Toxicity Effects of Nerium Oleander, Basic and Clinical Evidence: A Comprehensive Review

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Abstract: - *Nerium oleander* is a plant that is frequently grown in gardens and public areas. *N. oleander* is distributed originally in subtropical Asia but is now growing in many parts of the world, such as the United States, Australia, China, and Middle East countries. Pharmacological effects of plant including antinociceptive, anti-inflammatory, and anticancer activity were reported, but the potential toxic effects of all parts of the shrub either fresh or dried on animal and human body were documented. The data of this review article were obtained from Medline/Pubmed, Scopusand Google Scholar databases in English until September 2019. To include all publications in this field, keywords such as *N. oleander* and toxicity were used. The poisoning effects of plant or their active alkaloids induced infiltration of cells with hemorrhage and sever negative changes in the lung, induce lesions, and infiltration of inflammatory cells into the portal spaces with scattered necrosis of hepatocytes in the liver, cardiac toxicity of the plant in the heart were included, induced varying degrees of hemorrhage, myocardial degeneration, and necrosis. It also induced arrhythmia, sinus bradycardia, and prolonged P-R interval in electrocardiographic records. The toxic effects of *N. oleander* are mostly related to its inhibitory effects on the $Na^þ$-$K^þ$ ATPase pump in the cellular membrane. However, the exact molecular mechanism involved in the toxicity of *N. oleander* is not clear. As the world transitions to the digital age, the need for construction companies to adapt to different technological advancements is becoming more and more crucial. The presence and continuous developments of these technologies can help to automate repetitive tasks and streamline processes, which can increase efficiency and reduce the time it takes to complete construction projects. This can lead to cost savings for both builders and customers. This study aimed to evaluate the difficulties being encountered by workers in the construction sector and develop a project monitoring application which can be used by different private construction firms currently based in the Province of Pampanga. The data were gathered through 2-phase survey questionnaires. The findings of the first part of the study showed that the construction sector continuously encounter project monitoring-related problems such as communication, shipment and delivery of tools and equipment, and health and safety standards. These factors led to the development of ConCheck Project Monitoring application that primarily focused on the digitalization of project monitoring among construction projects. Among the features of the application are: Daily Weather Report, Delay Type, Daily Progress Report, and Accomplishment Report. The application was pilot tested to 5 private construction firms and the survey results showed that the application's functionality enabled users to monitor their construction projects in a more efficient way. Moreover, the data gathered strongly suggests that the application would be beneficial for the companies to adopt. The findings of the study will be beneficial to construction companies in their efforts to address the need for technological advancements in the sector. Further, the results may be used by different web-developers in establishing a more user-friendly application that can help the construction sector intervene in the 21st century landscape of the workforce.

Key Words: — ***Nerium oleander, toxicity, organs.***

I. INTRODUCTION

Nerium oleander is an ornamental shrub that is grown as an attractive plant frequently in gardens and public city areas. N. oleander have linear and leathery leaves with various colors from dark green to grey-green with separate light yellowish veins. The flowers of

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N. oleander are funnel-shaped and fragrant, with white to pink to deep red colors. Its fruit is a narrow sheath containing many silky-haired seeds (Figure 1). This plant distributed originally in the subtropical Asia and Mediterranean region but is now growing in many parts of the world, including the United States, Australia, China, and Middle East countries.1

Fig.1. Nerium oleander (white, pink, and red colors flowers)

N. oleander has several pharmacological activities. Ethanolic and aqueous extracts from dried and fresh flowers and leaves of the plant showed significant antinociceptive activity in variable degrees against *p*-benzoquinone-induced abdominal contractions. In addition, ethanolic extracts of dried and fresh flowers revealed potent anti-inflammatory effects against carrageenan-induced hind paw edema in mice model.[2] The ethanol extracts from *Oleander* flowers against four important plants pathogenic fungi showed anti-mycotic activity using agar dilution bioassay.[3] The methanolic extract of the fresh leaves of *N. oleander* showed depressant effect in central nervous system of mice.[4] Although several pharmacological activities of *N. oleander* was reported, it has several toxicity effects on human and animal body.

N. oleander is well-known for its toxicity, it has potential toxic effects after ingestion, all parts of the plant contain several toxic compounds, such as oleandrin, oleandrigenin, and other cardiac glyco- sides. *N. oleander* with red flowers in the flowering stage produces more cardiac glycosides than shrub with white flowers.[5] Several toxic exposures of humans and different domestic animals to *N. olean- der* in the different geographic regions were occurs.[6] Generally, animal poisoning occurs due to consumption of *N. oleander* toxic shrub by hungry animals or due to unplanned contamination of food with this plant.[7]

The lethal doses of *N. oleander* leaves were recognized, which differ among animal species, such as sheep and rats (250 and 4000 mg/kg body weight (b.w.), respectively).[6,8] Therefore, the aim of this study was to show the toxicity effects of *N. oleander* on the animal and human body.

II. Literature Review

2.1 Method

The data of this review article were obtained from published articles, books, and conference papers in English until September 2019 from Medline/Pubmed, Scopus, Embase, and Google Scholar databases. To include all publications in this field, keywords such as *N. oleander* and toxicity were used.

N. oleander constituents:

A pentacyclic triterpene, oleanderocioic acid, two flavonoid glycosides, such as quercetin and kaempferol, as well as cardenolide and oleandigoside were iso-oleanolic acid were isolated as the active componentsfrom flowers of the plant.[10]

2.2 Toxic properties of N. oleander

The toxicity of *N. oleander* has been found for years. All parts of the plant especially seeds and roots contain cardiac glycosides.[11] The structure of cardiac glyco- sides is similar to digitoxin of the foxglove plant.[11]

Several studies have indicated that *N. oleander* may act as insecticides, pesticides, rodenticides, and antimi- crobial agents.[11] Consumption of five *N. oleander* leaves can cause lethal poisoning.[11] However, it was reported that one *N. oleander* leaf had severe toxic effects in children. Controversially, ingestion of three leaves of *N. oleander* with a 7 years old child caused moderate poisoning with no complication. Mild toxi- city was observed in an adult woman following consumption of five leaves of *N. Oleander*, without severe symptoms. Thus, determination of the fatal dose for *N. oleander* toxicity has not fully understood and more studies should be done to found the lethal doses of the plant. The severity of *N. oleander* toxicity is related to several factors including the concentration of toxin in ingested part of the plant, age, and health condition of the subject who consumed the plant.[11]

2.3 Toxic mechanism of N. oleander

Cardiac glycosides component in *N. oleander* inhibits the "$Na^þ$-$K^þ$ ATPase pump" in the membrane of cardiomyocytes, resulting in an increase in intracellular $Na^þ$ concentration. Additionally, this increase changes the shift of $Na^þ$-$Ca^{2þ}$ channels, resulting in an elevation in intracellular $Ca^{2þ}$ and contraction force and also cardiac automaticity.[12] "$Na^þ$-$K^þ$ ATPase pump" inhibition changes the shift of $K^þ$, resulting in

increased level of K[þ].[12] Hyperkalemia indicates the severity of toxicity in acute cardiac glycosides poisoning.[12]

2.4 Toxic effects of N. oleander on lungs

Intramuscularly (IM) administration of *N. oleander* leaves extract (10 mL/kg) in both hind limbs of rats showed mononuclear cell infiltrates in the lung tissue section, most frequently around the blood vessel 3, 12, and 24 h after administration. Dilation and even collapse in some alveoli were observed in alveolar tissue 24 h after administration. Massive infiltration along with hemorrhage and extravasation of blood cells and severe negative changes were also observed in the study group. Alveoli, alveolar sacs, and broncus were observed in section of the control lung tissue.[13] The aqueous decoction of leaves extract of *N. olean- der* leaves extract (10 mL/kg) induced histopatholo- gical changes in the Wistar rats lung tissues including alterations in the pulmonary tissue with disruption of bronchus mucosal folds. Also, alveolar cells with extreme widening of lumen of the bronchiole and vascular lesions have been observed. Inflammatory cells, especially neutrophils, were frequently found in the bronchoalveolar region. In addition, lung sections of the control group showed normal histological architecture and numerous clear alveoli with thin interalveolar septa and alveolar sacs.[14]

The aqueous extracts of *N. oleander* flowers (11, 22, and 33 mg/kg, b.w.) induced severe congestion in blood vessels and edema around the esophagus in albino male mice, especially at the high dose of extract.[15] The aqueous leaves extract of *N. oleander* (10 mg/kg, b.w.) on healthy male New Zealand rab- bits for 4-week treatment showed pathological changes, such as interstitial pneumonia, alveolar space hemorrhage, disappearance of pulmonary alveolus, thickening of the lung matrix, and alveolar septa, while in control group, there were no signifi- cant abnormalities observed in the lung tissue.[16] Orally administration of *N. oleander* leaves at lethal dose (110 mg/kg, b.w.) to native female goats induced interstitial hemorrhage in the lung 1 h after receiving the oleander and also caused congestion and edema in the lung of sheep.[17] Administration of *N. oleander* leaves (110 mg/kg, b.w.) induced varying degrees of congestion or hemorrhage in the lungs of sheep.[18] The results of the above studies indicated that leaves or flowers of *N. oleander* have toxic effects in the lung tissue of exposed animal, such as induced congestion in blood vessels, disruption of bronchus mucosal, induced inflammatory cells and neutrophils in the bronchoalveolar, and induced congestion or hemor- rhage in the lung tissue. The toxic effect of *N. olean- der* on the lung tissue of animal models was summarized in Table 1.

2.5 Toxic effects of N. oleander on liver

The results of Prussian blue iron-stained sections after 3, 6, and 12 h of *N. oleander* leaves extract (10 mL/kg, IM) administration showed extensive iron accumulation but in section after 12 h of admin- istration, mild deposition in sinusoidal space was also observed particularly. Distinct bluish granules (ferritin) within hepatocytes 6 and 12 h after onset of acute phase response were observed.[13] The extracts of *N. oleander* flowers (33 mg/kg, b.w.) induced hydropic degenerations in the liver tissue. In addi- tion, mononuclear cell infiltration in the portal spaces with scattered necrosis of hepatocytes was induced by plant flower extract. Congestion and hemorrhage in some cases were also observed.[15]

Dried leaves of *N. oleander* (110 mg/kg, b.w.) induced lesions in the liver that caused fatty change and infiltration of inflammatory cells into the portal spaces with scattered necrosis of hepatocytes in female goats and male sheep.[6,17] In addition, mild bile duct hyperplasia was observed in two goats.[17]

N. oleander leaves (110 mg/kg, b.w.) induced varying degrees of hemorrhage, degeneration and focal necrosis of hepatocytes, necrosis of hepato- cytes, fatty degeneration, and infiltration of mono- nuclear inflammatory cells in liver.[18] Table 2 indicates the toxic effect of *N. oleander* on the liver tissue of animal models.

2.6 Toxic effects of N. oleander on heart

Oral administration of 100 mg of *N. oleander* ethano- lic extract showed diffuse mild interfascicular edema with congested vessels and many fragmentations of myofibrils in degenerated myocytes 14 days after treatment in heart muscles. In addition, 200 mg of *N. oleander* ethanolic extract showed moderate interfascicular edema with dilated congested vessels and few degenerated myocytes with focal striation loss and focal vacuolar degeneration in the heart muscles; 30 days treatments animals with 100 mg of *N. oleander* showed focal mild interfascicular edema with congested vessels and very few degenerated myocytes in the heart muscles, while 200 mg of *N. oleander* showed focal marked interfascicular edema with congested vessels and moderately degenerated myocytes with vacuolation of the muscle.[20]

Table.1. Toxic effects of *N. oleander* on lungs

Plant	Experimental model	Dose/duration of injection/exposure route	Findings	References
N. oleander leaves extract	Rat	10 mL/kg/3, 12, and 24 h/IM	Mononuclear infiltration in the lung, especially around the blood vessel After 24 h, massive cellular infiltration, hemorrhage, and extravasation of blood cells Alveoli, alveolar sacs, and abronchus	Abbasi et al.[13]
N. oleander leaves extract	Rat (Wistar)	10 mL/kg/6 h/IM	Histopathological changes in the lung tissues Alterations in the pulmonary architecture Impairment of bronchus mucosal folds Extreme flattened bronchiole lumen Vascular lesions Increased inflammatory cells in the bronchoalveolar	Abbasi et al.[14]
N. oleander flowers extract	Mice (male, albino)	11, 22, and 33 mg/kg/ 4 days/IM	Induced severe congestion in blood vessels and edema around the esophagus, especially at the high doseof the extract	Majeed[19]
N. oleander leaves extract	Rabbit (male, New Zealand)	10 mg/kg/4 weeks/oral	Induced pathological changes, such as interstitial pneumonia, alveolar hemorrhage, disappearance of the pulmonary alveolus, and stiffness of the lung	Taheri et al.[16]
N. oleander leaves extract	Sheep (female, goat)	110 mg/kg/1 h/oral	Induced interstitial hemorrhage in the lung 1 h after receiving the oleander Caused congestion and edema in the lung	Aslani et al.[6,17]
N. oleander leaves extract	Sheep (male)	110 mg/kg/41, 56, and 80 h/oral	Induced varying degrees of congestionor hemorrhage in the lungs	Ozmaie et al.[18]

N. oleander: *Nerium oleander*; IM: intramuscular.

Oral administration of aqueous leaf extract of *N. oleander* for 28 days induced pathomorphological changes in the heart in male rabbits. Mild granular degeneration of myocytes, coagulative necrosis, frag- mentation in the cardiac muscle, and loss of striations were observed in heart by photomicrograph. In addition, intra-sarcoplasmic vacuoles with myocyto- lysis were also observed in the heart samples in treated animals compared to the control group.[16]

N. oleander flowers aqueous extracts (22 and 33 mg/kg, b.w.) showed congestion and hemorrhage, especially in the myocardium regions. In addition, varying degrees of coagulative necrosis of cardiac muscle cells that were associated with the infiltration of mononuclear inflammatory cells in heart sections were observed.[15]

N. oleander (110 mg/kg, b.w.) induced congestion and severe hemorrhage especially in the subendocar- dial regions in the hearts of goats. Additionally, vary- ing degrees of coagulative necrosis of cardiac muscle cells associated with infiltration of inflammatory cells were also observed. The mononuclear inflammatory cell infiltration into the endoneurium of nerve fasci- cles and hemorrhages in the left ventricular endocard was observed.[17]

Table.2. Toxic effects of *N. oleander* on liver.

Plant	Experimental model	Dose/duration of injection/exposure route	Findings	References
N. oleander leaves extract	Rat	10 mL/kg/3, 6, and 12 h/IM	Induced extensive iron accumulation and deposition especially in sinusoidal space after 12 h Distinct bluish granules (ferritin) in liver cells after onset of acute-phase response	Abbasi et al.[13]
N. oleander flowers extract	Mice (male albino)	11, 22, and 33 mg/kg/ 4 days/IM	Induced hydropic degenerations in the liver tissue Infiltration of mononuclear cell in the portal spaces with scattered hepatocytes necrosis Congestion and hemorrhage	Majeed[19]
N. oleander leaves extract	Sheep (female, goat)	110 mg/kg/1 h/oral	Induced fatty change lesions in the liver Infiltration of inflammatory cells into the portal spaces with scattered necrosis of hepatocytes Observed mild bile duct hyperplasia in two goats	Aslani et al.[6,17]
N. oleander leaves extract	Sheep (male)	110 mg/kg/41, 56, and 80 h/oral	Induced varying degrees of hemorrhage, degeneration and focal necrosis of hepatocytes, necrosis of hepatocytes, fatty degeneration, and infiltration of mononuclear inflammatory cells in liver	Ozmaie et al.[18]

N. oleander: *Nerium oleander*; IM: intramuscular.

Administration of *N. oleander* leaves (110 mg/kg, b.w.) induced varying degrees of hemorrhage, myo- cardial degeneration, and necrosis in the heart of sheep.[18] An earlier study conducted by Aslani et al.[6] on the cardiotoxicity impact of *N. Oleander* (110 mg/kg, orally, single dose) in male sheep indi- cated that sinus bradycardia was seen as the first symptom in electrocardiogram (ECG) 0.5 h after receiving this plant.[6] Then, the sinus arrhythmia was observed. The second cardiac effect was moderate and consists of blockage of arterial/ventricular (AV) valve, sinus tachycardia, ST-segment depression, AV dissociation, ventricular tachycardia, and fibrillation.[6] Histopathological examination indicated degenera- tion and necrosis in the myocardium.[6] Botelho et al. investigated the cardiotoxic effect of *N. oleander* hydroalcoholic extract (150 and 300 mg/kg) in guinea pigs.[21] It was found that *N. oleander* caused death due to severe cardiac arrhythmias in some animals. In vitro studies indicated that *N. oleander* disturbed electromechanical function in the heart by sodium ($Na^þ$) and potassium ($K^þ$) pump inhibition, mito- chondrial swelling, and the sarcoplasmic $Ca^{2þ}$ ATPase impairment. A non-blinded, placebo- controlled study was designed to investigate the pro- tective effect of digoxin-specific Fab fragments (dsFab) against cardiotoxicity induced by *N. Olean- der* in dogs. *N. Oleander* leaves (30 mg/kg, intrave- nous (IV)) caused dysrhythmias during 27 min of starting the administration. However, dsFab reversed to normal condition during the first minutes of injec- tion.[22] Fattahi et al. indicated that *N. oleander* (100 mg/kg, orally) caused ventricular fibrillation in sheep, leading to death in two animals.

However, pretreatment with garlic extract improved arrhythmia in five sheep.[23] Khordadmehr et al. investigated cardiac toxicity of *N. oleander* (10, 12.5, 15, and 20 mg/kg, orally) in Wistar rats and Balb/c mice.[24] Creatine kinase (CK) and troponin levels increased in mice and rat received *N. oleander*. Hyperemia, hemorrhage, and myofibroblasts were seen in the cardiac tissue of animals. Table 3 indicates the toxic effect of *N. oleander* on the heart tissue of animal models.

Table.3. Toxic effects of *N. oleander* on heart.

Plant	Experimental model	Dose/duration of injection/exposure route	Findings	References
N. oleander leavesextract	Mice (male)	100 and 200 mg ofdried extract/kg/ 14 and 30 days/ oral	Induced diffuse moderate interfascicular edemaand congested vessels Myofibrils fragmentations in degeneratedmyocytes (100 mg, 14 days)	Abdou et al.[20]
			Moderate interfascicular edema with dilated congested vessels and few degenerated myocytes, focal vacuolar degeneration (200 mg, 14 days) Focal moderate interfascicular edema, moderate congested vessels, and small number of degenerated myocytes (100 mg,30 days) Focal sever interfascicular edema, dilated congested vessels, moderate degenerated myocytes, and muscle vacuolation (200 mg,30 days)	
N. oleander leaves extract	Rabbit (male, New Zealand)	10 mg/kg/4 weeks/ oral	Induced pathomorphological changes in the cardiac cell Moderate granular degeneration of myocytes, coagulative necrosis, cardiac muscle fragmentation, and loss of striations Induced intra-sarcoplasmic vacuoles, myocytolysis in the cardiac cells	Taheri et al.[16]
N. oleander flowers extract	Mice (male albino)	11, 22, and 33 mg/kg/ 4 days/IM	Induced congestion and hemorrhage especially in the myocardium regions Induced coagulative necrosis in the heart muscle cells Induced inflammatory cells infiltration	Majeed[19]
N. oleander leaves extract	Sheep (female, goat)	110 mg/kg/1 h/oral	Induced congestion and severe hemorrhage, particularly in the subendocardial in the hearts Induced coagulative necrosis of cardiac musclecells and inflammatory cells infiltration Induced mononuclear cell infiltration into the endoneurium of nerve fascicles of conductive system and hemorrhages in the left ventricular endocard	Aslani et al.[17]
N. oleander leaves extract	Sheep (male)	110 mg/kg/41, 56, and 80 h/oral	Induced varying degrees of hemorrhage, myocardial degeneration, and necrosis in the heart	Ozmaie et al.[18]
N. oleander leaves extract	Sheep (female, goat)	110 mg/kg/1 h/oral	Induced sinus bradycardia, sinus arrhythmia, blockage of AV valve, sinus tachycardia, ST-segment depression, AV dissociation, ventricular tachycardia, and fibrillation Degeneration and necrosis in the myocardium	Aslani et al.[8]
N. oleander leaves extract	Pig (male, guinea)	150 and 300 mg/kg/ 0, 45, 90, 135, and 180 min/oral	Induced death due to severe cardiac arrhythmias Disturbed electromechanical function in the heart by Na^+ and K^+ pump inhibition, mitochondrial swelling, and the sarcoplasmic Ca^{2+} ATPase impairment	Botelho et al.[21]
N. oleander leaves extract	Dog	30 and 60 mg/kg, IV/ 15, 30, 60, 120 and 160 min/oral	Induced dysrhythmias during 27 min of starting the administration	Clark et al.[22]
N. oleander leaves extract	Sheep	100 mg/kg/oral	Induced ventricular fibrillation, leading to death in two animals Improved arrhythmia pretreatment with garlic extract in five sheep	Fattahi et al.[23]
N. oleander leaves and flowers extract	Rat (Wistar) and mice (Balb/c)	10, 12.5, 15, and 20 mg/kg/1–4 days/oral	Increased CK and troponin levels in miceand rat Hyperemia, hemorrhage, and myofibroblastsin the cardiac tissue of animals	Khordadmehr and Nazifi[24]

N. oleander: *Nerium oleander*; AV: arterial/ventricular; Na^+: sodium; K^+: potassium; CK: creatine kinase.

2.7 Toxic effects of N. oleander *on blood parameters*

Oral administration of *N. oleander* alcoholic extract (100 and 200 mg of dried extract/kg) after 14 days significantly changed blood parameters including increased mean corpuscular hemoglobin (MCH) and decreased white blood cells (WBCs) at 200 mg of extract and also significantly decreased lymphocytes (%) at two doses of extracts. In addition, after 30 days of oral administration, mean corpuscular volume (MCV), WBCs, and platelet (PLT) count significantly elevated at 200 mg of extract. The percent of lymphocytes also significantly decreased at two doses of extracts.[20]

The aqueous extracts from boiling air-dried leaves of *N. oleander* in 0.9% NaCl solution (1:1, w/v) significantly altered hematological parameters such as red blood cells (RBCs), hemoglobin (Hb), hematocrit, MCV, lymphocyte, neutrophil, monocyte, and eosinophil count in the groups of *N. Oleander* oral intake for 3 and 7 days compared to the control group.[25]

The aqueous leaves extract of *N. Oleander* and flowers (25 mg/kg, b.w.) significantly increased WBCs, while decreased RBCs and Hb, after 2 and 4 weeks treatments in mice compared with the control group.[26]

Intraperitoneal administration alkaloid extract of *N. Oleander* leaves (20 mg/kg) per day for a period of 30 days significantly decreases b.w. after 10, 20, and 30 days of experience in treated female mice compared with control group. Alkaloid extract of *N. oleander* also significantly decreased packed cell volume (PCV), mean platelet volume, MCH, and Hb, while significantly increased RBC distribution width, MCH concentration (MCHC), plateletcrit, PLT, and WBC in treated female mice compared to the control group.[27]

The aqueous leaves extract of *N. Oleander* (10 mg/kg b.w.) once a day for 28 days significantly increased RBC and WBC counts and also mean Hb value in the treated rabbits compared to the control group. However, the PLTs count was decreased significantly in the treatment group compared to the control

group. The percent of PCV value was noticeably higher in treated rabbits, although it was not statistically significant.[16]

Table 4 indicates the toxic effect of *N. Oleander* on the blood parameters of animal models.

Table.4. Toxic effects of *N. oleander* on blood parameter

Plant	Experimental model	Dose/duration of injection/exposure route	Findings	References
N. oleander leaves extract	Mice (male)	100 and 200 mg of dried extract/kg/14 and30 days/oral	Increased MCH and decreased WBCs(at 200 mg of extract) Decreased lymphocytes (at two-doseof extracts) Increased MCV, WBCs, and PLT (at 200 mgof extract, after 30 days) Decreased the percent of lymphocytes(at two-dose of extracts)	Abdou et al.[20]
N. oleander leaves extract	Rat (Wistar)	Dried extract in 0.9% NaCl solution (1:1, w/v)/3 and 7 days/oral	Altered RBCs, Hb, HCT, MCV, lymphocyte, neutrophil, monocyte, and eosinophil count in the groups of *N. oleander*	Akhtar et al.[25]
N. oleander leaves and flowers extract	Mice	25 mg/kg/4 weeks/oral	Increased WBCs Decreased RBCs and Hb	Altaee[26]
N. oleander leaves extract	Mice	20 mg/kg/30 days/IP	Decreased body weight after 10, 20, and 30 days of experience in treated female mice Decreased PCV, MPV, MCH, and Hb Increased RDW, MCHC, PCT, PLT, and WBC in treated female mice	Hussein[27]
N. oleander leaves extract	Rabbit (male, New Zealand)	10 mg/kg/4 weeks/oral	Increased RBC and WBC counts and also mean Hb value Decreased the PLT count	Taheri et al.[16]

N. oleander: *Nerium oleander*; MCH: mean corpuscular hemoglobin; WBC: white blood cell; MCV: mean corpuscular volume; PLT: platelet; RBC: red blood cell; Hb: hemoglobin; HCT: hematocrit; PCV: packed cell volume; MPV: mean platelet volume; RDW: red blood cell distribution width; MCHC: mean corpuscular hemoglobin concentration; PCT: plateletcrit; IP: intraperitoneal.

2.8 Serum biochemical parameters

The toxic impact of *N. oleander* extract (100 and 200 mg of dried extract/kg, orally, for 14 and 30 days) was evaluated in mice. The findings indicated that interleukin 1 (IL-1), IL-6, tumor necrosis factor a (TNF-a), CK, and CK-MB were significantly increased at 200 mg of *N. oleander* ethanolic extract after 14 days of treatment, but C reactive protein (CRP) and lactate dehydrogenase (LDH) were significantly increased at 100 and 200 mg of *N. oleander* ethanolic extract. In addition, after 30 days of treatments, IL-6, TNF-a, CRP, aminotransferase (ALT), LDH, CK, and CK-MB levels were significantly increased at 100 and 200 mg of plant extract, while IL-1 was only significantly increased at 200 mg extract group compared to the control group.[20]

The oral administration of aqueous extract of *N. Oleander* leaves and flowers (25 mg/kg, b.w.) significantly increased alanine aminotransferase, aspartate aminotransferase (AST), glutamic- pyruvate transaminase (GPT), and glutamyl oxaloacetic transaminase (GOT) after 2- and 4-weeks treatments in mice compared with the saline- treated control group.[26] These changes were depended on the time of treatments.

Serum calcium levels decreased but not significantly after 2 weeks oral administration of the *N. oleander* summer and winter leaf extracts com- pared to control rabbits, while in 4 weeks after treatment showed winter leaf extracts group decreased calcium levels significantly compared to the control group. The winter extract group was more toxic than the summer group that may be due to the presence of different active ingredient of the plant. The time of treatment was similar between different treated groups.[28]

Serum $K^þ$ levels after 2 weeks significantly increase in summer and winter *N. oleander* leaf extracts compared to the control group, while there were no significant differences between summer and winter groups. Increased levels of $K^þ$ were depended on the time of treatment (2 and 4 weeks).[28]

The serum levels of ALT significantly increased between the two summer and winter *N. oleander* leaf extracts compared to the control, while there were no significant increase differences between winter and summer groups. Additionally, serum levels of AST and alkaline phosphatase were not significantly changed between the summer and winter *N. oleander* leaf extracts compared to the control.[28]

Table.5. Serum biochemical parameter.

Plant	Experimental model	Dose/duration of injection	Findings	References
N. oleander leaves extract	Mice (male)	100 and 200 mg of dried extract/kg/14 and 30 days/oral	Increased IL-1, IL-6, TNF-a, CK, and CK-MB (at 200 mg, 14 days) Increased CRP and LDH (at 100 and 200 mg, 14 days) Increased IL-6, TNF-a, CRP, ALT, LDH, CK, and CK-MB levels (at 100and 200 mg, 30 days) Increased IL-1 (at 200 mg)	Abdou et al.[20]
N. oleander leaves and flowers extract	Mice	25 mg/kg/4 weeks/oral	Increased ALT, AST, GPT, and GOT	Altaee[26]
N. oleander leaves extract	Rabbit	94.36 mg/kg for summer extract and 79.75 mg/kg for winter extract/2 and4 weeks/oral	Decreased serum calcium levels Increased serum $K^þ$ levels Increased the serum levels of ALT between the two summer and winter *N. oleander* leaf extracts compared to the control Not significantly changes in serum levels of AST and ALP between the two summer and winter *N. oleander* leaf extracts compared to the control	Salih and Alkhayyat[28]
N. oleander leaves extract	Rat (Wistar)	10 mL/kg/3, 12, and 24 h/IM	Enhanced total iron content in the serum with maximum increase 156.87% after 12 h Decreased the serum ferritin at 3 and24 h of injection with 29% and 23% Increased serum hepcidin concentration which reached thepeak at 12 h compared with the control group while decreased 9.53% value after 24 h	Abbasi et al.[29]
N. oleander leaves extract	Sheep (male)	110 mg/kg/41, 56, and 80 h/oral	Decreased serum glucose and urea concentration Increased serum activity of enzymes such as ALT and AST	Ozmaie et al.[18]

N. oleander: *Nerium oleander*; IL-1: interleukin 1; TNF-a: tumor necrosis factor a; CK: creatine kinase; CK-MB: creatine kinase MB; CRP: C reactive protein; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GPT: glutamic- pyruvate transaminase; GOT: glutamyl oxaloacetic transaminase; IM: intramuscular.

Administration of aqueous leaves extract of *N. oleander* (10 mL/kg, IM) significantly enhanced total iron content in the serum with maximum increase of 156.87% after 12 h and 100% rise was observed after 3 h, in male Wistar rats compared to

control group. The serum ferritin was declined at 3 and 24 h of injection with 29% and 23%, respectively, which were not significant differences with control group. Serum hepcidin concentration greatly increased which reached a peak at 12 h compared with the control group while decreased 9.53% value after 24 h.[29]

Administration of *N. oleander* leaves (110 mg/kg, b.w.) as lethal dose decreased serum glucose and urea concentration. Serum activity of enzymes such as ALT and AST was increased in experimental group compared to the control group.[18]

Table 5 indicates the toxic effect of *N. oleander* on the serum biochemical parameters of animal models.

2.9 Clinical toxicity of N. oleander

Human poisoning due to *N. oleander* may be caused by accidental or intentional consumption, consump- tion for medicinal purpose, or criminal poisoning. Oleander poisoning has been observed in some coun- tries, including Europe, United States, Asia, and Africa and also in Australia.[30] Few case report asso- ciated with *N. oleander* poisoning has been observed. In this context, a case of *N. oleander* poisoning was reported by Osterloh et al.[31] They reported a 96 years old woman who died following consumption of *N. oleander*. However, Driggers et al. reported a sur- vived 83 years old woman of *N. oleander* poisoning who ingested for suicide.[32]

It was reported death of 58 years old Caucasian woman due to consumption of *N. oleander* for self- poisoning. The pathological evaluation indicated petechiae, edema, and congestion in tongue, gastric, and lung.[33] PBI-05204, a *N. Oleander* extract comprising oleandrin, blocked the "a-3 subunit of Na/K ATPase, FGF-2 export, Akt and p70S6K," leading to alleviating the activity of mTOR. Grade 1 atrioven- tricular block was observed in 10 subjects and supra- ventricular tachycardia (grade II) in one patient.[34]

N. oleander poisoning was reported in a 21 years old woman. She was admitted to hospital with vomiting, lightheadedness, and cardiac block. Electrocardio- gram indicated P wave reversion in inferior and PR interval prolongation, with varying degree AV blocks.[35] Shumaik et al. presented a case report about self-poisoning with *N. Oleander*.[36] The main symptoms were bradycardia and sinoatrial nodal arrest inpatient. "Digoxin-specific Fab antibody fragments (Digibind®)" improved cardiac problems. It was also reported that a man was criminally administrated.

N. oleander roots extract for 8 weeks. The symptoms such as nausea, diarrhea, abdominal pain, and confusion were similar to acute toxicity. His clinical symptoms were moderate at the beginning, but elevated later. "Sinus tachycardia" with "diffuse ST depression" and inverted "T wave" were observed in ECG and also elevation in the levels of CK.[37]

III. CONCLUSION

N. oleander poisoning commonly occurred in animal and human; however, the fatal cases due to this plant toxicity were reported. Children are very susceptible to the toxic effect of *N. oleander*. Accidental ingestion in children and use of the plant for suicide are two main causes of *N. oleander* poisoning in the world. The important clinical characteristic of *N. oleander* consists of vomiting, nausea, abdominal pain, diarrhea, arrhythmias, and hyperkalemia. The important toxic impact of oleander poisoning is cardiotoxicity (ventricular arrhythmia, tachycardia, and bradycar- dia). Electrocardiography indicates an elevated "PR interval," a reduced "QRS-T interval," and "T wave inversion." Animal studies have also indicated that cardiac glycoside component, especially oleanderin, of this plant could disturb the normal heart function.

Additionally, this plant has hepatotoxic, hematotoxic, and respiratory toxic effects. The lethal dose of this plant in the animal studies is not similar as some studies used dried leaves and others used green plant. Additionally, the amount of toxic glycoside in the plant varies according to the size of leaves, season, and other environmental parameters in which that plant has grown. However, Osterloh et al.[31] reported the lethal dose of oleander leaf for their patient was approximately 4 g, but more studies should be done for calculating exact lethal dose. The toxic effects of

N. oleander are mostly related to its inhibitory effects on the "$Na^þ$-$K^þ$ ATPase pump" in the cellular mem- brane. However, the exact molecular mechanism involved in the toxicity of *N. oleander* is not clear.

In recent years, digoxin-specific Fab antibody frag- ments are found as a suitable agent for dysrhythmias and hyperkalemia in acute poisoning with *N. olean- der.* Additionally, animal studies suggested that plant with antioxidant activity could be suitable approach for ameliorating of cardiotoxicity induced by *N. oleander*. Overall, *N. oleander* is a toxic plant and should not be grown in gardens and public areas for protection of children and animals.

Limitations:

Due to limited studies conducted on the *N. oleander* poisoning and also a low number of animal and human that poisoned with this plant ingestion, the present study could not reveal all aspects related to *N. oleander* such as lethal doses for human with different age and various animal species. Therefore, more experimental studies are needed to clear these.

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