CHAPTER 114

Plants

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A 25-year-old man was found unconscious with sustained ventricular tachycardia. He was found with a printout from a web page describing the use of *Aconitum* spp (monkshood) from horticultural sources as a means of committing suicide. His vital signs were: blood pressure, 60 mm Hg palpable; pulse, 120–170 beats/min; respiratory rate, 22 breaths/min; temperature 99°F (37.3°C); and oxygen saturation 100% by pulse oximetry breathing 28% oxygen. His dysrhythmia was responsive to sodium bicarbonate and 100 mg lidocaine IV bolus followed by a 2-mg/min infusion. Urine toxicology for cocaine, amphetamine, salicylate, and acetaminophen was negative. Upon awakening, he would not describe what he had done. Although both urine and serum specimens were obtained, local public health and medical examiner laboratories and 3 commercial natural product laboratories were unable to analyze these specimens for aconitine, one of the active ingredients presumed responsible for his symptoms.

CLASSIFICATION OF PLANT XENOBIOTICS

Aconitine, from monkshood, exemplifies the rich history of plant toxicology. It was believed by the Greeks to be the first poison—"lycotonum"—created by the goddess Hecate from foam of the river Cerebrus.[18] Alkaloid constituents are responsible for its toxic (and therapeutic) effects. "Alkaloid" is one of several classes of organic molecules found in plants as defined by the science of pharmacognosy. The pharmacognosy approach is consistent with the literature of plant efficacy and is applied here to their toxicity (Table 114–1). Unfortunately, the "science" of pharmacognosy is not always straightforward and varies depending on the pharmacognosist. Hence our approach borrows primarily from two groups of authors[107,296] to keep the classification as consistent as possible. The major groups are as follows:

1. *Alkaloids:* Molecules that react as bases and contain nitrogen, usually in a heterocyclic structure. Alkaloids typically have strong pharmacologic activity that defines many major toxidromes.
2. *Glycosides:* Organic compounds that yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The aglycone is the basis of subclassification into saponin or steroidal glycosides (also called cardioactive steroids, Chap. 62), cyanogenic glycosides, anthraquinone glycosides, and others such as atractyloside and salicin.
3. *Terpenes and resins:* Assemblages of 5-carbon units (isoprene unit) with many types of functional groups (eg, alcohols, phenols, ketones, and esters) attached. These are the largest group of secondary metabolites; approximately 20,000 are identified. Most essential oils are mixtures of monoterpenes, and the terpene name depends on the number of assemblages. Monoterpenes have 2 units ($C_{10}H_{16}$), sesquiterpenes have 3 isoprene units (C_{15}), diterpenes have 4 isoprene units (C_{20}), triterpenes have 6 (C_{30}), etc... These molecules have an active role in plant defense mechanisms.
4. *Proteins, peptides, and lectins:* Proteins consist of amino acid units with various side chains, and peptides consist of linkages among amino acids. Lectins are glycoproteins classified according to the number of protein chains linked by disulfide bonds and by binding affinity for specific carbohydrate ligands, particularly galactosamines. The toxalbumins (eg, ricin) are lectins. These components tend to be neurotoxins, hemagglutinins, or cathartics.
5. *Phenols and phenylpropanoids:* Phenols have phenyl rings. Phenylpropanoids consist of a phenyl ring attached to a propane side chain. They are devoid of nitrogen, even though some are derived from phenylalanine and tyrosine. They constitute a major group of secondary metabolites and among plant toxins consist of *coumarins* (lactone side chains), *flavonoids* (built upon a flavan 2,3-dihydro-2-phenylbenzopyran nucleus, eg, naringenin and rutin), *lignans* (2 linked phenylpropanoids, eg, podophyllin), *lignins* (complex polymers of lignans that bind cellulose for woody bark and stem), and *tannins* (polymers that bind to protein and can be further hydrolyzed or condensed).

Plant chemistry is complex. Our simplified presentation of one toxin class per plant, per symptom group (Table 114–1) overlooks the fact that plants contain multiple chemicals and chemical classes that work independently or in concert. Additionally, different plant families may contain similar, if not identical, xenobiotics (a form of convergent evolution). In some cases, xenobiotics remain unidentified and are grouped in the section on Unidentified Toxins.

Dissimilar molecules from diverse pharmacognosy classes that share effects are grouped together for pragmatic purposes in the section on Effects Shared Among Diverse Classes of Xenobiotics. They are further categorized into Plant–Drug Interactions, Sodium Channel Effects, Antimitotic Alkaloids and Resins, and Plant-induced Dermatitis.

TABLE 114–1. Primary Toxicity of Common Important Plant Species

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Abrus precatorius (Euphorbiaceae)[a]	Prayer beans, rosary pea, Indian bean, crab's eye, Buddhist's rosary bead, prayer bead, jequirity pea	Gastrointestinal	Abrin	Protein, lectin, peptide, amino acid
Aconitum napellus and other *Aconitum* spp (Ranunculaceae)[a]	Monkshood and others	Cardiac, neurologic	Aconitine and related compounds	Alkaloid
Acorus calamus (Araliaceae)	Sweet flag, rat root, flag root, calamus	Gastrointestinal	Asarin	Phenol or phenylpropanoid
Aesculus hippocastanum (Hippocastanaceae)	Horse chestnut	Hematologic	Esculoside (6-β-D-glucopyranosyloxy-7-hydroxycoumarin)	Phenol or phenylpropanoid
Agave lecheguilla (Amaryllidaceae)	Agave	Dermatitis: hepatogenous photosensitivity in animals	Steroidal saponins (aglycones: smilagenin, sarsasapogenin)	Saponin glycoside
Aloe barbadensis, A. vera, others (Liliaceae/ Amaryllidaceae)	Aloe	Gastrointestinal	Barbaloin, iso-barbaloin, aloinosides	Anthraquinone glycoside
Anabaena and Aphanizomenon[a]	Blue green algae	Neurologic	Saxitoxin equivalents	Guanidinium compound
Anacardium occidentale, many others (Anacardaceae)	Cashew, many others	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Anthoxanthum odoratum (Poaceae)	Sweet vernal grass	Hematologic	Coumarin	Phenol or phenylpropanoid
Areca catechu (Aracaceae)	Betel	Cholinergic	Arecoline	Alkaloid
Argemone mexicana (Papaveraceae)	Mexican pricklepoppy	Gastrointestinal	Sanguinarine	Alkaloid
Argyreia nervosa	Hawaiian baby woodrose seeds	Neurologic	Lysergacidamide, lysergacidethylamide	Alkaloid
Argyreia spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid
Aristolochia reticulata, A. spp (Aristolochiaceae)[a]	Texan or Red River snake root, numerous	Renal, carcinogenic	Aristolochic acid	Alkaloid relative as derivative of isothebaine
Artemisia absinthium (Compositaceae/ Asteraceae)[a]	Absinthe	Neurologic	Thujone	Terpenoid
Asclepias spp (Asclepidaceae)[a]	Milk weed	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
Astragalus spp (Fabiaceae)[a]	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Atractylis gummifera (Compositaceae)[a]	Thistle	Hepatic	Atractyloside, gummiferine	Glycoside
Atropa belladonna (Solanaceae)[a]	Belladonna	Anticholinergic	Belladonna alkaloids	Alkaloid
Azalea spp (Ericaceae)[a,b]	Azalea	Cardiac, neurologic	Grayanotoxin	Terpenoid
Berberis spp (Ranunculaceae)	Barberry	Oxytocic, cardiovascular	Berberine	Alkaloid
Blighia sapida (Sapindaceae)[a]	Ackee fruit	Metabolic, gastrointestinal, neurotoxic	Hypoglycin	Protein, lectin, peptide, amino acid
Borago officinalis (Boragniaceae)[a]	Borage	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Brassaia spp[b]	Umbrella tree	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Brassica nigra (Brassicaceae)	Black mustard	Dermatitis: irritant	Sinigrin	Glucosinolate (isothiocyanate glycoside)
Brassica olearacea var. *capitata*	Cabbage	Metabolic (precursor to goitrin, antithyroid compound)	Progoitrin	Isothiocyanate glycoside
Cactus spp[b]	Cactus	Dermatitis: mechanical	Nontoxic	None
Caladium spp (Araceae)[b]	Caladium	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid

(*continued*)

TABLE 114–1. Primary Toxicity of Common Important Plant Species (continued)

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Calotropis spp (Asclepidaceae)[a]	Crown flower	Cardiac	Asclepin and related cardenolides	Cardioactive steroid
Camellia sinensis (Theaceae)	Tea, green tea	Cardiac, neurologic	Theophylline, caffeine	Alkaloid
Cannibis sativa	Cannibis, marijuana, Indian hemp, hashish, pot	Neurologic	Tetrahydrocannabinol	Terpenoid, resin, oleoresin
Capsicum frutescens, C. annuum, C. spp (Solanaceae)[b]	Capsicum, cayenne pepper	Dermatitis: irritant	Capsaicin	Phenol or phenylpropanoid
Cascara sagrada = *Rhamnus purshiana* = *R. cathartica* (Rhamnaceae)	Cascara, sacred bark, Chittern bark, common buckthorn	Gastrointestinal	Cascarosides, *O*-glycosides, emodin	Anthraquinone glycoside
Cassia senna, C. angustifolia (Fabaceae)	Senna	Gastrointestinal	Sennosides	Anthraquinone glycoside
Catha edulis (Celastaceae)	Khat	Cardiac, neurologic	Cathinone	Alkaloid
Catharanthus roseus (formerly *Vinca rosea*) (Apocynaceae)	Catharanthus, vinca, madagascar periwinkle	Gastrointestinal	Vincristine	Alkaloid
Caulophyllum thalictroides (Berberidaceae)	Blue cohosh	Nicotinic	*N*-Methylcytisine and related compounds	Alkaloid
Cephaelis ipecacuanha, C. acuminata (Rubiaceae)[a]	Ipecac	Gastrointestinal, cardiac	Emetine/cephaline	Alkaloid
Chlorophytum comosum[b]	Spider plant	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Chondrodendron spp, *Curarea* spp, *Strychnos* spp[a]	Tubocurare, curare	Neurologic	Tubocurarine	Alkaloid
Chrysanthemum spp, *Taraxacum officinale*, many other Compositaceae (Asteraceae)[b]	Chrysanthemum, dandelion, other Compositaceae	Dermatitis: contact, allergic	Sesquiterpene lactones	Terpenoid
Cicuta maculata (Apiaceae/Umbelliferae)[a]	Water hemlock	Neurologic	Cicutoxin	Alcohol
Cinchona spp (Rubiaceae)[a]	Cinchona	Cardiac, cinchonism	Quinidine	Alkaloid
Citrus aurantium (Rutaceae)[a]	Bitter orange	Cardiac, neurologic	Synephrine	Alkaloid
Citrus paradisi (Rutaceae)	Grapefruit	Hepatic drug interactions	Bergamottin, naringenin, or naringen	Phenol or phenylpropanoid
Claviceps purpurea, C. paspali (Claviceptacea = fungus)[a]	Ergot	Cardiac, neurologic, oxytocic	Ergotamine and related compounds	Alkaloid
Coffea arabica (Rubiaceae)	Coffee	Cardiac, neurologic	Caffeine	Alkaloid
Cola nitida, Cola spp (Sterculiaceae)	Kola nut	Cardiac, neurologic	Caffeine	Alkaloid
Colchicum autumnale (Liliaceae)[a]	Autumn crocus	Multisystem	Colchicine	Alkaloid
Conium maculatum (Apiaceae/Umbelliferae)[a]	Poison hemlock	Nicotinic, neurologic, respiratory, renal	Coniine	Alkaloid
Convallaria majalis[a]	Lily of the valley	Cardiac	Convallatoxin, strophanthin (~40 others)	Cardioactive steroid
Coptis spp (Ranunculaceae)	Goldenthread	Oxytocic, cardiovascular	Berberine	Alkaloid
Crassula spp[b]	Jade plant	Gastrointestinal	Nontoxic	None
Crotalaria spp (Fabaceae)[a]	Rattlebox	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Croton tiglium and C. spp (Euphorbiaceae)	Croton	Carcinogen, gastrointestinal	Croton oil	Lipid and fixed oil, also contains tropane alkaloid and diterpene
Cycas circinalis[a]	Queen sago, indu, cycad	Neurologic	Cyacasin	Glycosides
Cytisus scoparius (Fabaceae)[a]	Broom, Scotch broom	Nicotinic, oxytocic	Sparteine	Alkaloid
Datura stramonium (Solanaceae)[a]	Jimson weed, stramonium, locoweed	Anticholinergic	Belladonna alkaloids	Alkaloid
Delphinium spp (Ranunculaceae)[a]	Larkspur, others	Cardiac, neurologic	Methyllycaconitine and related compounds	Alkaloid

(*continued*)

TABLE 114–1. Primary Toxicity of Common Important Plant Species (continued)

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Dieffenbachia spp (Araceae)[b]	Dieffenbachia	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Digitalis lanata[a]	Grecian foxglove	Cardiac	Digoxin, Lanatosides A-E (contains ~70 cardiac glycosides)	Cardioactive steroid
Digitalis purpurea[a]	Purple foxglove, Grecian foxglove	Cardiac	Digitoxin	Cardioactive steroid
Dipteryx odorata, D. oppositifolia (Fabaceae/ Legumaceae)	Tonka beans	Hematologic	Coumarin	Phenol or phenylpropanoid
Ephedra spp, especially *sinensis* (Ephedraceae/ Gnetaceae = Gymnosperm)[a]	Ephedra, Ma-huang	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
Epipremnum aureum (Araceae)[b]	Pothos	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Erythroxylum coca	Coca	Neurologic, cardiac	Cocaine	Alkaloid
Eucalyptus globus or spp[b]	Eucalyptus	Dermatitis: contact, allergic	eucalyptol	Terpenoid
Euphorbia pulcherrima, E. spp (Eurphorbiaceae)[b]	Poinsettia	Dermatitis: contact, allergic	Phorbol esters	Terpenoid
Ficus benjamina[b]	Weeping fig tree	Nontoxic	Nontoxic	None
Galium triflorum (Rubiaceae)	Sweet-scented bedstraw	Hematologic	Coumarin	Phenol or phenylpropanoid
Ginkgo biloba (Ginkgoaceae)	Ginkgo	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Ginkgo biloba (Ginkgoaceae)[a]	Ginkgo	Hematologic	Ginkgolides A–C, M	Terpenoid
Ginkgo biloba (Ginkgoaceae)[a]	Ginkgo	Neurologic	4-Methoxypyridoxine in seeds only	Alkaloid, pyridine
Gloriosa superba (Liliaceae)[a]	Meadow saffron	Multisystem	Colchicine	Alkaloid
Glycyrrhiza glabra[a]	Licorice	Metabolic, renal	Glycyrrhizin	Saponin glycoside
Gossypium spp	Cotton, cottonseed oil	Metabolic	Gossypol	Terpenoid
Hedeoma pulegioides (Lamiaceae)[a]	Pennyroyal	Hepatic, neurologic, oxytoxic	Pulegone	Terpenoid
Hedera helix (Araliaceae)[b]	Common ivy	Not absorbed	Hederacoside C, α-hederin, hederagenin	Cardioactive steroid
Hedysarium alpinum (Fabiaceae)	Wild potato	Metabolic, neurologic	Swainsonine	Alkaloid
Heliotropium spp (Compositae/ Asteraceae)[a]	Ragwort	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Helleborus niger[a]	Black hellebore, Christmas rose	Cardiac	Hellebrin	Cardioactive steroid
Hydrastis canadensis (Ranunculaceae)[a]	Goldenseal	Neurologic, oxytocic, cardiovascular, respiratory	Hydrastine, berberine	Alkaloid
Hyoscyamus niger (Solanaceae)[a]	Henbane, hyoscyamus	Anticholinergic	Belladonna alkaloids	Alkaloid
Hypericum perforatum (Clusiaceae)	St. John's wort	Dermatitis: photosensitivity, neurologic, hepatic drug interactions	Hyperforin or other	Terpenoid
Ilex paraguariensis (Aquifoliaceae)	Maté, Yerba Maté, Paraguay tea	Cardiac, neurologic	Caffeine	Alkaloid
Ilex spp berries (Aquifoliaceae)[b]	Holly	Gastrointestinal	Mixture: Alkaloids, polyphenols, saponins, steroids, triterpenoids	Unidentified
Illicium anasatum (Illiciaceae)[a]	Japanese Star anise	Neurologic	Anasatin	Terpenoid
Ipomoea tricolor and other *Ipomoea* spp (Convolvulaceae)	Morning glory	Neurologic	Lysergic acid derivatives	Alkaloid
Jatropha curcas (Euphorbiaceae)	Black vomit nut, physic nut, purging nut	Gastrointestinal	Curcin	Protein, lectin, peptide, amino acid

(*continued*)

TABLE 114–1. Primary Toxicity of Common Important Plant Species (continued)

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Karwinskia humboldtiana[a]	Buckthorn, wild cherry, tullidora, coyatillo, capulincillo, others	Neurologic, respiratory	Toxin T-454, others	Phenol or phenylpropanoid
Laburnum anagyroides (syn. *Cytisus laburnum;* Fabaceae)[a]	Golden chain, laburnum	Nicotinic	Cytisine	Alkaloid
Lantana camara (Verbenaceae)	Lantana	Dermatitis: hepatogenous photosensitivity	Lantadene A and B, phylloerythrin	Terpenoid
Lathyrus sativus[a]	Grass pea	Neurologic, skeletal	β-*N*-oxalylamino-L-alanine (BOAA); β-aminopropionitrile (BAPN)	Protein, lectin, peptide, amino acid
Lobelia inflata (Campanulaceae)	Indian tobacco	Nicotinic	Lobeline	Alkaloid
Lophophora williamsii	Peyote or mescal buttons	Neurologic	Mescaline	Alkaloid
Lupinus latifolius and other *Lupinus* spp (Fabaceae)	Lupin	Nicotinic	Anagyrine	Alkaloid
Lycopersicon spp (Solanaceae)[a]	Tomato (green)	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine	Alkaloid
Mahonia spp (Ranunculaceae)	Oregon grape	Oxytocic, cardiovascular	Berberine	Alkaloid
Mandragora officinarum (Solanaceae)[a]	European or true mandrake	Anticholinergic	Belladonna alkaloids	Alkaloid
Manihot esculentus (Euphorbiaceae)[a]	Cassava, manihot, tapioca	Metabolic, neurotoxic: motor spastic paresis and vision disturbance with chronic use	Linamarin	Cyanogenic glycoside
Melilotus spp (Fabaceae/Legumaceae)	Sweet clover	Hematologic	Coumarin	Phenol or phenylpropanoid
Mentha pulegium (Lamiaceae)[a]	Pennyroyal	Hepatic, neurologic, oxytoxic	Pulegone	Terpenoid
Microcystis and Anabaena spp	Blue-green algae (planktonic cyanobacteria)	Hepatotoxic, dermatitis: photosensitivity	Microcystin	Protein, lectin, peptide, amino acid
Myristica fragrans	Nutmeg, pericarp = mace	Neurologic (hallucinations with 15 g)	Myristicin, elemicin	Terpenoid
Narcissus spp and other (Amaryllidaceae, Liliaceae)	Narcissus	Dermatitis: mechanical and cytotoxic	Lycorine, homolycorin	Alkaloid
Nerium oleander[a]	Oleander	Cardiac	Oleandrin	Cardioactive steroid
Nicotiana tabacum and other *Nicotiana* spp (Solanaceae)[a]	Tobacco	Nicotinic	Nicotine	Alkaloid
Oxytropis spp (Fabiaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Papaver somniferum	Poppy with opium derivatives	Neurologic	Morphine/other opium derivatives	Alkaloid
Paullinia cupana (Sapindaceae)	Guarana	Cardiac, neurologic	Caffeine	Alkaloid
Pausinystalia yohimbe (Rubiaceae)[a]	Yohimbe	Cardiac, cholinergic	Yohimbine	Alkaloid
Philodendron spp (Araceae)[b]	Philodendron	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Phoradendron spp (Loranthaceae or Viscaceae)	American mistletoe	Gastrointestinal	Phoratoxin, ligatoxin	Protein, lectin, peptide, amino acid
Physostigma venenosum (Fabaceae)[a]	Calabar bean, ordeal bean	Cholinergic	Physostigmine	Alkaloid
Phytolacca americana (Phytolaccaceae)[a]	Pokeweed, Indian poke, poke, inkberry, scoke, pigeonberry, garget, American cancer	Gastrointestinal	Phytolaccotoxin	Protein, lectin, peptide, amino acid
Pilocarpus jaborandi, P. pinnatifolius (Rutaceae)[a]	Pilocarpus, jaborandi	Cholinergic effects (muscarinic)	Pilocarpine	Alkaloid

(*continued*)

TABLE 114–1. Primary Toxicity of Common Important Plant Species (continued)

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenbiotic(s)	Class of Xenobiotic
Piper methysticum[a]	Kava kava	Hepatic, neurologic	Kawain, methysticine yangonin, other kava lactones	Terpenoid, resin, and oleoresin
Plantago spp seed husks (Plantaginaceae)	Plantago	Gastrointestinal	Psyllium	Carbohydrate
Podophyllum emodi (Berberidaceae)[a]	Wild mandrake	Multisystem	Podophyllin (lignan)	Phenol or phenylpropanoid
Podophyllum peltatum (Berberidaceae)[a]	Mayapple	Multisystem	Podophyllin (lignan)	Phenol or phenylpropanoid
Populus spp (Salicaceae)	Poplar species	Cinchonism	Salicin	Glycoside
Primula obconica (Primulaceae)	Primrose	Dermatitis: contact, allergic	Primin	Phenol or phenylpropanoid
Prunus armeniaca, Prunus spp, *Malus* spp (Rosaceae)[a]	Apricot seed pits, wild cherry, peach plum, pear, almond, apple and other seed kernels	Metabolic, acidosis, respiratory failure, coma, death	Amygdalin, emulsin	Cyanogenic glycoside
Pteridum spp (Polypodiaceae)	Brachen fern	Carcinogen, thiaminase	Ptaquiloside	Terpenoid
Pulsatilla spp (Ranunculaceae)	Pulsatilla	Dermatitis: contact	Ranunculin, protoanemonin	Glycoside
Quercus spp	Oak	Metabolic: oak toxicosis in livestock	Tannic acid	Phenol or phenylpropanoid
Ranunculus spp (Ranunculaceae)	Pilewort and other buttercups	Dermatitis: contact	Ranunculin, protoanemonin	Glycoside
Rauwolfia serpentina (Apocynaceae)	Indian snakeroot	Cardiac, neurologic	Reserpine	Alkaloid
Remijia pedunculata (Rubiaceae)[a]	Cuprea bark	Cardiac, cinchonism	Quinidine	Alkaloid
Rhamnus frangula (Rhamnaceae)	Frangula bark, alder buckthorn	Gastrointestinal	Frangulins	Anthraquinone glycoside
Rheum officinale, Rheum spp *(Polygonaceae)*	Rhubarb	Gastrointestinal	Rhein anthrones	Anthraquinone glycoside
Rheum spp (Polygonaceae)	Rhubarb species	Urologic	Oxalates	Carboxylic acid
Rhododendron spp (Ericaceae)[a]	Rhododendron	Cardiac, neurologic	Grayanotoxins	Terpenoid including resin and oleoresin
Ricinus communus (Euphorbiaceae)[a]	Castor or rosary seeds, purging nuts, physic nut, tick seeds	Gastrointestinal	Ricin, curcin	Protein, lectin, peptide, amino acid
Robinia pseudacacia (Fabiaceae)[a]	Black locust	Gastrointestinal	Robinia lectin	Protein, lectin, peptide, amino acid
Rumex spp (Polygonaceae)	Dock species	Urologic	Oxalates	Carboxylic acid
Saintpaulia spp[b]	African violet	Nontoxic	Nontoxic	None
Salix spp (Salicaceae)	Willow species	Cinchonism	Salicin	Glycosides: other
Sambucus spp (Caprifoliaceae)	Elderberry	Metabolic	Anthracyanins	Cyanogenic glycoside
Sanguinaria canadensis (Papaveraceae)	Sanguinaria, bloodroot	Gastrointestinal	Sanguinarine	Alkaloid
Schefflera spp (Araceae)[b]	Umbrella tree	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Schlumbergera bridgesii[b]	Christmas cactus	Dermatitis: mechanical	Nontoxic	None
Senecio spp (Compositae/ Asteraceae)[a]	Groundsel	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Sida carpinifolia (Malvaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Sida cordifolia (Malvaceae)[a]	Bala	Cardiac, neurologic	Ephedrine and related compounds	Alkaloid
Solanum americanum (Solanaceae)[a]	American nightshade	Gastrointestinal, neurologic, some anticholinergic possible	Solasodine, soladulcidine, solanine, chaconine	Alkaloid
Solanum dulcamara (Solanaceae)[a,b]	Deadly nightshade, bitter nightshade	Gastrointestinal, neurologic, some anticholinergic possible	Solanine, chaconine, belladonna alkaloids, eg, atropine	Alkaloid

(*continued*)

TABLE 114–1. Primary Toxicity of Common Important Plant Species (continued)

Plant Species (Family)	Typical Common Names	Primary Toxicity	Xenobiotic(s)	Class of Xenobiotic
Solanum nigrum (Solanaceae)[a]	Black nightshade, common nightshade	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine, belladonna alkaloids (atropine)	Alkaloid
Solanum tuberosum (Solanaceae)[a]	Potato (green)	Gastrointestinal, neurologic, some anticholinergic	Solanine, chaconine	Alkaloid
Spathiphyllum spp (Araceae)[b]	Peace lily	Dermatitis: mechanical and cytotoxic	Oxalate raphides	Carboxylic acid
Spinacia oleracea (Chenopodiaceae)	Spinach, others	Urologic	Oxalates	Carboxylic acid
Strychnos nux-vomica, S. ignatia (Loganiaceae)[a]	Nux vomica, Ignatia, St. Ignatius bean, vomit button	Neurologic	Strychnine and brucine	Alkaloid
Swainsonia spp (Fabiaceae)	Locoweed	Metabolic, neurologic	Swainsonine	Alkaloid
Symphytum spp (Boragniaceae)[a]	Comfrey	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Tanacetum vulgare (= *Chrysanthemum vulgare*; Compositaceae/ Asteraceae)[a]	Tansy	Neurologic	Thujone	Terpenoid
Taxus baccata, Taxus brevifolia, other *Taxus* spp (Taxaceae)[a]	English yew, Pacific yew, yew	Cardiac	Taxine	Alkaloid
Theobroma cacao (Sterculiaceae)	Cocoa	Cardiac, neurologic	Theobromine	Alkaloid
Thevetia peruviana[a]	Yellow oleander	Cardiac	Thevetin	Cardioactive steroid
Toxicodendron radicans, T. toxicarium, T. diversilobum, T. vernix, T. spp, many others (Anacardaceae)[b]	Poison ivy, oak, sumac, many others	Dermatitis: contact, allergic	Urushiol oleoresins	Terpenoid
Tribulus terrestris (Fabaceae)	Tribulus terrestris	Dermatitis: hepatogenous photosensitivity in animals	Steroidal saponins (aglycones: diosgenin, yamogenin)	Saponin glycoside
Trifolium pratense and other (Fabaceae/Legumaceae)	Red clover	Hematologic	Coumarin	Phenol or phenylpropanoid
Tussilago farfara (Compositae/ Asteraceae)[a]	Coltsfoot	Hepatic (venoocclusive disease)	Pyrrolizidine alkaloids	Alkaloid
Urginea maritima, U. indica[a]	Red, White, or Mediterranean squill, Indian squill	Cardiac	Scillaren A, B	Cardioactive steroid
Veratrum viride, V. album, V. californicum (Liliaceae)[a]	False hellebore, green hellebore, European hellbore, California hellbore	Cardiac	Veratridine	Alkaloid
Viscum album (Loranthaceae or Viscaceae)	European mistletoe	Gastrointestinal	Viscumin	Protein, lectin, peptide, amino acid, lignan, polypeptide
Wisteria floribunda (Fabiaceae)	Wisteria	Gastrointestinal	Cystatin	Protein, lectin, peptide, amino acid

[a]Reports of life-threatening effects from plant use.
[b]Plants reported commonly among calls to poison centers.

Our focus is on exposures to flowering plants (angiosperms) related to foraging, dietary, or occupational contact, except for some gymnosperms or algae and, rarely, medicinal contact (medicinal use as herbals is discussed in Chap. 43).[222] Because our understanding of plant toxicity is poor relative to that of pharmaceutical agents, we include animal research to provide a more comprehensive foundation for comparison to human experiences that may otherwise go unrecognized without such precedent or may likewise prove incorrect in time. The science of plant toxicology formally began in the United States as a response to significant poisonings of livestock.[360,361] The overall quality of literature for human exposures is poor and primarily available as case reports.[276]

Many of these cases lack clear links between toxin exposure and illness, and qualitative serum concentrations often are unavailable.[157] Uncertainty is compounded by the fact that plants themselves are inherently variable, and potency and type of toxin depend on the season, geography, local environment, plant part, and methods of processing.[6,126]

IDENTIFICATION OF PLANTS

Positive identification of the plant species should be attempted whenever possible, especially when the patient becomes symptomatic. Communication with an expert botanist or poison center is highly recommended and can be facilitated by transmission of digital images or a fax.[243] Provisionally, simple comparison of the species in question with pictures or descriptions from a field guide or flora may help exclude the plant's identity from among the most life-threatening in Table 114–1. A plant identification also can be compared with those searched in the PLANTOX database *(http://vm.cfsan.fda.gov/~djw/readme.html)* managed by the Food and Drug Administration.[75,359,361] Laboratory analysis is not timely enough to be useful except as a tool in an investigatory or forensic analysis.[133]

In cases where expert identification cannot be immediately achieved, crude recognition of taxonomic families of poisonous plants is the simplest first step to identify or exclude poisonous plants but is most easily achieved when the plant is in flower or fruit. For instance, if the flower is described or looks like a flower from a tomato or potato, it probably is in the Solanaceae family. Plants of this family typically produce gastroenteritis or anticholinergic findings following ingestion. It then would be prudent to begin expectant management (eg, prepare for use of physostigmine). This approach will be less useful for those xenobiotics (eg, pyrrolizidine alkaloids) that occur in numerous different families.

APPROACH TO THE EXPOSED PATIENT AND UNDERSTANDING RISK

Faced with the care of an individual who comes seeking medical care, health care givers must determine whether or not the patient needs treatment interventions. Potential symptoms listed in Table 114–1 are organized by plant name but with their *major* organ system effects for quick reference to types of symptoms and whether they might be life threatening.[35] For instance, life-threatening symptoms such as dysrhythmias or seizures can be searched by "cardi-" or "neuro-" in the first column and compared with the plant(s) in question. The plants and xenobiotics that present life-threatening symptoms are so noted. Exposures associated with one of these plants or xenobiotics or major organ system symptoms dictates the need for possible prompt gastric emptying, decontamination, individualized therapy, and hospitalization. Note that nonspecific symptoms such as nausea and vomiting are listed only when they are the sole cause of morbidity or mortality (toxalbumins such as ricin), but nausea and vomiting are nearly ubiquitous among acute poisonings of clinical consequence.

Identified plant species most frequently reported during a decade of Poison Center experience are indicated in Table 114–1. In most cases, these species provide reassurance because most offer benign outcomes, and only 2 among these can be life threatening depending on the circumstances of the exposure. Given the relatively poor understanding of toxins and in the absence of complete information about an exposure, expectant management and supportive care are the rule. Even if a plant is not marked as life threatening or commonly reported, the patient should undergo a period of observation and followup given the relatively immature science of plant toxicology relative to that of pharmaceuticals.

The difficult task in human plant toxicology is the lack of adequate data to determine risk (see examples in Chap. 124). Typically, evaluations of risk are based on poison center data and usually cite the numerous calls without clinical consequence as a part of the risk equation (Chap. 130).[208–213,260,363] However, poison center data are dominated by pediatric cases and other cases with unsubstantiated clinical manifestations (Chap. 130).[157] These cases often represent small or nonexistent exposures, and their inclusion in the database may mask real risks by diluting "true" hazardous exposures with trivial or nonexistent exposures. Furthermore, misidentification of the plant may occur because of either similar appearance or similar nomenclature.

In summary, basic decontamination and supportive care should be instituted as fits the situation, with appropriate consultation to a poison center. The most consequential and dangerous plant xenobiotics for humans are discussed here and those that can produce life-threatening signs acutely are denoted in Table 114–1.

TOXIC CONSTITUENTS IN PLANTS, TAXONOMIC ASSOCIATIONS, AND SELECTED SYMPTOMS

Alkaloids: Toxic Manifestations

The term *alkaloid* refers to nitrogen-containing basic xenobiotics of natural origin and limited distribution. They figure prominently in the history of human–plant interaction, ranging from epidemics of poisoning caused by ergot-infested rye bread in the Middle Ages, to addictions to cocaine, heroin, and nicotine in contemporary time. Numerous examples of toxic constituents of these families are given in the following discussion, which begins with a description of every major toxidrome that involves alkaloids. See also Sodium Channel Effects under Effects Shared Among Diverse Classes of Xenobiotics later in this chapter for description of additional life-threatening alkaloids.

Anticholinergic Effects: Belladonna Alkaloids. The belladonna alkaloids are all from the family Solanaceae and can be identified as members of this family by their characteristic flowers (most familiar from nightshade, potato, or tomato flowers). The belladonna alkaloids have potent antimuscarinic effects. Ingestion produces classic signs of this toxidrome: tachycardia, hypertension, hyperthermia, dry skin and mucous membranes, skin flushing, diminished bowel sounds, urinary retention, agitation, disorientation, and hallucinations (Chap. 3). Since the 1970s, the quest for recreational "highs" has surpassed unintentional ingestions as the main source of toxicity. Hallucinatory effects are sought in seeds and teas, especially in late summer, when jimsonweed *(Datura stramonium)* seeds (see ILDATURASTRAMONIUM1 and ILDATURASTRAMONIUM2 in the Image Library at goldfrankstoxicology.com) become available.[46,48,71,72,149,152,320] One hundred of these seeds contain up to 6 mg atropine and related alkaloids, and an ingestion of this amount can be fatal.[27]

Although various species and plants within species bear differing concentrations of diverse xenobiotics, the clinical manifestations usually are similar.[290,347] Onset of symptoms typically occurs 1–4 hours postingestion, or more rapidly if the plants are smoked or consumed as a tea infusion. The duration of effect is partly dose dependent and may last from a few hours to weeks.[152] The course of anticholinergic poisoning is altered by use of physostigmine, which when consequential may require repetitive dosing, necessitating observation and hospitalization.[307] Moreover, physostigmine may be lifesaving in patients with seizures or agitated delirium (Antidotes in Depth: Physostigmine Salicylate). Anticholinergic toxicity may be produced without detectable atropine, scopolamine, or hyoscyamine concentrations and is better left as a clinical and not a laboratory diagnosis.[320]

Solanine is contained in other members of the Solanaceae family, but it is not a belladonna alkaloid. It inhibits cholinesterase in vitro, although cholinergic symptoms are not noted clinically. Nonetheless, reports of solanine-induced central nervous system (CNS) toxicity includes hallucinations, delirium, and coma.[244,278] However, most symptomatic patients typically develop nausea, vomiting, diarrhea, and abdominal pain that begins 2–24 hours after ingestion, which, like CNS toxicity, may persist for several days.[80,278] Although solanine is present in most of the 1700 species in the genus *Solanum,* solanine toxicity in humans is uncommonly encountered. Green potatoes and green potato tops are most commonly associated with symptoms, which is not surprising because the alkaloids are most concentrated in those items. Most reports of death come from the older literature,[4,162] and consumption of 2–5 g of green components per kilogram body weight per day is not predicted to cause acute toxicity.[284]

Nicotine and Nicotine-like Alkaloids: Nicotine, Lobeline, Sparteine, *N*-Methylcytisine, Cytisine, and Coniine. Nicotine toxicity (other than from inhaled sources) occurs via ingestion of leaves of *Nicotiana tabacum,* cigarette remains, organic products and insecticides, and transdermally among farm workers harvesting tobacco (green tobacco sickness).[137,139,289] A dose as little as 1 mg/kg can be lethal to an adult.[238,282] Overstimulation of the nicotinic receptors by high doses of nicotine produces a toxidrome that progresses from gastrointestinal (GI) symptoms to diaphoresis, mydriasis, fasciculations, tachycardia, hypertension, hyperthermia, and seizures, respiratory depression, and death (Chap. 82). Wearing of protective clothing by tobacco farm workers best prevents green tobacco sickness.

These manifestations are also produced by alkaloids other than nicotine.[355] There are no recent reports of nicotinic toxicity from lobeline (found in all parts of *Lobelia inflata),* but its overenthusiastic use in the 18th century resulted in morbidity and mortality.[44]

Sparteine from broom *(Cytisus scoparius)*[349] and *N*-methylcytisine from blue cohosh *(Caulophyllum thalictroides)*[291] provide additional examples of nicotinelike alkaloids that may be teratogenic.[194] Laburnum or golden chain *(Cytisus laburnum)* contains cytisine, which reportedly is responsible for mass poisonings and fatalities in children and adults who eat the plants or parts thereof (even as little as 0.5 mg/kg, or a few peas).[138,259,293] Unfortunately, such reports have resulted in thousands of unnecessary hospital admissions for patients without morbidity and mortality after ingestion of this plant, demonstrating the difficulty in separating hazard from risk and in obtaining accurate dose–response information in the setting of plant exposures and human variability.[30,121]

The most famous description of the end stages of nicotinic toxicity dates from approximately 2400 years ago by an observer of Socrates' fatal ingestion of a decoction of poison hemlock *(Conium maculatum)*:[342]

> …the person who had administered the poison went up to him and examined for some little time his feet and legs, and then squeezing his foot strongly asked whether he felt him. Socrates replied that he did not and said to us when the effect of the poison reached his heart, Socrates would depart.

Birds do not experience coniine toxicity but provide a vector for poisoning. According to the book of Exodus, quail that fed on seeds (presumably from poison hemlock) became toxic and passed the toxicity on to the Israelites who ate the fowl. In the 20th century, people have succumbed to hemlock poisoning following their avian repasts. This is especially well documented in Italy, where the toxic alkaloid coniine subsequently was detected in the bird meat, as well as in the blood, urine, and tissue of some victims.[294,314]

The age of the plant seems to be directly correlated with increasing concentrations of coniine, whereas the toxin γ-coniceine occurs in greater amounts in new growth; hence, the plant remains toxic over the length of the growing season.[91,135] Fatal poisonings are reported on multiple continents,[91,34] and death may result from respiratory arrest.[23] Of 17 poisoned Italian patients, all had elevated liver aminotransferases and myoglobin concentrations, and 5 had acute tubular necrosis. Death developed 1–16 days following ingestion.[295]

Cholinergic Effects in Alkaloids: Arecoline, Physostigmine, and Pilocarpine. Betel chewing has been a habitual practice in the East since ancient times. The "quid" consists of betel nut *(Areca catechu)* and other ingredients. The effects of acute exposure to arecoline, the major alkaloid, include sweating, salivation, and hyperthermia. Effects of acute use are rarely reported, but are associated with death, at least in susceptible patients.[87] Prolonged use is linked to dental decay and oral cancer.[64,85,90,106,316] Physostigmine is an alkaloid derived from the Calabar bean *(Physostigma venenosum),* where it is present in concentrations of 0.15%. The miotic effects of physostigmine have been used to reverse mydriatic agents. Its efficacy as an anticholinesterase agent makes it a valuable antidote in anticholinergic poisoning (Antidotes in Depth: Physostigmine Salicylate). Pilocarpine is derived from *Pilocarpus jaborandi* from South America and possesses stimulatory effects on muscarinic receptors. It is of value in treatment of glaucoma.[106] Reversal of toxicity can be achieved by atropine.

Psychotropic Alkaloids: Lysergic Acid and Mescaline. Hallucinations from the direct serotonin effects of lysergic acid diethylamide (LSD) and its derivatives and from the amphetaminelike serotonin effects of the mescaline alkaloids are reported following ingestion of morning glory seeds (*Ipomoea* spp) and peyote cactus *(Lophophora williamsii),* respectively (Chap. 80). Ingestion of at least 150 morning glory seeds also produces nausea and vomiting.[68,179,369] Despite their chemical relatedness to LSD, molecules such as lysergacidamide and lysergacidethylamide, found in Hawaiian baby woodrose seeds *(Argyreia nervosa)* and sold for their hallucinogenic effects, produce a syndrome more similar to that of anticholinergic poisoning.[28]

Alkaloidal Central Nervous System Stimulants and Depressants: Ephedrine, Synephrine, Cathinone, and Narcotics. Use of ephedrine-containing *Ephedra* herbal products was banned by

the FDA in 2004 secondary to cardiovascular toxicity and deaths.[357] However, varieties of *Sida cordifolia* also contain ephedrine. Synephrine, another compound structurally related to ephedrine, occurs in *Citrus aurantium,* which is ingested as a plant or as a medicinal. Deaths are reported following ingestion of *C. aurantium* rinds by children.[240] Drug interactions can ensue from their use.[175] Another plant ingested for its CNS stimulant activity is khat *(Catha edulis)*. The plant contains cathinone (α-aminopropiophenone) and cathine [(+)-norpseudoephedrine]. In addition, narcotics derived from the poppy plant *(Papaver* spp) are prototypic CNS depressants and analgesics (Chap. 38).

Pyrrolizidine Alkaloids. Pyrrolizidine alkaloids are widely distributed both botanically and geographically. Approximately half of the 350 different pyrrolizidine alkaloids characterized to date are considered toxic. Pyrrolizidine alkaloids are found in 6000 plants and in 13 plant families but are most heavily represented within the Boraginaceae, Compositae, and Fabaceae families. Within these families, the genera *Heliotropium, Senecio,* and *Crotalaria,* respectively, are particularly notable for their content of toxic pyrrolizidine alkaloids.[332] These hepatotoxic alkaloids all contain an unsaturated 1-hydroxymethyl pyrrolizidine system.[370] The hepatic cytochrome P450 system converts these compounds to highly reactive pyrroles in vivo. Chronic exposures cause hepatic venoocclusive disease by stimulating proliferation of the intima of hepatic vasculature. Most poisonings occur as a result of contamination of food grain with seeds of pyrrolizidine alkaloid-containing plants or by use of pyrrolizidine alkaloid-rich plants for medicinal purposes. Acute poisoning probably is caused by an oxidant effect resulting in hepatic necrosis.[75,150] An estimated 20% of patients with acute pyrrolizidine alkaloid poisoning die, 50% recover completely, and the rest develop subacute or chronic manifestations of hepatic venoocclusive disease.[14] Pyrrolizidine alkaloids are teratogenic and are transmitted through breast milk.[301] Other types of plant-associated hepatic disorders are discussed in Effects Shared Among Diverse Classes of Xenobiotics.

Isoquinoline Alkaloids: Sanguinarine, Berberine, and Hydrastine. Sanguinarine was detected in 26 family members who consumed a mustard oil contaminated with seeds of *Argemone mexicana*.[322] All patients suffered GI distress followed by peripheral edema, skin darkening, erythema, skin lesions, perianal itching, anemia, and hepatomegaly. Ascites developed in 12%, and myocarditis and congestive heart failure occurred in approximately a third of affected individuals.[371] Medicinally, sanguinarine is used for dental hygiene.[164] In North America, sanguinarine is found in blood root *(Sanguinaria canadensis),* which, like *Argemone,* is in the Ranunculaceae family.

Berberine is structurally similar to sanguinarine and reportedly also has cardiac depressant effects. A number of medicinal plants contain berberine, including goldenseal *(Hydrastis canadensis),* Oregon grape *(Mahonia* spp), and barberry *(Berberis* spp). It causes myocardial and respiratory depression and contraction of smooth muscle in vasculature and the uterus.[240] Strychninelike movement disorders are described following ingestion of hydrastine, which composes 4% of goldenseal.

Miscellaneous Other Alkaloids: Emetine/Cephaline, Strychnine/Curare, and Swainsonine. Emetine and cephaline are derived from *Cephaelis ipecacuanha,* a tropical plant native to the forests of Bolivia and Brazil. They are the principal active constituents in syrup of ipecac, which produces emesis. Chronic use of syrup of ipecac, typically by patients with eating disorders or Munchausen syndrome by proxy,[13,111] can lead to cardiomyopathy, smooth muscle dysfunction, myopathies, electrolyte and acid–base disturbances related to excessive vomiting, and death [154,315] (Antidotes in Depth: Syrup of Ipecac). Poisoning in patients ingesting plant material is not reported.

Strychnine and curare are both derived from plants of the *Strychnos* genus but possess very different clinical effects. The alkaloids strychnine and brucine result in muscular spasms and rigidity by antagonizing glycine receptors in the spinal cord and brainstem and are derived from the seeds of *Strychnos nux-vomica*. The plant is used as an herbal remedy for arthritis called "maqianzi," which if processed in error produces muscle spasm and weakness, including respiratory muscles[59] (Chap. 108).

Curare is the name given to the unstandardized extract of the bark of certain members of the genera *Strychnos* and *Chondodendron.* The physiologically active principal of curare is (+)-tubocurarine chloride, a competitive antagonist of acetylcholine at nicotinic receptors in the neuromuscular junction. The pharmacology and potential applications of curare are great, as it is the molecule from which most nondepolarizing neuromuscular blockers are derived (Chap. 66). Plant poisoning is recorded solely with its traditional use as a hunting poison.[24,226,286]

Swainsonine is isolated from *Swainsonia canescens, Astragalus lentiginosis* (spotted locoweed), *Sida carpinifolia,* other species of *Swainsonia* and *Astragalus,* as well as several species in the genera *Oxytropis* and *Ipomoea,* and several fungi.[69,70] After subsisting on seeds containing swainsonine for nearly 4 months, a naturalist forager manifested profound muscular weakness and died in the wilderness.[207] The compound is teratogenic and causes chronic neurologic disease called "locoism," with weakness and failure to thrive in livestock. Swainsonine inhibits the glycosylation of glycoproteins by α-mannosidase II of the Golgi apparatus, resulting in a lysosomal storage disease. Swainsonine was used with some success in clinical trials for treatment of advanced neoplasms. Adverse effects included hepatic, pancreatic, and respiratory manifestations, as well as lethargy and nausea.[148]

Glycosides

Glycosides yield a sugar or sugar derivative (the glycone) and a nonsugar moiety (the aglycone) upon hydrolysis. The aglycone group is the basis of subclassification. The nonsugar or aglycone group determines the subtype of glycoside. For instance, the cardioactive steroids have saponin (steroid) aglycone groups and are among the saponin glycosides.

Saponin Glycosides: Cardioactive Steroids, Glycyrrhizin, *Ilex* Saponins
Cardioactive Steroids. Poisoning by virtually all *cardioactive steroids* is clinically indistinguishable from poisoning by digoxin (Chap. 62), which itself is derived from *Digitalis lanata*.[296] However, compared to toxicity from pharmaceutical digoxin, toxicity resulting from the cardioactive steroids found in plants has markedly different pharmacokinetic characteristics. For example, digitoxin in *Digitalis* species has a plasma half-life as long as 192 hours (average 168 hours).

The pharmacologic properties are true across taxonomic boundaries.[311] Poisonings by *Digitalis* spp,[267,292,324] squill (*Urginea* spp),[123,345] lily of the valley (*Convallaria* spp [see ILCONVALLARIAMAJALIS in the Image Library at goldfrankstoxicology.com]),[98,210,215] oleander (*Nerium* spp),[7,161,210,218,220] and yellow oleander (*Thevetia* spp [see ILTHEVETIAPERUVIANA1 and ILTHEVETIAPERUVIANA2 in the Image Library at goldfrankstoxicology.com]).[26,96,97,235,311,312] are clinically similar. The potency of these effects depends on the specific cardioactive steroid constituents and its dose. For instance, lily of the valley is rarely associated with morbidity or mortality,[98,219] whereas ingestion of only two seeds of yellow oleander by adults can produce severe symptoms, and expected outcome is grave if more than 4 seeds are consumed.[235,311] Poisonings by oleander and yellow oleander occur predominantly in the Mediterranean and in the Near and Far East. These two plants are attractive ornamentals popular in the United States and Europe, commonly resulting in poisoning in some of these regions.[82]

Patients experience vomiting within several hours, followed by hyperkalemia, conduction delays, and increased automaticity (bradycardia and tachydysrhythmias). Interestingly, the cardiac manifestations may be difficult to distinguish from those produced by plants with sodium channel blockers (see Effects Shared Among Diverse Classes of Toxins). Activated charcoal was beneficial in preventing death after suicide attempts with yellow oleander in Sri Lanka and its use should not be delayed in the face of uncertain plant identity.[86] Antibody therapy reduces mortality 3-fold from yellow oleander poisoning but is too expensive for developing countries where oleander-induced mortality is highest. In addition, various cardioactive steroids respond differently to therapeutic use of digoxin-specific antibody fragments (Fab). Use of very large doses of digoxin-specific antibody (up to 37 vials reported in one case[292]) may be necessary to capitalize on the therapeutic cross-reactivity between antibody and the nondigoxin cardioactive steroids. The potential for success should lead to use of antibody therapy without delay when available.[81,306] Similarly, there is variable cross-reactivity among the individual plant cardioactive steroids with regard to the degree to which each elevates diagnostic polyclonal digoxin assay measurements in clinical laboratories. These measurements can be used only as qualitative proof of exposure but not as quantitative indicators of the exposure, because the elevations can result in marked *underestimation* of the "functional digoxin concentrations." Until more is known, any positive digoxin concentration following exposure to a plant should be assumed to be significant and treated accordingly.

Because steroidal glycosides were found only in the stomach of a patient who died after ingestion of common ivy *(Hedera helix),* it was concluded that hederacoside C, α-hederin, and hederagenin did not cause death. Instead, the patient is believed to have asphyxiated on the leaves.[132]

Glycyrrhizin. Glycyrrhizin is a saponin glycoside derived from *Glycyrrhiza glabra* (licorice) and other *Glycyrrhiza* spp. Glycyrrhizin inhibits 11β-hydroxysteroid dehydrogenase, an enzyme that converts cortisol to cortisone. When large amounts of licorice root are consumed chronically, cortisol concentrations rise, resulting in pseudohyperaldosteronism because of its affinity for renal mineralocorticoid receptors.[109] Chronic use eventually leads to hypokalemia with muscle weakness, sodium and water retention, hypertension, and dysrhythmias[76,105,108,109,377] Assessment involves evaluation of the patient's fluid and electrolytes and electrocardiogram. Potassium replacement is the most common necessary intervention.

Ilex *Species.* Holly berries (from >300 *Ilex* spp) are a common and attractive ingestant among children, especially during winter holidays.[353] They contain a mixture of alkaloids, polyphenols, saponin glycosides, steroids, and triterpenes.[367] Saponin glycosides appear to be responsible for GI symptoms such as nausea, vomiting, diarrhea, and abdominal cramping that result from ingestion of the berries. Experimental data in animals describe hemolysis as well as cardiotonic effects similar to those of digoxin.[15,362] CNS depression was reported in a case in which a child consumed a "handful" of berries; however, this child was also treated with syrup of ipecac.[298] The toxic dose has been suggested to be just two berries,[125] but one study suggested that no untoward effects are to be expected for ingestions of <6 berries.[362] Symptoms may be expected to be restricted to GI effects, and treatment is supportive.

Cyanogenic Glycosides: *(S)*-Sambunigrin, Amygdalin, Linamarin, and Cyacasin. Cyanogenic glycosides yield hydrogen cyanide on complete hydrolysis. These glycosides are represented in a broad range of taxa and in approximately 2500 plant species.[354] The species that are most important to humans are cassava (*Manihot esculenta* [see ILMANIHOTESCULENTA in the Image Library at goldfrankstoxicology.com]), which contains linamarin, and *Prunus* spp, which contain amygdalin. Cycad toxins are neurotoxic or pseudocyanogenic. Rare reports of cyanide poisoning associated with *(S)*-sambunigrin in European elderberry *(Sambucus nigra;* sambunigrin) are more severe when these ingestions include leaves as well as berries.[39,49]

Many North American species of plants contain cyanogenic compounds, including ornamental *Pyracantha, Passiflora,* and *Hydrangea* spp, which either do not release cyanide or are rarely consumed in quantities sufficient to result in toxicity.[146] On the other hand, although the fleshy fruit of *Prunus* spp in the Rosaceae are nontoxic (apricots, peaches, pears, apples, and plums), the leaves, bark, and seed kernels contain amygdalin, which is metabolized to cyanide.[43] Amygdalin was the active ingredient of Laetrile, an apricot pit extract, promoted in the 1970s for its supposed selective toxicity to tumor cells. Its sale was restricted in the United States because it lacked efficacy and safety.[258] However, patients continued to travel to other countries for laetrile therapy, also marketed as "vitamin B-17," and it once again is available through alternative medicine providers.[372] Ingestions of, and poisoning from, *Prunus* seeds continue today.[281,304,336] The manifestations of cyanide poisoning and treatment involving use of the cyanide antidote kit are detailed elsewhere (Chap. 121 and Antidotes in Depth: Nitrates, Sodium Thiosulfate, and Hydroxcobolanin).

Acute and chronic cyanide toxicity (including deaths) associated with consumption of inadequately prepared cassava (*M. esculenta* [see ILMANIHOTESCULENTA in the Image Library at goldfrankstoxicology.com]) are reported worldwide (Chap. 121).[2,303] Chronic manifestations include visual disturbances (amblyopia), upper motor neuron disease with spastic paraparesis, and hypothyroidism. These findings are associated with protein-deficient states and use of tobacco and alcohol. The ataxic neuropathy resembles that produced by lathyrism (see Proteins, Peptides, and Lectins). A unifying hypothesis about the etiology of these 2 similar diseases from seemingly very different sources is that thiocyanate accumulation may lead to degeneration of the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)-containing neurons that are first stimulated and then destroyed in neurolathyrism.[326,329]

Similarly, seeds of cycads contain cycasin and neocycasin, which belong to the family of cyanogenic glycosides, as well as neurotoxins associated with consumption of indigenous food. The cyanogenic glycosides of cycads are considered pseudocyanogenic, with little potential to liberate hydrogen cyanide, but most typically produce violent vomiting 30 minutes to 7 hours after ingestion of 1–30 seeds.[58] On the island of Guam, indigenous peoples develop a devastating amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) that appears associated with ingestion of *Cycas circinalis* seeds or the flying foxas that feed extensively upon the cycads.[333] The implicated toxin originally was believed to be an amino acid[33] but more recently is identified as a sterol glycoside.[195] Research on the mechanism of this cycad-induced disease is ongoing, with the goal of understanding potential mechanisms of this disease and its links to ALS and Parkinson disease.[321]

Anthraquinone Glycosides: Sennoside and Others. Anthraquinone laxatives are regulated both as nonprescription pharmaceutical ingredients and as dietary supplements. These glycosides, such as sennoside, are metabolized in the bowel to produce derivatives that stimulate colonic motility, probably by inhibiting Na^+–K^+–ATPase in the intestine, which also promote accumulation of water and electrolytes in the gut lumen, producing fluid and electrolyte shifts that can be life threatening.[108]

Other Glycosides: Salicin and Atractyloside. Salicin is an inactive glycoside until it is hydrolyzed to produce salicylic acid (Chap. 35). The glycosidic bond is relatively resistant to stomach acid, and the hydrolysis must be accomplished by gut flora. The ability of individual human flora to produce the necessary enzymes varies significantly, resulting in variable clinical effects. However, sufficient hydrolysis to transform salicylic acid occurs in all individuals.

Atractylis gummifera was a favorite agent for homicide during the reign of the Borgias. Atractyloside, the active ingredient, decreases concentrations of cytochrome P450. It also inhibits oxidative phosphorylation in the liver by inhibiting the ADP/ATP antiporter blocking influx of adenosine diphosphate (ADP) into hepatic mitochondria and outflow of ATP to the rest of the cell (Chap. 13). Death or severe illness as a result of liver failure or hepatorenal disease following ingestion is reported.[156,166]

The effects of the glycosides sinigrin (from *Brassica nigra* seed and *Alliaria officinalis* [horseradish] root) and naringen (a polyphenolic glycoside from the grapefruit *Citrus paradisi*) are discussed in the sections on Plant-Induced Dermatitis and Plant–Drug Interactions, respectively.

Terpenoids and Resins: Ginkgolides, Kava Lactones, Thujone, Anisatin, Ptaquiloside/Thiaminase, and Gossypol

Ginkgolides in *Ginkgo biloba* are associated with antiplatelet aggregation effects. Three reports of spontaneous bleeding associated with ingestion of *Ginkgo* leaf products as an herbal medicine are perhaps explained by this property.[300,302,351] Another xenobiotic found only in the seed, 4-methoxypyridoxine (pyridine alkaloid), is associated with seizures. A mechanism similar to isoniazid-induced seizures is plausible.[129,188,255,358] These cases suggest treatment with pyridoxine phosphate (Chap. 55 and Antidotes in Depth: Pyridoxine). The dermal effects of *Ginkgo* are discussed in Plant-Induced Dermatitis.

Kava lactones are a family of terpene lactones found in kava kava *(Piper methysticum)* that causes central and peripheral nervous system effects or hepatotoxicity.[66] Kava kava has enjoyed a long ceremonial history among islanders of the South Pacific, and observers visiting Oceania have recorded its acute and chronic effects (both pleasant and unpleasant) over the centuries. Importation of kava kava to Australia in 1983 was a measure to assist Aborigines with alcohol abuse problems. However, the kava kava itself became abused, and its subsequent ban has resulted in the growth of a black market for kava kava.[12,45] Proposed mechanisms to explain the effects of kava lactones include effects at $GABA_A$ and $GABA_B$ receptors[83,186] or, more likely, local anesthetic effects.[38,142,275] Acute symptoms following ingestion include peripheral numbness, weakness, and sedation. Chronic use leads to kava dermopathy and weight loss.[36] More than 70 cases of hepatotoxicity, several requiring liver transplantation, are associated with both acute and chronic effects of the kava lactones on cytochrome oxygenases or other yet to be defined etiologies and prompted regulatory health measures in Europe and North America.[47]

Thujone is one of many terpenes associated with seizures.[34] It is found in the wormwood plant *(Artemisia absinthium)* and its derivative absinthe, and in some strains of tansy *(Tanacetum vulgare).* The α- and β-isomers of thujone are believed to act much like camphor to produce CNS depression and seizures. Invoking the structural similarity of thujone to tetrahydrocannabinol (THC), one of the terpenoids of marijuana, to explain the psychoactive effects is controversial[250] (Chap. 81).

Absinthism is characterized by seizures and hallucinations, permanent cognitive impairment, and personality changes. Acute and chronic absinthism led to a worldwide ban of the alcoholic beverage absinthe, which contained thujone, in the early 1900s. The essential oil of wormwood is composed almost exclusively of thujone. Wormwood oil currently is available over the Internet and is responsible for at least 2 reports of adverse reactions in people seeking its hallucinatory or euphoriant effects[21,365]

Anisatin found in *Illicium* spp. This terpenoid produces seizures as a noncompetitive GABA antagonist. The Chinese star anise *(Illicium verum)* is sometimes used in teas and occasionally is confused or contaminated with other species of *Illicium,* particularly Japanese star anise *Illicium anisatum.*[140,180] These contaminations have resulted in small epidemics of tonic–clonic seizures, particularly but not exclusively of infants after use of the tea to treat their infantile colic. Recently, in the United States, a case series of at least 40 individuals who had consumed teas brewed from "Star anise" experienced seizures, motor disturbances, other neurologic effects, and vomiting. These cases include at least 15 infants treated for infantile colic with this home remedy. This trend prompted the FDA to issue an advisory regarding the health risk from remedies sharing the common name "Star anise."[180]

Ptaquilosides are found in the bracken fern *(Pteridium aquilinum),* a plant that is extending its range and density worldwide. In foraging animals, consumption of ptaquilosides results in acute hemorrhage secondary to profound thrombocytopenia whereas thiaminases produce cerebral disease.[108,290] Although no acute human poisonings are reported, these xenobiotics are transmitted through cow's milk and are associated with increased prevalence of gastric and esophageal cancer in areas where fern is endemic and consumed by cows whose milk is not diluted. Chronic toxicity through spore inhalation also produces pulmonary adenomas in animals [325,374] More recently, research defined links between alimentary cancer in humans who previously consumed bracken fiddleheads.[5]

Gossypol is a sesquiterpene that is derived from cottonseed oil. It is used experimentally as a reversible male contraceptive. The mechanism for its spermicidal effect is unclear,[75] but the effects have been attributed to inhibition of plasminogen activation and plasmin activity in acrosomal tissue.[337] These effects are not currently reported to produce systemic bleeding. Gossypol also inhibits 11β-hydroxysteroid dehydrogenase, as does glycyrrhizin, but typically results in only isolated hypokalemia.[74]

Proteins, Peptides, and Lectins: Ricin and Ricinlike, Pokeweed, Mistletoe, Hypoglycin, Lathyrins, and Microcystins

Lectins are glycoproteins that are classified according to their binding affinity for specific carbohydrate ligands, particularly galactosamines, and by the number of protein chains linked by disulfide bonds. Toxalbumins such as ricin and abrin, are lectins that are such potent cytotoxins that they used as biologic weapons (Chap. 126). Ricin, extracted from the castor bean (*Ricinus communi* [see ILRICINUSCOMMUNIS1 and RICINUSCOMMUNIS2 in the Image Library at goldfrankstoxicology.com]), exerts its cytotoxicity by 2 separate mechanisms. The compound is a large molecule that consists of 2 polypeptide chains bound by disulfide bonds. It must enter the cell to exert its toxic effect. The B chain binds to the terminal galactose of cell surface glycolipids and glycoproteins. The bound toxin then undergoes endocytosis and is transported via endosomes to the Golgi apparatus and the endoplasmic reticulum.[309] There the A chain is translocated to the cytosol, where it stops protein synthesis by inhibiting the 28S subunit of the 60S ribosome. In addition to the GI manifestations of vomiting, diarrhea, and dehydration, ricin can cause cardiac, hematologic, hepatic, and renal toxicity. All contribute to death in humans and animals.[7,52,189,203,274] Despite the obvious toxicity of this compound, death probably can be prevented by early and aggressive fluid and electrolyte replacement after oral ingestion (but not injection or inhalation, Chap. 126). Allergic reactions to some of these lectin-bearing plants are noted, particularly to *R. communis*.[265] Occupational exposures to castor oil are a particular hazard,[84,346] and the plant's pollen may be a pneumoallergen.[135]

Just how lethal are ingestions of the ornamental seeds? The highest concentration of xenobiotic is in the hard, brown-mottled seeds. These seeds are both tempting and available, even to children in the United States, because they are attractive enough to be used to make jewelry, and their parent plants are showy enough to have been exported for horticultural purposes outside of their native India (including to the United States).[199] Although mastication of one seed by a child liberates enough ricin to produce death,[203] this outcome (or even serious toxicity) is uncommon, even if the seeds are chewed, probably because GI absorption of the xenobiotic is poor and supportive care is effective.[9,52] Activated charcoal should be administered promptly.

Other *ricinlike lectins* are found in *Abrus precatorius* (jequirity pea, rosary pea [see ILABRUSPRECATORIUS in the Image Library at goldfrankstoxicology.com]),[17,82] *Jatropha* spp,[221] *Trichosanthes* spp (eg, *kirilowii* or Chinese cucumber),[187] *Robinia pseudoacacia* (black locust),[73,248] *Phoradendron* spp (American mistletoe), *Viscum album* (European mistletoe),[94,102] and *Wisteria* spp (wisteria).[171,299] These all produce at least one double-chain lectin that binds to galactose-containing structures in the gut or inhibits protein synthesis in a manner similar to ricin.

Pokeweed mitogen of *Phytolacca americana* (pokeweed [see ILPHYTOLACCAAMERICANA in the Image Library at goldfrankstoxicology.com]) is a single-chain protein that inhibits ribosomal RNA by removing purine groups.[16,177] Given their mechanism, it is not surprising that the lectins are capable of producing GI symptoms, and they otherwise have toxic profiles with variable degrees of overlap in pattern and severity with ricin in humans and animals.

The most commonly ingested toxic plant lectins in the United States are from pokeweed, which is eaten as a vegetable but rarely causes toxicity or death. *Phytolacca* toxin and pokeweed mitogen are found in all plant parts, but the highest concentrations are found in the plant root. The mature deep purple berries are less toxic.[16] Pokeweed leaves are consumed after boiling without toxic effect if the water is changed between the first and second boiling (parboiling). When this detoxification technique is not followed, as in preparation of poke salad or pokeroot tea, violent GI effects can ensue 0.5–6 hours after ingestion. Nausea, vomiting, abdominal cramping, diarrhea, hemorrhagic gastritis, and death may occur. In addition, bradycardia and hypotension, perhaps induced by an increase in vagal tone, may be associated with nausea and vomiting.[159,297] More often than not, toxicity is limited to the GI tract. The mitogen produces a lymphocytosis 2–4 days after ingestion that may take up to 10 days to clear, but this is without clinical consequence.[16]

Mistletoe berries, both American and European, can produce severe gastroenteritis, especially when delivered as teas or extracts, or particularly as parenteral antineoplastic medicinal agents in Europe.[95] As festive holiday plants they become seasonally available for children. Poison Center data suggest that ingestion of 3–5 berries or 1–5 leaves of the American species may not cause toxicity, but these suggestions are based on limited evidence. (See Chap. 130.)[214] Despite single reports of seizure, ataxia, hepatotoxicity, and death,[156,327] most authors performing such retrospective examinations[155,219,327] conclude that mistletoe exposures are not a highly consequential risk.

Hypoglycin A (β-methylene cyclopropyl-L-α-aminopropionic acid) and *hypoglycin B* (dipeptide of hypoglycin A and glutamic acid) are found in the unripe ackee fruit and seeds of *Blighia sapida* (Euphorbiaceae). (See ILBLIGHIASAPIDA in the Image Library at goldfrankstoxicology.com.) The tree is native to Africa but was imported to Jamaica in 1778 by the botanist Thomas Clarke. The scientific name of the plant derives from Captain William Bligh, the British explorer.[32] The tree is also naturalized in Central America, southern California, and Florida. Epidemics of illness (Jamaican vomiting sickness) associated with consumption of the unripe ackee fruit (raw and cooked) occur in Africa but are more common in Jamaica, where ackee is the national dish.[50,246] The most toxic part is the yellow oily aril of the fruit, which contains three large shiny black seeds.[53] Cases in the United States usually are associated with canned fruit.[245] Hypoglycin A is metabolized to methylene cyclopropyl acetic acid, which competitively inhibits the carnitine–acyl coenzyme (CoA) transferase system.[1,31,32] This prevents importation of long-chain fatty acids into the mitochondria, preventing their β-oxidation to precursors of gluconeogenesis. β-Oxidation and gluconeogenesis are further arrested by inhibition of various enzymes,[31,101] such as glutaryl CoA dehydrogenase, which blocks the malate shunt (Chap. 13). In addition, increased concentrations of glutaric acid may inhibit glutamic acid decarboxylase, which produces GABA from glutamic acid. This not only depletes GABA but also increases concentrations of excitatory glutamate to produce seizures.[1,193] Insulin concentrations remain unaffected by hypoglycin and metabolites.[253] Carboxylic and other organic acid substrates build up in the urine and serum as a

result of these metabolic perturbations. Detection of these acids can help corroborate the diagnosis.[143]

Jamaican vomiting sickness is characterized by epigastric discomfort and the onset of vomiting starting 2–6 hours after ingestion. Convulsions, coma, and death can ensue, with death occurring approximately 12 hours following consumption. Laboratory findings are notable for profound hepatic aminotransferase and bilirubin abnormalities, and aciduria and acidemia without ketonemia. Cholestatic hepatitis can occur and is reported with chronic use.[219] Autopsy reveals fatty degeneration of liver, particularly microvesicular steatosis, and other organs with depletion of glycogen stores.[170] Left untreated, patient mortality reaches 80%, with 85% of the fatal cases suffering seizures. Treatment with glucose and fluid replacement is essential. Benzodiazepines can control seizures, perhaps directly if the seizures are related to depletion of GABA. L-Carnitine therapy may exert a theoretical therapeutic role similar to that noted with valproic acid toxicity,[104,223] whereas glycine therapy shows some beneficial effects in rats (Chap. 47).[319]

The *lathyrins* β-*N*-oxalylamino-L-alanine (BOAA) and β-aminopropionitrile (BAPN) are peptides from the grass pea *(Lathyrus* sativus) found in the seeds and leaves, respectively. BOAA produces neurolathyrism (seeds) and BAPN produces osteolathyrism (leaves) in individuals with a dietary dependence on this plant. Neurolathyrism is clinically indistinguishable from spastic paresis associated with consumption of improperly prepared cassava (see Cyanogenic Glycosides: *(S)*-Sambunigrin, Amygdalin, Linamarin, and Cyacasin). Thiol oxidation with depletion of nicotinamide adenine dinucleotide (NADH) dehydrogenase at the level of neuronal mitochondria (ie, excitatory AMPA receptors) may be the common etiology.[246,273,326] Epidemics occur in Bangladesh, Ethiopia, Israel, and India.[137,226] Exposure to BOAA results in degeneration of corresponding corticospinal pathways that becomes irreversible if consumption of undetoxified grass peas is not stopped early. BOAA stimulates the AMPA class of glutamate receptors to provide constant neuronal stimulation, eventual degeneration, and hence spasticity. BAPN affects bone matrix and leads to bone pain and skeletal deformities that develop in adulthood.[163] These diseases occur in areas where the plants are endemic, the food is consumed for two months or more, and when diets are otherwise poor in protein and possibly in zinc.[214]

Microcystins are found in several cyanobacteria (blue-green algae) belonging to various species of the genera *Microcystis, Anabaena, Nodularia, Nostoc*, and *Oscillatoria*. [42] They elaborate a series of peptide xenobiotics called microcystins and nodularins *(Nodularia spumigena)*. These xenobiotics produce hepatotoxicity by causing deterioration of the microfilament function in hepatocytes, leading to cell shrinkage and bleeding into the hepatic sinusoids. Evidence indicates that these peptides are carcinogenic to humans.[90] Although most cases of untoward effects from blue-green algae occur in animals, the potential for harm was demonstrated by use of microcystin-contaminated water in a dialysis unit in Brazil.[184] Unfiltered water was identified as the risk factor for liver disease in 100 patients who attended the dialysis center (Chap.10). Fifty of these patients died of acute liver failure following early signs of nausea, vomiting, and visual disturbances. The concern for poisoning is heightened because certain species of *Cyanobacteria* are harvested and consumed as health foods[43,142,191] or may be consumed secondarily in fish.[231] In addition to the sodium channel and acetylcholinesterase effects, ingestion of the genus *Microcystis* produces photosensitivity.[119]

Phenols and Phenylpropanoids: Coumarins, Capsaicin, Karwinskia Toxins, Naringenin and Bergamottin, Asarin, Nordihydroguaiaretic Acid, Podophyllin, Psoralen, and Esculoside

Phenols and phenylpropanoids represent one of the largest groups of secondary metabolites.[107,296] Coumarins and their isomers are phenylpropanoids that are discussed in Chap. 57. Some coumarins are warfarinlike in their activity and are capable of producing a bleeding diathesis when plants are consumed in sufficiently large quantities.[174,216] Lignans are formed when phenylpropanoid side chains react to form bisphenylpropanoid derivatives. Lignins are high-molecular-weight polymers of phenylpropanoids that bind to cellulose and provide strength to cell walls of stem and bark. Tannins are polymers that bind to proteins and divide into 2 groups: hydrolyzable and condensed (called *proanthocyanidins*, eg, karwinol).

Capsaicin is derived from *Capsicum annuum* or other species of chile or cayenne peppers. It is a simple phenylpropanoid that causes release of the neuropeptide substance P from sensory C-type nerve fibers. The immediate response to capsaicin is intense local pain and is the rationale for its use in pepper spray. Eventual depletion of substance P prevents local transmission of pain impulses from these receptors to the spinal cord, blocking perception of pain by the brain, explaining its use in postherpetic neuralgia.[364]

Painful exposures to capsaicin-containing peppers are among the most common plant-related exposures presented to poison centers. They cause burning or stinging pain to the skin. If ingested in large amounts by adults or small amounts by children, they can produce nausea, vomiting, abdominal pain, and burning diarrhea.[89,364] Eye exposures produce intense tearing, pain, conjunctivitis, and blepharospasm.[344]

Skin irrigation, dermal aloe gel, analgesics, and oral antacids are therapeutic agents that may be helpful as appropriate, but patients can be reassured that the effects are transitory and produce no long-term damage. Irritated eyes can be treated with irrigation and local analgesia, but generally resolve without sequelae within 24 hours.[185]

Karwinskia toxins from plants commonly named Buckthorn, coyotillo, tullidora, wild cherry, or capulincillo *(Karwinskia humboldtiana)*. These xenobiotics are identified by their molecular weights (T-514, T-496, T-516, T-544). Toxicity has been known for more than 200 years. In 1920, an epidemic of deaths was reported after 20% of 106 Mexican soldiers died following ingestion of foraged *Karwinskia* fruits.[196,234] The fruits are attractive to children; epidemic poisonings have been reported in Central America[11] and are possible wherever the shrub is found (in semidesert areas throughout the southwestern United States and Caribbean, Mexico, and Central America). Recently, poisonings from this plant in Mexico have increased from a total of 72 cases reported between 1990 and 1994 to 40 cases per year currently reported in northern Mexico.[234,264] Uncoupling of oxidative phosphorylation or dysfunction of peroxisome assembly and integrity is described for Schwann cells.[353,368] Each xenobiotic exhibits similar cytotoxic effects at the cellular level, but with trophism for different organs in animal models.[234]

Within a few days of ingestion, a symmetric motor neuropathy ascends from the lower extremities to produce a bulbar paralysis that may lead to death. Deep-tendon reflexes are abolished in affected areas, but cranial nerve findings are absent. Distinction of this demyelinating motor neuropathy from Guillain-Barré syndrome,

poliomyelitis, solvent, and other polyneuropathies is best assisted by detection of T-514 in the blood of affected patients.[29,196,234] The other recognized toxins are not detected in blood. Occasionally, axonal damage is observed, but demyelination is the predominant finding on biopsy. Nerve conduction studies always demonstrate loss or abolition of function in fast-conducting axons. Cerebrospinal fluid demonstrates normal protein, glucose, and cytology. Treatment is supportive, with mechanical ventilation as needed, and recovery typically is slow.

Naringenin and *bergamottin* are phenylpropanoids derived from grapefruit that inhibit CYP3A4 in gut and liver.[128] Grapefruit juice consumption can increase circulating concentrations of drugs reliant on 3A4 for metabolic elimination, including terfenadine, carbamazepine, and felodipine. These effects are maximally achieved by a single glass of grapefruit juice.[228]

Hyperforin is another phenylpropanoid found in St. John's wort *(Hypericum perforatum)* and is associated with plant–drug interactions.

Asarin is found in the sweet flag plant tuber *(Acorus calamus).* Putative euphoric and hallucinogenic effects that motivate ingestion are in contrast to confirmed reports of unpleasant GI effects.[352]

Nordihydroguaiaretic acid (NDGA) is associated with hepatotoxicity after ingestions of chaparral *(Larrea tridentata).*[317] Podophyllin and psoralens are phenylpropanoids discussed in Antimitotic Alkaloids and Resins and in Plant-Induced Dermatitis, respectively.

Esculoside (also called *esculin* or *aesculin)* has triterpene saponin side chains and is believed to be the toxic component in horse chestnut *(Aesculus hippocastanum).* Horse chestnut extracts are used medicinally in patients with venous insufficiency. Its therapeutic use at high doses (>340 μg/kg) is associated with renal failure or a lupuslike syndrome.[151,168] Leaves, twigs, or horse chestnuts ingested by children or infused as teas result in a syndrome that resembles nicotine intoxication. The syndrome consists of vomiting, diarrhea, muscle twitching, weakness, lack of coordination, dilated pupils, paralysis, and stupor.[262] The mechanism of toxicity is not defined, but ingestion of chestnut approximately 1% of a child's weight is suggested to be poisonous to a child.

Carboxylic Acids: Oxalic Acid and Oxalate Raphides

Oxalic acid is the strongest acid among the carboxylic acids found in living organisms. It forms poorly soluble chelates with calcium and other divalent cations. Higher plants have varying ability to accumulate these products of metabolism. Oxalates are mainly found in certain plant families, such as the Araceae, Chenopodiaceae, Polygonaceae, Amaranthaceae, and several of the grass families. Human dietary sources include rhubarb, spinach, strawberries, chocolate, tea, and nuts.[236] Human consumption of soluble oxalate-rich foods correlates with kidney stone formation.[169]

The insoluble calcium oxalate raphides that are present in certain plants, usually in the Araceae family, are found in conjunction with a protein toxin that increases the painful irritation to skin or mucous membranes. This special manifestation is discussed in greater detail in Plant-Induced Dermatitis.

Alcohols: Cicutoxin

Cicutoxin, a diacetylenic diol, is found in the water hemlock *(Cicuta maculata)* and other *Cicuta* spp. Ingestion of any part of the plant constitutes the most common form of lethal plant ingestion in the United States. In a series of 83 ingestions from 1900–1975, the case fatality rate was 30%, and it dominated plant-related fatalities among the most recent 10-year reviews of the Toxic Exposure Surveillance System (TESS) and Centers for Disease Control (CDC) plant-poisoning records (Chap. 130).[213,252] In contrast to most plant exposures in humans (which tend to involve children), these ingestions usually involve adults who incorrectly identify the plant as wild parsnip, turnip, parsley, or ginseng. All plant parts are poisonous at all times, but the tuber is especially toxic, and more so during the winter and early spring.[145,252] Absorption of cicutoxin is rapid and occurs through the skin as well as through the gut.[200] Ingestion of as little as a 2-cm section of the sweet-tasting root of *Cicuta* can produce fatal status epilepticus, the mechanism of which remains unclear.[25,41,165,270,335]

Symptoms of mild or early poisonings consist of GI symptoms (nausea, vomiting, epigastric discomfort) and begin as early as 15 minutes after ingestion. Emesis may diminish the toxic load in the gut. Diaphoresis, flushing, dizziness, excessive salivation, bradycardia, hypotension, bronchial secretions with respiratory distress, and cyanosis occur and rapidly progress to violent seizures. Complications include rhabdomyolysis with renal failure and severe acidemia.[41] Immediate gastric evacuation should be performed, and benzodiazepines should be administered for seizures. Case reports recommend diverse treatments such as hemodialysis, anticholinergic therapy, and sodium thiopentone infusion as potential lifesaving measures.[205,270,294,330]

Unidentified Toxins

Consistent with the inherent complexity of plants and the relatively early stage of the science, identification of the active ingredient(s) involved in poisoning is not always possible. An epidemic of the irreversible lung disease bronchiolitis obliterans developed in 1994. It involved more than 200 dieters who had been eating *Sauropus androgynous* as a weight-loss vegetable. The effects were dose related (usually~100 g/d) and manifested by month 7 after approximately 10 weeks of use.[176] The cases were associated with at least 4 deaths and, in addition to pulmonary disease, included 3 cases of torsade de pointes.[54,227] This last complication is consistent with the plant's high concentration of papaverine, a toxin that produces dysrhythmias in animals, but papaverine does not cause the lung disease.[375] Steroid and bronchodilator therapy consistently failed to improve pulmonary symptoms, and lung transplantation remains the only effective treatment for advanced cases.[227]

Milk sickness is an historic poisoning described by pioneer farmers. It was caused by transmission of the nontoxic ketone tremetone to humans via milk of animals grazing on white snakeroot plants *(Eupatorium rugosum).*[242,318] Tremetone is transformed into an unknown, unstable toxin by hepatic microsomal enzymes.[19,20] Toxicity is cumulative. Milk sickness can be fatal in 1–21 days or is associated with a slow recovery marked by weakness for months or years, relapsing sometimes to death. A delay in the lactating animal's symptoms provided a lag time when xenobiotic-laden milk was taken from presymptomatic animals and thereby transmitted to humans before the problem was detected. Reports in animals but not humans may be found in the literature.

Breynia officinalis,[224] black cohosh *(Actaea racemosa)*,[341] and the yam *(Dioscorea bulbifera)*[338] are implicated as agents producing hepatotoxicity. Unidentified components of the plant

Achyranthes aspera are associated with production of hypotension and bradycardia.[161] Additional studies are needed to verify these effects.

Consumption of the food star fruit *(Averrhoa carambola)* and preexisting renal insufficiency are associated with development of intractable hiccups, vomiting, motor disabilities, paresthesias, confusion, seizures, and death unless patients receive supportive care and hemodialysis.[61,266,348] The unidentified toxin appears to be neuroexcitatory and active in the thalamus and right temporooccipital cortex.[57]

EFFECTS SHARED AMONG DIFFERENT CLASSES OF XENOBIOTICS

Plant–Drug Interactions

By increasing the metabolic rate of CYP enzymes,[302] hyperforin in St. John's wort *(H. perforatum)* decreases concentrations of (1) cyclosporin, (2) digoxin, (3)warfarin, (4) theophylline, (5) oral contraceptives, and (6) indivir. Activity of some of these 6 drugs and others (eg, amitriptyline and theophylline) may be reduced by flavonoids in St. John's wort, which increases drug elimination by increasing the activity of P-glycoprotein.[181] On the other hand, bergamottin and naringenin from grapefruit reduce activity of the CYP system enzymes and increase drug concentrations. Other *Citrus* species also appear to increase drug concentrations.[175]

Additive effects may be responsible for serotonin excess or mild serotonin syndrome when St. John's wort is used concurrently with tryptophan or serotonin reuptake inhibitors. Additive effects also appear to be responsible for increased prothrombin time in patients taking *Ginkgo biloba* and various dugs to affect coagulation (eg, warfarin or aspirin) because the ginkgolides have antiplatelet activity.[79,127,181,251] Hawthorn (*Crataegus* spp), used medicinally for cardiac disorders, may produce an additive effect when taken concomitantly with digoxin, producing bradycardia.[173] Excessive intake of broccoli provides enough vitamin K to competitively inhibit the negative effects of warfarin on vitamin K activation.[79]

Sodium Channel Effects: Aconitine, Veratridine, Zygacine, Taxine, and Grayanotoxins

Several unrelated plants produce xenobiotics that affect the flow of sodium at the sodium channel. For instance, aconitine and veratrum alkaloids tend to open the channels to influx of sodium, whereas others (eg, taxine) tend to block the flow, and grayanotoxins both increase and block sodium flow. The sodium channel opener aconitine from *Aconitum* spp or.(See ILACONITUM-RAPELLUS in the Image Library at goldfrankstoxicology.com) *Delphinium* spp has the most persistent toxicity and the lowest therapeutic index among the many active alkaloid ingredients of the toxin called aconite. Some of these related alkaloids are controlled medicinal substances in the People's Republic of China and Taiwan.[88] Aconite has been abused for its psychoactive "out of body" effects[110,343] and for suicide and homicide.[101,106] Properly processed aconite is supposedly less cardiotoxic than unprocessed material, because processing results in production of the less toxic dehydroaconitine. This xenobiotic should be suspected in potentially poisoned patients who manifest cardiac toxicity, paresthesias, and seizures.[60,110,256]

The mechanism of action depends on the individual alkaloid. Some compounds block and others activate sodium channels.[6,313] Aconitine itself opens the voltage-dependent sodium channel at binding site 2 of the α-subunit, initially increasing cellular excitability.[6] By prolonging sodium current influx, neuronal and cardiac repolarization eventually slows. It also has calcium channel-opening effects. Asian prescription medicines use the alkaloids to treat dysrhythmias and pain by reducing the excitability of the cardiac conducting system and sensory neurons, respectively. Enhanced activity of the vagus nerve results in bradycardia, which is treated successfully by atropine.[197,283] Approximately one teaspoon (2–5 mg) of the root may cause death by paralyzing the respiratory center or cardiac muscle.

The aconitine alkaloids are rapidly absorbed from the GI tract. Cardiovascular symptoms typically progress from bradycardia and hypotension to tachydysrhythmias and cardiac arrest. CNS symptoms typically progress from paresthesias to CNS depression, respiratory muscle depression, paralysis, and seizures.[6] Nausea, vomiting, diarrhea, and abdominal cramping occur.[56,110,206,269,378] Cardiac toxicity resembles that caused by cardioactive steroids, with atrioventricular conduction blockade and increased ventricular automaticity resulting in a variety of rapid ventricular rates, from multifocal premature ventricular contractions to ventricular fibrillation and torsade de pointes. A history of paresthesias may be useful in differentiating aconitine toxicity from that caused by a cardioactive steroids, but empiric use of digoxin-specific antibody fragments should not be delayed if there is any doubt. These antibodies, however, are ineffectual against aconitine. Orogastric lavage, activated charcoal, and preparation for cardiac pacing, bypass, or balloon pump assist are warranted given the potential for rapid cardiovascular deterioration.[118,271] Success with amiodarone is reported.

Ingestion of veratridine and other veratrum alkaloids (from *Veratrum viride* and other *Veratrum* spp) generally results from foraging errors where the root appears similar to leeks *(Allium porrum)* and above-ground parts appear similar to gentian *(Gentiana lutea)* used for teas and wines in Europe.[40,115,120,125,287] The mechanism of action is like that of aconitine (sodium channel opening) but with shorter duration.[247,350] Although severe toxicity is reported, management is supportive with fluids, atropine, and pressors. Deaths are rare.[75,183,232]

Zygacine from *Zigadenus* spp (death camus) and other members of the lily family produces the same toxic effects as veratridine alkaloids (vomiting, hypotension, and bradycardia). Symptoms begin 1–2 hours after ingestion[167,328] and usually result from errors while foraging for onions because of the plant's look-alike bulb. Treatment options are the same as above with Veratrum alkaloids. Fatalities among Native Americans in the western United States caused by *Zigadenus* were recorded after interviews conducted in the 19th century.

Taxine is another alkaloid mixture of sodium channel effectors that tend to close the channel.[340,373] It is derived from the yew (*Taxus baccata* [see ILTAXUS spp in the Image Library at goldfrankstoxicology.com]). Suicide using leaves is reported despite the large number of leaves required.[112,261,331,366,371] Toxic alkaloid is contained within the hard central seed but not in the surrounding fleshy red aril, which partly explains the low rate of toxicity in reported cases. [363]

Paclitaxel (Taxol) is an alkaloid component of the relatively rare Pacific yew *(Taxus brevifolia)* that is used as an antitumor chemotherapeutic agent because of its ability to promote the assembly of microtubules and to inhibit the tubulin disassembly

process in mitotic cells. Within 1 hour after ingestion, toxicity progresses from nausea, abdominal pain, bradycardia, and cardiac conduction delays to wide-complex ventricular dysrhythmias, paresthesias, ataxia, and mental status changes.[111,269] Four prisoners who drank an extract of yew experienced profound hypokalemia, and 2 died of cardiac arrest.[111,269] Animal models indicate that bradycardia is responsive to atropine,[289] but wide-complex tachydysrhythmia is unresponsive to sodium bicarbonate.[305]

Grayanotoxins (formerly termed *andromedotoxins*) are a series of 18 toxic diterpenoids present in leaves of various species of *Rhododendron, Azalea, Kalmia* (see ILKALMIA sp Image Library at goldfrankstoxicology.com), and *Leucothoe* (Ericaceae). They exert their toxic effects via sodium channels, which they open or close, depending on the toxin.[263] Grayanotoxin I increases membrane permeability to sodium and affected calcium channels in a manner similar to that of veratridine (and batrachotoxin).[92,131,198] Grayanotoxins become concentrated in honey made from the plants, mainly in the Mediterranean. Accounts of poisoning by honey date back to at least 401 B.C., when Xenophon's troops were incapacitated after they consumed honey made from nectar of *Rhododendron luteum.* These accounts are echoed by modern accounts of toxic honey in the same region.[22,289, 376] Bradycardia, hypotension, GI manifestations, mental status changes ("mad honey"), and seizures are described in patients or animals suffering grayanotoxin toxicity.[23,201,217,288,289,332,376]

Antimitotic Alkaloids and Resins: Colchicine, Vincristine, and Podophyllum

Consumption of colchicine from plant sources such as autumn crocus *(Colchicum autumnale)* produces a spectrum of symptoms, including nausea, vomiting, watery diarrhea, hypotension, bradycardia, electrocardiographic abnormalities, diaphoresis, alopecia, bone marrow depression, renal failure, hepatic necrosis, hemorrhagic acute lung injury, convulsions, and death.[130,147,202,249]

Colchicine-induced deaths from ingestion of *Gloriosa superba* are among the most common plant-associated fatalities in Sri Lanka.[114] Confusion of the bulbs or leaves of this plant with those of wild onions or garlic occur as a foraging error. Unintentional consumption by children, or ingestion with suicidal intent, accounts for the other cases involving morbidity or mortality.[3] The mechanism of toxicity is disruption of microtubule formation in mitotic cells.

Vincristine and vinblastine are two other indole alkaloids that are used as antineoplastics and are both isolated from the Madagascar periwinkle *(Catharanthus roseus)*. No reports of poisoning by these alkaloids following ingestion of the plant could be found (Chap. 52).

Podophyllum resin is the dry, alcoholic extract of the rhizomes and roots of mayapple (*Podophyllum peltatum* [see ILPODOPHYLLUMPELTATUM in the Image Library at goldfrankstoxicology.com]). The dry resin consists of up to 20% podophyllotoxin, α- and β-peltatin, desoxypodophyllotoxin, and dehydropodophyllotoxin. These xenobiotics are originally present in the plant as β-D-glucosides. Podophyllum resin containing podophyllin is available by prescription for topical treatment of venereal warts. Its medicinal derivatives (eg, etoposide) are used for a range of neoplastic diseases. It is used as a popular traditional Chinese medicine and may produce toxicity even in "therapeutic" doses.[191] Podophyllotoxins make up 20% of the resin from the roots of mayapple *(P. peltatum)*. As a group, they disrupt tubulin formation, producing multisystem organ failure. Poisonings are caused by misidentification and adulteration, possibly because the list of common names by which it is known includes mayapple, as well as mandrake, wild mandrake, American mandrake, and European mandrake.[37,124] Catharsis is prominent after ingestion, but onset of symptoms may be delayed (10 hours in a fatal ingestion[44]). Acute severe sensorimotor neuropathy and bone marrow suppression following transient leukocytosis can occur even after one-time acute exposures and may be directly related to inhibition of microtubule assembly. Lethargy, confusion, encephalopathy, autonomic instability, sensory ataxia, and death are described following large exposures,[268] but poisoning also can occur after "therapeutic" doses of a popular traditional Chinese medicine.[191] Glutamic acid has been used to prevent vincristine-induced peripheral neuropathy and would be a reasonable therapy following podophyllin ingestion.[182]

Plant-Induced Dermatitis

A large number of plants result in undesirable dermal, mucous membrane, and ocular effects (Chap. 29), the most common adverse effects reported to US poison centers and occupational health centers. Plant-induced dermal disorders can be categorized[106,254,310,334] into 4 mechanistic groups, that is, dermatis that results from (1) mechanical injury, (2) irritant molecules that penetrate the skin, (3) allergy, or (4) photosensitivity (direct and hepatogenous).

There is much overlap between these categories (some plants can produce all types). Clinicians may have difficulty distinguishing between plant-induced dermatitis and skin disorders[237,239] or between plant-induced dermatitis and pseudophytodermatitides caused by arthropods, pesticides, or wax (used in fruit and vegetable packaging).[334] Agents that cause adverse skin reactions can also cause eye and local gastric mucosal irritation.

Dermatitis from *mechanical injury* often is combined with primary or allergic contact dermatitis. Stinging nettles *(Urtica dioica* and other species) have a specialized apparatus in the form of an elongated silicious cell (glandular trichome) that acts like a hypodermic syringe to deliver irritant chemicals into the skin. Contact with these stinging hairs shears off the tip of the hair, producing micromechanical injury and releasing irritant contents: acetylcholine, histamine, and 5-hydroxytryptamine.[272] The proteinase mucunain is released from the barbed trichomes of *Mucuna* spp (cowhage),[105] and workers who handpick pineapples are subject to fissuring and loss of fingerprints after bromelain is introduced following dermal abrasion by raphides.[204]

Exposures to commonly available household plants such as dumbcane (*Dieffenbachia* spp), *Philodendron* spp,[241] and *Narcissus* bulbs can lead to mechanical injury and painful microtrauma produced by bundles of tiny needlelike calcium oxalate crystals called *raphides.* Packages of hundreds of raphides called *idioblasts* contain proteolytic enzymes. *Dieffenbachia* (>30 species [see ILDIFFENBACHIA sp. in the Image Library at goldfrankstoxicology.com]) exposures are commonly reported household or malicious plant exposures.[10,285] These exposures are rarely serious.[280] When the leaves are chewed, immediate oropharyngeal pain and swelling occur. Severe oral exposures can be excruciating and progress to profuse salivation, dysphagia, and loss of speech. Soothing liquids, ice, parenteral opioids, corticosteroids, and airway protection may be indicated, but antihistamines provide little relief. The edema and pain typically begin to subside after 4–8 days.[241] Ocular exposure to the sap may produce chemical conjunctivitis, corneal abrasions, and, rarely, permanent corneal opacifications.

Similar exposures to oxalate raphide-containing household plants in the same family *(Philodendron*, *Brassaia*, *Epipremnum aureum*, *Spathiphyllum,* and *Scheflera* spp) are not as painful as to dumbcane, presumably because the crystals are packaged differently and do not simultaneously deliver proteolytic enzymes.[204,260] One exception to their lower severity is a report of death in an 11-month-old following complications arising from esophageal lesions induced by philodendron.

Irritant dermatitis results from low-molecular-weight xenobiotics such as phorbol esters (Euphorbiaceae) that directly penetrate the skin without antecedent mechanical injury. Similar penetrance is achieved by products of glycoside hydrolysis. For instance, hydrolysis of ranunculin gives rise to anemonin in Ranunculaceae, the buttercup family, and hydrolysis of sinigrin in plants in the mustard family Brassicaceae yields allyl isothiocyanate. Although one death is attributed to prolonged contact with sinigrin in mustard plaster,[254] exposures to primary irritants in Brassicaceae and Ranuculaceae usually are mild. Alternatively, dermatitis can occur without contact, as in cases of airborne contact dermatitis, in which typically exposed sites are the upper eyelids, neck, uncovered extremities, including antecubital fossae, and other skin folds[63,310] (Chap. 29).

Phorbol esters found in spurges (Euphorbiaceae) are contained in milky sap that is capable of producing erythema, desquamation, and bullae. The saps of some species are more irritating than others.[100] For instance, the manchineel tree *(Hippomane mancinella),* found in the Caribbean and Florida, once was planted on graves to deter grave robbers, and juice from the tree has been used to brand animals and to blind people.[254] In addition to dermal and ocular injury, ingestion of some spurges can induce severe GI injury. Poinsettia *(Euphorbia pulcherrima),* crown of thorns *(E. splendens),* candelabra cactus *(E. lacteal),* and pencil tree *(E. tirucalli)* are spurges found in the home as holiday or other ornamentation that rarely produce serious injury, despite reputations to the contrary. The poinsettia plant, for instance, gained a reputation of significant toxicity based on a single, inadequately documented case report from Hawaii in 1919, involving the death of a 2-year-old child. In a subsequent case, an 8-month-old child developed oral mucosal burns after chewing poinsettia.[99] Contact dermatitis, irritation of mucous membranes, and GI complaints (eg, nausea, vomiting, and abdominal pain)[78,99] are rare findings among the many reported exposures to poinsettia.[212]

Allergic contact dermatitis results from type IV hypersensitivity response and, unlike irritant dermatitis, requires repeat exposures to the agent before symptoms manifest. The most infamous of these xenobiotics are the urushiol oleoresins derived from catechols that are found in *G. biloba* (Ginkgoaceae) and members of the Proteaceae (eg, *Macadamia integrifolia*) and the Anacardaceae.[105] The latter family is notable for inclusion of poison ivy *(Toxicodendron radicans),* poison oak *(T. toxicarium, T. diversilobum),* and poison sumac *(T. vernix),*[67,116,117,233,339] as well as mango *(Mangifera indica),* pistachio *(Pistacia vera),* cashew *(Anacardium occidentale),* and Indian marking nut "Bhilawanol" *(Semecarpus anacardium).*[144] Upon first exposure, urushiol resins penetrate the skin and react with proteins to form antigens to which the body forms antibodies. Upon reexposure to urushiol resins, inflammatory mediators are released, leading to urticaria, itching, swelling, and pain. In extreme cases, these reactions can progress to type I hypersensitivity, as demonstrated by a 6% rate of anaphylaxis to mango among 580 patients who previously had mango-induced contact dermatitis.[8] Cross-reactivity between allergens is possible, and particular vigilance is required in sensitive individuals.[113,160,230] Prevention by removal of exposed objects that act as fomites for the oils and use of protective ointments are appropriate.[233,356] Therapy includes washing with soap and water and corticosteroid creams and, for those frequently exposed, desensitization (Chap. 29).[115,257]

Allergic contact dermatitis is the most common plant-induced occupational injury. In the United States, 33% of 462 floral shops surveyed reported that at least one employee had developed contact dermatitis.[310] Reactions are reported following exposure to tulips, *Narcissus,* Peruvian lily (*Alstroemeria* spp), and primroses (*Primula* spp). Exposure to the glycoside tuliposide A results in "tulip fingers," the dry, painfully fissured hyperkeratosis of fingers observed in horticultural workers who chronically handle tulips.[172] Upon hydrolysis, this compound yields α-methylene-butyrolactone, the true allergen. Cross-reactivity is possible among some of these xenobiotics. *Alstroemeria* spp, a common ornamental called *Peruvian lily,* contain tuliposide A and thus can cross-react with antigens in those persons already allergic to tulips, producing an allergic contact dermatitis. Primin (2-methoxy-6-*n*-pentyl-*p*-benzoquinone) from members of the Primulaceae[62,225] was responsible for the most frequently reported allergic plant dermatitis in northern Europe until workers refused to stock primroses. The "wood cutters dermatitis" of loggers occurs with development of sensitivity to compounds in liverwort (*Frullania* spp), which is cross-reactive to ursinic acid in lichens and mosses found on the wood.[358] Cross-reactivity with common weeds such as ragweed (*Ambrosia* spp) or dandelion (*Taraxacum* spp) initiate the risk of hypersensitivity from members of the Composite family. A myriad of other types of plants are involved in producing occupational dermatitides.[134,189,190,279,308]

Sensitivity to Compositae (daisy family) involves more than 600 sesquiterpene lactones in at least 200 of the 25,000 species in the family and is as ubiquitous as the distribution of species. *Chrysanthemum* allergy is a common occupational hazard in Europe,[153,334]

Direct photosensitivity dermatitis is produced when compounds such as psoralen or other linear furocoumarins come into direct contact with the skin or is digested and becomes bloodborne to dermal capillary beds, where it interacts with sunlight.[65] These photosensitizing agents are activated by ultraviolet A (320–400 nm), producing singlet oxygen and DNA adducts. In addition to severe sunburnlike symptoms (erythema, epidermal bullae), hyperpigmentation lasting for several months may result from exposure to these compounds. The mechanism by which this reaction is produced is unknown, but depletion of glutathione is postulated to indirectly stimulate melanogenesis by disinhibiting the normally suppressant tyrosinase.[87,310] More than 200 of these xenobiotics have been identified in at least 15 plant families, including food sources, such as Apiaceae (anise, caraway, carrot, celery, chervil, dill, fennel, parsley, and parsnip), Rutaceae (grapefruit, lemon, lime, bergamot, and orange), Solanaceae (potato), and Moraceae (figs) family.[229,310] A 45-year-old woman died of complications of severe burns received in a tanning salon following exposure to psoralen,[87] but most other human reactions are sequelae to handling crop plants or retail produce. Humans using St. John's wort *(H. perforatum)* may be susceptible to this syndrome.[93,139,202]

Hepatogenous photosensitivity is produced when a xenobiotic that normally is harmlessly ingested, absorbed, and hepatically excreted gains access to the peripheral circulation through failure of a liver excretion or detoxification mechanism. An example is

the photosensitivity that occurs when phylloerythrin, a product of chlorophyll digestion normally eliminated in the bile, accumulates in the blood as a result of liver dysfunction. The cyanobacterium *Microcystis aeruginosa,* as well as the plants *Lantana camara, Tribulus terrestris,* and *Agave lecheuilla,* reportedly cause this type of photosensitization in animals.[119]

SUMMARY

Plant xenobiotics, as well as therapeutic ingredients, can be organized using a pharmacognosy approach. Examples are provided in which the toxin has therapeutic use (colchicine, taxine, physostigmine, pilocarpine, and others). Some xenobiotics act directly or are metabolized to toxic principals (tremetone), whereas others are toxic through secondary contact in animal meat or milk (coniine, tremetone, nitrates, pyrollizidine alkaloids, and ptaquiloside).[192,277,323]

This analysis should not lead to the false conclusion that all toxic plants, all xenobiotics in plants, or all toxic mechanisms are known. Some reassurance can be achieved by excluding exposure to most life-threatening plants and plant xenobiotics or ascertaining whether a common exposure is toxic. This determination can be aided by basic taxonomy while awaiting expert input. Management should balance the relative risks of using invasive gastric emptying and use of activated charcoal if the plant induces sedation or vomiting or is nontoxic. Potentially fatal ingestions warrant gastric emptying in addition to standard decontamination with activated charcoal and supportive measures. Xenobiotics from sodium channel effectors, cicutoxin, or high-dose belladonna alkaloids necessitate expert toxicologic care and consultation for cardiac support devices and hemodialysis, respectively. Physostigmine should be at hand for serious anticholinergic toxicity. Seizures can be controlled with benzodiazepines, with knowledge that some plants may require pyridoxine (Ginkgo seeds) or possibly thiamine (ginkgolides, ptaquilosides). Hepatotoxicity should be treated empirically with *N*-acetylcysteine. Other xenobiotic-specific measures are noted throughout this chapter, but most patients require supportive management, the intensity of which is dictated by the patient's condition and plant identification. Laboratory diagnostic assays are published for many plant xenobiotics but in most cases are impractical to perform.

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