Toxicology International, *Vol 28(4), 385-401, 2021, DOI: 10.18311/ti/2021/v28i4/28028*

Original Review
ISSN (Print): 0971-6580
ISSN (Online): 0976-5131

A Comprehensive Review on Globally Present Cardiotoxic Plants

Sanjukta Rajhans*, Himanshu Pandya and Archana Mankad

Department of Botany, Bioinformatics and Climate Change Impacts Management, Gujarat University, Ahmedabad – 380009, Gujarat, India; rajhanssanjukta@gujaratuniversity.ac.in

History: Received 2021-06-24; Accepted 2021-07-07; Published 2021-12-22

Abstract

In this review, an attempt was made to compile and include published data of cardiotoxic plants from all over the world. The plants have been listed with their scientificand common names, a family from which they belong, their parts that specifically contain toxic active principles causing cardiotoxicity. Moreover, the review also has specific symptoms, which can provide great help in understanding the patient's condition and help in providing medicinal aid and treatment. This review is the first of its kind involving the details of the cardiotoxic plants worldwide. A short description of how the toxins affect the heart and possible treatments for dealing with the symptoms have also been presented here.

Keywords: Cardiotoxicity, Plant Family, Toxic Parts, Symptoms

1. Introduction

Plants have certain active principles that provide them protection against predators and pathogens. These active principles are secondary metabolites like Cardiac Glycosides, Alkaloids, Grayanotoxins Cyanide, Oxalic acid, Phorbol esters, Lectins, etc. These active principles on contact, inhalation and ingestion are capable of causing harm to humans and animals. The toxicity varies from plant to plant and differs based on chemical compounds present in them[1]. The degree of intoxication varies greatly depending upon a physical condition, age, weight, and degree of exposure to the toxic substance. Most of the poisonings are characterized by dermatitis, diarrhea, nausea, and vomiting. In extreme conditions, these poisonous substances can claim a life of an individual[2]. The cases of poisoning are either intentional (suicidal) or accidental. In both circumstances, it is vital to identify the symptoms and provide treatment accordingly. This review aims to present a collection of all cardiotoxic plants around the world with their details. The details of the secondary metabolites that are primarily responsible for cardiotoxicity have also been presented here.

2. Methodology

(Literature source, keywords used, data inclusion and exclusion criteria)

2.1 Cardioactive Substances and their Effects on the Heart

Cardioactive components can affect the integrity of cardiac myocytes or the nerves controlling the heart and the heart rate. Depending upon the specific compound and its actions on the heart, the outcomes can be positive or negative. Cardiac neurons are present in the form of networks all over the heart, involved in the intrinsic electrical conduction[3–5]. These neurons generate an action potential. Electric activation of the cardiomyocytes occurs in the same way as in nerve cells, i.e., influx of sodium ions across the membrane. Changes in the electrolytes trigger inflammation, vasoactive, antioxidant, and apoptotic

*Author for correspondence

cascades in the heart, which further establishes either cardiotoxicity or cardio protection to the heart[6].

2.2 Toxicity of the Plants

Humans developed skills to use poisonous plants belonging togenus *Acokanthera, Strophanthus* and *Adenium* for murder, abortions, executions and suicide in early civilizations. These plants were rich in compounds like alkaloids, cardiac glycosides, phorbol esters, lectins, and cyanogenic glycosides and wereknown to be highly toxic in nature[1].

2.3 Plant-induced Cardiotoxicity

Ingestion of cardio-toxic plants either with the intention of suicide or by accidental ways is the primary cause of cardiotoxicity. All plants contain some or the other toxic principal compounds which further protect them from animals and insects. The toxicity effect varies from genus to genus, geographical distribution, seasonal variation, environmental condition, and part(s) of the plants. The *Cinchona* spp. (Rubiaceae), the *Apocynum* spp. (Apocynaceae), the *Asclepias* spp. (Apocynaceae), the *Plumeria* spp. (Apocynaceae), and the *Ornithogalum* spp. (Asparagaceae) are of plant species belonging to specific plant families that are known to cause cardiotoxic effects[7]. Plants with cardiotoxic effects have been listed in Table 1.

Table 1. Plants with cardiotoxic effects

S.No.	Scientific name	Common name	Family	Plant Parts	Type of Toxic or Active Principles	Symptoms	References
1	*Abrus precatorius* L.	Rosary pea	Fabaceae	Leaves, Roots, Seeds and Seed Coat	Lectins- Abrin, Abrine and Abrasine	Bloody diarrhea, Convulsions Nausea, Trembling of Legs and Vomiting	18,33–36
2	*Acokanthera oblongifolia* (Hochst.) Benth.& Hook.f. ex B.D. Jacks.; *Acokanthera oppositifolia*(Lam.) Codd; *Acokanthera schimperi*(A.DC.) Schweinf.	African wintersweet; Bushman's poison; Arrow poison tree	Apocynaceae	All parts are toxic in nature	Cardiac glycoside- Acovenoside A, B, C and Ouabain	Cardiac dysrhythmia, Exhaustion, Hyperkalemia, Nausea, Purging, Retching and Salivation	1,6,37
3	*Aconitum ferox* Wall. ex Ser.; *Aconitum napellus* L.	Indian Aconite; Monk's-hood	Ranunculaceae	Roots	Steroid alkaloids-, Aconitine, Aconines, Benzoylaconines, Deoxyaconitine Hypaconitine, Jesaconitine, Lappaconitine, Mesaconitine, Methyllycaconitine, Napelline, Ranaconitine and Sinomontanitines and Vunaconitine	Arrhythmias, Bidirectional tachycardia, Bradycardia, Blood pressure abnormalities, Burning in the mouth after ingestion, Chest discomfort, Coma, Conduction disturbances, Convulsions, Diarrhea, Dimness of vision, Headache, Increased salivation, Muscular weakness, Myocardial depression, Ventricular tachycardia, Vomiting and Death	1,12,38,39
4	*Adenium obesum* (Forssk.) Roem. & Schult.	Desert rose	Apocynaceae	Leaves, Roots and Stems	Cardiac glycosides- Obeside B, C, D, obebioside A, B, C and D	Hyperthermia, Hyperventilation, Collapse and Death	1,40
5	*Adonis macrocarpa* DC.	Red chamomile	Ranunculaceae	Seeds	Cardenolide- Adonitoxin	Arrhythmias, Bradycardia, Hyperkalemia and Vomiting	6,36,41

6	*Allamanda cathartica* L.	Golden trumpet	Apocynaceae	Leaves	Cardio-toxic glycosides-apocyanamarin, apocynein and cymarin	Cytotoxicity, Diarrhea, Genotoxicity and Skin problems	42–44
7	*Apocynum androsaemifolium* L.	Spreading dogbane	Apocynaceae	All parts are poisonous especially the roots	Cardiac glycoside-Cymarin and k-strophanthin-β	Apathy, Convulsions, Diarrhea, Frequent Urination, High Blood Pressure, Irregular Pulse, Low Body Temperature, Sweating, Vomiting and Death	35
8	*Areca catechu* L.	Betel tree	Arecaceae	Seeds	Alkaloids- Arecoline, Arecaidine, Guvacoline and Guvacine	Cardiac arrhythmias, Damage to neurons, Euphoria, Hyperlipidemia, Increased heart rate, Increased blood pressure, Myocardial ischemia and Vasospasm	15,45,46
9	*Argemone mexicana* L.	Mexican prickly poppy	Papaveraceae	All parts are poisonous, especially the seeds	Alkaloids- Berberine, Dihydrosangunarine Protopine and Sanguinarine	Abortion, Acute Inflammation of Gastro intestinal tract, Alopecia, Anemia, Blindness, Cardiac Failure, Diarrhea, Sleepiness and Vomiting	35,47–50
10	*Asclepias curassavica* L	Tropical milkweed	Apocynaceae	Latex, Leaves, Roots and Stems	Cardiac glycoside-Asclepain, Asclepin, Asclepine, AsclepogeninCalactin, Calotropin, Calotroposide, Calotropagenin, Clepogenin, Coroglaucigenin, Corotoxigenin, Curassavogenin, Desglucouzarin, Galitoxin, Kidjolanin, Uscharidin, Uzarin and Uzarigenin	Cardiotoxicity, Corneal endothelial dysfunction, Inhibitory effect on Na^+–K^+ATPase and Toxic to human skin	36,51–53
11	*Astragalus* L.	Locoweed	Fabaceae	Roots	Indolizidine alkaloid-Swainsonine	Congestive right-heart failure	14,54–56
12	*Atropa belladonna* L.	Deadly nightshade	Solanaceae	All parts	Tropane alkaloids-Atropine, Belladonnine, Hyoscyamine and Scopolamine	Blurred Vision, Confusion, Constipation, Convulsions, Delirium, Dilated Pupils, Dry Mouth and Throat, Flushing, Hallucinations, Headache, Loss of Balance, Rash, Sensitivity to Light, Slurred Speech, Staggering,Tachycardia and Urinary Retention	6,57,35
13	*Bersama abyssinica* Fresen.	Winged bersama	Francoceae	Leaves and Roots	Isoquinoline alkaloids-Berberine and Magnoflorine	Hyperaesthesia, Irregular shallow respirations, Limb weakness, Paralysis, Weak irregular pulse and Death	1,58

14	*Bowie avolubilis Harv.* ex Hook. f.	Climbing potato	Asparagaceae	Bulbs	Cardiac glycosides- Bufodienolide- Bovogenin A	Excessive salivation, Irregular heart palpitations, Purging and Vomiting	1,50,59
15	*Calotropis procera* (Aiton) W.T. Aiton	Sodom apple	Apocynaceae	Latex and Leaves	Cardenolides-Calotropin, Calactin, Calotoxin, Usharin, Usharidin and Voruscharin	Cardiac arrhythmias, Bradycardia, Flaccid heart, Hydropericardium, Multi-focal coagulation, Myocardial infarction, Necrosis of cardiac fibers and Tachycardia	35,36
16	*Cascabela thevetia* (L.) Lippold	Yellow oleander	Apocynaceae	Whole plant, especially the Leaves and Seeds	Cardiac glycosides- Aucubine, Cereberoside, Cerebroside, Neriifolin, Peruvoside, Ruvoside,Thevetin, Thevetin A, Thevetin B, Thevetin C and Thevetoxin	Abdominal pain, Accelerated junctional rhythms, Anxiety Burning in the mouth, Cardiac dysrhythmias, Coma, Convulsion, Diarrhea, High-degree AV block, Hyperkalemia, Nausea, Significant ventricular ectopy, Sinoatrial blocks, Yellow vision changes and Vomiting	6,7,35, 47,60–62
17	*Catha edulis* (Vahl) Forssk. Ex Endl.	Qat	Celastraceae	Leaves	Alkaloids- Cathinone and Cathine	Acute myocardial infarction, Elevation in arterial blood pressure, Elevation in the heart rate, Peripheral and coronary vasoconstriction and Tachycardia	7,63
18	*Catharanthus roseus* (L.) G. Don	Madagascar periwinkle	Apocynaceae	Leaves, Roots, and Stems	Alkaloids- Vincristine, Vinblastine, Vindesine, Vinflunine and Vinorelbine	Cardiac ischemic pain, electrocardiographic abnormalities and Myocardial infarction	1,35,47
19	*Cerbera manghas* L.	Sea mango	Apocynaceae	Leaves, Latex and seeds of dried ripe fruits	Cardiac glycoside- Ascerberin, Cerberin, Cerberoside, Deacetylcerberin, Deacetyltanghinin, Neriifolin and Tanghinin	Abdominal pain, Bradycardia, Cardiac dysrhythmias, Diarrhoea, Dizziness, Dysrhythmia, Hyperkalaemia, Hypotension, Vomiting and Death	64–68
20	*Cerbera odollam* Gaertn.	Suicide tree	Apocynaceae	Leaves and Seeds	Cardiac glycoside- Cerberin, Deacetyltanghinin and Neriifolin	Abdominal pain, Bradycardia, Diarrhoea, Dizziness, Dysrhythmia Hyperkalaemia, Hypotension, and Vomiting	7,67,69–71
21	*Cicuta maculata* L.	Spotted water hemlock	Apiaceae	All the parts	Alkaloids- Cicutoxin and Oenanthotoxin	Bradycardia, Cardiac dysrhythmias, Central nervous system disruption, Coma, Diarrhea, Hypotension, Hypertension Mydriasis, Nausea, Renal failure, Respiratory impairment, Respiratory failure, Rhabdomyolysis, Tachycardia, Ventricular fibrillation and Vomiting	72–74

22	*Cinchona officinalis* L.	Red cinchona	Rubiaceae	Bark	Alkaloids- Quinine and Quinidine	Cardiac complications and Cardiac dysrhythmias	7,14,75
23	*Cleistanthus collinus* (Roxb.) Benth. ex Hook.f.	Oduvanthalai	Phyllanthaceae	All parts of the plant	Lignan lactones- Arylnaphthalene, Cleistanthin A and B, Collinusin, Diphyllin and Ellagic acid	Acute Respiratory Distress Syndrome (ARDS), Acidosis, Asystole, Cardiac arrest, Cardiac rhythm abnormalities, Dysrhythmia, Fatal ventricular Hypokalemia, Hypotension, Respiratory failure, Sinus bradycardia, Sinus tachycardia and Vasodilatory shock	76–78
24	*Colchicum* L. (C. autumnale)	Autumn crocus	Colchicaceae	All parts are poisonous, especially bulbs and seeds	Alkaloid- Colchicine and Colchicoside	Bone marrow suppression, Cardiovascular collapse, Initial oropharyngeal pain followed by intense gastrointestinal symptoms and Peripheral neuropathy	72,79–81
25	*Conium maculatum* L.	Hemlock	Apiaceae	Fruits Leaves and Stems	Conium alkaloids- Coniine Piperidine alkaloids and Cyanapine	Coma, Coldness, Depression, Gastrointestinal irritation, Hyperpnea, Loss of coordination, Nervousness, Respiratory failure, Trembling, Tachycardia, Staggering and death.	74,82–85
26	*Convallaria majalis* L.	Lily of the valley	Asparagaceae	All the parts	Cardiac glycosides- Convallarin Concallamarin, Convallatoxins and Convallamarin	Arrhythmia, Bradycardia, Cardiac dysfunction, Cardiac insufficiency, Cardiac shock, Diarrhea, Heart becomes hyperirritable, Mild gastrointestinal perturbation, Sinus tachycardia and Vomiting	14,37,61
27	*Cytisus scoparius* (L.) Link; *Cytisus striatus* (Hill) Rothm.; *Genista monspessulana* (L.) O. Bolos & Vigo; *Spartium junceum* L.	Common broom; Hairy-fruited broom; French broom; Spanish broom	Fabaceae	All parts of the plant	Quinolizidine alkaloids- Cytisine and Sparteine	Depression, Paralysis, Reduced sensitivity and conductivity of the cardiac muscle	87,88
28	*Datura stramonium* L.; *Datura ferox* L.; and *Datura innoxia* Mill.	Jimsonweed; Fierce thorn-apple; Downy thorn-apple	Solanaceae	All parts of the plant and particularly the seeds	Tropane Alkaloids- Atropine, Hyoscine, Hyoscyamine, L-hyoscyamine, and Scopolamine	Hypotensive, Heart failure and Multiple organ failure	72,73,79,89,90
29	*Delphinium* L.	Larkspur	Ranunculaceae	Herbal parts, Roots and Seeds	Alkaloids- Lycoctonine, MDL (7,8-methylenedioxyly-coctonine) and MSAL (methylsuccinylan-thranoyllycoctonine)	Fever, Hypotension and Rapid and irregular heartbeat, Respiratory depression, Seizures and Ventricular tachycardia	72,79,91

30	*Digitalis purpurea* L.	Foxglove	Plantaginaceae	Flowers, Leaves, Seeds and Stems	Cardiac glycosides- Digitoxin and Digoxin	Abdominal pains, Advanced Cardiac Rhythm Disturbances, Arrhythmias, Congestion of lungs, Changes in vision. Convulsions, Diarrhea, Dyspnea, Extreme fatigue, Headaches Hyperkalemia, Nausea, Strange dreams, Visual disturbances, Vomiting, Weakness and Death	6,14,35, 42,72,92
31	*Drimia* Jacq. ex Willd.	Sea squill	Asparagaceae	Bulbs	Bufadienolides- 12-β-hydroxyscillirosidin	Cardiac arrest, Diarrhoea, Haematuria, Nausea, Rash, Vomiting and Death	37
32	*Erythrina caffra*Thunb.	Coast coral tree	Fabaceae	Whole plant specially barks and stem	Isoquinoline alkaloid- Erythraline and Erysotrine	Cardiac arrest, Disturbance of gastrointestinal (GI) tract and CNS, Dyspnea, Paralysis effect on skeletal muscles, Spasm, Trembling and Unrest	1
33	*Erythrophleum lasianthum* Corbishley	Maputaland ordeal tree	Fabaceae	Aerial parts, Bark and Seeds	Diterpenoid alkaloid- Cassaine and Erthrophleine	Cardiac arrest, Diarrhea, Hypertension, Vomiting and Death	1
34	*Erythroxylum coca* Lam.	Amazonian coca	Erythroxylaceae	Leaves	Alkaloid- Cocaine	Hypertension, Increase in blood pressure, Myocardial ischemia, Myocardial infarction, Tachycardia and Vasoconstriction of coronary artery	93,94
35	*Gloriosa superba* L.	Glory lily	Colchicaceae	Tubers	Alkaloids- Colchicine and Gloriosine	Cardiac arrhythmias, Fast rhythm, Hypotension and Tachycardia	47,95–99
36	*Gomphocarpus fruticosus* (L.) W.T.Aiton	Balloon cotton	Apocynaceae	Whole plant	Cardiac glycosides- Gomphotin and Gomphotoxin	Cardiac arrest and Diarrhea	1
37	*Hyoscyamus niger* L.	Henbane	Solanaceae	Fruits, Leaves, Roots and Seeds	Tropane alkaloids- Hyoscyamine	Irregular heartbeat, Stomach complaints, Toothaches, Ulcers and Tumors	100–103
38	*Jatropha curcas* L.	Poison nut	Euphorbiaceae	Seed oil	Phorbol esters	Muscle shock, Increase in heart rate and Weakening of visual capacity	6,24,25
39	*Kalanchoe laciniata* (L.) DC.; *Kalanchoe delagoensis* Eckl.&Zeyh.	Christmas tree plant; Mother of millions	Crassulaceae	All the parts	Cardiac glycosides (Bufadienolides)- Bryotoxins, BryophyllinsBersalgenins and Daigremontianin	Anorexia, Depression, Diarrhea, Dyspnea Inhibition of Na1/K1-adenosine triphosphatase following decrease in the transportation of sodium- potassium across the cell membranes and finally decrease in the cardiac function, Lethargy, Tachycardia, Vocalization, Vomiting and Weakness	104

40	*Kalmia latifolia* L.	Mountain laurel	Ericaceae	Leaves and Flowers	Grayanotoxins-Andromedotoxin; Rhodotoxin	Anoxia, Bradycardia, burning sensation in mouth and pharynx, Coma, Dimness of vision, Emesis, Hypotension, Muscular weakness, Respiratory paralysis, Increased Salivation and Death	18,72,105
41	*Melianthus comosus*Vahl,	Honey flower	Francoceae	Roots	Cardiac glycosides (Bufadienolides)-Hellebrigenin-3- acetate, Melianthugenin and Melianthusigenin	Cardiac symptoms, Colic and gastrointestinal disturbance, Exhaustion, Foaming vomit, Nausea, Purging, Respiration and Salivation	1,106
42	*Merwilla natalensis* (Planch.) Speta	Inguduza	Hyacinthaceae	Bulbs	Cadiac glycoside-Transvaalin (same compound as scillaren A)	Cardiac arrest, Diarrhoea, Haematuria, Nausea, Rash, Vomiting and Death	107,108
43	*Mitragyna speciosa* (Korth.) Havil.	Kratom	Rubiaceae	Leaves	Alkaloid- Mitragynine	Hypotension and Ventricular tachyarrhythmia	109,110,111
44	*Nerium oleander* L.	Oleander	Apocynaceae	All the parts	Cardiac glycosides-Convallatoxin and Convallosid and Oxalic acid (further forming Calcium oxalate crystals)	Abdominal pain, Bradycardia, Cardiac arrhythmias Cramps, Coma Depression, Drowsiness Diarrhea, Emesis, Eye and skin irritant, Hyperkalemia, Increased heart rate. Irregular Heartbeat, Nausea, Pain in the oral cavity, Paralysis of the Lungs, Pupil Dilation, Severe gastroenteritis, sweating, Tachycardia, Trembling, Ventricular fibrillation, Ventricular myocardial necrosis, Vomiting, Weakness and Death	37,41,47, 112–116
45	*Ornithogalum* L.	Star of Bethlehem	Asparagaceae	Bulbs	Cardiac glycosides-Convallotoxin and Convallosid and Oxalic acid (further forming Calcium oxalate crystals)	Cardiac arrhythmia, Diarrhea, Dyspnea, Heart-block and Tachycardia	7,117–119
46	*Plumeria* L.	Frangipani	Apocynaceae	Latex and Leaves	Cardiac glycosides-Kaneroside and Oleandrin	Diarrhea, Vomiting and Ventricular tachycardia	7,120–122
47	*Rauvolfia serpentina* (L.) Benth. ex Kurz; *Rauwolfia vomitaria* Afzel.	Indian snakeroot; Poison devil's pepper	Apocynaceae	Roots	Alkaloids- Reserpine, Reserpidine, Reserpinine and Serpentine	Bradycardia, Diarrhea, Drowsiness, Hyper gastric Secretion, Nasal Congestion, Nausea and Severe Depression	18,35,48,123
48	*Rhodondendron* L.	Rose tree	Ericaceae	All parts	Grayanotoxin	Abdominal pain, Bradycardia, Cardiac arrhythmias, Cardiopulmonary arrest, Cardiovascular collapse Depression, Diarrhea, Dyspnea, Hypotension, Lethargy, Pulmonary edema, Seizures, Shock Weak heart rate, Weakness, Vomiting and death	7,124

49	*Ricinus communis* L.	Castor bean	Euphorbiaceae	Seeds	Lectin- Ricin	Bradycardia, Calcium hemostasis in the heart, Cytotoxicity, Decrease in systolic and diastolic left ventricular function, Rise in vascular permeability and Hypotension	72,79
50	*Solanum nigrum* L.	Black nightshade	Solanaceae	All parts are toxic except the ripe fruits	Glycoalkaloid- Solanine	Abdominal pain, Arrhythmias, Asystole Bradycardia, Diarrhea, Heart block, Hypotension and Vomiting	72,79
51	*Sorghum halepense* (L.) Pers.	Johnson grass	Poaceae	Green portions	Cyanogenic glycoside- Dhurrin	Cardiac Arrhythmia, Coma, Convulsions, Dizziness, Difficult Breathing, Headache and Vomiting	35,79
52	*Strophanthus hispidus* DC.	Hispid strophanthus	Apocynaceae	Latex and Seeds	Cardiac glycosides- Ouabain and Strophanthins	Cause the heart to arrest in systole and Hypertension	6,125
53	*Taxus baccata* L., *Taxus brevifolia* Nutt., *Taxus cuspidata* Siebold & Zucc. *Taxus wallichiana* Zucc., T*axus sumatrana* (Miquel) de Laub.	Common yew, Pacific yew, Japanese yew, Himalayan yew, Chinese yew	Taxaceae	Entire plant except fleshy berry (the seeds are poisonous)	Alkaloids- Ephedrine, Isotaxine B, Paclitaxel, Taxine A, Taxine B, Taxol A and B, Taxicatine	Arrhythmias, Ataxia, Blue Lips, Bradycardia, Bradypnea, Cardiac arrest, Collapse, Coma, Convulsions, Cramps, Dark tarry blood in left heart, Decreased myocardial contractility, Diarrhea, Diastolic cardiac standstill, Dizziness, Dry mouth, Dyspnea, Empty right heart, Heart Arrhythmia, Hypotension, Muscle weakness, Low Blood Pressure, Nervousness, Pale Face, Pupil dilation, Respiratory paralysis, Salivation, Seizures, Trembling, Ventricular tachycardia, Ventricular fibrillation Vomiting and Death	10,61,126–129
54	*Thaumatophyllum bipinnatifidum*(Schott ex Endl.) Sakur., Calazans& Mayo	Horsehead Phillodendron	Araceae	All the parts	Oxalic acid (further forming Calcium oxalate crystals)	Cardiac arrhythmia, Coma, Depression, Difficulty in swallowing, Hypersalivation, Inappetence, Mydriasis, Oral pain, Swelling of the oral cavity, Vomiting and Death	21–23
55	*Toxicoscordion venenosum*(S. Watson) Rydb.	Death Camas	Melanthiaceae	Bulbs and Foliage	Cevanine Steroidal alkaloid - Zigacine	Bradycardia, Cardiovascular failure, Irregular pulse, Low blood pressure and Necrosis of cardiac muscle	130,131

56	*Veratrum album* L., *Veratrum californicum* Durand, *Veratrum nigrum* L., *Veratrum fimbriatum* A.Gray, *Veratrum viride* Aiton	White hellebore, California false hellebore, Black false hellebore, Fringed false hellebore, Indian poke	Melanthiaceae	Leaves, Rhizomes and Roots	Alkaloids- Cevadine, Cevine, Germine, Germerine, Germidine, Isorubrijervine, Jervine, Pseudojervine, Protoverine Veratridine, Veratramine, Veratrosine, Veracerine, Zygadenine,	Abdominal pain, Bradycardia, Coma, Diaphoresis, Headache, Hypotension, Nausea, Numbness, Paresthesia, Seizures, Visual disturbance and Vomiting	132–135

2.3.1 Plants ContainingCardiac Glycosides

Highly toxic cardiac glycosides are found in several plants. These cardiac glycosides are made of aglycones that are linked to one or more sugar molecules. Aglycones are structurally associated to steroid hormones and can be further divided into two chemical groups i.e., the cardenolides and bufadienolides.The plants containing these glycosides are known, since ages for their toxicity to humans and animals. In 11 plant families the cardiac glycosides are found to be present, and in 34 genera of these families, cardiotoxic compounds are found in almost all the parts. The most famous plant is *Digitalis purpurea* L., commonly known as foxglove. Digoxin, digitoxin, digitonin and digitalin are some of the cardiac glycosides of this plant. Although digoxin is used to treat congestive heart failure, it is toxic, and high doses can claim the life of the patient[6]. Stronger but slower cardiac contractions, prolonged diastole, pulse, and cardiac rhythm abnormalities, hyperkalemia, ventricular tachycardia are some of the symptoms of intoxication of *Digitalis purpurea* L.[8]. *Acokanthera* spp., *Adonis macrocarpa* DC., *Asclepias curassavica* L., *Bersama abyssinica* Fresen., *Bowiea volubilis* Harv. ex Hook. f., *Cascabela thevetia* (L.) Lippold, *Drimia*Jacq. ex Willd., *Kalanchoe laciniata* (L.) DC., *Kalanchoe delagoensis* Eckl. and Zeyh., *Nerium oleander* L., etc.are examples of rich plants in cardiac glycosides[1,6].

These cardiac glycosides affect the heart by making changes in the functioning of the ion's channels leading to arrhythmias, and cause other cardiac problems. These glycosides increase the intracellular Na1 and Ca21 levels, by inhibiting the Na1/K1-ATPase i.e., the cellular membrane-bound enzyme system. Inhibition of Na1/K1-ATPase in baroreceptor and skeletal muscle cells results in an increased vagal tone which clinically manifests as bradycardia and hyperkalemia. The increase in intracellular Ca21 results in the interaction of troponin C of the actin-myosin complex, further increasing ventricular contractions[9]. Other symptoms of cardiac glycoside poisoning are gastro-intestinal, nervous system, and neuromuscular disorders[1].

2.3.2 Plants Containing Alkaloids and Grayanotoxins

Among the alkaloid-containing plants yews (*Taxus* species) are significantly known. The chief phytochemicals are taxine A and B, which are alkaloidal in nature[6]. Symptoms of intoxication include arrhythmias, culminating in cardiac failure[10]. Plants of *Datura* spp. (*Datura stramonium* L.; *Datura ferox* L.; and *Datura innoxia* Mill.) are rich in tropane alkaloids. Overdoses of tropane alkaloids like atropine and scopolamine can act as poisons for humans[6]. Tropane alkaloids are also found in *Atropa belladonna* L.[11]. In the *Aconitum* plants, e.g., *Aconitum ferox* Wall. ex Ser.; *Aconitum napellus* L., the dried rootstocks are known as aconites[12].The toxicity of aconite is associated with the steroid alkaloids like aconitine, deoxyaconitine, mesaconitine, hypaconitine, and vunaconitine[13]. These steroidal alkaloids open sodium channels and affect excitable membranes of cardiac, muscle, and neural tissues similarly, in *Toxicoscordion venenosum* (S. Watson) Rydb. (Death Camas) the principal toxic compounds are the steroidal alkaloids, Cevanine and Zygacine[14]. Symptoms of intoxication include irregular pulse, bradycardia, low blood pressure, necrosis of cardiac muscle, and cardiovascular failure. To date, no known treatment is there for Death Camas poisoning. It is interesting that *Areca catechu* L. contains an alkaloid arecoline which is capable of causing ventricular arrhythmia[15].

Other cardiotoxic plants that are known for their alkaloid contents are the plants of genus *Astragalus*, *Cinchona officinalis* L.[14], *Cicuta maculata* L., *Delphinium* L.[16], *Argemone mexicana* L., *Bersama abyssinica* Fresen., *Catharanthus roseus* (L.) G. Don, *Catha edulis* (Vahl) Forssk. Ex Endl. *Conium maculatum* L., *Gloriosa superba* L., *Hyoscyamus*

niger L. *Rauvolfia serpentina* (L.) Benth. ex Kurz, *Rauwolfia vomitaria* Afzel., and plants of genus *Veratrum*.

Grayanotoxins are found in *Rhodondendron* L. and the plants like *Kalmia latifolia* L., these toxins show similar effects as the steroidal alkaloids of the *Aconitum* spp. Other names for grayanotoxins are andromedotoxin, acetylandromedol, and rhodotoxin. There are 18 different forms of grayanotoxins which are diterpenoids by nature[17]. Like the steroidal alkaloids these toxins also affect the sodium channels in the cell membranes[18]. Bradycardia, cardiovascular collapse, hypotension, cardiac arrhythmias, and weak heart rate are some of the symptoms caused by the grayanotoxins.

2.3.3 Plants Containing Cyanide (Cyanogenic glycosides)

Around 2500 plants comprise cyanogenic glycosides in them[19]. *Sorghum halepense* (L.) Pers. is an example of a plant rich in hydrocyanic acid or prussic acid. The amount of hydrocyanic acid production varies from plant to plant, and thus the level of toxicity also varies. Cyanide acts rapidly and hinders the action of cytochrome oxidase whose chief function is to make oxygen reach the erythrocytes. It can be said that cyanide induces cellular hypoxia. Symptoms of cyanide poisoning are tachycardia, dysarrhythmia, and petechial hemorrhage of the heart. The ECG changes are observed as the shortening of the ST-segment and fusion of T-wave and QRS segment[20].

2.3.4 Plants Containing Oxalic Acid

Oxalic acid combines with calcium and forms crystals which are primarily deposited in the kidneys. But, in special conditions they can also get deposited in other organs like the heart. In humans, oxalosis, i.e., accumulation of oxalate crystals in kidney, leads to cardiac abnormalities along with the declination of renal functioning[21]. Oxalosis also causes blockage in the heart[22]. The formation of calcium oxalates leads to hypocalcemia, which interferes with the action potential by inhibiting the Ca21 pump resulting in the relaxation of the heart muscles and further leading to cardiac arrest. Other symptoms are weak and irregular pulse, hypotension, necrosis of the myocardium, and cardiovascular collapse. *Thaumatophyllum bipinnatifidum*(Schott ex Endl.) Sakur., Calazans and Mayo, and the genus *Ornithogalum* L. plants are known to contain oxalic acid[23].

2.3.5 Plants Containing Phorbol Esters and Lectins

Phorbol esters are tetracyclic diterpenoids. *Jatropha curcas* L. contains phorbol esters in the seed oil. The symptoms of intoxication in humans include muscle shock, weakening of visual capacity, and increased heart rate[6,24,25]. Lectins are proteins of nonimmune origin that possess the ability to bind with certain carbohydrates[26]. *Abrus precatorius* L. and *Ricinus communis* L. contain lectins in them that are cardiotoxic in nature.

2.3.6 Mycotoxins

Mushrooms are basidiomycete fungi; out of several thousand species, only less than 100 are toxic. The principal toxin in mushrooms is amatoxin which is a bicyclic octapeptide in nature[27]. Amatoxin inactivates RNA polymerase II present in cell nuclei and DNA transcription, preventing protein synthesis, and curtailing cell metabolism. Symptoms of amatoxin intoxication are elevated cardiac enzymes[28] including CK-MB (Creatine kinase-MB) isoenzyme and myoglobin, and heart block, bradycardia, sinus tachycardia, hypotension, and lowering of calcium and phosphate levels. Among the edible mushrooms also there are some mycotoxins found to be present. Flammutoxin is a cardiotoxin; found in an edible mushroom known as *Flammulina velutipes*. This toxin interferes with the voltage-gated ion channels causing depression of the ST segment and inversion of T waves[29,30]. Similarly, volvatoxin A2, a unique pore-forming cardiotoxic protein isolated from the edible mushroom *Volvariella volvacea* is known to cause cardiac arrest by the initiation of Ca21-dependent ATPase activity[31].

2.4 Treatment

The first step in the treatment process is the immediate stoppage of further exposure to the toxic substance. Toxicity induced due to the ingestion of a particular toxic substance should be stopped before it gets absorbed in the gastrointestinal tract. Vomiting can help somewhat get rid of the toxin, but this can only be helpful if the toxin is present in the upper Gastrointestinal tract. It has been found that doses of activated charcoal are effective against further absorption of the toxin(s); for example, in the treatment for amatoxin intoxication administration of the activated charcoal, along with maintenance of hydration in the body, is required[28]. Dyselectrolytemia, i.e, imbalance of the electrolytes present in the blood is seen upon consumption of cardiac glycosides. Therefore, the next step is to monitor electrolyte levels and provide the patient with electrolyte supplements if required. The following step is the rectification of hyperkalemia by providing insulin and dextrose. As the patients have a high risk of arrhythmias, 24 hours monitoring is a must. The ultimate therapy in cases of cardiac glycoside poisoning is digoxin-specific Fab fragments (e.g., Digibind and DigiFab). These Fab antibody fragments bind to the circulating cardiac glycosides in the body and limit its toxicity. With the help of atropine and

β-adrenergic agents, Bradyarrhythmias can be managed. With the usage of these agents, patients may fall into increased risks of tachyarrhythmias; therefore, cautiously, these agents should be given to the patients[32]. In the case of tachyarrhythmias the drug Lidocaine is suggested. In cases of cyanide poisoning, antidotes include sodium nitrate and sodium thiosulfate. Recommended treatment for oxalate poisoning includes oral dosing with calcium lactate followed by an emetic (binding the unabsorbed oxalates to calcium and removing them from the body)[14]. Furthermore, treating of all kinds of poisonings requires antidotes of that particular kind, if known and if available[18].

3. Concluding Remarks and Future Directions

There are very few available published research and review papers that deal with the principle toxic compounds of the cardiotoxic plants. Further studies are required for the identification of the symptoms in human beings and other animals on the consumptions of these plants or plant part(s). The list of cardiotoxic plants is endless as each year, new plants are discovered throughout the world, but many details are missing. Therefore, further investigation and study are required. The detailed research on proper identification, specification and possible treatments of the cardiotoxic plants still needed. It is essential to guide the general public regarding the identification of the toxic plants and their harmful effects so that people become more aware of themselves and their livestock. Cases of intoxication should be reported immediately so that medical practitioners can have detailed studies and develop possible treatments for these types of conditions.

4. Acknowledgment

The authors are grateful to the staff of The Department of Botany, Bioinformatics and Climate Change Impacts Management, Ahmedabad, Gujarat University for their timely help and support.

5. Conflict of Interest

The authors hereby declare no conflict of interest.

7. References

1. Ndhlala AR, Ncube B, Okem A, Mulaudzi RB, Staden JV. Toxicology of some important medicinal plants in southern Africa. Food Chem Toxicol. 2013; 62(1): 609–21. https://doi.org/10.1016/j.fct.2013.09.027. PMid:24075916
2. Serrano R. Toxic plants: Knowledge, Medicinal uses and potential human health risks. Environ Ecol Res. 2018; 6(5):487–92. https://doi.org/10.13189/eer.2018.060509
3. Hall JE, Guyton AC. Hall textbook of medical physiology. 11th ed. Philadelphia, Pennsylvania: Elsevier Saunders; 2006.
4. Parameswaran S, Kumar S, Verma RS, Sharma RK. Cardiomyocyte culture: An update on the in vitro cardiovascular model and future challenges. Can J Physiol Pharmacol. 2013; 91(12):985–98. https://doi.org/10.1139/cjpp-2013-0161. PMid:24289068
5. Barrett K, Barman S, Boitano S, Brooks H. Ganong's review of medical physiology. New York: McGraw-Hill; 2010.
6. Akinmoladun AC, Olaleye MT, Farombi EO. Cardiotoxicity and cardioprotective effects of African Medicinal plants. In: Kuete V. Toxicological Survey of African Medicinal Plants. Elsevier; 2014. https://doi.org/10.1016/B978-0-12-800018-2.00013-3
7. Senthilkumaran S, Meenakshisundaram R, Thirumalaikolundusubramanian P. Plant toxins and the heart. In: Ramachandran M. Heart and Toxins. Academic Press; 2015. https://doi.org/10.1016/B978-0-12-416595-3.00005-0
8. Lin CC, Yang CC, Phua DH, Deng JF, Lu LH. An outbreak of foxglove leaf poisoning. J Chinese Med Assoc. 2010; 73(2):97–100. https://doi.org/10.1016/S1726-4901(10)70009-5
9. Page E. The actions of cardiac glycosides on heart muscle cells. Circulation. 1964; 30(2):237–51. https://doi.org/10.1161/01.CIR.30.2.237. PMid:14205552
10. Wilson CR, Sauer J, Hooser SB. Taxines: A review of the mechanism and toxicity of yew (*Taxus* spp.) alkaloids. Toxicon. 2001; 39(2–3):175–85. https://doi.org/10.1016/S0041-0101(00)00146-X
11. Caksen H, Odaba SD, Akbayram S, Cesur Y, Arslan S, Uner A, Oner AF. Deadly nightshade (*Atropa Belladonna*) intoxication: An analysis of 49 children. Hum Exp Toxicol. 2003; 22(12):665–68. https://doi.org/10.1191/0960327103ht404oa. PMid:14992329
12. Tai YT, But RR, Young K, Lau CR. Cardiotoxicity after accidental herb-induced aconite poisoning. Lancet. 1992; 340(8830):1254–56. https://doi.org/10.1016/0140-6736(92)92951-B
13. Lai CK, Poon WT, Chan YW. Hidden aconite poisoning: Identification of yunaconitine and related *Aconitum* alkaloids in urine by liquid chromatography-tandem

mass spectrometry. J Anal Toxicol. 2006; 30(7):426–33. https://doi.org/10.1093/jat/30.7.426. PMid:16959134

14. Zoltani CK. Cardiovascular toxicity. In: Gupta RC. Veterinary Toxicology. Academic Press; 2018. https://doi.org/10.1016/B978-0-12-811410-0.00014-3
15. Dwivedi S, Aggarwal A, Sharma V. Cardiotoxicity from 'safe' herbomineral formulations. Trop Doct. 2011; 41(2):113–15. https://doi.org/10.1258/td.2010.100304. PMid:21262956
16. Pfister JA, Stegelmeier BL, Cheney CD, Gardner DR. Effect of previous locoweed (*Astragalus* and *Oxytropis* species) intoxication on conditioned taste aversions in horses and sheep. J Anim Sci. 2007; 85(7):1836–41. https://doi.org/10.2527/jas.2007-0046. PMid:17431041
17. Koca I, Koca AF. Poisoning by mad honey: A brief review. Food Chem Toxicol. 2007; 45(8): 1315–18. https://doi.org/10.1016/j.fct.2007.04.006. PMid:17540490
18. Bhalla A, Thirumalaikolundusubramanian P, Fung J, Cordero-Schmidt G, Soghoian S, Sikka VK, Dhindsa HS, Singh S. Native medicines and cardiovascular toxicity. In: Ramachandran M. The heart and toxins. Academic Press; 2015. https://doi.org/10.1016/B978-0-12-416595-3.00006-2
19. Vetter J. Plant cyanogenic glycosides. Toxicon. 2000; 38(1):11–36. https://doi.org/10.1016/S0041-0101(99)00128-2
20. Holstege CP, Forrester JD, Borek HA, Lawrence DT. A case of cyanide poisoning and the use of arterial blood gas analysis to direct therapy. Hosp Pract. 2010; 38(4):69–74. https://doi.org/10.3810/hp.2010.11.342. PMid:21068529
21. Mookadam F, Smith T, Jiamsripong P, Moustafa SE, Monico CG, Lieske JC, Milliner DS. Cardiac abnormalities in primary hyperoxaluria. Circ J. 2010; 74(11):2403–09. https://doi.org/10.1253/circj.CJ-10-0107. PMid:20921818 PMCid:PMC5929473
22. Coltart DJ, Hudson REB.Primary oxalosis of the heart: A cause of heart block. Br Heart J. 1971; 33(2):315–19. https://doi.org/10.1136/hrt.33.2.315. PMid:5572669 PMCid:PMC487183
23. Burg RV. Toxicology Update. J App Tox. 1994; 14(3):233–37. https://doi.org/10.1002/jat.2550140315. PMid:8083486
24. Goel G, Harinder PSM, Francis G, Becker K. Phorbol esters: Structure, biological activity, and toxicity in animals. Int J Toxicol. 2007; 26(4):279–88. https://doi.org/10.1080/10915810701464641. PMid:17661218
25. Fujiki H, Suttajit M, Rawangkan A, Iida K, Limtrakul P, Umsumarng S, Suganuma M. Phorbol esters in seed oil of *Jatropha curcas* L. (saboodam in Thai) and their association with cancer prevention: From the initial investigation to the present topics. J Cancer Res Clin Oncol. 2017; 143(8):1359–69. https://doi.org/10.1007/s00432-017-2341-6. PMid:28124725 PMCid:PMC5504133
26. Goldstein IJ, Hughes RC, Monsigny M, Osawa T, Sharon N. What should be called a lectin? Nature. 1980; 285:66. https://doi.org/10.1038/285066b0
27. Berger K, Guss D. Mycotoxins revisited: Part 1. J Emerg Med. 2005; 28(1):53–62. https://doi.org/10.1016/j.jemermed.2004.08.013. PMid:15657006
28. Unverir P, Soner BC, Dedeoglu E, Karcioglu O, Boztok K, Tuncok Y. Renal and hepatic injury with elevated cardiac enzymes in *Amanita phalloides* poisoning: A case report. Hum Exp Toxicol. 2007; 26(9): 757–61. https://doi.org/10.1177/0960327107083972. PMid:17984148
29. Tadjibaeva G, Sabirov R, Tomita T. Flammutoxin, a cytolysin from the edible mushroom Flammulina velutipes, forms two different types of voltage-gated channels in lipid bilayer membranes. Biochim Biophys Acta. 2000; 1467(2):431–43. https://doi.org/10.1016/S0005-2736(00)00240-6
30. Lin JY, Lin YJ, Chen CC, Wu HL, Shi GY, Jeng TW. Cardiotoxic protein from edible mushrooms. Nature. 1974; 252:235–37. https://doi.org/10.1038/252235a0. PMid:4472852
31. Weng YP, Lin YP, Hsu CI, Lin JY. Functional domains of a pore-forming cardiotoxic protein, Volvatoxin A2. J Biol Chem. 2004; 279(8):6805–14. https://doi.org/10.1074/jbc.M308675200. PMid:14645370
32. Rajapakse S. Management of yellow oleander poisoning. Clin Toxicol (Phila). 2009; 47(3):206–12. https://doi.org/10.1080/15563650902824001. PMid:19306191
33. Adelowotan O, Aibinu I, Adenipekun E, Odugbemi T. The in-vitro antimicrobial activity of *Abrus precatorius* (L) fabaceae extract on some clinical pathogens. Niger Postgrad Med J. 2008; 15(1):32–7.
34. Zore GB, Awad V, Thakre AD, Halde UK, Meshram NS, Surwase BS, Karuppayil SM. Activity directed-fractionation and isolation of four antibacterial compounds from *Abrus precatorius* L., roots. Nat Prod Res. 2007; 21(9):933–40. https://doi.org/10.1080/14786410701474928. PMid:17763102

35. Pandita D, Pandita A, Pandita S. The Phytochemistry, Toxicology and warning signs of the poisonous flora of Jammu and Kashmir, India. International Journal of Indigenous Medicinal Plants. 2014; 47(2):1621–39.
36. Dalefield R. Poisonous plants. In: Dalefield R. Veterinary Toxicology for Australia and New Zealand. Elsevier; 2017. https://doi.org/10.1016/B978-0-12-420227-6.00023-2
37. Bijl PVD. Cardiotoxicity of plants in South Africa. Cardiovasc J Afr. 2012; 23(9):476–7.
38. Dhesi P, Ng R, Shehata MM, Shah PK. Ventricular tachycardia after ingestion of ayurveda herbal antidiarrheal medication containing *Aconitum*. Arch Intern Med. 2010; 170(3):303–5. https://doi.org/10.1001/archinternmed.2009.518. PMid:20142579
39. Chan TYK. Aconite poisoning. Clin Toxicol (Phila). 2009; 47(4):279–85. https://doi.org/10.1080/15563650902904407. PMid:19514874
40. Versiani MA, Ahmeda SK, Ikrama A, Ali ST, Yasmeena K, Faizib S. Chemical constituents and biological activities of *Adenium obesum* (FORSK.) ROEM. et SCHULT. Chem Biodivers. 2014; 11(2):171–80. https://doi.org/10.1002/cbdv.201200254. PMid:24591309
41. Aslani MR, Movassaghi AR, Mohri M, Abbasian A, Zarehpour M. Clinical and pathological aspects of experimental oleander (*Nerium oleander*) toxicosis in sheep. Vet Res Commun. 2004; 28(7):609–16. https://doi.org/10.1023/B:VERC.0000042870.30142.56. PMid:15563108
42. Anadón A, Martínez-Larrañaga MR, Ares I, Martínez MA. Poisonous plants of the Europe. In: Gupta RC. Veterinary Toxicology. Academic Press; 2018. https://doi.org/10.1016/B978-0-12-811410-0.00062-3
43. Petricevich VL, Abarca-Vargas R. Allamanda cathartica: A review of the phytochemistry, pharmacology, toxicology, and biotechnology. Molecules. 2019; 24(7):1–22. https://doi.org/10.3390/molecules24071238. PMid:30934947 PMCid:PMC6480200
44. Ghosh C, Hazra L, Nag SK, Sil S, Dutta A, Biswas S, Biswas M, Ghosh P, Chatterjee S. *Allamanda cathartica* Linn. Apocynaceae: A mini review. International Journal of Herbal Medicine. 2019; 7(4):29–33.
45. Deng JF, Ger J, Tsai WJ, Kao WF, Yang CC. Acute toxicities of betel nut: Rare but probably overlooked events. J Toxicol Clin Toxicol. 2001; 39(4):355–60. https://doi.org/10.1081/CLT-100105155. PMid:11527229
46. Chu NS. Effects of betel chewing on the central and autonomic nervous systems. J Biomed Sci. 2001; 8(3):106–10. https://doi.org/10.1007/BF02256596. PMid:11385294
47. Sikdar A, Mondal AK, Rajan K, Tripathi N. Survey of common poisonous plants of Birbhum, Burdwan, and Nadia Districts of West Bengal, India. International Journal of Plant Research. 2015; 5(5):103–6.
48. Bakhlet AO, Adam SAI. Therapeutic utility, constituents and toxicity of some medicinal plants: A review. Vet Human Toxicol. 1995; 37(3):255–8.
49. Brink AJ, Lewis CM, Weber HW. Myocardiopathy in *Argemone mexicana* Poisoning. S Afr Med J. 1965; 39:108–14.
50. Bothaa CJ, Penrithb ML. Poisonous plants of veterinary and human importance in southern Africa J Ethnopharmacol. 2008; 119(3):549–58. https://doi.org/10.1016/j.jep.2008.07.022. PMid:18706990
51. Groeneveld HW, Van der Made LA. Cardenolide and triterpene synthesis in the laticifers of *Asclepias curassavica* L. Acta Bot Neerl. 1982; 31(1/2):5–10. https://doi.org/10.1111/j.1438-8677.1982.tb01589.x
52. Lee YJ, Han SB, Hyon JY. Corneal endothelial dysfunction caused by *Asclepias curassavica* in a young farmer. Am J Ophthalmol Case Rep. 2019; 16:1–4. https://doi.org/10.1016/j.ajoc.2019.100564. PMid:31692682 PMCid:PMC6806376
53. Al-Snafi AE. Chemical constituents and pharmacological effects of *Asclepias Curassavica* - A review. Asian J Pharm Res. 2015; 5(2):83–7.
54. Pfister JA, Stegelmeier BL, Cheney CD, Gardner DR. Effect of previous locoweed (*Astragalus* and *Oxytropis* species) intoxication on conditioned taste aversions in horses and sheep. J Anim Sci. 2007; 85(7):1836–41. https://doi.org/10.2527/jas.2007-0046. PMid:17431041
55. Rios JL, Waterman PG. A review of the pharmacology and toxicology of *Astragalus*. Phytother Res. 1997; 11(6):411–18. https://doi.org/10.1002/(SICI)1099-1573(199709)11:6<411::AID-PTR132>3.0.CO;2-6
56. Li X, Qu L, Dong Y, Han L, Liu E, Fang S, Zhang Y, Wang T. A review of recent research progress on the *Astragalus* Genus. Molecules. 2014; 19(11):18850–80. https://doi.org/10.3390/molecules191118850.PMid:25407722 PMCid:PMC6270929
57. Singh MK, Bharati KA, Kumar R. Folk medicinal plants of Sikkim Himalayas and their pharmacological use. Int J Econ Plants. 2015; 2(2):035–045.

58. Bene K, Kra AKM, Konan KF, Zirihi GN. *Bersama abyssinica* Fresen. (Melianthaceae): Antifungal activity on Aflatoxin B1-producing mold. Br J Pharm Res. 2017; 15(1):1–6. https://doi.org/10.9734/BJPR/2017/31695

59. Masondo NA, Ndhlala AR, Aremu AO, Staden JV, Finnie JF. A comparison of the pharmacological properties of garden cultivated and muthi market-sold Bowiea volubilis. S Afr J Bot. 2013; 86():135–8. https://doi.org/10.1016/j.sajb.2013.02.169

60. Bose TK, Basu RK, Biswas B, De JN, Majumdar BC, Datta S. Cardiovascular effects of yellow oleander ingestion. J Indian Med Assoc. 1999; 97(10):407–10.

61. Aslani MR. Cardiotoxicity of plants in Iran: A review. Iran J Veterinary Sci Technol. 2018; 10(1):1–11.

62. Eddleston M, Ariaratnam CA, Sjostrom L, Jayalath S, Rajakanthan K, Rajapakse S, *et al.* Acute yellow oleander (*Thevetia peruviana*) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. Heart. 2000; 83(3):301–6. https://doi.org/10.1136/heart.83.3.301. PMid:10677410 PMCid:PMC1729329

63. Kalix P. *Catha edulis*, a plant that has amphetamine effects. Pharm World Sci. 1996; 18(2):69–73. https://doi.org/10.1007/BF00579708. PMid:8739260

64. Eddleston M, Haggalla S. Fatal injury in eastern Sri Lanka, with special reference to cardenolide self-poisoning with *Cerbera manghas* fruits. Clin Toxicol. 2008; 46(8):745–8. https://doi.org/10.1080/15563650701668617. PMid:18803087

65. Cheenpracha S, Karalai C, Rat-A-Pa Y, Ponglimanont C, Chantrapromma K. New cytotoxic cardenolide glycoside from the seeds of *Cerbera manghas*. Chem Pharm Bull (Tokyo). 2004; 52(8):1023–5. https://doi.org/10.1248/cpb.52.1023. PMid:15305009

66. Eddleston M, Persson H. Acute plant poisoning and antitoxin antibodies. J Toxicol Clin Toxicol. 2003; 41(3):309–15. https://doi.org/10.1081/CLT-120021116. PMid:12807314 PMCid:PMC1950598

67. Chan EWC, Wong SK, Chan HT, Baba S, Kezuka M. *Cerbera* are coastal trees with promising anticancer properties but lethal toxicity: A short review. J Chin Pharm Sci. 2016; 25(3):161–9. https://doi.org/10.5246/jcps.2016.03.019

68. Selladurai P, Thadsanamoorthy S, Ariaranee G. Epidemic Self-Poisoning with Seeds of *Cerbera manghas* in Eastern Sri Lanka: An Analysis of Admissions and Outcome. J Clin Toxicol. 2016; 6(2):1-4. https://doi.org/10.4172/2161-0495.1000287

69. Iyer GV, Narendranath M. A preliminary report on the neurological manifestations of *Cerbera odollam* poisoning. J Med Res. 1975; 63(2):312–14.

70. Gaillard Y, Krishnamoorthy A, Bevalot F. *Cerbera odollam*: A 'suicide tree' and cause of death in the state of Kerala, India. J Ethnopharmacol. 2004; 95(2–3):123–6. https://doi.org/10.1016/j.jep.2004.08.004. PMid:15507323

71. Guruswami MN, Ganapathy MN, Thampai CK. A preliminary study of the pharmacological actions and toxicity of "*Cerbera odollam*". Indian J Med Sci. 1970; 24(2):82–7.

72. Nelson LS, Shih RD, Balick MJ. Handbook of poisonous and injurious plants. New York: Springer; 2007.

73. Panter KE, Welch KD, Gardner DR, Lee ST, Green BT, Pfister JA, Cook D, Davis TZ. Poisonous plants of the United States. In: Gupta RC. Veterinary Toxicology. Academic Press; 2018. https://doi.org/10.1016/B978-0-12-811410-0.00061-1

74. Panter KE, Keeler RF, Baker DC. Toxicoses in Livestock from the Hemlocks (*Conium* and *Cicuta* Spp.). J Anim Sci. 1988; 66(9):2407–13. https://doi.org/10.2527/jas1988.6692407x. PMid:3049497

75. Eyal S. The fever tree: From malaria to neurological diseases. Toxins. 2018; 10(12):1–12. https://doi.org/10.3390/toxins10120491. PMid:30477182 PMCid:PMC6316520

76. Chrispal A. *Cleistanthus collinus* poisoning. J Emerg Trauma Shock. 2012; 5(2):160-166. https://doi.org/10.4103/0974-2700.96486 PMid:22787347

77. Benjamin SP, Fernando ME, Jayanth JJ, Preetha B. *Cleistanthus collinus* poisoning. J Assoc Physicians India. 2006; 54(9):742-744.

78. Nagraj S. Cardiac toxicity of Oduvanthalai (*Cleistanthus collinus*) common leaves poisoning in Tamil Nadu (Report of 25 cases). Antiseptic. 1987; 84:33-5.

79. Larrea MISA, Larrea MDSA, Fernandez CR. Plants, Poisonous (Animals). In: Wexler P. Encyclopedia of Toxicology. Academic Press 2014.

80. Lin S, Qin D, Zhang Y, Zheng Q, Yang L, Cheng D, Huang S, Chen J, Zhang Z. Toxicity and Sublethal Effects of Autumn Crocus (*Colchicum autumnale*) Bulb Powder on Red Imported Fire Ants (*Solenopsis invicta*). Toxins. 2020; 12(11):1-12. https://doi.org/10.3390/toxins12110731 PMid:33233472 PMCid:PMC7700203

81. Brvar M, Ploj T, Kozelj G, Mozina M, Noc M, Bunc M. Case report: fatal poisoning with *Colchicum autumnale*. Crit Care. 2004; 8:R56-R59. https://doi.org/10.1186/cc2427 PMid:14975056 PMCid:PMC420069

82. Keelar RF, Balls LD. Teratogenic Effects in Cattle of *Conium maculatum* and *Conium* Alkaloids and Analogs. Clin Toxicol. 1978; 12(1):49-64. https://doi.org/10.3109/15563657809149583 PMid:630821

83. Al-Barwani FM, Eltayeb EA. Antifungal compounds from induced *Conium maculatum* L. plants. Biochem Sys Ecol. 2004; 32(12):1097-1108. https://doi.org/10.1016/j.bse.2004.02.011

84. López TA, Cid MS, Bianchini ML. Biochemistry of hemlock (*Conium maculatum* L.) alkaloids and their acute and chronic toxicity in livestock. A review. Toxicon. 1999; 37(6): 841-865. https://doi.org/10.1016/S0041-0101(98)00204-9

85. Frank BS, Michelson WB, Panter KE, Gardner DR. Ingestion of Poison Hemlock (*Conium maculatum*). West J Med. 1995; 163(6):573-574.

86 Welsh KJ, Huang RSP, Actor JK, Dasgupta A. Rapid detection of the active cardiac glycoside convallatoxin of lily of the valley using LOCI digoxin assay. Am J Clin Pathol. 2014; 142(3):307-312. https://doi.org/10.1309/AJCPCOXF0O5XXTKD PMid:25125619

87. Boido CC, Tasso B, Boido V, Sparatore F. Cytisine derivatives as ligands for neuronal nicotine receptors and with various pharmacological activities. Farmaco. 2003 58(3):265-277. https://doi.org/10.1016/S0014-827X(03)00017-X

88. Riccardi A, Frumento F, Ghinatti M, Guiddo G, Lerza R. Spanish Broom flower ingestion: a very unusual poisoning. Eur J Emerg Med. 2006;13(5):317-318. https://doi.org/10.1097/00063110-200610000-00018 PMid:16969244

89. DeFrates LJ, Hoehns JD, Sakornbut EL, Glascock DG, Tew AR. Antimuscarinic intoxication resulting from the ingestion of moonflower seeds. Ann Pharmacother. 2005; 39(1):173-176. https://doi.org/10.1345/aph.1D536 PMid:15572604

90. Krenzelok EP. Aspects of *Datura* poisoning and treatment. Clin Toxicol. 2010; 48(2):104-110. https://doi.org/10.3109/15563651003630672 PMid:20229618

91. Green BT, Pfister JA, Cook D, Welch KD, Stegelmeier BL, Lee ST, Gardner DR, Knoppel EL, Panter KE. Serum elimination profiles of methyllycaconitine and deltaline in cattle following oral administration of larkspur (*Delphinium barbeyi*). Am J Vet Res. 2009;70(7):539-546. https://doi.org/10.2460/ajvr.70.7.926 PMid:19566479

92. Davies MK, Hollman A. *Digitalis* and *Strophanthus* cardiac glycosides. Heart. 1998; 80(1):4. https://doi.org/10.1136/hrt.80.1.4 PMid:9764048 PMCid:PMC1728766

93. Stolberg VB. The use of coca: prehistory, history, and ethnography. J. Ethn. Subst. Abuse. 2011; 10(2), 126-146. https://doi.org/10.1080/15332640.2011.573310 PMid:21678146

94. Havakuk O, Rezkalla SH, Kloner RA. The Cardiovascular Effects of Cocaine. J Am Coll Cardiol. 2017; 70(1):101-113. https://doi.org/10.1016/j.jacc.2017.05.014 PMid:28662796

95. Angunawela RM, Fernando HA. Acute ascending polyneuropathy and dermatitis following poisoning by tubers of *Gloriosa superba*. Ceylon Med J. 1971; 16(4):233-235.

96. Gooneratne BW. Massive generalized alopecia after poisoning by *Gloriosa superba*. Br Med J. 1966; 1:1023-1024. https://doi.org/10.1136/bmj.1.5494.1023 PMid:5909848 PMCid:PMC1844473

97. Panghal M, Arya V, Yadav S, Kumar S, Yadav JP. Indigenous knowledge of medicinal plants used by Saperas community of Khetawas, Jhajjar District, Haryana, India. J Ethnobiol Ethnomedicine. 2010; 6(4):1-11. https://doi.org/10.1186/1746-4269-6-4 PMid:20109179 PMCid:PMC2826346

98. Mendis S. Colchicine cardiotoxicity following ingestion of *Gloriosa superba* tubers. Postgrad Med J. 1989; 65(768):752-755. https://doi.org/10.1136/pgmj.65.768.752 PMid:2694138 PMCid:PMC2429836

99. Aleem HM. *Gloriosa superba* poisoning. J Assoc Physicians India. 1992; 40(8):541-542.

100. Khan AU, Gilani AH. Cardiovascular inhibitory effects of *Hyoscyamus niger*. Methods Find Exp Clin Pharmacol. 2008; 30(4):295-300. https://doi.org/10.1358/mf.2008.30.4.1186075 PMid:18773124

101. Drummer OH. Autopsy Findings: Organic Toxins. In: Payne-James J, Byard RW. Encyclopedia of Forensic and Legal Medicine. Elsevier 2016. https://doi.org/10.1016/B978-0-12-800034-2.00046-X

102. Friedman M, Roitman JN, Kozukue N. Glycoalkaloid and calystegine contents of eight potato cultivars. J Agric Food Chem. 2003; 51(10):2964-2973. https://doi.org/10.1021/jf021146f PMid:12720378

103. Pomilioa AB, Falzonia EM, Vitaleb AA. Toxic Chemical Compounds of the Solanaceae. Nat Prod Commun. 2008; 3(4):593-628. https://doi.org/10.1177/1934578X0800300420

104. García-Pérez P, Lozano-Milo E, Landin M, Gallego PP. From Ethnomedicine to Plant Biotechnology and Machine Learning: The Valorization of the Medicinal

Plant *Bryophyllum* sp. Pharmaceuticals. 2020; 13:1-23. https://doi.org/10.3390/ph13120444 PMid:33291844 PMCid:PMC7762000

105. Ito S, Nakazato Y, Ohga A. Further evidence for the involvement of Na+ channels in the release of adrenal catecholamine: the effect of scorpion venom and grayanotoxin I. Br J Pharmacol. 1981; 72(1):61-67. https://doi.org/10.1111/j.1476-5381.1981.tb09105.x PMid:6261866 PMCid:PMC2071538
106. Kelmanson JE, Jager AK, Staden JV. Zulu medicinal plants with antibacterial activity. J Ethnopharmacol. 2000; 69(3):241-246. https://doi.org/10.1016/S0378-8741(99)00147-6
107. Sparg SG, Staden JV, Jager AK. Pharmacological and phytochemical screening of two Hyacinthaceae species: *Scilla natalensis* and *Ledebouria ovatifolia*. J Ethnopharmacol. 2002; 80(1):95-101. https://doi.org/10.1016/S0378-8741(02)00007-7
108. Taylor JLS, Elgorashi EE, Maes A, Van UG, De NK, Van JS, Verschaeve L. Investigating the safety of plants used in South African traditional medicine: testing for genotoxicity in the micronucleus and alkaline comet assays. Environ Mol Mutagen. 2003; 42(3):144-154. https://doi.org/10.1002/em.10184PMid:14556222
109. Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. J Am Osteopath Assoc. 2012; 112(12):792-799.
110. Jun L, Heming W, Jianjun W, Jamil MFA, Tan ML, Adenan MI, Wong P, Shim W. Evaluation of the Cardiotoxicity of Mitragynine and Its Analogues using Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes. Plos One. 2014; 9(12):1-18. https://doi.org/10.1371/journal.pone.0115648 PMid:25535742 PMCid:PMC4275233
111. Takayama H. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*. Chem Pharm Bull. 2004 52(8):916-928. https://doi.org/10.1248/cpb.52.916 PMid:15304982
112. Farooqui S, Tyagi T. *Nerium oleander*: Its Application in Basic and Applied Science: A Review. International Journal of Pharmacy and Pharmaceutical Sciences. 2018; 10(3):1-4. https://doi.org/10.22159/ijpps.2018v10i3.22505
113. 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 *Thevetia peruviana* (yellow oleander) poisoning. Toxicon. 2010; 56(1):273-281. https://doi.org/10.1016/j.toxicon.2010.03.026 PMid:20438743
114. Barbosa RR, Fontenele-Neto JD, Soto-Blanco B. Toxicity in goats caused by oleander (*Nerium oleander*). Res Vet Sci. 2008(2); 85: 279-281. https://doi.org/10.1016/j.rvsc.2007.10.004 PMid:18031775
115. Langford S, Boor P. Oleander toxicity: an examination of human and animal toxic exposures. Toxicology. 1996; 109(1):1-13. https://doi.org/10.1016/0300-483X(95)03296-R
116. Oryan A, Maham M, Rezakhani A, Maleki M. Morphological Studies on Experimental Oleander Poisoning in Cattle. J Vet Med A. 1996;43(1-10):625-634. https://doi.org/10.1111/j.1439-0442.1996.tb00496.x PMid:9011151
117. Plančić M, Božin B, Kladar N, Rat M, Srđenović B. Phytochemical profile and biological activities of the genus *Ornithogalum* L. (Hyacinthaceae). Biol Serb. 2014; 36(1-2):3-17.
118. Kanji S, MacLean RD. Cardiac glycoside toxicity: more than 200 years and counting. Crit Care Clin. 2012; 28(4):527-535. https://doi.org/10.1016/j.ccc.2012.07.005 PMid:22998989
119. Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE. Goldfrank's Toxicologic Emergencies. New York: McGraw-Hill; 2011.
120. Saleem M, Akhtar N, Riaz N, Ali MS, Jabbar A. Isolation and characterization of secondary metabolites from *Plumeria obtusa*. J Asian Nat Prod Res. 2011; 13(12):1122-1127. https://doi.org/10.1080/10286020.2011.618452 PMid:22115036
121. Nunes FCR, Batista JS, Soto-Blanco B. Pathological effects of *Cryptostegia venusta* toxicity in goats and rats. Res Vet Sci. 2011;90(3):474-476. https://doi.org/10.1016/j.rvsc.2010.07.005 PMid:20678785
122. Alonso-Castro AJ, Domínguez F, Ruiz-Padilla AJ, Campos-Xolalpa N, Ramón Zapata-Morales J, Carranza-Alvarez C, Maldonado-Miranda JJ. Medicinal Plants from North and Central America and the Caribbean Considered Toxic for Humans: The Other Side of the Coin. Evid Based Compl Alt. 2017; 14:1-28. https://doi.org/10.1155/2017/9439868 PMid:29234446 PMCid:PMC5688365
123. Chandran R, Nagrajan A, Bakare S. Evaluation of the Haematological Properties and effects of crude *Rauwolfia vomitoria*. International Journal for Research in Applied Sciences and Biotechnology. 2014; 1:10-16.

124. Akera T, Ku DD, Frank M, Brody TM, Iwasa J. Effects of Grayanotoxin I on cardiac Na^+ K^+ -adenosine triphosphatase activity, transmembrane potential and myocardial contractile force. J Pharmacol Exp Ther. 1976; 199(1):247-254.

125 Gundamaraju R, Vemuri RC, Singla RK, Manikam R, Rao R, Sekaran SD. *Strophanthus hispidus* attenuates the Ischemia-Reperfusion induced myocardial Infarction and reduces mean arterial pressure in renal artery occlusion. Phcog Mag. 2014; 10(39):557-562. https://doi.org/10.4103/0973-1296.139782 PMid:25298674 PMCid:PMC4189272

126. Shi QW, Sauriol F, Mamer O, Lolita OZ. New Taxanes from the Needles of *Taxus canadensis*. J Nat Prod. 2003; 66(4):470-476. https://doi.org/10.1021/np020361n PMid:12713395

127. Zhang J, Sauriol F, Mamer O, Lolita OZ. Taxoids from the needles of the Canadian yew. Phytochem. 2000; 54(2):221-230. https://doi.org/10.1016/S0031-9422(00)00079-0

128. Jones R, Jones J, Causer J, Ewins D, Goenka N, Joseph F. Yew tree poisoning: a near-fatal lesson from history. Clin Med. 2011; 11(2):173-175. https://doi.org/10.7861/clinmedicine.11-2-173 PMid:21526705 PMCid:PMC5922745

129. Ogden L. *Taxus* (yews)--a highly toxic plant. Vet Hum Toxicol. 1988; 30(6):563-564.

130. Peterson MC, Rasmussen GJ. Intoxication with foothill camas (*Zigadenus paniculatus*). J Toxicol Clin Toxicol. 2003; 41(1):63-65. https://doi.org/10.1081/CLT-120018272 PMid:12645969

131. Majak W, McDiarmid RE, Cristofoli W, Sun F, Benn M. Content of zygacine in *Zygadenus venenosus* at different stages of growth. Phytochem. 1992; 31(10):3417-3418. https://doi.org/10.1016/0031-9422(92)83697-W

132. Gilotta I, Brvar M. Accidental poisoning with Veratrum album mistaken for wild garlic (*Allium ursinum*). Clin Toxicol. 2010; 48(9):949-952. https://doi.org/10.3109/15563650.2010.533675 PMid:21171854

133. Marinov A, Koev P, Mirchev N. Electrocardiographic studies of patients with acute hellebore (*Veratrum album*) poisoning. Vutr Boles. 1987; 26(6):36-39.

134. Jaffe AM, Gephardt D, Courtemanche L. Poisoning due to ingestion of *Veratrum viride* (false hellebore). J Emerg Med. 1990; 8(2):161-167. https://doi.org/10.1016/0736-4679(90)90226-L

135. Schep LJ, Schmierer DM, Fountain JS. *Veratrum* poisoning. Toxicol Rev. 2006; 25(2):73-78. https://doi.org/10.2165/00139709-200625020-00001 PMid:16958554