10.4.4 Poisonous plants 1828

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SECTION 10 Environmental medicine, occupational medicine, and poisoning 1828 10.4.4 Poisonous plants Michael Eddleston and Hans Persson ESSENTIALS Many plants contain toxic substances—heterogeneous in chemical composition and diverse in toxic effects. When classifying plant pois- onings, a pragmatic approach is to look at the main clinical effects, but it should be emphasized that few plant toxins produce just one type of symptom and that symptomatology is often multiple, with some features predominating. Ingestion of, or contact with, poisonous plants is common but ser- ious plant poisoning is rare worldwide because most plant exposures are accidental: the majority occur in small children, the ingested dose is usually small, and no treatment is required. Globally, severe plant poisoning usually results from intentional exposure. Toxic plants are ingested for self-harm in certain regions (e.g. in Sri Lanka and India), where cardiac glycosides in yellow ole- ander Cascabela thevetia and odollam Cerbera manghas and diphyllin glycosides in oduvan Cleisthanthus collinis are responsible for much morbidity and mortality. Other intentional and serious poisonings occur with, for example, Aconitum and Colchicum spp.. Plants with psychotropic and hallucinogenic effects, for example, Datura and Cannabis spp., are abused as recreational drugs or used in food or drinks to render travellers unconscious for robbery. Severe unintentional poisoning has resulted from the use of herbal medicines or foods containing, or contaminated by, plant toxins
(e.g. aconitine in China, cyanide (cassava) in Africa, and aristolochic acid (Aristolochia spp.) in Europe). Food insecurity in lower in- come countries results in outbreaks of poisoning, often in children
(e.g. with pyrrolizidine alkaloids in Heliotrope species, mitochondrial toxins in Xanthium strumarium, a hepatotoxin in Blighia sapida, and cyanogenic glycosides in toxic Detarium senegalense). Treatment of severe plant poisoning includes careful de- contamination and symptomatic and supportive care. Specific antidotes are only available for poisoning by plants containing belladonna alkaloids (physostigmine), cardiac glycosides (digoxin- specific Fab fragments), and cyanogenic agents (dicobalt edetate, hydroxocobalamin). Aetiology and epidemiology The most common exposure to toxic plants, particularly in the West, is in young children as they explore their environment. Few of these exposures result in serious harm. In other

parts of the world, par- ticularly Asia, the most common plant exposures are from self-harm in adolescents and adults, sometimes with fatal outcome. Deaths also occur after children (although rarely adults) eat poisonous plants as food, especially where there is food insecurity. Herbal medicines containing toxic principles cause accidental plant poisoning, while recreational ingestion or smoking of psychoactive plants is popular in industrialized countries. A clinically oriented overview of the main plant toxins is given in Table 10.4.4.1. Neurotoxic plants Anticholinergic toxins Belladonna alkaloids (atropine, hyoscyamine, scopolamine) occur in a variety of plants, including deadly nightshade Atropa bella- donna, henbane Hyoscyamus niger, thorn apple/jimson weed Datura stramonium, and angels' trumpets Brugmansia suaveolens. These al- kaloids are muscarinic acetylcholine receptor antagonists, causing central and peripheral anticholinergic effects. Poisoning can occur unintentionally in children or, in some localities, as part of drugging a person for robbery; most commonly, toxicity occurs after recre- ational use in young people ingesting Datura or Brugmansia spp. The anticholinergic toxidrome includes tachycardia, fever, agita- tion, flushing, mydriasis, delirium, hallucinations, and urinary re- tention. The latter can make confused patients even more distressed and should be actively sought. Rarely, seizures and coma ensue. Differential diagnoses include sympathomimetic or serotinergic toxidromes, common after poisoning with amphetamines and other central nervous system stimulants, and central nervous system infection. Nurse in a quiet calm environment; diazepam may be required for sedation. Physostigmine given by slow intravenous push (adults Table 10.4.4.1 Classification of the main plant toxins Neurotoxins Anticholinergic alkaloids Hallucinogenic toxins Convulsants Nicotinic agonists Cardiotoxins Aconitine Grayanotoxins Cardiac glycosides Taxanes Cytotoxic agents Colchicine Toxalbumins Cyanogenic glycosides Diterpenoid glucosides Epidemic dropsy alkaloids Hepatotoxins Pyrrolizidine alkaloids Senna occidentalis toxins Hypoglycin Nephrotoxins Aristolochic acid Diphyllin glycosides Terpenes Antraquinone glycosides Oxalic acid Gastrointestinal irritants Calcium oxalate Oxalic acid Diterpene esters Dermatotoxins Calcium oxalate Oxalic acid Phototoxic psoralens

 1–2 mg, children 0.02–0.04 mg/kg) can reverse marked central anticholinergic toxicity that is not settling with time and diazepam. The dose may be repeated as required. Physostigmine should be withheld if cardiotoxic agents have been co-ingested, if the pa- tient has a bradycardia, or if there are signs of cardiac conduction abnormalities. Unilateral mydriasis may occur in people (often gardeners, hence 'gardeners' mydriasis') who handle plants of this type and happen to rub their eye. This has caused confusion on presentation to hospital and unnecessary, expensive investigations. Hallucinogenic toxins Some plant toxins are particularly popular among abusers because of their hallucinogenic properties. Examples are tetrahydrocannabinols in cannabis Cannabis sativa, alkaloids in khat Catha edulis, mes- caline in peyote Lophophora williamsii, and myristicin in nutmeg Myristica fragrans. Ayahuasca is a hallucinogenic brew made from Banisteriopsis caapi vine and Psychotria viridis leaves in South America. After absorption, the usual first pass breakdown of dimethyltryptamine from P. viridis is inhibited by monoamine oxi- dase inhibitors in B caapi, markedly potentiating the effect of the former. Treatment is symptomatic, with a calm environment and benzodiazepines as necessary. Convulsants The γ-aminobutyric acid (GABA) antagonists, cicutoxin and oenanthotoxin, are some of the most potent convulsants known. Cicutoxin occurs in cowbane Cicuta virosa, water hemlock C mac- ulata, and western water hemlock C douglasii, while oenanthotoxin occurs in hemlock water dropwort Oenanthe crocata. Severe poisoning has occurred in adults eating one of these plants after mistaking it for an edible plant. Typical symptoms include gastrointestinal upset, increased

salivation, diaphoresis, and violent, recurrent, and long-lasting tonic–clonic convulsions. These may result in hypoxia, severe metabolic acidosis, coma, cir- culatory instability, rhabdomyolysis, joint dislocations, and rectal prolapse. Diagnosis is typically based on the presence of recurrent seiz- ures together with the history of plant ingestion. Treatment re- quires careful symptomatic and intensive care, with emphasis on combating convulsions with benzodiazepines, barbiturates, and general anaesthesia, correction of acidosis, and maintenance of urinary output. Other toxins reported to cause coma and/or seizures include coriamyrtin in Coriaria myrtifolia in the Western Mediterranean, terpenes in chinaberry Melia azedarach in South East Asia, the alkaloid dauricine in moonseed Menispermum canadense and podophylloresin in may apple Podophyllum peltatum, both in North America, strychnine in the nux vomica or strychnine tree (Strychnos nux-vomica) in South and South East Asia, and un- known toxins in Urobotrya siamensis Hiepko in South East Asia and star fruit Averrhoa carambola in patients with chronic kidney disease in East Asia. Treatment is symptomatic and supportive. Nicotinic agonists The tobacco plant Nicotiana tabacum and hemlock Conium macula- tum contain multiple alkaloids with nicotinic receptor agonist effects, particularly nicotine in the former and coniine and γ-coniceine in the latter. Their unpleasant taste should reduce the risk of poisoning by ingestion; nevertheless, they are sporadically confused with herbs and eaten in salads. Early symptoms are vertigo, agitation, thirst, tachy- cardia, hypertension, salivation, diaphoresis, vomiting, and diarrhoea. Muscle fasciculation, convulsions, hypotension, bradydysrhythmias, ascending weakness, paralysis, and coma may follow. Careful symp- tomatic and supportive care, including assisted ventilation, may be required. Cytisine in Laburnum spp. (e.g. golden chain) and lobeline in Lobelia spp. cause mild nicotine-like effects. However, the most common symptoms after ingestion are vomiting and diarrhoea. Childhood exposures are frequent and symptoms mostly mild or moderate. Treatment is symptomatic. Other neurotoxins Toxins in fruit of the buckthorn or tullidora bush, Karwinskia hum- boldtiana, in Central America produce a flaccid, symmetric, ascending paralysis of the lower limbs. The dimeric hydroxyanthracenone peroxisomicine A1 appears to be cytotoxic but the precise mechanism of the peripheral neuropathy is not yet known. Buckthorn poisoning can easily be mistaken for Guillain-Barré syndrome unless there is a history of fruit ingestion. Treatment is supportive until the peripheral neuropathy resolves, with careful monitoring for impending ventila- tory failure. Gelsemine in lemuan Gelsemium elegans in China and yellow jessamine G sempervirens in North America is a glycine agonist. Patients present with dizziness and eye manifestations (blurred vi- sion, diplopia, nystagmus, ptosis), progressing to coma, seizures, and respiratory failure requiring mechanical ventilation. Treatment requires supportive and intensive care. Cardiotoxic plants Aconitine Aconitine is one of the most potent plant toxins known, occurring in multiple Aconitum spp. (e.g. monkshood, A napellus) native to mountainous parts of the northern hemisphere and now grown widely in gardens. The toxin binds to voltage-gated sodium chan- nels causing persistent sodium influx and depolarization of cardiac and neurological tissue. Serious poisoning results from intentional ingestion of the plant, homicidal administration of aconitine in food, and from unintentional overdose of Asian herbal medica- tions. It is also used in arrow poisons (e.g. Bikh in Nepal). Ingestion results in rapid onset of burning and tingling in the lips, mouth, and pharynx, followed by numbness and paraesthesia of the limbs, hypersalivation, and gastrointestinal symptoms in particular severe and protracted vomiting. Many kinds of dys- rhythmias occur, but particularly ventricular ectopy leading to ventricular tachycardia and fibrillation that may be refractory to treatment. Cardiac failure and shock often develop; coma, mus- cular weakness, neuromuscular failure, and seizures also occur. Considering the extreme toxicity of this plant, gastrointestinal decontamination should be performed. Treatment includes optimal symptomatic

and supportive care, directed at dysrhythmias and cardiac failure, including magnesium, flecainide, or lidocaine, and extracorporeal membrane oxygenation.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1830 Grayanotoxins Grayanotoxins occur in multiple Rhodedendron spp. Pollen from these plants are incorporated by bees into ‘mad’ honey particularly around the Black Sea and Himalayas. The toxic dose is reported to be 20–200 g of honey, with a clear dose response. Similar to acon- itine, the toxin binds to and activates voltage-gated sodium channels on nerve, muscle, and heart cells. Strong vagal effects cause brady- cardia. Toxicity often lasts for 2–3 days, with occurrence of car- diac dysrhythmias, dizziness, diplopia, reduced consciousness, and rarely respiratory failure. Treatment is supportive. Grayanotoxins also occur in mountain laurel Kalmia latifolia, Menziesia spp., and Pieris spp. Cardiac glycosides Cardiac glycosides occur in multiple foxglove spp., including Digitalis purpurea and D lanata, common oleander Nerium ole- ander, yellow oleander Cascabela thevetia, sea mango or odollam tree Cerbera manghas, lily of the valley Convallaria majalis, and red squill Urginea maritima. Cardiac glycoside poisoning is particularly common in South Asia where C. thevetia and C. manghas are com- monly used for self-harm, resulting in hundreds of deaths each year; poisoning with other cardiac glycoside containing plants is more usually unintentional. Ingestion results in severe gastrointestinal features, with ab- dominal pain, profuse vomiting, and diarrhoea common. The toxins’ inhibition of the Na+/K+ ATPase on cardiomyocytes results in hyperkalaemia, as well as raised intracellular sodium and then raised intracellular calcium concentration. Bradycardia with sinus and AV blocks are common; death occurs in 5–10% of patients, likely due to catecholaminergic polymorphic ventricular tachy- cardia. Where available, digitalis-specific antibodies (ovine Fab fragments) are highly effective (Fig. 10.4.4.1). Where not avail- able, management focuses on symptomatic care and treatment of hyperkalaemia. Taxanes Taxin alkaloids in yew Taxus spp. block Na+ and Ca+ channels, inducing QRS prolongation, atrioventricular block, ventricular fib- rillation, and cardiac arrest. They also block Na+ channels and dis- rupt microtubule function, inhibiting cell division, causing central nervous system and gastrointestinal effects. Treatment involves supportive care, with extracorporeal membrane oxygenation if available. Other cardiotoxins Other cardiotoxins include veratrine in Veratrum and Zigadenus spp. and phoratoxin in American mistletoes Phoradendron spp. Cytotoxic plants Colchicine Colchicine occurs in autumn crocus/meadow saffron Colchicum autumnale and glory lily Gloriosa superba. It binds to β-tubulin, producing antimitotic effects on cells with high metabolism (e.g. gut and bone marrow), but also direct toxicity on heart, liver, and kidneys. Intentional exposures may result in severe poisoning. The clinical course has different phases. After an initial delay— sometimes of many hours—there is onset of intense gastrointestinal symptoms, followed by dysrhythmias, circulatory failure, seizures, central nervous system depression, and muscular weakness. There may be signs of renal and hepatic damage and, after a few days, bone marrow depression. Patients who survive the acute phase may lose their hair and develop a peripheral neuropathy. Multiple-dose activated charcoal may enhance elimination, but intensive care is crucial together with measures to encourage bone marrow recovery. Anticolchicine Fab fragments have been studied but are not yet available in clinical practice. Toxalbumins Ricin in the castor plant Ricinus communis and abrin in je- quirity bean Abrus precatorius are water-soluble proteins known as toxalbumins. Ricin is so toxic that it has been placed on the Chemical Weapons Convention List. These compounds block protein synthesis by inhibiting ribosome function, causing cell death, with the gut as the primary target organ. Intact beans are not toxic as they pass through the gut without releasing toxin. However, beans that have been chewed are highly toxic, with just a few

sufficient to cause severe poisoning. A few hours after inges- tion, severe gastroenteritis may occur with heavy fluid and elec- trolyte loss, resulting in renal failure, circulatory instability, and hepatic damage. Treatment is symptomatic with vigorous fluid replacement. Baseline t = 30 min t = 60 min t = 2 h t = 8 h t = 48 h Fig. 10.4.4.1 Resolution of atrioventricular conduction block after treatment with 1200 mg of digoxin-specific Fab fragments. Reprinted from The Lancet, Vol. 355, No. 9208, Eddleston M et al., Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial, pages 967–72, Copyright © 2000, with permission from Elsevier.

10.4.4 Poisonous plants 1831 Cyanogenic glycosides Over 25 cyanogenic glycosides are known, occurring in more than 2500 species of plants distributed across the world. They occur in kernels or fruits of Prunus spp. such as bitter almonds, apricots, cherries, and peaches as well as non-Prunus spp. such as loquat Eriobotrya japonica, cassava (Manihot spp.), elderberry Sambucus nigra, and toxic fruits of the tallow tree Detarium senegalense. Even apple pips Malus spp. contain small amounts of cyanogenic glyco- sides, but large amounts are required to cause poisoning. After the kernels are chewed and swallowed, barriers between the cyanogenic glycoside and enzyme break down, resulting in enzymatic release of cyanide in the stomach. This is a slow process, and symptoms of poisoning may be delayed for many hours. Cyanide poisoning from plants is unusual but, should it occur, treatment is as outlined else- where for cyanide (see Chapter 10.4.1). Inappropriately prepared cassava M. esculenta represents a spe- cial, large-scale problem of chronic cyanide exposure, producing neurological disorders such as tropical ataxic neuropathy and konzo. It was observed in Nigeria in the 1930s, and subsequently in other African countries. Food insecurity results in atypical ways of preparing cassava, producing small outbreaks from time to time. Diterpenoid glucosides The diterpenoid glucosides, atractyloside and carboxyatractyloside, have been identified in bird-lime or blue thistle Atractylis gummif- era in north Africa and in the cocklebur thistle Xanthium strumar- ium in Bangladesh (Fig. 10.4.4.2). These plants are usually eaten by children when food is short. These toxins block the adenine nu- cleotide translocator in mitochondria, inhibiting mitochondrial oxidative phosphorylation. Patients develop vomiting, abdom- inal pain, and diarrhoea, then headache, convulsions, coma, car- diovascular collapse, and liver failure. The published case fatality is high, with most deaths occurring within 24 hrs. Treatment is supportive. Epidemic dropsy alkaloids The alkaloids sanguinarine and dihydrosanguinarine in seeds of the Mexican prickly poppy Argemone mexicana cause epidemic dropsy in populations, particularly South Asian, that cook with mustard oil Brassica nigra. Dropsy occurs when B nigra seeds become contaminated with A mexicana seeds, either acciden- tally due to A mexicana growing in or near B nigra cultivation or due to intentional adulteration. The alkaloids damage capillaries, leading to vascular protein loss and oedema. Patients present with diarrhoea, cough, and marked bilateral pitting oedema of the legs; right sided congestive cardiac failure may occur. Treatment is symptomatic. Hepatotoxic plants Pyrrolizidine alkaloids Hepatotoxicity most commonly occurs when people ingest plants containing pyrrolizidine alkaloids. These toxins cause veno-occlusive disease and occur in many Senecio, Crotalaria, Heliotropium, and Symphytum spp. Cases are reported from Afghanistan, countries of the old USSR, India, and Jamaica; large epidemics have occurred in west Asia when Heliotropium plants have contaminated grain fields producing contamination of flour with pyrrolizidine-containing seeds. Outbreaks have also occurred when misidentification of plants has resulted in them being incorporated into herbal medi- cines. Treatment is supportive. Senna occidentalis toxins Epidemics of acute hepatomyoencephalopathy have been noted in young children in India. Previously thought to be

due to virus in- fection, they are now recognized to be due to ingestion of beans from Senna (prev Cassia) occidentalis. The plant contains a var- iety of toxins (anthraquinones, emodin, glycosides, toxalbumins, alkaloids). Previously healthy children present with vomiting, agi- tation, and abnormal movements that rapidly progress to coma. Blood tests show markedly raised alanine transaminase and cre- atine kinase. In a study of 55 children, 42 (76%) died. Treatment is supportive. Hypoglycin Hypoglycin found in unripe fruit of the ackee Blighia sapida tree causes a reduction in liver fatty acid β oxidation, production of toxic metabolites, and liver steatosis. Patients present with vomiting, sometimes severe hypoglycaemia, coma, and convulsions. Many cases, including localized outbreaks, have been reported from West Africa, Haiti, and Jamaica (where it is termed the Jamaican vomiting disease). Treatment involves correction of hypoglycaemia and intensive care. OH O O O O O O H COOH OH CH2 H O O CH3 CH3 H3C O O S S HO HO (a) (b) Fig. 10.4.4.2 (a) Atractylis gummifera L. (chardon a glu, bird-lime, or blue thistle). (b) The plant’s toxin, atractyloside, which is a mitochondrial adenine nucleotide translocator inhibitor. (a) Courtesy of Luis Nunes Alberto, licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

Nephrotoxic plants Aristolochic acid Balkan endemic nephropathy is due to dietary exposure to seeds of the European birthwort Aristolochia clematitis, which grows intermingled with the wheat used for bread. During the early 1990s, hundreds of patients in Belgium and the United Kingdom developed renal failure after Aristolochia fangchi was mistakenly incorporated into a herbal weight loss treatment instead of Stephania tetrandra. The mechanism of aristolochic acid induced nephropathy is not known. Treatment is supportive. Diphyllin glycosides Self-poisoning with leaves of the oduvan Cleistanthus colli- nus tree in south India is responsible for perhaps hundreds of deaths each year. The plant contains the diphyllin glycosides cleistanthins A and B which cause severe hypokalaemia (via kaliuresis) and metabolic acidosis (due to renal tubular acid- osis), acute respiratory distress syndrome, cardiovascular shock, rhabdomyolysis, and neuromuscular weakness that may require ventilation. Deaths occur from cardiac dysrhythmias; the prog- nosis is worse when water from boiled leaves is drunk. There is no antidote although K+ replacement & acetylcysteine have been tried. Other nephrotoxins Spurge laurel Daphne laureda, mezereon Daphne mezereum, and savin Juniperus sabina contain terpenes that cause intense irritation and blistering in the mouth and gastrointestinal tract, but also renal inflammation with haematuria and proteinuria. Anthraquinone glycosides and oxalic acid in rhubarb Rheum rhabarbarum cause irritation in the mouth and gastrointestinal tract; transient renal impairment and metabolic acidosis may follow ingestion of large amounts of raw leaves or stems. Rumex spp. (docks and sorrels) also contain oxalates; food based on these plants may result in similar toxic effects. Gastrointestinal irritants Popular plants with sap containing calcium oxalate and oxalic acid are elephant’s ear Philodendron spp., cuckoo pint Arum maculatum, and dumb cane Dieffenbachia spp. The needle-shaped calcium ox- alate crystals damage mucous membranes mechanically. Euphorbia and Daphne spp. contain irritating diterpene esters that cause pain, burning sensations in the mouth and pharynx, salivation, reddening, blistering, and uncommonly, in very large expos- ures, nephritis. Dysphagia, vomiting, and diarrhoea may follow. Treatment is rinsing of the mouth and oral fluids for dilution. Dermatotoxic plants Euphorbia and Dieffenbachia spp. damage skin as described earlier for mucous membranes. Hypersensitivity to plant allergens may also cause impressive skin reactions. Examples are poison ivy Rhus radicans, western poison oak Toxicodendron diversilobum, Primula obconica, and citrus plants and fruit. Treatment involves rinsing with water and symptomatic care. The giant hogweed and other Heracleum spp., rue Ruta

graveo- lens, and gas plant Dictamnus albus contain phototoxic psoralens. Contact with sap and subsequent solar radiation can provoke in- tense phototoxic reactions with eczematous skin lesions and large, painful bullae. The best treatment is to rinse the skin directly after exposure and avoid sunlight. When skin damage is already estab- lished, treatment is the same as for chemical burns.

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