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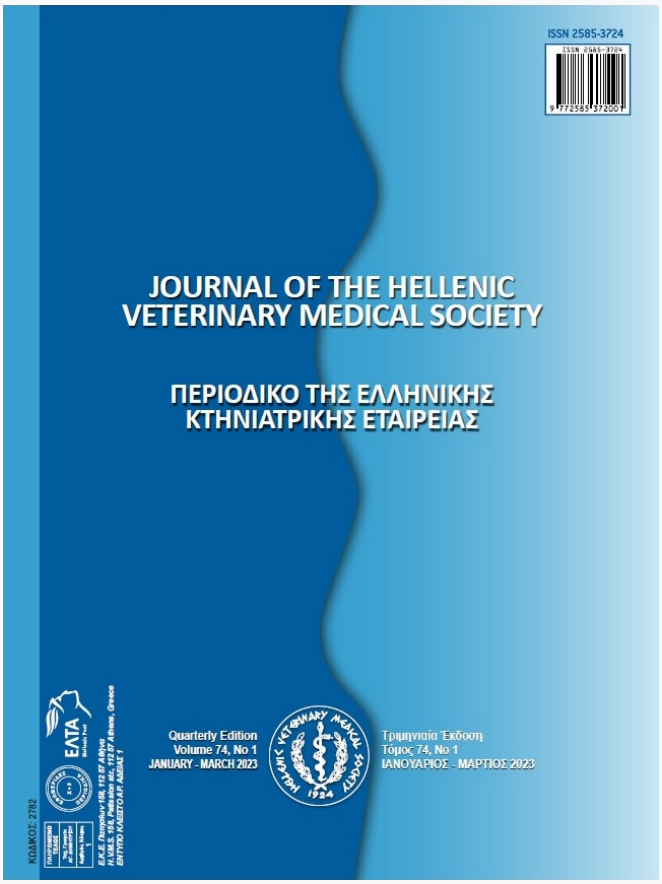

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Review article
Ανασκόπηση

Accidental oleandrum (*Nerium oleander L.*) ingestion: anatomo-pathological consequences in livestock species

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ABSTRACT: The oleander (*Nerium oleander* L.) is a flowering and evergreen shrub or small tree, belonging to the Dogbane family, cultivated as ornamental plants in gardens and public city areas. These plants, distributed originally in Asia and the Mediterranean area, grow in many parts of the world, particularly in warm temperate and subtropical regions. Oleander is considered a noxious weed and its toxicity has been known since ancient times.All parts of plants, including stems, leaves, young shoots, flowers, nectar, sap and products induced by combustion are toxic.The poisoning effects of plants induce severe negative changes especially in the heart, also in the lung, liver and kidney. Accidental and experimental cases of oleander poisonings have been described in many species. Several cases of accidental ingestion in human and animals have been reported from across the world. Therefore, this review summarizes the main anatomo-pathological effects found in livestock species after accidental oleandrum poisoning.

Keywords: Oleander; Poisoning; Pathological lesions; Livestock species

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INTRODUCTION

The oleander (*Nerium oleander* L.) is a flowering and evergreen shrub or small tree,belonging to the Dogbane family, *Apocynaceae*, cultivated as ornamental plants in gardens and public city areas. These plants, distributed originally in Asia and the Mediterranean region, grow in many parts of the world, particularly in warm temperate and subtropical regions (Derwich *et al.* 2010).

There are two common oleanders, *Nerium oleander* and *Thevetia peruviana*, with numerous varieties existing within each species(Shepherd, 2004; Kiran and Prasad 2014). *Nerium oleander* grows rapidly and is often used for highway barriers, roadsides and other areas that require screening from noise and pollution (Omidi *et al*. 2012; Santo *et al.* 2019).There are three varieties that can be easily distinguished according to the color of the flower (red, white, and pink-flowered varieties).

In some parts of the world, oleanders are considered a noxious weed (Shepherd 2004). Its toxicity has been known since ancient times: in BC India, the shrub was called Kajamaraka, "the herb that makes the horse die"(Ceruti *et al.*1993;Ceci *et al.* 2020).

All parts of the plant, including stems, leaves, young shoots, flowers, nectar, sap and products induce by combustion are toxic and contain a variety of cardiac glycosides, the most prominent of which are oleandrin and nerine, collectively referred to ascardenolides (Galey *et al*. 1996; Langford and Boor 1996; Begum *et al*. 1999; Oji and Okafor 2000; Bandara *et al*. 2010) (Table 1). Due to relatively high lipophilicity resulting in a rapid and extensive gastrointestinal absorption and a slow urinary excretion rate, the most active molecule is oleandrin (Ceci *et al*.2020).

Table 1. Cardiac glycosides found in oleander species (adapted from Karawya et al.1973; Langford and Boor 1996; Kyerematen et al. 1985,Yamauchi et al. 1983).

Common oleander (*N. oleander*)	**Yellow oleander** (*T. peruviana)*
Oleandrin	Thevetin A
Folineriin	Thevetin B
Adynerin	Thevetoxin
Digitoxigenin	Neriifolin
	Peruvoside
	Ruvoside

In a study, Karawya *et al*. (1973)reported that seeds and roots of *N. oleander* contained the highest percentage of cardiac glycosides followed by fruits and leaves. Dry leaves are about as toxic as green ones (Galey *et al*. 1999). Glycoside's mechanism of action consists in an inhibition of the Na^+-K^+ATPase pump in the membrane of cardiomyocytes, resulting in an increase of intracellular Na^+ and Ca^{2+} concentration, and determining a positive inotropic effect, as well as a rise of the resting membrane potential with consequent augmented excitability and automaticity of myocardial cells (Farkhondeh *et al.* 2020; Ceci *et al*.2020). Interference with the vagal tone leading to slow atrioventricular conduction and ventricular arrhythmias has been also documented (Bandara *et al*.2010). Non-digitalis cardiac glycosides, contained throughout the plant, are among the most poisonous compounds found in plants and have toxic and sometimes fatal side effects, including gastric disorders (vomiting, nausea and burning), bradycardia, and increased respiratory rate and central nervous system disorders, including lethargy (Rubini *et al.,* 2019). Fractions of a methanol extract from the leaves were found to produce a reduction in locomotor activity, rotarod performance and potentiation of hexobarbital sleeping time in mice (Zia et al., 1995).

The main pathological findings included disseminated hyperemia and hemorrhages, degeneration and necrosis of the cardiac muscle fibers, enteritis, hepato- and nephropathy, pulmonary congestion (Lubian *et al.* 2021).

Despite their toxicity, both *N. oleander* and *T. peruviana* have several pharmacological activities and they have been used as an abortifacients, a treatment for dropsy (congestive heart failure), leprosy, malaria, ringworm, venereal disease and even as a suicide instrument (Osterloh *et al.* 1982; Langford and Boor 1996; Kostadinović *et al.* 2019; Farkhondeh *et al*. 2020; Aslanipour *et al*. 2020).Some researchers reported their potentiality as antibacterial agents, insecticides, rodenticides, and molluscicides(Osterloh *et al*. 1982; Obasi and Igoboechi 1991;Oji and Okafor 2000). The potential of oleander extract as a chemotherapeutic agent has been studied (Nasua *et al*. 2002,Winnicka *et al*.2006; Newman *etal*. 2007; Pan *et al.* 2015; Aslanipout *et al*.2020; Kanval *et al* 2020; Ayogu *et al*. 2020).Antiviral activity of oleandrin and a defined extract of Nerium oleander against SARS-CoV-2 has been evaluated (Plante *et al*. 2020).

Oleanders areone of the leading causes of poisoning cases and they are potentially lethal to different species of insects, domestic animals, and human be-

ings: ingestion, inhalation, and contact with all parts of the plant can cause much adverse toxicities and lethal effects (Langford *et al*., 1996; Aslani *et al*. 2004; Soto-Blanco *et al*. 2006). El-Shazly, Nassar & El-Sherief (1996) and El- Shazly, Rfeaei & Shaurub (1997) reported that ethanolic extracts of the leaves of *Nerium oleander* were lethal to the larvae of *Muscina stabulans* (Diptera-Muscidea) and to the second instar nymphs of *Spilostethus pandurus* (Heteroptera-Lygaeidae) when incorporated into the diet of these insects. The insecticidal activity of this plant has also been reported by Satphathi & Ghatak (1990), Satphathi, Ghatak & Bhusam (1991), Pushpafatha & Muthukrishnan (1995) and Hiremath, Young, Joon, Kim-Soon & Kim (1997).

Examination of toxic exposures of humans and animals to *N. oleander* has been discussed by Jaspersen-Schib *et al*. (1996) and Longford and Boor (1996). Toxic exposure of humans and different species of domestic animals to oleander cardenolides occurs commonly throughout the geographic regions where this plant grows. Human mortality associated with exposure to oleander is generally very low, however, accidental poisonings have been described, particularly in children, where one leaf can be lethal (Langford *et al*. 1996; Bandara *et al* 2010).The lethal dose of dried *Nerium oleander* leaves varies according to the animal species. Animals are often found dead owing to cardiac dysfunction, or they present with rapidly developing nonspecific signs (Farzaei *et al*. 2020). Clinical manifestations include mainly cardiac and gastrointestinal symptoms such as sinus bradycardia, atrioventricular blocks, paroxysmal ventricular tachycardia, acute renal failure, vomiting, nausea, apathy, abdominal pain, diarrhea, ataxia and tremors, coma, respiratory arrest, and death (Galey *et al*. 1996; Kozikowski *et al*. 2009; Reiner *et al*. 2013; Salih *et al.* 2017; Ceci *et al*. 2020).

Moreover, *N. oleander* is described as an unpalatable plant because of it releases a type of triterpenoid glycoside (saponins) when the fresh leaves are chewed, which produces an unpleasant burning sensation on contact with the oral mucosa (Mack 1984). Despite its poor palatability, the ingestion of toxic plants is a common occurrence found in domestic animals and livestock species (Kozikowski *et al*. 2009; Cortinovis *et al.* 2013; Reiner *et al.*2013). It can be consumed voluntarily by animals when they are hungry or when there is scarcity of fodder (Al-Farwachi *et al*. 2008; Flores *et al.* 2019; Ceci *et al*. 2020).However, poisoning can also be attributed to human managerial errors when oleander is unintentionally mowed, crushed, and mixed with feed. Animals can also be intoxicated after the ingestion of water containing fallen and macerated leaves(Ceci *et al*. 2020).

Several toxic exposures of humans and different domestic animals to *N. oleander r*in different geographic regions occurred (Aslani *et al*.2004).

Accidental and experimental cases of oleander poisonings have been described in several species, such as horses, chicken, geese, cattle, dogs, rabbits and bears (Ratigan 1921; Williams 1957; Trautvetter *et al*. 1969; Mahin *et al*. 1984; Alfonso *et al*.1994; Omidi *et al.* 2011; Caloni *et al*.2015;Taheri *et al.* 2013; Ceci *et al*. 2020). Experimental toxicosis with oleander has been induced in cats (Burton *et al.* 1965), dogs and goats (Szabuniewez *et al*.1971; Barbosa *et al*. 2008), monkey (Scwarts *et al.* 1974), camels (Vashista and Singh, 1977). The frequency and severity of mortality have been mostly studied in ruminants with reported mortalities between 41-100 % (Fazzio *et al*.2007; Soto-Blanco *et al.* 2006;). It seems that bovines are more sensitive compared to small ruminants, the LD being 50 mg/kg for cattle, 110 mg/kg for goats, and 250 mg/kg for sheep (Oryan *et al.* 1996; Adam 2001; Aslani *et al*. 2004).Other experimental toxicosis induced in cattle (Oryan *et al*. 1996) and sheep (Aslani *et al*.2004) demonstrated that sheep are highly sensitive to oleander toxicity (Aslani *et al*. 2004). In monogastric species, the risk of poisoning is reduced by the presence of saponins, which may facilitate the elimination of the ingested toxic vegetables (Mack 1984).

Therefore, the current review summarizes the anatomo-pathological consequences after accidental oleandrum poisoning, potentially hazardous plants inanimalfeed.

Anatomo-pathological consequences by oleander ingestion

In a study, Hughes *et al.*(2002) reported clinical signs, routine laboratory procedure results, ECG, changes and postmortem findings in a case of suspected cardiac glycoside toxicity from oleander ingestion in a horse (Arabian gelding) who died approximately 24 hours after presentation signs of rapidly progressive cardiovascular collapse, including hypothermia, ventricular tachyarrhythmia and weak pulses. The horse had exposure to *Nerium oleander* clippings for the 24 hours preceding presentation and died soon af-

ter. Ascites, multiple areas of full thickness ventricular myocardial haemorrhage up to 2cm in diameter and multiple subendocardial and subepicardial haemorrhages were present at necropsy examination. Histologically, there were multiple areas of myocardial degeneration and necrosis involving the ventricles. (Hughes *et al*. 2002).

Recently, Flores Olivares *et al.* (2020) reported the death of eight goats after accidental consumption of *N. oleander* administered by the feedlot manager. About 54% of the flock showed clinical signs that include agalactia, apathy, sternal decubitus, severe dehydration, anorexia, and/or head pressing. The autopsy findings revealed pale areas without clear limitations and a slightly elevated level of ventricular myocardium and papillary muscles on the left side. Both lungs showed an increase in their touch consistency and a presence of foam in the bronchial bifurcation and first tracheal portion. They also showed marked ruminal and abomasal distension with solid content and a fibrous aspect with remains of leaves that could not be identified at that time, as well as petechiae, hemorrhage in the abdominal serosa, duodenal mucosa, and the first portion of jejunum with marked congestion and slightly thickened walls and edematized in the first duodenal portion and its lumen. The large intestine presented greenish to brown content of low liquid consistency as well as reddened and enlarged mesenteric lymph nodes (twice its normal size). There were no alterations in size and morphology at the hepatic level. Histopathological lesions included marked multifocal necrosis of contractile myocardiocytes, rupture of myofibrils; edema and mild diffuse interstitial hemorrhage in the lung and in the kidney; in the reticulum, rumen, omasum, and abomasum, mild mononuclear inflammatory infiltrate, hyperemia, congestion, and bleeding in the lamina propria were also noted. Hepatocytes, hydrophilic and vacuolar degeneration was found in the centrilobular area(Flores Olivares *et al.* 2020).

Recently, Ceci *et al* (2020) described the occurrence of a cattle herd intoxication in Southern Italy due to the accidental presence of oleander leaves mixed with fodderin the hay. Animals died showing pedaling, convulsive movements, increased frequency of bellowing, and coma. The necropsy performed on all the dead animals showed a diffuse congestion of visceral organs including liver, kidneys, lungs, abomasum, and intestine. Multifocal, mild hemorrhages in the ventricular endocardium were also observed. The lungs were edematous, with frothy contents in the bronchi. Mild hydrothorax, hydropericardium, and ascites were also present. At the histological examination, all the cardiac areas showed mild multifocal hyperemia and hemorrhages and interstitial inflammatory infiltrates, kidneys showed diffuse passive hyperemia and mild, multifocal hemorrhages, and multifocal tubular degeneration were also detected. In the liver, perilobular nonsuppurative acute hepatitis with moderate diffuse hyperemia was observed. Regarding the gastrointestinal tract, signs of chronic enteritis were found. (Ceci *et al*. 2020).

Oleander toxicosis is rarely reported in avian species, with symptoms including cardiac, neurological and gastrointestinal manifestations. Experimental works demonstrated its effects in canaries, budgerigars and broiler chickens, with clinical symptoms and pathological findings similar to those reported in mammals (Arai *et al.* 1992; Omidi *et al.* 2011; Lubian *et al.* 2021). Alfonso *et al*. (1994) reports a case of an acute accidental intoxication that affected 21.9% of 5000 geese appeared in a breeding center. At necropsy, abundant hemorrhages in parenchymatous organs were found (Alfonso *et al.* 1994). Further, Omidi *et al*. (2011)evaluated an experimental oleander (*N. oleander*) intoxication in broiler chickens after giving a single dose of 500 mg/kg body weight to 20 clinically healthy male chickens. Pathological findings were generally consistent with those reported in turkeys (Aslani *et al*. 2007). Sudden death in broiler chickens occurred 1 hour after receiving oleander. During necropsy, there were congestion and hemorrhages in the visceral organs particularly in heart, liver, kidney, and lung (Omidi *et al*. 2011).In a recent article, Lubian *et al.*(2021) described a 6-month-old domestic goose (*Anser anserdomesticus*) presenting depression, anorexia, permanent sternal recumbency, weakness and incoordination. The owners witnessed the ingestion of oleander leaves. Despite the absence of evident cardiac symptoms, biochemical hematological findings showed significant increase of CPK, AST, LDH, and troponin. The animal didn't die because of an adequate therapy(Lubian *et al*. 2021).

Poisoning from both *N. oleander* and *T. peruviana* is a common toxicological emergency in tropical and subtropical parts of the world and commonly occurred in human and animals. Clinical symptoms and pathological findings are similar in mammals and avian species. As oleander contains cardiac glycosides, the heart is the most affected organ but congestion of

kidney, liver, lungs, and intestine, hydrothorax, hydropericardium, and ascites have also been reported. Lethal dose is not similar between animals, but this may be related to variation in the dose of the ingested poison: more studies should be done for calculating it. Identification of the plant and evidence of its consumption is essential to arrive at a confirmatory diagnosis of the poisoning because clinicopathological changes and necropsy findings are usually like other intoxications. Definitive diagnosis is only provided by laboratory testing (Bandara *et al*. 2010;Bothelo *et al.* 2018; Ceci *et al*. 2020).

CONCLUSION

Based on literature review and data available, far more research has to be done especially to establish the oleander lethal doses in the different livestock species. Although, it was reported for the first time the transfer into milk and dairy products from poisoned cattle, suggesting a potential risk for the consumers, the lack of information about the toxicity of oleanders suggests that it is necessary to deeply investigate this topic.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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