an extensive root system and are often used to stabilize soil in warmer areas. Oil prepared from the root bark is used in treatment of leprosy and skin diseases of a scaly nature. Seeds are poisonous, abortifacient and alternative. They are used as purgative in dropsy and rheumatism. The whole plant is said to have anticancer properties. Oleander has also been used in the treatment of cancer, the flowers, leaves, leaf juice or latex, bark and roots have been used against corns, warts, cancerous ulcers, carcinoma, ulcerating or hard tumors.

CONCLUSION

Understanding of the interactions between drugs, herbs and food is still in its infancy. People are using herbal medicines from centuries for safety, efficacy, cultural acceptability for lesser side effects. Plants and plant products have utilized with varying success to cure and prevent diseases throughout history.

Major plunge by the pharmaceutical industry is focused towards design and development of new innovative/ indigenous plant based drugs through investigation leads from traditional system of medicine.
The oleander plant is commonly known as ‘Kaner’, its parts are used as traditional remedy in various diseases. Oleander contains glycosides with digoxin like activity. Cardiac glycosides blocks electric impulses by inhibiting the Na⁺/K⁺-ATPase sodium-potassium ion pump. Therapeutic use of herbal cardiac glycosides continues to be a source of toxicity.

There is an urgent requirement for a concerted effort to enlarge forensic and toxicological databases to include methods for detection of poisoning by these cardiotoxic plants.

The significance of this review on such studies of plants and their toxicity will help forensic investigators in solving the crimes and searching the poisoning-plant materials on the crime spot. It can lead to the reason related to the poisoning- suicidal, accidental or homicidal, by the parts of plants may or may not be found at crime spot like forest/garden, symptoms of poisoning can help to direct the investigation to right path. On the basis of analysis and plant origin toxicity, forensic team can opine whether the case was suicidal, homicidal or of accidental type.

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