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ARTICLE

An Evidence-Based Systematic Review of Elderberry and Elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration

Catherine Ulbricht, PharmD[1], Ethan Basch, MD, MPhil[2], Lisa Cheung, PharmD[3], Harley Goldberg, DO[4], Paul Hammerness, MD[5], Richard Isaac[6], Karta Purkh Singh Khalsa, DN-C, RH[7], Aviva Romm, BSc, CPM, RH (AHG)[8], Idalia Rychlik, PharmD[9], Minney Varghese, BS[10], Wendy Weissner, BA[6], Regina C. Windsor, MPH[6], & Jayme Wortley, PharmD[11]

[1]Massachusetts General Hospital, Boston, MA, USA, [2]Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA, [3]University of Rhode Island, 45 Upper College Road, Kingston, RI 02881, USA, [4]Kaiser Permanente, Oakland, CA, USA, [5]Harvard Medical School, 25 Shattuck St, Boston, MA, [6]Natural Standard Research Collaboration, Somerville, MA, [7]Bastyr University, 14500 Juanita Drive Northeast, Kenmore, WA 98028-4966, USA, [8]American Herbalists Guild, Canton, GA, USA, [9]Massachusetts College of Pharmacy, 179 Longwood Ave, Boston, MA 02115, USA, [10]Northeastern University, 360 Huntington Ave, Boston, MA, [11]East Tennessee State University, Gatton College of Pharmacy, 807 University Pkwy, Johnson City, TN

ABSTRACT. An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration consolidates the safety and efficacy data available in the scientific literature using a validated, reproducible grading rationale. This article includes written and statistical analysis of clinical trials, plus a compilation of expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. Adverse effects, dosing, elder, elderberry, elderflower, evidence-based, interactions, pharmacodynamics, pharmacology, pharmacokinetics, Sambucus nigra, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOM, the

Address correspondence to: Catherine Ulbricht, PharmD, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (E-mail: ulbricht@naturalstandard.com).

Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to July 2013. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts and consulted experts when applicable. Authors of studies were contacted when clarification was required.

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Synonyms/Common Names/Related Substances

- Almindelig hyld (Danish), alpha-amyrenone, alpha-amyrin, anthocyanins, baccae, baises de sureau (French), battree, beta-sitosterol, betulin, black berried alder, black elder, black elderberry, boor tree, bountry, boure tree, busine (Russian), Caprifoliaceae (family), cyanidin-3-glucoside, cyanidin-3-glucoside monoglucuronide, cyanidin-3-sambubioside, devil's eye, elderberry, elderberry anthocyanins, elderberry bark agglutinin, elderberry juice, ellanwood, ellhorn, European alder, European elder, European elder fruit, European elderberry, European elderflower, frau holloe, German elder, Holunderbeeren (German),

Holunderblüten (German), hyperoside, inking elder, lady elder, mucilage, nigrin b, *N*-phenylpropenoyl-L-amino acid amides, old gal, old lady, oleanolic acid, peonidin monoglucuronide, peonidin-3-glucoside, peonidin-3-sambubioside, pipe tree, plastocyanin, quercetin, Rubini® (elderberry extract), rutin, Sambreo, *Sambuci* flos, *Sambuci* fructus, *Sambucipunct sambucus*, sambuco (Italian), *Sambucus sieboldiana* (Japanese red elder), schwarzer Holunder (German), sambunigrin, sieboldin-b, suco (Spanish), sureau noir (French), sweet elder, tannins, tetrameric, tree of doom, yakori bengestro.

- **Selected combination products**: OptiBerry IH141 (contains wild blueberry, strawberry, cranberry, wild bilberry, elderberry, raspberry extracts), Sinupret® (contains *Sambucus nigra* flowers, gentian root, verbena, cowslip flower, and sorrel), Sambucol® Active Defense (contains elderberry extract, vitamin C, zinc *Echinacea angustifolia*, *Echinacea purpurea*, and propolis); Sambucol® Immune System (contains elderberry, *Echinacea angustifolia* root, *Echinacea purpurea*, propolis, vitamin C, zinc); Sambucol® for Kids (contains elderberry, *Echinacea purpurea*, *Echinacea angustifolia* root, propolis). A phytotherapeutic compound contained *Pimpinella anisum*, *Foeniculum vulgare*, *Sambucus nigra*, and *Cassia angustifolia*.
- **Note**: Several species of *Sambucus* produce elderberries. Most scientific literature pertains to *Sambucus nigra*. Other species with similar chemical components include the American elder or common elder (*Sambucus canadensis*), antelope brush (*Sambucus tridentata*), blue elderberry (*Sambucus caerulea*), danewort (*Sambucus ebulus*), dwarf elder (*Sambucus ebulus*), red-fruited elder (*Sambucus pubens*, *Sambucus racemosa*), and *Sambucus formosana*. American elder (*S. canadensis*) and European elder (*S. nigra*) are often discussed simultaneously in the literature, since they have many of the same uses and contain common constituents.
- **Note**: This review does not include *Sambucus nigra* agglutinin (SNA) affinity chromatography.

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- Several species of *Sambucus* produce elderberries. Most research and publications refer to *Sambucus nigra*. Other species with similar chemical components include the American elder or common elder (*Sambucus canadensis*), antelope brush (*Sambucus tridentata*), blue elderberry (*Sambucus caerulea*), danewort (*Sambucus ebulus*), dwarf elder (*Sambucus ebulus*), red-fruited elder (*Sambucus pubens*, *Sambucus racemosa*), and *Sambucus formosana*. American elder (*S. canadensis*) and European elder (*S. nigra*) are often discussed simultaneously in the literature, because they have many of the same uses and contain common constituents.
- According to secondary sources, European elder grows up to 30 ft tall and is native to Europe, but has been naturalized to the Americas. Historically, the flowers and leaves have been used for pain relief, swelling, inflammation, and diuresis

(urine production), and as a diaphoretic or expectorant. The leaves have been used externally for sitz baths. The bark, when aged, has been used as a diuretic, laxative, or emetic (to induce vomiting). The berries have been used traditionally in food as flavoring and in the preparation of elderberry wine and pies.

- According to secondary sources, the flowers and berries (blue and black only) are used most often medicinally. They contain flavonoids, which have been found preclinically to possess a variety of biochemical and pharmacological actions, including antioxidant and immunologic properties that have shown benefit in treating influenza, bacterial sinusitis, and bronchitis. Although it has been hypothesized to be beneficial, definitive evidence from well-conducted human clinical trials is currently lacking regarding the use of elder, especially as monotherapy.
- The bark, leaves, seeds, and raw or unripe fruit contain the cyanogenic glycoside sambunigrin, which is potentially toxic.

Scientific Evidence

Influenza	B
Bacterial sinusitis	C
Bronchitis	C
Cardiovascular disease risk	C
Constipation	C
Gingivitis	C
Hyperlipidemia	C
Obesity	C

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1 to 2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case–control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory.

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Level of Evidence Grade	Criteria
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case–control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case–control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the five-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996; 17[1]:1–12).
†Listed separately in the "Historical or Theoretical Uses That Lack Sufficient Evidence" section.

Historical or Theoretical Uses That Lack Sufficient Evidence

- Alzheimer's disease, angiogenesis (antiangiogenic) (Bagchi, Sen, Bagchi, & Atalay, 2004; Roy et al., 2002), anti-inflammatory (Harokopakis, Albzreh, Haase, Scannapieco & Hajishengallis, 2006; Mascolo et al., 1987), antioxidant (Cao & Prior, 1999; Kaack & Austed, 1998), antispasmodic, asthma, astringent, blood pressure control (Chrubasik et al., 2008; Hasani-Ranjbar, Nayebi, Larijani, & Abdollahi, 2009), blood vessel disorders, burns, cancer (de Benito et al., 1998; Lukash et al., 1997), circulatory stimulant, colds (Roxas & Jurenka, 2007), colic, cough suppressant, diabetes, diaphoretic (Zakay-Rones et al., 1995), diuretic (Beaux, Fleurentin, & Mortier, 1999), edema, epilepsy, fever, flavoring, fragrance, gastrointestinal disorders, gout, hair dye, hay fever, headache, *Helicobacter pylori*, herpes simplex virus, HIV (Konlee, 1998), immune stimulant (Barak, Halperin, & Kalickman, 2001), insomnia, joint swelling, kidney disease, laryngitis, liver disease, measles, migraines, mosquito repellant, nerve pain, osteoporosis, psoriasis, respiratory distress, sedative, skin infections, skin irritation (chafing), stress reduction, syphilis, toothache, ulcerative colitis, vomiting.

Expert Opinion and Historic/Folkloric Precedent

- According to an ethnobotanical survey, *Sambucus nigra* is one of the plants most commonly used for medicinal purposes (Jaric et al., 2007). Historically, the leaves have been considered to relieve pain and promote healing when applied as a poultice. Native Americans used elder for infections, coughs, and skin conditions. Elderflower has been used as an insect repellent. When mixed with sage, lemon juice, vinegar, and honey, elder has been used as a gargle for coughs, head colds, laryngitis, flu-like symptoms, and shortness of breath. It has been used on the skin as an astringent in rheumatism and for swelling or inflammation. When mixed with peppermint and honey, hot elder has been used to induce diaphoresis to

treat colds. Ancient Egyptians used elder flowers to improve complexion and heal burns.

- According to secondary sources, elder extracts are used as flavoring in foods and beverages, and in perfumes, hair dyes, scented ointments, skin lotions, and insect repellent. Elder has also been used in wine, pies, and lemonade.
- Elderflower has approval status by the German Commission E for colds. The bark, leaves, and berries of the plant are lacking approval by the World Health Organization (WHO), the European Scientific Cooperative on Phytotherapy (ESCOP), and the German Commission E for any use (Akerreta, Cavero, & Calvo, 2007).
- Marz et al. published a review of the evidence regarding the use of Sinupret® for sinusitis (Marz, Ismail, & Popp, 1999). The authors cited preclinical reports of secretolytic, anti-inflammatory, immunomodulatory, and antiviral effects. They also noted human research suggesting a favorable safety profile and efficacy when combination products containing elder, such as Sinupret®, were added to antibiotics and conventional decongestant drugs.
- *Sambucus canadensis* L., or elderflower, used as a flavoring or seasoning, is on the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list. Other species of elderberry are not listed on the FDA GRAS list.

Brief Safety Summary

- Likely safe: According to secondary sources, when cooked berries are consumed in amounts usually found in foods. According to secondary sources, flowers are believed to be safe for use in food, provided that hydrogen cyanide (HCN) levels are below 25 ppm. Short-term use of elder flowers has not been associated with adverse effects in the available literature. Marz et al. reported a favorable safety and efficacy profile when combination products containing elder, such as Sinupret®, were added to antibiotics and conventional decongestant medications (Marz et al., 1999).
- Possibly unsafe: Elderberry products should be used under the direction of a qualified healthcare provider, due to the risk of cyanide toxicity, especially from elder bark, root, leaves, or juice (Anonymous, 1984; Kunitz, Melton, Updyke et al., (1984)). According to secondary sources, the berries must be cooked sufficiently to avoid the risk of nausea or vomiting or cyanide toxicity. When used in patients with arrhythmias or cardiovascular disease, due to the potential of tachycardia from cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984). When used in patients on blood pressure medications, due to the potential of blood pressure lowering, according to human research (Chrubasik et al., 2008; Hasani-Ranjbar, Nayebi, Larijani, & Abdollahi, 2009). When used in patients on chemotherapy agents, due to the potential of increased adverse effects (de Benito et al., 1998; Lukash et al., 1997). When used in patients with CNS disorders, due to the potential for CNS depression from cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984). When used in patients with dermatological conditions, due to the potential for application site reactions from patches, according to human research (Grbic, Wexler, Celenti, Altman, & Saffer, 2011). When used in patients with diabetes or those taking antidiabetic agents, due to stimulation of glucose metabolism and

promotion of insulin secretion from beta cells in vitro (Gray, Abdel-Wahab, & Flatt, 2000). When used in patients with diarrhea or conditions causing diarrhea, due to the potential of laxative effects, according to human research (Picon et al., 2010). When used in patients taking diuretics, due to the diuretic properties of elder, according to animal research (Beaux, Fleurentin, & Mortier, 1999). When used in patients with eating disorders or those who are underweight, due to the potential for anorexia or decreased mean body mass, according to human research (Chrubasik et al., 2008; Grbic et al., 2011; Hasani-Ranjbar et al., 2009). When used in patients who are female, due to the potential for dysmenorrhea, according to human research (Grbic et al., 2011). When used in patients with gastrointestinal disorders, due to the potential for gastrointestinal distress or upset, diarrhea, nausea, vomiting, abdominal cramps, and dyspepsia (Anonymous, 1984; Grbic et al., 2011; Kunitz et al., 1984; Tsui, Dennehy, & Tsourounis, 2001). When used in patients with hypokalemia, due to the potential for decreased potassium, according to human research (Picon et al., 2010). When used in patients with migraines, due to the potential for headache, according to human research (Grbic et al., 2011). When used in patients with muscle pain, due to the potential for backaches, according to human research (Grbic et al., 2011). When used in patients with respiratory disorders, due to the potential for respiratory depression from cyanide poisoning (Anonymous, 1984; Kunitz, et al., 1984) or coughing, according to human research (Grbic et al., 2011). When used in patients taking theophylline, due to the potential to inhibit xanthine oxidase and affect levels, according to secondary sources.

- Likely unsafe: according to secondary sources, when the bark, roots, leaves, and unripe berries of the elder plant are consumed, due to the risk of cyanide poisoning. With known allergy or hypersensitivity to elder, as well as plants in the Caprifoliaceae (honeysuckle) family, according to secondary sources.

DOSING/TOXICOLOGY

General

- Doses may be based on those most commonly used in available trials or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- According to secondary sources, dried elderflower is often standardized to contain at least 0.8% total flavonoids calculated as isoquercitrin. Dried flower preparations often contain at least 25% water-soluble extract.
- The standardized elderberry product Sambucol® is a 38% standardized black elderberry extract containing three flavonoids. For children, Sambucol® is a 19% standardized black elderberry juice (Zakay-Rones et al., 1995).

- According to secondary sources, Sambucol® Active Defense™ contains a 38% standardized black elderberry extract, plus vitamin C, zinc, propolis, and a proprietary blend of *Echinacea angustifolia* and *Echinacea purpurea*.
- The standardized elderberry product Sinupret® (Quanterra® Sinus Defense) is an herbal mixture containing 18 mg of flos *Sambucus nigra* (elderflower), 18 mg of herba *Verbenae off*. (vervain wort), 6 mg of radix *Gentianae luteae* (gentian root), 18 mg of flos *Primulae veris cum calycibus* (cowslip flowers with calyx), and 18 mg of herba *Rumicis acetosae* (sorrel) (Neubauer & März, 1994).

Dosing

Adult (age ≥18)

Oral.

- **General**: according to secondary sources, a dose of 3–5 g of dried elder flowers steeped in one cup of boiling water for 10–15 min has been taken by mouth three times daily. Be aware of possible toxicity.
- **Cardiovascular disease risk**: patients received two capsules (500 mg) of elderberry extract (containing 125 mg of anthocyanin (cyanidin-3-glucoside), equivalent to anthocyanin levels measured in 25 g of elderberries, 140 g of blackberries, and 100 g of blueberries) twice daily (in the morning and at night) for 12 weeks (Curtis et al., 2009).
- **Hyperlipidemia**: patients were given 400 mg of spray-dried powder capsules containing 10% anthocyanins three times daily equivalent to 5 mL of elderberry juice for two weeks (Mulleder, Murkovic, & Pfannhauser, 2002). Patients were given spray-dried elderberry juice containing 120–4,000 mg of anthocyanins daily for 2–3 weeks (Vlachojannis, Cameron, & Chrubasik, 2010).
- **Influenza**: Patients received 175 mg of proprietary elderberry extract lozenge four times daily for two days (Kong, 2009). Patients were given 15 mL of elderberry syrup four times daily for five days for influenza symptoms in another clinical trial by the same author group (Zakay-Rones, Thom, Wollan, & Wadstein, 2004).

Topical

- **General**: according to secondary sources, cream has been prepared by taking several handfuls of fresh elder flowers, mixing in liquefied petroleum jelly, simmering for 40 min, filtering, and allowing the formula to solidify. This has been applied to the hands at bedtime.

Children (age <18).

- Insufficient available evidence.

Toxicology.

- The bark, root, and leaves of *S. nigra* contain the cyanogenic glycoside sambunigrin, which is potentially toxic, and contact may lead to cyanide poisoning. Flowers may be used in food provided hydrogen cyanide (HCN) levels are below

25 ppm. Purified galactose-specific lectin from *S. nigra* flowers at 2 mg/mL possesses mutagenic activity (Lukash et al., 1997).

- **Overdose**: according to secondary sources, Ipecac (within 30 min) has been recommended following ingestion of elder leaves, roots, bark, or unripe fruit. Activated charcoal with cathartic may be used, although cathartics may be inadvisable if diarrhea has developed. Emesis and gastric lavage are recommended in cases of cyanide toxicity. Amyl nitrate, sodium nitrate, and sodium thiosulfate may also be used.
- At a dose of 3 g/kg, *S. nigra* extract did not modify the growth rate of rats (Mascolo et al., 1987).

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

- According to secondary sources, avoid in individuals with known allergy or hypersensitivity to elder, as well as plants in the Caprifoliaceae (honeysuckle) family.
- Elderberry allergy elicited by 33 kDa allergen, present in pollen, flower, and berry extracts with significant homology to ribosomal inactivating proteins, has been observed (Forster-Waldl et al., 2003).
- According to secondary sources, there are anecdotal reports of allergies in children playing with toys made from fresh elder stems. In theory, according to in vitro research, lectins from *Sambucus nigra* may have the ability to stimulate cytokine release and induce type 1 hypersensitivity (Haas et al., 1999).
- In human research, three patients reported application site reaction during use of a combination transmucosal herbal periodontal patch (THPP) (Grbic et al., 2011).

Adverse Effects

- **General**: the bark, root, and leaves of *S. nigra* contain the cyanogenic glycoside sambunigrin, which is potentially toxic, and contact may lead to cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984). Elderberry products should be used under the direction of a qualified healthcare provider, due to the risk of cyanide toxicity, especially from elder bark, root, leaves, or juice (Anonymous, 1984; Kunitz et al., 1984). According to secondary sources, the berries must be cooked to prevent nausea or cyanide toxicity.
- **Cardiovascular**: cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz et al., 1984), including tachycardia.
- **Dermatologic**: in human research, three patients reported application site reaction during use of a combination THPP (Grbic, Wexler, Celenti, Altman, & Saffer, 2011).
- **Endocrine**: in vitro research (Gray et al., 2000) refuted earlier research (Swanston-Flatt, Day, Flatt, Gould, & Bailey, 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Gastrointestinal**: there are reports of gastrointestinal distress, diarrhea, vomiting, abdominal cramps, and weakness after drinking elderberry juice made from crushed leaves, stems, and uncooked elderberries (Anonymous, 1984; Kunitz

et al., 1984; Tsui et al., 2001). According to secondary sources, elder may also possess laxative effects. According to secondary sources, the combination formula Sinupret®, which contains elder in combination with gentian root, sorrel, verbena, and cowslip flower, is anecdotally said to be well tolerated, although infrequent cases of gastrointestinal upset have been reported. In human research, dyspepsia ($N = 1$), nausea ($N = 1$), nausea and/or vomiting ($N = 1$), taste perversion ($N = 6$), and pharyngitis ($N = 1$) were reported during use of a combination THPP (Grbic et al., 2011). In human research, patients using a mouthwash containing *S. nigra* reported teeth staining and discoloration ($N = 3$) and mouth sensitivity ($N = 1$) (Samuels, Grbic, Saffer, Wexler, & Williams, 2012).

- **Genitourinary**: in human research, a patient reported dysmenorrhea during use of a combination THPP (Grbic et al., 2011).
- **Musculoskeletal**: in human research, backache ($N = 1$), anorexia ($N = 1$), and accidental injury ($N = 3$) were reported during use of a combination THPP (Grbic et al., 2011).
- **Neurologic/CNS**: cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz et al., 1984), including CNS and respiratory depression, and weakness. Three patients reported headaches during use of a combination THPP (Grbic et al., 2011).
- **Renal**: in theory, high-dose or long-term use of elder flowers may have diuretic effects (Beaux et al., 1999).
- **Respiratory**: a patient reported increased coughing during use of a combination THPP (Grbic et al., 2011).

Precautions/Warnings/Contraindications

- Elderberry products should be used under the direction of a qualified healthcare provider, due to the risk of cyanide toxicity, including from elder bark, root, leaves, uncooked berries, or juice (Anonymous, 1984; Kunitz et al., 1984).
- Use cautiously in patients with arrhythmias or cardiovascular disease, due to the potential of tachycardia from cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984).
- Use cautiously in patients on blood pressure medications, due to the potential of blood pressure lowering, according to human research (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).
- Use cautiously in patients on chemotherapy agents, due to the potential of increased adverse effects (de Benito et al., 1998; Lukash et al., 1997).
- Use cautiously in patients with CNS disorders, due to the potential for CNS depression from cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984).
- Use cautiously in patients with dermatological conditions, due to the potential for application site reactions from patches, according to human research (Grbic et al., 2011).
- Use cautiously in patients with diabetes or those taking antidiabetic agents, due to stimulation of glucose metabolism and promotion of insulin secretion from beta cells in vitro (Gray et al., 2000).
- Use cautiously in patients with diarrhea or conditions causing diarrhea, due to the potential of laxative effects, according to human research (Picon et al., 2010).

- Use cautiously in patients taking diuretics, due to the diuretic properties of elder, according to animal research (Beaux, Fleurentin, & Mortier, 1999).
- Use cautiously in patients with eating disorders or those who are underweight, due to the potential for anorexia or decreased mean body mass, according to human research (Chrubasik et al., 2008; Grbic et al., 2011; Hasani-Ranjbar et al., 2009).
- Use cautiously in patients who are female, due to the potential for dysmenorrhea, according to human research (Grbic et al., 2011).
- Use cautiously in patients with gastrointestinal disorders, due to the potential for gastrointestinal distress or upset, diarrhea, nausea, vomiting, abdominal cramps, and dyspepsia (Anonymous, 1984; Grbic et al., 2011; Kunitz et al., 1984; Tsui et al., 2001).
- Use cautiously in patients with hypokalemia, due to the potential for decreased potassium, according to human research (Picon et al., 2010).
- Use cautiously in patients with migraines, due to the potential for headache, according to human research (Grbic et al., 2011).
- Use cautiously in patients with muscle pain, due to the potential for backaches, according to human research (Grbic et al., 2011).
- Use cautiously in patients with respiratory disorders, due to the potential for respiratory depression from cyanide poisoning (Anonymous, 1984; Kunitz et al., 1984) or coughing, according to human research (Grbic et al., 2011).
- Use cautiously in patients taking theophylline, due to the potential to inhibit xanthine oxidase and affect levels, according to secondary sources.
- Avoid in individuals with known allergy or hypersensitivity to elder, as well as plants in the Caprifoliaceae (honeysuckle) family, according to secondary sources.

Pregnancy & Lactation

- There is a lack of sufficient data on the use of elderberry during pregnancy or lactation. One study reported gastrointestinal discomfort in pregnant women taking elderberry (Tsui et al., 2001). A surveillance study of the multi-ingredient product Sinupret® in pregnant women reported no excess teratogenicity compared to controls not using Sinupret® (Ismail, Wiesel, Marz, & Queisser-Luft, 2003).
- Information on elder's effects on lactation is lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

INTERACTIONS

Elder/Drug Interactions

- **Antibiotics**: in human research, concurrent use of doxycycline with Quanterra® Sinus Defense or Sinupret® has been shown to synergistically improve outcomes in patients with acute bacterial sinusitis (Neubauer & Mrz, 1994).
- **Antidiabetic agents**: in vitro research (Gray et al., 2000) refuted earlier research (Swanston-Flatt et al., 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Antihypertensive agents**: in human research, elderberry improved blood pressure (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).

- **Anti-inflammatory agents**: anti-inflammatory properties have been demonstrated in animal studies using elder flowers (Mascolo et al., 1987). *S. nigra* is reported to modulate the inflammatory cytokines IL-1 and TNF-alpha in vitro (Mascolo et al., 1987; Yesilada et al., 1997); increase human basophil secretion of IL-4, IL-13, and histamine (Haas et al., 1999); alter function of human neutrophils (Timoshenko & Cherenkevich, 1995); and inhibit macrophage release of proinflammatory cytokines and nuclear transcription factor-kB and phosphatidylinositol 3-kinase in vitro (Harokopakis et al., 2006).
- **Antilipemics**: in human research, elderberry juice reduced postprandial lipid levels (Vlachojannis, Cameron, & Chrubasik, 2010). In human research, elderberry juice decreased cholesterol concentrations and had minor effect on other serum lipids (Mulleder et al., 2002).
- **Antineoplastic agents**: preclinical research reports that elder may increase the effects and possible adverse effects of some cancer chemotherapies, including alkylating agents (de Benito et al., 1998; Lukash et al., 1997). In vitro, *S. nigra* inhibited nuclear protein transport in neuroblastoma cells (Emig, Schmalz, Shakibaei, & Buchner, 1995).
- **Antiobesity agents**: in human research, an *S. nigra* (elderberry)-containing product decreased mean body weight (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).
- **Antivirals**: in laboratory, animal, and human research, elder had antiviral effects (Kong, 2009; Konlee, 1998; Serkedjieva et al., 1990; Vlachojannis et al., 2010; Zakay-Rones et al., 1995).
- **Caffeine**: according to secondary sources, the flavonoid quercetin, which is found in elder, has been reported to inhibit xanthine oxidase and may affect caffeine levels.
- **Cardiovascular agents**: in human research, cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz, Melton, Updyke, et al., 1984), including tachycardia.
- **Decongestants**: according to secondary sources, according to preliminary research in patients, increased benefits may be seen when elder is used in combination with decongestants, such as oxymetazoline (Afrin®) and antibiotics.
- **Dental agents**: in human research, an *S. nigra*-containing mouthwash decreased the gingival index score (Samuels, Grbic, Saffer, Wexler, & Williams, 2012)
- **Diuretics**: according to animal research, elder may possess diuretic properties and should be used cautiously with drugs that increase urination (Beaux, Fleurentin, & Mortier, 1999).
- **Electrolyte modulators**: in human research, an *S. nigra*-containing product produced a small reduction in potassium during treatment; however, the study did claim that there were no significant differences and whether these effects were from the combination product (Picon et al., 2010).
- **Gastrointestinal agents**: in human research, there are reports of gastrointestinal distress, diarrhea, vomiting, abdominal cramps, and weakness after drinking elderberry juice made from crushed leaves, stems, and uncooked elderberries (Anonymous, 1984; Kunitz et al., 1984; Tsui et al., 2001). According to secondary sources, elder may also possess laxative effects and should be used cautiously with other laxatives.

- **HIV agents**: in human research, Sambucol® decreased viral load (Konlee, 1998).
- **Laxatives**: according to secondary studies, elder may possess laxative effects and should be used cautiously with other laxatives. In human research, an *S. nigra*-containing product decreased colonic transit time (CTT) and increased daily evacuations (Picon et al., 2010).
- **Methylxanthines**: according to secondary studies, the flavonoid quercetin, which is found in elder, has been reported to inhibit xanthine oxidase and may affect caffeine and theophylline levels.
- **Neurologic agents**: in human research, cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz et al., 1984), including CNS and respiratory depression, and weakness.
- **Vascular endothelial growth factor (VEGF) inhibitors**: n vitro, OptiBerry IH141 inhibited TNF-alpha-induced VEGF (Bagchi, Sen, Bagchi, & Atalay, 2004).

Elder/Herb/Supplement Interactions

- **Antibacterials**: in human research, concurrent use of doxycycline with Quanterra® Sinus Defense or Sinupret® has been shown to synergistically improve outcomes in patients with acute bacterial sinusitis (Neubauer & Mrz, 1994). Additional supporting evidence in this area is limited.
- **Anti-inflammatory herbs**: anti-inflammatory properties have been demonstrated in in vitro and animal studies using elder flowers (Haas et al., 1999; Harokopakis et al., 2006; Mascolo et al., 1987; Timoshenko & Cherenkevich, 1995; Yesilada et al., 1997).
- **Antilipemics**: in human research, anthocyanidin reduced postprandial lipid levels (Vlachojannis et al., 2010). In human research, elderberry juice decreased cholesterol concentrations and had minor effect on other serum lipids (Mulleder et al., 2002).
- **Antineoplastic herbs**: preclinical research reports that elder may increase the effects and possible adverse effects of some cancer chemotherapies, including alkylating agents (de Benito et al., 1998; Lukash et al., 1997). In vitro, *S. nigra* inhibited nuclear protein transport in neuroblastoma cells (Emig et al., 1995).
- **Antiobesity herbs**: in human research, an *S. nigra* (elderberry)-containing product decreased mean body weight (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).
- **Antioxidants**: elder preparations may exert antioxidant activity, and increased effects may be seen when elder is used in combination with other antioxidants, according to laboratory research (Cao & Prior, 1999; Kaack & Austed, 1998).
- **Antivirals**: in laboratory, animal, and human research, elder had antiviral effects (Kong, 2009; Konlee, 1998; Serkedjieva et al., 1990; Vlachojannis et al., 2010; Zakay-Rones et al., 1995).
- **Caffeine**: according to secondary sources, the flavonoid quercetin, which is found in elder, has been reported to inhibit xanthine oxidase and may affect caffeine levels.
- **Cardiovascular agents**: in human research, cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz et al., 1984), including tachycardia.
- **Decongestants**: in theory, increased benefits may be seen when elder is used in combination with decongestants.

- **Dental agents**: in human research, an *S. nigra*-containing mouthwash decreased the gingival index score (Samuels et al., 2012).
- **Diuretics**: elder may possess diuretic effects and should be used cautiously with other agents that increase urination (Beaux et al., 1999).
- **Electrolyte supplements**: in human research, an *S. nigra*-containing product reported a small reduction in potassium during treatment; however, the study did claim that there were no significant differences and whether these effects were from the combination product (Picon et al., 2010).
- **Gastrointestinal agents**: in human research, there are reports of gastrointestinal distress, diarrhea, vomiting, abdominal cramps, and weakness after drinking elderberry juice made from crushed leaves, stems, and uncooked elderberries (Anonymous, 1984; Kunitz et al., 1984; Tsui et al., 2001). According to secondary sources, elder may also possess laxative effects and should be used cautiously with other laxatives.
- **Hypoglycemics**: in vitro research (Gray et al., 2000) refuted earlier research (Swanston-Flatt et al., 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Hypotensives**: in human research, elderberry improved blood pressure (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).
- **Laxatives**: according to secondary sources, elder may possess laxative effects and should be used cautiously with other laxatives in human research, an *S. nigra*-containing product decreased CTT and increased daily evacuations (Picon et al., 2010).
- **Neurologic agents**: in human research, cyanide poisoning from bark, root, leaves, or juice may lead to toxicity (Anonymous, 1984; Kunitz et al., 1984), including CNS and respiratory depression, and weakness.

Elder/Food Interactions

- **Anthocyanin-rich foods**: certain foods rich in anthocyanin may increase effects of elder (Curtis et al., 2009). These include raspberries, blueberries, red grapes, plums, radishes, and red cabbage, as well as products with these ingredients (Curtis et al., 2009).
- **Sucrose**: ingestion of sucrose concomitantly with elderberry has been seen to reduce the excretion of anthocyanins found in elder (Mulleder et al., 2002).

Elder/Lab Interactions

- **Bilirubin**: in human research, elderberry (anthocyanins) produced significant change in plasma bilirubin, but the clinical impact was minimal, as the bilirubin levels were still within normal physiological levels (Curtis et al., 2009).
- **Blood glucose**: in vitro research (Gray et al., 2000) refuted earlier research (Swanston-Flatt et al., 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Blood pressure**: in human research, elderberry improved blood pressure (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).
- **Cholesterol**: in human research, elderberry juice reported reduced postprandial lipid levels (Vlachojannis et al., 2010). In human research, elderberry juice decreased cholesterol concentrations and had minor effect on other serum lipids (Mulleder et al., 2002).

- **Colonic transit time (CTT)**: in human research, an *S. nigra*-containing product decreased CTT (Picon et al., 2010).
- **Electrolytes**: in human research, an *S. nigra*-containing product reported a small reduction in potassium during treatment; however, the study did claim that there were no significant differences and whether these effects were from the combination product (Picon et al., 2010).

Elder/Nutrient Depletion:

- **Glucose**: in vitro research (Gray et al., 2000) refuted earlier research (Swanston-Flatt et al., 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Lipids**: in human research, elderberry juice reported reduced postprandial lipid levels (Vlachojannis et al., 2010). In human research, elderberry juice decreased cholesterol concentrations and had minor effect on other serum lipids (Mulleder et al., 2002).

MECHANISM OF ACTION

Pharmacology

- **Constituents**: there are multiple chemical and biochemical studies of chemical constituents in *S. nigra*. The bark contains alpha-amyrenone, alpha-amyrin, betulin, oleanolic acid, and beta-sitosterol (Lawrie, McLean & Paton, 1964), as well as nigrin b, a lectin similar to ricin, and other type 2 ribosome inactivating proteins (RIPs) that are less toxic to cells and animals (Battelli et al., 1997). The flowers and leaves contain flavonoids, including quercetin (up to 3%), rutin, hyperoside (Davidek, 1961), and anthocyanins (Mulleder et al., 2002), as well as essential oils (responsible for the muscat aroma characteristic of elder flowers) (Toulemonde & Richard, 1983), mucilage, tannins (3%), organic acids, glycoside (0.042% by weight), plastocyanin (Scawen, Ramshaw, Brown, & Boulter, 1974), and sambunigrin (0.042% by weight). High amounts of *N*-phenylpropenoyl-L-amino acid amides were found in the flowers of *Sambucus nigra* (Hensel et al., 2007).
- The fruit contains the protein *Sambucus nigra* agglutinin Ivf (SNAIVf), which is homologous to type 2 RIP (van Damme, Roy, Barre, Rouge et al., 1997), while the bark contains a novel type 2 RIP (SNLRP), consisting of an A-chain with *N*-glycosidase activity and a B-chain devoid of carbohydrate-binding activity normally present (van Damme, Barre, Rouge, van Leuven, & Peumans, 1997; van Damme, Roy, Barre, Citores et al., 1997). Two additional RIPs were further identified in bark (SNAI and SNAI') (van Damme, Roy, Barre, Citores et al., 1997), demonstrating the complexity of type 2 RIP and lectin mixture in *S. nigra*. The lectin isolated from bark is tetrameric with two distinct subunits and is rich in glutamine, glutamic acid, valine, and leucine (Broekaert, Nsimba-Lubaki, Peeters, & Peumans, 1984). The fruit type 2 RIP lectin is 10 amino acids longer than the bark lectin (Peumans, 1998). Elder RIPs with *N*-glycosidase activity are reported to inhibit protein synthesis in rabbits, but not in plants (de Benito et al., 1998).
- Quercetin is also present in elder and has been shown to be a potent inhibitor of xanthine oxidase (Chang, Lee, Lu, & Chiang 1993). *S. nigra* has been shown to bind heavy metals (Coupe, Taylor, & Roberts, 1995).

- According to secondary sources, additional elderberry constituents include cyanidin-3-glucoside and cyanidin-3-sambubioside, as well as four metabolites: peonidin-3-glucoside, peonidin-3-sambubioside, peonidin monoglucuronide, and cyanidin-3-glucoside monoglucuronide.
- **Experimental assays**: the lectin of *S. nigra* has been used in multiple experimental clinical assays, due to its carbohydrate binding properties and its ability to precipitate highly sialylated glycoproteins (Shibuya et al., 1987), including the use of *S. nigra* agglutinin binding to identify pregnant women at risk for preterm delivery (by detecting fibronectin in cervicovaginal secretions using a glycoprotein lectin immunoabsorbent assay) (Hampel, Kottgen, Dudenhausen, & Kottgen, 1999); distinguishing normal from stone-forming kidneys (using *N*-acetylneuraminic acid:calcium binding ratios) (Hofbauer et al, 1998); examining colorectal carcinoma by examining rates of colonic mucin sialylation (by comparing alpha 2,6-linked sialic acid vs. sialyl-Tn antigen) (Murayama et al., 1997); evaluating ulcerative colitis by monitoring differences in sialylation in Asian vs. European colitis patients (McMahon et al., 1997); examining increased beta-galactoside alpha 2,6-sialyltransferase activity (by detection of dioxigenin-conjugated *S. nigra* agglutinin) (Dall'Olio & Trere, 1993); evaluating SNA levels in women with breast and ovarian cancer (Goodarzi & Turner, 1995); glycohistochemically identifying microglial cells from Alzheimer's disease samples (Zambenedetti, Giordano, & Zatta, 1998); measuring decreased sialylation of glycoproteins in nasal glands of patients with sinusitis (Ueno et al., 1997); monitoring elevated serum sialic acids associated with increased cardiovascular mortality (Crook, Goldman, Dalziel, Madden, & McKenna, 1997); and enriching stem cell samples and depleting T cells in bone marrow harvests (Mumcuoglu, Manor, & Slavin, 1986).
- **Anti-inflammatory effects**: *S. nigra* is reported to modulate the inflammatory cytokines IL-1 and TNF-alpha in vitro (Mascolo et al., 1987; Yesilada et al., 1997); increase human basophil secretion of IL-4, IL-13, and histamine (Haas et al., 1999); alter function of human neutrophils (Timoshenko and Cherenkevich, 1995); and inhibit macrophage release of proinflammatory cytokines and nuclear transcription factor-kB and phosphatidylinositol 3-kinase in vitro (Harokopakis, Albzreh, Haase, Scannapieco, & Hajishengallis, 2006).
- **Antioxidant effects**: elderberries contain flavonoids (flavone, flavanone, isoflavone derivatives, and anthocyanins), which are reported to possess antioxidant activity and to protect against oxidative stressors, such as hydrogen peroxide, 2-amidinopropane, dihydrochloride (AAPH), ferrous sulfate, and ascorbic acid (Abuja, Murkovic, & Pfannhauser, 1998; Middleton & Kandaswami, 1992; Murkovic, Adam, & Pfannhauser, 2000; Youdim, Martin, & Joseph, 2000).
- **Antiproliferative effects**: in vitro, *S. nigra* agglutinin has been reported to inhibit nuclear protein transport in neuroblastoma cells, suggesting a functional significance of sialylation (Emig et al., 1995).
- **Antiviral effects**: in laboratory and animal research, *S. nigra* had antiviral effects by inhibiting influenza virus types A and B and herpes simplex-1 virus (Serkedjieva et al., 1990), reducing hemagglutination of red blood cells, and inhibiting replication of several strains of influenza A and B (Zakay-Rones et al., 1995). A case report exists of an HIV-positive woman, taking no HIV drugs, who

experienced a viral load drop from 17,000 to 4,000 after ingestion of Sambucol® with olive leaf extract (Konlee, 1998). The report also included a placebo controlled, double-blind study of Sambucol® associated with a rapid recovery from influenza and inhibited replications of nine other strains of the flu virus by elderberry. The mechanism is believed to be rendering viruses nonfunctional by staining and coating them. According to a review, in vitro and animal research reported that elderberry fruit (*Sambuci* fructus) had an effect on influenza, other viral infections, and increased antibody titers (Vlachojannis, Cameron, & Chrubasik, 2010). Human studies reported the efficacy of elderberry extract for flu-like symptoms (Kong, 2009).

- **Blood pressure effects**: in human research, an *S. nigra* (elderberry)-containing product improved blood pressure (Chrubasik et al., 2008; Hasani-Ranjbar, Nayebi, Larijani, & Abdollahi, 2009); however, details are lacking on whether these results were due to a decrease in mean body weight.
- **Cardioprotective effects**: in human research, elderberry (anthocyanins) lacked cardioprotective benefit in cardiovascular disease (CVD) after 12 weeks (Curtis et al., 2009). Significant changes in plasma levels of inflammatory biomarkers, vascular measures (including platelet reactivity, endothelin-1, blood pressure, and pulse), and concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and glucose, as well as renal and hepatic function, were lacking.
- **Diuretic effects**: in animal research, diuretic effects and sodium excretion were associated with an extract of *S. nigra* flowers (Beaux, Fleurentin, & Mortier, 1999).
- **Electrolyte effects**: in human research, an *S. nigra*-containing product reported a small reduction in potassium during treatment, however, the study did claim that there were no significant differences and whether these effects were from the combination product (Picon et al., 2010). The effects of *S. nigra* alone are unclear.
- **Gingival effects**: in human research, an *S. nigra*-containing mouthwash demonstrated a minimal, nonsignificant decrease in gingival index scores (Samuels, Grbic, Saffer, Wexler, & Williams, 2012).
- **Glucose/insulin metabolism**: in vitro research (Gray, Abdel-Wahab, & Flatt, 2000) refuted earlier research (Swanston-Flatt et al., 1989) and reported stimulation of glucose metabolism and promotion of insulin secretion from beta cells.
- **Hepatic effects**: in human research, elderberry (anthocyanins) lacked significant effects on levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and albumin; however, a significant change in plasma bilirubin was measured, but the clinical impact was minimal, as the bilirubin levels were still within normal physiological levels (Curtis et al., 2009).
- **Laxative effects**: in human research, an *S. nigra*-containing product decreased CTT and increased daily evacuations in patients with chronic constipation (Picon et al., 2010). The effects of *S. nigra* alone are unclear.
- **Lipid-lowering effects**: in human research, elderberry juice reduced postprandial lipid levels (Vlachojannis et al., 2010). In human research, elderberry juice decreased cholesterol concentrations and had minor effect on serum lipids (Mulleder et al., 2002).

- **Renal effects**: in human research, elderberry (anthocyanins) lacked significant effects on urea and creatinine (Curtis et al., 2009).
- **Vascular effects**: in vitro, the multi-ingredient product OptiBerry IH141 has been shown to possess antiangiogenic properties via inhibition of H_2O_2- and TNF-alpha-induced VEGF (Bagchi et al., 2004). In another study, elderberry extracts were associated with significantly impaired angiogenesis in human dermal microvascular endothelial cells (Roy et al., 2002).
- **Weight loss effects**: in human research, an *S. nigra* (elderberry)-containing product decreased mean body weight (Chrubasik et al., 2008; Hasani-Ranjbar et al., 2009).

Pharmacodynamics/Kinetics

- **Absorption**: anthocyanins, which are potent flavonoid antioxidants found in elder, are not absorbed in their unchanged glycosylated forms in humans (Milbury et al., 2002). The maximum concentration of anthocyanins found in blood after injection of a highly concentrated solution was 35 mg/mL at 1 hr, followed by a quick decay (Murkovic et al., 2000). In human research, 4 hr after the consumption, the two major anthocyanins in elderberry extract, cyanidin-3-glucoside and cyanidin-3-sambubioside (including the metabolites peonidin-3-glucoside, peonidin-3-sambubioside, peonidin monoglucuronide, and cyanidin-3-glucoside monoglucuronide) were detected in urine (Wu, Cao, & Prior, 2002).
- **Metabolism**: in human research, total elderberry extract anthocyanins demonstrated a low excretion of 554 ± 90 mcg (mean $\pm$ SD, $n = 4$) (0.077% of intake/4h, wt/wt) (Wu, Cao, & Prior, 2002).
- **Elimination**: the elimination of plasma anthocyanins appears to follow first-order kinetics, and most anthocyanin compounds are excreted in urine within 4 hr after ingestion (Milbury et al., 2002). After ingestion of about 30 mL of elderberry extract (147.3 mg of total anthocyanins), the $t_{1/2}$ was 1.74 hr (Bitsch, Janssen, Netzel, Strass, & Frank, 2004). The urinary excretion rate of intact anthocyanins was fast and appeared to be monoexponential, with high variability.

HISTORY

- According to secondary sources, legend states that Judas Iscariot was hanged from an elder tree and that the cross on which Jesus was hanged was made of elder. Traditionally, elder was used to ward off evil influences, witches, spirits, and death in England and Russia. Knots made from elder twigs were sometimes carried as charms to protect from rheumatism in England. The Serbs considered elder to be good luck.
- *Sambucus nigra* is a still commonly gathered in Poland (Luczaj & Szymanski, 2007) and Italy (Guarrera, 2005) for its food and medical uses.
- Inhabitants of the South-Slavic diaspora of Mundimitar (Montemitro) (southern Italy) use elderberry tree (*S. nigra*) for treating erysipelas in pigs (di Tizio, Luczaj, Quave, Redzic, & Pieroni, 2012).

EVIDENCE TABLE

Condition Treated	Study Type	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit (how strong is the effect?)	Absolute Risk Reduction	Number of Patients Needed to Treat for One Outcome	Comments
Influenza	Systematic review	Vlachojannis, 2010	Three trials	NA	NA	NA	NA	NA	Improvements were seen in patients after three to five days of treatment with Sambucol® or anthocyanidin.
Influenza	Randomized, double-blind, placebo controlled trial	Kong, 2009	64	Yes	4	Large	28	4	After 24 hr of treatment, symptoms of fever, headache, muscle aches, and nasal congestion were significant ($p < .0001$). Coughing and mucus discharge lacked significance. Improvement in all symptoms was seen at 48 hr in 28% of patients taking elderberry vs. placebo.
Influenza	Randomized double-blind, placebo controlled trial	Zakay-Rones, 1995	27	Yes	3	Large	53	2	Improved symptoms after three days in the elderberry group vs. six days in controls. Intent-to-treat analysis was lacking (40 subjects initially randomized).
Influenza	Randomized, double-blind, placebo controlled trial	Zakay-Rones, 2004	60	Yes	2	NA	NA	NA	Symptoms were relieved on average four days earlier, and use of rescue medication was significantly less than placebo group. Intent-to-treat analysis was lacking, and there was a small sample.
Bacterial sinusitis	Systematic review and meta-analysis	Melzer, 2006	Four trials, 900 patients	Yes	NA	Medium	NA	NA	BNO-101 (Sinupret®) had a favorable risk-benefit ratio when used as an add-on to antibacterial treatment; incidence of adverse events was similar to placebo.
Bacterial sinusitis	Randomized, double-blind, placebo controlled trial	Neubauer, 1994	160	Yes	4	Medium	28	4	Improved X-rays and symptoms after two weeks with herbal combination Sinupret® vs. placebo; all subjects received antibiotics and decongestants.
Bacterial sinusitis	Randomized, double-blind, placebo controlled trial	Richstein, 1980	31	Yes	2	Unclear	Unclear	Unclear	Lack of clear description of analysis precludes ability to calculate ARR and NNT.

Cardiovascular disease risk	Randomized, double-bind, placebo controlled, parallel trial	Curtis, 2009	57	No	4	NA	NA	NA	Most outcome measures lacked significance vs. placebo. Anthocyanin supplementation was safe but lacked additional cardioprotective benefits after 12 weeks of therapy in healthy, postmenopausal women.
Constipation	Randomized, single-blind, placebo controlled crossover trial	Picon, 2010	20	Yes	2	Medium	NA	NA	Patients taking a combination product containing 5.0 g of *Sambucus nigra* (*sabugueiro*) flower, had statistical improvements in colonic transit time of 62.9%.
Gingivitis	Phase II, randomized, double-blind, placebo controlled, crossover trial	Grbic, 2011	53	Yes	4	Small	NA	NA	A transmucosal herbal periodontal patch (THPP) significantly decreased gingival index scores at days 4 and 15.
Gingivitis	Randomized, double-blind, placebo controlled trial	Samuels, 2012	62	Yes	3	Large	NA	NA	HM-302 was the only active treatment to demonstrate a significantly better change in gingival index score and percent change.
Hyperlipidemia	Systematic review	Vlachojannis, 2010	Three trials	NA	NA	NA	NA	NA	A study in the systematic review reported a reduction in postprandial lipid levels in individuals taking 4,000 mg of anthocyanidin daily (*p*-value unclear).
Hyperlipidemia	Randomized, placebo controlled trial	Mülleder, 2004	34	No	2	NA	NA	NA	Two weeks was too short to determine benefit. Patients were not blinded.
Obesity	Systemic review	Hasani-Ranjbar, 2009	One trial	NA	NA	NA	NA	NA	Elderberry reported significant improvement in weight loss, blood pressure, and quality of life.

Explanation of columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study Design	Author, Year	*N*	Statistically Significant?	Quality of Study 0–2 = poor 3–4 = good 5 = excellent	Magnitude of Benefit	Absolute Risk Reduction	Number Needed to Treat	Comments

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- Randomized controlled trial (RCT): an experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- Equivalence trial: an RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care and may not include a placebo arm.
- Before and after comparison: a study that reports only the change in outcome in each group of a study and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- Case series: a description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterward). Case series are considered weak evidence of efficacy.
- Case–control study: a study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- Cohort study: a study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- Meta-analysis: a pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in

particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- Review: an author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- Systematic review: a review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically significant?

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p*-values). *P* = pending verification.

Quality of study

- A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 1996;17[1]:1–12). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad score calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:
  - Large: if >1 SD
  - Medium: if 0.5 to 0.9 SD
  - Small: if 0.2 to 0.4 SD.
- In many cases, studies do not report the SD of change of the outcome measure. However, the change in the SD of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled SD (effect size = [mean treatment − mean placebo]/SDp).

Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate − experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. P = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the absolute risk reduction into 1 (1/ARR). *P* = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

Note

- Due to the common use and study of elder in combination products, meta-analyses, systematic reviews, and randomized controlled trials of elder in combination products are included in the Evidence Table. Nonrandomized studies of elder as a monotherapy, as well as elder in combination products, are not included in the Evidence Table, but are briefly discussed in the Evidence Discussion.

Influenza

- **Summary**: in laboratory and animal research, *S. nigra* had antiviral effects by inhibiting influenza virus types A and B and herpes simplex-1 virus (Serkedjieva, Manolova, Zgorniak-Nowosielska et al., 1990), reducing hemagglutination of red blood cells, and inhibiting replication of several strains of influenza A and B (Zakay-Rones et al., 1995). An available study reported that elderberry juice may improve flu-like symptoms, such as fever, fatigue, headache, sore throat, cough, and aches, in less than half the time that it normally takes to recover from the flu (Zakay-Rones et al., 1995). However, the study was small and had design flaws, and it should be noted that the berries must be cooked to prevent nausea or cyanide toxicity. In another study, patients taking elderberry for 48 hr had a significant eradication of all investigated symptoms such as cough, fever, headache, mucus discharge, muscle aches, or nasal congestion (Kong, 2009). It remains unclear whether there is any benefit from elder for this condition. Additional research with further well-designed clinical trials is needed in this area before a firm conclusion may be reached. Elder should not be used in the place of other more proven therapies, and patients are advised to discuss influenza vaccination with their primary healthcare provider.
- **Systematic review**: Vlachojannis et al. conducted a systematic review of 22 studies to assess the clinical efficacy and pharmacological effects of elderberry fruit (*Sambuci* fructus) in disease prevention and treatment (Vlachojannis et al., 2010). The effects of elderberry were evaluated in 22 articles, including in vitro and animal studies; however, only three articles assessed the effects of elderberry

in humans (Murkovic, et al., 2004; Zakay-Rones et al., 2004; Zakay-Rones et al., 1995). The authors identified relevant studies using CENTRAL, Ovid (MEDLINE), PubMed, and SilverPlatter databases. The references of the pooled articles were reviewed to identify additional relevant studies, and a manual review of literature that was lacking from the electronic databases was conducted. In a study, participants were administered spray-dried elderberry juice containing 120–4,000 mg of anthocyanins daily for 2–3 weeks. In other studies, participants were administered Sambucol® syrup containing elderberry, raspberry extract, honey, glucose, and citric acid. These participants were treated with 4 tbsp. of Sambucol® by mouth daily for 3–5 days. Information on standardization and allergies for these three trials was lacking. For all three studies, adverse effects were reported to be lacking. Information on toxic effects, dropouts, and interactions was lacking. Outcome measures included fasting and postprandial levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides, as well as clinical symptoms of influenza or viral upper respiratory tract infections and antibody titers. A study reported a reduction in postprandial lipid levels in individuals taking 4,000 mg of anthocyanidin daily (p-value was unclear). Two other studies reported moderate effectiveness of Sambucol® in individuals with influenza or other viral infections when started within 24 hr of symptom onset and taken for 3–5 days. In one of these studies, participants in the Sambucol® treatment group exhibited a significant symptomatic improvement and increased antibody titers. In the other study, participants treated with Sambucol® showed symptom relief four days sooner, as well as a decreased use of rescue medications. The significance of these results was unclear from the review. The authors concluded that elderberry fruit has poor-to-moderate effectiveness based on results from the included studies. Limitations of the review included a lack of information on dropouts, standardization, allergies, and interactions, and an overall lack of statistical values to confirm significance claims. Further research is needed in this area. The effect of elder alone is not clear.

- **Evidence**: Kong conducted a randomized, double-blind, placebo controlled trial to examine the efficacy of a proprietary elderberry extract for the treatment of flu-like symptoms ($N = 64$) (Kong, 2009). Individuals aged 16–60 years and presenting with a minimum of three predesignated flu symptoms (coughing, fever, headache, mucus discharge, muscle aches, or nasal congestion) for $\leq$24 hr were included in this trial. Individuals with known chronic diseases, suspected bacterial infections, concurrent participation in another clinical trial, or recent use of antiviral therapy, flu medication, or influenza vaccination were excluded from this trial. Eligible participants were randomly assigned via a computer-generated randomization code to receive either a 175 mg of a proprietary elderberry extract lozenge ($N = 32$) or a placebo lozenge ($N = 32$), indistinguishable by appearance, taste, or composition of nonactive ingredients. Both treatment lozenges were administered four times daily for two days and supplied by HerbalScience Singapore Pte. Ltd. Information on standardization was lacking. Adverse events were reportedly lacking in either group. Information on toxic effects, dropouts, and interactions was lacking. Primary outcome assessed was changed in self-reported symptom severity on a 0–10 visual analog scale (VAS). After 24 hr of treatment, mean VAS score significantly improved (lower) in the elderberry group

compared to the placebo group for symptoms of fever, headache, muscle aches, and nasal congestion ($p < .0001$ for all); however, statistically significant between-group differences were lacking for coughing ($p = .1556$) and mucus discharge ($p = .1513$). By 48 hr, a statistically significant between-group improvement in VAS score was seen for all investigated symptoms ($p < .0001$ for all). In total, 28% of participants receiving elderberry vs. 0% of participants receiving placebo demonstrated complete eradication of all symptoms after 48 hr of treatment. Investigators concluded that elderberry extract was effective in attenuating flu symptoms in otherwise healthy individuals. This trial was limited by a lack of objective outcome measures and a lack of description of dropouts. Also, this trial was sponsored by HerbalScience Singapore Pte. Ltd., the supplier of both the active elderberry and placebo lozenges used.

- Zakay-Rones et al. conducted a randomized, double-blind, placebo controlled study of Sambucol® (a syrup containing elderberry juice, raspberry extract, glucose, citric acid, and honey) in the treatment of influenza in otherwise healthy individuals (children and adults) not previously vaccinated against the flu, located in an Israeli agricultural community ($N = 40$; Zakay-Rones et al., 1995). Patients were included who had at least three symptoms (fever, myalgia, nasal discharge, cough) of less than 24 hr' duration. Children received 2 tbsp. daily and adults received 4 tbsp. daily for three days. Age range and mean age were similar between groups. An intent-to-treat analysis was lacking, and out of 40 subjects who were initially enrolled and randomized, 13 were disqualified prior to analysis, due to crossover or protocol violations (five in the treatment group and eight in the placebo group). In subjects who were analyzed, convalescent phase serologies demonstrated higher antibody titers to influenza B in the group treated with Sambucol®, although statistically significant changes were lacking and only demonstrated a trend in favor of the treatment group. Follow-up of symptoms was adequately recorded over six days, and significant improvement in symptoms was observed in 93.3% of treated patients within two days, vs. the control group, in which it took six days to see improvement in 92.7% of patients ($p < .001$). A complete cure was seen within 2–3 days in Sambucol®-treated patients (90%), whereas six days were needed in the placebo group. Although randomization and blinding were adequately described, this study was limited by the small sample size, lack of intent-to-treat analysis, and use of influenza B rather than influenza A titer measurement. Results seemed promising. The effect of elder alone is not clear.
- Zakay-Rones et al. conducted a randomized, double-blind, placebo controlled study of oral elderberry syrup in the treatment of influenza A and B virus infections during the influenza season of 1999–2000 in Norway ($N = 60$) (Zakay-Rones et al., 2004). Patients 18–54 years old with influenza-like symptoms for 48 hr or less were enrolled. Patients were given 15 mL of elderberry or placebo syrup four times daily for five days and recorded their symptoms using a visual analog scale. An intent-to-treat analysis was lacking. Symptoms were relieved on average four days earlier, and use of rescue medication was significantly less in those receiving elderberry extract compared with placebo. The authors concluded that elderberry extract seems to offer an efficient, safe, and cost-effective treatment for influenza. Although the study was randomized and blinded, this study was

limited by the small sample size, lack of intent-to-treat analysis, and failure to report any adverse effects or lack of compliance. Although these results were positive, additional research is needed in this area before a firm conclusion may be drawn.

Bacterial Sinusitis

- **Summary**: Elder has been observed to reduce excessive sinus mucus secretion in laboratory studies (Ueno et al., 1997), and use of elder for bacterial sinusitis has been the topic of a review (Marz et al., 1999). There is only limited research specifically using elder to treat sinusitis in humans. Combination products containing elder and other herbs (such as Sinupret®) have been reported to have beneficial effects when used with antibiotics to treat sinus infections, although these results require confirmation with additional research (Ernst, Marz & Sieder, 1997; Neubauer & Mrz, 1994). Research suggests that herbal preparations containing elder may result in less swelling of mucus membranes, better drainage, milder headache, and decreased nasal congestion. Evidence is lacking regarding the effects of elder when used alone for treatment of this condition, and further well-designed clinical trials are required before conclusions may be made.
- **Systematic review and meta-analysis (Sinupret®)**: Melzer et al. conducted a systematic review and meta-analysis to assess the effects of BNO-101 (Sinupret®) in the treatment of sinusitis (Melzer, Saller, Schapowal, & Brignoli, 2006). Of the 22 studies reviewed, six controlled trials on sinusitis were reassessed according to predefined criteria. Four trials, comprising 900 patients, could be examined by meta-analysis. After two weeks of treatment, verum was significantly superior to placebo (2 RCTs, 159 vs. 160 patients, both add-on to antibacterial treatment). The benefit was based on the patients' assessment ("cured": verum = 61.1%, placebo = 34.5%), reduction of drain obstruction, headache, and radiological signs (all $p < .05$). There were no apparent differences between BNO-101 and ambroxol after two weeks, although results favored BNO-101 in chronic cases ("cured": BNO-101 = 37.1%, ambroxol = 12.5%; $p < .05$). Individuals using BNO-101 also had less pyorrhea and headache ($p < .05$). The authors concluded that BNO-101, combined with standard antibacterial therapy, significantly reduced the acute symptoms and signs of sinusitis. In the trials investigated, BNO-101 had a favorable risk–benefit ratio and an incidence of adverse events that was similar to placebo. The effect of elder alone is not clear.
- **Evidence (Sinupret®)**: Neubauer and Marz conducted a two-week randomized, double-blind, placebo-controlled trial to examine the adjunct effects of a combination herbal preparation, Sinupret®, on conventional antimicrobials and decongestants for the treatment of acute bacterial sinusitis ($N = 160$) (Neubauer & Marz, 1994). The inclusion criterion for this trial consisted of a confirmed clinical diagnosis of acute sinusitis associated with plain sinus radiogram opacification. Individuals with pronounced anatomical nasal septum deviations or those with a known intolerance of doxycycline were excluded from this trial. All eligible participants received antibiotic treatment with Vibramycin® (doxycycline) and decongestant treatment with Otriven® (xylometazoline). Additionally, participants were randomly assigned via computer program to receive two Sinupret® tablets

($N = 81$) or identical placebo tablets ($N = 79$) three times daily for two weeks. Each Sinupret® tablet was sugar-coated and contained 6 mg of radix *Gentianae luteae*, 18 mg of flos *Sambuci nigra*, 8 mg of flos *Primulae veris cum calycibus*, 18 mg of herba *Rumicis acetosae*, and 18 mg of herba *Verbenae off*. Information on allergies, adverse effects, and toxic effects was lacking. Information on dropouts was also lacking, although investigators stated that the reasons for missing data in both groups were unrelated to treatment. Although 10% of subjects used nose-drops during the study (a protocol violation), this noncompliance was distributed equally among groups. Investigators also stated that, according to the results obtained from this trial, possible negative interactions between Sinupret® and conventional therapy were lacking. Primary outcomes investigated were radiographic opacification and self-reported assessment of the therapy. Various clinical findings, including mucosa swelling, secretions, patency of the nose, nasal obstruction, and headache, were assessed as secondary outcomes. Compared to placebo, radiographic changes in opacification significantly favored Sinupret® when considering all observed outcomes ($X2 = 15.5049$; $df = 5$; $p = .0084$) and when grouping outcomes based on effect vs. lack of effect ($X2 = 5.1152$; $df = 1$; $p = .02372$). Following treatment, the percentage of participants who improved from opaque or shadowed radiographic findings to lack of detectable abnormalities was 64.1% for the treatment group and 36.4% for the placebo group. Similarly for self-reported assessments, Sinupret® was significantly favored vs. placebo ($X2 = 21.45517$; $df = 2$; $p = .000$). Following treatment, the percent of asymptomatic participants was 60.3% in the treatment group and 25.0% in the placebo group. With respect to clinical symptoms, a statistically significant between-group difference in favor of Sinupret® was seen for mucosa swelling, nasal obstruction, and headache but was lacking for nasal patency and secretions. Investigators concluded that the combination herbal therapy Sinupret® enhanced the treatment efficacy of conventional antimicrobial and decongestant agents in individuals with acute bacterial sinusitis. Strengths of this trial included the use of both objective and subjective outcome measures; however, its methodological rigor was limited by a lack of description regarding dropouts. The use of a combination product left open the question of elder's activity as a monotherapy. The short follow-up period left open the question of longer-term efficacy and safety. Due to limited descriptions of methods and statistical analysis, additional research is needed in this area before a firm conclusion may be drawn.

- Richstein et al. conducted a double-blind, placebo-controlled study to assess the efficacy of Sinupret® in patients with rhinorrhea and headache ($N = 31$) (Richstein & Mann, 1980). Patients were administered Sinupret® or placebo in either liquid or tablet form: two Sinupret® tablets three times daily, 50 drops of Sinupret® liquid two times daily, or placebo for seven days. Objective and subjective measurements were taken, including measures of symptoms pertaining to headache, congestion, and changes in radiologic1al findings. Using a chi-squared analysis, the authors found that there was a significant effect in objective ($p = .001$) and subjective ($p = .025$) measurements. The lack of description of clinical symptom scoring, dropouts, power calculations, use of double dummy, and statistical analysis made interpretation of these results difficult. The effect of elder alone is not clear.

Bronchitis

- **Summary**: reliable human evidence evaluating elder monotherapy as a treatment for bronchitis is currently lacking. However, elder is an ingredient in the combination herbal product Sinupret®. This proprietary formula has been used historically in Europe for the treatment of acute bronchitis and bacterial sinusitis. Although studies comparing the combination product to placebo are lacking, there is initial evidence from a comparison trial of various expectorants vs. Sinupret® in the treatment of acute bronchitis (Ernst et al., 1997). Additional evidence and well-designed clinical trials are necessary before a firm conclusion may be drawn regarding the use of sorrel or Sinupret® in the management of bronchitis.
- **Studies of lesser methodological quality (not included in the Evidence Table)**: Ernst et al. conducted a comparison trial to evaluate the safety and efficacy of Sinupret® vs. 72 commonly prescribed expectorants, chosen freely by physicians at the point of care (for example, products containing acetylcysteine, bromhexine, or carbocysteine) (Ernst et al., 1997). The trial was open (nonblinded, nonrandomized) and included 3,187 patients with acute, uncomplicated bronchitis, 1–94 years old. The product was administered for 10 days, and the primary outcome was improvement in bronchitis-related symptoms. The authors reported that Sinupret® was superior to the mean improvement seen in the reference drugs, both in terms of efficacy and adverse effects. However, Sinupret® was not compared to individual expectorants. A subgroup analysis of 535 patients with bronchitis demonstrated lower efficacy of both Sinupret® and the reference expectorants. Further details are lacking. Because Sinupret® was compared to multiple agents and the study was neither randomized nor blinded, the results may only be considered preliminary. The effect of elder alone is not clear.

Cardiovascular Disease Risk

- **Summary**: a randomized clinical trial suggested that long-term consumption of elderberry lacks additional cardioprotective benefit in postmenopausal women (Curtis et al., 2009). Further well-designed clinical trials are required before conclusions may be made.
- **Evidence**: Curtis et al. conducted a randomized, double-blind, placebo-controlled, parallel-designed study to assess the effects of long-term consumption of elderberry (anthocyanins) on cardiovascular disease (CVD) risks in postmenopausal women ($N = 57$) (Curtis et al., 2009). The authors included postmenopausal women <70 years of age who lacked menstruation for at least 12 months. Only women with a BMI between 20 and 32 kg/m^2 were included in the trial. Women who had taken hormone replacement therapy within the previous six months or smoked within the previous 12 months were excluded. Furthermore, women who had a history of diabetes or cardiac, digestive, kidney, liver, pulmonary, neurologic, thyroid, hematologic, or psychiatric illnesses were excluded. Those taking anti-inflammatory drugs, steroids, antibiotics, vaccines, or dietary supplements were excluded. Women on weight loss diets or already participating in a clinical trial within the previous four months were excluded. Lastly, individuals with anemia, abnormal levels on renal and hepatic tests, untreated hypertension, or abnormal levels of lipid and glucose were ineligible

to participate. Individuals were randomized to receive two capsules of elderberry or placebo by mouth twice daily (in the morning and at night) for a duration of 12 weeks. Elderberry extract capsules each contained 125 mg of anthocyanin (cyanidin-3-glucoside). The daily dose of 500 mg was equivalent to anthocyanin levels measured in 25 g of elderberries, 140 g of blackberries, and 100 g of blueberries. Information on allergies was lacking. One participant in the placebo group reported anal irritation. Information regarding toxic effect was lacking. Overall, five participants withdrew from the study (two in the treatment group, three in the placebo group). One woman in the placebo group discovered a lump secondary to a routine breast exam and withdrew thereafter. Two individuals were removed from the study by the researchers due to poor compliance ($N = 1$ in the treatment group) and recurrence of an undisclosed condition ($N = 1$ in the placebo group). One participant in the placebo group withdrew due to adverse events, and one individual in the treatment group was lost to follow-up. Interactions with food were minimized by the researchers via enforcement of dietary restrictions starting seven days prior to the inception and lasting for the 12-week duration of the study. Participants were to avoid anthocyanin-rich berries, fruits, and vegetables, including raspberries, blueberries, red grapes, plums, radishes, and red cabbage, as well as products with these ingredients. Furthermore, the authors encouraged participants to minimize intake of lower-anthocyanin-yield products, including black olives, red apples, nectarines, and aubergine (eggplant). Any foods that may alter CVD biomarkers, such as tea, oily fish, and dark chocolate, were restricted. The authors provided a list of freely available foods as well as guidelines to maintain normal lifestyle and exercise routines. Compliance was measured using a food diary for four days. Other information on interactions was lacking. Levels of anthocyanins and biomarkers for CVD risk were measured using fasting blood samples. These markers included inflammatory, lipid, platelet, and glucose levels, as well as measures of hepatic and renal function using albumin, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), urea, and creatinine. Blood samples were drawn 1, 2, and 3 hr after the initial bolus. The authors also measured baseline characteristics such as height, weight, blood pressure, and pulse. Blood pressure measurements were also taken before and after each blood draw. Following treatment, a significantly higher plasma concentration of anthocyanin metabolites was observed in the treatment group vs. placebo ($p = .02$). However, plasma levels of the parent compound (anthocyanin) lacked significant between-group differences. Additionally, significant changes in plasma levels of the following inflammatory biomarkers, vascular measures (including platelet reactivity, endothelin-1, blood pressure, and pulse), and concentrations of total cholesterol, high-density lipoprotein cholesterol, LDL-C, triglycerides, and glucose were lacking. Furthermore, significant effects of elderberry on renal and hepatic function, as determined by urea, creatinine, albumin, ALP, ALT, and GGT, were lacking. A significant change in plasma bilirubin was measured between the anthocyanin treatment group and the placebo group ($p < .05$) after 12 weeks. However, the authors reported that the clinical impact of this difference was minimal, as the bilirubin levels were still within normal physiological levels for this population of women. The authors concluded that anthocyanin

supplementation was safe but lacked additional cardioprotective benefits after 12 weeks of therapy in healthy, postmenopausal women. Limitations of this study included the extensive exclusion data (thus low generalizability of the results) and a lack of information on adverse and toxic effects. Further research is needed in this area.

Constipation

- **Summary**: a randomized clinical trial suggests that a combination product containing *Sambucus nigra* may help treat chronic constipation in as little as two days (Picon et al., 2010). Significant results were reported in CTT and daily evacuations; however, impact on the quality of life in patients was lacking. Further well-designed clinical trials are required before conclusions may be made.
- **Evidence**: Picon et al. conducted a randomized, single-blind, placebo-controlled crossover study to assess the effects of a combination treatment containing *Sambucus nigra* L. on constipation ($N = 20$) (Picon et al., 2010). Individuals aged 18–50 years who experienced chronic constipation (based on American Gastroenterology Association criteria) were recruited for this study. Participants were included in the study if they had normal laboratory measurements and were using appropriate anticonception methods (if they were fertile). Participants were excluded from the study if they currently used medications that could cause constipation, if they had a history of abusing drugs or alcohol, or if they presented with other diseases that lacked proper control. Participants were randomized using a computer-generated randomization list to receive 150 mL of tea that was infused with 1 g of the active compound or placebo tea three times daily for five days. Following a nine-day wash-out period, participants were crossed over to the other study arm. Each 15 g portion of the active compound contained a homogenous blend of the following components: 2 g of *Pimpinella anisum* (green anises) fruit, 2.0 g of *Foeniculum vulgare* (fennel) fruit, 5.0 g of *Sambucus nigra* (*sabugueiro*) flower, and 6.0 g of *Cassia angustifolia* (senna) flower. The placebo tea was prepared my adding seven drops of caramel color plus 10 drops of orange essence to 1,600 mL of boiling water. According to the investigators, adverse events were lacking. According to laboratory measurements, treatment with the combination tea resulted in significant reduction in serum potassium levels (from 4.5 mEq/L to 3.96 mEq/L, $p < .001$). Information regarding dropouts and interactions were lacking. The primary outcome measure was CTT, which was measured using a radiological technique 48 hr after the injection of the last treatment for each phase of the study. Secondary outcome measures included daily symptoms, quality of life, frequency of adverse events, and use of laxatives during the washout period. Following treatment, mean CTT was 15.7 hr (95% CI: 11.1–20.2 hr) for the active treatment group and 42.3 hr (95% CI: 33.5–51.1 hr) for the placebo group. The mean difference between these two groups was statistically significant (26.6 hr, 95% CI: 18.7–34.6 hr), with the treatment group showing an improvement of 62.9%. With regard to the frequency of bowel movements over a 24-hr time period, 42% of participants in the placebo group and 14% of participants in the treatment group answered "none"; this between-group difference was significant ($p < .001$). Also, participants in the active treatment group showed

a significant improvement in the perception of bowel function compared to the placebo group ($p = .03$). Significant between-group differences in the use of laxatives during the washout period or quality of life during treatment phases were lacking. Limitations of this study include a lack of blinding and lack of information regarding dropouts. The effect of elder alone is not clear.

Gingivitis

- **Summary**: *Sambucus nigra*, in combination with other products, has been reported to decrease gingivitis and gingival inflammation in human trials (Grbic et al., 2011). Significant results were seen four days after treatment. A combination mouthwash containing *Sambucus nigra* significantly decreased gingival index scores when used three times daily for 14 days (Samuels et al., 2012). It remains unclear whether there is any benefit from elder for this condition. Additional research with further well-designed clinical trials is needed in this area before a firm conclusion may be reached.
- **Evidence**: Grbic et al. conducted a phase II, randomized, double-blind, placebo-controlled, crossover study to examine the safety and efficacy of a combination THPP on gingival inflammation ($N = 53$) (Grbic, Wexler, Celenti, Altman & Saffer, 2011). Males and females aged 18–65 years participated in this study. Inclusion criteria consisted of at least three posterior teeth per maxillary quadrant and a mean gingival index (GI) score >1 (as per Löe and Silness's methodology). Conversely, prospective participants were excluded on the basis of known allergies to any patch components; concomitant use of antibiotics, anti-inflammatories, or hormonal therapies; existing systemic conditions (e.g., diabetes); or evidence of severe periodontal disease, as characterized by ≥7 mm probing depth on posterior maxillary teeth with the exception of third molars. Eligible participants were randomly assigned to receive either a THPP patch of *Sambucus nigra*, *Centella asiatica*, and *Echinacea purpurea*, or a placebo patch with an identical delivery system but lacking any plant extracts. A total of five patches for both treatments were administered over three days. One patch was administered by the clinical investigator and two by the participants on day 1, then one patch was administered by the participants on days 2 and 3 each. Information on standardization was lacking. Serious adverse events were lacking in either treatment group. Mild adverse events possibly related to THHP included accidental injury ($N = 2$), anorexia ($N = 1$), back pain ($N = 1$), increased coughing ($N = 1$), dysmenorrhea ($N = 1$), dyspepsia ($N = 1$), headache ($N = 3$), nausea ($N = 1$), nausea and/or vomiting ($N = 1$), pharyngitis ($N = 1$), reactivity of the application site ($N = 3$), and taste perversion ($N = 6$). Information on toxic effects was lacking. Three participants dropped out of the study. Two dropouts were due to protocol noncompliance, and one was due to an unrelated injury. Information on interactions was lacking. The primary efficacy outcome investigated was change in GI score. Secondary outcomes included treatment response (as defined by a minimum one point increase in GI score) and change in beta-glucuronidase (BG) levels. All efficacy outcomes were evaluated according to a per-protocol (PP) analysis and reported only for phase 1 of the crossover, as investigators noted that GI scores lacked a return to baseline during washout.

Compared to baseline, both THPP and placebo were shown to decrease mean GI scores; however, a significantly greater decrease was seen with THPP vs. placebo at days 4 and 15 ($p < .05$ for both days). Similarly, significantly more participants receiving THPP demonstrated a positive treatment response compared to those receiving placebo on days 4 (38% vs. 22%, respectively; $p = .036$) and 15 ($p = .014$). With regard to gingival enzyme activity, a significantly larger decrease in BG level was observed with THPP vs. placebo on days 4 ($p = .048$) and 8 ($p = .04$). Investigators concluded that THPP safely and effectively reduced topical gingival inflammation. This study was strengthened by the use of both clinical and laboratory assessments of gingival inflammation but was limited by an unsuccessful crossover and a lack of description regarding randomization procedure. The effect of elder alone is not clear.

- Samuels et al. conducted a randomized, double-blind, placebo-controlled trial to examine the safety and efficacy of a proprietary combination herbal formulation (HM-302) for the treatment of experimentally induced gingivitis ($N = 62$) (Samuels et al., 2012). Individuals aged 14–75 years with clinically confirmed gingivitis were included in this trial. Exclusion criteria consisted of smoking; comorbid chronic illnesses, including diabetes, heart disease, or inflammatory conditions; concomitant use of anti-inflammatory or antibiotic medications; or evidence of less than 24 teeth or severe periodontitis, as characterized by >5 mm periodontal pockets in more than three areas. Eligible participants were randomly assigned according to the Moses–Oakford algorithm to receive one of four mouth rinses: (Abuja et al., 1998) HM-302 rinse with extracts from *Sambucus nigra*, *Centella asiatica*, and *Echinacea purpurea* (Izun Pharmaceuticals Corp., Israel; $N = 15$); (Akerreta et al., 2007) a water-based cetylpyridinium chloride (CPC) rinse ($N = 14$); (Anonymous, 1984) an alcohol-based essential oil (EO) rinse (Listerine®, Johnson & Johnson; $N = 17$), or; (Bagchi et al., 2004) a water-based negative control rinse ($N = 16$). All treatment mouth rinses were taken in 15 mL aliquots three times daily for 14 days. All other oral hygiene techniques, including flossing, use of breath mints, and use of commercial mouth rinses, were prohibited during this trial. Information on standardization was lacking. HM-302 was reportedly well tolerated and lacked evidence of any serious adverse effects. Teeth staining and discoloration was the most commonly reported adverse effect across all treatments, but it lacked a statistically significant between-group difference in frequency ($N = 3$ with HM-302). One incidence of mouth sensitivity was also reported with HM-302. Information regarding toxic effects, dropouts, and interactions was lacking. The primary outcome assessed was change in gingival index (GI). Secondary outcomes included change in plaque index (PI) and the number of bleeding sites. Compared to baseline, HM-302 demonstrated a minimal, nonsignificant decrease in GI score, whereas all other groups demonstrated an increased (worsening) GI score. Compared to the water control, HM-302 was the only active treatment to demonstrate a significantly better change in GI score (0.213 ± 0.23 vs. -0.026 ± 0.22 for water vs. HM-302, respectively; $p = .007$) and percent change in GI score (31.8 ± 37.2 vs. $-1.80 \pm 31.8\%$, respectively; $p = .013$). HM-302 also demonstrated the smallest increase (exacerbation) in PI score from baseline, whereas all other groups demonstrated a statistically significant or nearly significant increase. However, a statistically significant between-group

difference was lacking between HM-302 and the water control with respect to change in PI score ($p = .081$) or percent change in GI score ($p = 0.126$) from baseline. With regard to gingival bleeding, HM-302 demonstrated a minimal change in the number of bleeding sites from baseline and the highest proportion of participants with a reduction of bleeding sites post-treatment (i.e., response rate). Between groups, a statistically significant difference in change of bleeding sites from baseline was seen with HM-302 vs. water control (0.2 ± 1.07 vs. 9.5 ± 12.3, respectively; $p = 0.035$). Investigators concluded that combination herbal HM-302 mouth rinse attenuated gingival inflammation in otherwise healthy individuals. Limitations of this trial included a lack of description regarding blinding procedures and participant dropouts. Also, Izun Pharmaceuticals Corp., the developers of HM-302 and affiliated employer of two study investigators, provided funding for the statistical analysis of this trial. The effect of elder alone is not clear.

- **Studies of lesser methodological quality (not included in the Evidence Table)**: Samuels et al. conducted a pilot trial to assess the localized effects of a topical gingival patch on gingival inflammation ($N = 26$) (Samuels, Saffer, Wexler, & Oberbaum, 2012). Patients were included in the trial if site inflammation was identified on subjects with moderate-to-severe chronic periodontitis. A topical patch was placed on 22 of 36 identified sites for 24 hr. Reports on adverse effects were lacking in both groups. The primary outcome assessed was inflammation (measured by neutrophilic activity using gingival crevicular fluid (GCF) beta-glucuronidase (b-glu) levels) and clinical response (measured by gingival index (GI)). In 17 of 22 sites, GCF b-glu levels significantly reduced patch placement ($p = .002$), compared to 3 of 14 sites in the control group. A significant reduction in mean b-glu levels and percent change from baseline were seen during patch replacement (-2.52 ± 1.62 and 29.7%, respectively); however; an increase was seen in the mean b-glu levels and percent change from baseline in the control group (2.14 ± 0.89 and 33%, respectively). Eighteen of 21 sites vs. 7 of 14 sites had a significantly better GI response rate at 24 hr ($p = .053$). Further details are lacking. The effect of elder alone is not clear.

Hyperlipidemia

- **Summary**: Reliable human evidence evaluating elder monotherapy as a treatment for hyperlipidemia is currently lacking. A randomized control trial reported that elderberry juice may decrease in serum cholesterol concentrations and increase in LDL stability (Mulleder, Murkovic, & Pfannhauser, 2002). However, this study was a pilot design of small sample population. It remains unclear whether there is any benefit from elder for this condition. Additional research is needed in this area before a firm conclusion may be reached.
- **Systematic review**: Vlachojannis et al. conducted a systematic review of 22 studies to assess the clinical efficacy and pharmacological effects of elderberry fruit (*Sambuci* fructus) in disease prevention and treatment (Vlachojannis et al., 2010). The effects of elderberry were evaluated in 22 articles, including in vitro and animal studies; however, only three articles assessed the effects of elderberry in humans (Murkovic et al., 2004; Zakay-Rones et al., 2004; Zakay-Rones et al.,

1995). The authors identified relevant studies using Central, Ovid (MEDLINE), PubMed, and SilverPlatter databases. The references of the pooled articles were reviewed to identify additional relevant studies, and a manual review of literature that was lacking from the electronic databases was conducted. In a study assessed, participants were administered spray-dried elderberry juice containing 120–4,000 mg of anthocyanins daily for 2–3 weeks. In other studies, participants were administered Sambucol® syrup containing elderberry, raspberry extract, honey, glucose, and citric acid. These participants were treated with 4 tbsp. Sambucol® by mouth daily for 3–5 days. Information on standardization and allergies for these three trials was lacking. For all three studies, adverse effects were reported to be lacking. Information on toxic effects, dropouts, and interactions was lacking. Outcome measures included fasting and postprandial levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides, as well as clinical symptoms of influenza or viral upper respiratory tract infections and antibody titers. A study reported a reduction in postprandial lipid levels in individuals taking 4,000 mg of anthocyanidin daily (p-value was unclear). Two other studies reported moderate effectiveness of Sambucol® in individuals with influenza or other viral infections when started within 24 hr of symptom onset and taken for 3–5 days. In one of these studies, participants in the Sambucol® treatment group exhibited a significant symptomatic improvement and increased antibody titers. In the other study, participants treated with Sambucol® showed symptom relief four days sooner, as well as a decreased use of rescue medications. The significance of these results was unclear from the review. The authors concluded that elderberry fruit has poor-to-moderate effectiveness based on results from the included studies. Limitations of the review included lack of information on dropouts, standardization, allergies, and interactions, and an overall lack of statistical values to confirm significance claims. Further research is needed in this area. The effect of elder alone is not clear.

- **Evidence**: Mülleder et al. conducted a pilot, randomized, placebo controlled trial of elderberry juice in the treatment of hyperlipidemia in otherwise healthy individuals ($N = 16$) (Mulleder et al., 2002). Patients were given 400 mg of spray-dried powder capsules containing 10% anthocyanins three times daily, equivalent to 5 mL of elderberry juice for two weeks. This was not an intent-to-treat analysis. There was only a statistically insignificant change in cholesterol concentrations in the elderberry group (from 199 to 190 mg/dL) compared to the placebo group (from 192 to 196 mg/dL). Elderberry spray-dried extract at a low dose exerted a minor effect on serum lipids. Higher but nutritionally relevant doses might significantly reduce postprandial serum lipids. Although randomization and blinding were adequately described, this study is limited by the small sample size, lack of intent-to-treat analysis, and use of a low dose of elderberry extract. Additional research is needed in this area before a firm conclusion may be drawn.

Obesity

- **Summary**: a literature review evaluated a study on the effects of elderberry on obesity (Hasani-Ranjbar et al., 2009). A significant difference was seen not only in body weight, but in blood pressure and quality of life as well (Chrubasik et al.,

2008). Further well-designed clinical trials are required before conclusions may be made.

- **Systematic review**: Hasani-Ranjbar et al. conducted a systematic review of 77 articles to assess the safety and efficacy of herbal medications in the treatment of obesity (Hasani-Ranjbar et al., 2009). The authors included a variety of antiobesity herbs tested in animals and humans; one study focused on the effects of *Sambucus nigra* (elderberry) in humans (Chrubasik et al., 2008). Relevant articles published prior to December 30, 2008, that assessed the effects of herbal or plant medicines on obesity in animals or humans were pooled from the PubMed, Google Scholar, Scopus, IranMedex, and Web of Science databases. Relevant outcomes included antiobesity effects such as changes in body weight, body fat, percentage of body fat or adipose tissue, thickness of triceps skin folds, circumference of the waist or hips, and changes in appetite or food intake. Studies evaluating other disease states, such as diabetes, were included if the outcomes matched those above. Inclusion required the use of a herbal medicine defined as the raw or refined product of a plant or plant part, including the stems, leaves, flowers, buds, tubers, or roots, used for medicinal purposes. In vitro studies were excluded from the review, as were letters to the editor, unpublished data, articles without available abstracts, and review articles. Individuals in the treatment group received a combination of *Sambucus nigra* and *Asparagus officinalis* in the form of 19 mg of saponin daily. The duration of treatment was unclear. The daily dose of the combination treatment provided 1 mg of anthocyanin, 370 mg of flavonol, 150 mg of hydroxycinnamate from *Sambucus nigra*, and 19 mg of saponin from *Asparagus officinalis*. Information regarding allergies, adverse effects toxic effects, dropouts, and interactions was lacking. Outcomes included mean changes in body weight, blood pressure, quality of life, and emotional and physical wellness. A significant decrease in mean body weight was measured (p-value was unclear). Furthermore, a significant improvement in blood pressure values, quality of life, and physical and emotional wellness was reported (p-values were unclear). The authors concluded that multiple herbal supplements have beneficial effects on obese animals and humans. Specific conclusions regarding the clinical benefits of *Sambucus nigra* were lacking. Limitations of this literature review include lack of information regarding the duration of therapy, adverse effects, allergies, interactions, and dropouts. Further research is needed in this area. The effect of elder alone is not clear.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Rubini® BioFlavonoides Elderberry Extract (Zertifikationsnr: IT-CDX 5987) is a monotherapy derived from elderberries, with no additives from animals or colorings, and no preservatives (Youdim et al., 2000).
- Sambucol® (Razei Bar Industries, Jerusalem, Israel) is a syrup containing elderberry juice extract standardized to contain three flavonoids, raspberry extract, glucose, citric acid, and honey (Barak et al., 2001).
- Sinupret® (Quanterra® Sinus Defense) is an herbal mixture of 18 mg of flos *Sambucus nigra* (elderflower), 18 mg of herba *Verbenae off.* (vervain wort), 6 mg of radix *Gentianae luteae* (gentian root), 18 mg of flos *Primulae veris cum*

calycibus (cowslip flowers with calyx), and 18 mg of herba *Rumicis acetosae* (sorrel) (Neubauer & Mrz, 1994; Richstein & Mann, 1980).

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ABOUT THE AUTHORS

Catherine Ulbricht, PharmD, Massachusetts General Hospital, Boston, MA, USA. **Ethan Basch**, MD, MPhil, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. **Lisa Cheung**, PharmD, University of Rhode Island, 45 Upper College Road, Kingston, RI 02881, USA. **Harley Goldberg**, DO, Kaiser Permanente, Oakland, CA, USA. **Paul Hammerness**, MD, Harvard Medical School, 25 Shattuck St, Boston, MA. **Richard Isaac**, **Wendy Weissner**, BA, and **Regina C. Windsor**, Natural Standard Research Collaboration, Somerville, MA. **Karta Purkh Singh Khalsa**, DN-C, RH, Bastyr University, 14500 Juanita Drive Northeast, Kenmore, WA 98028-4966, USA. **Aviva Romm**, BSc, CPM, RH (AHG), American Herbalists Guild, Canton, GA, USA. **Edward Mills**, DPH, MSc, Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto M2K 1E2, Canada. **Idalia Rychlik**, PharmD, Massachusetts College of Pharmacy, 179 Longwood Avenue, Boston, MA 02115, USA. **Minney Varghese**, BS, Northeastern University, 360 Huntington Ave, Boston, MA. **Jayme Wortley**, PharmD, East Tennessee State University, Gatton College of Pharmacy, 807 University Pkwy, Johnson City, TN.

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Notice of Correction

Changes have been made to this article since its original online publication date of 10 January 2014.