**Sambucus nigra — a promising natural source for human health**

Sara Cunha, Diana Meireles, Jorge Machado

1 ICBAS - Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal.
2 CIIMAR – Centro Interdisciplinar de Investigação Marinha e Ambiental, Universidade do Porto, Portugal

**Abstract**

*Sambucus nigra* (S.nigra) is a species belonging to Caprifoliaceae family, geographically distributed in Europe but also in the far north and northwest Africa and southwest Asia. In Portugal it occurs in almost all the territory, mainly in the North region. Tarouca, Armamar, Lamego, Tabuço and Moimenta da Beira are examples of producing regions. Its berries, commonly known as "soft fruits", have a diameter up to 6mm and, when mature, have a dark purple colour.

*Sambucus nigra* (S.nigra) has been used in products for human consumption (e.g. jam, syrup, juice, wine, pies) and traditional medicine all over the years, with described compounds contributing to its pharmacological activity. It is a good source of proteins, fibers, vitamins and minerals. Its richness in flavonoids and phenolic acids makes it also a very good source of antioxidants, contributing positively for several diseases, reason why different brands commercialize elderberry based supplements and homeopathic products. Researchers showed that *S. nigra* exhibit antiviral, antioxidant, antidepressant, anti-UV and anti-Toxoplasma gondii activity, positive effects on obesity, diabetes and immune system.

**Keywords:** *Sambucus nigra*; Elderberry; Flavonoid; Antioxidant; Antiviral.

**Introduction**

*Sambucus nigra* (S.nigra), also known as elder, elderberry, black elder or European elder, is one of the eighteen species from the Genus *Sambucus*, Caprifoliaceae family, that grows in most parts of Europe, Asia, United States and North Africa (1). The plant (Figure 1 A) can reach up to 6 meters in height, developing small white flowers in early summer. Elderberry fruits mature in late summer and consists of dark purple berries, with a diameter up to 6 mm (Figure 1 B) (2).

*S. nigra* has been widely used in culinary and in phytotherapy, having several compounds responsible for its pharmacological activity. The use of natural products as therapy being a good way of avoiding the unpleasant side-effects of chemical drugs, elderberry appears to be promising in this field. Several studies have been made, showing the enormous benefits of its leaves and fruits for human health (3).

Despite its benefits, some care should be taken before consuming elderberry. Consumption of raw berries or juice in high quantity may cause nausea, vomiting and diarrhea. Thus, berries should be consumed in controlled doses and should be cooked before consumption. Furthermore, its leaves, stems, flowers and roots contain certain possibly poisoning components. Again, the cooking process of the raw materials prevents the poisoning (4, 5).

The elder fruit is a healthy food, being a good source of proteins (3) and with several vitamins (e.g. vitamins C, folic acid and pantothenic acid) (6), as shown in Table 1. Elderberry seed oil has unsaturated fatty acids as linolenic acid (40.7g / 100g oil), linoleic (34.3 g / 100g oil) and oleic acid (13.8 g / 100g oil), and the tocopherols α-tocopherol (0.49 µg / g oil) and γ-tocopherol (2.63 µg / g oil). This fruit contains many primary metabolites, as sugars and organic acids, and secondary metabolites, as flavonoids (kaempferol, astragalin, quercetin, rutin, ...
Anthocyanins, a class of flavonoid compounds, are natural colorants distributed among flowers, fruits (especially berries) and vegetables, and are responsible for their orange, red and blue colors (8). Beyond the color effect, anthocyanins are also important for plants because they play a role in attracting animals for pollination and for seed dispersion and may also interfere in the plant mechanism for resisting insect attacks (9). The anthocyanins presented in S. nigra are cyanidin-3-glucoside (C3G), cyanidin-3-sambubioside (C3S), cyanidin 3-sambubioside-5-glucoside (C3S5G), cyanidin 3, 5-diglucoside (C3, 5-DIG), cyanidin 3-rutinoside (C3R), pelargonidin 3-glucoside (P3G), pelargonidin 3-sambubioside (P3S) and delphinidin-3-rutinoside (D3R) (3). Other active constituents found to influence pharmacological activity are the flavonoids quercetin and rutin, the hemagglutinin protein Sambucus nigra III (SNA-III), cyanogenic glycosides and vitamins A and C (1).

In traditional medicine elderberry has been used against cold, as laxative, as diaphoretic and as a diuretic (5). Several studies have been made corroborating some of these uses but also exploring other benefits to human health, as applications against viruses and the parasitic protozoan Toxoplasma gondii, in diabetes, in obesity, in depression, among others.

**Benefits for human health**

**Antiviral activity**

*Sambucus nigra* has long been studied, with antiviral properties and actions described (10). One of the most researched fields is the ability of elderberry to inhibit the influenza viruses. Elder berries flavonoids exhibited *in vitro* activity against Human Influenza A Virus (H1N1), in a study that had isolated the major flavonoids that binds to H1N1 virions, blocking the virus ability to infect host cells. The identified compounds were 5,7,30,40-tetra-O-methylquercetin and 5,7-dihydroxy-4-oxo-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-3,4,5-trihydroxycyclohexanecarboxylate, and their activity against H1N1 was favorable when compared to the common anti-Influenza drugs, Oseltamivir (Tamiflu®; 0.32 lM) and Amantadine (27 lM) (11).

Zakay-Rones et al. also showed that elderberry extract syrup has *in vitro* activity against several strains of influenza viruses type A and B, in a study where cell cultures were infected with said viruses (12). Furthermore, in a clinical study they concluded that elderberry extract reduced the illness symptoms within 2 days while placebo group only showed improved symptoms within 6 days. In 2009 another clinical trial was conducted in which
a proprietary elderberry extract formulated as a slow-dissolve lozenge was given to the patients. Patients ameliorate the symptoms within 2 days, with results revealing similar or superior efficacy in symptom mitigation than common anti-viral drugs, as oseltamivir or zanamivir (10).

Considering the results obtained in vitro in both studies, as well as in the two clinical trials, elderberry extracts showed activity against influenza viruses and ability to soothe flu symptoms in infected patients, whereby it may be a hypothesis for treatment for influenza virus.

Another virus that appears to possibly be treated with *S. nigra* is the feline immunodeficiency virus (FIV), a lentivirus of domestic cats with several biological and pathogenic similarities with the human immunodeficiency virus (HIV). FIV infection has been proposed as an animal model for HIV infection studies, reason why it is important to find effective drugs against this virus. Uncini Manganelli et al. studied the capability of elderberry bark extract to inhibit replication of FIV in Crandell feline kidney (CrFK) cells, showing that *S. nigra* may have activity against that virus (13).

**Antidepressant activity**

A 2014 study has tested the antidepressant activity of *Sambucus nigra* leaf and fruit extracts in mice. A plant extract was made with percolation using methanol, a method to extract plant components such as flavonoids, which are described to have antidepressant activity (14, 15). Groups of mice were tested with different doses of *S. nigra* leaf and fruit extracts while other groups were tested with imipramine, a tricyclic antidepressant. The results showed that leaf extract at 1200 mg Kg-1 had the same activity as imipramine at 10 mg Kg-1, while fruit extract showed better activity than imipramine (16). Thus, this study indicated that this natural source may be a good alternative to chemical antidepressant drugs.

**Anti-UV activity**

Inflorescences of elderflower are rich in phenolic compounds, as phenolic acids, flavonoids, catechins and proanthocyanidins, which appear to have a good application in cosmetic sunscreens (17). Polyphenols are capable of absorbing UV radiation (18), reducing its penetration on skin, hence they reduce inflammation, reactive oxygen species (ROS) formation and DNA damage (19, 20). The richness of elderflower in polyphenols makes it a good natural source of protection against UV radiation, both UVA and UVB, for cosmetic sunscreens. Jarzycka et al. studied the *in vitro* effectiveness and photostability of a cosmetic emulsion containing *S. nigra* extracts, taking into account sun protection factor (SPF), UVA protection factor, UVA/UVB ratio and critical wavelength before and after UV irradiation. This study showed that the formulations tested with *S. nigra* extract have the necessary requirements for a sunscreen product, indicating that this plant can be used for this type of formulation.

**Elderberry effect on obesity and diabetes**

*S. nigra* has a high content in anthocyanins, with cyaniding-3-glucoside (C3G) and 3-sambubioside being two of the major (21). Anthocyanins appear to be inversely related with inflammation and insulin resistance in humans (22), and C3G showed capability of enhancing adipocyte function and protecting them from metabolic stress *in vitro* (23-25). Thus, elderberry effects on metabolic disturbances associated with obesity were studied, using a high-fat diet (HFD) induced obese mouse model. For the study, four groups of animals were subjected to different diets during 16 weeks. One group was a low fat diet (LFD) control group, another was a HFD control group, and the other two were HFD with two different percentages of black elderberry extract (BEE). Farrell et al. verified several beneficial effects of BEE in mice. In terms of HFD animal weight it had not been affected by BEE when compared to HFD control group, although a decrease was observed in liver weight of animals fed with BEE; mice fed with BEE showed an attenuation of insulin resistance and systemic inflammation and lower serum TAG levels (26). Thus, this study showed that elderberry extracts may have potential benefits for metabolic disturbances resultant from obesity.

Extracts of *Sambucus nigra* flowers (elderflowers) showed capability to stimulate glucose uptake (GU) in porcine myotubes, in the presence and absence of insulin, and to reduce fat accumulation (FAc) *in vivo* in *Caenorhabditis elegans*. Elderberry extracts seems to have components that may be used in metabolic syndrome, which is characterized by elevated blood glucose levels and increased visceral obesity, because of its ability to modulate glucose and lipid metabolism (27).

A diet supplemented with *S. nigra* and *Asparagus officinalis* also seems to have benefits in decreasing obesity. For that conclusion, a group of volunteers had a diet supplemented with tablets containing 225 mg of *S. nigra* berry powder and 600 mg of flower extract, and tablets with 2.7 g of *Asparagus officinalis* powder. This diet showed an improvement of participant’s body mass index, blood pressure, well-being and quality of life. As such, a diet supplemented with elder and asparagus may be a good way of decreasing obesity (28).

Diabetes mellitus is a syndrome with a great oxidative stress involvement. As a result, the antioxidant properties of *S. nigra* were studied in diabetes field. Diabetes-induced rats were administered with an elder fruit extract which resulted in a reduction of glucose levels, in an increase of antioxidant enzymes activity, in a decrease of free radicals, and a decrease of lipid peroxides in the serum. Thus, elderberry can have benefits for diabetes, reducing hyperglycemia and oxidative stress (28).

**Anti Toxoplasma gondii activity**

Toxoplasmosis is a serious health problem with a wide geographical distribution (29), caused by *Toxoplasma gondii*, an obligatory intracellular protozoan parasite (30). Toxoplasmosis is a problem
especially for immunocompromised patients (31) and pregnant women, potentially leading to fetal death or serious problems in the infants (32). The common drugs for toxoplasmosis are not completely effective (33) and have several side effects reported (34, 35), reason why it is important to study alternatives for the treatment of this disease. Different concentrations of \textit{S. nigra} leaves and fruit extracts were tested for its ability to kill \textit{Toxoplasma gondii} tachyzoites, by incubation of extracts with infected macrophages. The fruit extract proved more efficient than leaves extract, killing 100\% of the tachyzoites in the higher concentration tested (50 mg/mL) after 30 minutes, while leaves extract killed 94\% of the tachyzoites after 60 min (30). Thus, \textit{S. nigra} fruit extract has efficacy \textit{in vitro} against \textit{Toxoplasma gondii} tachyzoites, and seems to be promising for toxoplasmosis treatment.

**Antioxidant activity and Immunological Properties**

\textit{Sambucus nigra} is rich in flavonoids and phenolic acids, secondary metabolites with a high antioxidant activity and, consequently, with several benefits for multiple diseases.

A comparative study of phenolic compounds extracted of elderflower was made, in which three different extractions were prepared, one with methanol and two with water. The water extractions were a syrup – 1kg of sucrose, 16.7g of citric acid, 140 g of elderflowers and 1L of water; and sabesa – 150g of sucrose, 1 g of citric acid, 50 mL of acetic acid, 14 g of fresh elderflowers and 1L of water. Methanol is the standard solvent for phenolic extraction, and it allowed to identify 37 different phenolic compounds, of which 15 hydroxycinnamic acid derivatives and 18 glycosides of kaempferol, quercetin and isorhamnetin. The beverages prepared were tested for its antioxidant activity and concluded that elderberry beverages have higher antioxidant activity than apple or strawberry juice, with the syrup being the richest beverage in antioxidant activity (36).

\textit{Sambucus nigra} polyphenols have influence on several immune system components, revealing potential to regulate defense mechanisms. Studies showed that elderberry revealed capability to decrease IL-1\(\beta\), an interleukin responsible for long-term inflammation in chronic diseases, in diabetic-induced mice (28); stimulate the production of cytokines IL-1\(\beta\), IL-6, IL-8 and IL-10 and TNF-\(\alpha\) (37); increase TNF-\(\alpha\) and IFN-\(\gamma\) in healthy and diabetic rats (38). Other research showed that the administration of \textit{Sambucus nigra} in diabetic-induced rats can improve their immune defense, because the elderberry led to an increase of lymphocytes (39).

**Supplements**

\textit{Sambucus nigra} has lots of benefits for human health and has been used in traditional medicine all over the years. With scientific evolution, elderberry became an interesting source of study resulting in proved evidence about its benefits and several supplements and homeopathic preparations being created (Table 2). Sambucol\textsuperscript{®}, developed in 1991, is one of the most researched elderberry products in the world, having scientific evidences of its properties against influenza virus both \textit{in vitro} (12, 40, 41) and \textit{in vivo} - clinical trials (12, 40), antioxidant activity (42) and immune enhancing-properties (37, 43). Nature’s way\textsuperscript{®}, gaia Herbs\textsuperscript{®}, quantum health\textsuperscript{®}, now\textsuperscript{®} foods and Maine medicinals are other examples of brands that commercialize elderberry based products (Table 2). A range of elderberry products can be found in each of these brands, with syrups or lozenges for adults and kids, specific for contributing for the support of the immune system, relief of flu symptoms, helping to have a restful sleep, helping to maintain health and well-being, giving a support for a healthy sinus function, among others, by combining elderberry with vitamins, zinc, honey or other plants extracts.

<table>
<thead>
<tr>
<th>Table 2: List of some commercialized elderberry products.</th>
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<tbody>
<tr>
<td><strong>Product name</strong></td>
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<tr>
<td>Sambucol\textsuperscript{®}</td>
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<tr>
<td>Sambucol Cold &amp; Flu Relief</td>
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<tr>
<td>Sambucol Immuno Forte</td>
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<tr>
<td>Sambucol FluCare</td>
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<tr>
<td>Sambucus Immune</td>
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<tr>
<td>Sambucus NightTime\textsuperscript{TM}</td>
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<tr>
<td>Black Elderberry</td>
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<tr>
<td>Black Elderberry Nighttime Syrup</td>
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<tr>
<td>GaaKid\textsuperscript{®} Sniffle Support</td>
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<tr>
<td>Herbal Drops</td>
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<tr>
<td>Quantum Elderberry Capsule</td>
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<tr>
<td>Elderberry Syrup</td>
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<tr>
<td>Elderberry &amp; Zing</td>
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<tr>
<td>Elderberry Liquid</td>
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<tr>
<td>asthimmune\textsuperscript{™} Organic</td>
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<tr>
<td>Elderberry Syrup</td>
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Conclusion

*Sambucus nigra* has a high quantity of flavonoids, which contribute to its several properties. Elderberry exhibit antiviral activity, with flavonoids 5,7,30,40-tetra-O-methylqueretin and 5,7-dihydroxy-4-oxo-2-(3,4,5,6,9 trihydroxyphenyl)chroman-3-yl-3,4,5-trihydroxycyclohexanecarboxylic acid bound to H1N1 viruses and blocking its ability to infect host cells and with flu symptoms being reduced within 2 days in infected patients. Depression could also benefit with elderberry extracts, however existing studies were only made in mice, reason why more research is needed on this field. The elder extracts appears to have a beneficial contribution in obesity and diabetes because it reduced liver weight and serum TAG levels and attenuated insulin resistance and systemic inflammation in mice; it stimulated glucose uptake in porcine myotubes; it reduced fat accumulation in *Caenorhabditis elegans*; it improved body mass index, blood pressure, well-being and quality of life in humans and it reduced lipid peroxides in serum of diabetes-induced rats.

Thus, elderberry appears to be a good natural source for the maintenance of health and immune system, as well as a promising source for development of natural medicines for influenza infections, toxoplasmosis, depression, obesity disturbances and diabetes.

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