WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 6, 794-806. Review Article ISSN 2277–7105

A REVIEW: *NERIUM INDICUM* OR *NERIUM OLEANDER* AND ITS TOXICITY IN VERTEBRATES

Krishma Chaudhary*, Veena Batra Kushwaha and Sunil Kumar Srivastav

Department of Zoology, Deen Dayal Upadhyay Gorakhpur University, Gorakhpur.

Article Received on
03 February 2024,

Revised on 23 Feb. 2024,
Accepted on 13 March 2024

DOI: 10.20959/wjpr20246-31728

***Corresponding Author**
Krishma Chaudhary
Department of Zoology,
Deen Dayal Upadhyay
Gorakhpur University,
Gorakhpur.

ABSTRACT

In this review article has been evaluated toxicity of *Nerium indicum* or *Nerium oleander* in the body organs of different animal. In recent year the population of India is in the first place all over the world so the demand of food is increasing also. To cope of food necessity the farmers uses different type of synthetics pesticides and botanical pesticides in agricultural fields. *Nerium indicum* considered to be very toxic due to secondary metabolites present in the plants. It is a great replacement of synthetics pesticides because it's easily availability in nature. *Nerium indicum* could be a great fertilizers if uses brilliantly. The toxicity of *Nerium indicum* plant is mild to severe which causes death to the animals and human being also. It crosses blood-brain barrier and block Na+K+ATPases which causes effects on vital organs and muscles of body. Decrease in sperm formation in seminiferous tubules, necrosis, inflammation in kidney, liver, heart, mucus formation in lungs. Additionally, ROS formation and free radicals, decline in calcium, inorganic phosphate, albumin and increase in bilirubin, creatinine, LDH, Uric acid, urea, SGOT and SGPT.

KEYWORDS: *Nerium indicum*, toxicity, Botanical pesticide, Cardiac glycosides, vertebrate.

INTRODUCTION

Nerium indicum is glycosides bearing toxic plant in which secondary metabolites are present mostly found at the Gangetic region, Himalayan areas of Nepal to Kashmir and Mediterranean countries.[1,2] *Nerium oleander* grows very fast, planted as highway barriers and roadsides which act as noise silencer and pollution controller.[3] Cardiac glycosides

inhibit Na+K+ATPase pump in animals which cause toxic effect in their biological system.[4,5]

Nerium indicum commonly known as Kaner in Hindi, surkh kaner in Unani, Gauri Pushpa in Ayurveda.[6] It is a large evergreen flowering shrub. A studies shows *Nerium oleander* contain oleandrin, theventin A, thevetin B and neriifolin, odoroside, odoroside H, odoroside A, neritaloside, vanderoside, monoglycocidic cardenolides, adynerin, daneric acid, neriucoumaric acid and 12β-D-hydroxypregna4,6,16-trien-3,2,20-dione.[7,8,9]

Accidental consumption of Nerium leaves, flowers are very toxic to animals which causes severe damage, sometimes caused death in cow.[10,11,4,5] A case study showed oleandrin causes effect in heart, brain, kidney and liver of on Guinea pig (*Cavia porcellus*).[12] *Nerium oleander* shows negative effect in digestive system, blood pressure, cardiac function and causes hyperkalemia, hypoglycemia in dog.[13,14] A case of death is reported due to hemorrhage and necrosis in kidney, heart, liver and mesentery in a child.[15] An increase level of inflammatory marker c-reactive protein (CRP) and pro-inflammatory cytokines interleukin-1, interleukin-6 and tumor necrosis factor α (TNF α) in mice.[16]

Besides their toxicity *Nerium oleander* have antioxidant, anticancerous, antimalarial, anti-inflammatory, hepatoprotective and cardioprotetive properties[17,18], antidiabitic.[1,19,18,20,17] Different studies show anti-anxiety properties of *Nerium oleander* by binding of flavonoids in GABA receptors BZD in brain cell.[21]

Toxic Properties

Nerium contains several lethal toxins, neroside and oleandroside, the cardiac glycosides oleandrigenin. It was reported that the toxins of this plant, upon ingestion, shut down the cardiovascular and nervous system, after causing severe nausea and projecting vomiting.

***Nerium indicum* toxicity in different organs of vertebrates**

Toxic effect on fishes

Different studies on *Nerium indicum shows* decline in pyruvate, acetylcholine esterase enzyme, DNA, RNA, protein, alkaline phosphatase and increase in lactate, Aspartate aminotransferase, Alanine aminotransferase, proteases activity, free amino acid in liver and muscle of *Chana punctuates, Chana maurilius, Colisa fasciatus*.[22,23,24] In *Heteropneustes fossilis* decrease in nuclear volume, degeneration and necrosis in ultimobranchial gland is

observed after administrated with Nerium leaves.[25,26] Mortality in zebra fishes (*Brachydanio rerio*) is observed due to severe effect of Nerium leaves.[27] *Nerium indicum* latex effect the size and number of fishes *Mystus mystus* and *Chhana punctatus.*[28,29] and declined in level of Acetylcholine esterase and alkaline phosphatases in *Chhana marulius* brain tissue.[30] In fishes Nerium leaves caused toxic effect, increase in dermal mucus secretion, frequent opening of gill, and loss of body equilibrium.[22]

Nerium Toxicity in Birds

Researchers noted oleander toxicity caused neurological problems, discontinuous myofibril, RBCs infiltration and pycnotic in cardiac cell and hemorrhage, degeneration in tubules in the kidney of Franconia geese (*Anser anser*)[31] and *Gallus gallus.*[3] Omidi and his coworkers also observed degeneration in hepatocytes and hemorrhage in liver in broiler chickens.[3] Behavioural changes like depression, weakness, atrophy and increase in lactate dehydrogenase, troponin Ⅰ and AST due to Nerium poisoning in *Anser anser domesticus.*[32]

***Nerium indicum or oleander* toxicity in mammal**

Toxicity in lung: Lung is the one of the organs which is affected by toxicants lesions and damage caused by oxidative stress of cells due to toxic nature of *Nerium oleander*. Oleander poisoning causes effect on bronchioles, lumen widening expansion of alveolar cell and hemorrhage in lung in rat.[33] Accumulation of mucus hemorrhage blockage and edema in lungs[34] of mice and pneumonia in rabbit[35,36], in cow[4,5] after treatment with *Nerium oleander* leaves. Nerium contains oleandrin, neriin and digitoxigenin causes fatal toxic effect shows diarrhea, anemia and swelling in interstitial and alveolar tissues in lungs and even death in cow.[37]

Toxic effect on digestive organs

Oral administration of *Nerium oleander* shows degradation and necrosis in gastric glands in rabbit after exposure.[36] A case study by some researchers shows hemorrhage in abdominal serosa, jejunum and duodenum in goat after oleander consumption with foliage.[38] Unidentified red nodule like structure is noticed in case of cow treated with Nerium leaves and flower with fodder.[4] Another report of congestion, hemorrhage, mononuclear cell infiltration of intestine in cows due to N. oleander toxicity.[37]

Toxicity in kidney

Kidney is a vital organ in a mammal it's have an important role in homeostasis and excretion of waste product outside the body. Most of the pesticides direct effect in kidney function. After exposure with *Nerium oleander* leaves necrosis, inflammation, cell aggregation, hemorrhage in kidney are reported in different animals like mice[39,40,41,42,34,43,44], rat[39,33], sheep[45,2], horse[46] and goat.[38,47] Another study in rat exhibits kidney necrosis and changes in fatty acid after treatment of mustard oil extract with root barks.[48] It has been noted necrosis and lesions in corticomedullary in kidney of horses after oleander administration.[46]

Toxicity in liver

Nucleus fragmentation in Hepatocytes of liver is noticed by[49] after rat exposed with *Nerium oleander* leaves. A study shows increase in serum hepcidin, necrosis, over granulation, blood accumulation in hepatic cell, inflammation in hepatocytes is noticed in rats after exposure of *Nerium oleander.*[50,51,33,52,49,39] *Nerium indicum* leaves shows hepatic necrosis and broadening of sinusoidal spaces due to ROS formation in rat.[53] Focal degeneration, hemorrhage, hyperplasia in hepatocytes and enlargement of semi sinuses is observed by[39,34,41,42,43,44,54] and[55] in liver on mice after administration of *Nerium oleander* leaves and flower. Dermal administration of root barks of oleander shows fatty acid depletion and inflammation in rat.[48] Another study shows effect of *Nerium oleander* causes hemorrhage, focal degeneration in liver of cow.[4,37] Other investigators indicated fatty acid accumulation, degeneration the liver of sheep.[45,2] Toxic damage caused by Inflammation in kupffer's cell, fatal vacuolization in hepatocytes and nucleus are found in periphery of hepatic lobules.[52] Some researchers noted increased cell damage; hemorrhage causes apoptosis and congestion in liver when high doses of oleander given to mice.[56]

Toxic effect in heart

Multifocal cardiac necrosis, cardiac degeneration and the condition of picnosis due to imbalance in Na+/Ca+ ion channel is caused by *Nerium oleander* poisoning in goat.[38,47] Vacuolization, infiltration of mononuclear cell, swelling in pericardium cardiac muscles of rabbit.[57,58,35,36] A studies shows coagulation, degeneration and vacuolization in myocytes of mice[16,41,59,34,43,44] and rat[20] after exposure of *Nerium oleander* leaves and flower. Increase in mean corpuscular volume, Case studies on Bison (Bovine animal) shows hemorrhage, cardiomyocyte necrosis and focal degeneration in cardiac after administration of *Nerium indicum* with fodder.[60] Another report of cardiotoxicity sometimes caused edema,

hemorrhage, necrosis, degeneration in myocytes in cow[4,5,37,10] and horse[46] are observed due to oleander plants. Nerium exposed dogs showed abnormal heart beat and blockage in atrioventricular.[13] Electro cardio graph (ECG) studied done by some investigators shows tachyarrhythmia in donkey due to inhibition of Na+K+ pump causes overload of calcium in heart.[61] Some investigators Yellow oleander or *Thevetia cerebra* seed poisoning observed in patients in Kerala, India shows symptoms like abnormality in ECG due to inhibition in Na+K+ATPase function in body due to cardiac glycosides present in oleander species.[62]

Effects on brain

An observation conducted by shows negative effect in brain tissues in mice and focal degeneration in rat brain noticed by[41,34,59] A researcher observed oleander toxicity caused lack of motor impairment in central nervous system in rats and mice due to Nerium block the synaptic transfer by enhancing GABA receptor in CNS.[61] Some investigators showed degeneration, hyperemia, swelling and degeneration in neurons in brain of cows due to oleander poisoning.[37] Researcher noted congestion, cluster of cells around hemorrhage and cell proliferation in damaged cell of brain due to Nerium poisoning occur in mice.[40]

Toxic effect on spleen

Report of spleen enlargement in mice[55] and necrosis and reduction in splenic follicles in rat is observed after administration of *Nerium oleander* leaves.[33]

Effect on reproductive organs

Nerium oleander administration exhibits necrosis in seminiferous tubules, block the formation of primary spermatozoa causes reduction in spermatogenesis or germ cells in rat.[63,48] A study conducted in sheep observed abnormality in sperm structure, function, decrease in sperm count and mobility due to toxic effect of oleander.[64] In yellow oleander kaempferol and quercetin inhibit fertility by declining progesterone level in female rat.[65]

Effects on Biochemical parameters

Animal	Plant parts	Effects on blood parameters	References
Charles foster rat	*Nerium indicum* roots	No any changes are reported in SGOT, bilirubin, creatinine, uric acid, calcium, albumin, globulin but increase in SGPT and cholesterol.	[48]
Wistar rats	*Nerium indicum* Leaves	Decrease in calcium and phosphate level	[66]
Albino rat	*Thevetia*	Induced in serum urea and creatinine level	[67]

	peruviana (seeds)	but no alteration in bilirubin	
Sheep	*Nerium oleander* Leaves	Increase in bilirubin, urea, lactate dehydrogenase and decrease in albumin level	[45]
Albino rat	*Nerium oleander* Leaves	Increase in liver enzymes ALP, AST and decrease in albumin	[49,68]
Mice	*Nerium oleander*	Induce in enzymes Alanine transaminase, urea, aspartate transaminase and creatinine	[54]
Cow	*Nerium oleander* leaves	Creatinine, urea, alkaline phosphatase, lactate dehydrogenase, total protein level is increased and diminished in calcium level	[10]
Sheep	Nerium oleander leaves	Induced liver enzymes AST, ALT and increase in Urea, Uric acid, Creatinine, bilirubin, triglyceride, glucose due to enormous release of catecholamins by autonomous nervous system	[2]
Rats	*Thevetia Peruviana* seeds	*Thevetia peruviana* seeds in rats exhibit decrease in creatinine, no changes in ALP, SGPT, SGOT and Bilirubin	[69]
Wistar rats	*Nerium oleander* leaves	Increase in monocyte, eosinophils, neutrophils is noted due to immune response	[53]
Heteropneustes fossilis	*Nerium indicum* Leaves	Decline in calcium and inorganic phosphate	[25,26]
Rabbit	*Nerium indicum* Leaves	Decrease in albumin, protein and increase in blood urea and creatinine	[70]
Mice	*Nerium indicum* Leaves	Increase in Aspartate aminotransferase, Alkaline phosphatase and Alanine aminotransferase	[2]
Mice (*Musmusculus*)	*Nerium oleander* leaves	Decline in red blood cells, hemoglobin and increase in platelets	[71]
Rabbit	*Nerium oleander* leaves	reduction in calcium and decrease in K+, ALP, ALT and AST	[72]
Donkey	*Nerium oleander*	increase level of serum creatinine, Alkaline phosphatase, Aspartate amino transferase	[61]

ACKNOWLEDGMENT: Authors are very much thankful to H.O.D. Department of Zoology for providing research facilities.

Conflict of Interest: Declared no conflict of interests.

REFERENCES

1. Sikarwar MS, Patil MB, Kokate CK, Sharma S and Bhat V. Antidiabetic activity of *Nerium indicum* leaf extract in alloxan-induced diabetic rats. Journal of Young Pharmacists, 2009; 1(4): 330-335.
2. Ozmaie S, Akbari G, Asghari A, Sakha M, Mortazavi P. Experimental oleander (*Nerium oleander*) poisoning in sheep: Serum biochemical changes and pathological study Annals of Biological Research, 2013; 4(1): 194-198.
3. Omidi A, Razavizadeh AT, Movassaghi AR and Aslani MR. Experimental oleander (*Nerium oleander*) intoxication in broiler chickens (*Gallus gallus*). Human & experimental toxicology, 2012; 31(8): 853-858.
4. Rajbanshi, BR, Mishra C, Adhikari J, Timalsina S, Pokhrel P and Bashyal K. Oleander Poisoning in Cattle in Devghat, Nepal-A Case Report. Nepa. Vet. Journal, 2023; 38: 224-229.
5. Zorzan A, Perosa F, Cecco B S, Santos IR, Menegatt JC, Bandinelli MB, Dalto AG, Pavarini SP and Panziera W. Intoxication by *Nerium oleander* in Cattel: use of immunohistochemistry for troponin C as auxiliary diagnostic method. Ciencia Rural, 2023; 54(5): 1-6.
6. Kumar GS and Gupta D. Hepatoprotective and antioxidant activity of methanolic extract of flowers of *Nerium oleander* against CCl4–induced liver injury in rats. Asian Pacific Journal of Tropical Medicine, 2012; 5(9): 677-685.
7. Bandara V, Weisttein SA, White J and Eddleston M. A review of the natural history, toxinology, diagnosis and clinical management of *Nerium oleander* (common oleander) and *Thevetia peruviana* (yellow oleander) poisoning. Toxicon, 2010; 56(3): 273-281.
8. Rashan J, Ozenver N, Boulos JC, Dawood M, Roos WP, Franke K, Papasotiriou I, Wessjohann LA, Fiebig H and Efferth T. Molecular Modes of Action of an Aqueous *Nerium oleander* extract in cancer cells In Vitro and In Vivo. Molecules, 2023; 28(4): 1871.
9. Banerjee A A, Vasu K K, Pancholi H, Rajani M and Nivsarkar M A. Detoxification of *Nerium indicum* roots based on Indian system of medicine: Phytochemical and toxicity evaluations. Acta Pol Pharm, 2011; 68: 905-11.
10. Ceci L, Girolami F, Capucchio MT, Colombino E, Nebbia C, Gosetti F, Marengo E, Iarussi F, Carelli G. Outbreak of Oleander (*Nerium oleander*) Poisoning in Dairy Cattle: Clinical and Food Safety Implications. Toxins, 2020; 12(8): 471.

11. Fabio G, Nebbia C, Ceci L, Carelli G and Marengo E. UHPLC-ms/ms determination of Oleandrin in blood and tissue of dairy cattle poisoned by oleander (*Nerium oleander*). Anal. Methods, 2019; 11(43): 5562-5567.
12. Botelho AF, Oliveira F A, Fiuza AT, Pedroza HP, Branco SE, Pierezan F and Soto-Blanco B. Improved method for diagnosis of *Nerium oleander* poisoning in necropsy tissues. Pesquisa Vaterinaria Brasileira, 2018; 38: 967-972.
13. Camplesi AC, Bellodi C, Socha JM, Hatayde MR, Sobreira MF, Araujo GH and Araujo CF. Dogs poisoned with *Nerium oleander* fresh leaves: clinical and electrocardiographic findings. Ciencia rural, 2017; 47(6): 1-6.
14. Page C & Murtaugh RJ. Hypoglycemia associated with oleander toxicity in a dog. Journal of Medical Toxicology, 2015; 11(1): 141-143.
15. Ayyappan, SN and Toi PC. Accidental fatal poisoning in a child due to ingestion of *Nerium oleander* leaf. Forensic Science. Medicine and Pathology, 2023; 2023: 1-5.
16. Abdou RH, Basha WA and Khalil WF. Subacute toxicity of *Nerium oleander* ethanolic extract in mice. Toxicological research, 2019; 35: 233-239.
17. Singhal KG and Gupta GD. Hepatoprotective and antioxidant activity of methanolic extract of flowers of *Nerium oleander* against CCl4–induced liver injury in rats. Asian Pacific Journal of Tropical Medicine, 2012; 5(9): 677-685.
18. Shafiq Y, Naqvi B, Rizwani GH, Asghar MA, Bushra R, Ghayas S, Rehman A and Asghar AM. A mechanistic study on the inhibition of bacterial growth and inflammation by *Nerium oleander* extract with comprehensive in vivo safety profile Complementary Medicine and Therapies, 2021; 21(135): 1-19.
19. Ishikawa A, Yamashita H, Hiemori M, Inagaki E, Kimoto M, Okamoto M, Tsuji H, Menon AN, Mohammadi A and Natori Y. Characterization of Inhibitors *of* Postprandial Hyperglycemia from the Leaves of *Nerium indicum*. Journal of Nutritional Science and Vitaminology, 2007; 53(2): 166-173.
20. Gayathri V, Ananthi S, Chandronitha C, Ramakrishnan G, Sundaram RL, Vasanthi HR. Cardioprotective Effect of *Nerium oleander* Flower Against Isoproterenol-Induced Myocardial Oxidative Stress in Experimental Rats. Journal of Cardiovascular Pharmacology and Therapeutics, 2011; 16(1): 96-104.
21. Shashikala GH, Shilpa BN and Mansi J. Shah Evaluation of anxiolytic activity of aqueous extract of *Nerium oleander* flowers in albino rats. International Journal of Basic & Clinical Pharmacology, 2018; 7(9): 1797-1802.

22. Tiwari S and Singh A. Control of common freshwater predatory fish, *Channa punctatus*, through *Nerium indicum* leaf extracts. Chemosphere, 2003; 53(8): 865-875.
23. Tiwari S and Singh A. Piscicidal activity of alcoholic extract of *Nerium indicum* leaf and their biochemical stress response on fish metabolism. Complementary and Alternative Medicines. African Journal of Traditional, 2004; 1(1): 15-29.
24. Tiwari S and Singh A. Changes in some biochemical parameters in the liver and muscle of *Colisa fasciatus* due to toxicity of ethanolic extract of *Nerium indicum* Mill. (Lal Kaner) latex. Natural product Radiance, 2009; 8(1): 48-54.
25. Prasad M, Kumar A, Srivastav SK and Srivastav AK. *Nerium indicum*, a botanical pesticide affects ultimobranchial gland of the catfish *Heteropneustes fossilis*. Environmental toxicology, 2013; 28(12): 661-665.
26. Prasad M, Kumar A, Mishra D, Srivastav SK and Srivastava AK. Alteration in blood electrolytes of a freshwater catfish *Heteropneustes fossilis* in response to treatment with a botanical pesticide, *Nerium indicum* leaves extract. Fish physiology and biochemistry, 2011; 37: 505-510.
27. Jian-Ming C, Yue-Ping HE, Jue-Feng Z and Lie-Zhong C. Toxic evaluation on ethanol extracts from leaves of Oleander, *Nerium indicum* Mill. To Zebra fish, BrachyDanio rerio. Acta Hydrobiologica Sinica, 2011; 35(5): 835-840
28. Kumar K and Singh A. Effect of Fish Size and Treatment Conditions on the Piscicidal Activity of *Nerium indicum* Latex Powder. Int. J. Life. Sci. Scienti. Res., 2015; 2(5): 583-587.
29. Kumar K and Singh A. Effect of fish size and treatment conditions on the Piscicidal activity of *Nerium indicum* latex powder. Int. J. Life. Sci. Scienti. Res., 2016; 2(5): 583-587.
30. Singh D and Singh A. The toxicity of four native Indian plants: Effect on AChE and acid/alkaline phosphatase level in fish *Channa maurilius*. Chemosphere, 2005; 60(1): 135-140.
31. Pugliese N, Tinelli A, Crescenzo G, Nieddu M, Baralla E, Schiavone A and Camarda A. Poisoning by *Nerium oleander* L. in Franconia Geese. Animals, 2024; 14(4): 1-12.
32. Lubian E, Capitelli R, Nappi S, Esposito R S, Russo R P, Lodi G and Bardi E. Use of intralipid emulsion therapy to treat suspected oleander toxicosis in a domestic goose (*Anser anser domesticus*). Journal of Exotic Pet Medicine, 2021; 39: 78-80.

33. Abbasi MH, Fatima S Khawar MB, Jahan S and Sheikh N. An In Vivo Study on intoxicating effects on *Nerium oleander* Water based extract on multiorgans of Wistar rat. Canadian Journal of Gastroenterology and Hepatology, 2018; 2018(4739637): 1-7.
34. Saliem AH. Effect of median lethal dose of ethanolic extract of (*Nerium oleander*) leaves on the Histopathology features of the vital organs in a mice. The Iraqi journal of Veterinary medicine, 2010; 34(2): 103-109.
35. Taheri S, Solati A, Moradi P. Toxic effects of *Nerium oleander* aqueous leaf extract on haematological parameters and histopathological changes of the lungs and heart in rabbits. Comp Clin Pathol, 2013; 22: 1189–1193.
36. Hassan DF and Kadhim FM. Acute Toxicity of leaves Ethanolic extract of *Nerium oleander* (Aldefla) in Local Iraqi Rabbots (*Lepus cuniculus*). Plant Archives, 2020; 20(2): 7840-7846.
37. Ozdemir O, Ciftci MK and Maden M. Oleander poisoning in cattle. Eurasian Journal of Veterinary Sciences, 2011; 27(1): 73-76.
38. Olivares CA, Muñoz CA, Eldredge F, Morales JI, Figueroa LA, Latorre, CA and Rodríguez S. Accidental poisoning with Nerium oleander in dairy goat in the Santiago metropolitan region in Chile. Revista de Medicina Veterinaria, 2019; 39: 43-48.
39. Khordadmehr M, Nazifi S, Mansourian M, Basiri S and Kolahian S. Experimental *Nerium oleander* poisoning in Balb/c mice and Wistar rat: comparative hepatotoxicity and nephrotoxicity effects based on biochemical and pathological studies. Turk J Biochem, 2017; 42(4): 427–434.
40. Abdalhadi BA and Jassim BA. Histological Study of *Nerium oleander* on the Kidney, small Intestine and Brain in the Male White Mice. Annals of the Romanian Society for Cell Biology, 2021; 25(1): 6045-6056.
41. Majeed LJ. Histopathological effects of aqueous extract of oleander (*Nerium oleander*) flower in albino male mice. Al-Mustansiriya J. Sci., 2012; 23(1): 29-38.
42. Mezban NA and Hussein AM. Comparative study to some of the biochemical and histological effects of alkaloids extracts from *Nerium oleander* and *Apium graveolens* in females mice. *Mus musculus*. World Journal of Pharmaceutical Research, 2015; 4(5): 219-238.
43. Alhazmi A, Salih M, Aldairi A, Alghamdi, A, Almalki, A, Almehmadi, M, Alomery A, Dahlawi H, Almasmoum, H, Gharib A and Alyamani R. Protective and therapeutic effect of zamzam water on various organs in mice induced by ethanolic extract of *Nerium oleander*. Fresenius Environmental Bulletin, 2021; 30(7A): 9197-9205.

44. Alhazmi A, Aldairi A, Mansour M, Alghamdi A, Almalki A, Almehmadi M and Almaimani R. Antioxidant activity of magnetized water in mice injected with *Nerium oleander* ethanolic extract. Fresenius Environ. Bull, 2021; 30: 9771-9779.
45. Adam SE, Al-Yahya MA and Al-Farhan AH. Response of Najdi sheep to oral administration of *Citrullus colocynthis* fruits, *Nerium oleander* leaves or their mixture. Small Ruminant Research, 2001; 40(3): 239–244.
46. Sykes A, Uzal F A, Mete A, Ochoa J, Filigenzi M, Robert H, Poppenga RH and Asin J. Renal Lesions in Horses with Oleander (*Nerium oleander*) Poisoning. Animals, 2022; 12(11): 1443.
47. Barbosa RR, Fontenele-Neto JD, & Soto-Blanco B. Toxicity in goats caused by oleander (*Nerium oleander*). Research in veterinary science, 2008; 85(2): 279-281.
48. Patel VK, Acharya R, Kumari A and Nariya M. Assessment of dermal toxicity of mustard oil based formulation of *Nerium indicum* Mill. Indian Journal of Traditional Knowledge (IJTK), 2023; 22(1): 76-82.
49. Rizk M, Kholy EI, Thorea D and Thanaa A. A study of the effects of garlic [*Allium Sativum*] and black seed [*Nigella Sativa*] on some liver functions and histopathology in *Nerium oleander* induced hepatotoxicity in albino rats, 2000; 36(4): 381-390.
50. Abbasi MH, Fatima SA, Naz N, Malik IA and Sheikh N. Effect of *Nerium oleander* (NO) leaves extract on serum hepcidin, total iron and infiltration of ED1 positive cells in albino rat. BioMed Research International, 2013; 2013(125671): 1-8.
51. Abbasi MH, Fatima S, Khawar MB, Naz N, Mujeeb KA, Akhtar T and Sheikh N. Dose-Dependent Acute Phase of response of aqueous leaf decoction of *Nerium oleander* in Wistar rats. Journal of biological regulators and homeostatic agents, 2017; 31(4): 985-989.
52. Al-Saadi SA, Al-Derawi KH and Alrasool SA. The effect of steroidal extract of *Nerium oleander* on the liver tissue structure of albino mice. Journal of Pharmacy and Biological Sciences, 2017; 12: 2(I): 52-55.
53. Akhtar T, Sheikh N and Abbasi MH. Clinical and pathological features of *Nerium oleander* extract toxicosis in Wistar rats. BMC Res Notes, 2014; 7(947): 1-6.
54. Abdalhadi B A and Jasim, B A. Histopathological and Physiological Study of *Nerium oleander* and Lead on the Liver in the Male Albino Mice. MJPS, 2021; 8(2): 112-125.
55. Altaee M F. In vivo toxicity study of *Nerium oleander*'s leaves and flowers aqueous extracts in mice (cytogenetic, Biochemical and Hematological study). Baghdad Science Journal, 2011; 8(1): 366-372.

56. Al-Hakak Z M, Khaleel Z I and Fadel M A. Study the effect of the toxic alcoholic extract of *Nerium oleander* on the liver cancer cell line in vivo and the effects on the liver histology in Mus Musculus. Journal of Pharmaceutical Sciences and Research, 2019; 11(1): 201-205.
57. Alkhayyat AA, Kafi LA and Hatif ZA. Acute toxicity study of three type of *Nerium oleander* leaves of hexane extract in mice:. The Iraqi Journal of Veterinary Medicine, 2010; 34(2): 194-201.
58. Alkhayyat A and Salih RA. Toxic effects of subacute exposure to *Nerium oleander* leaves hexane extract on the heart of rabbits. Iraqi Journal of Vet Medicune, 2017; 41(2): 54-60.
59. Khaleel ZI, Mohammed ZH and AL-Samarraie MQ. Histological effects of the Alcoholic Extract of *Nerium oleander* in the heart and brain in Mice and its effect on the Lymphocytes (In Vitro). Indian Journal of Public health, 2019; 10(8): 2362-2366.
60. Streitenberger N, Asin J, Navarro MA, Poppenga RH and Uzal FA. Oleander (*Nerium oleander*) intoxication in a bison. Braz J Vet Pathol, 2022; 15(1): 65-68.
61. Smith PA, Aldridge BM and Kittleson MD. Oleander toxicosis in a donkey. Journal of veterinary internal medicine, 2003; 17(1): 111-114.
62. Radhika RH. Cerebra Thevetia poisoning: a prospective study at a tertiary care hospital, Kerala. Ind. J Forensic community Med., 2018; 5(2): 123-126.
63. Kumar M. Triterpenoids of *Nerium oleander* shows antifertility effect in male albino rats. Journal of Advanced Laboratory Research in Biology, 2019; 10(4): 104-110.
64. Kiruthika SA and Sornaraj R. Spermicidal activity of Nerium oleander flower extract. World Journal of Pharmaceutical Research, 2020; 9(4): 1865-1872.
65. Samanta J, Bhattacharya S and Rana AC. Antifertility activity of *Thevetia peruviana* (Pers.) K. Schum leaf in female Sprague-Dawley rat. Indian journal of pharmacology, 2016; 48(6): 669.
66. Chaudhary K, Kushwaha VB and Srivastava SK. Turmeric (*Curcuma longa*) rhizome extract and selenium protect effects of *Nerium indicum* leaf extract on serum calcium and phosphate of male Wistar rats. Intern. J. Zool. Invest, 2023; 9(2): 1355-1364.
67. Kesharwani L and Gupta AK. Effect of mechanical antidote on toxicity of seed extract of *Thevetia peruviana* in albino rat- forensic consideration. Ind. J. Sci. Res. And Tech, 2014; 2(5): 25-28.
68. Al-Maiali HK, Al-Hmedawi HA, Al-Lebawi, ZI. The effect of alcoholic extract of *Nerium oleander* leafs on some biochemical parameters and function of liver and kidney in white rats. Journal of Wasit for Science and Medicine, 2010; 3(2): 1-9.

69. Nesy E, Padikkala J and Mathew L. Acute and Subacute studies of *Thevetia peruviana* seed methanol extracts on Wistar Male Albino Rats. Indian J Pharm Sci., 2021; 83(5): 1000-1006.
70. Rhaymah MS, Al-Farwachi MI and Al-Bandrani BA. Chronic toxicity of *Nerium oleander* aqueous leaf extract in rabbits. Al-Anbar J Vet Sci., 2011; 4: 88-93.
71. Hussein AM. The study of alkaloid extracts effect of *Nerium oleander* and *Apium graveolens* in the body weight and blood paramerters in laboratory mice females *Mus musculus* L, Int J Agric Sci Re., 2016; 6(2): 87-96.
72. Salih RA and Alkhayyat AA. Toxic effect of *Nerium Oleander* leaves extract on biochemical parameters in rabbit serum. Al-Anbar J. Vet. Sci., 2016; 9(2): 1-8.