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REVIEW

A Review of the Antiviral Properties of Black Elder (*Sambucus nigra* L.) Products

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Black elder (*Sambucus nigra* L.) has a long ethnobotanical history across many disparate cultures as a treatment for viral infection and is currently one of the most-used medicinal plants worldwide. Until recently, however, substantial scientific research concerning its antiviral properties has been lacking. Here, we evaluate the state of current scientific research concerning the use of elderberry extract and related products as antivirals, particularly in the treatment of influenza, as well as their safety and health impacts as dietary supplements. While the extent of black elder's antiviral effects are not well known, antiviral and antimicrobial properties have been demonstrated in these extracts, and the safety of black elder is reflected by the United States Food and Drug Administration approval as generally recognized as safe. A deficit of studies comparing these *S. nigra* products and standard antiviral medications makes informed and detailed recommendations for use of *S. nigra* extracts in medical applications currently impractical. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: black elder; *Sambucus nigra*; antiviral; review; influenza; elderberry.

BOTANICAL INFORMATION

Black elder [*Sambucus nigra* L., Fam. Adoxaceae (previously Caprifoliaceae); sometimes called European elder] is a deciduous shrub or small tree, reaching 10 m in height with numerous erect stems from a base. Tutin *et al.* (1976) describe it as having brownish-gray corky bark with whitish pith and arching branches; pinnate leaves with 5–7 ovate, ovate-lanceolate or ovate-elliptical leaflets, with serrate margins and sparse abaxial pubescence; fly-pollinated flowers with white petals and light yellow anthers; and dark violet drupes. An example of the plant, its flowers, and its fruit can be seen in Fig. 1. *S. nigra* is found across Europe, northern Africa, west and central Asia, and North America. (It is noteworthy that some – e.g., The Plants Database of the USDA – classify *S. nigra*, *Sambacus canadensis*, and *Sambacus cerula* instead as the cryptic species *S. nigra* ssp. *nigra*, *S. nigra* ssp. *canadensis*, and *S. nigra* ssp. *cerula*. We shall follow The Plant List in listing these as separate species.)

HISTORY OF USE

Various parts of the *S. nigra* plant have been used for thousands of years by Native Americans (Ulbricht *et al.,* 2014) and people of the Mediterranean basin and surrounding regions (Agustí, 1617; Vallès *et al.,* 2004; Jarić *et al.,* 2007). While the primary concern of this review is its use in the treatment of influenza and other viral and bacterial infections, it has also been used for various other medicinal and dietary applications by these and other ethnic and cultural groups dating back at least to the Ancient Egyptians (Ulbricht *et al.,* 2014). It continues to be commonly gathered as food and medicine and, according to ethnobotanical research, is currently one of the most-used medicinal plants worldwide (Jarić *et al.,* 2007).

CURRENT STATUS

Not all constituents of the *S. nigra* plant are safe for use. Only *S. canadensis* and *S. nigra* flowers have been approved by the United States Food and Drug Administration (FDA) as Generally Recognized as Safe (GRAS) for use as a flavoring ingredient (U.S. Food and Drug Administration, 2016). Further, *S. nigra* flowers have been approved by Commission E of the German Federal Institute for Drugs and Medical Devices for the treatment of viral infections, but other parts of the plant have not (Ulbricht *et al.,* 2014). While the fruit is not on the FDA GRAS list or approved by the German Commission E, analyses of flowers and of cooked fruit have consistently indicated safety; other parts of the plant are less suitable for use (Jensen and Nielsen, 1973; van Damme *et al.,* 1997; de Benito *et al.,* 1998; Ulbricht *et al.,* 2014; Tejero *et al.,* 2015). While there are dosage recommendations for dried *S. nigra* flower, extract, and fruit syrup based on studies of efficacy and toxicology, these are not well standardized. Thus, commercially available black elder products with known chemical ratios and compositions may be preferable to *S. nigra*-containing home remedies. Such

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Figure 1. *Sambucus nigra*, with inset images of its flowers and fruit. The images are reprinted with permission from their original authors: Pennie Logemann of the New England Wild Flower Society (NEWFS) for the image of the whole plant, Glen Mittelhauser of the Maine Natural History Observatory for the inset image of *S. nigra* flowers, and Lawrence Newcomb of NEWFS for the inset image of *S. nigra* fruit. The original images are available from https://gobotany.newenglandwild.org/species/sambucus/nigra/. [Colour figure can be viewed at wileyonlinelibrary.com]

products include Sambucol® (Sambucol, Copyright 2011, Pharmacare US Inc., San Diego, CA, USA) (Saphira-Nahor *et al.,* 1995; Zakay-Rones *et al.,* 1995; Morag *et al.,* 1997; Ito *et al.,* 1997; Konlee, 1998; Burge *et al.,* 1999; Barak *et al.,* 2001, 2002; Zakay-Rones *et al.,* 2004; Mandenius *et al.,* 2008), Rubini® (Rubini, Copyright Iprona AG Via Industria LANA (BZ), Italy) (Krawitz *et al.,* 2011; Tiralongo *et al.,* 2016), and other *S. nigra* extracts or syrups (Chatterjee *et al.,* 2004), and black elder-containing multi-herb products such as Sinupret® (Sinupret, Copyright 2014, Bioforce USA, Ghent, NY, USA) (Richstein and Mann, 1980; Neubauer and März, 1994; Ernst *et al.,* 1997; März *et al.,* 1999; Ismail *et al.,* 2003; Melzer *et al.,* 2006; Glatthaar-Saalmüller *et al.,* 2011; Ulbricht *et al.,* 2014). While less research has been carried out on the whole plant, properly prepared *S. nigra* fruit and flowers do appear safe to consume in the absence of contraindications; this is discussed further in the Safety section of this review.

It should be noted that current studies concerning *S. nigra* health properties and use focus primarily on these elderberry extracts and commercial elder-containing multi-herb products and do not use the berries or flowers of the plant directly. This could potentially confound the generalizability of results to the effectiveness of the plant itself; however, as these extracts (although not the multi-herb products) typically contain only such ingredients as glucose syrup, purified water, citric acid, and potassium sorbate (as in the case of Sambucol), in addition to elderberry extract, it will be assumed for the purposes of this review that antimicrobial, antiviral, and general health properties found in such products are due to components of the *S. nigra* extract contained therein. This paper will focus on these extracts as what have been most studied and determined to display these properties; however, all research related to the health effects of *S. nigra* will be discussed. Research comparing the efficacy and safety of these products to *S. nigra* flowers and fruits is lacking.

CONSTITUENTS

Tables 1 and 2 list the known constituents of *S. nigra* fruit and flowers (respectively); Figs 2 and 3 depict the chemical structures of the most-studied compounds in the fruit and flowers – certain anthocyanins in the fruit, and certain flavonols in the flowers and fruit. *S. nigra* agglutinins (SNAs), although also heavily studied, have more complex structures as proteins and have not been depicted. Flavonoids, separated in the tables into anthocyanins, proanthocyanidins/flavanols, flavonols, flavanones, and flavones, are polyphenolic antioxidants, which, along with other *S. nigra* phenolic acids, display considerable protection against oxidative stress *in vitro*, but debated protection *in vivo* (Laranjinha *et al.,* 1994; Nardini *et al.,* 1995; Youdim *et al.,* 2000; Olthof *et al.,* 2001; Netzel *et al.,* 2002; Williams *et al.,* 2004; Valko *et al.,* 2006; Ding *et al.,* 2006; Lotito and Frei, 2006; González-Segovia *et al.,* 2008; EFSA, 2010; Izzi *et al.,* 2012; Gomes *et al.,* 2012; Chang *et al.,* 2014). In addition, many of these compounds have antiinflammatory (González-Segovia *et al.,* 2008; Izzi *et al.,* 2012; Gomes *et al.,* 2012), anticancer (Yang *et al.,* 2001; López-Lázaro, 2002; Galati and O'Brien, 2004; Valko *et al.,* 2006; Moon *et al.,* 2006; Marczylo *et al.,* 2009; Zamora-Ros *et al.,* 2012; González *et al.,* 2013; Woo and Kim, 2013), anti-diabetic (Christensen *et al.,* 2010; van Dam *et al.,* 2013; Bhattacharya *et al.,* 2013), neuroprotective (Youdim *et al.,* 2002; Schroeter *et al.,* 2002; Chang *et al.,* 2014), and cardiovascular health-promoting properties (Laranjinha *et al.,* 1994; Nardini *et al.,* 1995; Morton *et al.,* 2000; Olthof *et al.,* 2001;

Table 1. Chemical constituents of *Sambucus nigra* fruit

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Anthocyanins				
Cyanidin-3-sambubioside	Brønnum-Hansen and Hansen, 1983	32.4% of anthocyanins	0.1 M HCl	1
	Macheix *et al.*, 1990			1
	Fiorini, 1995	59.8% of anthocyanins	Methanol (room temperature)	1
	Kaack and Austed, 1998	[269, 656] mg/100 g	Acetonitrile	13
	Youdim *et al.*, 2000	32.39 or 38.19 mg/g depending on quantization method	Rubini elderberry extract	1
	Nakajima *et al.*, 2004		Ethanol (room temperature)	1
	Wu *et al.*, 2004	545.9 mg/100 g fresh weight	Acetone	1
	Dawidowicz *et al.*, 2006	2.70 g/kg	Ethanol (20)	1
		2.77 g/kg	Ethanol (100)	1
	Lee and Finn, 2007	[122.2, 143.0]; [268.1, 269.1] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.*, 2009	[270.8, 630.8] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.*, 2010	397.55 mg/L	Aqueous sucrose (100)	1
Chrysanthemin	Brønnum-Hansen and Hansen, 1983	65.7% of anthocyanins	0.1 M HCl	1
	Macheix *et al.*, 1990			1
	Fiorini, 1995	90.7% of anthocyanins	Methanol (room temperature)	1
	Kaack and Austed, 1998	[361, 1266] mg/100 g	Acetonitrile	13
	Youdim *et al.*, 2000	36.31 or 42.81 mg/g depending on quantization method	Rubini elderberry extract	1
	Wu *et al.*, 2004	739.8 mg/100 g fresh weight	Acetone	1
	Dawidowicz *et al.*, 2006	2.14 g/kg	Ethanol (20)	1
		2.52 g/kg	Ethanol (100)	1
	Lee and Finn, 2007	[204.6, 253.7]; [309.7, 481.4] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.*, 2009	[221.4, 586.4] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.*, 2010	350.07 mg/L	Aqueous sucrose (100)	1
Cyanidin-3,5-diglucoside	Brønnum-Hansen and Hansen, 1983	0.8% of anthocyanins	0.1 M HCl	1
	Macheix *et al.*, 1990			1
	Fiorini, 1995	15.7% of anthocyanins	Methanol (room temperature)	1
	Kaack and Austed, 1998	[5, 36] mg/100 g	Acetonitrile	13
	Youdim *et al.*, 2000	11.85 or 8.07 mg/g depending on quantization method	Rubini elderberry extract	1
	Nakajima *et al.*, 2004		Ethanol (room temperature)	1
	Wu *et al.*, 2004		Acetone	1
	Lee and Finn, 2007	[8.2, 11.2]; [18.3, 19.5] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.*, 2009	[7.41, 23.29] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.*, 2010	139.46 mg/L	Aqueous sucrose (100)	1

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Cyanidin-3-sambubioside-5-glucoside	Brønnum-Hansen and Hansen, 1983	1.1% of anthocyanins	0.1 M HCl	1
	Macheix *et al.*, 1990			1
	Kaack and Austed, 1998	[14, 47] mg/100 g	Acetonitrile	13
	Youdim *et al.*, 2000	19.48 or 10.93 mg/g depending on quantization method	Rubini elderberry extract	1
	Wu *et al.*, 2004	82.6 mg/100 g fresh weight	Acetone	1
	Lee and Finn, 2007	[16.0, 32.2]; [37.3, 59.2] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.*, 2009	[19.52, 53.49] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.*, 2010	58.99 mg/L	Aqueous sucrose (100)	1
Antirrhinin	Wu *et al.*, 2004	4.40 mg/100 g fresh weight	Acetone	1
	Lee and Finn, 2007	[0, 0.3) mg/100 g fresh weight across two growing seasons	Acidified methanol	2
	Veberic *et al.*, 2009	[1.49, 9.63] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.*, 2010	19.22 mg/L	Aqueous sucrose (100)	1
Callistephin	Wu *et al.*, 2004	1.80 mg/100 g fresh weight	Acetone	1
	Lee and Finn, 2007	<0.3 mg/100 g fresh weight across two growing seasons	Acidified methanol	2
Tulipanin	Lee and Finn, 2007	[0, 0.3] mg/100 g fresh weight across two growing seasons	Acidified methanol	2
Pelargonidin-3-sambubioside	Wu *et al.*, 2004	<0.025 mg/100 g fresh weight	Acetone	1
Peonidin-3-glucoside	Ulbricht *et al.*, 2014 (secondary source)			
Peonidin-3-sambubioside	Ulbricht *et al.*, 2014 (secondary source)			
Peonidin monoglucuronide	Ulbricht *et al.*, 2014 (secondary source)			
Chrysanthemin monoglucuronide	Ulbricht *et al.*, 2014 (secondary source)			
Proanthocyanidins/Flavanols				
Epicatechin (a monomer)	Mikulic-Petkovsek *et al.*, 2015	63.71 mg/kg fresh weight	Acidified methanol	1
Monomers	Wu *et al.*, 2004	1.44 mg/kg fresh weight	Acetone	1
Dimers	Wu *et al.*, 2004	10.62 mg/kg fresh weight	Acetone	1
Trimers	Wu *et al.*, 2004	5.63 mg/kg fresh weight	Acetone	1
4-6mers	Wu *et al.*, 2004	10.80 mg/kg fresh weight	Acetone	1

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Flavonols				
Rutin	Dawidowicz *et al.,* 2006	1.09 g/kg	Ethanol (20)	1
		1.54 g/kg	Ethanol (100)	1
	Lee and Finn, 2007	[46.5, 72.7]; [42.6, 95.6] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.,* 2009	[35.59, 52.02] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.,* 2010	109.57 mg/L	Aqueous sucrose (100)	1
	Mikulic-Petkovsek *et al.,* 2015	313.30 mg/kg fresh weight	Acidified methanol	1
Isoquercetin	Dawidowicz *et al.,* 2006	0.18 g/kg	Ethanol (20)	1
		0.30 g/kg	Ethanol (100)	1
	Lee and Finn, 2007	[3.9, 9.5]; [5.2, 14.9] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Veberic *et al.,* 2009	[6.38, 26.52] mg/100 g fresh weight	Acidified methanol	5
	Schmitzer *et al.,* 2010	7.79 mg/L	Aqueous sucrose (100)	1
	Mikulic-Petkovsek *et al.,* 2015	43.52 mg/kg fresh weight	Acidified methanol	1
Kaempferol-3-*O*-rutinoside	Lee and Finn, 2007	0.7; [1.1, 1.2] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Schmitzer *et al.,* 2010	0.74 mg/L	Aqueous sucrose (100)	1
	Mikulic-Petkovsek *et al.,* 2015	4.2 mg/kg fresh weight	Acidified methanol	1
Isorhamnetin-3-*O*-rutinoside	Lee and Finn, 2007	[0.3, 0.7]; [0.7, 2.2] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Mikulic-Petkovsek *et al.,* 2015	2.03 mg/kg fresh weight	Acidified methanol	1
Quercetin	Kaack and Austed, 1998	[29, 60] mg/100 g	Acetonitrile	13
	Veberic *et al.,* 2009	[2.70, 4.50] mg/100 g fresh weight	Acidified methanol	5
Astragalin	Dawidowicz *et al.,* 2006	0.11 g/kg	Ethanol (20)	1
		0.18 g/kg	Ethanol (100)	1
Unidentified quercetin acetylhexosides	Mikulic-Petkovsek *et al.,* 2015	4.66 mg/kg fresh weight (This was the concentration of one out of two noted but unidentified quercetin acetylhexosides)	Acidified methanol	1
Unidentified quercetin hexoside pentosides	Mikulic-Petkovsek *et al.,* 2015	3.36 mg/kg fresh weight (This was the concentration of one out of two noted but unidentified quercetin hexoside pentosides)	Acidified methanol	1
5,7,3′,4′-tetra-*O*-methylquercetin	Roschek *et al.,* 2009		Supercritical CO_2; ethanol	1
5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-3,4,5-trihydroxycyclohexanecarboxylate	Roschek *et al.,* 2009		Supercritical CO_2; ethanol	1
Isorhamnetin-3-*O*-glucoside	Lee and Finn, 2007	[0, 0.1]; [0, 0.3] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Flavanones				
Unidentified naringenin hexosides	Mikulic-Petkovsek *et al.*, 2015		Acidified methanol	1
Phenolic acids				
5-*O*-*trans*-caffeoylquinic acid	Lee and Finn, 2007	[26.4, 28.1]; [34.7, 35.9] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Schmitzer *et al.*, 2010	15.46 mg/L	Aqueous sucrose (100)	1
	Mikulic-Petkovsek *et al.*, 2015	153.80 mg/kg fresh weight	Acidified methanol	1
3-*O*-caffeoylquinic acid	Lee and Finn, 2007	[0.7, 1.1]; [0.9, 4.4] mg/100 g fresh weight (two growing seasons)	Acidified methanol	2
	Schmitzer *et al.*, 2010	42.76 mg/L	Aqueous sucrose (100)	1
	Mikulic-Petkovsek *et al.*, 2015	88.41 mg/kg fresh weight	Acidified methanol	1
4-*O*-caffeoylquinic acid	Lee and Finn, 2007	[1.2, 1.6]; [1.9, 2.5] mg/100 g fresh weight fresh weight (two growing seasons)	Acidified methanol	2
	Mikulic-Petkovsek *et al.*, 2015	28.68 mg/kg fresh weight	Acidified methanol	1
5-*O*-*cis*-caffeoylquinic acid	Mikulic-Petkovsek *et al.*, 2015	40.13 mg/kg fresh weight	Acidified methanol	1
3-*O*-feruloylquinic acid	Mikulic-Petkovsek *et al.*, 2015	18.78 mg/kg fresh weight	Acidified methanol	1
3-*O*-*p*-coumaroylquinic acid	Mikulic-Petkovsek *et al.*, 2015	11.94 mg/kg fresh weight	ACIDIFIED methanol	1
4-*O*-*cis*-*p*-coumaroylquinic acid	Mikulic-Petkovsek *et al.*, 2015	10.20 mg/kg fresh weight (It is uncertain whether this concentration was for the *cis*- or *trans*- form of the molecule; the concentration of only one form was obtained.)	Acidified methanol	1
4-*O*-*trans*-*p*-coumaroylquinic acid	Mikulic-Petkovsek *et al.*, 2015	10.20 mg/kg fresh weight (It is uncertain whether this concentration was for the *cis*- or *trans*- form of the molecule; the concentration of only one form was obtained.)	Acidified methanol	1
3,5-di-*O*-caffeoylquinic acid	Mikulic-Petkovsek *et al.*, 2015	3.43 mg/kg fresh weight	Acidified methanol	1
4,5-di-*O*-caffeoylquinic acid	Mikulic-Petkovsek *et al.*, 2015	2.29 mg/kg fresh weight	Acidified methanol	1
Additional organic acids				
Shikimic acid	Veberic *et al.*, 2009	[0.14, 0.93] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	44.48 mg/kg fresh weight	Aqueous (room temperature)	1
Fumaric acid	Veberic *et al.*, 2009	[0.10, 0.29] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	19.83 mg/kg fresh weight	aqueous (room temperature)	1
Citric acid	Veberic *et al.*, 2009	[3.08, 4.81] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	9.66 g/kg fresh weight	Aqueous (room temperature)	1
Malic acid	Veberic *et al.*, 2009	[0.97, 1.31] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	8.82 g/kg fresh weight	Aqueous (room temperature)	1
Tartaric acid	Mikulic-Petkovsek *et al.*, 2016	1.52 g/kg fresh weight	Aqueous (room temperature)	1
Valeric acid	Duke, 1985			1

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Vitamins				
Ascorbic acid	Duke, 1985			1
	Kaack and Austed, 1998	[6, 25] mg/100 g	Acetonitrile	13
	Jabłońska-Ryś *et al.*, 2009	116.70 mg/100 g fresh weight		1
Retinol	Duke, 1985			1
Sugars				
Peptic polysaccharides (containing Ara, Rha, Xyl, Man, Gal, Glc, GlcA, GalA, and 4-*O*-Me-GlcA; AG-II and other proteins; and phenols)	Ho *et al.*, 2015		Ethanol (70, 50); aqueous (50, 100)	1
	Ho *et al.*, 2016		Ethanol (70, 50); aqueous (50, 100)	1
Glucose	Veberic *et al.*, 2009	[33.33, 50.23] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	29.03 g/kg fresh weight	Aqueous (room temperature)	1
Fructose	Veberic *et al.*, 2009	[33.99, 52.25] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	26.81 g/kg fresh weight	Aqueous (room temperature)	1
Sucrose	Veberic *et al.*, 2009	[0.47, 1.68] g/kg fresh weight	Aqueous (room temperature)	5
	Mikulic-Petkovsek *et al.*, 2016	10.46 g/kg fresh weight	Aqueous (room temperature)	1
Lectins				
SNA-IV (*Sambucus nigra* agglutinin-IV)	Mach *et al.*, 1991		Phosphate-buffered saline (4)	1
	Mach *et al.*, 1996		Phosphate-buffered saline (4)	1
	Girbés *et al.*, 1996			1
	van Damme *et al.*, 1997		Aqueous	1
	Tejero *et al.*, 2015			1
	Shang *et al.*, 2015		Phosphate-buffered saline (4)	1
SNA-V (*Sambucus nigra* agglutinin-V)	Girbés *et al.*, 1996			1
	Citores *et al.*, 1996		Saline	1
	van Damme *et al.*, 1997		Aqueous	1
	Tejero *et al.*, 2015			1

Table 2. Chemical constituents of *Sambucus nigra* flowers

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Flavonols				
Rutin	Davídek, 1961	3% of dry weight	Methanol	1
	Seitz and Bonn, 1991		Methanol (60)	1
	Pietta *et al.*, 1992		Methanol (room temperature)	1
	Dawidowicz *et al.*, 2006	13.27 g/kg	Ethanol (20)	1
		20.21 g/kg	Ethanol (100)	1
	Christensen *et al.*, 2008	[11.6, 42.3] mg/g dry weight	Aqueous MeCN	16
		[1.1, 63.0] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Isoquercetin	Seitz and Bonn, 1991		Methanol (60)	1
	Pietta *et al.*, 1992		Methanol (room temperature)	1
	Dawidowicz *et al.*, 2006	0.54 g/kg	Ethanol (20)	1
		0.97 g/kg	Ethanol (100)	1
	Christensen *et al.*, 2008	[0.4, 1.9] mg/g dry weight	Aqueous MeCN	16
		[0.2, 8.6] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Isorhamnetin-3-*O*-rutinoside	Lamaison *et al.*, 1991			1
	Christensen *et al.*, 2008	[2.0, 7.5] mg/g dry weight	Aqueous MeCN	16
		[0.3, 2.7] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Quercetin-3-*O*-6″-acetylglucoside	Christensen *et al.*, 2008	[0.9, 2.8] mg/g dry weight	Aqueous MeCN	16
		[0.4, 8.0] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Isorhamnetin-3-*O*-glucoside	Lamaison *et al.*, 1991			1
	Christensen *et al.*, 2008	[0.2, 1.0] mg/g dry weight	Aqueous MeCN	16
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Kaempferol-3-*O*-rutinoside	Christensen *et al.*, 2008	[0.2, 3.0] mg/g dry weight	Aqueous MeCN	16
		[0.6, 21.5] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
Astragalin	Dawidowicz *et al.*, 2006	0.13 g/kg	Ethanol (20)	1
		0.25 g/kg	Ethanol (100)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Kaempferol	Seitz and Bonn, 1991		Methanol (60)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Hyperoside	Seitz and Bonn, 1991		Methanol (60)	1
Flavanones				
Naringenin	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Flavones				
Luteolin	Seitz and Bonn, 1991		Methanol (60)	1
Phenolic acids				
5-*O*-*trans*-caffeoylquinic acid	Petitjean-Freytet *et al.*, 1991			1
	Urbánek *et al.*, 2002		Methanol	1
	Hawrył *et al.*, 2002			1
	Christensen *et al.*, 2008	[10.1, 20.7] mg/g dry weight	Aqueous MeCN	16
		[1.0, 63.8] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
3,5-di-*O*-caffeoylquinic acid	Hawrył *et al.*, 2002			1
	Christensen *et al.*, 2008	[0.5, 3.2] mg/g dry weight	Aqueous MeCN	16
		[0.1, 0.7] mg/g dry weight	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
p-coumaric acid	Urbánek *et al.*, 2002		Methanol	1
	Hawrył *et al.*, 2002			1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
5-*O*-*p*-coumaroylquinic acid	Christensen *et al.*, 2008	[0.5, 1.2] mg/g dry weight	Aqueous MeCN	16
		[1.7, 5.9] mg/g dry weight	Aqueous (25 *w*/w %) (70)	44
	Christensen *et al.*, 2010		Methanol (5)	1
3-*O*-caffeoylquinic acid	Seitz and Bonn, 1991		Methanol (60)	1
	Christensen *et al.*, 2008	[0.8, 2.4] mg/g dry weight	Aqueous MeCN	16
		[0.3, 13.6] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
Ferulic acid	Seitz and Bonn, 1991		Methanol (60)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Caffeic acid	Seitz and Bonn, 1991		Methanol (60)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
1,5-di-*O*-caffeoylquinic acid	Christensen *et al.*, 2008	[8.0, 13.9] mg/g dry weight	Aqueous MeCN	16
		[0.6, 11.9] mg/g dry weight	Aqueous (25 *w*/w %) (70)	44
4-*O*-caffeoylquinic acid	Christensen *et al.*, 2008	[0.6, 1.5] mg/g dry weight	Aqueous MeCN	16
		[0.2, 2.3] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
3,4-di-*O*-caffeoylquinic acid	Christensen *et al.*, 2008	[0.4, 1.2] mg/g dry weight	Aqueous MeCN	16
		[0.2, 14.3] mg/g dry weight	Aqueous (25 *w*/w %) (70)	44
3-*O*-*p*-coumaroylquinic acid	Christensen *et al.*, 2008	[0.4, 1.9] mg/g dry weight	Aqueous MeCN	16
		[0.2, 0.6] mg/100 g extract	Aqueous (25 *w*/w %) (70)	44
4,5-di-*O*-caffeoylquinic acid	Christensen *et al.*, 2008	[0.1, 1.5] mg/g dry weight	Aqueous MeCN	16
p-coumaric acid hexoside	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Essential fatty acids				
α-Linolenic acid	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1
Linoleic acid	Christensen *et al.*, 2010		Methanol (5)	1
	Bhattacharya *et al.*, 2013		Dichloromethane; methanol (5)	1

Compound	Study	Concentration	Extract type (temperature in °C)	Number of *Sambucus nigra* varieties tested
Additional organic acids				
Malic acid	Mikulic-Petkovsek *et al.,* 2016	30.19 g/kg dry weight	Aqueous (room temperature)	1
Citric acid	Mikulic-Petkovsek *et al.,* 2016	7.86 g/kg dry weight	Aqueous (room temperature)	1
Tartaric acid	Mikulic-Petkovsek *et al.,* 2016	3.29 g/kg dry weight	Aqueous (room temperature)	1
Shikimic acid	Mikulic-Petkovsek *et al.,* 2016	2.35 g/kg dry weight	Aqueous (room temperature)	1
Fumaric acid	Mikulic-Petkovsek *et al.,* 2016	0.43 g/kg dry weight	Aqueous (room temperature)	1
Palmitic acid	Toulemonde and Richard, 1983	11.3% of distilled oil	Steam-distilled oil	1
Sugars				
Sucrose	Mikulic-Petkovsek *et al.,* 2016	27.35 g/kg dry weight	Aqueous (room temperature)	1
Fructose	Mikulic-Petkovsek *et al.,* 2016	24.28 g/kg dry weight	Aqueous (room temperature)	1
Glucose	Mikulic-Petkovsek *et al.,* 2016	19.71 g/kg dry weight	Aqueous (room temperature)	1
Terpenes				
Epoxylinalool	Bhattacharya *et al.,* 2013		Dichloromethane; methanol (5)	1
Linalool	Toulemonde and Richard, 1983	3.7% of distilled oil	Steam-distilled oil	1
cis-rose oxide	Toulemonde and Richard, 1983	3.4% of distilled oil	Steam-distilled oil	1
trans-rose oxide	Toulemonde and Richard, 1983	1.7% of distilled oil	Steam-distilled oil	1
Additional alcohols				
Trans-3,7-dimethyl- l,3,7-octatrien-3-ol	Toulemonde and Richard, 1983	13.0% of distilled oil	Steam-distilled oil	1
cis-hexenol	Toulemonde and Richard, 1983	2.5% of distilled oil	Steam-distilled oil	1

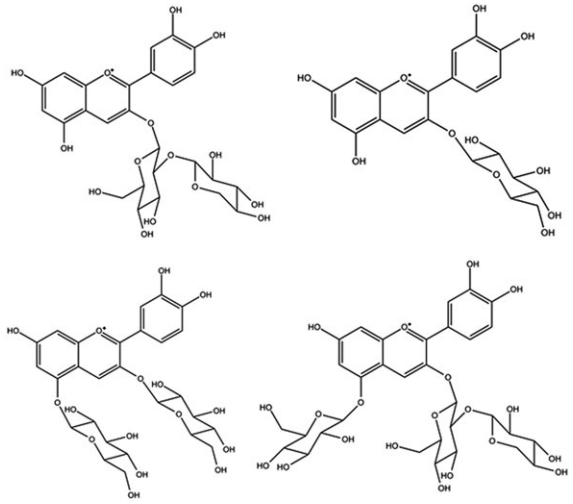

Figure 2. Most-studied anthocyanins of *Sambucus nigra* fruit. Clockwise from top left: cyanidin-3-sambubioside, chrysanthemin, cyanidin-3-sambubioside-5-glucoside, and cyanidin-3,5-diglucoside.

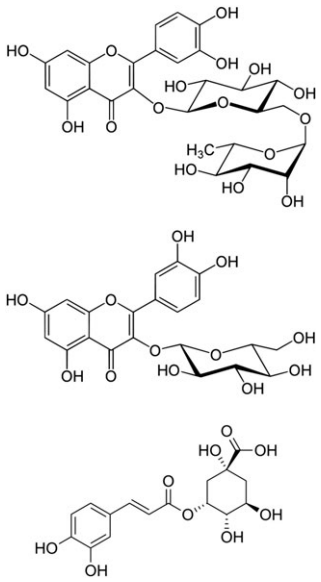

Figure 3. Most-studied flavonols of *Sambucus nigra* flowers and fruit. From top to bottom: rutin, isoquercetin, and 5-*O*-*trans*-caffeoylquinic acid.

Steinberg *et al.,* 2003; van Dam *et al.,* 2013; Siasos *et al.,* 2013; Tangney and Rasmussen, 2013; Chang *et al.,* 2014; Cappello *et al.,* 2016). Most pertinent to the purposes of this study are the immune-stimulating, antimicrobial and antiviral effects of these flavonoids, as well as the varied polyphenolic constituents of the plant (Nagai *et al.,* 1990; Middleton and Kandaswami, 1992; Nagai *et al.,* 1992; Amoros *et al.,* 1992; Mahmood *et al.,* 1993; Hernández *et al.,* 2000; Choi *et al.,* 2007; González-Segovia *et al.,* 2008; Oh *et al.,* 2010). Of particular interest are the effects of the *S. nigra* flavonoids kaempferol, against herpes simplex virus type 1 (HSV-1) (Amoros *et al.,* 1992); quercetin, against HSV-1 (Amoros *et al.,* 1992) and *Helicobacter pylori* (González-Segovia *et al.,* 2008); epicatechin, against the human immunodeficiency virus (HIV) (Mahmood *et al.,* 1993); and 5,7,3′,4′-tetra-*O*-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-3,4,5-trihydroxycyclohexanecarboxylate against influenza (Roschek *et al.,* 2009). While it is uncertain what mechanisms are primarily responsible for *S. nigra*'s inhibition of influenza, its high flavonoid content is one possibility.

Another extremely important group of black elder constituents is that of SNAs, which are lectins and ribosome-inactivating proteins (RIPs). It is important to note that while nonspecific RIPs found in other plants have the potential for great toxicity, highly specific RIPs, such as those found in *S. nigra* fruit, have the potential to target specific cells, and are thus often good candidates to act as therapeutic agents (Girbés *et al.,* 1996; van Damme *et al.,* 1996; Citores *et al.,* 1996; van Damme *et al.,* 1997; Girbés *et al.,* 2003; Stirpe and Battelli, 2006; Tejero *et al.,* 2015). *S. nigra* bark SNAs have been studied, which show high affinity for sialic acid-α-2,6-galactose (SAα2,6Gal) – and specifically *N*-Acetylneuraminic acid-α-2,6-galactose (Neu5Acα2,6Gal) – to which many pathogens bind in order to initiate pathogenesis (Shibuya *et al.,* 1987; Rogerieux *et al.,* 1993; Haseley *et al.,* 1999; Nicholls *et al.,* 2007; Chen *et al.,* 2007; Song *et al.,* 2011; Narla and Sun, 2012; Gregorio-Jauregui *et al.,* 2014). This study does not list the constituents of *S. nigra* bark, as it is inadvisable to consume the bark of the plant (van Damme *et al.,* 1997; de Benito *et al.,* 1998; Ulbricht *et al.,* 2014; Tejero *et al.,* 2015). However, these SNAs are mentioned here because, if isolated, they could be beneficial in the inhibition of pathogens; further, these bark SNAs are very similar to SNAs found in the fruit of the plant, SNA-IV and SNA-V, which have been shown to be non-toxic in murine and human cellular models (Mach *et al.,* 1991; Girbés *et al.,* 1996; Mach *et al.,* 1996; Citores *et al.,* 1996; van Damme *et al.,* 1997; Girbés *et al.,* 2003; Tejero *et al.,* 2015). Many RIPs have been isolated, which display antiviral and antitumor effects, and SNA-IV shows homology to some such antiviral RIPs (McGrath *et al.,* 1989; Collins *et al.,* 1990; Lee-Huang *et al.,* 1991; Girbés *et al.,* 1996; Au *et al.,* 2000; Wang *et al.,* 2000; Girbés *et al.,* 2003). SNA-V shows high homology to the Neu5Acα2,6Gal-specific *S. nigra* bark lectin SNA-I (van Damme *et al.,* 1996) and may display antiviral properties (Vandenbussche *et al.,* 2004). More specifically, SNA-IV interacts with SAα2,6Gals similarly to *S. nigra* bark lectins, and SNA-V with Gal and NAcGal residues, indicating competitive inhibition of pathogens, which utilize these galactose residues, as is seen with bark SNAs (van Damme *et al.,* 1996; Shang *et al.,* 2015). The extent of this potential inhibition is unknown, but it is unlikely to be the only antiviral mechanism in the plant, as *S. nigra* flowers have not been shown to contain these SNAs, yet have shown antiviral activity, as discussed in the Antiviral Properties section of this review.

In addition to flavonoids, phenolic acids, and SNAs, *S. nigra* fruit contains peptic polysaccharides, which also appear to play a role in the interaction of *S. nigra* with the human immune system through the stimulation of macrophages (Ho *et al.,* 2015; Ho *et al.,* 2016). Further research is needed to determine the extent of these properties.

It is noteworthy that based on chemical makeup alone, *S. nigra* appears to be the best candidate among studied *Sambucus* species as a therapeutic agent and general dietary supplement. Compared with *S. canadensis*, *S. nigra* has higher concentrations of cinnamic acids, flavonol glycosides, and polyphenolic

compounds in general (Lee and Finn, 2007). In other studies, *S. nigra* was shown to have the most organic acids and smallest sugars to organic acids ratio across seven *Sambucus* species and hybrids (Mikulic-Petkovsek *et al.,* 2016), and by far the highest flavonol concentration, as well as a favorable phenolic composition, across 13 *Sambucus* species and hybrids (Mikulic-Petkovsek *et al.,* 2015). Further, while some other members of the genus have been reported to display similar medicinal effects, many have higher concentrations of toxins and are considered unsafe for use (Hardin and Arena, 1974; Vigneaux, 1985; Mulet, 1990; Agelet, 2000; Boada and Romanillos, 1999; Bruneton, 2001; Vallès *et al.,* 2004). While more research is needed, the hypothesis that *S. nigra* is the safest and healthiest member of the genus is also consistent with ethnobotanical history of *Sambucus* species usage, in which *S. nigra* is heavily favored.

GENERAL HEALTH PROPERTIES

Because of its high flavonoid and polyphenolics content, *S. nigra* has received some attention for its antioxidant properties. Preparations from both *S. nigra* flowers and fruit have been shown to provide antioxidant effects *in vitro*, although the extent of this antioxidant activity *in vivo* is debated, as discussed in the Constituents section of this review in the case of flavonoids in general (Abuja *et al.,* 1998; Cao and Prior, 1999; Pool-Zobel *et al.,* 1999; Youdim *et al.,* 2000; Murkovic *et al.,* 2001; Milbury *et al.,* 2002; Roy *et al.,* 2002; Wu *et al.,* 2002; Lugasi and Hóvári, 2003; Wu *et al.,* 2004; Ginsburg *et al.,* 2004; Nakajima *et al.,* 2004; Lichtenthäler and Marx, 2005; Dawidowicz *et al.,* 2006; Jabłońska-Ryś *et al.,* 2009; Shipp and Abdel-Aal, 2010; Schmitzer *et al.,* 2010; Bratu *et al.,* 2012; Jimenez *et al.,* 2014; Topoľská *et al.,* 2015). *S. nigra* has also shown promise as a treatment for many other conditions. Multiple studies have demonstrated the antiinflammatory effects of *S. nigra* (Mascolo *et al.,* 1987; Timoshenko and Cherenkevich, 1995; Yesilada *et al.,* 1997; Haas *et al.,* 1999; Barak *et al.,* 2001; Bobek *et al.,* 2001; Barak *et al.,* 2002; Harokopakis *et al.,* 2006; Thole *et al.,* 2006; Ulbricht *et al.,* 2014). It appears to act as a diuretic (Beaux *et al.,* 1999), and to lower blood pressure (Chrubasik *et al.,* 2008; Hasani-Ranjbar *et al.,* 2009). It may have potential in the reduction of certain genotoxin levels (Cheng *et al.,* 2007) and shows promise in the inhibition of certain cancers (Emig *et al.,* 1995; Thole *et al.,* 2006). Black elder has great potential in treating obesity, as its use appears to reduce post-meal lipid levels (Vlachojannis *et al.,* 2010), decrease cholesterol concentration and serum lipids (Mülleder *et al.,* 2002; Murkovic *et al.,* 2004), and decrease mean body weight in obese patients (Chrubasik *et al.,* 2008; Hasani-Ranjbar *et al.,* 2009). Further, it has been shown to promote insulin secretion and cellular glucose uptake and thus shows potential in treating diabetes mellitus (Gray *et al.,* 2000; Christensen *et al.,* 2009; Christensen *et al.,* 2010; Bhattacharya *et al.,* 2013). Less certain are its potential as a laxative (Picon *et al.,* 2010) and in the inhibition of gingivitis (Grbic *et al.,* 2011; Samuels *et al.,* 2012a; Samuels *et al.,* 2012b). It also has the potential to prevent endothelial dysfunction, atherosclerosis, and gout through XO inhibition of its constituent quercetin (Chang *et al.,* 1993; Lü *et al.,* 2010; Lin *et al.,* 2008; Schröder *et al.,* 2006). While there are thus many conditions that *S. nigra* has shown initial promise in treating or preventing, its efficacy in these potential treatments has not yet been fully determined, and most of these studies are preliminary; further research is required.

ANTIMICROBIAL PROPERTIES

As discussed in the Constituents section of this review, *S. nigra* fruit contains lectins with affinity for SAα2,6Gal residues, and which may thus competitively inhibit pathogens that attach to these residues on host cells. *Helicobacter pylori* (Ilver *et al.,* 2003), *Escherichia coli* (Vimr and Troy, 1985; Ilver *et al.,* 2003; Vimr *et al.,* 2004), *Streptococcus pneumoniae* (Kahane and Ofek, 1996; Sharon, 2006), *Plasmodium falciparum* (Varki and Varki, 2007), *Haemophilus ducreyi* (Post *et al.,* 2005), *Haemophilus influenza* (Severi *et al.,* 2007), and a great many other bacterial and fungal pathogens (Kahane and Ofek, 1996; Schauer, 2000; Angata and Varki, 2002; Sharon, 2006; Severi *et al.,* 2007; Varki, 2007; Varki, 2008) all utilize these sialic acids as important aspects of their pathogenicity and virulence and thus may be inhibited by *S. nigra* fruit lectins. However, sufficient research verifying this hypothesis as to the antipathogenic activity of fruit SNAs is lacking.

While there is little research as to the mechanisms, several studies have shown the efficacy of *S. nigra* against select microbial pathogens. *In vitro*, an elderberry extract from InterHealth Nutraceuticals Incorporated has been shown to inhibit the pathogenic bacterium *Helicobacter pylori* (Chatterjee *et al.,* 2004), and Rubini elderberry extract has been shown to inhibit the pathogenic bacteria *Streptococcus pyogenes*, group C and G *Streptococci*, *Branhamella caterrhalis*, and *Haemophilus influenza* (Krawitz *et al.,* 2011). The latter study also found that Rubini does not appear to significantly inhibit certain other pathogenic bacteria, such as *Staphylococcus aureus*, *Streptococcus mutans*, or *Haemophilus parainfluenzae* (Krawitz *et al.,* 2011). *S. nigra* also appears to lessen symptoms of bacterial sinusitis (although many of the studies indicating this are confounded by use of a multi-herb treatment instead of *S. nigra* alone; Sinupret, of which *S. nigra* flowers constitute 3/13 of the herbal constituents (Neubauer and März, 1994), was most studied); *S. nigra* also appears to improve the efficacy of doxycycline against bacterial infections (Richstein and Mann, 1980; Neubauer and März, 1994; Ueno *et al.,* 1997; Ernst *et al.,* 1997; März *et al.,* 1999; Melzer *et al.,* 2006). Sinupret additionally shows promise in the treatment of bronchitis (Ernst *et al.,* 1997). While initial research indicates the potential of *S. nigra* to inhibit certain pathogens, further *in vitro* and clinical studies are required to determine the extent of such effects, and which bacterial and fungal pathogens are susceptible.

ANTIVIRAL PROPERTIES

The high affinity of SNAs for SAα2,6Gals and particularly Neu5Acα2,6Gal, discussed previously in reference

to bacterial and fungal infection, is extremely important in many viral pathogeneses as well. As with bacteria and fungi, a great many viral pathogens have been identified, which use these sialic acids as important aspects of their pathogenicity and virulence (Kahane and Ofek, 1996; Schauer, 2000; Angata and Varki, 2002; Sharon, 2006; Varki, 2007; Severi *et al.,* 2007; Varki, 2008.). Perhaps most notable are human parainfluenza viruses (Fukushima *et al.,* 2014) and influenza viruses (discussed further later). *S. nigra* flavonoids, polyphenolic compounds, and immunomodulating peptic polysaccharides may also be important in viral inhibition, as discussed in the Constituents section of this review. Regardless of the mechanisms, black elder fruit extracts and flower infusions have shown effectiveness in mitigating symptoms of and quickly curing multiple viral infections.

Sambucol is a 38% *S. nigra* fruit extract in a solution of glucose syrup, purified water, citric acid, and potassium sorbate; it also contained small amounts of raspberry extract as late as the Zakay-Rones *et al.* study in 2004, although the raspberry extract is not believed to have played a significant part in the effect of the extract because of its small dosage and is no longer contained in Sambucol (Zakay-Rones *et al.,* 1995, 2004). Sambucol has been shown *in vitro* to significantly inhibit HSV-1 even in strains resistant to multiple traditional antiviral medications (Morag *et al.,* 1997). Sambucol has also been shown to have a significant antiviral effect against HIV *in vitro* (Saphira-Nahor *et al.,* 1995), and in combination with olive leaf extract, it demonstrated a 17,000 to 4000 particle/mL drop in viral load in one HIV-infected patient (Konlee, 1998). Another patient saw a drop in viral load from 39,000 to non-detectable levels in 10 days while ingesting boiled elderberry extract, glucosamine sulfate, chondroitin, and the commercial product Thymate (promoted as an immune booster) (No authors listed, 1998). An infusion of *S. nigra* flowers, *Hypericum perforatum* aerial components, and *Saponaria officinalis* roots also showed promising results, inhibiting HSV-1 *in vitro* and influenza A and B both *in vitro* and in animal models (Serkedjieva *et al.,* 1990; Serkedjieva, 1996). Sinupret likewise displayed impressive antiviral activity against a broad spectrum of pathogenic viruses *in vitro*, inhibiting the replication of both DNA and RNA viruses (Glatthaar-Saalmüller *et al.,* 2011) – in contrast to most other plant-derived substances, which typically inhibit either DNA or RNA viruses but rarely both. More studies are needed, which focus on *S. nigra* alone, as most of the promising results seen are confounded by use of a multi-herb treatment. Further research is also needed to determine the efficacy of *S. nigra* as a broad-spectrum antiviral, as most studies focus on one or two specific viral pathogens.

Influenza: mechanisms and *in vitro* studies

The effects of *S. nigra* against influenza have been most heavily studied, but research in this field is still typically considered only B-level, as substantial research is still needed in certain areas (Ulbricht *et al.,* 2014; B-level rating is according to the National Standard Evidence-Based Validated Grading Rationale). Few mechanisms have been detailed explaining the influenza-inhibiting effects of various black elder constituents. At least two *S. nigra* flavonoids have been shown *in vitro* to bind to influenza virions of at least one strain (H1N1), as discussed previously, and strongly inhibit host cell entry or recognition, effectively rendering the virus inert in the host (Roschek *et al.,* 2009; Ulbricht *et al.,* 2014). *S. nigra* fruit lectins appear to also be important in inhibiting influenza's pathogenesis. SAα2,6Gals, and particularly Neu5Acα2,6Gal, are extremely important in the pathogenicity of the influenza virus, as influenza virus hemagluttinin (HA) binds to these sialic acids (Rogers and Paulson, 1983; Rogers *et al.,* 1983; Rogers and D'Souza, 1989; Connor *et al.,* 1994; Gambaryan *et al.,* 1997; Brinkman-Van der Linden *et al.,* 2002; Wagner *et al.,* 2002; Shinya *et al.,* 2006; Yamada *et al.,* 2006; Gamblin and Skehel, 2010) as a precursor to entering the host cell, which occurs once HA is cleaved by host proteases and the virus is endocytosed (Steinhauer, 1999). Thus, *S. nigra* fruit SNAs appear to prevent influenza infection by competitively inhibiting the influenza virus' binding to host cells to begin its pathogenesis. HA is also responsible for the virus' capacity to induce hemagglutination in human hosts (Ito *et al.,* 1997; Mandenius *et al.,* 2008), which Sambucol has been shown *in vitro* to inhibit fourfold to 16-fold depending on the strain of influenza (Zakay-Rones *et al.,* 1995). Studies have also indicated that elderberry's effectiveness against infection may be due to immune stimulation (Kinoshita *et al.,* 2012; Ho *et al.,* 2015; Ho *et al.,* 2016). In order to move toward the best possible treatment for influenza, more research is needed to determine to what extent *S. nigra* antiviral effects are due to each chemical constituent of the plant, and if synergistic effects exist between combinations of these constituents to increase their therapeutic potential.

Multiple *in vitro* studies using standardized elderberry extracts have found them to inhibit influenza. One study found dilutions of Sambucol of between 1:8 and 1:16 to significantly inhibit the replication of all 16 tested influenza A and B strains based on dosage and to inhibit virally instigated hemaggluttination of all of four tested influenza A and B strains (Zakay-Rones *et al.,* 1995). Another study found Sambucol to inhibit avian influenza titer by 99% to greater than 99.9% when incubated for 30 seconds in a 1:4 and 1:8 dilution, respectively, and greater than 99.99% when incubated for 1 h (the longest incubation time tested (Balasingam *et al.,* 2006). The same study found that host cells incubated 4 h in Sambucol showed little toxicity at such dilutions, and no cytoxicity at dilutions of 1:80 or lower; no tests for cytotoxicity were carried out for incubations of a shorter duration. Konlee (1998) likewise found Sambucol to inhibit nine tested strains of influenza, although this study was less detailed overall. Rubini similarly displays reduced influenza spread and titre, one study finding that a 1:100 dilution resulted in 30% inhibition of one influenza A strain and 25% inhibition of one influenza B strain (Krawitz *et al.,* 2011). Another study found that concentrated elderberry juice inhibited influenza when introduced alongside the influenza infection, but had little effect when it was introduced post-infection (Kinoshita *et al.,* 2012). This may indicate that *S. nigra* may be more effective preventatively than if first administered during an existing infection or could simply show that the reported clinical efficacy of *S. nigra* against influenza (discussed later) is not primarily the result of direct interaction between *S. nigra* constituents and the

virus, but more complex interactions in the host, such as immune stimulation; however, this study is also the only study using elderberry juice instead of an extract to study the ability of *S. nigra* to inhibit influenza, and such results may be due to this difference in treatment. While initial *in vitro* results on *S. nigra* extracts are promising and supported by research on individual compounds contained in such extracts, more *in vitro* studies are needed to determine with certainty the efficacy and mechanisms of action of the whole extract in influenza inhibition and its safety to host cells.

Influenza: clinical and animal studies

Human clinical studies on the effects of *S. nigra* against influenza are summarized in Table 3. Zakay-Rones *et al.* have published two clinical studies (Zakay-Rones *et al.,* 1995; Zakay-Rones *et al.,* 2004) indicating rapid recovery from influenza A and B with the use of Sambucol. A randomized, double-blind, placebo-controlled clinical study against influenza A and B symptoms and illness duration (as well as that of adenovirus and human respiratory syncytial virus) in 27 Israeli patients, aged 5–50 years, found that patients in the treatment group recovered from fever in 4 days on average as opposed to 6 days in the control group ($p < 0.01$), showed symptomatic improvement in 2 days opposed to at least 5 days in the control group ($p < 0.001$), and were completely cured in 2 to 3 days opposed to at least 5 days in the control group ($p < 0.001$) (Zakay-Rones *et al.,* 1995). The same study also found that healthy adults given Sambucol at this dosage (4 tsp daily) showed no side effects ($n = 35$). It is notable, however, that this study has been criticized by some for its relatively small sample size and lack of an intent-to-treat analysis (Ulbricht *et al.,* 2014). Zakay-Rones *et al.* later (Zakay-Rones *et al.,* 2004) performed a larger study ($n = 60$) of the same design on adult (18–54 years old) Norwegian influenza patients, which, utilizing global assessments and visual analog scales to determine efficacy, found pronounced improvement in individual symptomatic visual analog scales and global assessment in 2 to 4 days opposed to 7 to 8 days in the placebo control ($p < 0.001$ for both). The study also found the treatment group to use much less rescue medications for their symptoms ($p < 0.001$). This study has also been criticized by Ulbricht *et al.* (2014) as being relatively small and lacking an intent-to-treat analysis. These results are statistically significant in these populations; however, while larger studies are needed, these initial studies are both promising and sound in design. [Ulbricht *et al.* (2014) further criticized the study as failing to report adverse effects or compliance, but these complaints are unfounded as the study clearly addresses both issues, stating that no patients noted any adverse effects and all patients were compliant in taking at least 80% of the prescribed doses.] Konlee (1998) verified the lessened duration of influenza-related illness with another randomized, double-blind, placebo-controlled clinical study of Sambucol against influenza A and B, although it was primarily concerned with *in vitro* effects against influenza and clinical and *in vitro* studies against HIV, discussed previously. These studies all clearly support Sambucol, the most heavily studied commercial *S. nigra* product, as a treatment for influenza.

Yet another randomized, double-blind, placebo-controlled study used an elderberry extract lozenge from HerbalScience Singapore Pte Ltd, containing 175 mg of extract, to determine *S. nigra*'s effectiveness

Table 3. Human clinical studies on the effects of various *Sambucus nigra* treatments against influenza

Study	Treatment	dosage	*n*	Results	*p*
Zakay-Rones *et al.,* 1995	Sambucol®	4 tsp (all adults) once daily for 2 days	25	Absence of side-effects in healthy adults	
		4 tsp (adults) or 2 tsp (children) once daily for 2 days	27	Recovery from fever in 4 days instead of 6 or more days	<0.01
				Symptomatic improvement in 2 days instead of 5 or more days	<0.001
				Complete recovery in 2–3 days instead of 5 or more days	<0.001
Konlee, 1998	Sambucol®			Lessened duration of illness	
Zakay-Rones *et al.,* 2004	Sambucol®	15 mL four times daily for 5 days	60	All individual symptoms relieved in 2–4 days instead of 7–8 days	<0.001
				Global assessment showed pronounced improvement after 3 days instead of 7 days	<0.001
				Less use of rescue medication than control	<0.001
				Absence of side-effects in patients	
Kong, 2009	Elderberry extract lozenge from HerbalScience Singapore Pte. Ltd.	4 lozenges daily for 2 days	64	24 h: significant improvement in all symptoms except coughing and mucus discharge	<0.0001
				48 h: significant improvement in all symptoms	<0.0001
				48 h: complete eradication of all symptoms in 28% of treatment group and 0% of control group	
				Absence of side effects in patients	
Tiralongo *et al.,* 2016	Rubini capsules	2 capsules/day priming (9 days), then 3 capsules/day (6 days)	29	Lessened symptom severity	0.05
				Lessened illness duration	0.02
				No significant difference in use of rescue medications	0.9
			312	Less occurrence of illness in treatment group (not significant)	0.2

All studies were randomized, double-blinded, and placebo-controlled, with acceptable patient compliance.

in relieving flu-like symptoms (determined through visual analog scales) in 64 patients aged 16 to 60 years (without any identification of the influenza virus as the causative agent being required) (Kong, 2009). The study demonstrated pronounced improvement in most symptoms (fever, headache, muscle aches, and nasal congestion) within 24 h of treatment using elderberry extract (and complete cure of fever in more than half of the treatment group within 24 h), and pronounced improvement in all investigated symptoms (in addition to the aforementioned symptoms, cough and mucus discharge) within 48 h (and complete cure of fever in all treated patients, and of mucus discharge, muscle aches, and headache in at least half of all treated patients). The control group showed a worsening of symptoms over 48 h, and the difference between treatment and control groups was statistically significant at 24 h for all symptoms except cough and mucus discharge ($p < 0.0001$ for all others), and for all symptoms at 48 h ($p < 0.0001$ for all). The treatment group reported no adverse effects of the lozenge. This is the only study using an elderberry extract lozenge.

A randomized, double-blind, placebo-controlled study of Rubini (in capsule form; 300 mg elderberry extract per capsule) analyzed its efficacy in the prevention and treatment of influenza and "colds" during international travel, determined by self-reported symptomatic scales (Tiralongo *et al.,* 2016). The study found a non-significant difference ($p = 0.4$) in the occurrence of illness between the treatment and control groups; because only 29 of the 312 volunteers (healthy adults of 18 years and older) became ill, it is possible that the smaller incidence of illness in the treatment group that was observed would have been statistically significant with a larger sample size. Rubini was also found in this study to decrease the mean duration of these colds by 2 days ($p = 0.05$) and to greatly reduce symptom severity ($p = 0.02$). [Interestingly, the study also found that physical health declined over the duration of travel ($p = 0.005$) in the control group while it remained statistically stable in those taking Rubini ($p = 0.9$). However, the physical health of the treatment group was lower at baseline, and by the end of travel, physical health between the two groups was not significantly different ($p = 0.27$); thus, it is indeterminate whether Rubini may prevent a decline in physical health during travel.] While this study indicates the effectiveness of Rubini in reducing symptom severity and length, further clinical studies on the efficacy of Rubini are needed to verify these initial results.

Despite the non-significant results of the Tiralongo *et al.* (2016) study, other studies have suggested that *S. nigra* may prevent influenza and general viral infection. An exploratory study on healthy chimpanzees ($n = 8$) of aged 4 to 31 years found that untreated animals showed three times the likelihood of illness of individuals receiving 10 mL of Sambucol daily; this supplementation was carried out for approximately 6 months (Burge *et al.,* 1999). When symptoms occurred, the dosage of animals in the treatment group was raised to 15 mL twice daily; it was noted that illnesses in the treatment group lasted an average of only half as long as in the control group. While this is the longest duration study of *S. nigra* extract use against influenza, it is limited by sample size, and similar but larger studies on humans are needed to determine its potential as a preventative for human influenza and other viral infections. Additional evidence supports that *S. nigra* may have a strong preventative effect against viral infection, and in particular, influenza A; this effect was primarily seen *in vivo* in mice, although it was weak in cell cultures, a difference speculated to have originated from immunostimulating effects of the extract in the host (Kinoshita *et al.,* 2012). Again, however, further research on the potential preventative antiviral effects of *S. nigra* is needed to verify the results of these promising initial studies in humans.

SAFETY

Some *S. nigra* constituents are potentially hazardous. The fruit contains a small concentration of an RIP with slight cytotoxic effects, SNA-V, which is found in higher concentrations in the unripe fruit (Citores *et al.,* 1996; Tejero *et al.,* 2015). This is one of multiple RIPs that may harbor slight toxicity (van Damme *et al.,* 1997; de Benito *et al.,* 1998; Tejero *et al.,* 2015; Shang *et al.,* 2015). Thoroughly cooking the fruit (or boiling the juice) before use, however, should denature such proteins; while this has not yet been experimentally demonstrated with *S. nigra* RIPs, a study on *S. ebulus* berries found that heating the fruit sufficiently inhibited toxic effects from a lectin, which shows high homology to the *S. nigra* RIP Sam n1 (Jimenez *et al.,* 2014). Other cytotoxic and genotoxic effects have been suggested at very high doses, but not at those which would be recommended for use (Bratu *et al.,* 2012). Overall, concerns with the safety of *S. nigra* can be avoided with proper preparation of the plant and proper dosing.

Reports of adverse effects of *S. nigra* use typically result from use of a non-prescribed part of the plant, overdosage, or eating uncooked fruit, and reports of adverse effects with proper usage of the plant are anecdotal and unverified (Kunitz *et al.,* 1984; Ulbricht *et al.,* 2014). Symptoms of *S. nigra* misuse are typically limited to nausea, vomiting, and diarrhea (Lust, 1974; Ulbricht *et al.,* 2014); these issues are all easily avoided by using a properly processed commercial *S. nigra* extract, syrup, or combination therapy. In theory, high-dose or long-term *S. nigra* flower use could pose a risk of excessive diuresis (Beaux *et al.,* 1999). In the treatment of acute viral infection, however, neither high-dose nor long-term prescription would typically be recommended. The only recorded case of *Sambucus* fruit poisoning in recent reports was from uncooked juice from pressed berries, leaves, and branches, which was then left out overnight before consumption, and likely from *S. mexicana* or possibly *S. canadensis*, but doubtfully *S. nigra* (Kunitz *et al.,* 1984). While this was cited by Ulbricht *et al.* (2014) as cause for concern of cyanide toxicity in *S. nigra* fruit and flowers, the potential cyanogenic compounds in question, L-prunasin and D-prunasin, found in non-prescribed parts of the plant and perhaps the unripe fruit, have not been reported in ripe fruit or flowers (Tables 1 and 2); the patients in this incident did not have elevated cyanide levels, although this was tested for; and the fruit, which was picked from wild elder, was not verified as *S. nigra*, which is not native to the region of the incident (while *S. mexicana* is). Further, any potential cyanogenic

compounds would be more likely to have come from the leaves and branches pressed with the juice, which do contain such potentially cyanogenic compounds. Considering the lack of any substantiated claims for concern with regards to cyanide toxicity in ripe fruit or in flowers, it is unlikely that cyanide toxicity is a safety concern in properly consumed *S. nigra*. Further, considering the lack of any verified reports of adverse effects of *S. nigra* flower, ripe cooked fruit, or fruit extract use, and the lack of known potentially harmful compounds at any reasonable dosage, *S. nigra* is likely safe for use temporarily or as a continuous dietary supplement in the absence of contraindications.

Research on potential contraindications is tentative and conservative. Initial research on the use of black elder in pregnancy indicated no teratogenicity (Ismail *et al.,* 2003), and the only noted complication was gastrointestinal distress (Tsui *et al.,* 2001). However, sufficient research to verify the safety of black elder in fetal and early post-natal development is lacking, and *S. nigra* is not recommended for such individuals. *S. nigra* may marginally impair angiogenesis (Roy *et al.,* 2002; Bagchi *et al.,* 2004); more research is needed to determine if the degree of impairment could result in clinically relevant pathologies. *S. nigra* is not recommended for patients allergic or hypersensitive to Adoxaceae or Caprifoliaceae plants because of the risk of allergic reaction (Förster-Waldl *et al.,* 2003; Ulbricht *et al.,* 2014). Chemotherapy patients are cautioned because of the potential for increased adverse effects in general during chemotherapy (Lukash *et al.,* 1997; de Benito *et al.,* 1998; Ulbricht *et al.,* 2014). Hypokalemics are cautioned against *S. nigra* use because of a possible risk of decreased potassium with its use (Picon *et al.,* 2010). As *S. nigra* stimulates cellular glucose uptake and promotes insulin secretion by beta cells, its use would need to be closely monitored alongside other medications in diabetic patients (Gray *et al.,* 2000; Christensen *et al.,* 2009; Christensen *et al.,* 2010; Bhattacharya *et al.,* 2013). Patients on blood pressure-lowering medications, diuretics, laxatives, or XO inhibitors would likewise need to be monitored closely with *S. nigra* usage, as constituents of the plant have the potential to act synergistically with these medications (Beaux *et al.,* 1999; Chrubasik *et al.,* 2008; Hasani-Ranjbar *et al.,* 2009; Picon *et al.,* 2010; Ulbricht *et al.,* 2014). *S. nigra* has also been implicated as a potential causative agent for gastrointestinal distress or upset and related disorders (Tsui *et al.,* 2001; Grbic *et al.,* 2011; Ulbricht *et al.,* 2014), and possibly dysmenorrhea, migraines, and dorsal muscular pain (Grbic *et al.,* 2011; Ulbricht *et al.,* 2014). Occurrence of complications even in these cases of potential caution appears quite low, although most studies had insufficient sample size to determine the rate of occurrence with high precision or certainty (Lukash *et al.,* 1997; de Benito *et al.,* 1998; Beaux *et al.,* 1999; Gray *et al.,* 2000; Tsui *et al.,* 2001; Roy *et al.,* 2002; Bagchi *et al.,* 2004; Chrubasik *et al.,* 2008; Hasani-Ranjbar *et al.,* 2009; Picon *et al.,* 2010; Grbic *et al.,* 2011; Ulbricht *et al.,* 2014). However, more research is needed to determine the extent of these potential contraindications. Further, because of possible drug interactions in these contraindicated cases, as is often an issue with the use of herbal remedies (which are typically very chemically complex) (Izzo *et al.,* 2016), *S. nigra* should not be prescribed in these cases until research has verified their safe use. In absence of these contraindications, *S. nigra* flowers and ripe cooked fruit, and standardized elderberry extracts, are likely safe for normal consumption.

RECOMMENDATIONS FOR USE

Adding *S. nigra* flowers or cooked ripe fruit to one's diet in the absence of contraindications appears safe because of its long history of use throughout disparate cultures in medicine and cuisine without report of ill effect (Agustí, 1617; Vallès *et al.,* 2004; Jarić *et al.,* 2007; Ulbricht *et al.,* 2014) and the denaturation of the only known constituents, which could be potentially toxic, SNAs, as discussed previously. Plant constituents other than flowers and ripe fruit are generally considered unsafe for consumption. Known-dosage, properly prepared fruit or flower extracts that denature potentially harmful lectins also appear safe to use in individuals without contraindications and have been indicated as beneficial in preventing and fighting many pathogens, including influenza. It is uncertain whether elderberry extracts or properly prepared fruit or flowers is preferential, because of a lack of clinical research using the fresh plant.

As the probability of complications appears low, because most of the complications indicated are relatively minor (Lukash *et al.,* 1997; de Benito *et al.,* 1998; Beaux *et al.,* 1999; Gray *et al.,* 2000; Tsui *et al.,* 2001; Roy *et al.,* 2002; Ismail *et al.,* 2003; Bagchi *et al.,* 2004; Chrubasik *et al.,* 2008; Hasani-Ranjbar *et al.,* 2009; Picon *et al.,* 2010; Grbic *et al.,* 2011; Ulbricht *et al.,* 2014), and because of noted benefits in the treatment of influenza and other pathogens, *S. nigra*, at proper dosages and in a prepared and well-studied product such as Sambucol or Sinupret may be an optimal choice in the treatment of influenza.

Comparisons with standard antiviral medications

While current research is sufficient to substantiate claims of its preventative effects against viral pathogens, studies directly comparing *S. nigra* and its constituents with conventional antiviral medications are greatly lacking, and thus, its potential as a clinical antiviral medication has not been well established. Perhaps the most important issues to consider between *S. nigra* and traditional antivirals are safety, cost, efficacy, and viral resistance.

It has been noted that herbal remedies are typically better tolerated than synthetic drugs (Izzo *et al.,* 2016). *S. nigra* appears very well tolerated and safe based on a lack of adverse effects seen in clinical studies or other reports, and its long ethnobotanical history as a food and medicinal herb.

The cost of *S. nigra* extract is quite low, as one would expect of an extraction of a common fruit, compared with synthetically manufactured antiviral medications.

Comparative efficacy is best determined through comparative clinical and mechanistic studies. One study comparing the multi-herb treatment TheraMax® (TheraMax, Copyright 2008, Therabiogen, Inc., New York, NY, USA), which contains elderberry extract, to the neuraminidase inhibitor oseltamivir phosphate (Tamiflu®, Tamiflu, Copyright 2017, Genentech, Inc.,

South San Francisco, CA, USA) in influenza-infected mice found that oseltamivir prevented death and mitigated weight loss while most animals treated with TheraMax did not survive (although a treatment containing TheraMax combined directly with the virus prior to inoculation of the mice performed similarly to oseltamivir) (Smee *et al.,* 2011). Another study found the *in vitro* influenza-inhibiting activity of *S. nigra* flavonoids 5,7,3′,4′-tetra-*O*-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-3,4,5-trihydroxycyclohexanecarboxylate similar or preferable to oseltamivir and preferable to amantadine (Roschek *et al.,* 2009) – another neuraminidase inhibitor used against influenza infection before seasonal influenza developed almost complete resistance to the drug (CDC, 2006; Deyde *et al.,* 2007; CDC, 2009). One study on synergistic effects between amantadine and a multiherb treatment containing *S. nigra* flowers found that synergistic effects exists between the herbal treatment and several amantadine treatments against influenza *in vitro* (Serkedjieva and Zgorniak-Nowosielska, 1993). A study comparing oseltamivir with concentrated elderberry juice in influenza-infected mice found that the elderberry juice significantly inhibited the infection, and that while oseltamivir may have had slightly greater inhibition, elderberry worked at least in part by stimulating an immune response, while oseltamivir lessened immune response compared with a control group by directly inhibiting viral neuraminidase (Kinoshita *et al.,* 2012). However, these few studies alone are insufficient to accurately determine the potential of *S. nigra* or its constituents in comparison with accepted antiviral medications, and more research is needed in this area.

Viral resistance can develop easily in cases of medicine being used unnecessarily or preventatively, especially at low doses over long periods of time; thus, most traditional antivirals, such as oseltamivir, are not recommended preventatively (Burch *et al.,* 2009). Thus, if the promising results of early studies as to *S. nigra*'s preventative effects (Burge *et al.,* 1999; Kinoshita *et al.,* 2012) prove accurate, it could be of great benefit to public health. While preventative use of most traditional antivirals could provide an opportunity for pathogenic viruses to develop resistance to the drug (Memoli *et al.,* 2010; American Academy of Pediatrics, 2015), *S. nigra* displays the biochemical complexity of most plants' antimicrobial defensive mechanisms, in which multiple compounds and mechanisms simultaneously inhibit the activity of susceptible pathogens. As it is highly unlikely that any individual virion would have adequate defenses against all these mechanisms, as would be necessary to begin the evolution of resistance, these pathogens would be unlikely to develop any resistance to *S. nigra*. However, more research is needed to verify or disprove this claim. *S. nigra* also stimulates natural immune responses in the host, as opposed to neuraminidase inhibitors (Kinoshita *et al.,* 2012), and has been shown to be effective against neuraminidase inhibitor-resistant viruses (Morag *et al.,* 1997). By stimulating a host immune response, *S. nigra* adds additional mechanisms targeting the virus, thus making it even more unlikely for viruses to develop resistance; the inhibited immune response seen in neuraminidase inhibitors (because the drug acts directly on the virion, reducing stress on the host immune system) has the opposite effect. At the least, *S. nigra* could be a suitable treatment against oseltamivir-resistant viruses. Further, any potential evolution of resistance to *S. nigra* by influenza viruses or other viral pathogens would be unlikely to provide a detrimental impact on public health compared with its current state (by providing increased fitness to the virus against other treatment options), although this claim would need to be verified before the potential to benefit public health by preventative prescription of *S. nigra* extract could be properly evaluated.

CONCLUSION

Black elder has many constituents beneficial to general health and is implicated in the relief of a wide variety of health disorders. Despite the need for more research in many areas, *S. nigra* is promising as an inexpensive and low-risk treatment for influenza and other viral and non-viral pathogens – and potentially as a preventative for acute viral infections as well.

Ethics

This review conforms to the Committee on Publication Ethics Codes of Conduct and Best Practice Guidelines.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

Abuja PM, Murkovic M, Pfannhauser W. 1998. Antioxidant and prooxidant activities of elderberry (*Sambucus nigra*) extract in low density lipoprotein oxidation. *J Agric Food Chem* **46**: 4091–4096.

Agelet A. 2000. Estudis d'etnobotànica farmacèutica al Pallars. *Revista d'etnologia de Catalunya* **17**: 120–123.

Agustí M. 1617. Libre Dels Secrets de Agricultura, Casa Rústica y Pastoril, Facsimile edition: 1988 edn. Alta Fulla: Barcelona. Esteve Liberós: Barcelona.

American Academy of Pediatrics. 2015. Recommendations for prevention and control of influenza in children, 2014–2015. *Pediatrics* **134**(5): e1503–e1519.

Amoros M, Simões CM, Girre L, Sauvager F, Cormier M. 1992. Synergistic effect of flavones and flavonols against herpes simplex virus type 1 in cell culture. Comparison with the antiviral activity of propolis. *J Nat Prod* **55**(12): 1732–1740.

Angata T, Varki A. 2002. Chemical diversity in the sialic acids and related α-keto acids: an evolutionary perspective. *Chem Rev* **102**(2): 439–469.

Au TK, Collins RA, Lam TL, Ng TB, Fong WP, Wan DC. 2000. The plant ribosome inactivating proteins luffin and saporin are potent inhibitors of HIV-1 integrase. *FEBS Lett* **471**(2–3): 169–172.

Bagchi D, Sen CK, Bagchi M, Atalay M. 2004. Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula. *Biochemistry (Mosc)* **69**(1): 75–80.

Balasingam S, Lamkin R, Safirman D, Mumcuoglu M, Oxford JS. 2006. Neutralizing activity of Sambucol® against avian NIBRG-14 (H5N1) influenza virus. In IV International Conference on Influenza, Preventing the Pandemic, Bird Flu Vaccines. London; 23–24.*June*

Barak V, Halperin T, Kalickman I. 2001. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. *Eur Cytokine Netw* **12**(2): 290–296.

Barak V, Birkenfeld S, Halperin T, Kalickman I. 2002. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J* **4**(11 Suppl): 919–922.

Beaux D, Fleurentin J, Mortier F. 1999. Effect of extracts of *Orthosiphon stamineus* benth, *Hieracium pilosella* L., *Sambucus nigra* L. and *Arctostaphylos uva-ursi* (L.) spreng. in rats. *Phytother Res* **13**(3): 222–225.

Bhattacharya S, Christensen KB, Olsen LC, *et al.* 2013. Bioactive components from flowers of *Sambucus nigra* L. increase glucose uptake in primary porcine myotube cultures and reduce fat accumulation in *Caenorhabditis elegans*. *J Agric Food Chem* **61**(46): 11033–11040.

Boada M, Romanillos T. 1999. Les Plantes Tòxiques de Catalunya. Portic: Barcelona.

Bobek P, Nosalova V, Cerna S. 2001. Influence of diet containing extract of black elder (*Sambucus nigra*) on colitis in rats. *Biol Bratislava* **56**: 643–648.

Bratu MM, Doroftei E, Negreanu-Pirjol T, Hostina C, Porta S. 2012. Determination of antioxidant activity and toxicity of *Sambucus nigra* fruit extract using alternative methods. *Food Technol Biotechnol* **50**(2): 177–182.

Brinkman-Van der Linden ECM, Sonnenburg JL, Varki A. 2002. Effects of sialic acid substitutions on recognition by *Sambucus nigra* agglutinin and *Maackia amurensis* hemagglutinin. *Anal Biochem* **303**(1): 98–104.

Brønnum-Hansen K, Hansen SH. 1983. High-performance liquid chromatographic separation of anthocyanins of *Sambucus nigra* L. *J Chromatogr A* **262**: 385–392.

Bruneton J. 2001. Plantas Tóxicas: Vegetales Peligrosos Para el Hombre. Zaragoza: Editorial Acribia.

Burch J, Corbett M, Stock C, *et al.* 2009. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet Infect Dis* **9**(9): 537–545.

Burge B, Mumcuoglu M, Simmons T. 1999. The effect of Sambucol on flu-like symptoms in chimpanzees: prophylactic and symptom-dependent treatment. *Int Zoo News* **46**: 16–19.

Cao G, Prior RL. 1999. Anthocyanins are detected in human plasma after oral administration of an elderberry extract. *Clin Chem* **45**(4): 574–576.

Cappello AR, Dolce V, Iacopetta D, *et al.* 2016. Bergamot (*Citrus bergamia* Risso) flavonoids and their potential benefits in human hyperlipidemia and atherosclerosis: an overview. *Mini Rev Med Chem* **16**(8): 619–629.

CDC (Centers for Disease Control and Prevention). 2006. CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the United States during the 2005–06 influenza season. *CDC Health Alert* [serial on the Internet]. 14 Jan, 2006 [cited 17 Nov, 2016]. Available from https://web.archive.org/web/20080503092840/http://www.cdc.gov/flu/han011406.htm

CDC (Centers for Disease Control and Prevention). 2009. 2008–2009 influenza season week 35 ending September 5, 2009. *FluView* [serial on the Internet]. 27 Aug, 2009 [cited 17 Nov, 2016]. Available from http://www.cdc.gov/flu/weekly/weeklyarchives2008-2009/weekly35.htm

Chang WS, Lee YJ, Lu FJ, Chiang HC. 1993. Inhibitory effects of flavonoids on xanthine oxidase. *Anticancer Res* **13**: 2165–2170.

Chang C-F, Cho S, Wang J. 2014. (−)-Epicatechin protects hemorrhagic brain via synergistic Nrf2 pathways. *Ann Clin Transl Neurol* **1**(4): 258–271.

Chatterjee A, Yasmin T, Bagchi D, Stohs SJ. 2004. Inhibition of *Helicobacter pylori in vitro* by various berry extracts, with enhanced susceptibility to clarithromycin. *Mol Cell Biochem* **265**: 19–26.

Chen S, Zheng T, Shortreed MR, Alexander C, Smith LM. 2007. Analysis of cell surface carbohydrate expression patterns in normal and tumorigenic human breast cell lines using lectin arrays. *Anal Chem* **79**(15): 5698–5702.

Cheng KW, Wu Q, Zheng ZP, *et al.* 2007. Inhibitory effect of fruit extracts on the formation of heterocyclic amines. *J Agric Food Chem* **55**: 10359–10365.

Choi O, Yahiro K, Morinaga N, Miyazaki M, Noda M. 2007. Inhibitory effects of various plant polyphenols on the toxicity of Staphylococcal α-toxin. *Microb Pathog* **42**(5–6): 215–224.

Christensen LP, Kaack K, Fretté XC. 2008. Selection of elderberry (*Sambucus nigra* L.) genotypes best suited for the preparation of elderflower extracts rich in flavonoids and phenolic acids. *Eur Food Res Technol* **227**(1): 293–305.

Christensen KB, Minet A, Svenstrup H, *et al.* 2009. Identification of plant extracts with potential antidiabetic properties: effect on human peroxisome proliferator-activated receptor (PPAR), adipocyte differentiation and insulin-stimulated glucose uptake. *Phytother Res* **23**(9): 1316–1329.

Christensen KB, Petersen RK, Kristiansen K, Christensen LP. 2010. Identification of bioactive compounds from flowers of black elder (*Sambucus nigra* L.) that activate the human peroxisome proliferator-activated receptor (PRAR) γ. *Phytother Res* **24**(Suppl 2): S129–S132.

Chrubasik C, Maier T, Dawid C, *et al.* 2008. An observational study and quantification of the actives in a supplement with *Sambucus nigra* and *Asparagus officinalis* used for weight reduction. *Phytother Res* **22**(7): 913–918.

Citores L, de Benito FM, Iglesias R, *et al.* 1996. Isolation and characterization of a new non-toxic two-chain ribosome-inactivating protein from fruits of elder (*Sambucus nigra* L.). *J Exp Bot* **47**(303): 1577–1585.

Collins EJ, Robertus JD, Presti ML, *et al.* 1990. Primary amino acid sequence of α-trichosanthin and molecular models for abrin A-chain and α-trichosanthin. *J Biol Chem* **265**(15): 8665–8669.

Connor RJ, Kawaoka Y, Webster RG, Paulson JC. 1994. Receptor specificity in human, avian, and equine H2 and H3 influenza virus isolates. *Virology* **205**(1): 17–23.

Davídek J. 1961. Isolation of chromatographically pure rutin from flowers of elder. *Nature* **189**(4763): 487–488.

Dawidowicz AL, Wianowska D, Baraniak B. 2006. The antioxidant properties of alcoholic extracts from *Sambucus nigra* L. (antioxidant properties of extracts). *LWT Food Sci Technol* **39**(3): 308–315.

de Benito FM, Iglesias R, Ferreras JM, *et al.* 1998. Constitutive and inducible type 1 ribosome-inactivating proteins (RIPs) in elderberry (*Sambucus nigra* L.). *FEBS Lett* **428**(1–2): 75–79.

Deyde VM, Xu X, Bright RA, *et al.* 2007. Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide. *J Infect Dis* **196**(2): 249–257.

Ding M, Feng R, Wang SY, Bowman L, Lu Y, Qian Y, Castranova V, Jiang BH, Shi X. 2006. Cyanidin-3-glucoside, a natural product derived from blackberry, exhibits chemopreventive and chemotherapeutic activity. **281**(25): 17359–17368.

Duke JA. 1985. CRC Handbook of Medicinal Herbs. CRC Press: Boca Raton.

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Agostoni C, Bresson J-L, *et al.* 2010. Scientific opinion on the substantiation of health claims related to various food(s)/food constituent(s) and protection of cells from premature aging, antioxidant activity, antioxidant content and antioxidant properties, and protection of DNA, proteins and lipids from oxidative damage pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA J* **8**(2): 1489.

Emig S, Schmalz D, Shakibaei M, Buchner K. 1995. The nuclear pore complex protein p62 is one of several sialic acid-containing proteins of the nuclear envelope. *J Biol Chem* **270**(23): 13787–13793.

Ernst E, März RW, Sieder C. 1997. Vergleichende Anwendungsbeobachtung gegenüber üblichen Expektoranzien bei 3.187 Patienten. *Fortschr Med* **115**(11): 52–53.

Fiorini M. 1995. Preparative high-performance liquid chromatography for the purification of natural anthocyanins. *J Chromatogr A* **692**(1–2): 213–219.

Förster-Waldl E, Marchetti M, Schöll I, *et al.* 2003. Type I allergy to elderberry (*Sambucus nigra*) is elicited by a 33.2 kDa allergen with significant homology to ribosomal inactivating proteins. *Clin Exp Allergy* **33**(12): 1703–1710.

Fukushima K, Takahashi T, Ito S, *et al.* 2014. Terminal sialic acid linkages determine different cell infectivities of human parainfluenza virus type 1 and type 3. *Virology* **464-465**: 424–431.

Galati G, O'Brien PJ. 2004. Potential toxicity of flavonoids and other dietary phenolics: significance for their chemopreventive and anticancer properties. *Free Radic Biol Med* **37**(3): 287–303.

Gambaryan AS, Tuzikov AB, Piskarev VE, *et al.* 1997. Specification of receptor-binding phenotypes of influenza virus isolates from different hosts using synthetic sialylglycopolymers: non-

egg-adapted human H1 and H3 influenza A and influenza B viruses share a common high binding affinity for 6'-sialyl(*N*-acetyllactosamine). *Virology* **232**(2): 345–350.
Gamblin SJ, Skehel JJ. 2010. Influenza hemagglutinin and neuraminidase membrane glycoproteins. *J Biol Chem* **285**(37): 28403–28409.
Ginsburg I, Sadovnic M, Oron M, Kohen R. 2004. Novel chemiluminescence-inducing cocktails, part II: measurement of the anti-oxidant capacity of vitamins, thiols, body fluids, alcoholic beverages and edible oils. *Inflammopharmacol* **12**: 305–320.
Girbés T, Citores L, de Benito FM, Inglesias R, Ferreras JM. 1996. A non-toxic two-chain ribosome-inactivating protein co-exists with a structure-related monomeric lectin (SNA III) in elder (*Sambucus nigra*) fruits. *Biochem J* **315**(Pt 1): 343–344.
Girbés T, Ferreras JM, Arias FJ, *et al.* 2003. Non-toxic type 2 ribosome-inactivating proteins (RIPs) from *Sambucus*: occurrence, cellular and molecular activities and potential uses. *Cell Mol Biol (Noisy-le-Grand)* **49**(4): 537–545.
Glatthaar-Saalmüller B, Rauchhaus U, Rode S, Haunschild J, Saalmüller A. 2011. Antiviral activity in vitro of two preparations of the herbal medicinal product Sinupret® against viruses causing respiratory infections. *Phytomed* **19**(1): 1–7.
Gomes A, Couto D, Alves A, *et al.* 2012. Trihydroxyflavones with antioxidant and anti-inflammatory efficacy. *Biofactors* **38**(5): 378–386.
González CA, Sala N, Rokkas T. 2013. Gastric cancer: epidemiologic aspects. *Helicobacter* **18**(Suppl 1): 34–38.
González-Segovia R, Quintanar JL, Salinas E, Ceballos-Salazar R, Aviles-Jiménez F, Torres-López J. 2008. Effect of the flavonoid quercetin on inflammation and lipid peroxidation induced by *Helicobacter pylori* in gastric mucosa of guinea pig. *J Gastroenterol* **43**(6): 441–447.
Gray AM, Abdel-Wahab YH, Flatt PR. 2000. The traditional plant treatment, *Sambucus nigra* (elder), exhibits insulin-like and insulin-releasing actions in vitro. *J Nutr* **130**(1): 15–20.
Grbic J, Wexler I, Celenti R, Altman J, Saffer A. 2011. A phase II trial of a transmucosal herbal patch for the treatment of gingivitis. *J Am Dent Assoc* **142**(10): 1168–1175.
Gregorio-Jauregui KM, Carrizalez-Alvarez SA, Rivera-Salinas JE, *et al.* 2014. Extraction and immobilization of SA-α-2,6-Gal receptors on magnetic nanoparticles to study receptor stability and interaction with *Sambucus nigra* lectin. *Appl Biochem Biotechnol* **172**(8): 3721–3735.
Haas H, Falcone FH, Schramm G, *et al.* 1999. Dietary lectins can induce in vitro release of IL-4 and IL-13 from human basophils. *Eur J Immunol* **29**(3): 918–927.
Hardin JW, Arena JM. 1974. Human Poisoning from Native and Cultivated Plants. Duke University Press: Durham.
Harokopakis E, Albzreh MH, Haase EM, Scannapieco FA, Hajishengallis G. 2006. Inhibition of proinflammatory activities of major periodontal pathogens by aqueous extracts from elder flower (*Sambucus nigra*). *J Periodontol* **77**(2): 271–279.
Hasani-Ranjbar S, Nayebi N, Larijani B, Abdollahi M. 2009. A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. *World J Gastroenterol* **15**(25): 3073–3085.
Haseley SR, Talaga P, Kamerling JP, Vliegenthart JF. 1999. Characterization of the carbohydrate binding specificity and kinetic parameters of lectins by using surface plasmon resonance. *Anal Biochem* **274**(2): 203–210.
Hawrył M, Hawrył A, Soczewiński E. 2002. Application of normal- and reversed-phase 2d TLC on a cyanopropyl-bonded polar stationary phase for separation of phenolic compounds from the flowers of *Sambucus nigra* L. *JPC – J Planar Chromat* **15**(1): 4–10.
Hernández NE, Tereschuk ML, Abdala LR. 2000. Antimicrobial activity of flavonoids in medicinal plants from Tafí del Valle (Tucumán, Argentina). *J Ethnopharmacol* **73**(1–2): 317–322.
Ho GT, Ahmed A, Zou YF, Aslaksen TH, Wangensteen G, Barsett H. 2015. Structure–activity relationship of immunomodulating pectings from elderberries. *Carbohydr Polym* **125**: 314–322.
Ho GT, Zou YF, Aslaksen TH, Wangensteen G, Barsett H. 2016. Structural characterization of bioactive pectic polysaccharides from elderflowers (*Sambuci* flos). *Carbohydr Polym* **135**: 128–137.
Ilver D, Johansson P, Miller-Podraza H, Nyholm PG, Teneberg S, Karlsson KA. 2003. Bacterium-host protein-carbohydrate interactions. *Methods Enzymol* **363**: 134–157.
Ismail C, Wiesel A, März RW, Queisser-Luft A. 2003. Surveillance study of Sinupret in comparison with data of the Mainz birth registry. *Arch Gynecol Obstet* **267**(4): 196–201.
Ito T, Suzuki Y, Mitnaul L, Vines A, Kida H, Kawaoka Y. 1997. Receptor specificity of influenza A viruses correlates with the agglutination of erythrocytes from different animal species. *Virology* **227**(2): 493–499.
Izzi V, Masuelli L, Tresoldi I, *et al.* 2012. The effects of dietary flavonoids on the regulation of redox inflammatory networks. *Front Biosci (Landmark Ed)* **17**: 2396–2418.
Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM. 2016. A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. *Phytother Res* **30**(5): 691–700.
Jabłońska-Ryś E, Zalewska-Korona M, Kalbarczyk J. 2009. Antioxidant capacity, ascorbic acid and phenolics content in wild edible fruits. *J Fruit Ornam Plant Res* **17**(2): 115–120.
Jarić S, Popović Z, Mačukanović-Jocić M, *et al.* 2007. An ethnobotanical study on the usage of wild medicinal herbs from Kopaonik Mountain (Central Serbia). *JEthnopharmacol* **111**: 160–175.
Jensen SR, Nielsen BJ. 1973. Cyanogenic glucosides in *Sambucus nigra* L. *Acta Chem Scand* **27**(7): 2661–2662.
Jimenez P, Cabrero P, Basterrechea JE, *et al.* 2014. Effects of short-term heating on total polyphenols, anthocyanins, antioxidant activity and lectins of different parts of dwarf elder (*Sambucus ebulus* L.). *Plant Foods Hum Nutr* **69**(2): 168–174.
Kaack K, Austed T. 1998. Interaction of vitamin C and flavonoids in elderberry (*Sambucus nigra* L.) during juice processing. *Plant Foods Hum Nutr* **52**(3): 187–198.
Kahane I, Ofek I (Eds). 1996. Advances in Experimental Medicine and Biology. Vol 408, Toward Anti-Adhesion Therapy for Microbial Diseases. Plenum Press: New York.
Kinoshita E, Hayashi K, Katayama H, Hayashi T, Obata A. 2012. Anti-influenza virus effects of elderberry juice and its fractions. *Biosci Biotechnol Biochem* **76**(9): 1633–1638.
Kong F. 2009. Pilot clinical study on a proprietary elderberry extract: efficacy in addressing influenza symptoms. *Online J Pharmacol Pharmacokinet* **5**: 32–43.
Konlee M. 1998. A new triple combination therapy. *Posit Health News* **17**: 12–14.
Krawitz C, Mraheil MA, Stein M, *et al.* 2011. Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses. *BMC Complement Altern Med* **11**: 16.
Kunitz S, Melton RJ, Updyke T, Breedlove D, Werner SB. 1984. Poisoning from elderberry juice. *MMWR* **33**(13): 173–174.
Lamaison JL, Petitjeat-Freytet C, Carnat A. 1991. Presence of isorhamnetin 3-glucoside and 3-rutinoside in *Sambucus nigra* L. flowers. *Ann Pharm Fr* **49**(5): 258–262.
Laranjinha JA, Almeida LM, Madeira VM. 1994. Reactivity of dietary phenolic acids with peroxyl radicals: antioxidant activity upon low density lipoprotein peroxidation. *Biochem Pharmacol* **48**(3): 487–494.
Lee J, Finn CE. 2007. Anthocyanins and other polyphenolics in American elderberry (*Sambucus canadensis*) and European elderberry (*S. nigra*) cultivars. *J Sci Food Agric* **87**(14): 2665–2675.
Lee-Huang S, Huang PL, Kung HF, *et al.* 1991. TAP 29: an anti-human immunodeficiency virus protein from *Trichosanthes kirilowii* that is nontoxic to intact cells. *Proc Natl Acad Sci U S A* **88**(15): 6570–6574.
Lichtenthäler R, Marx F. 2005. Total oxidant scavenging capacities of common European fruit and vegetable juices. *J Agric Food Chem* **53**: 103–110.
Lin H-C, Tsai S-H, Chen C-S, *et al.* 2008. Structure–activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities. *Biochem Pharmacol* **75**: 1416–1425.
López-Lázaro M. 2002. Flavonoids as anticancer agents: structure–activity relationship study. *Curr Med Chem Anticancer Agents* **2**(6): 691–714.
Lotito SB, Frei B. 2006. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? *Free Radic Biol Med* **41**(12): 1727–1746.

Lü J-M, Lin PH, Yao Q, Chen C. 2010. Chemical and molecular mechanisms of antioxidants: experimental approaches and model systems. *J Cell Mol Med* **14**(4): 840–860.
Lugasi A, Hóvári J. 2003. Antioxidant properties of commercial alcoholic and nonalcoholic beverages. *Nahrung* **47**: 79–86.
Lukash LL, Karpova IS, Miroshnichenko OS, *et al.* 1997. The effect of the lectin from *Sambucus nigra* inflorescences on spontaneous and alkylating agent-induced mutagenesis in mammalian somatic cells. *Tsitol Genet* **31**(5): 52–60.
Lust J. 1974. The Herb Book. Cox and Wyman Ltd.: Reading; 174.
Mach L, Waltraud S, Ammann M, *et al.* 1991. Purification and partial characterization of a novel lectin from elder (*Sambucus nigra* L.) fruit. *Biochem J* **278**(Pt 3): 667–671.
Mach L, Kerschbaumer R, Schwihla H, Glössl J. 1996. Elder (*Sambucus nigra* L.)-fruit lectin (SNA-IV) occurs in monomeric, dimeric and oligomeric isoforms. *Biochem J* **315**(Pt 3): 1061.
Macheix JJ, Fleuriet A, Billot J. 1990. Fruit Phenolics. CRC Press: Boca Raton.
Mahmood N, Pizza C, Aquino R, *et al.* 1993. Inhibition of HIV infection by flavanoids. *Antiviral Res* **22**(2–3): 189–199.
Mandenius CF, Wang R, Aldén A, *et al.* 2008. Monitoring of influenza virus hemagglutinin in process samples using weak affinity ligands and surface plasmon resonance. *Anal Chim Acta* **623**(1): 66–75.
Marczylo TH, Cooke D, Brown K, Steward WP, Gescher AJ. 2009. Pharmacokinetics and metabolism of the putative cancer chemopreventive agent cyanidin-3-glucoside in mice. *Cancer Chemother Pharmacol* **64**(6): 1261–1268.
März RW, Ismail C, Popp MA. 1999. Wirkprofil und Wirksamkeit eines pflanzlichen Kombinationspräparates zur Behandlung der Sinusitis. *Wien Med Wochenschr* **149**(8–10): 202–208.
Mascolo N, Autore G, Capasso F, Menghini A, Palmira FM. 1987. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytother Res* **1**(1): 28–31.
McGrath MS, Hwang KM, Caldwell SE, *et al.* 1989. GLQ223: an inhibitor of human immunodeficiency virus replication in acutely and chronically infected cells of lymphocyte and mononuclear phagocyte lineage. *Proc Natl Acad Sci U S A* **86**(8): 2844–2848.
Melzer J, Saller R, Schapowal A, Brignoli R. 2006. Systematic review of clinical data with BNO-101 (Sinupret) in the treatment of sinusitis. *Forsch Komplement Med* **13**(2): 78–87.
Memoli M, Hrabal R, Hassantoufighi A, Eichelberger M, Taubenberger J. 2010. Rapid selection of oseltamivir and peramivir resistant pandemic H1N1 during therapy in two immunocompromised hosts. *Clin Infect Dis* **50**(9): 1252–1255.
Middleton E Jr, Kandaswami C. 1992. Effects of flavonoids on immune and inflammatory cell functions. *Biochem Pharmacol* **43**(6): 1167–1179.
Mikulic-Petkovsek M, Ivancic A, Todorovic B, Veberic R, Stampar F. 2015. Fruit phenolic composition of different elderberry species and hybrids. *J Food Sci* **80**(10): C2180–C2190.
Mikulic-Petkovsek M, Ivancic A, Schmitzer V, Veberic R, Stampar F. 2016. Comparison of major taste compounds and antioxidative properties of fruits and flowers of different *Sambucus* species and interspecific hybrids. *Food Chem* **200**: 134–140.
Milbury PE, Cao G, Prior RL, Blumberg J. 2002. Bioavailability of elderberry anthocyanins. *Mech Ageing Dev* **123**(8): 997–1006.
Moon YJ, Wang X, Morris ME. 2006. Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. *Toxicol In Vitro* **20**(2): 187–210.
Morag AM, Mumcuoglu M, Baybikov T, Schlesinger M, Zakay-Rones Z. 1997. Inhibition of sensitive and acyclovir-resistant HSV-1 strains by an elderberry extract *in vitro*. Xth International Congress of Virology Jerusalem, Israel; 11–16 August 1996. *Z Phytother* **25**: 97–98.
Morton LW, Abu-Amsha Caccetta R, Puddey IB, Croft KD. 2000. Chemistry and biological effects of dietary phenolic compounds: relevance to cardiovascular disease. *Clin Exp Pharmacol Physiol* **27**(3): 152–159.
Mulet L. 1990. *Aportaciones al Conocimiento Etnobotánico de la Provincia de Castellón* [dissertation]. University of València: València.
Mülleder U, Murkovic M, Pfannhauser W. 2002. Urinary excretion of cyanidin glycosides. *J Biochem Biophys Methods* **53**(1–3): 61–66.
Murkovic M, Mülleder U, Adam U, Pfannhauser W. 2001. Detection of anthocyanins from elderberry juice in human urine. *J Sci Food Agric* **81**(9): 934–937.
Murkovic M, Abuja PM, Bergmann AR, *et al.* 2004. Effects of elderberry juice on fasting and postprandial serum lipids and low-density lipoprotein oxidation in healthy volunteers: a randomized, double-blind, placebo-controlled study. *Eur J Clin Nutr* **58**: 244–249.
Nagai T, Miyaichi Y, Tomimori T, Suzuki Y, Yamada H. 1990. Inhibition of influenza virus sialidase and anti-influenza virus activity by plant flavonoids. *Chem Pharm Bull* **38**(5): 1329–1332.
Nagai T, Miyaichi Y, Tomimori T, Suzuki Y, Yamada H. 1992. *In vivo* anti-influenza virus activity of plant flavonoids possessing inhibitory activity for influenza virus sialidase. *Antiviral Res* **19**(3): 207–217.
Nakajima JI, Tanaka I, Seo S, Yamazaki M, Saito K. 2004. LC/PDA/ESI-MS profiling and radical scavenging activity of anthocyanins in various berries. *J Biomed Biotechnol* **2004**: 241–247.
Nardini M, D'Aquino M, Tomassi G, Gentili V, Di Felice M, Scaccini C. 1995. Inhibition of human low-density lipoprotein oxidation by caffeic acid and other hydroxycinnamic acid derivatives. *Free Radic Biol Med* **19**(5): 541–552.
Narla SN, Sun XL. 2012. Immobilized sialyloligo-macroligand and its protein binding specificity. *Biomacromolecules* **13**(5): 1675–1682.
Netzel M, Strass G, Kaul C, Bitsch I, Dietrich H, Bitsch R. 2002. In vivo antioxidative capacity of a composite berry juice. *Food Res Int* **35**(2–3): 213–216.
Neubauer N, März RW. 1994. Placebo-controlled, randomized double-blind clinical trial with Sinupret® sugar coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. *Phytomed* **1**(3): 177–181.
Nicholls JM, Bourne AJ, Chen H, Guan Y, Peiris JS. 2007. Sialic acid receptor detection in the human respiratory tract: evidence for widespread distribution of potential binding sites for human and avian influenza viruses. *Respir Res* **8**: 73.
No authors listed. 1998. Anecdotal reports: elderberry extract plus chondroitin and glucosamine sulfate and Thy-mate reduces viral load to non-detectable levels in 10 days. *Posit Health News* **17**: 7–11.
Oh DR, Kim JR, Kim YR. 2010. Genistein inhibits *Vibrio vulnificus* adhesion and cytotoxicity to HeLa cells. *Arch Pharm Res* **33**(5): 787–792.
Olthof MR, Hollman PC, Katan MB. 2001. Chlorogenic acid and caffeic acid are absorbed in humans. *J Nutr* **131**(1): 66–71.
Petitjean-Freytet C, Carnat A, Lamaison L. 1991. Teneurs en flavonoides et en derives hydroxycinnamiques de la fleur de *Sambucus nigra* L. *J Pharm Belg* **46**(4): 241–246.
Picon PD, Picon RV, Costa AF, *et al.* 2010. Randomized clinical trial of a phytotherapic compound containing *Pimpinella anisum*, *Foeniculum vulgare*, *Sambucus nigra*, and *Cassia augustifolia* for chronic constipation. *BMC Complement Altern Med* **10**: 17.
Pietta P, Bruno A, Mauri P, Rava A. 1992. Separation of flavonol-2-O-glycosides from *Calendula officinalis* and *Sambucus nigra* by high-performance liquid and micellar electrokinetic capillary chromatography. *J Chromatogr* **593**(1–2): 165–170.
Pool-Zobel BL, Bub A, Schröder N, Rechkemmer G. 1999. Anthocyanins are potent antioxidants in model systems but do not reduce endogenous oxidative DNA damage in human colon cells. *Eur J Nutr* **38**: 227–234.
Post DM, Mungur R, Gibson BW, Munson RS Jr. 2005. Identification of a novel sialic acid transporter in *Haemophilus ducreyi*. *Infect Immun* **73**(10): 6727–6735.
Richstein A, Mann W. 1980. Zur Behandlung der chronischen Sinusitis mit Sinupret. *Ther Ggw* **119**(9): 1055–1060.
Rogerieux F, Belaise M, Terzidis-Trabelsi H, Greffard A, Pilatte Y, Lambré CR. 1993. Determination of the sialic acid linkage specificity of sialidases using lectins in a solid phase assay. *Anal Biochem* **211**(2): 200–204.
Rogers GN, D'Souza BL. 1989. Receptor binding properties of human and animal H1 influenza virus isolates. *Virology* **173**(1): 317–322.
Rogers GN, Paulson JC. 1983. Receptor determinants of human and animal influenza virus isolates: differences in receptor specificity of the H3 hemagglutinin based on species of origin. *Virology* **127**(2): 361–373.
Rogers GN, Paulson JC, Daniels RS, Skehel JJ, Wilson IA, Wiley DC. 1983. Single amino acid substitutions in influenza haemagglutinin change receptor binding specificity. *Nature* **304**(5921): 76–78.

Roschek B Jr, Fink RC, McMichael MD, Li D, Alberte RS. 2009. Elderberry flavonoids bind to and prevent H1N1 infection *in vitro*. *Phytochemistry* **70**(10): 1255–1261.
Roy S, Khanna S, Alessio HM, *et al.* 2002. Anti-angiogenic property of edible berries. *Free Radic Res* **36**(9): 1023–1031.
Samuels N, Grbic JT, Saffer AJ, Wexler ID, Williams RC. 2012a. Effect of an herbal mouth rinse in preventing periodontal inflammation in an experimental gingivitis model: a pilot study. *Compend Contin Educ Dent* **33**(3): 204–211.
Samuels N, Saffer A, Wexler ID, Oberbaum M. 2012b. Localized reduction of gingival inflammation using site-specific therapy with a topical gingival patch. *J Clin Dent* **23**(2): 64–67.
Saphira-Nahor O, Zakay-Rones Z, Mamcuoglu M. 1995. The effects of Sambicol® on HIV infection *in vitro*. *Ann Israel Congress Microbiol, February 6–7.*
Schauer R. 2000. Achievements and challenges of sialic acid research. *Glycoconj J* **17**(7–9): 485–499.
Schmitzer V, Veberic R, Slatnar A, Stampar F. 2010. Elderberry (*Sambucus nigra* L.) wine: a product rich in health promoting compounds. *J Agric Food Chem* **58**(18): 10143–10146.
Schröder K, Vecchione C, Jung O, *et al.* 2006. Xanthine oxidase inhibitor tungsten prevents the development of atherosclerosis in ApoE knockout mice fed a Western-type diet. *Free Radic Biol Med* **41**: 1353–1360.
Schroeter H, Boyd C, Spencer JP, Williams RJ, Cadenas E, Rice-Evans C. 2002. MAPK signaling in neurodegeneration: influences of flavonoids and of nitric oxide. *Neurobiol Aging* **23**(5): 861–880.
Seitz U, Bonn G. 1991. Isotachophoretic analysis of flavonoids and phenolcarboxylic acids of relevance to phytopharmaceutical industry. *J Chromatogr A* **559**(1–2): 499–504.
Serkedjieva J. 1996. In vitro antiinfluenza virus effect of a plant preparation SHS-174. *Fitoterapia* **67**(4): 351–358.
Serkedjieva J, Zgorniak-Nowosielska I. 1993. Combined antiinfluenza activity of a plant preparation SHS-174 and amantadine derivatives. *Acta Virol* **37**(4): 258–264.
Serkedjieva J, Manolova N, Zgórniak-Nowosielska I, Zawili'nska B, Grzybek J. 1990. Antiviral activity of the infusion (SHS-174) from flowers of *Sambucus nigra* L., aerial parts of *Hypericum perforatum* L., roots of *Saponaria officinalis* L. against influenza and herpes simplex viruses. *Phytother Res* **4**(3): 97–100.
Severi E, Hood DW, Thomas GH. 2007. Sialic acid utilization by bacterial pathogens. *Microbiology* **153**(Pt 9): 2817–2822.
Shang C, Chen Q, Dell A, Saslam SM, de Vos WH, van Damme EJ. 2015. The cytotoxicity of elderberry ribosome-inactivating proteins is not solely determined by their protein translation inhibition activity. *PLoS One* **10**(7): e0132389.
Sharon N. 2006. Carbohydrates as future anti-adhesion drugs for infectious diseases. *Biochim Biophys Acta* **1760**(4): 527–537.
Shibuya N, Goldstein IJ, Broekaert WF, Nsimba-Lubaki M, Peeters B, Peumans WJ. 1987. The elderberry (*Sambucus nigra* L.) bark lectin recognizes the Neu5Ac(α2-6)Gal/GalNAc sequence. *J Biol Chem* **262**(4): 1596–1601.
Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. 2006. Avian flu: influenza virus receptors in the human airway. *Nature* **440**(7083): 435–436.
Shipp J, Abdel-Aal E-SM. 2010. Food applications and physiological effects of anthocyanins as functional food ingredients. *Open Food Sci J* **4**(1): 7–22.
Siasos G, Tousoulis D, Tsigkou V, *et al.* 2013. Flavonoids in atherosclerosis: an overview of their mechanisms of action. *Curr Med Chem* **20**(21): 2641–2660.
Smee DF, Hurst BL, Wong MH. 2011. Effects of TheraMax on influenza virus infections in cell culture and in mice. *Antivir Chem Chemother* **21**(6): 231–237.
Song X, Yu H, Chen X, *et al.* 2011. A sialylated glycan microarray reveals novel interactions of modified sialic acids with proteins and viruses. *J Biol Chem* **286**(36): 31610–31622.
Steinberg FM, Bearden MM, Keen CL. 2003. Cocoa and chocolate flavonoids: implications for cardiovascular health. *J Am Diet Assoc* **103**(2): 215–223.
Steinhauer DA. 1999. Role of hemagglutinin cleavage for the pathogenicity of influenza virus. *Virology* **258**(1): 1–20.
Stirpe F, Battelli MG. 2006. Ribosome-inactivating proteins: progress and problems. *Cell Mol Life Sci* **63**(16): 1850–1866.
Tangney C, Rasmussen HE. 2013. Polyphenols, inflammation, and cardiovascular disease. *Curr Atheroscler Rep* **15**(5): 324.
Tejero J, Jiménez P, Quinto EJ, *et al.* 2015. Elderberries: a source of ribosome-inactivating proteins with lectin activity. *Molecules* **20**(2): 2364–2387.
Thole JM, Kraft TF, Sueiro LA Kang YH, *et al.* 2006. A comparative evaluation of the anticancer properties of European and American elderberry fruits. *J Med Food* **9**: 498–504.
Timoshenko AV, Cherenkevich SN. 1995. H_2O_2 generation and human neutrophil aggregation as affected by lectins. *Gematol Transfuziol* **40**(4): 32–35.
Tiralongo E, Wee SS, Lea RA. 2016. Elderberry supplementation reduces cold duration and symptoms in air-travellers: A randomized, double-blind placebo-controlled clinical trial. *Nutrients* **8**(4): e182.
Topoľská D, Valachová K, Rapta P, *et al.* 2015. Antioxidative properties of *Sambucus nigra* extracts. *Chem Pap* **69**(9): 1202–1210.
Toulemonde B, Richard HMJ. 1983. Volatile constituents of dry elder (*Sambucus nigra* L.) flowers. *J Agric Food Chem* **31**(2): 365–370.
Tsui B, Dennehy CE, Tsourounis C. 2001. A survey of dietary supplement use during pregnancy at an academic medical center. *Am J Obstet Gynecol* **185**(2): 433–437.
Tutin TG, Heywood VH, Burges NA, *et al.* 1976. Flora Europaea. Cambridge University Press: Cambridge.
U.S. Food and Drug Administration. 2016. Code of Federal Regulations, Title 21, Volume 3, Chapter 1. Part 182, Substances Generally Recognized as Safe, Subpart A, General Provision, Section 182.20, Essential oils, oleoresins (solvent free), and natural extractives (including distillates). Office of the Federal Register National Archives and Records; U.S. Government Publishing Office: Washington, DC.
Ueno K, Wang ZH, Hanamure Y, *et al.* 1997. Reduced sialylation of glycoproteins in nasal glands of patients with chronic sinusitis. *Acta Otolaryngol* **17**(3): 420–423.
Ulbricht C, Basch E, Cheung L, *et al.* 2014. An evidence-based systematic review of elderberry and elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration. *J Diet Suppl* **11**(1): 80–120.
Urbánek M, Pospíšilová M, Polaášek M. 2002. On-line coupling of capillary isotachophoresis and zone electrophoresis for the assay of phenolic compounds in plant extracts. *Electrophoresis* **23**(7–8): 1045–1052.
Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact* **160**(1): 1–40.
Vallès J, Bonet MÀ, Agelet A. 2004. Ethnobotany of *Sambucus nigra* L. in Catalonia (Iberian Peninsula): the integral exploitation of a natural resource in mountain regions. *Econ Bot* **58**(3): 456–469.
van Dam RM, Naidoo N, Landberg R. 2013. Dietary flavonoids and the development of type 2 diabetes and cardiovascular diseases: review of recent findings. *Curr Opin Lipidol* **24**(1): 25–33.
van Damme EJ, Barre A, Rougé P, Van Leuven F, Peumans WJ. 1996. Characterization and molecular cloning of *Sambucus nigra* agglutinin V (nigrin b), a GalNAc-specific type-2 ribosome-inactivating protein from the bark of elderberry (*Sambucus nigra*). *Eur J Biochem* **237**(2): 505–513.
van Damme EJ, Roy S, Barre A, Rouge P, van Leuven F, Peumans WJ. 1997. The major elderberry (*Sambucus nigra*) fruit protein is a lectin derived from a truncated type 2 ribosome-inactivating protein. *Plant J* **12**(6): 1251–1260.
Vandenbussche F, Desmyter S, Ciani M, Proost P, Peumans WJ, Van Damme EJ. 2004. Analysis of the in planta antiviral activity of elderberry ribosome-inactivating proteins. *Eur J Biochem* **271**(8): 1508–1515.
Varki A. 2007. Glycan-based interactions involving vertebrate sialic-acid-recognizing proteins. *Nature* **446**: 1023–1029.
Varki A. 2008. Sialic acids in human health and disease. *Trends Mol Med* **14**(8): 351–360.
Varki NM, Varki A. 2007. Diversity in cell surface sialic acid presentations: implications for biology and disease. *Lab Invest* **87**(9): 851–857.
Veberic R, Jakopic J, Stampar F, Schmitzer V. 2009. European elderberry (*Sambucus nigra* L.) rich in sugars, organic acids, anthocyanins and selected polyphenols. *Food Chem* **114**(2): 511–515.
Vigneaux C. 1985. Plantes Médicinales: Thérapeutique – Toxicité. Masson: Paris.

Vimr ER, Troy FA. 1985. Identification of an inducible catabolic system for sialic acids (*nan*) in *Escherichia coli*. *J Bacteriol* **164**(2): 845–853.

Vimr ER, Kalivoda KA, Deszo EL, Steenbergen SM. 2004. Diversity of microbial sialic acid metabolism. *Microbiol Mol Biol Rev* **68**(1): 132–153.

Vlachojannis JE, Cameron M, Chrubasik S. 2010. A systematic review on the sambuci fructus effect and efficacy profiles. *Phytother Res* **24**(1): 1–8.

Wagner R, Matrosovich M, Klenk HD. 2002. Functional balance between haemagglutinin and neuraminidase in influenza virus infections. *Rev Med Virol* **12**(3): 159–166.

Wang YX, Jacob J, Wingfield PT, *et al.* 2000. AntiHIV and antitumor protein MAP30, a 30 kDa single-strand type-I RIP, shares similar secondary structure and beta-sheet topology with the A chain of ricin, a type-II RIP. *Protein Sci* **9**(1): 138–144.

Williams RJ, Spencer JPE, Rice-Evans C. 2004. Flavonoids: antioxidants or signalling molecules? *Free Radic Biol Med* **36**(1): 838–849.

Woo HD, Kim J. 2013. Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis. *PLoS One* **8**(9): e75604.

Wu X, Cao G, Prior RL. 2002. Absorption and metabolism of anthocyanins in elderly women after consumption of elderberry or blueberry. *J Nutr* **132**: 1865–1871.

Wu X, Gu L, Prior RL, McKay S. 2004. Characterization of anthocyanins and proanthocyanidins in some cultivars of *Ribes*, *Aronia*, and *Sambucus* and their antioxidant capacity. *J Agric Food Chem* **52**: 7846–7856.

Yamada S, Suzuki Y, Suzuki T, *et al.* 2006. Haemagglutinin mutations responsible for the binding of H5N1 influenza A viruses to human-type receptors. *Nature* **444**(7117): 378–382.

Yang CS, Landau JM, Huang MT, Newmark HL. 2001. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu Rev Nutr* **21**: 381–406.

Yesilada E, Ustun O, Sezik E, Takaishi Y, Ono Y, Honda G. 1997. Inhibitory effects of Turkish folk remedies on inflammatory cytokines: interleukin-1α, interleukin-1β and tumor necrosis factor α. *J Ethnopharmacol* **58**(1): 59–73.

Youdim KA, Martin A, Joseph JA. 2000. Incorporation of the elderberry anthocyanins by endothelial cells increases protection against oxidative stress. *Free Radic Biol Med* **29**(1): 51–60.

Youdim KA, Spencer JPE, Schroeter H, Rice-Evans C. 2002. Dietary flavonoids as potential neuroprotectants. *Biol Chem* **383**(3–4): 503–519.

Zakay-Rones Z, Varsano N, Zlotnik M, *et al.* 1995. Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. *J Altern Complement Med* **1**(4): 361–369.

Zakay-Rones Z, Thom E, Wollan T, Wadstein J. 2004. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res* **32**(2): 132–140.

Zamora-Ros R, Agudo A, Luján-Barroso L, *et al.* 2012. Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* **96**(6): 1398–1408.