Plant Toxin

Plant and bacterial toxins are typically very potent and have no inherent tumor selectivity as their receptors are expressed on many cell types.

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Related terms:
Antibody, Protein, Toxin, Ingestion, Immunotoxin, Mycotoxin, Toxicity, Intoxication, Ricin, Bacterium

Plant Toxins

Ahmed Mohamed Galal Osman, ... Ikhlas A. Khan, in Foodborne Infections and Intoxications (Fourth Edition), 2013

Introduction

Food poisoning caused by plant toxins has been thoroughly documented for many decades. Intoxication due to food contamination by poisonous plants has been associated with several different classes of plant constituents. Furthermore, the upsurge in usage of a number of dietary supplements and traditional herbal medicines has been associated with health risks due to the intrinsic or extrinsic presence of phytotoxins, in addition to their possible adverse interactions with prescription drugs. The majority of plant species in the world are not edible, largely owing to the existence of toxins they produce. The process of domestication has diminished the levels of these toxic compounds over time. As a result, the plant foods we consume today are far less toxic than their wild parents. Plant toxins are usually secondary metabolites that are produced and secreted by plants. These metabolites are either accumulated in the tissues or deposited on the plant surface. Levels of toxic substances vary considerably in plants for several reasons, including ontogenic, ecotypic, genotypic, and chemotypic factors.

Phytotoxic food poisoning occurs for the following reasons:

1. *Inedible plants*: Certain wild plants, such as wild mushrooms and giant elephant ears, contain potent toxins that are not easily destroyed by cooking. These wild plants may be inadvertently ingested as edible plants.
2. *Edible plants without proper processing or cooking*: Certain food plants such as green beans and the cyanogenic plants, namely bitter apricot seeds, need sufficient heating to destroy the toxic substances. For other plants such as cassava and bamboo shoots, toxic cyanide can be removed more effectively by soaking in water or by cutting the plant into small pieces before cooking.
3.

Heat-resistant toxins: Consumption of food plants containing toxins that are resistant to heat of cooking, for instance green potatoes or their sprouts.

The symptoms of poisoning extend from mild gastrointestinal disorders to severe effects on the central nervous system. The degree of intoxication is contingent on the amount of the plant consumed, the concentration of toxins present, and the susceptibility of the individual.

One of the ecological functions of phytotoxins is the defense against potential enemies, such as insects, pathogenic microorganisms, and herbivorous animals. In addition, phytotoxins may, as their primary role, promote the survival of the plant against abiotic environmental stresses such as ultraviolet radiation [1].

Chemically, plant toxins display a diverse range of structures from small organic molecules to large peptides and proteins. This chapter will provide an overview of the plant toxin classes, including alkaloids, cyanogenic glycosides, glucosinolates, isothiocyanates, and furanocoumarins that are most frequently encountered in food poisoning. The discussion will focus on their natural occurrence, chemistry, adverse effects, implications on health, and clinical relevance. Particular emphasis will be placed on pyrrolizidine alkaloids as they are the most common and geographically widespread cause of phytotoxic food poisoning.

Poisoning: Overview and Statistics

A.L. Jones, P.I. Dargan, in Encyclopedia of Forensic and Legal Medicine (Second Edition), 2016

Plants

Plant poisoning is globally uncommon but locally popular in some areas. For example, in Sri Lanka there are thousands of cases each year of yellow oleander (*Thevetia* peruviana) poisoning and it causes 4.1% of deaths due to poisoning. Ingestion of oduvan (*Clistanthus collinus*) is a common self-harm practice in India. *Datura* strammonium poisoning has been reported in the tropics and is increasing in prevalence in the West because of the known hallucinogenic properties. In India, plant poisoning accounts for 1.5% of calls to a poisons center; *Datura* is the most commonly ingested plant being reported.

Plant Toxins and the Heart

Subramanian Senthilkumaran, ... Ponniah Thirumalaikolundusubramanian, in Heart and Toxins, 2015

5.12.1 Prevention of Plant Poisoning

Plant poisoning contributes to 3 to 10% of all poisoning. Since plant toxins affect various parts of the body including risk for life, the best strategy is to avoid plant poisoning altogether. Some suggestions for prevention include the following:

- Children and the public have to be educated and informed “never put any plant parts/materials (e.g., twigs, berries, flowers, leaves) in the mouth” and make them aware that it is not safe to do so.
- People should be informed not to suck nectar from flowers or make tea or decoction from unknown plant materials.
-

People should be aware of the names of household plants and should learn about new plants if brought home.

- Keep plants and plant materials out of the reach of the children.
- Educate the community not to be lured by folklores and proverbs on plants or plant materials.
- Avoid exposure to smoke from burning plant materials as the toxins may enter the system through inhalation.
- Inform the community that heating or cooking toxic plants or plant materials does not destroy the toxins or toxic substances always.
- When someone develops symptoms and signs of toxicity following exposure to plants, bring all parts of the plant sample when the patient is brought for treatment.
- Educate the community not to apply plant medicine over raw surfaces of the skin and mucosa, as the toxins may get absorbed transcutaneously.

Acute and Subacute Toxicities of African Medicinal Plants

Gerald Ngo Teke, Victor Kuete, in Toxicological Survey of African Medicinal Plants, 2014

5.1 Introduction

Plant poisoning in animals is usually accidental, and most frequently occurs during unfavorable conditions when pastures are poor due to drought, veldt fires, and overstocking and trampling of the grazing. In humans, it may be accidental or intentional. Accidental poisoning in humans may be due to confusing poisonous with edible plants, contamination of food with poisonous plants, or by the use of plants as remedies. Toxic principles in plants can affect the entire spectrum of organ systems; the dominant effect may depend on the condition, growth stage or part of the plant, the amount consumed, and the species and susceptibility of the victim. Considering the fact that herbal medicine as preparations derived from naturally occurring plants with medicinal or preventive properties are a major component in all indigenous peoples' traditional medicine across Africa and the world at large, pharmacological and toxicological evaluations of medicinal plants are essential for drug safety and development. The main types of toxicological evaluations include: acute toxicity, subacute toxicity, subchronic toxicity, and chronic toxicity studies. We will emphasize the acute and subacute toxicities of African medicinal plants.

Acute toxicity refers to those adverse effects occurring following oral or dermal (topical) administration of a single dose of a substance or medicinal plant extract, or multiple doses given within 24 h, or a single uninterrupted exposure by inhalation over a short period of time [1,2]. Subacute toxicity is an adverse effect occurring as a result of repeated daily dosing of a chemical, or exposure to the chemical, over a period of several days or weeks [3]. The study of the toxicities of medicinal plants is important in predicting their safety. Most of the methods used in the evaluation of acute and subacute toxicities of chemicals are based on the routes of administration/exposure to humans: oral; dermal; intraperitoneal (IP), inhalation; and the eye irritation assays. The inhalation and eye irritation tests are not very common in Africa [4–7]. In most acute toxicity tests, each test animal is administered a single (relatively high) dose of the test substance, observed for 1 or 2 weeks for signs of

treatment-related effects, then necropsied. Some acute toxicity tests (such as the "classical" LD_{50} test) are designed to determine the mean lethal dose of the test substance. The median lethal dose (or LD_{50}) is defined as the dose of a test substance that is lethal for 50% of the animals in a dose group.

Hepatic Toxicology

S.B. Yee, R.A. Roth, in Comprehensive Toxicology, 2010

9.27.6 Conclusions

PA phytotoxins, found in PA-containing plants throughout the world, represent a significant health risk to both animals and humans. For toxicity to occur, PAs must be bioactivated in the liver by CYPs to toxic pyrrolic metabolites. Differences in bioactivation and detoxification underlie the diverse species susceptibility to PA intoxication. Exposure to PA-contaminated food sources or PA-containing alternative medicines and dietary supplements results primarily in liver injury, often marked by the development of HVOD, leading to cirrhosis and liver failure. Exposure to PAs can also result in extrahepatic toxicities, including pulmonary hypertension, and potentially cancer. Careful monitoring of food sources, development of rapid and efficient diagnostic techniques, better recognition of the symptoms of PA poisoning, consumer education to the dangers of PAs (especially to PA-containing alternative medicines), and more definitive regulations concerning PA intake will lessen the public health risk to these hepatotoxic plant toxins.

Chemical Ecology

Hisakazu Yamane, ... Hideaki Oikawa, in Comprehensive Natural Products II, 2010

4.08.3.4 Terpenoids

Terpenoid phytotoxins, including diverse fungal diterpenoids and sesquiterpenoids, are produced by many phytopathogenic fungi. In general, the biosynthesis of terpenes starts with the formation of the molecular skeleton with terpene cyclase to afford cyclic hydrocarbon, which is usually hydroxylated and subsequently modified by alkylation, acylation, and glycosylation. Some of these phytotoxins show useful biological activity, and are used as plant growth regulators in agriculture and as biochemical agents for plant and cell physiology (**Figure 34**).

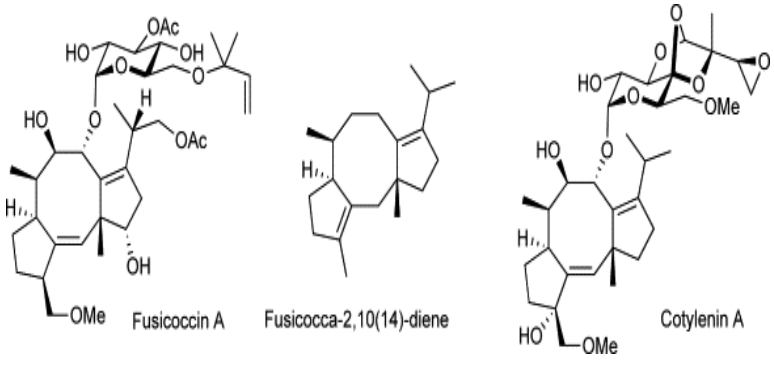

Figure 34. Structures of terpenoid phytotoxins.

Diterpene glucoside fusicoccin is produced by *Phomopsis* (*Fusicoccum*) *amygdali* as a principal toxin implicated in the wilting disease of almond and peach in Italy, and a fusicoccin-producing *P. amygdali* Niigata 2 is newly found in a peach *Fusicoccum* canker fungus in Japan. Fusicoccin A shows potent phytohormone-like activities and is used as a biochemical agent for plant physiology. It permanently activates plasma membrane H^+-ATPase in all higher plants and its mode of action is investigated by X-ray crystallographic analysis of the ternary complex of a plant 14-3-3 adapter protein, fusicoccin, and a synthetic phosphopeptide of the C-terminus of H^+-ATPase.[318] Current biosynthetic studies of fusicoccin aglycone indicate the presence of the genuine biosynthetic tricyclic hydrocarbon intermediate (+)-fusicocca-2,10(14)-diene in the mycelia of *P. amygdali* Niigata 2.[319] Cloning of fusicoccadiene synthase gene and its expression allowed elucidation of the highly unusual multistep conversion of C_5 isoprene units into fusicoccadiene, showing that fusicoccadiene synthase possesses both prenyltransferase and terpene cyclase activities.[320] Fusicoccin biosynthetic gene cluster has been identified by chromosomal walking. In connection with structure and bioactivities of fusicoccin, its sole congener cotylenin A, a plant growth regulator isolated from a fungus *Cladosporium* sp. 501-7W, is originally characterized as a potent differentiation-inducing substance in mammalian cells and an antitumor agent against human lung carcinoma cells.[321]

The plant hormones gibberellins $GA_{1/3}$ and GA_4 are produced by *Gibberella fujikuroi*, a Bakanae disease fungus of rice, and *Sphaceloma* manihoticola, a super-elongation disease fungus of cassava, respectively. Fungal gibberellins GA_3 and GA_4 are used as plant growth regulators for horticultural production. The biosynthesis of gibberellins in *G. fujikuroi* is determined at the molecular level; biosynthetic enzymes responsible for GA_1 formation include only *ent*-kaurene synthase and four cytochrome P-450 enzymes.[322] This pathway is totally different from the corresponding plant counterpart. Another gibberellin-producing fungus *Phaeosphaeria* sp. L487, known as one of the phytopathogenic fungi, produces GA_1 in plant-like gibberellin biosynthetic pathway through GA_9 and $GA_{4/20}$. Its *ent*-kaurene synthase in the GA_1 biosynthesis catalyzes the formation of *ent*-kaurene from GGDP through *ent*-copalyl diphosphate[323] (**Figure 35**).

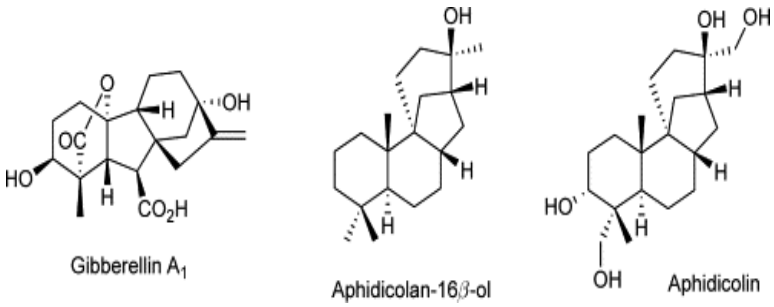

Figure 35. Structures of terpenoid phytotoxins (continued).

Aphidicolin, a well-known biochemical agent that functions as a specific inhibitor of DNA polymerase α, is produced by *Phoma* betae, a fungal pathogen of beet. Its biosynthetic precursors, including aphidicolan-16β-ol, were elucidated by treatment of *P. betae* with cytochrome P-450 inhibitors.[324] From this fungus, a cDNA encoding aphidicolan-16β-ol synthase was cloned, and its recombinant fusion protein was found to catalyze the direct formation of 16β-ol from GGDP through *syn*-copalyl

diphosphate.[325] Furthermore, chromosomal walking adjacent to the aphidicolol synthase gene allowed to identify the aphidicolin biosynthetic gene cluster.

Diterpene phytotoxins sphaeropsidins A–F, tri- and tetracyclic unrearranged pimarane skeleton, are isolated from *Sphaeropsis sapinea*, a fungus that causes a canker disease of Italian cypress. Sphaeropsidin A is the major toxic substance showing nonhost-selective phytotoxic activity[326] (**Figure 36**).

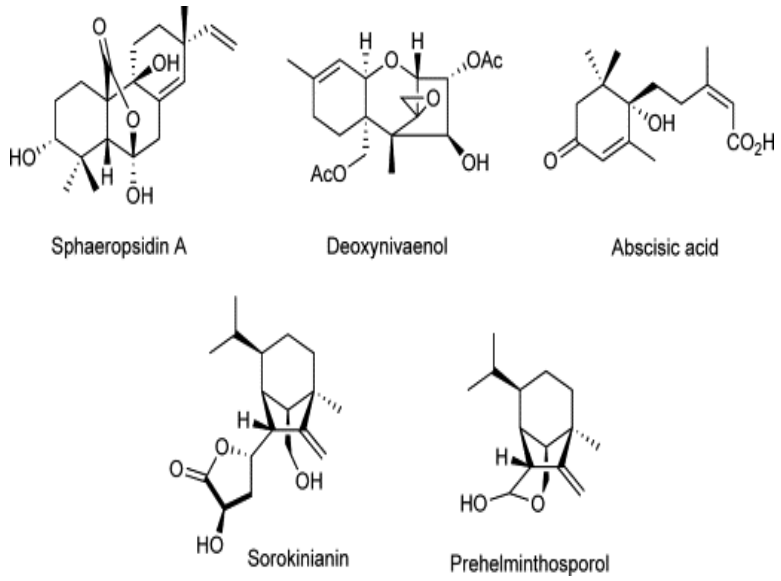

Figure 36. Structures of terpenoid phytotoxins (continued).

Trichothecene phytotoxins such as deoxynivaenol are produced by some phytopathogenic species of *Fusarium*. Biosynthetic studies on this phytotoxin show that a bicyclic hydrocarbon intermediate trichodiene, formed from FDP, and the subsequent oxidations with a series of cytochrome P-450s such as Tri4 give isotrichodiol, isotrichotriol, and deoxynivaenol.[302] The gene cluster responsible for trichothecene biosynthesis was found in *Fusarium* and *Myrothecium* fungi.

Another phytohormone abscisic acid is produced by phytopathogenic fungi *Cercospora* cruenta, *C. cruenta*, and *Botrytis cinerea*. These fungi biosynthesize abscisic acid by oxidation of ionylideneethane with molecular oxygen following cyclization of allofarnesene.[327] This direct pathway via ionylideneethane and subsequent ionylideneethanol is common among abscisic acid-producing fungi.

Sorokinianin, an unusual sesquiterpenoid, is isolated from *Bipolaris sorokiniana*, a fungal phytopathogen that causes spot blotch or foot and root rot diseases in wheat, barley, and oat. It is biosynthesized from phytotoxic prehelminthosporol and C_3 unit derived from oxaloacetic acid.[328] Prehelminthosporol itself was isolated as a phytotoxin of *Helminthosporium* sativum. Sorokinianin is more phytotoxic than prehelminthosporol in inhibiting the germination of barley seeds.

Introduction to Forensic Plant Science

Jane H. Bock, David O. Norris, in Forensic Plant Science, 2016

3.1.1.1 Colchicine

One plant poison favored by the Greeks and Romans came from a species of crocus (*Colchicum* spp., family: Iridaceae). These plants are the source of the alkaloid drug colchicine (Figure 1.6) that sometimes is prescribed today for the treatment of gout, arthritis, and constipation-predominant irritable bowel syndrome. Colchicine is known to most biologists as an inhibitor of cell division. The drug comes from crocus corms and seeds. Colchicine can be deadly if misused as there is no known antidote for colchicine poisoning. Multiple system failures occur in 24–72 h after consumption of a lethal dose. An unfortunate case of colchicine poisoning occurred in Colorado when a thief misread the label on a bottle he had stolen from a doctor's safe, and he died after ingesting the pills (Bock, personal observation).

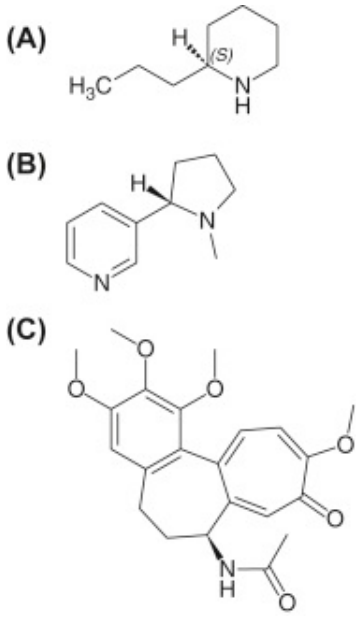

Figure 1.6. Alakaloid toxins. (A) Coniine; (B) Nicotine; (C) Colchicine.

Immunotoxin Therapy for Brain Tumors

V. Chandramohan, ... D.D. Bigner, in Translational Immunotherapy of Brain Tumors, 2017

Ricin

The plant toxin ricin is extracted from the seeds of *Ricinus communis*. Ricin is synthesized as a 576 amino acids precursor protein, consisting of N-terminal signal sequence (35 amino acids), A chain (267 amino acids), linker (12 amino acids), and B chain (262 amino acids)[40,41] (Fig. 10.2). During biosynthesis, the signal sequence and linker are removed to yield the mature protein, which is held together by a single disulfide bond. Ricin A chain carries the rRNA-specific N-glycosidase activity and the B chain, which is a d-galactose- and *N*-acetylgalactosamine-specific lectin that binds to the galactose-containing receptors on the cell surface.[42,43] Upon binding to its cognate receptor, ricin is internalized by endocytosis and undergoes retrograde transport from Golgi to endoplasmic reticulum (ER).[44] Cleavage of ricin A chain from B chain is catalyzed by the enzyme protein disulfide-isomerase in the lumen of ER; ricin A chain then enters the cytoplasm by utilizing the ER associated protein

degradation pathway.[44] Once the A chain reaches the cytosol of the target cell, it enzymatically attacks the adenine residue at position 4324 within the 28S rRNA in the 60S ribosomal subunit, leading to the inactivation of ribosomes and protein synthesis inhibition.[18,45,46] ITs are generated by chemical cross-linking of the intact ricin or the recombinant ricin A chain to antibodies directed to antigens overexpressed on the tumor cell surface.

Harmful and Protective Effects of Terpenoids from African Medicinal Plants

Armelle T. Mbaveng, ... Victor Kuete, in Toxicological Survey of African Medicinal Plants, 2014

19.3 Toxic Terpenoids and Their Mode of Action

Chemically, plant poisons are not only peptides but also low molecular weight compounds, belonging to alkaloids, terpenoids, phenolics, or other secondary metabolites. Plants produce a wide variety of secondary metabolites which can interfere with the biochemistry and physiology of herbivores on the one hand and some with bacteria, fungi, viruses, and even competing plants on the other hand [13]. Plants produce and accumulate not only single entities but mixtures of secondary metabolites that mostly belong to several classes [13]. The plants' defenses against herbivores include repellence, deterrence, toxicity, and growth inhibition as well as toxicity against microorganisms [13].

Toxins and poisons are classified in four categories according to their oral toxicity determined in rat experiments:

1. Class Ia: extremely hazardous (5 mg or less per kilogram body weight).
2. Class Ib: highly hazardous (5–50 mg/kg body weight).
3. Class II: moderately hazardous (50–500 mg/kg body weight).
4. Class III: slightly hazardous (500 mg and more per kilogram body weight) [13].

In this classification, toxins, which fall into the classes Ia, Ib, and II, interfere with central functions in animals. The most poisonous substances are neurotoxins which affect the nervous system, followed by cytotoxins and metabolic poisons that disturb liver, heart, kidneys, respiration, muscles, and reproduction. It has been shown that the morbidity and mortality associated with exposure to toxic terpenes is largely related to the degree of CNS depression when the compound is aspired [14]. However, it should be noted that morbidity induced by terpenoids is extremely low.

19.3.1 Neurotoxicity

A seizure is an episode of neurologic dysfunction caused by abnormal neuronal activity that results in a sudden change in behavior, sensory perception, or motor activity. The so-called "epilepsy" is the recurrent, unprovoked seizure from known or unknown causes, while "ictus" describes the period in which the seizure occurs, and "postictal" refers to the period after the seizure has ended, but before the patient has returned to his or her baseline mental status [9]. It has been demonstrated that neurotoxins can affect important ion channels of neuronal cells, such as Na^+, K^+, and Ca^{2+} channels, either by activating or inactivating them permanently [13]. Both actions will stop neuronal signal transduction and thus block the activity of the CNS but also neuromuscular signaling [13], which eventually leads to paralysis of both striated and smooth muscles of heart, lungs, and skeleton. A special case is the Na^+, K^+-ATPase, which is the most important ion pump in neuronal and other cells to

maintain an ion gradient important for action potentials and transport mechanisms [13]. Cardiac glycosides, the secondary metabolites used in the treatment of congestive heart failure and cardiac arrhythmia, occurring in several plant families and even in toad skins (genus *Bufo*), are strong inhibitors of this pump. Due to the fact that this pump is extremely important, cardiac glycosides are considered to be toxins of class Ia. It should be noted that drugs such as ouabain (**1**) and digoxin (**2**) are cardiac glycosides (Figure 19.1). However, compound **1** from the foxglove plant is used clinically, whereas compound **2** is used only experimentally due to its extremely high potency. The sesquiterpenes 13-*O*-acetylsolstitialin A (**3**) and cynaropicrin (**4**) (Figure 19.1), isolated from *Centaurea* solstitialis, were found to be responsible for the ability of the plant to cause neurodegenerative changes in the brain of horses [15].

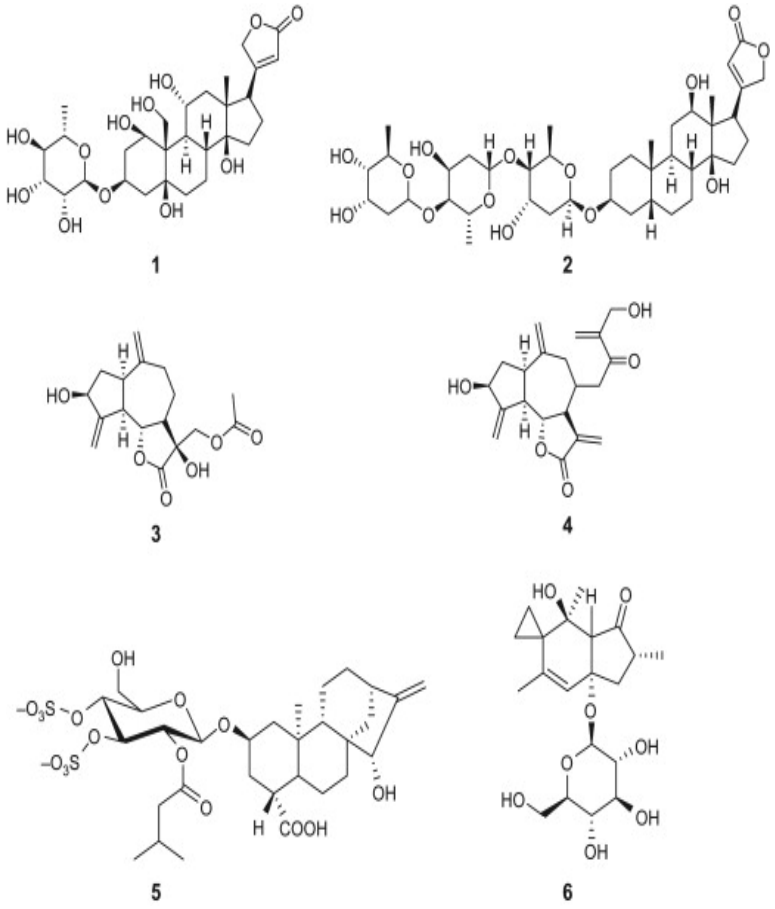

Figure 19.1. Chemical structures of some known toxic terpenoids. Ouabain (**1**), digoxin (**2**), 13-*O*-acetylsolstitialin A (**3**), cynaropicrin (**4**), atractyloside (**5**), ptaquiloside (**6**).

19.3.2 Inhibition of Cellular Respiration

In cellular respiration, taking place in mitochondria, ATP is generated. This energy is essential for all cellular and organic functions making respiration a vulnerable target in animals. Plant metabolites can attack this target with HCN, which binds to iron ions of the terminal cytochrome oxidase in the mitochondrial respiratory chain [13]. HCN does not occur in a free form, but is stored as cyanogenic glycosides in plant vacuoles [13]. A plant's cytosolic enzymes, such as β-glucosidase and nitrilase,

hydrolyze the cyanogenic glycosides and the extremely toxic HCN is released [13]. The diterpene atractyloside (**5**) (Figure 19.1) is a potent inhibitor of the mitochondrial ADP/ATP transporter and thus inhibits the ATP supply of a cell [13]. Atractyloside is an inhibitor of the adenine nucleotide translocator that inhibits oxidative phosphorylation by blocking the transfer of adenosine nucleotides through the mitochondrial membrane [16].

19.3.3 Cytotoxins

A cytotoxin is any substance that has a toxic effect on an important cellular function, such as venom or a chemical agent. An important target in this context are biomembranes, which regulate the import and export of metabolites and ions [13]. Membrane fluidity and integrity can be severely disturbed by both steroidal and triterpenoid saponins. Saponins are usually stored as inactive bidesmosidic saponins in plant vacuoles; upon wounding and decompartmentation, they are converted into the membrane-active monodesmosidic saponins, which are amphiphilic holding detergent activities [13]. Within cells, other important targets include several enzymes and proteins but also DNA/RNA.

19.3.4 Alkylating and Intercalating DNA Toxins

An unstable glycoside ptaquiloside (**6**) (Figure 19.1), containing a reactive cyclopropane ring, has been isolated from ferns and is a potent carcinogenic agent [17]. Many plant alkaloids were also found to act as alkylating agents (see Chapter 21).

19.3.5 Toxins of Skin and Mucosal Tissues

Phytochemicals also can affect the skin and mucosal tissue of animals. The diterpenes known as phorbol esters from the Euphorbiaceae and Thymelaeaceae, which resemble the endogenous signal compound diacylglycerol, are activators of the key enzyme protein kinase C [13]. When in contact with skin, mucosal tissue, or the eyes, they cause severe and painful inflammation, with ulcers and blister formation [13].

GABAA Receptor Structure–Function Studies: A Reexamination in Light of New Acetylcholine Receptor Structures

Myles H. Akabas, in International Review of Neurobiology, 2004

d A picrotoxin binding site is located near the cytoplasmic 2′ position in the channel

Picrotoxin is a plant toxin that noncompetitively inhibits $GABA_A$ receptors (Newland and Cull-Candy, 1992; Ticku *et al*., 1978). It binds in a use-dependent manner indicating that it preferentially binds in the open–activated receptor conformation (Newland and Cull-Candy, 1992). Picrotoxin's affinity is in the micromolar range, but it has slow on and off rates and thus an unexpectedly long bound duration (Newland and Cull-Candy, 1992). The toxin is uncharged and, therefore, its interaction is not voltage-dependent. At the single channel level, picrotoxin reduces burst duration and the number of openings per burst (Twyman *et al*., 1989b).

Several lines of evidence indicate that picrotoxin binds in the channel. Picrotoxin co-applied with $pCMBS^-$ protected a Cys substituted for α_1V257 (2′) from modification by $pCMBS^-$ but did not protect a Cys substituted for the adjacent, more extracellular channel-lining position, α_1T261 (6′), or any other channel-lining position (Xu *et al*.,

1995). Additional evidence that picrotoxin binds in the channel includes (1) substitution of phenylalanine at the 6′ position in α-, β-, or γ-inhibited picrotoxin block of $GABA_A$ receptors (Gurley *et al.*, 1995); (2) mutations in insect $GABA_A$ receptors at the 2′ position cause resistance to the cyclodiene insecticide dieldrin and also cause picrotoxin insensitivity (French-Constant *et al.*, 1993; Hosie *et al.*, 1995; Zhang *et al.*, 1994); (3) sulfhydryl-reactive insecticide derivatives react with 2′ engineered Cys (Perret *et al.*, 1999); (4) mutation of the 2′ proline in GABA ρ_1 alters picrotoxin block (Enz and Bormann, 1995); and (5) similar results are found in glycine receptors (Pribilla *et al.*, 1992; Shan *et al.*, 2001). Picrotoxin is a rigid, roughly spherical molecule that is ~9 Å in diameter. Its ability to bind at the 2′ level indicates that the open channel must be at least 9 Å in diameter from the extracellular end to the 2′ level (Xu *et al.*, 1995). The largest permeant anion is ~5.6 Å in diameter (Bormann *et al.*, 1987), which implies either that the channel narrows at a more cytoplasmic location or that anions permeate in a partially hydrated form. Because the ACh-receptor structure is in the closed state, the structure does not provide an answer to this issue.