Paper No. 01

Paper Title: Food Chemistry

Module-34: Natural plant toxicants

Our food contains, in addition to the many well-known major (protein, fat, carbohydrate, and fiber) and minor (vitamins, minerals, and nonessential compounds) nutrients, thousands of naturally present toxic plant compounds. Some are known or strongly suspected to cause cancer in laboratory animals and, thus, may be potentially carcinogenic in people. Many of these compounds are commonly termed "nature's pesticides" because they are often toxic to predators, such as insects and animals, thereby conferring a competitive advantage to the plant that produces them. Other natural toxins in plants have no known role. Although these chemicals are in every meal we eat, they have received little attention compared to that given to minute residues of synthetic chemicals such as PCBs and pesticides. Our food contains significantly greater amounts of natural plant toxins and carcinogens than the synthetic kind, and our bodies aren't able to distinguish between the two. Still, while popular notion remains that "natural is good," it is clear that natural toxins pose a far greater health risk than that posed by synthetic chemicals in our foods.

Natural Plant Toxins in Foods

The following are some of the most well-studied and characterized plant toxins.

Canavanine

Despite the notion that they are the ultimate health food, alfalfa sprouts contain up to 15,000 ppm canavanine. Canavanine is produced in other legumes as well, such as the jack bean. It is an analog of arginine and, as such, can substitute for this amino acid in cellular proteins, thereby compromising their function. Canavanine inhibits the enzyme nitric oxide synthetase and induces heat-shock proteins in human cells *in vitro*. Due to its action as an anti-metabolite, it is under current consideration as an antitumor drug in combination with other anti-metabolites such as 5-fluorouracil, but has not yet been tested for carcinogenicity. Canavanine is suspected of causing autoimmune disorders in people, such as lupus erythematosus. Primates fed alfalfa sprouts develop a severe toxic syndrome resembling human lupus.

Cyanogenic Glycosides

Cyanogenic glycosides are cyanide-containing compounds naturally present in seeds from apples, apricots, cherries, peaches, pears, plums, quinces, and also in almonds, sorghum, lima beans, cassava, corn, yams, chickpeas, cashew nuts, and kirsch. High cyanide varieties, distinguished by their bitter taste, may contain over 600 ppm cyanide on a dry weight basis, while "sweet" varieties contain much less. There are several such cyanogenic glycosides, of which linamarin, amygdalin, and dhurrin are examples (Figure.34.1). In the 1970s, amygdalin, as laetrile, gained notoriety as a fad remedy and preventative for cancer and other ailments. Cyanogenic glycosides are toxic by virtue of the release of free hydrogen cyanide which occurs when the plant tissue is disturbed as during chopping, processing, or ingestion. These conditions initiate the hydrolysis of the glycoside by the action of β – glucuronidases and other enzymes naturally present in the plant tissue and in the intestinal lumen. The process also can be initiated by acid, but this doesn't appear to occur in the digestive tract to any great extent despite the acid environment in the stomach. Hydrolysis by β-glucuronidases produces the sugar and a cyanohydrin, the latter spontaneously or enzymatically degrades to form free hydrogen cyanide. The scheme of release of hydrogen cyanide is depicted in Figure 34.1.

Cyanide is one of the most acutely toxic chemicals. It binds to and inactivates heme enzymes, the most critical of which is mitochondiral cytochrome oxidase, resulting in an acute, life-threatening anoxia. The two-step therapy is initiated with sodium nitrite, which induces methemoglobinemia permitting the release of cyanide from heme proteins, followed by sodium thiosulfate, which acts as a substrate for rhodanese, an endogenous hepatic enzyme that catalyzes the conversion of free cyanide to the less toxic thiocyanate. Cases of acute human poisoning from the cyanide released from certain varieties of lima beans, cassava, and bitter almonds are a regular occurrence. Due to the importance as a subsistence crop in Africa and South America, cyanogenic glycosides in cassava probably represents the greatest health risk. Traditional methods of processing cassava, such as sun-drying, soaking, boiling, and fermenting, eliminate most of the cyanide. In addition to regular cases of human deaths, cyanogenic glycosides in cassava may be responsible for birth defects, endemic goiter, and "konzo," an upper myelopathic motor neuron disease endemic to East Africa. Cyanogenic glycosides also have been implicated as a causative agent of diabetes.

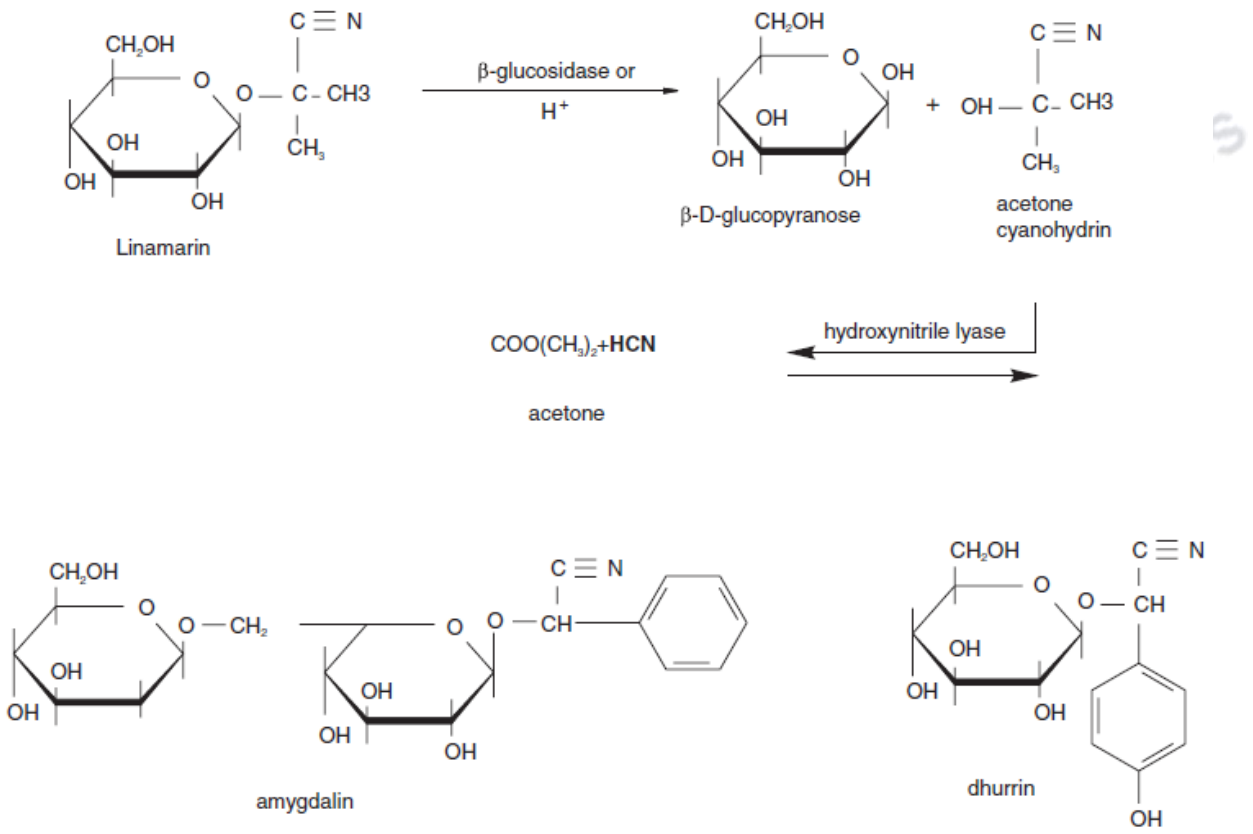


Figure 34.1. Mechanism of formation of cyanide from linamarin. Chemical structures of amygdalin and dhurrin.

Allyl Isothiocyanates

Allyl isothiocyanates are a group of major naturally occurring compounds that confer a pungent flavor to foods, such as mustard and horseradish, where it is present at about 50 to 100 ppm. It is also present at much lower levels in Brassica vegetables such as broccoli and cabbage, and in cassava and other tropical staple foods. In high doses, it is carcinogenic in rats, but it is nonmutagenic in bacteria. Isothiocyanates occur in cruciferous vegetables as glucosinolate conjugates that are hydrolyzed when the plant releases enzymes such as during chewing (Figure 34.2). Isothiocyanates are toxic goitrogens which inhibit binding of iodine in the thyroid gland. Because iodine is required for the formation of the critical thyroid hormones thyroxine (T4) and triiodothyronine (T3), isothiocyanate-induced hyperthyroidism (goiter) mimics iodine deficiency. Hyperthyroidism is a physiological response as the thyroid attempts to compensate for reductions in

both T4 and T3 production. Normal dietary exposures to isothiocyanate-containing foods releases milligram amounts of isothiocyanates. As in the case of cyanogenic glycosides, normal processing steps (chopping, rinsing, milling) results in a safe product. Endemic goiter is seen in geographical areas like India and Africa, where consumption of poorly processed foods is coincident with iodine deficiency.

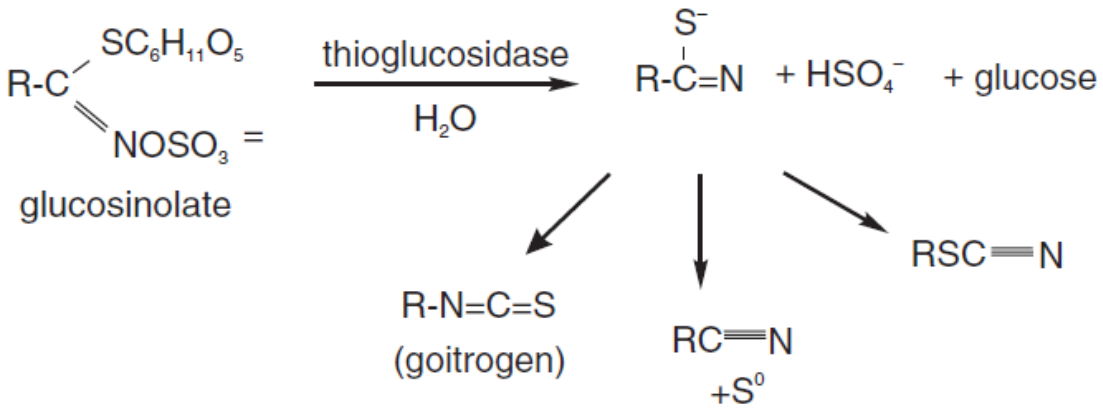


Figure.34.2. Enzymatic formation of goitrigenic isothiocyanate from glucosinolate

Hydrazines and Other Toxins in Edible Mushrooms

The three most commonly eaten mushrooms are the cultivated mushroom *(Agaricus bisporus)*, the shiitake mushroom *(Cortinellus shiitake*), and the false morel *(Gyromitra esculenta).* All contain substantial amounts of compounds in the hydrazine family (Figure 34.3), many of which are potent liver toxins and animal carcinogens. N-methyl-N formylhydrazine is commonly found in concentrations of 500 ppm and causes lung tumors in mice and hamstersl. People consuming a 100 g serving and, therefore, ingesting 50 mg would be getting very nearly the same dose on a per kilogram (kg) body weight basis as that giving cancer to mice upon sustained daily exposure.

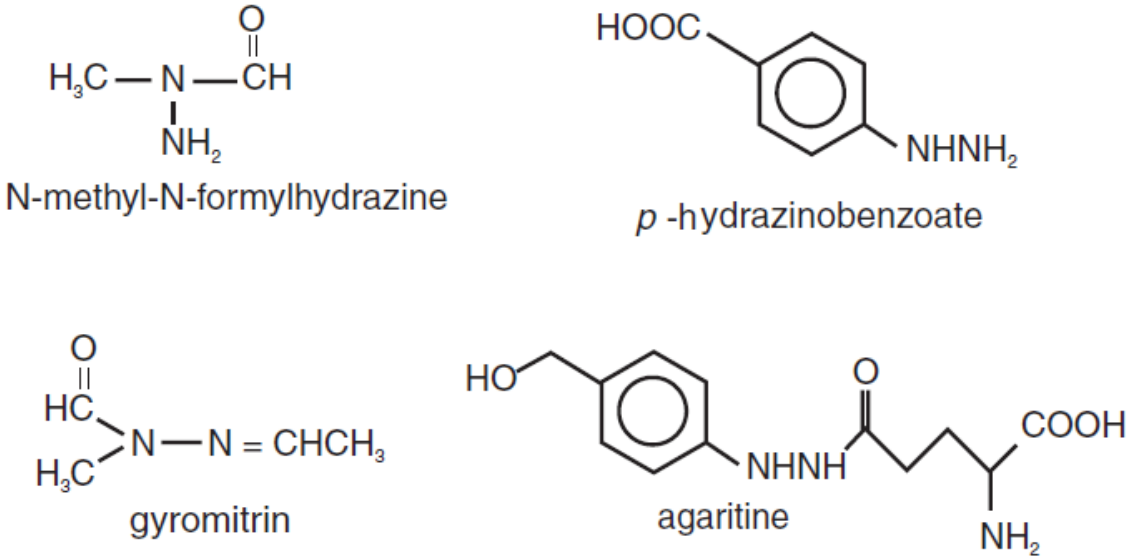


Figure.34.3. Carcinogenic hydrazine in commercial mushrooms

Shiitake mushrooms and the cultivated mushroom contain up to 3000 ppm agaritine. A metabolic product of agaritine (a diazonium derivative) is a potent carcinogen and a mutagen. Gyromitrin (acetaldehyde-N-methyl-Nformylhydrazone), the major carcinogenic hydrazine in the false morel, also is present in similar concentrations. Other carcinogenic hydrazines include *p* - hydrazinobenzoate (present in *A. bisporus* at 10 ppm) and 4-(hydroxymethyl) benzenediazoate

(HMBD), the latter shown to induce DNA strand breaks presumably through a carbon-centered, free-radical intermediate, a possible mechanism of the carcinogenic action of hydrazines in general.

Another carcinogenic hydrazine, methylhydrazine, is present in smaller concentrations (14 ppm). Whole mushrooms have been shown in numerous studies to cause cancer in laboratory animals, but whether they are a significant cause of cancer in people is uncertain.

Toxic Substances in Spices and Flavoring Agents

Safrole, estragole, myristicin, β−asarone, piperine, and isosafrole (Figure 34.4) are closely related alkenylbenzenes found in many spices, essential oils, and herbs. They also are present, in much lower levels, in parsnips, parsley, and sesame seeds. All are weak to moderate rodent hepatocarcinogens.

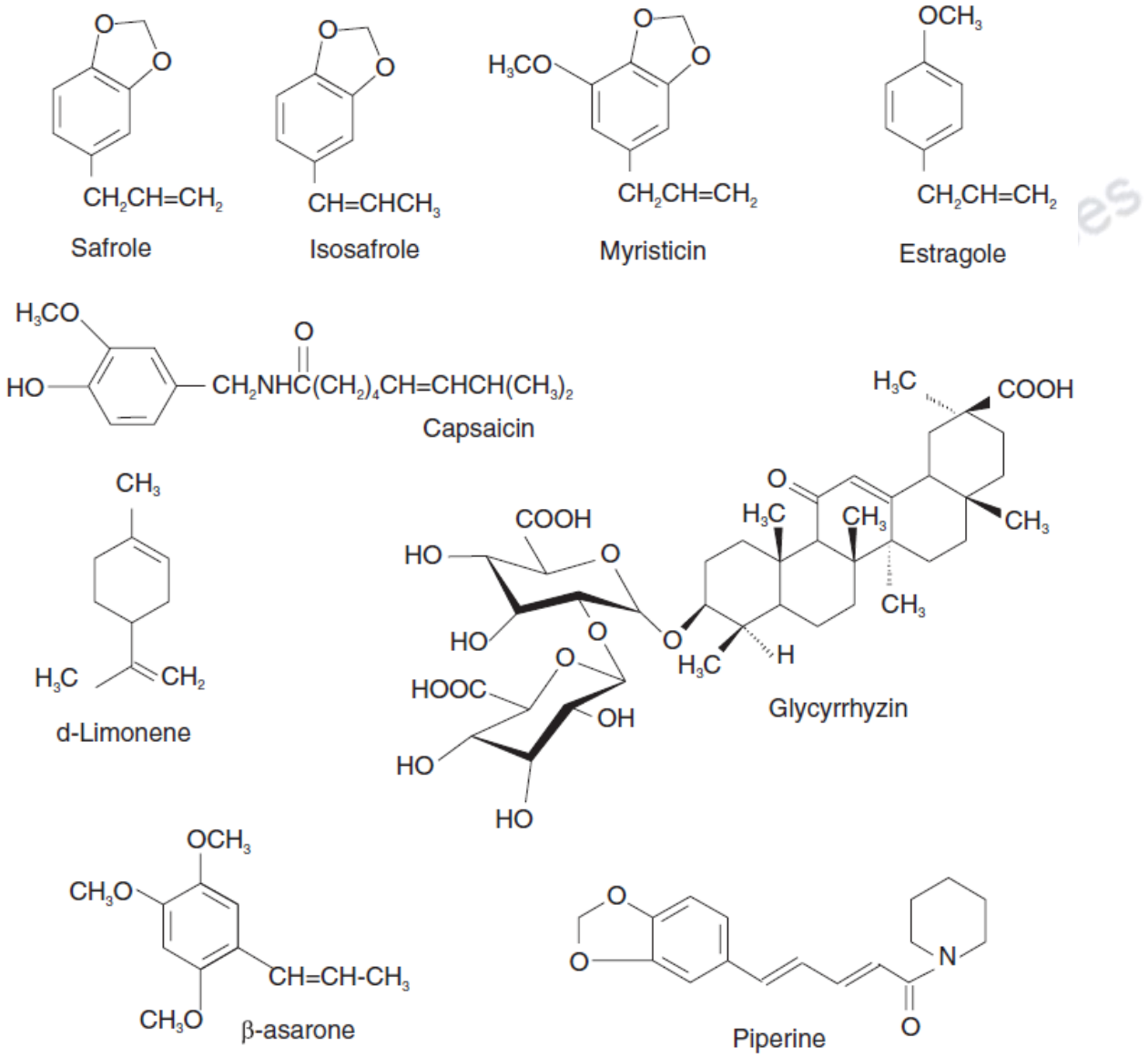


Figure 34.4. Natural toxins in spices and flavouring agents

Safrole is found in sassafras tea and makes up 85% of oil of sassafras (*Sassafras albidum*), which was once used to flavor root beer. It has been banned as a flavor additive since 1960, but is a minor, natural component of nutmeg, mace, star anise, cinnamon, and black pepper. Sassafras bark is an ingredient in filé powder used to make gumbo, a spicy Cajun dish. Estragole, a related aromatic flavor agent, is found in tarragon, basil, and fennel, and is likewise a weak carcinogen. Safrole is bioactivated to a DNA-binding species via hydroxylation of benzyl carbon, conjugation with

sulfate, and then alkylation of DNA with displacement of the sulfate group. Another route of bioactivation involving a rearrangement to electrophilic quinone methides has been identified for safrole and is presumed to occur with related flavor compounds. Epoxidation at the allylic side chain is another activation route identified for safrole, estragole, and eugenol. Epoxide intermediates of these compounds degrade to form covalent adducts with guanine *in vitro.*

Isosafrole, a component of ylang-ylang (*Cananga odorata*) oil, a flavorant and scent, is carcinogenic in mice. Many of these alkenylbenzenes interact with cytochrome P-450 (CYP) mediated metabolism. For example, both isosafrole and safrole are powerful inducers of 1A family CYP enzymes. Safrole and isosafrole also inhibit CYP 2E1 enzymes and, in so doing, protect against carbon tetrachloride liver toxicity in mice. Piperonyl butoxide, a related synthetic alkenylbenzene, is a commercial CYP inhibitor used as a synergist with pyrethroid and carbamate insecticides.

β-asarone is a major component of oil of calamus (derived from the *Acorus calamus* root which is a folk remedy for indigestion), and was once used to flavor vermouth and bitters. It causes intestinal tumors in rats.

Myristicin is a major flavor component of nutmeg, derived from the dried, ripe seed of the tree *Myristica fragrans*. Approximately 2% of nutmeg is myristicin, which is present in the volatile oil distilled with steam from the dried seeds. Mace, a closely related spice, is derived from the arrilode, or outer coating of the seed. The world's principal commercial supply of nutmeg is grown in the Malay peninsula. Myristicin is found in black pepper, parsley, celery, dill, and carrots as well. While not thought to be carcinogenic, large amounts of nutmeg, equivalent to two whole nutmeg seeds (ca. 15 g) are intoxicating and allegedly hallucinogenic. However, large doses also are associated with undesirable side effects, such as tachycardia, flushed skin, and dry mouth. Pure myristicin is not as hallucinogenic as nutmeg. Thus, it is assumed that other components in nutmeg may contribute to its potential psychoactive properties.

Piperine, an alkaloid present in high concentrations (10%) in black pepper (*Piper nigrum* and other sp.), is largely responsible for the pungent "bite" of this condiment. Powdered *P. cubeba* berries are added to cigarettes and smoked as a remedy for throat irritation, and oil derived from these berries is added to some throat lozenges. Reports of the cancer-causing ability of this compound are conflicting. Extracts of black pepper caused cancer in mice at several sites in skin painting tests, while orally injected piperine did not. Furthermore, piperine is not mutagenic in a number of *in vitro* screening assays. However, under appropriate conditions, piperine is chemically converted to potentially carcinogenic intermediates. In the presence of nitrite, piperine is nitrosated to form highly mutagenic nitrosamine intermediates *in vitro,* which may have potential carcinogenic activity. Like the related alkenylbenzenes, piperine also affects CYP expression and activity. For example, piperine specifically inhibits CYP 2E1, while specifically inducing the expression and activities of CYP 1A and 2B.

Capsaicin is the extremely pungent ingredient (up to about 0.5%) in red and yellow chili peppers: *Capsicum frutescens, C. conoides,* and *C. annum.* Due to its irritating qualities to the eyes and mucous membranes, a solution of capsaicin in an aerosol spray is a popular dog repellent for mail carriers. Topical creams containing capsaicin (0.025%) are commercially available as an analgesic. Although its pain relieving qualities are debatable, it has been shown to cause a local depletion of *substance P*, an endogenous neuropeptide known to transmit pain impulses. Thus, even though the physiological conditions causing pain may persist, capsaicin prevents pain impulses from reaching the brain.

Glycyrrhyzin is a saponin-like glycoside derived from the dried roots of *Glycyrrhiza glabra*, popularly known as licorice. Licorice is one of the oldest folk medicines traditionally used as an expectorant, flavoring agent (also used to mask the bitter taste of medicines), and demulcent. Cuneiform tablets dating to about 4000 B.C. mention the medicinal use of licorice by the Sumerians, and pieces of licorice root was found in King Tut's tomb. The one caveat to the many benefits of licorice is that it promotes hypertension. Glycyrrhizin is thought to be responsible for the hypertensive properties of licorice, which is brought about by the inhibition of the enzyme β-hydroxysteroid dehydrogenase. This enzyme acts as a protective modulator in certain mineralocorticoid receptor-rich tissues — particularly kidneys, colon, and salivary gland — by metabolizing receptor-active glucocorticoids such as cortisol to 11-keto derivatives (e.g., cortisone) which are not receptor agonists. A condition of excess glucocorticoids brought about by inhibition of the dehydrogenase leads to severe sodium retention, hypokalemia, and hypertension. Licorice reportedly has been responsible for fatal episodes of acute hypertension in people. Consequently, people with heart problems or hypertension should avoid licorice; as little as 100 to 200 g/day can cause persistent, heightened mineralocorticoid activity.

d-Limonene is a major constituent of citrus oils and also is found, in much lower amounts, in other fruits and vegetables. The major sources of d-limonene are oils of orange, grapefruit, and lemon. Citrus peel oil can contain as much as 95% d-limonene. d-Limonene per se or citrus oils where d-limonene is the major constituent have been widely used as flavoring agents and/or as fragrances in perfumes and soaps, and in a variety of foods such as ice cream, soft drinks, baked goods, gelatin, chewing gum, and puddings. It is also the active ingredient in "natural" citrus-based degreasing solvents and in insect repellents. Animal studies show that d-limonene is nephrotoxic to male animals. d-Limonene binds specifically, but reversibly to $\alpha_{2\mu}$-globulin which is the major low molecular weight protein produced by the renal proximal tubules and, hence, excreted in the urine of the male rat. Female rats excrete much less $\alpha_{2\mu}$-globulin. Accordingly, male rats that do not excrete $\alpha_{2\mu}$-globulin (NBR strain) do not exhibit nephrotoxicity following d-limonene treatment. Some animal studies indicate that d-limonene causes renal tumors in rodents. When administered orally, d-limonene induced renal adenomas and carcinomas in male rats, but not in mice. Oral d-limonene also was shown to significantly promote the development of N-nitrosoethylhydroxyethylamine - induced renal tumors in male rats. However, the toxicity and carcinogenicity of d-limonene appear to be absolutely species and gender specific due to the specific binding of this natural compound with $\alpha_{2\mu}$-globulin. Because humans do not excrete $\alpha_{2\mu}$-globulin, d-limonene is not thought to be harmful to people. Indeed, several studies have shown d-limonene to possess chemoprotective properties.

Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids (PAs) are common plant toxins produced by over 200 species of flowering plants, from genera such as *Senecio*, *Crotalaria,* and *Cynoglossum*. They are often present at very high levels — as much as 5 % of the plant's dry weight. Pyrrolizidine alkaloid-containing plants pose significant health hazards to people who consume some kinds of "natural" herbal teas and traditional folk remedies and those who eat grain-based foods contaminated with PA-containing plant parts. Some PAs have been investigated in clinical trials for their anticancer potential.

DNA cross-links are probably a critical event in PA bioactivity in that the cytotoxic, antimitotic, and megalocytic activity of PAs closely correspond with the formation of cross-links *in vitro.* Pyrrolizidine alkaloids form both DNA interstrand and DNA-protein cross-links in equal amounts *in vitro.* Structure-activity studies have revealed that the presence of a continuous macrocyclic diester and α, β-unsaturation are important structural determinants for DNA cross-link formation. Thus, PAs like senecionine are more potent cross-linkers than monocrotaline, which is more potent than open diesters such as latifoline and heliosupine. Of those examined, the simple necine retronecine is the least active cross-linker. The pattern of proteins cross-linked by PAs is similar to

those cross-linked by other bifunctional compounds, such as *cis* platinum and mitomycin C; actin has been postulated to be one of the proteins involved in the PA-induced cross-links.

Petasitenine is found in *Petasites japonicus*, a medicinal herb used as an expectorant and cough suppressant. The flower stalks of this herb are used as a food or herbal remedy. When incorporated into the diet, dried stalks are hepatocarcinogenic to rats. Purified petasitenine is also hepatocarcinogenic in rats as well as mutagenic in bacteria.
Tussilago farfara (coltsfoot) is a common herb used for centuries as a medicine for coughs and bronchitis in Europe and Asia. (*Tussilago* is the ancient Roman name for "cough suppresser.") The plant contains the pyrrolizidine alkaloid senkirkine at concentrations as high as 150 ppm, as well as high concentrations of senecionine, another very toxic and carcinogenic PA. Again, both the dried buds of coltsfoot (when ground and mixed in the diet) and purified senkirkine or senecionine cause liver tumors in rats, and both are bacterial mutagens.

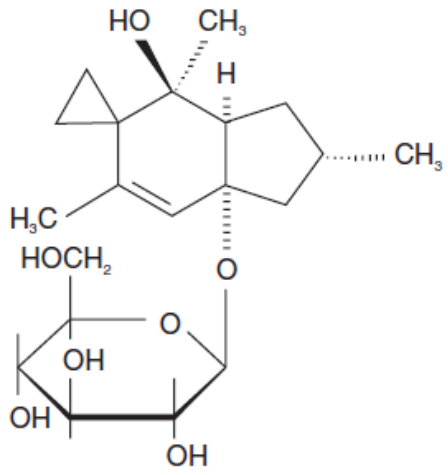
Human intoxication by PA-containing plants is well recognized and reported in the medical literature, and is endemic in Jamaica, India, and parts of Africa. Diseases, such as liver cirrhosis, veno-occlusive disease, and liver cancer, are linked to consumption of PA-containing plants. Hispanic and Native American populations in the west and southwest U.S. are at high risk for PA intoxications due to their traditional widespread use of herbs, occasional lack of confidence in traditional medicine, and, more commonly, lack of access to medical care.

Comfrey (*Symphytum officinale*) is a nearly universal herb commonly sold not only in health food stores and by herbalists, but also in supermarkets. Since ancient Greek and Roman times, both leaves and roots have been used to make teas and compress pastes to treat a variety of external and internal diseases, such as healing of wounds, skin disorders, and respiratory diseases. Numerous vegetarian recipes call for comfrey leaves to make soufflés, salads, and breads. Comfrey leaves and roots contain up to 0.3% pyrrolizidine alkaloids such as intermedine, lycopsamine, symphytine, and others. Diets containing powder from dried leaves and roots caused liver tumors in rats.

Additionally, these pure pyrrolizidine alkaloids also are animal carcinogens and bacterial mutagens. There are several cases cited in the medical literature of comfrey-related intoxications in people. The well-demonstrated reported toxicity and carcinogenicity of comfrey is such a significant cause for concern that the governments of Australia, Canada, Great Britain, and Germany either restrict comfrey's availability or have banned its sale entirely.

Substances in Bracken Fern
Bracken fern *(Pteridium aquilinum, esculentum,* and others) is widely used as human food in greens or salads in many countries such as New Zealand, Australia, Canada, the U.S., and especially Japan. It is also a forage plant for sheep and cattle. It first attracted the attention of veterinary scientists who noticed severe toxicity — bladder cancer, bone marrow depression, severe leukemia, thromocytopenia, and a hemorrhagic syndrome — in livestock grazing on this plant. When fed to rodents, bracken is a strong bladder, lung, and intestinal carcinogen. Lactating cows fed bracken fern produced milk that was carcinogenic to rats, showing that human exposure also may occur through cow's milk. Human consumption of bracken fern has been linked to an increased incidence of esophageal cancer in Japan.

The major carcinogen in bracken is believed to be *ptaquiloside* (Figure 34.5), a potent norsesqiterpenoid glucoside that is present at often high concentrations (up to 1.3% dry weight) in the plant. Ptaquiloside is a potent alkylator of DNA that appears to interact primarily with adenines at codon 61 in the *Ha*-ras oncogene in ptaquiloside-fed sheep. The plant also contains quercetin, kaempferol, and other mutagenic compounds of the flavonoid family which may contribute to its carcinogenicity. It also contains toxic tannins.



Ptaquiloside

Figure 34.5. Chemical structure of Ptaquiloside, the major carcinogen in the Bracken fern.

Acetylcholinesterase Inhibitors in Potatoes

Members of the family Solanaceae contain a variety of toxic glycoalkaloids. Potatoes (*Solanum tuberosum*) are an important food staple in many parts of the world and, under certain conditions, produce a variety of glycoalkaloids. Potatoes that have been damaged, exposed to light (green), or sprouted contain the glycoalkaloids α-solanine and α-chaconine (Figure 34.6) that can exceed concentrations of 100 ppm. Like physostigmine, solanine and chaconine are highly potent inhibitors of the enzyme acetylcholineesterase. Higher amounts of solanine and chaconine are present in the potato greens (tops). Healthy potatoes contain negligible amounts of these toxins. Episodes of human poisoning by green potatoes have been documented. Poisoning symptoms — gastric pain, weakness, nausea, vomiting, labored breathing — are consistent with acetylcholinesterase inhibition. These symptoms have been duplicated in clinical trials with human volunteers. Studies have indicated that the acetylcholinesterase inhibitory activity of solanine is probably insufficient to cause these toxic effects, which are probably due to the combined toxicity of solanine with other cholinesterae inhibitors in the potato, such as chaconine.

Most cases of human poisoning and deaths have occurred in Europe, but are occasionally seen in the Western Hemisphere. Poisoning episodes are not infrequent in animals fed damaged potatoes or peel, greens, or trim. A small number of studies in which animals are fed toxic doses of blighted potatoes or pure glycoalkaloid have indicated that these compounds may have weak teratogenic activity.

Tannins

Tannins long have been known as plant materials that confer a dark color when applied to animal hides thereby turning them into “tanned” leather. Although a precise definition is difficult due to their diverse and polymeric nature, one working definition is that tannins are a large group of water-soluble polyphenolic compounds with a molecular weight greater than 500 that have the ability to bind to and/or precipitate proteins. It is their ability to bind to proteins that is of toxicological and nutritional concern. Tannins also strongly bind to metals, such as iron, copper, and zinc, and reduce the gastrointestinal absorption of these metals. The two major classes of tannins are the proanthocyanidins (or “condensed tannins”) which are flavonoid polymers, and hydrolyzable tannins, which are polymers of gallic or ellagic acid esterified to either glucose or a polyphenol, such as catechin. Some polyphenolic compounds also are beneficial in that they can prevent cancer in certain animals.

Tannins occur in nearly every plant-derived food, but they are particularly high in bananas, raisins, spinach, red wines, bracken fern, coffee, and tea. Tea is an especially rich source of tannins. Green tea has about 4%, while black tea may contain as much as 33% tannin; adding milk to tea will bind the tannins so that they will be less absorbable. A normal diet will provide several grams per week from fruits and vegetables. Tannins also are high in traditional herbal stimulant drinks such as those derived from Brazilian guarana (*Paullinia cupana*), betel nut (*Areca catechu*), and kola nut (*Cola nitida* and C. *acuminata*). In animal studies, tannins cause a diminished weight gain and lowered efficiency of nutrient utilization. The major biochemical basis for these effects appears not to be inhibition of dietary protein digestion but rather a systemic inhibition of the metabolism of digested and absorbed nutrients.

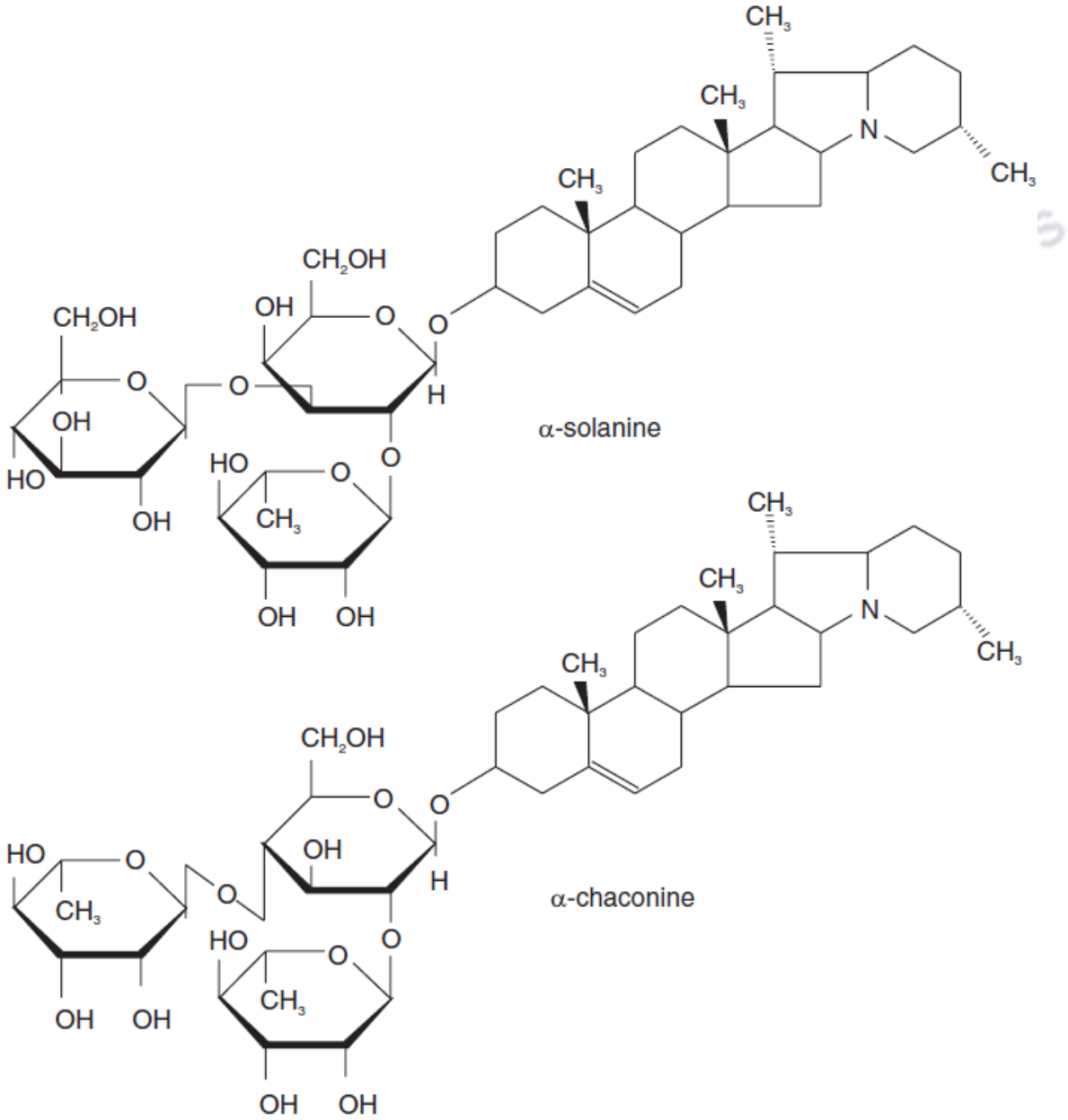


Figure 34.6. Potato glycoalkaloids α-solanine and α-chaconine

Tannins are liver carcinogens as well in rats and mice. Habitual chewers of betel nut (primarily in India, Pakistan, and Southeast Asia) have a high incidence of carcinoma of the mouth which has been linked to the high tannin content (10 to 25%) of this nut, although other components may be involved. An extract of betel nut causes cancer in hamsters. A high incidence of esophageal cancer

in the Transkei in South Africa has been associated with the consumption of high-tannin varieties of sorghum.

Caffeic Acid and Chlorogenic Acid

Caffeic and its quinic acid conjugate chlorogenic acid occur in an extremely wide range of fruits and vegetables. Other minor conjugates of caffeic acid also are known to exist. Upon ingestion, chlorogenic acid is hydrolyzed in the gastrointestinal tract to yield caffeic and quinic acids. In humans, caffeic acid is metabolized to *o*-methylated derivatives, such as ferulic, dihydroferulic, and vanillic acids, and *meta*-hydroxyphenyl derivatives, which are excreted in the urine. Caffeic acid and conjugates are present in high concentrations (over 1500 ppm) in many seasonings (thyme, basil, anise, caraway, rosemary, tarragon, marjoram, sage, and dill); vegetables (lettuce, potatoes, radishes, and celery); and fruits (grapes, berries, eggplant, and tomatoes). Coffee is particularly rich in these phenolics, in addition to many other compounds. A cup of coffee contains about 190 mg of chlorogenic acid. Caffeic acid inhibits 5-lipoxygenase which is a key enzyme in the biosynthesis of various eicosanoids, such as leukotrienes and thromboxanes. These eicosanoids are mediators of a wide variety of physiological and disease states and are involved in immune-regulation, asthma, inflammation, and platelet aggregation. At high doses (2% in the diet), caffeic acid caused a significant incidence of forestomach squamous cell papillomas and carcinomas in both sexes of rats and mice, renal tubular cell hyperplasia in male rats and female mice, and alveolar type II cell tumors in male mice. Oral caffeic acid also can enhance (or inhibit) the carcinogenic activity of known carcinogens. Chlorogenic acid has been shown to be mutagenic in bacteria, but has not been tested for carcinogenicity.

Coumarin and Psoralen

Coumarin is widely found in plants such as cabbage, radish, and spinach, and in plants traditionally used as flavoring agents, such as lavender and sweet woodruff (*Asperula odorata*); the latter is an essential herb for making May wine, which is a popular German drink used to salute the coming of Spring. Coumarin is widely found in herb teas based on tonka beans (*Dipteryx odorata*) and sweet clover (*Melilotus albus* and *officinalis*) called "melilot." The name "coumarin" originates from *coumarou*, the Carribean name for tonka beans. Purified coumarin was once used as a food additive, but this use was banned by the FDA after it was discovered that high doses caused liver damage in test animals. Coumarin is a powerful anticoagulant and is, in fact, the active ingredient in many brands of rodent baits. It also is used in human medicines as a blood thinning agent. Coumarin has been reported to cause bile duct carcinomas in rats as well.

Psoralens are a group of phototoxic furocoumarins widespread in a number of plant families such as Apiaceae (formerly Umbelliferae — celery and parsnips), Rutaceae (e.g., bergamot, limes, cloves), and Moraceae (e.g., figs). Celery contains 100 ppb psoralens, while parsnips contain approximately 40ppm. When activated by sunlight, psoralens are mutagenic, presumably due to their ability to form interstrand and protein cross-links with DNA. Many members of this chemical family are carcinogenic as well, including 5-methoxypsoralen and 8-methoxypsoralen (also called methoxsalen, xanthotoxin). Dietary exposure to psoralens is probably not a significant health risk; however, the margin of safety is thought to be narrow. Human volunteers who ingested 300 g of celery root (with a total phototoxic furocoumarin content of 28 ppm) experience no skin reactions after UVA exposure, and the blood levels of psoralen, methoxsalen, and 5-methoxypsoralen were below the analytical detection limit.

Lathyrogens

Lathyrogens, found in legumes such as chick peas and vetch, are derivatives of amino acids that act as metabolic antagonists of glutamic acid, a neurotransmitter in the brain. When lathyrogens are ingested in large amounts by humans or animals, they cause a crippling paralysis of the lower limbs and may result in death. Lathyrism only occurs on a impoverished diet of vetch, sweet pea, or grass pea and is characterized by bone thinning and leg paralysis.

Amylase inhibitors
Wheat contains a group of anti-enzymes capable of inhibiting amylase, an enzyme present in saliva and the intestinal tract which breaks down starch. Although wheat is rarely eaten raw, and heat destroys anti-amylases, anti-amylase has been found in the center of loaves of bread and in some wheat-based breakfast cereals. Animal experiments and human trials have shown no effect, but could, like protease inhibitors, produce pancreatic hypertrophy if present in large enough quantities.

Protease inhibitors
Protease inhibitors interfere with the action of trypsin and chymostrypsin, enzymes produced by the pancreas to break down ingested proteins. They are found to some extent in cereal grains (oats, barley, and maize), Brussels sprouts, onion, beetroot, wheat, finger millet, and peanuts. They have caused pancreatic hypertrophy in chicks and rats, but no ill effects have been observed in calves, pigs and dogs. Raw soybeans have high levels of trypsin inhibitors. Soybean fractions high in trypsin inhibitors depressed the growth of rats, chicks, and mice. Cooking heat largely destroys the trypsin inhibitors in soybeans, but 5 to 20% of the original trypsin inhibitor activity may be retained in commercially available soybean food products. For example, while raw soy flour contains 52.1 TI (trypsin inhibitor activity) per gram of sample, toasted soy flour contains 3.2-7.9 TI per g.

Phytohemagglutinins
Lectin proteins (phytohemagglutinins) are proteins present in leguminous species that can agglutinate red blood cells in various species of animals. These lectins are in many species of beans, especially red kidney beans and castor beans. Poisoning can occur if those beans are eaten raw or not completely cooked.

Miscellaneous Flavonoids: Quercetin, Ellagic Acid, Kaempferol, and Rutin
This family of chemicals is widespread in plant-derived foods, including fruits and fruit juices, vegetables, buckwheat, tea, cocoa, red wine, dill, soybeans, bracken fern, and others. The estimated average daily intake of flavonoids is 1 g. None of these has yet been conclusively shown to be carcinogenic, but both quercetin and kaempferol are mutagenic. Rutin is not mutagenic in itself, but it can be metabolized by intestinal bacteria to yield quercetin. Quercetin also has some anticarcinogenic properties.

Conclusion
Our food contains many naturally occurring plant compounds that have been shown to be toxic and/or carcinogenic in animals and people. Because it is practically impossible to avoid all plant-derived toxins in a normal diet, the best way to minimize potential hazard would be to eat a wide variety of foods, but not too much of any one dietary item. Because natural chemopreventives are associated with a reduction in risk to many types of cancer, it is also important to include generous servings of fruits and vegetables in the daily diet.

*****