Chapter 5
Medicinal Attributes of American Elderberry

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Abstract American elderberry (Sambucus nigra subsp. canadensis) is a common fruiting shrub native to much of Eastern North America. While the fruit and flowers have been used for eons as food and medicine by both early and contemporary North Americans, its use is seeing a resurgence. This has resulted in a renewed interest in horticultural development and cultivation of elderberry, with numerous new products developed especially in the form of dietary supplements. Recent scientific research continues to underscore the health-benefitting attributes of both elderberry fruit and flowers, and is further fueling the development of a significant elderberry value chain from production, to processing, marketing, and consumption.

Keywords Sambucus · Dietary supplement · Anti-oxidant · Elderflower
5.1 Introduction

American elderberry is a common deciduous woody shrub native to much of Eastern North America, ranging from Florida to Québec, and west to Manitoba and New Mexico (Allen et al. 2002; Hosie 1979; Small et al. 2004). It is also found in Mexico and Central America, where it may have been introduced by humans (e.g., Bolli 1994; Mejicanos and Ziller 1994; Pedraza and Williams-Linera 2003). The taxonomy of the widespread elderberry genus, *Sambucus* L., is much-debated. While *Sambucus* was formerly placed in the family Caprifoliaceae, molecular phylogenetic data have shown that it is best placed in a smaller segregate family (e.g., Donoghue et al. 2001; Angiosperm Phylogeny Group et al. 2016), which was formerly known as Adoxaceae but is now properly called Viburnaceae (Wilson 2016; Turland et al. 2017). Most botanists now concur that American elderberry is best considered a subspecies of the European elderberry (*Sambucus nigra* L., now best called *Sambucus nigra* subsp. *nigra*) and is most correctly called *Sambucus nigra* L. subsp. *canadensis* (L.) Bolli (Applequist 2015). Even the USDA National Plant Germplasm System (2019) officially changed the name of American elderberry accordingly in 2013. Nevertheless, American elderberry is still frequently called *Sambucus canadensis* L. in both popular and scientific literature.

Other North American *Sambucus* taxa include red elderberry (*S. racemosa* L., a very widespread species when broadly circumscribed, the eastern North American populations being *S. racemosa* subsp. *pubens* (Michx.) Hultén or *S. pubens* Michx.), and blue or Mexican elderberry (*S. cerulea* Raf., whose synonyms include *S. nigra* subsp. *cerulea* (Raf.) Bolli). Red elderberry fruit is considered poisonous but was nevertheless widely consumed by Native Americans after cooking and removal of seeds (Losey et al. 2003). Blue elderberry is commonly consumed by humans as both a food and medicine, and was tentatively proposed as a horticultural crop by the well-known plant breeder Luther Burbank (Hummer et al. 2012). This report focuses on the North American taxon commonly called American elderberry (*Sambucus nigra* subsp. *canadensis*), which will often be referred to herein simply as “elderberry”.

American elderberry typically occurs at the edge of wooded areas, in fence-rows, in openings near streams and waterways, and on the upper edges of road-side ditches where water is abundant but does not stand for extended periods. Elderberry thrives in areas that are mowed annually, such as roadsides, where competing woody vegetation is kept to a minimum. Occasionally elderberry is found in open dry areas where weedy vegetation is moderated by either animal grazing or mowing. While elderberry can grow in shade, it rarely flowers or fruits abundantly therein. Once established, American elderberry can vigorously re-grow from ground-level buds, and produce flowers and fruit in one season (Thomas et al. 2009), whereas European elderberry does not flower on new seasonal growth. American elderberry tends to sucker and spread as a multi-stemmed shrub if conditions allow, usually reaching heights of 2–3 m, and sometimes taller in southern climates. It produces abundant, large, flat corymbs of creamy white, perfect flowers (Figs. 5.1 and 5.2) typically in
June in the Midwest, followed by dark, glossy purple to black berries (Fig. 5.3) from late July through early September. The juicy berries are small, generally ranging from 70–90 mg, with several hundred berries produced per corymb (Finn et al. 2008). Pollination of elderberry has not been well-studied, but appears to combine wind pollination (likely the major factor) with some assistance from insects (Way 1981). While small solitary bees are often seen on elderflowers, honeybees are infrequent visitors (A.L.T. pers. obs. 22 years). Elderberries are of great benefit to wildlife, providing excellent cover and habitat for small mammals, birds, and beneficial insects, and nutritious food for birds and deer. The berries are edible and considered highly nutritious and beneficial to humans due to their high content of anthocyanins, polyphenols, and vitamins. The nutritious flowers are also consumed either cooked or more often in beverages, teas, and liqueurs. Both fruit and flowers are also of increasing interest for use as natural food colorants. During the last 15 years, American elderberry has emerged as an important specialty crop primarily grown for fruit used in health-promoting dietary supplements; a trip to most any North American health store will reveal an abundance of elderberry dietary supplement products for sale, most at a high price. However, the majority of those products are still coming from Europe.
5.2 Traditional and Historic Use as Food and Medicine

The close biological relationship between European and American elderberry should prompt the reader to incorporate records of elderberry use as a food and medicine in Europe (e.g., Knudsen and Kaack 2015a, b) to approximate the history of human elderberry use in North America. European records cite the human use of European elder since ancient times for a plethora of food, medicinal, and spiritual purposes (Salamon and Grulova 2015). American elderberry has a similar and extensive history of use among nearly 100 North American indigenous nations and tribes (Moerman 1998), and subsequently among the peoples who migrated more recently to North America from Europe. The latter group’s long-established use of European elderberry as food and medicine was likely and logically perpetuated upon encountering the closely related North American subspecies. Nevertheless, despite this history, American elderberry remains relatively unknown to the North American public and the agricultural industry alike. While many of the reported medicinal effects still lack adequate scientific validation, there is an increasing number of studies supporting important medicinal or therapeutic properties associated with American elderberry, as described herein.

The documented medicinal uses of elderberry by indigenous Americans include the following areas: emetic, laxative, anti-rheumatic, cathartic, dermatological, burn
dressing, diaphoretic, diuretic, pediatric aid, liver aid, breast treatment, blood purifier, gastrointestinal aid, analgesic, tonic, febrifuge, heart medicine, measles, venereal aid, gynecological aid, sedative, toothache, ceremonial medicine, urinary aid, herbal steam, anti-diarrheal, anti-hemorrhagic, tuberculosis, and cold remedy (Moerman 1998). Note that the several species and varieties cited by Moerman (1998) are now mostly recognized as being members of *S. nigra* subsp. *canadensis*; the variation being considered more representative of ecotype formation. While the use of elderberry fruits is most frequently cited in traditional medicine practice, there is evidence of use of the flowers (and leaves) for pain relief, swelling, inflammation, and diuresis (urine production), and as a diaphoretic or expectorant (Ulbricht et al. 2014). Readers are also directed to the condensed coverage of traditional medicinal uses of American elderberry in Duke (2002), the PDR (Physicians’ Desk Reference) for Herbal Medicines (Thomson Healthcare 2007), and the evidence-based systematic review of elderberry and elderflower by the Natural Standard Research Collaboration (Ulbricht et al. 2014).

Food uses by both indigenous and neo-Americans include juice and beverages, fresh and dried fruit, pie, bread, cake, jam, jelly, sauce, relish, and in yoghurt, syrup, and ice cream. The flowers are dried for use in making beverages or teas, or consumed fresh – often battered and fried in the form of “fritters”. The flowers are also used to flavor alcoholic spirits and in soaps for their medicinal and fragrant attributes. Excellent wines can be made from both the fruit and flowers; numerous North
American wineries now produce and market a variety of dry and sweet wine products that are popular with North American consumers.

5.3 Modern Science-Based Health Claims

Clinical and preclinical research to confirm the traditional uses of elderberry is limited, and the large majority has been done in Europe with the European subspecies, *Sambucus nigra* subsp. *nigra*. The two subspecies are chemically distinct but contain the same major compound classes (e.g., Lee and Finn 2007), and there is no reason to presume that the American subsp. *canadensis*, which is widely used medicinally and for similar purposes, lacks the bioactivities of the European subspecies. Both subspecies contain chlorogenic acid and rutin as “major” polyphenolic compounds, with American elderberry also containing substantial amounts of neochlorogenic acid and isorhamnetin 3-rutinoside (Johnson et al. 2017; Lee and Finn 2007). In one *in vitro* study, extracts of fruits of American elderberry demonstrated a greater number of anticancer bioactivities than European elderberry (Thole et al. 2006). Similarly, flowers of both subspecies contain numerous acyl spermidines, though they have distinct fingerprints (Kite et al. 2013).

A second confounding issue is that most published clinical trials are of multispecies products. It is common in herbal medicine, both in formalized professional modalities such as Traditional Chinese Medicine and in traditional herbalism, for multiple plant species to be used in formulas. Such formulas are believed to have greater efficacy, and sometimes also tolerability, than a high dose of a single species, much as a botanical extract containing multiple compounds may have a better effect profile than any one chemical from that extract. This creates challenges for the evaluation of those formulas. The insistence that only one species at a time should be tested is not rationally justifiable, as it would mean that botanical medicines as they were really used would not be tested, and their full potential benefit might never be revealed. However, when a multicomponent product is tested, it is not yet possible to know to what degree the observed benefits are derived from the individual activity of any one component or synergistic activities requiring that component’s presence. Therefore, single-species products should not be presumed to have the same efficacy as tested multispecies products that contain those species. The use of “omics” technology is promoted as a means of elucidating putative synergistic molecular activity in the context of animal-based physiological models (Khakimov et al. 2012).

The most common and best-supported medicinal use of elderberry is for upper respiratory infections (URIs). Clinical trials of elderberry alone for treatment of URI symptoms have been favorable, but most have been small. A meta-analysis of trials of elderberry for URIs reported a “large mean effect size” (Hawkins et al. 2019); however, the trials included in that analysis had only 180 participants. At least two placebo-controlled human trials have tested the standardized extract Sambucol® (Razei Bar, Jerusalem, Israel) for influenza; recovery was up to 4 days...
faster in elderberry users (Zakay-Rones et al. 1995, 2004). Elderberry is also effective against influenza in mice (Kinoshita et al. 2012).

A larger placebo-controlled trial gave elderberry or a placebo prophylactically to 312 airline passengers traveling economy class from Australia to overseas destinations (Tiralongo et al. 2016). Though the number of colds was not significantly reduced in those who consumed a standardized elderberry extract (12 vs. 17 in the placebo group), the number of days of illness was halved (57 vs. 117, P = 0.02) and average symptoms suffered by those who were ill also substantially lowered (P = 0.05).

Perhaps the best-tested elderberry-containing product is Echinaforce Hotdrink® (A. Vogel Bioforce AG, Roggwil, Switzerland). This syrup contains 240 mg of a standardized hydroethanolic extract of Echinacea purpurea (L.) Moench (echinacea) and 276.5 mg elderberry extract per mL; it is made into a hot drink by adding 5 mL to hot water. In a large clinical trial, 473 people with early influenza were randomized to take Echinaforce Hotdrink or the anti-influenza drug oseltamivir (Rauš et al. 2015). Blinding was created by having each participant take both a hot beverage, five times a day for 3 days, then three times a day for 7 days, and capsules twice a day for 10 days. The Echinaforce group received Echinaforce Hotdrink syrup plus placebo capsules; the oseltamivir group received a placebo syrup and 5 days of drug capsules followed by 5 days of placebo capsules. The two treatments were similar in efficacy, with 1.5% vs. 4.1% reporting recovery (absent or only mild symptoms) after 1 day, 50.2% vs. 48.8% after 5 days, and 90.1% vs. 84.8% after 10 days. The incidence of complications was near-significantly lower with Echinaforce (2.46% vs. 6.45%; P = 0.076), and nausea and vomiting were five times more frequent with oseltamivir, sometimes necessitating discontinuation.

Rauš et al. (2015) technically demonstrated only that Echinaforce Hotdrink is not inferior to oseltamivir in efficacy. However, the additional considerations of oseltamivir’s lesser accessibility, greater cost, and neurological and psychiatric side effects (Ishii et al. 2008; Jefferson et al. 2014) would support a consumers’-perspective conclusion that Echinaforce Hotdrink is superior to the pharmaceutical alternative when all costs and outcomes are considered. Most other Echinaforce® branded products contain only echinacea, which has been subjected to far more clinical trials than elderberry, and has been well demonstrated to reduce incidence and severity of URIs when correctly used (Shah et al. 2007; Schapowal et al. 2015). Perhaps because echinacea is so much better known, Rauš et al. (2015: 66) referred to the tested product as “Echinacea purpurea-based.” However, the likely contribution of elderberry, with its well-demonstrated anti-influenza mechanisms of action (see below), to the efficacy of this and similar formulae should not be minimized.

Bark of American and European elderberry has been used as a purgative, while twigs and fruits are used for a laxative effect and flower infusions used for stomach upset and given to babies with colic (Moerman 1998). There are no clinical trials of single-species products for these effects. A placebo-controlled crossover trial of a four-species formula for chronic constipation found that the formula reduced mean colonic transit time from 42.3 h during placebo treatment to 15.7 h during active treatment (Picon et al. 2010). Frequency of elimination and patient perception of
bowel function also improved significantly. That botanical formula, sold commercially in Brazil since 1926, contains one-third elderflower by weight, with the remainder flowers of Cassia angustifolia Vahl (= Senna alexandrina Mill., senna) and fruits of Pimpinella anisum L. (anise) and Foeniculum vulgare Mill. (fennel). Because senna leaf is a well-known laxative, it may be suspected of being the most potent part of this formula, which does not mean that the other species have no benefit; they could serve to support efficacy while mitigating side effects.

American and European elderberry have occasionally been used as diuretics; the inner bark is sometimes the part used (Moerman 1998), but sometimes the fruit is used. European elderberry has been shown to be a true diuretic in rodents, leading to increased sodium excretion as well as increased urinary output (Beaux et al. 1999). A European formulation of four botanicals including elderflower (Herbensurina®; Deiters Laboratories, Badalona, Spain) has been reported to reduce induced calcium oxalate crystal formation, microcalcifications, and kidney fibrosis in male rats, with the middle tested dosage of 125 mg/kg being most effective (Crescenti et al. 2015). However, there are no human trials.

PerioPatch® (Izun Pharmaceuticals Ltd., Jerusalem, Israel, and New York City, USA) is a topical herbal patch containing elderberry, echinacea, and Centella asiatica (L.) Urb. (gotu kola), which is used for treatment of oral wounds and ulcerations. A clinical trial in humans with gingivitis (Grbic et al. 2011) found that use for 3 days reduced the gingival index, compared to users of a placebo patch, on days 4 and 15, though not on day 8. The trial was intended to be a crossover trial, but because gingival inflammation in some users of the active patch had not rebounded to the baseline level by day 15, results from the second half were not reported. A study in rats compared PerioPatch to a placebo patch and no patch for treatment of oral surgical wounds. After 12 days, the herbal patch group had smaller epithelial gaps and greater collagen deposition and angiogenesis at the flap site (Chaushu et al. 2015). In a human trial, an herbal mouth rinse, HM-302, developed by the same company and containing the same species, reduced the development of gingivitis significantly better than a water rinse and nonsignificantly better than essential oil or cetylpyridinium rinses (Samuels et al. 2012).

5.4 Mechanisms of Bioactivity

Sambucus nigra has direct antiviral activity, especially against a wide range of influenza viruses, in which hemagglutination is reduced and replication is inhibited (Zakay-Rones et al. 1995; Krawitz et al. 2011). Strains against which the commercial extract Sambucol is effective in vitro include multiple H1N1, H3N2, and type B strains, an H5N1 strain, and animal strains from European swine and turkeys. Elderberry also inhibits an H9N2 strain in human epithelial cell culture (Shahsavandi et al. 2017), possibly preventing viral spread between cells by interfering with lipid raft association. Flavonoids from elderberry bind to H1N1 virions, inhibiting their ability to penetrate host cells (Roschek et al. 2009). In one study, the IC50 for the
direct H1N1 inhibitory activity of fruit extract was $252 \pm 34 \, \mu g/mL$, while two isolated flavonoids displayed inhibitory activity at concentrations comparable to oseltamivir and amantadine respectively (Roschek et al. 2009). Contrarily, Kinoshita et al. (2012) reported that \textit{in vitro} anti-influenza activity of elderberry was relatively weak, compared with its benefits in mice \textit{in vivo}, which were therefore attributed primarily to immune stimulation.

Elderberry is also directly active against infectious bronchitis virus, a coronavirus causing illness in chickens; treatment with \textit{S. nigra} extracts reduced viral titers in Vero cells by four to six orders of magnitude (Chen et al. 2014). The standardized extract Rubini® (BerryPharma AG, Leichlingen, Germany), which, like Sambucol, is made from the European subspecies, inhibits growth of four bacterial species that can cause upper respiratory tract infections, including \textit{Streptococcus pyogenes}, group C and G \textit{Streptococci}, and \textit{Branhamella catarrhalis} (Krawitz et al. 2011). Elderberry therefore might reduce complications of influenza in part by impeding development of secondary infections.

Some studies have reported that elderberry and elderflower reduce inflammation both \textit{in vitro} and \textit{in vivo}. Nitric oxide (NO) inhibition and complement fixing activities were demonstrated \textit{in vitro} (e.g., Ho et al. 2017a). In obese mice, the inflammatory marker tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) was significantly reduced by elderberry extract (Farrell et al. 2015b). However, Sambucol products have been reported to be pro-inflammatory \textit{in vitro} (Barak et al. 2001; Waknine-Grinberg et al. 2009), increasing production of both anti- and pro-inflammatory cytokines and TNF-\(\alpha\) (Barak et al. 2001, 2002). Mice that consumed Sambucol both before and after infection with malaria had an increased incidence of cerebral malaria, which is thought to be caused by inflammatory response, although Sambucol protected mice from leishmaniasis (Waknine-Grinberg et al. 2009). Another study reported that elderberry extract increased TNF-\(\alpha\) in a diabetic rat model, which was inexplicably reported as indicating “anti-inflammatory effects” (Badescu et al. 2015).

Elderberry has not been shown to be pro-inflammatory (or anti-inflammatory) in humans, and it is not clear whether the manufacturing of Sambucol may affect its bioactivities. Some symptoms of influenza stem from the inflammatory response to the illness, so a product that did increase cytokine production might be expected to worsen symptoms rather than improve them. Hypothetically, this might provide a good rationale for the herbal practice of combining elderberry with echinacea. Echinacea is well demonstrated to reduce production of pro-inflammatory cytokines (e.g., Sharma et al. 2009a, b; Vimalanathan et al. 2017) so in addition to adding a different direct anti-influenza activity (Pleschka et al. 2009), it might counteract any potential side effects of the elderberry.

Though anthocyanins or flavonoids are sometimes presumed to be “the” active compounds in elderberry, pectic polysaccharides in elderberry and elderflower provide complement fixing and macrophage stimulating activities (Ho et al. 2015, 2016). In mice, also, the elderberry fraction containing polysaccharides was reported to be the strongest in reducing viral load and increasing antibody production (Kinoshita et al. 2012), but other fractions also evidently had some activity. Whole
elderberry products or crude extracts are therefore likely to be preferable to products that isolate a single subset of constituents.

5.5 Emerging Health Benefits

Recent scientific studies provide data suggesting that elderberry might be useful not only in treating acute conditions, but in preventing or ameliorating some of the chronic degenerative diseases associated with the Western diet and lifestyle. These include dementia, diabetes, cardiovascular disease (CVD), liver disease, and/or obesity, which often plays a causal role in the development of these chronic diseases. Though the evidence for prophylactic benefits of elderberry is far from definitive, it is certainly enough to demonstrate that further research is called for.

In particular, an ever-increasing amount of research indicates that consumption of berry fruits is beneficial for brain health. Elderberry has been relatively little studied in this context. However, promising preclinical research exists. Mice fed diets containing American elderberry suffered substantially less disability after 24 h and less neuronal cell death after 3 days in response to global cerebral ischemia (effectively, an induced stroke) than non-supplemented mice (Chuang et al. 2014). Flowers of *Sambucus cerulea*, which was once treated as a subspecies of *S. nigra* though it is morphologically distinct (Applequist 2015), are used by members of the North American Lumbee tribe to alleviate symptoms of Parkinson’s disease, and *in vitro* the extract has neuroprotective activities, including improvement of mitochondrial function in neurons and protection against rotenone neurotoxicity (de Rus Jacquet et al. 2017).

Methanolic extracts, especially of elder bark and leaf, reduce convulsions in mice induced by pentylenetetrazole and electroshock, and protect against mortality as well as diazepam (Ataee et al. 2016). Fruit and leaf extracts demonstrate substantial activity in mouse models of depression (Mahmoudi et al. 2014); results of that study are not relevant to humans because acute doses of up to 1200 mg/kg body weight were injected intraperitoneally.

An extract of *Sambucus nigra* had antioxidant activity in isolated neurons *in vitro* (Spagnuolo et al. 2016). Ethanolic extracts of American elderberry inhibit microglial activation (Simonyi et al. 2015) and sometimes reduce the production of reactive oxygen species (ROS) in microglial cells. However, when a variety of juice extracts were tested, some actually increased NO production (Jiang et al. 2015), so the antioxidant activity may not be ubiquitous.

Elderflower tea is reported to have particularly high antioxidant potential, suggesting that it might be beneficial for mitigating many potential health problems caused by chronic oxidative stress (e.g., Loizzo et al. 2016; Viapiana and Wesolowski 2017). Elderflower aqueous extracts can also inhibit the pro-inflammatory activities of bacteria responsible for gum disease (Harokopakis et al. 2006), perhaps contributing to the reported anti-gingivitis effects.
European elderberry is sometimes used traditionally to treat diabetes, but there is no relevant human research to date. In vitro, elderberry and elderflower increase glucose uptake in human skeletal muscle and liver carcinoma cells; multiple components, including flavonoids and phenolic acids, and their metabolites inhibit 15-lipoxygenase, α-amylase, and α-glucosidase, the latter two better than acarbose (Ho et al. 2017b, c). In isolated mouse muscles, an aqueous extract increases 2-deoxy-glucose transport, glucose oxidation, glycogenesis, and insulin secretion; activities derive from multiple constituents (Gray et al. 2000). Increased glucose uptake in porcine myotube cultures is attributed at least partly to phenolic compounds, including naringenin and 5-O-caffeoylquinic acid (Bhattacharya et al. 2013). Elderflower extracts can activate peroxisome proliferator-activated receptor-γ; three constituents known to have this activity, including naringenin and fatty acids, are present but are not wholly responsible for the activity (Christensen et al. 2010).

In vivo studies have shown inconsistent effects. In one study of type 2 diabetic rats, a polar extract reduced hyperglycemia and a lipophilic extract reduced insulin secretion; both lowered insulin resistance (Salvador et al. 2016). In obese mice fed a high-fat diet, an elderberry extract reduced insulin resistance (Farrell et al. 2015a). However, in a different mouse model no significant benefit was reported for elderberry (Swanston-Flatt et al. 1989). In hyperlipidemic mice deprived of the apolipoprotein E gene, elderberry reduced fasting glucose (Farrell et al. 2015b). In a diabetic mouse model of neuropathic pain, aqueous extract of elderflower, administered by intraperitoneal injection, reduced blood sugar better than a pharmaceutical control and reduced pain (Raafat and El-Lakany 2015). Elderberry may also improve bone density in diabetic rats (Badescu et al. 2012).

In a rat model of hypertension, a polyphenol-rich European elderberry extract reduced blood pressure; also, antioxidant activity was improved by the combination of elderberry extract and the pharmaceutical aliskiren better than by either alone (Ciocolu et al. 2016). In hamsters with hyperlipidemia due to fish oil feeding, elderberry decreased plasma and hepatic lipids and lipid peroxidation (Dubey et al. 2012). In mice fed a high-fat diet, elderberry extract reduced lipid synthesis (Farrell et al. 2015b). Two studies in mice deprived of the apolipoprotein E gene have had partly contradictory results. In one, in which the mice were fed a low-fat diet, elderberry supplementation increased non-HDL cholesterol (Millar et al. 2018). However, HDL function was improved, as were measures of liver inflammation and atherosclerotic plaque formation. In the other, serum lipids did not change, but aspartate transaminase and cholesterol content in the aorta (a measure of atherosclerosis progression) were reduced (Farrell et al. 2015b).

In a placebo-controlled human study, a product equivalent to 5 mL elderberry juice per day, taken for 2 weeks by young subjects, reduced cholesterol only non-significantly (from a mean of 199 to 190 mg/dL, vs. a slight increase in the placebo group) (Murkovic et al. 2004). However, that study used a very small dose and a very short treatment period. A 12-week placebo-controlled trial in healthy post-menopausal women tested the effects of 500 mg/day extracted anthocyanins as cyanidin glycosides, equivalent to the amount contained in 25 g/day elderberries, on
biomarkers of CVD risk (Curtis et al. 2009). No statistically significant differences were seen in any biomarkers for CVD risk, including blood pressure, serum lipids or glucose, markers of inflammation, or platelet reactivity, or markers of liver and kidney function. However, the authors acknowledged that other studies testing anthocyanin-rich fruits containing a broader array of constituents, rather than one isolated fraction, in people with higher baseline inflammation levels have had positive results. No human trial, therefore, has yet effectively tested the potential benefits of elderberry, as consumers might use it, for CVD.

The possible effect of elderberry on body fat or weight is unclear. Elderflower extract reduces fat accumulation in *Caenorhabditis elegans* (a nematode worm), with phenolic compounds partly responsible for bioactivity (Bhattacharya et al. 2013). In a human study, the combination of elderberry and asparagus products was reported to result in improvements in weight and blood pressure (Chrubasik et al. 2008); unfortunately, the study design was inadequate to allow clear assessment of causality.

### 5.6 Negative Perceptions or Possible Side Effects from Elderberry Consumption

Conventional wisdom suggests that American elderberry contains cyanide, or specifically cyanogenic glycosides, and that consuming leaves, stems, green berries, and even unprocessed ripe berries can be harmful. Similar claims suggest that cooking, processing, or fermenting elderberries or elderberry juice mitigates such putative cyanide occurrence. This perception has been immortalized by a well-known incident in 1983 where a group of worshipers in California consumed a beverage made from raw elderberry fruits, leaves, and stems (likely *S. cerulea*), along with other ingredients, resulting in emergency hospitalization of eight people (Centers for Disease Control 1984). While cyanide poisoning was initially suspected as the cause, all victims had normal serum cyanide levels and recovered quickly. Nevertheless, this incident is frequently cited as a basis for the alleged occurrence of cyanide in elderberries. Countless websites state that elderberry contains cyanide or cyanogenic glycosides, and that the fruit should not be consumed raw; however, the scientific literature supporting such claims is scant.

Cyanogenic glycosides are naturally occurring organic compounds that are found in more than 2600 plant species (Irchhaiya et al. 2015), as well as in some insects, especially Lepidoptera (Zagrobelny et al. 2004). They are nitrogenous secondary metabolites consisting of an aglycone and a sugar moiety, with a nitrile functional group (R-CN). Cyanogenic glycosides are believed to play roles in plant defense mechanisms against herbivory, and in both pest and disease resistance and response (Nahrstedt 1985). The cyanogenic glycosides in plant tissues are generally considered safe and stable, but when such tissues are disrupted by herbivory or
infection, endogenous enzymes can be activated resulting in the release of toxic hydrogen cyanide from these compounds (Bak et al. 2006).

Dellagreca et al. (2000) and Senica et al. (2016) have documented the occurrence of notable and possibly toxic levels of cyanogenic glycosides in European elderberry (subsp. nigra) leaves, which are not considered edible, and are rarely used medicinally. Senica et al. (2017) quantified cyanogenic glycosides in leaf, flower, and fruit of European elderberry; levels of sambunigrin (a common cyanogenic glycoside) ranged from 29–210 μg/g in leaves, 7–19 μg/g in flowers, and from 0.08–0.59 μg/g in fruits (all generally increasing with altitude where plants were growing). Using the picrate paper test to evaluate American elderberry (subsp. canadensis) leaves, Buhrmester et al. (2000) found consistent detectable levels of evolved hydrogen cyanide (HCN) in only one population of wild elderberry collected in Illinois (USA), whereas eight other populations either tested negative or were inconsistent in detectable amounts of evolved HCN. Little research has been published on the occurrence of cyanogenic glycosides in American elderberry fruit. Bolarinwa et al. (2015) reported levels of 1–7 μg cyanide equivalents/g in commercial apple juice, and 10–40 μg/g in fresh apple juice pressed from 15 varieties. Appenteng et al. (manuscript in preparation) documented levels of cyanogenic glycosides in American elderberry juice at or below levels found in concurrent analyses of commercial apple juice. Frozen and canned commercial apple juice produced 0.16–0.21 μg cyanide equivalents/g juice in picrate paper tests, whereas dissected American elderberry fruits from two cultivars produced levels of 0.03–0.24 μg/g in juice, 0.01–0.24 μg/g in seeds, 0.01–0.64 μg/g in fruit skins, and 0.05–0.54 μg/g in pedicels (small green stems attaching the berry to the corymb). Further study found mean levels of 0.25 and 0.37 μg cyanide equivalents/g of green (unripe) berries and pedicels, respectively, thus suggesting that unripe elderberries and associated stems have slightly higher levels of cyanogenic glycosides compared with commercial apple juice. These levels are still well below published numbers for S. nigra fresh and processed juice (18.8 and 10.6 μg/g, respectively) (Senica et al. 2016). Elderberry processors already eschew incorporating unripe berries and stems in their products because they degrade quality, taste, and appearance; therefore, American elderberry products are very unlikely to contain any appreciable amount of cyanogenic glycosides or cyanide.

Thermal processing and fermenting of foods containing cyanogenic glycosides have indeed been shown to render them safe to consume. For example, cassava (Manihot esculenta Crantz), one of the world’s most important staple food crops, is highly toxic in its unprocessed state due to cyanogenic glycosides, but is safe to consume after processing or cooking (Montagnac et al. 2009). Senica et al. (2016) documented a 44% reduction in sambunigrin content in heat-treated subsp. nigra juice, and a 96% reduction in processed liqueur and fruit spread products.

The internet also abounds with claims that elderberries contain alkaloids, and suggesting that the purported alkaloids therein are toxic. For example, the USDA-NRCS Plant Guide for American Elderberry (2003) states “The active alkaloids in elderberry plants are hydrocyanic acid and sambucine. Both alkaloids will cause nausea so care should be observed with this plant.” However, there is no scientific
citation to support this statement, nor can a definitive corroborating published work be found. Nevertheless, such assertions are widely perpetuated throughout the internet and popular media. In fact, hydrocyanic acid is NOT considered an alkaloid, but is a weak acid formed by dissolving HCN (a gas) in water [National Research Council (US) Subcommittee on Acute Exposure Guideline Levels 2002]. As stated above, the potential occurrence of HCN in American elderberry fruit is very low; therefore, the formation of harmful amounts of hydrocyanic acid in either raw or processed elderberry products is inherently unlikely. Similarly, sambucine (also known as sambucin, antirrhinin, and cyanidin 3-O-rutinoside) is also not an alkaloid, but rather an anthocyanin (red pigment) that can act as an anti-oxidant in the human body upon consumption (Lila 2004). In high doses, however, sambucine may react in the human body in the presence of certain enzymes to produce an alkaloid that would be considered toxic (Kamsteeg et al. 1978).

The authors are aware of some rare anecdotal incidents where people who consumed large amounts of raw elderberries experienced upset stomach. The cause of this may be related to individual sensitivities to elderberry fruits in general, or possibly to one or more specific compounds in elderberry. The bottom line is that more research is needed to understand not only the health-benefitting metabolites and attributes of elderberry, but also to scientifically confirm or debunk the widespread unsubstantiated claims regarding the supposed toxicity and potential negative side-effects of elderberry consumption.

5.7 Horticulture and Developing Markets

Historically, much of the American elderberry crop was harvested from wild plants under minimal management. While commercial-scale European elderberry production is well-established in Europe, American elderberry remained a largely undeveloped crop until interest in use of the fruit and flowers in dietary supplements surged in the early 2000s (Charlebois 2007). American elderberry is well-suited to horticultural production in and near its native environment, provided adequate management is employed. The rapidly growing need for standardized quality parameters in fruit and flower production intended for commercial processed products has given rise to the development of improved elderberry cultivars and recommended production practices (Byers et al. 2014; Thomas et al. 2015a). Additionally, the importance of sustainable and profitable production has helped drive farmers and elderberry researchers into increasingly intensive management of American elderberry. Production practices developed in the twentieth century focused primarily on maximizing raw fruit production for processing markets (jelly, jam, juice, wine). More recently, as interest in the medicinal attributes of American elderberry has grown, emphasis has shifted to production practices that not only emphasize productivity, but also influence a range of elderberry bioactive compounds found in fruit and flowers. An overview of modern production practices is detailed in Charlebois et al. (2010).
Among the many production practices available to farmers, cultivar selection has perhaps the greatest influence on not only profitability, but also fruit and flower quality parameters. Cultivar selection with American elderberry is a recent development (Charlebois et al. 2010), and, in part, reflects the need among elderberry farmers and processors for uniform raw materials. Selecting cultivars with regional adaptation can help drive elderberry production in new areas; the success of the Missouri (USA) industry is due in part to the release of cultivars adapted to that region (Byers et al. 2010; Byers and Thomas 2011). While genotype has a demonstrated effect on the spectrum and levels of bioactive compounds found in American elderberry cultivars (Thomas et al. 2015b), establishing a planting that consistently produces fruit or flowers that meet quality standards is confounded by the interaction of genotype with environment (Finn et al. 2008; Perkins-Veazie et al. 2015; Thomas et al. 2008; Thomas et al. 2013).

Production practices that enhance productivity have a role to play in sustainable American elderberry production (Byers et al. 2014). Pruning and fertility management practices that influence plant growth and harvest efficiency by promoting uniform ripening have the potential to improve the consistency of processed products. For example, research at the University of Missouri/Missouri State University (Thomas et al. 2009) demonstrated that, for many American elderberry genotypes, removal of plants to the ground during the winter resulted in regrowth the following season that produced a fruit crop that ripened uniformly. This approach to pruning, while widely adopted by elderberry farmers in the central USA, may have limitations in production areas with shorter growing seasons. Elderberry fertility management has an important influence on plant growth and quality parameters in flowers and fruit. Initial studies by Byers et al. (2015) suggest that elemental content of elderberry plant parts could help guide a fertility management plan, thus giving farmers a useful management tool. Additional research is needed to determine optimum nutrient application rates and timing. While much of the American elderberry industry targets fruit production, elderberry flowers are of growing interest as a medicinal product. McGowan et al. (2019) demonstrated that management practices can be implemented that offer the potential of both a fruit and flower harvest from the same plant.

Pest and disease issues have the potential to reduce profitability of elderberry production and influence flower and fruit quality, but little research has been published exclusively on American elderberry. Warmund et al. (2019) confirmed that elderberry rust (Puccinia sambuci) requires an alternate host (sedge; Carex sp.) to complete its life cycle, and documented potential economic losses and reduction to fruit quality at various levels of infection; for even moderate incidences of rust, control measures may be warranted. Microscopic Eriophyid mites are a well-known pest of European elderberry in Europe (Vaněčková-Skuhravá 1996), and are also problematic in North America on American elderberry. Warmund and Amrine (2015) studied two mite species (Phyllocoptes wisconsinensis and a new, unnamed species of Phyllocoptes) on American elderberry and determined that the majority of over-wintering female protogynes shelter under leaf buds 14–24 cm from the terminus of the stem. Thus, they propose that pruning and removal of over-wintering...
stems may provide adequate mite control. Keller et al. (2015) surveyed viruses in American elderberry samples from Missouri and identified two new Carlavirus in most of the samples. The economic impact of these viruses, if any, is unknown. The researchers were able to use meristem culture to eliminate the viruses from several cultivars. Insects noted to be of particular concern with American elderberry include spotted wing drosophila (*Drosophila suzukii*), Japanese beetle (*Popillia japonica*), elder shoot borer (*Achatodes zeae*), elderberry sawfly (*Tenthredo grandis*), and elderberry longhorn beetle (*Desmocerus palliatus*) (Byers et al. 2014). Even with native crops such as elderberry, when plants are brought together into monocultures for efficient and economic production, pests and diseases must be monitored and addressed.

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