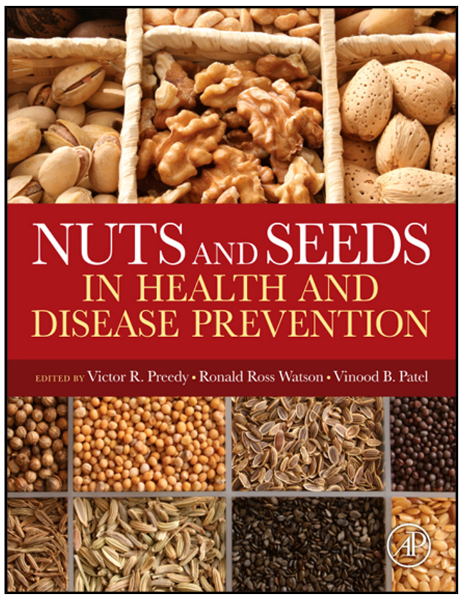

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CHAPTER 14

Cyanogenic Glycosides in Nuts and Seeds

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LIST OF ABBREVIATIONS

BMAA, β-methylamino-L-alanine
HCN, hydrogen cyanide
HDL, high density lipoprotein cholesterin
INC, International Nut and Dried Fruit Foundation
LDL, low density lipoprotein cholesterin
USDA, United States Department of Agriculture
WP ALS-PD, Western Pacific Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex

INTRODUCTION

Cyanide production by plants is widespread. While all higher plants probably form low levels of hydrogen cyanide (HCN) as a coproduct of ethylene biosynthesis in leaves and fruits, many plant species actively synthesize and accumulate cyanide-containing compounds. These cyanogenic plants have the ability to release HCN up to toxic thresholds in response to cell disintegration — for example, when damaged by herbivores (Ballhorn *et al.*, 2009). Over 3000 species, representing more than 550 genera and 130 families, produce cyanide-containing

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compounds, including many economically important food plants (Jones, 1998). The enzymatically accelerated release of HCN from these inactive precursors is called cyanogenesis. While in certain sapindaceous seeds HCN may arise during cyanolipid hydrolysis, HCN production in plants frequently results from the catabolism of cyanogenic glycosides. The approximately 75 documented cyanogenic glycosides are all *O*-β-glycosidic derivatives of α-hydroxynitriles (Poulton, 1990). Most cyanogenic glycosides are derived from the five hydrophobic protein amino acids, tyrosine, phenylalanine, valine, leucine, and isoleucine (Figure 14.1). In the course of the biosynthetic pathway the specific amino acids are hydroxylated to *N*-hydroxylamino acids, aldoximes, and then to nitriles serving as intermediates. In addition to cyanogenic monosaccharides, in which the unstable cyanohydrin moiety is stabilized by glycosidic linkage to a single sugar residue (e.g., prunasin, linamarin, dhurrin; Figure 14.1), cyanogenic disaccharids (e.g., amygdalin and linustatin; Figure 14.1) or trisaccharides (e.g., xeranthin) occur. Because HCN generally is toxic to all eukaryotes – including the plant itself – the accumulation of this toxin as inactive precursors is essential to prevent autotoxicity. To avoid uncontrolled release of HCN, in the intact plant cyanogenic glycosides are separated on cellular or tissue level from specific β-glucosidases. In case of cell disentegration, β-glucosidases are brought into contact with the cyanogenic glycosides. By hydrolysis of the glycosides, α-hydroxynitriles are formed that are relatively unstable, and dissociate either spontaneously or are enzymatically accelerated by α-hydroxynitrile lyases into HCN and an aldehyde or a ketone (Figure 14.2). Thus, the production of HCN from cyanogenic plants depends both on the biosynthesis of cyanogenic glycosides and the coexistence of one or more degrading enzymes.

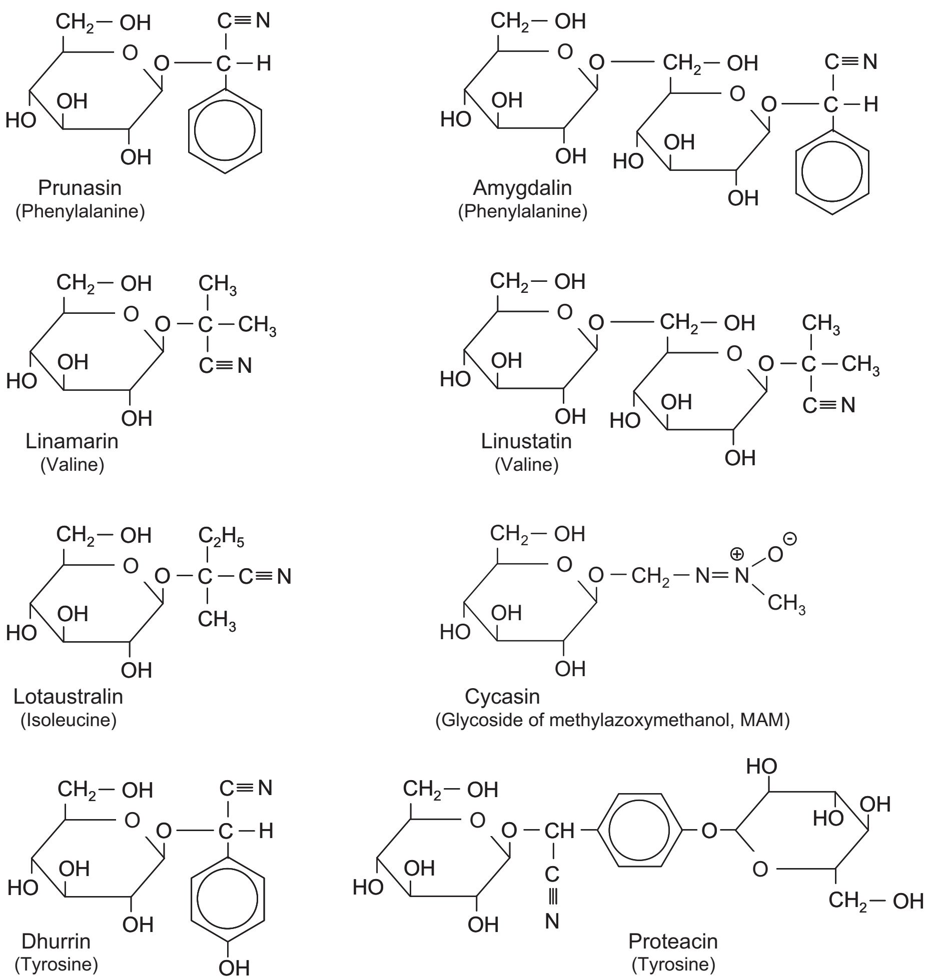

FIGURE 14.1
Important cyanogenic glycosides in food plants. Prunasin and amygdalin are central cyanogenic glycosides in rosaceous plants such as almonds, apricots, peaches, cherries, plums, and apples. Linamarin, linustatin, and lotaustralin occur in a wide range of different families (such as Fabaceae, Linaceae, Euphorbiaceae), for example in lima bean, flaxseed, and cassava. Cycasin (which is not a true cyanogenic glycoside since it does not contain a cyano group) is found in cycad seeds, whereas dhurrin occurs in *Sorghum* sp. and – together with proteacin – in macadamia nuts. The amino acid precursors of the respective cyanogenic glycosides are given in parentheses.

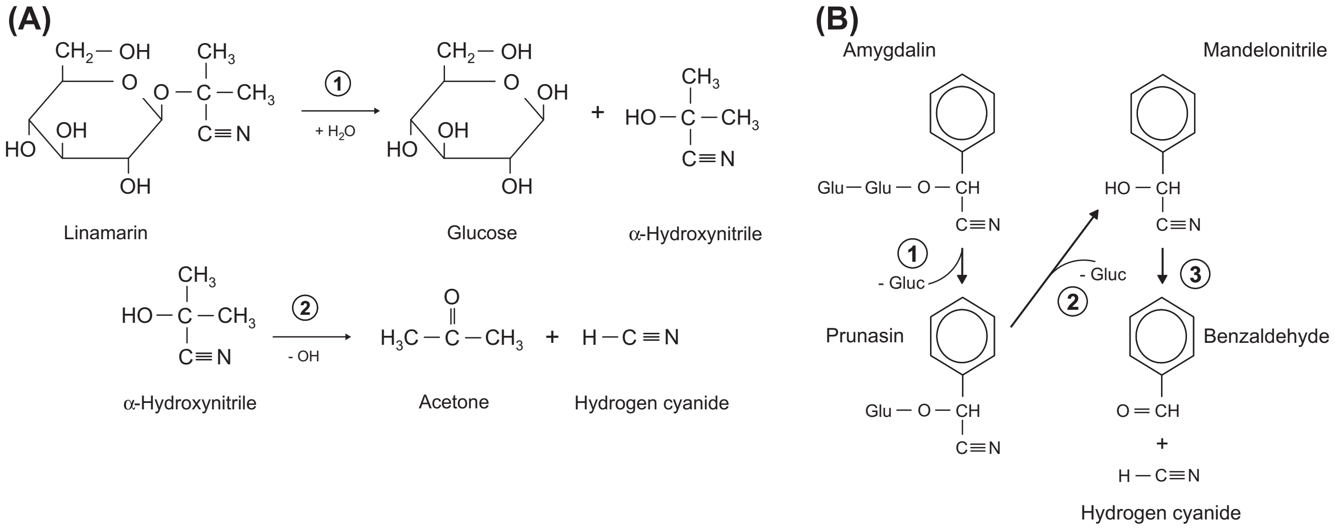

FIGURE 14.2

Release of HCN from cyanide-containing precursors. In response to cell damage, HCN is released by a two-step (A) or three-step (B) mechanism, depending on the type of the cyanogenic glycoside. In the case of cyanogenic monoglycosides such as linamarin (A), by the activity of β-glucosidases (1) unstable α-hydroxynitriles are formed that dissociate either spontaneously or are enzymatically accelerated by α-hydroxynitrile lyases (2) into HCN and a corresponding carbonyl compound. In the case of the cyanogenic diglycoside amygdalin (B), amygdalin hydrolase (1) and prunasin hydrolase (2) are β-glycosidases that catalyze the hydrolysis of the compound in a stepwise reaction by removing two glucose residues and producing mandelonitrile. This decomposes, enzymatically accelerated by a mandelonitrile lyase (3) into benzaldehyde and HCN.

While cyanide production in leaves can doubtlessly be attributed to herbivore defense (Ballhorn *et al.*, 2009), the ecological function of cyanogenic precursors in seeds is less understood. It appears reasonable that during seed germination, the defensive cyanide-containing compounds are transferred to the growing seedling for its defense. However, in addition to defense-associated functions, cyanogenic glycosides may serve as storage compounds for nitrogen that is required for seedling growth, or they may act as germination inhibitors.

Many plants store cyanogenic precursors in their seeds. Prominent and economically important examples presented in this chapter are various species belonging to the Rosaceae, for example *Prunus amygdalus* (almond), *P. armeniaca* (apricot), and *P. persica* (peach); Linaceae, for example *Linum usitatissimum* (flax); Fabaceae, for example *Phaseolus lunatus* (lima bean); and Proteaceae, such as *Macadamia integrifolia* and *M. tetraphylla* (macadamia nuts). In addition to these world-economically important plants, regional species such as *Cycas* sp. (e.g., *Cycas revoluta*) are known to produce cyanogenic seeds.

BOTANICAL DESCRIPTION, HISTORICAL AND PRESENT-DAY CULTIVATION

Almonds, Apricots, and Peaches

These rosaceous plants have long been known to contain cyanogenic compounds in their seeds. Almonds (*Prunus amygdalus*) originated in the Middle East and have been cultivated for 4000 years, mostly in temperate and subtropical regions, with an annual worldwide production in 2007 of $2.1 * 10^6$ tonnes (with shell) (FAOSTAT, 2009). The almond plant is a small deciduous tree, growing to 4–10 meters in height, with a trunk of up to 30 centimeters in diameter. In botanical terms, an almond is a stone fruit (not a nut). In contrast to other species of the genus *Prunus*, such as the peach, apricot, plum, and cherry, which show fleshy mesocarp, the mesocarp of almonds is a thick leathery greyish to greenish coat with a hairy epidermis. The endocarp is sclerotisized, and covers the edible seed. Like almonds, apricots (*Prunus armeniaca*) and peaches (*Prunus persica*) originated from Asia and have been cultivated for 3000–4000 years. Both species are small trees that require a temperate continental to subtropical climate. Although mainly produced for their fruits, the seeds (kernels), especially of apricots, are also used for human consumption.

Flaxseed

Flax (Linaceae: *Linum usitatissimum*) is an annual herbaceous plant of 30–120 cm in height that is native to the region extending from the eastern Mediterranean to India. Today flax is an important crop mainly in Europe and the US. The worldwide production of flaxseed in 2007 amounted $1.9 * 10^6$ tonnes (FAOSTAT, 2009).

Lima bean

The lima bean *Phaseolus lunatus* (Fabaceae) is a herbaceous bush, 30–90 cm in height, or a twining vine 2–4 m long with trifoliate leaves, white or violet flowers, and pods of 5–12 cm containing two to four seeds. The lima bean is a grain legume of Andean and Mesoamerican origin. Two separate domestication events are believed to have occurred; one in the Andes around 2000 BC, and one in Mesoamerica most likely around AD 800. The South American genotypes produce large seeds (Lima type), while the Mesoamerican varieties produce small seeds (Sieva type). By 1301 cultivation had spread to North America, and in the 16th century the plant began to be cultivated in the Eastern Hemisphere. Today, lima beans are cultivated in the tropics and subtropics around the world.

Macadamia nuts

Macadamia nut trees (Proteaceae) are small to medium-sized trees growing 2–12 m in height. They are native to tropical rainforests in eastern Australia (seven species), New Caledonia (one species, *M. neurophylla*), and Sulawesi in Indonesia (one species, *M. hildebrandii*). *Macadamia* sp. prefer fertile, well-drained soils, a rainfall of 1000–2000 mm, and temperatures not falling below 10°C, with an optimum temperature of 25°C. Only two species, *Macadamia integrifolia* and *Macadamia tetraphylla*, are of commercial importance, and these are in fact the only native Australian food plants of economic importance. According to the International Nut and Dried Fruit Foundation (http://www.nutfruit.org/), the annual production of macadamia nuts in 2008 was about 26,000 tonnes worldwide.

Cycad seeds

Cycas plants belong to the order Cycadales (family Cycadaceae), which consists of 11 genera of tropical and subtropical plants that produce terminal oblong cones containing orange-yellow seeds. Within the Cycadales, *C. revoluta* is the most cultivated species. It is sometimes named the "Sago palm" or "King Sago palm," which is misleading, since the common Sago palm, *Metroxylon sagu*, belongs to the Arecaceae. *Cycas revoluta* is a slow-growing plant that reaches 2–5 m in height. It is native to southern Japan, and has been naturalized throughout temperate and tropical habitats.

APPLICATIONS TO HEALTH PROMOTION AND DISEASE PREVENTION – ADVERSE EFFECTS AND REACTIONS

Almonds, Apricots, and Peaches

Seeds from sweet almonds are a valuable food source. They contain very low levels of carbohydrates, and may therefore be made into flour for low-carbohydrate diets or for patients suffering from diabetes mellitus or any other form of glycosuria. Almond flour is gluten-free, and is therefore a popular ingredient in cookery in place of wheat flour for gluten-sensitive people, and people with wheat allergies and celiac disease. In addition, almonds are a rich source of riboflavin, magnesium, manganese, and, especially, vitamin E (alpha tocopherol), containing 24 mg/100 g (USDA, 2008). They are also rich in monounsaturated fatty acids, and almonds in the daily diet reduced LDL cholesterol by as much as 9.4%, reduced the LDL : HDL ratio by 12.0%, and increased HDL cholesterol by 4.6% (Jenkins *et al.*, 2002). Claimed health benefits of almonds furthermore include improved complexion, improved transition of food through the colon, and even the prevention of cancer. Recent research associates the inclusion of almonds in the diet with elevating the blood levels of beneficial high density lipoproteins, and lowering the levels of low density lipoproteins. High concentrations of phenolics and flavonoids in the testa provide for antioxidative efficacy (Wijeratne *et al.*, 2006). Bitter almonds (*Prunus amygdalus* var. *amara*) in particular accumulate substantial amounts of the cyanogenic di-glycoside amygdalin (D-mandelonitrile-β-D-gentiobioside; Figure 14.1) in their seeds. The seeds can contain up to 5% amygdalin (~1 mg hydrogen cyanide per seed), and 10–15 seeds are considered lethal for children while 50–60 seeds represent a critical amount for adults (for lethal dose of cyanide, see below). Seeds of sweet almonds (*Prunus amygdalus* var. *dulcis*) contain much lower levels of cyanide; however, up to 2% of sweet almond seeds are bitter – i.e., contain amounts of amygdalin comparable to *P. amygdalus* var. *amara*.

Like almonds, both *Prunus armeniaca* (apricot) and *P. persica* (peach) accumulate amygdalin in their seeds. The amount of cyanide in seeds of apricots ranges from 0.05 to about 4 mg/g, with an average amount of 0.5 mg of cyanide, but varies widely depending on a variety of poorly defined factors, including cultivation practices, variety, and moisture content. In general, the HCN content in peach kernels is lower than in bitter almond or apricot kernels, and ranges from 0.4 to 2.6 mg/g. In addition to amygdalin, apricot and peach seeds also contain prunasin (the corresponding monoglycoside) and several minor cyanogenic glycosides, including amygdalinic acid, mandelic acid β-D-glucopyranoside, benzyl β-gentiobioside, and benzyl β-D-glucopyranoside (Fukuda *et al.*, 2003). Like bitter almonds, apricot kernels can sometimes be strongly bitter tasting. Consumed excessively, they can produce severe symptoms of cyanide poisoning or even death.

Flaxseed

Flaxseed (or linseed) is a valuable oil seed that is very low in cholesterol and sodium (USDA, 2008). It is also a good source of magnesium, phosphorus, and copper, and an excellent source of dietary fiber, thiamin, and manganese. At the same time, flaxseed can contain considerable amounts of cyanogenic diglycosides, primarily linustatin and neolinustatin, together with the corresponding monoglycosides linamarin and, at lower concentrations, lotaustralin (Figure 14.1). The cyanide content of different cultivars of flaxseed can range from 124 to 196 μg/g (Chadha *et al.*, 1995). The seeds contain about 35–45% oil, and are a desirable food product because of the high content of α-linolenic acid and lignans. Cyanogenic compounds are generally not detectable in processed flaxseed oil.

Lima bean

Dry, mature lima bean seeds are very low in saturated fat, cholesterol, and sodium (USDA, 2008). They are also a good source of protein, iron, magnesium, phosphorus, potassium, copper, dietary fiber, folate, and manganese (USDA, 2008). Depending on genotype, lima beans contain varying concentrations of cyanogenic glycosides, primarily linamarin (Figure 14.1), ranging from 2.1 (white seeds from Burma) to 3.1 mg HCN/g in seeds from Puerto Rico (black). The modern high-yielding and generally white varieties contain much less cyanide. Clinical toxicity in humans following the ingestion of lima beans is not well documented.

Macadamia nuts

These seeds are a valuable food due to their very low cholesterol and sodium content. Furthermore, they are rich in thiamin, and an excellent source of manganese (USDA, 2008). All *Macadamia* spp. acumulate cyanogenic glycosides (proteacin and dhurrin, Figure 14.1) in their seeds. Cyanide concentrations in the commercially used seeds are low (~4.05 μg HCN/g fresh weight), while *Macadamia whelanii* and *M. ternifolia* accumulate considerably higher amounts of cyanogenic glycosides in their seeds (260 µg/g in *M. ternifolia*) and are considered inedible (Dahler *et al.*, 1995). Indigenous people in Australia, however, process these seeds to reduce the cyanide content so they can use these species as well.

Cycad seeds

The cycad plants have a long history of use as food and medicine. In traditional Chinese medicine, cycad seeds are used to treat hypertension, musculoskeletal disorders, gastrointestinal distress, cough, and amenorrhea. Although the seeds are also frequently consumed as a source of carbohydrates, detailed data on nutritional facts are not available. Cycad seeds contain the toxic compounds cycasin (0.2–0.3%; Figure 14.1) and neocycasin (methylazoxymethanol β-D-glycosides), which are unique toxins present in cycad species (DeLuca *et al.*, 1980). These azoxyglucosides are glycosides of the same aglycone, methylazoxymethanol. The glycosides do not contain cyano groups, and thus are considered "pseudocyanogens," but can decompose to yield HCN. However, the liberation of cyanide from this process is a minor pathway compared to the formation of nitrogen gas, formaldehyde, and methanol. While acute poisoning has been observed arising after consumption of cycad seeds, the role of HCN as the agent determining toxicity is not fully resolved. Patients suffering from acute poisoning after consumption of cycad seeds and tested for blood cyanide concentrations had elevated blood cyanide levels, but the blood cyanide concentrations were below the values (0.5–1 mg/l) causing serious toxicity. In addition to acute poisoning, neuro-degenerative diseases (WP ALS-PD; Western Pacific Amyotrophic Lateral Sclerosis/Parkinsonism-Dementia Complex) associated with consumption of cycad seeds have been reported (Cox & Sacks, 2002). However, the non-protein amino acid β-methylamino-L-alanine (BMAA) is the most likely neurotoxic compound, rather than a cyanogenic compound.

TOXICITY AND DETOXIFICATION OF CYANIDE

In general, cyanide-containing compounds in nuts and seeds are detrimental rather than beneficial agents. However, since many cyanogenic nuts and seeds are of high nutritive value, these edibles have been used for a long time and in many cases food safety has been substantially improved by breeding low-cyanogenic plant varieties. Today, extremely low-cyanogenic cultivars of naturally sometimes high-cyanogenic plants, such as *Prunus* sp., lima bean, and *Macadamia* spp., exist. Cyanogenic nuts and seeds used for human consumption, or the products derived from them, generally – if properly processed – are below critical cyanide thresholds.

When consumed in low (i.e., sub-lethal) doses, hydrogen cyanide in mammals can be efficiently metabolized. The major defense of the organism to counter the toxic effects of cyanide is its conversion to thiocyanate, mediated by the enzyme rhodanese (sulfur transferase) located in mitochondria. The enzymatic detoxification requires sulfur donors, which are mostly provided from the dietary sulfur amino acids cysteine and methionine. Rhodanese catalyzes *in vitro* the formation of thiocyanate and sulfite from cyanide and thiosulfate or other suitable sulfur donors (Figure 14.3), while *in vivo* the enzyme is multifunctional.

$$\underset{\text{Hydrogen cyanide}}{HCN} + \underset{\text{Thiosulfate}}{S_2O_3^{2-}} \xrightarrow{\text{Rhodanese}} \underset{\text{Sulfite}}{SO_3^{2-}} + \underset{\text{Thiocyanate}}{SCN^-}$$

FIGURE 14.3
Detoxification of cyanide. Rhodanese is a mitochondrial enzyme which detoxifies cyanide by converting it to thiocyanate. The enzyme contains an active disulfide group, which reacts with the thiosulfate and cyanide. This detoxification requires sulfur donors, which are provided by dietary sulfur-containing amino acids. Thiocyanate is excreted in the urine.

Although most cyanogenic foods in industrialized countries are safe, and lower doses of hydrogen cyanide can be efficiently metabolized by humans, HCN released from cyanide-containing precursors is a strong respiratory poison, and the potential toxicity of cyanogenic food plants should be kept in mind. The toxicity of cyanide to vertebrates is mainly based on inhibition of the mitochondrial respiration pathway. Hydrogen cyanide inactivates the enzyme cytochrome oxidase in the mitochondria of cells by binding to the Fe^{3+}/Fe^{2+} ion contained in the enzyme. This causes a decrease in the utilization of oxygen in the tissues. Cyanide causes an increase in blood glucose and lactic acid levels, and a decrease in the ATP/ADP ratio, indicating a shift from aerobic to anaerobic metabolism. Cyanide activates glycogenolysis and shunts glucose to the pentose phosphate pathway, decreasing the rate of glycolysis and inhibiting the tricarboxylic acid cycle. Hydrogen cyanide ingestion reduces the energy availability in all cells, but its effect is most immediate on the respiratory system and the heart. This effect is further supported by the occupation of the oxygen-binding site in hemoglobin by cyanide, thus reducing oxygen transport capacities in blood. Beyond this, cyanide can inhibit several other metalloenzymes, most of which contain iron, copper, or molybdenum (e.g., alkaline phosphatase), as well as enzymes containing Schiff base intermediates (e.g., 2-keto-4-hydroxyglutarate aldolase). Cyanide that is released from cyanogenic glycosides in the gastrointestinal tract is readily absorbed by most animals. Oral lethal doses of HCN are 2.0 mg/kg body weight for a cat, 2.0 mg/kg for a sheep, 3.7 mg/kg for a mouse, 4.0 mg/kg for a dog, and 10 mg/kg for a rat. The oral lethal dose of HCN for humans is 0.5–3.5 mg/kg body weight, or about 50–250 mg for a typical adult human (Ballhorn *et al.*, 2009, and references therein).

In humans, the clinical features associated with the ingestion of cyanogenic glycosides mimic cyanide poisoning, and the severity of the intoxication correlates to the dose of active cyanogenic compounds. The onset of vomiting, abdominal pain, weakness, dyspnea, and diaphoresis, followed by convulsions, stupor, disorientation, hypotension, metabolic acidosis, coma, respiratory failure, and cardiovascular collapse, develops after exposure to high doses of cyanogenic glycosides (Akintonwa & Tunwashe, 1992). In addition to acute cyanide poisoning, chronic sub-lethal dietary cyanide frequently cause neuronal diseases, such as tropical ataxic polyneuropathy, Konzo, or WP ALS-PD, as well as reproductive effects including lower birth rates and increased numbers of neonatal deaths (Cox & Sacks, 2002).

Despite their potential to release highly toxic HCN, cyanogenic glycosides have been used as nutritional supplements and in cancer treatment. However, amygdalin, also sometimes falsely referred to as vitamin B17 or laetrile, is neither a vitamin nor an efficient pharmaceutical. Amygdalin and laetrile generally are different chemical compounds. Laetrile, which was patented in the US, is a semi-synthetic molecule sharing part of the amygdalin structure, while the "laetrile" made in Mexico is usually amygdalin – the natural product obtained from crushed apricot pits, or neoamygdalin. Clinical trials of amygdalin revealed no beneficial effect in cancer treatment, and considerable numbers of patients included in the studies suffered from cyanide toxicity (Milazzo *et al.*, 2006).

SUMMARY POINTS

- Many cyanogenic nuts and seeds have a long history of use as a food source or medicine, and nowadays some species are crop plants of world-economic importance.
- The concentrations of cyanide-containing compounds in nuts and seeds vary widely; however, in some species, such as *Prunus amygdalus* (almonds), *P. armeniaca* (apricots), and *Phaseolus lunatus* (lima bean), they can reach toxic thresholds.
- Although potentially toxic, cyanogenic nuts and seeds are often characterized by exceptionally high nutritive values. All of the economically most important cyanogenic nuts and seeds (i.e., almonds, macadamia nuts, lima beans, and flaxseed) contain health-promoting compositions of fatty acids, minerals, vitamins, and carbohydrates.

- Taking into consideration the possible health risk arising from consumption of inappropiately processed plant materials or the selection of highly cyanogenic crop plant genotypes, cyanogenic nuts and seeds represent excellent food sources.

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