Review Article

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Cardiotoxicity of Plants in Iran: a Review

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Keywords

Oleander poisoning, yew poisoning, cardiac glycosides, taxines, cardiac arrhythmia

Abstract

In this review an attempt has been made to review the cardiotoxic effects of poisonous plants which are found in Iran. Among various plant species growing in different regions of Iran, a large number of plants contain chemical compounds which are toxic to animals and humans. Among those poisonous plants, cardiotoxic plants are important due to the acute nature of their toxicity and frequent lethal livestock and human intoxications. Cardiotoxic plants of Apocynaceae family, Nerium oleander, N. indicum and Thevetia peruviana contain cardiac glycosides including oleandrin, oleandroside and thevetin A-C. Plants of Taxaceae family, Taxus baccata and T. brevifolia contain taxine alkaloids, including taxine A and B. The toxic effects of cardiac glycosides are primarily attributed to inhibition of plasmalemmal Na^+/K^+-ATPase which results into the accumulation of intracellular Ca^{2+} and, depending to its severity, inotropic or arrhythmic effects are seen. Taxine B, the prominent alkaloid in Taxus spp. block sodium and calcium channels preferentially in cardiac myocytes, thus causing conduction abnormalities. Various cardiac arrhythmias in acute cases of poisoning with aforementioned plants result in acute heart failure and death. Post mortem findings are non-diagnostic and toxicological analysis of gastrointestinal tract content or body fluids is used for detection of cardiac glycosides and taxines.

Abbreviations

CGs: cardiac glycosides
Na^+/K^+-ATPase: sodium/potassium adenosine triphosphatase
SR: sarcoplasmic reticulum
RyR2: ryanodine receptor 2
AV: atrioventricular
ECG: electrocardiography
GI tract: gastrointestinal tract
TLC: thin layer chromatography
LC-MS/MS: liquid chromatograpgy tandem mass spectrometry

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Introduction

Different phytogeographic regions in Iranian plateau have caused massive genetic flow in this area resulting to the generation of a variety of plant species. Total Taxa in Iran are about 8,000 which include about 6417 species, 611 subspecies, 465 varieties, and 83 hybrids [1], many of which have the potential to be toxic to animals and humans [2]. Economic and financial losses caused by poisonous plants have been significant over the years and require more attention and research efforts. These losses result from death of livestock, weight loss, decreased production, birth defects, management alternations and medical costs [2, 3, 4]. Many plant species are also poisonous to humans and intentional or accidental exposure leading to illness and fatality are occasionally seen, particularly in rural areas [5, 6]. Among the poisonous plants, cardiotoxic plants are important due to the acute nature of their toxicity and frequent lethal intoxications in livestock and human [2, 7]. The present review article describes various features and aspects of poisoning with the most important cardiotoxic plants in Iran.

Cardiac glycoside-containing plants

Several species of plants found in Iran contain cardiac glycosides (CGs) (Table 1), however, the toxic effects on animal or human health differ widely among these plant species. Three species of *Apocynaceae* (Dogbane family), *Nerium oleander, N. indicum and Thevetia peruviana* contain CGs, and are known as extremely toxic plants, causing lethal intoxication in animals and humans. These species are perennial evergreen ornamental plants and are planted as large flowering shrub or small ornamental trees in gardens, parks and roadsides. *Nerium* species, particularly *N. oleander* are wildly grown as ornamental plants in most parts of Iran, while cultivation of *T. peruviana*, yellow oleander, is limited to the southern lowland regions [2, 8].

Table 1.
Plants containing CGs found in Iran [2].

Plant species	Plant family
Adonis spp.	*Ranuculaceae*
Calotropice procera	*Apocynaceae*
Cheiranthus cheiri	*Crucifeae*
Convallaria majalis	*Convallariaceae*
Corchorus olitorius	*Malvaceae*
Coronilla varia	*Fabaceae*
Digitalis purpurea	*Plantaginaceae*
Euonymus europaeus	*Celastaceae*
Nerium indicum	*Apocynaceae*
Nerium oleander	*Apocynaceae*
Periploca graeca	*Apocynaceae*
Scrophularia aquatic	*Scrophuriaceae*
Thevetia peruviana	*Apocynaceae*

Botanical description

Nerium species vary in size from shrubs to small trees, 2-4 m in height, with erect stems and branches. Leaves are elongated, dark green to grey green in color, leathery, about 1 cm wide and 8 to 22 cm long with a prominent mid rib. Flowers are white to pink to deep red, with 5 spreading petals (Figure 1). The fruit is a narrow pod and contains many silky-haired seeds. The sap is thick, gummy and clear [7]. The color and the type of flowers are used to distinguish different varieties; the presence of variegated leaves and the growth habits can also be differentiating criteria [9].

Figure 1.
Nerium oleander, red and white flowers. Photograph by M.R. Aslani.

Figure 2.
Thevetia peruviana, light orange and yellow flowers and fruits. Photograph by M.R. Aslani.

T. peruviana is mostly seen as a small ornamental tree, with diffusely branched and dense crown and 2.5 -2.3 m height. The leaves are dark green, linear, spirally arranged, glossy and about 13-15 cm in length. Flowers are in small clusters at the tip of twigs, funnel-shaped with 5 petal lobs and yellow to dull orange color (Figure 2). The fruits which are somewhat globular, slightly fleshy, green in color with a diameter of 4-5 cm, become black on ripening and contain 2 seeds. All parts of the plant contain the milky juice [7].

Toxic constituents

Cardioactive steroids or CGs are the most noticeable naturally-occurring compounds identified in *Nerium* species and *T. peruviana* (Table 2). All parts

Table 2.
CGs found in *Nerium* species and *T. peruviana* [14, 15, 16].

***Nerium* species**	***T. peruviana***
Oleandrin	Thevetin A
Oleandrosid	Thevetin B
Nerioside	Thevetin C
Adynerin	Neriifolin
Odorosides	Digitoxin
Neriziside	Acetylthevetin A-C
Nertaloside	Peruvoside
Adigoside	Ruvoside
Rosaginoside	Thevetoxin
Neriantin	
Digitoxigenin	

of these plants whether fresh, dried or boiled contain cardiac glycosides of cardenolide class and are toxic. About 30 types of CGs from *N. oleander* and 15-18 types of CGs from *T. peruviana* have been isolated which were unevenly distributed throughout the plant, some being common in all parts of the plants [10, 11]. These glycosides are structurally derived from the tetracyclic 10,3-dimethylcyclopentanoperhydrophenanterene ring system with a 5 or 6 membered unsaturated lactone ring attached at the 17-position and sugar molecules which usually attached at the 3-position (Figure 3). The sugar molecules influence pharmacokinetic characteristics including water solubility, cell penetrability and duration of action, while pharmacological and toxicological properties of the glycosides reside principally in the unsaturated

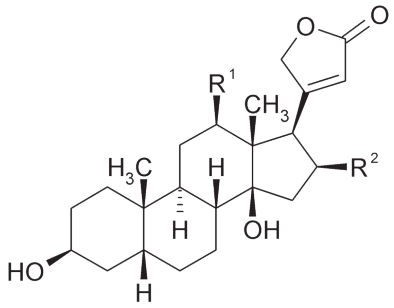

Figure 3.
General structure of cardenolids.

lactone ring at C-17 [12]. Acid hydrolysis leads to a cleavage of the glycoside into aglycones and sugar residues, which strongly decreases the biological activity of the glycoside, while more rigid conditions (alkaline hydrolysis) lead to cleavage of the lactone ring and to a total loss of its activity [13].

The most prominent CGs of *Nerium* species are oleandrin, nerioside and oleandroside. Oleandrin is the most studied CGs in these plants and it is a complex molecule that is very similar to digoxin and digitoxin, cardiac glycosides originated from *Digitalis* species which are used for treatment of congestive heart failure. It has been demonstrated that *T. peruviana* seeds contain a mixture of at least six CGs in-

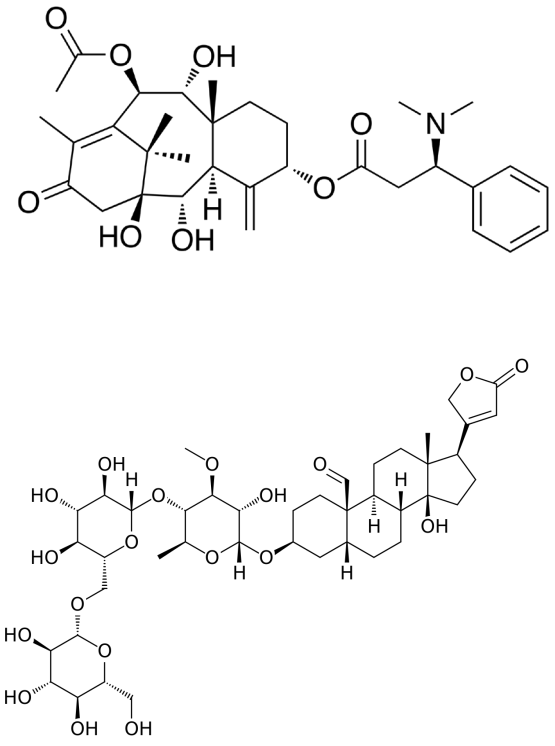

Figure 4.
Chemical structure of oleandrin (top) and Thevetin A (bottom).

cluding thevetin A, B and C, and neriifolin [14, 17] (Figure 4). It has been reported that in *N. oleander* the leaves contain the highest oleandrin contents and roots and seeds typically containing the highest contents of CGs. On the other hand, a significant variability of oleandrin has been indicated depending on varieties, a parameter which is related to the genetic variability between the wild shrub and different cultivars which differentiated by color and morphology. The plant height and some habitat conditions such as rate of light exposure or the type of soil are also factors that may influence the content of the oleandrin in the plant [18].

Plant toxicity

Oleander leaves have a bitter taste and it is said that is not palatable for livestock, and these animals seldom eat the plant voluntarily. Mastication of oleander leaves releases saponins that are surface active agents, and cause a burning sensation upon contact with tissues of the oral cavity, thus, rendering the leaves unpalatable [20]. However, extremely hungry cattle, sheep, and goats have been poisoned when grazing a strange pasture containing little forage but oleander. Apparently dry leaves more readily accepted by livestock, particularly when prunings are mixed with grass clippings or incorporated in baled hay, and the bitter taste is disguised [21]. In fact, dried oleander leaves mixed with forage is the common cause of oleander poisoning in herbivorous animals.

Various factors affects the amount of toxic glycosides within oleanders, therefore, it is difficult to determine a lethal dose for these plants poisoning in animals or humans. In this regards, Rezakhani and Maham reported the lethal dose of dry oleander leaves as 30 and 50 mg/kg body weight for donkeys and cattle, respectively [22], while other experimental studies have suggested the lethal dose of dry oleander leaves as 110 mg/kg body weight for calves, sheep and goats [23, 24, 25].

The determination of lethal dose of oleanders poisoning for humans is more difficult because of few published case reports that contain data sufficient to asses specific quantities of ingested doses. Although one leaf has been considered potentially lethal, ingestion of larger amounts is probably necessary to produce serious toxicity [13]. Ingestion of 5-15 *N. oleander* leaves or 8-10 *T. peruviana* seeds has resulted in fatal poisoning in adults [7]. Inhalation of smoke from burning oleander leaves and twigs, use of the sticks to roast meat or marshmallows, drinking of water in which the flowers or leaves have been soaked, partaking of a soup that was stirred with an oleander branch, and the ingestion of sap or honey produced from oleanders has resulted in poisonings of humans [26, 27]. Cutaneous, oral and trans-rectal use of some oleander preparations as indigenous herbal medicine has also been resulted in human intoxication [28, 29].

Little is known about toxicokinetics of cardenolides during oleander intoxication in animals. There are some evidence in experimentally induced oleander intoxications that the glycosides rapidly absorbed from gastrointestinal tract so that massive doses of leaves may kill an animal within 1 hour [30]. It has been suggested that after yellow oleander seed ingestion and absorption of glycosides into the systemic circulation, oleander glycosides are re-secreted into the gut lumen and disrupting the enterohepatic cycling will increase elimination of toxic glycosides [31]. In murine model, a considerable amount of oleandrin (approximately 60%) is excreted via biliary system through feces, whereas urinary excretion is not considered a major route of elimination (>10%). It has also been suggested that components within the oleander may enhance the transport of oleandrin across the blood brain barrier [32].

The CGs such as digoxin in humans are excreted from the udder and its concentration in the breast milk is approximately equal to the unbound plasma digoxin concentration [33]. Cardiac arrhythmias has been observed in suckling calves of oleander poisoned cattle, suggesting the passage of the oleander glycoside through the milk [34, 35].

Risk factors

There is substantial variation in the sensitivity to oleander poisoning among animal species. Generally, ruminants are less sensitive than monogastric animals. In ruminants solubilized CGs in the rumen can lead to noticeable loss of action as a result of hydrolytic splitting of the digitoxin. Dogs, cats, monkeys, and humans are relatively sensitive to the effects of oleander - derived cardenolides, whereas rodents and avian species are relatively insensitive [13]. The similarity in sensitivity to CGs between humans and dogs is probably due to the very close structural similarity of the Na^+/K^+-ATPases found in these two species. In contrast, it has been shown that the rat cardiac Na^+/K^+-ATPase exhibits a low affinity towards cardiac glycosides [20]. The time until the onset of symptoms, severity and outcome of intoxication all depend on parts and amount of the ingested plant. On the other hand, frequent vomiting in humans and animals such as dogs is a protective mechanism, helping to survive the intoxicated cases [2].

Hypomagnesemia can worsen CGs toxicity and

predispose to dangerous arrhythmias, therefore, monitoring of serum magnesium level and its correction to normal may be advisable [36]. In this regards, administration of magnesium has often been found to abolish arrhythmias caused by CGs [37]. Inversely, intravenous administration of calcium containing fluids is dangerous in cases of CGs poisoning [11]. Since the intracellular level of Ca^{2+} is elevated in CGs intoxication, administration of calcium may worsen cardiac arrhythmia and animal data have reported increased toxicity including death, which may relate to sustained cardiac contraction, also known as 'stone heart' [36, 38].

Pathophysiology

The Mg^{2+} dependent Na^+/K^+-ATPase in cardiac myocytes that supplies energy for the active pumping of Na^+ outward and K^+ inward the cell membrane, is believed to be the cellular receptor for cardiac glycosides [39]. All cardiac glycosides bind specifically to and inhibit the sarcolemmal Na^+/K^+-ATPase. The inhibition of Na^+/K^+-ATPase results in the accumulation of the Na^+ within the cardiac myocytes. This local accumulation of Na^+, in turn, causes an increase in Ca^{2+} concentrations as the Na^+–Ca^{2+} exchanger promotes Ca^{2+} influx over efflux. Elevation of cellular Ca^{2+} concentration is responsible for the inotropic action of cardiac glycosides such as digoxin.

The toxic effects (ie, arrhythmias) occur when the cytoplasmic Ca^{2+} increases to concentrations exceeding the storage capacity of the sarcoplasmic reticulum. As a consequence of this internal Ca^{2+} overload, spontaneous release of Ca^{2+} (Ca^{2+} waves) from the sarcoplasmic reticulum (SR) through ryanodine receptor 2 (RyR2) channels occur as a process known as store overload-induced calcium release. In addition, high internal concentrations of Ca^{2+} activate a depolarizing (inward) current corresponding to the forward mode of the electrogenic Na^+–Ca^{2+} exchanger (3Na/2Ca). This current generates delayed after-depolarizations that give rise to extra-systoles and polymorphic ventricular tachyarrhythmias due to triggered activity [40, 41, 42].

Furthermore, recent studies have suggested an alternative mechanism for pro-arrhythmic alterations in myocyte Ca^{2+} handling caused by CGs involving the generation of reactive oxygen species (ROS). The ROS release from mitochondria upon exposure to CGs. CG-induced ROS activate Ca^{2+}/calmodulin-dependent protein kinase II resulting in increase phosphorylation of RyR2 and pro-arrhythmic Ca^{2+} waves [43].

From an electrophysiological perspective, the negative chronotropic activity of CGs is largely attributed to the increased vagal tone, which decreases the rate of sinoatrial node depolarization and increased refractory period of the atrioventricular node (AV). The result is a reduction in sinoatrial and AV conduction [44].

Clinical findings

Many animals exposed to oleanders are often found dead. Clinical signs in experimental cases develop about 1.5 hours after ingestion of the oleander leaves. In accidental cases it may be delayed depending on the type of plant material ingested and the level of mastication of that materials. The signs may persist up to 7 days in nonfatal cases. Pollakiuria is the first sign that appears after plant exposure, concurrently, bradycardia with strength beats are noticeable in heart auscultation that may be transient in some cases. Then, abdominal pain is developed and progressed in severity and manifested by restlessness, dental granting and grating, forelimb pawing the ground, kicking at the belly, swishing of the tail, frequent lying and getting up, humped posture, flank-watching, frequent defecation and tenesmus. Initial bradycardia followed by heart blocks, ventricular premature beats and ventricular tachycardia and, ventricular fibrillation is the end stage of the poisoning.

Affected animal also shows some degrees of salivation, frothing of the mouth, tremor, depression and lethargy, ruminal atony with moderate bloat and diarrhea. Blood is often appeared as clots or streaks in feces in later stages. In some cases heart beats may be audible without the stethoscope. Rectal temperature may be normal or slightly subnormal. Lethal dose of oleander leads to death in most cases of ruminants within 12 hours. Death occurs following prostration and severe convulsive movements, general spasm and bellowing [2, 24, 25, 35].

Horses may develop clinical signs of toxicosis within a few hours after ingestion of oleander leaves [30]. However, sudden death is the most common finding attributed to oleander poisoning in equines. The most commonly reported signs are nonspecific initially and may include lethargy and depression with either profuse watery diarrhea, decreased intestinal motility or ileus. Other signs may include muscle tremors, profuse sweating, ataxia, weakness, colic, elevation of capillary refill time and seizures along with a variable degree of bradycardia and heart blocks. In later stages, hypothermia, recumbency, ventricular tachyarrhythmias, and dyspnea are seen. Death usually occurs within 12–36 hours after the development of signs due to cardiac dysfunction [45, 46].

The clinical signs of oleander poisoning in dogs occur very fast, within an hour, after the ingestion of the leaves. The first and most common clinical sign is vomiting. Other clinical signs of oleander poisoning in dogs may include loss of appetite, salivation, nausea, apathy, congestion of conjunctiva, dehydration, abdominal pain, tremor, diarrhea and tenesmus [11, 47]. Signs of oleander cardiotoxicity in dog is manifested as variety of dysrhythmias including sinus bradycardia, 2nd degree atrioventricular block, ventricular premature complexes, sinus tachycardia and ventricular tachycardia [11].

Oleander poisoning has been described in camelids including one humped camels, llamas and alpacas. The toxicity in one humped camel is manifested by dullness, vomiting, shivering, yawning, ataxia, excitement or convulsion followed by diarrhea and coma in severely affected cases [48]. Clinical findings of oleander poisoning including anorexia, lethargy, decreased to absent auscultable gastrointestinal tract motility, diarrhea, bradycardia, sinus arrhythmia, 2nd degree A-V block, azotemia and hyperglycemia have been recorded in new world camelids [49].

Ingestion of any part of oleander plants can result in a variety of signs similar to digoxin poisoning in humans. The onset and severity of intoxication depends on parts and amount of ingested plant, preparations and individual susceptibility [7, 13]. Clinical signs appear within a few hours following ingestion of plants. The GI signs includes excessive vomiting, nausea, abdominal pain, diarrhea, dry mouth, burning of the mouth and paraesthesias of the tongue. As other species, the most common serious complication of oleander poisoning in humans is disruption of cardiac conduction featured as sinus bradycardia, SA and AV blocks, atrial fibrillation which may persist 3-6 days. Life-threatening ventricular tachyarrhythmias and fibrillation, cardiovascular collapse or cardiogenic shock may occur in severe oleander intoxication [7, 13, 17]. Neurological signs of oleander plants intoxication seen in humans include blurred vision, visual disturbances such as halos, weakness, tremor confusion, dizziness, headache, fainting, depression, drowsiness and lethargy [7].

Electrocardiographic abnormalities

ECG abnormalities in cases of oleander poisoning include sinus bradycardia, prolonged P-R interval, sino-atrial block, 1st and 2nd degree A-V blocks, A-V dissociation and sinus tachycardia. In acute cases of oleander poisoning those findings are transient, but more dangerous cardiac arrhythmias including unifocal and multifocal ventricular premature contractions (Figure 5), ventricular tachycardia, depression or elevation of S-T segment and ventricular fibrillation in the end stage are seen [22, 23, 24, 25].

Clinical pathology and toxicological analysis

Elevation of serum glucose, BUN and creatinine have been reported in horses and new world camelids poisoned with oleanders [45, 49].

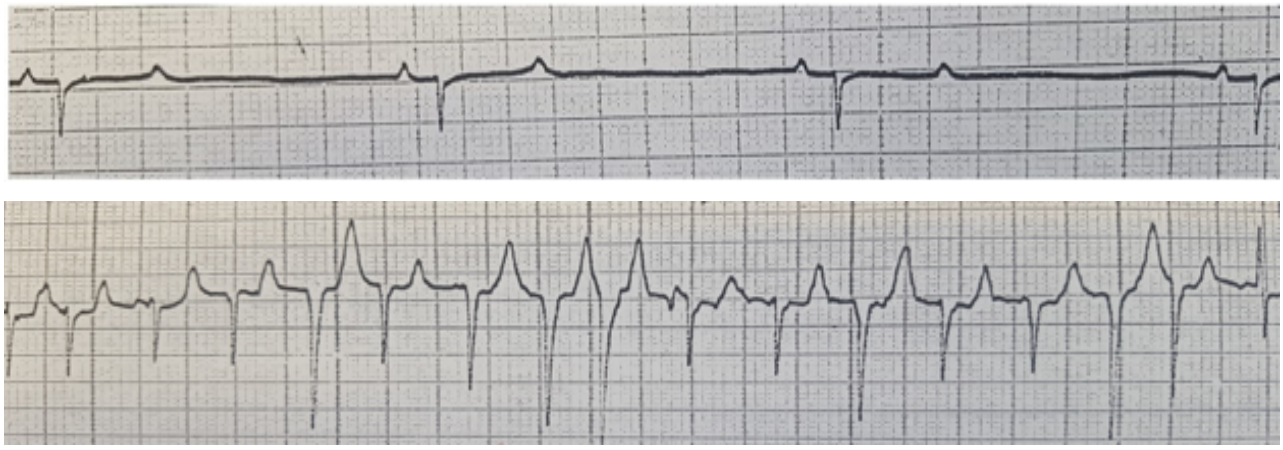

Figure 5.
ECGs of calves intoxicated with 110mg/kg body weight of oleander leaves showing sinus bradycardia (top) and multifocal ventricular premature beats (bottom) (Base apex leads; sensitivity 10 mm/mv and paper speed 25mm/s) [2].

Two-dimentional thin layer chromatography (TLC) has been used for identification of oleandrin in tissue samples and GI contents of livestock poisoned with oleander [50]. The high performance TLC has also been described as a simple, rapid and efficient method for the isolation and residual determination of oleandrin from oleander plant and autopsy samples [19].

For detection of oleander cardiac glycosides in blood fluorescence polarization immunoassay has widely been used in human intoxicated cases [7]. A

Figure 6
Taxus baccata. Photograph by M.R. Aslani.

rapid liquid chromatography tandem mass spectrometry (LC-MS/MS) method, using a triple-quadrupole/linear ion trap mass spectrometer, has been developed for the quantitative determination of oleandrin in serum, urine, and tissue samples and suggested to be the method of choice for toxicological investigations of oleander poisoning [51].

Pathology

Postmortem lesions of animals died due to intoxication with oleanders is not pathognomonic. Findings at gross are often associated to acute heart failure as fluids in body cavities, congestion and hemorrhages of the subdermal tissues, epicardium and endocardium, liver, kidneys and gastrointestinal tract. Lungs are also congested and edematous [24, 25]. Fragments of the oleander leaves may be recognized in forestomachs/stomach contents [52]. Histologically, evidence of myocardial degeneration and necrosis associated with hemorrhage and infiltration of mononuclear inflammatory cells in the heart, fatty changes, focal degeneration and necrosis of hepatocytes, congestion and tubular epithelial necrosis in the kidneys and perivascular and perineuronal edema and hemorrhages in cerebrum have been reported in oleander poisoning in animals [24, 25].

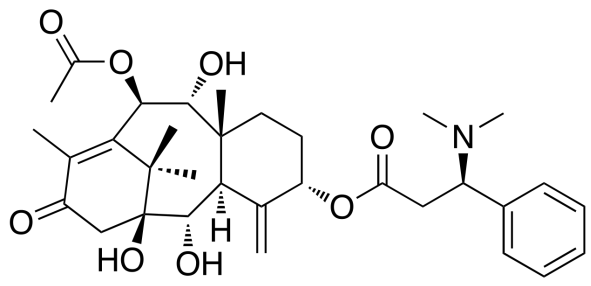

Figure 7.
Chemical structure of taxine B.

Cardiotoxic alkaloid-containing plants

Plant description

Yews (*Taxus spp.*) are popular evergreen trees or shrubs with high longevity and slow growth, belonging to the family of *Taxaceae* and used as ornamental landscaping plants in many parts of world. Two species of genus *Taxus*, *T. baccata* and *T. brevifolia* are found in Iran of which only *T. baccata* is native. *T. baccata* grows in northern parts of Iran in 900-1800 meters above sea level and because of reddish-brown bark, is known indigenously as Sorkhdar [53, 53]. The height of the plant reaches up to 28m. Leaves are small needle-like in opposite pairs, waxy, linear, dark green, 1-3cm long and 2-3mm wide with midrib prominent on both side and cane live up to 8 years. Branches are long and not whorled (Figure 6). Yew produces soft, bright berry like structure fruit called an aril, contains a single seed and has sweet taste which matures within 6 to 9 months [55].

Toxic constituents

Yews contain at least 10 taxine alkaloids with taxine A and taxine B the most widely recognized as cardiotoxins [52]. Of the two, taxine B constitutes about 30% (approx. 1.2% of dry weight in leaves) and taxine A only constitutes approximately 1.3% of total alkaloids. Taxine B alkaloids have much more cardioxicity than taxine A [56, 57]. Taxines are a mixture of alkaloids formed from nitrogen-free polyhydroxylic diterpenes esterified with β-dimethylamino- β-phenylpropionic acid and acetic acid. Taxines are particularly instable in neutral and alkaline environment and their toxicity decreases over time. These compounds are only slightly soluble in water but are readily soluble in alcohols, chloroform, dilute acids, low ketones and low esters [57].

Plant toxicity and risk factors

Fresh or dried yew plants are highly toxic throughout the year and have been implicated in poisonings and fatalities in different animals as well as humans. All parts of the plant exception the scarlet aril (berry) surrounding the seed contains toxic alkaloid. The seeds within the aril are extremely toxic [57]. However, the seeds are not toxic if swallowed in whole because the seed coat resist digestive enzymes. The maximal concentration of taxines in the foliage occurs during the winter season and the mature leaves are more toxic than the new ones [58]. It has also been reported that taxines are relatively abundant in *T. baccata* while minimal amounts are found in *T. brevifolia* [59, 60]. Poisoning in animals is often accidental and is frequently occur following exposure to discarded yew foliage of trimmings near their pasture or when livestock have access to landscape plot [61].

Yews are toxic to all animals to varying degrees. Horse are the most sensitive species and chickens are the least sensitive animals [57]. Most cases of poisonings have involved cattle and horses, however is has been reported in variety of animal species including canine and birds [61]. Some species of *Cervidae* including white-tailed deer (*Odocoileus virginianus*) and roe deer (*Capreolus capreolus*) eat yew over time without any adverse effects, due to elevation of ruminal and hepatic adaptation to detoxify taxines[57]. The minimal toxic dose of yew leaves for horses is 0.2-0.4, for cows 2, for sheep 2.5, for goats 12, for chicken 16.5 g/kg body weight [52, 57].

The incidence of yew poisoning may be higher in the winter when the other green plant materials are not available for animals to eat, the alkaloid content of the plant is highest and relative palatability of the leaves increases. Animals with hepatic disease may also be at higher risk of poisoning because the taxines are metabolized in the liver by conjugation and excreted in the bile and urine [60, 62, 63].

Pathophysiology

The taxine alkaloids are absorbed through the digestive tract rapidly, and the signs of poisoning are seen after 30-90 minutes [64]. Because of instability, purified taxine A and B are not available and crude extract of yew is used for study on the mechanism of action of taxines. From the experimental studies it has been concluded that the mechanism of action of taxines is primarily based on their sodium and calcium channel antagonistic properties, preferentially in cardiac myocytes, thus causing conduction abnormalities [57]. The inhibition of those channels results in decreased intracellular calcium within the myocardial cells which cause slowing of conduction, decreased atrial and ventricular contractility, bradycardia, arrhythmia, diastolic cardiac arrest and decreased cardiac output. Decreased cardiac output coupled with vasodilative effect of taxine result in profound hypotension [65]. On the other hand, interference of taxine alkaloids with potassium ion channels leading to hyperkalemia and absence of P wave and long duration of QRS complex in ECG has also been speculated [66].

Clinical findings

In most cases of acute poisoning, animals are often found dead or die within 3-4 hours after ingestion of the plant materials with no evidence of struggle. Subacute cases of yew intoxication in cattle which are seen infrequently is characterized by ataxia, bradycardia, anxiety or depression, dyspnea, muscle tremors, weakness, hypothermia, rumen hypotony which progressed to atony in later stages, sternal or lateral recumbency, and collapse and death without any struggling [52, 57, 61, 67]. Abortion has been reported in late-term pregnant cattle within 4 days of yew ingestion [61]. In cases of yew poisoning in horses, symptoms of intoxication are less or more similar to those observed in ruminants. The onset of signs may occur within an hour of yew ingestion and the course of clinical intoxication may last 15 to 45 minutes. Clinical signs include incoordination, weak pulse, nervousness, dyspnea, respiratory grunt, trembling of legs, decreased lip and tail tone, collapse and recumbency [58, 61]. The clinical signs in a nonfatal case of yew ingestion in a dog included mydriasis, tetanic seizures, increased aggressiveness and gastroenteritis lasting for one week [68].

Yew leaves and seeds have been used in humans for homicide, suicide or folk medicine. Clinical signs of poisoning in those cases may include nausea, vomiting, dizziness, diffuse abdominal pain, pupil dilation, muscle weakness, seizures, tachycardia (initially), cardiac arrest, respiratory paralysis and death. These signs can proceed to bradycardia, bradypnea, diastolic cardiac standstill or death [57, 69].

Electrocardiographic abnormalities

In experimentally intoxicated sheep by yew leaves ECG abnormalities include sinus tachycardia, sinus bradycardia, ventricular premature beats, multifocal ventricular tachycardia, idioventricular and idiojunctinal rhythm with arrest and silent atria, atrial fibrillation, atrial tachycardia, S-T segment slurring, QRS and T widening, AV dissociation, S-T segment

depression, episodes of cardiac pacemaker arrest, R on T phenomenon, inverted T and ventricular fibrillation [67, 70, 71].

Clinical pathology and toxicological analysis

Serum chemistry changes are limited in acute cases of yew poisoning. Hyperkalemia may be seen in some cases [66, 67]. Chemical analysis of GI content including stomach/rumen content by GC/MS, LC/MS or TLC can be used to confirm the presence of taxine alkaloids [57].

Pathology

Generally, the postmortem evaluation is usually unremarkable, because sudden death occur in most cases of yew poisoning and gross or microscopic lesions are rarely observed. Yew leaves or fragments are found in GI content particularly in stomach or rumen content of most cases which can be considered as a basic for diagnosis [52, 58, 69] Some degrees of hemorrhage on the cardiac surface, pulmonary edema and myocardial necrosis have been observed in accidental yew poisoning in horse and calves [58, 62]. General vascular dilation, hepatic and splenic congestion; pulmonary edema, petechial hemorrhages on the epicardium and endocardium, multifocal nonsuppurative interstitial myocarditis with mild focal cardiac muscle cell degeneration and necrosis as well as hyperemia and focal hemorrhages, moderate to severe interstitial edema with inflammation of the sinoatrial node and the AV-node, the bundle branches and the His-bundle have also been identified in sheep experimentally intoxicated with yew leaves [67].

Conflict of interest

The author declares that there is no conflict of interest.

References

1. Ghahreman A, Attar F. Biodiversity of plant species in Iran. 2000; vol. 1. Tehran University publications.

2. Aslani MR. Poisonous plants of Iran and their effects on Animals. 2004; Ferdowsi University of Mashhad Press, Mashhad.

3. Aslani MR, Movassaghi AR, Najarnezhad V, Janati- Pirouz H, Heidaipour-Bami M. Acute oxalate intoxication associated to ingestion of Eshnan (Seidlitzia rosmarinus) in sheep. Tropical Animimal Health and Production 2011; 43, 1065-1068.

4. Aslani MR, Maleki M, Mohri M, Najjar-Nazhad V, Afshari E. Castor bean (Ricinus communis) toxicosis in a sheep flock. Toxicon 2007; 49: 400-406.

5. Afshari A, Majdzadeh R, Balali-Moog M. Patterns of acute poisoning in Mashhad, Iran 1993-2000. Journal Toxicology. Clinical Toxicolology 2004; 42: 965-975.

6. Amini M, Khosrojerdi H, Afshari R. Acute Datura Stramonium poisoning in east of Iran-a case series. Avicenna Journal of Phytomedicine 2012; 2: 86-89.

7. Bandara V, Weinstein SA, White J, Eddleston M. A review of the natural history, toxinology, diagnosis and clinical management of Nerium oleander(common oleander) and Thevetiaperuviana(yellow oleander) poisoning. Toxicon 2010; 56: 273-281.

8. Aslani MR, Binas N, Shaterzadeh H. Thevetia peruviana, a poisonous plant in Iran. 6th congress of Iranian Veterinary Practitioners 2008; 28-30 July, Tabriz.

9. Portis E, Comino C, Lenzi A, Lombardi P, Tesi R, Lanteri S. Amplified fragment length polymorphism fro variety identification and genetic diversity assessment in oleander (Nerium oleander L.). Euphytica 2004; 136: 125-137.

10. Nesy EA, Lizzy M. HPLC profiling of cardiac glycosides if Thevetia peruviana leaf extracts of three morphovariant plants grown in Kerala, India. International Journal of Pharmacology and Pharmacological Sciences 2015; 7: 191-195.

11. Camplesi AC, Bellodi C, Socha JJM, Hatayde MR, Sobreira MFR, Araujo GSM, Araujo CFM. Dogs poisoned with Nerium oleander fresh leaves: clinical and electrocardiographic findings. Ciência Rural, Santa Maria 2017; 47: 06. E2016o970.

12. Miller M, Adams HR. Digitals, Positive Inotropes and Vasodilators. In: Veterinary Pharmacology and Therapeutics. 2009; 9thEdn, Ed By RiviereJE.,Papich MG., Adams HR., Willey-Blackwell.

13. Baeceloux DG. Medical Toxicology and Natural Substances: Foods, Fungi, Medicinal Herbs, Plants, and Venomous Animals. 2008; Wiley, New Jersy,

14. KohlsS, Scholz-Bottcher BM, Teske J, Zark P, Rullkotter J. Isolation and quantification of six cardiac glycosides from seeds of Thevetia peruviana provide a basis for toxicological survey. Indian Journal of Chemistry 2015; 54B: 1502-1510.

15. Kumar A, De T., Mishra A, Mishra AK. Oleandrin: A cardiac glycosides with potent cytotoxicity. Pharmacognosy Reviews 2013; 7: 131-139.

16. Siddiqui BS, Sultana R, Begum S, Zia A, Suri A. Cardenolides from the methanolic extract of Nerium oleander leaves possessing central nervous system depressant activity in

mice. Journal of Natural Production 1997; 60, 540-544.

17. Sundaragiri S, Tandur S. Electrocardiographic Profile of Cardiotoxic Plants and Animals. International Journal of Medical Research and Health Sciences, 2016; 11:719-725.

18. Nadji S, Abdaoui A, Ouerdane H, Azzouz M, Abtroun R, Reggab M, Alamir B. Determination of oleandrin levels by HPLC-DAD in vegetal material collected throughout Algeria and the study of some influencing factors. Research Journal of Phytochemistry 2017; 26: 74-84.

19. Praveen US, Gowtham MD, Yogaraje-Gowda CV, Nayak VG, Mohan BM. Detection of residues of cardenolides of Nerium oleander by high-performance thin-layer chromatography in autopsy samples. International Journal of Medical Toxicology and Forensic Medicine 2012; 2:135-142.

20. Langford SD, Boor PJ. Oleander toxicity: an examination of human and animal toxic exposures. Toxicology 1996; 109: 1-13.

21. Casteel SW, Schaffer JW. Collapse and sudden death. In: Large Animal Internal Medicine, 5th Edn, Ed By Smith B,

22. Rezakhani A, Maham M. Cardiac manifestation of oleander poisoning in cattle and donkeys. In: Colegate, SM and Darling, PR (Eds.), Plant associated toxins agricultural, phytochemical and ecological aspects. (1st. Edn.), London, CAB International 1994; PP: 538-540.

23. Aslani MR. Study on the mechanism of V285 treatment of experimental oleander poisoning in calves. PhD thesis 1995, School of Veterinary Medicine, University of Shiraz, Iran.

24. Aslani MR, Movassaghi AR, Mohri M, Abbasian A, Zaerpour M. Clinical and pathological aspects of experimental oleander (Nerium oleander) toxicosis in sheep. Veterinary Research Communication 2004; 28: 609-6016.

25. Aslani MR, Movassaghi AR, Janati-Pirouz H., Karazma M. Experimental oleander (Nerium oleander) poisoning in goats: a clinical and pathological study. Irish Journal of Veterinary Research 2007; 8: 58-63.

26. Senthilkumaran S, Meenakshisundaram R, Michaels AD, Thirumalaikolundusubramanian P. Electrocardiographic changes during inhalational oleander toxicity. Journal of Electrocardiology 2011; 44: 470–472.

27. Nelson LS, Shih RD, Balick MJ. Handbook of poisonous and Injurious Plants. 2007, 2nd Edn, Springer, NewYork.

28. Senthilkumaran S, Saravanakumar S, Thirumalaikolundusubramanian P. Cutaneous absorption of oleander: Fact or fiction. Journal of Emergencies, Trauma and Shock. 2009; 2: 43–45.

29. Bijl PVD. Cardiotoxicity of plants in South Africa. Cardiovascular Journal of Africa 2012; 23: 476–477.

30. Galey DF. Cardiac glycosides. In: Plumlee KH., Veterinary Clinical Toxicology. 2007 Elsevier, St Louis.

31. Peiris-John RJ, Wickremasinghe AR. Efficacy of activated charcoal in yellow oleander poisoning. Ceylon Medical Journal 2008; 53: 33-35.

32. Ni D, Madden TL, Johansen M, Felix E, Ho DH, Newman RA. Murine pharmacokinetics and metabolism of oleandrin, a cytotoxic component of Nerium oleander. Journal of Experimental Therapeutic Oncolology 2002; 2:278-85.

33. Marcus FL, Huang SK. Digitalis. In: The Heart, Arteries and Veins, Ed by Hurst JW, Schlant RC, 1990; McGrew-Hill Information Service Company, New York.

34. Rezakhani A, Maham M. Oleander poisoning in cattle of the Fars Province, Iran. Veterinary and Human Toxicology 1992; 34: 549.

35. Aslani MR, Rezakhani A. A case report of oleander (Nerium oleander) intoxication in Cattle. International Journal of Tropical Agriculture 2000; 18: 185-187.

36. Rajapakse S. Management of yellow oleander poisoning. Clinical Toxicology 2009; 47: 206-212.

37. Mannineh V, Nyberg L. Interaction between cardiac glycosides and other substances in the body. In: Cardiac Glycosides, part II: Pharmacokinetics and Clinical pharmacology, Ed by Greef K 1981, Springer, New York.

38. Roberts AM, Gallapatthy G, Dunuwille A, Chan BS. Pharmacological treatment of cardiac glycoside poisoning. British Journal of Clinical Pharmacology 2016; 81: 488–495

39. Miller MW, Adams HR. Digitalis, Positive Inotropes and Vasodilators. In: Veterinary Pharmacology and Therapeutics, 9th Edn, Ed by Riviere JE, Papich MG, 2009; Wiley-Blackwell.

40. Konstantinou DM, Karvounis H, Giannakoulas G. Digoxin in Heart Failure with a Reduced Ejection Fraction: A Risk Factor or a Risk Marker? Cardiology 2016; 134:311-319.

41. Lelie`vre LG, Lechat Ph. Mechanisms, manifestations, and management of digoxin toxicity. Heart and Metabism 2007; 35: 9–11.

42. Wasserstrom JA, Aistrup GL. Digitalis: new actions for an old drug. American Journal Physiology- Heart and Circulatory Physiology 2005; 289: H1781–H1793.

43. Ho HT, Liu B, Snyder JS, Lou Q, Brundage EA, Velez-Cortes F, Wang H, Ziolo MT, Anderson ME, Sen CK, Wehrens XHT, Fedorov VV, Biesiadecki BJ, Hund TJ, Gyorke S. Ryanodine receptor phosphorylation by oxidized CaMKII contributes to the cardiotoxic effects of cardiac glycosides. Cardiovascular Research 2014; 101: 165–174.

44. Kanji S, McLean RD. Cardiac glycoside toxicity: More than 200 years and counting. Critical Care Clinics 2012; 28: 527–535.

45. Renier AC, Cass PhH., Magdesian KG., Madigan JE., Aleman M., Pusterla N. Oleander toxicosis in equids: 30 cases (1995–2010). Journal of American Veterinary Medical Association 2013; 242: 540-549.

46. Butler J, Khan S, Scarzella G. Fatal oleander toxicosis in two miniature horses. Journal of American Animal Hospital Association 2016; 42: 398-402.

47. Page C, Murtaugh RJ. Hypoglycemia Associated With Oleander Toxicity in a Dog. Journal of Medical Toxicology 2015; 11:141–143.

48. Vashishta MS, Singh RP. Camel Disease in India. 1977, Scientific Book Agency, Calcutta.

49. Kosikowski TA, Magdesian G, Puschner B. Oleander intoxication in New World Camelids: 12 cases (1995-2006). Journal of American Veterinary Medical Association 2009; 235: 305-310.

50. Galey FD, Holstege DM, Plumlee KH, Tor E, Johnson B, Anderson ML, Blanchard PC, Brown F. Diagnosis of oleander poisoning in livestock. Journal of Veterinary Diagnosis Investigation 1996; 8: 358-364.

51. Tor ER, Filigenzi MS, Puschner B. Determination of oleandrin in tissues and biological fluids by liquid chromatography-electrospray tandem mass spectrometry. Journal of Agriculture and Food Chemistry 2005; 53: 4322-5.

52. Constable PD, Hinchkliff KW, Done SH, Grunberg W. Veterinary Medicine, A Textbook of the Diseases of Cattle, Horses, Sheep, Pigs and Goats. 11th Edn, 2017; Elsevier, St Louis.

53. Yazdiani D, Shahnazi S, Rezazadeh SH, Pir Ali Hamedani M. A review on T. baccata. Journal of Medicinal Plants 2005; 4: 1-8.

54. Janfaza S, Pourmajidiyan MR, Moradi M. Study of the ecological status of Iranian yew herbal towards its revival in Iran and the word in recent years. Annals of Biological Research 2014; 5: 68-71.

55. Thomas PA, Polwart A. Biological flora of the British Isles: Taxus baccata. Journal of Ecolology 2003; 91: 489-524.

56. Labossiere AW, Thompson DF. A review of the clinical toxicology of yew poisoning. Annals of Pharmacology 2018; 1-9, DOI: 10.1177/1060028017754225 .

57. Wilson CR, Hooser SB. Toxicity of yew (Taxus spp) alkaloids. In: Gupta RC, Veterinary Toxicology; Basic and Clinical Principles. 2012; 2nd edition, Academic press.

58. Tiwary AK, Puschner B, Kinde H, Tor ER. (2005) Diagnosis of Taxus (Yew) poisoning in a horse. Journal of Veterinary Diagnostic Investigation 17; 252-255.

59. Itokawa H, Lee KH. Taxus: The Genus Taxus. 2003; Tylor & Francis, London; pp 153-156.

60. Sufness M. Taxol: Science and Applications. 1995; CRC Press, Boca Raton, pp 7/8-311/312.

61. Casteel SW. Taxine alkaloids. In: Plumlee KH, Veterinary Clinical Toxicology. 2007; Elsevier, St Louis.

62. Sula MJM, Morgan S, Baily KL, Schumpert M, Njaa BL. Characterization of cardiac lesions in calves after ingestion of Japanese yew (Taxus cuspidate). Journal of Veterinary Diagnostic Investigation 2013; 25: 522-526.

63. Persico A, Bacis G, Uberti F, Panzeri C, Lorenzo CD, Moro E, Restani P. Identification of taxine derivatives in biological fluids from a patient after attempted suicide by ingestion of yew (Taxus baccata) leaves. Journal of Analytical Toxicology 2011; 35: 238-241.

64. Valis M, Koci J, Tucek D, Lutonsky T, Kopova J, Barton P, Vysata O, Krajickova D, Korabekny J, Masopust J, Klzo L. Common yew intoxication: a case report. Journal of Medical Case Report 2015; 8: 1/4.

65. Holstege CP, Eldridge DL, Rowden AK. ECG manifestations: the poisoned patient. Emergency Medicine Clinics of North America 2006; 24: 159-177.

66. Andersen KB. Future perspectives of the role of taxines derived from the yew (Taxus baccata) in research and therapy. Journal of Pre-Clinical and Clinical Research 2009; 3: 1-4.

67. Aslani MR, Taghavi-Rezavi-Zadeh AR, Mohri M, Movassaghi AR, Nabipour A, Rezakhani A, Yaghoobi-Faz S, Andalib A, Ahmadi F. Clinical and pathological study on experimentally induced yew (Taxus baccata) poisoning in sheep. Iranian Journal of Veterinary Science and Technology 2011; 3: 11-22.

68. Evans KL, Cooke IR. Japanese yew poisoning in a dog. Journal of American Animal Hospital Association 1991; 27; 300-302.

69. Perju-Dumbrava D, Morar S, Chiroban O, Lechintan E, Cioca A. Suicidal poisoning by ingestion of Taxus Baccata leaves. Case report and literature review. Romanian Journal of Legal Medicine 2013; 21: 115-118.

70. Piskac O, Stříbrnýb J, Rakocova H, Malý M, Cardiotoxicity of Yew. Cor et Vasa 2015; 57: 234-238.

71. Cerrato M, Calzolaria G, Tizzani P, Perinetto EA, Dellavalle A, Aluffi E. Bizarre and scary ECG in yew leaves poisoning: Report of successful treatment. Ann Noninvasive Electrocardiol. 2018;e12535. doi.org/10.1111/anec.12535.