

# Elderberry

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## INTRODUCTION

*Sambucus nigra* Linnaeus is a small deciduous tree, which grows widely in Europe, Western and Central Asia, and North Africa. It is often planted as a decorative tree in gardens and public parks. The English name Elder comes from the Anglo-Saxon word "aeld," which means fire. The hollow stems of the young branches were used for building a fire (1). The generic name *Sambucus* comes from the Greek word "Sambuca," an ancient musical instrument, made from the wood of this tree (1).

All parts of the tree have long been used in traditional medicine, that is, the bark, the fresh and dried leaves, the dried flowers, the fresh and dried fruits, and the dried roots. The tree is propagated by seeds sown in autumn, as well as by greenwood cuttings in early summer and by hardwood cuttings in winter. The flowers contain flavonoids, cyanogenic glycosides, triterpenes, phenolic acids, tannin, mucilage, pectin and sugar. They possess diuretic, diaphoretic, mild anti-inflammatory, and antiviral properties. The flowers are used to treat colds and catarrh of the upper respiratory tract. The fruits are rich in flavonoids, anthocyanin glycosides, and essential oils. They possess antiviral, immunostimulatory, and antioxidant activity. The fruits are used to treat flu and to boost the immune system. The standardized extract, Sambucol, has been shown to inhibit hemagglutination and replication of influenza viruses in vitro and to reduce the severity and duration of flu in clinical trials. The flowers and fruits, including the Sambucol extract, are safe, and can be administered to infants and children.

## BACKGROUND

*Sambucus nigra* L. is a member of the family, Adoxaceae, and its pharmacopeial name is *Sambuci flos* or *Sambuci fructus*. Common names include Elderflower, European Elder flower, Black Elder flower, and Elderberry. The parts used are the flowers, fruits, and leaves.

The tree grows to a height of between three and seven meters. The bark is light brown to gray and fissured. The leaves are narrow, dark green, and serrated. The flowers are small, white, and fragrant (Fig. 1). They grow in large clusters in flat, umbrella-like umbels. Each flower has five petals, five stamens, and one inferior ovary. The flowering tops are gathered in the wild and dried and separated by sorting them into individual flowers. The peduncles are discarded (2,3). The flowers have a characteristic odor and a mild sweet taste.

The fruits are round like a ball, 4 to 7 mm long (Fig. 2). The young fruits are green and they change from dark purple to black when they ripen. Each fruit contains one to three brownish, egg-shaped seeds. The fruits are sweet (slightly bitter), mucilaginous, and acidic with a characteristic aroma (4,5).

In **traditional medicine**, the flowers are used as a diuretic, laxative, and diaphoretic, as well as a gentle astringent for the skin. They are used as an infusion, a gargle for mouthwash, and for respiratory disorders such as coughs, colds, laryngitis, flu, and shortness of breath. Infusions and lotions from the flowers are used for clearing the skin of freckles and sunburn (1). The aqueous extract of the flowers is used for washing hands and face, as well as to whiten and soften the skin. Externally, herbal pillows are used for subduing swelling and inflammation. The fresh flowers are used for the distillation of Elder Flower Water, which is prepared made from 100 parts of fresh flowers and 500 parts of water. The product is a mild astringent and a gentle stimulant. It is used as a vehicle for eye and skin lotions (1). Vinegar prepared from the flowers of Elder is a known old remedy for sore throat.

## CHEMISTRY AND PREPARATION OF THE PRODUCTS

The flowers contain:

- Flavonoids (up to 3%) composed mainly of flavonoid glycosides (astragalín, hyperoside, isoquercetin, and rutin) and free aglycones (quercetin and kaempferol) (Fig. 3)
- Cyanogenic glycosides (glycosides of 2-hydroxy-2-phenylacetonitrile, such as sambunigrin)
- Triterpenes approximately 1% including  $\alpha$ - and  $\beta$ -amyrin, oleanolic, and ursolic acids
- Essential oils up to 0.3%, including 66% fatty acids (mainly linoleic, linolenic, and palmitic acids), alkanes (7%) and more than 60 other constituents including ethers, oxides, ketones, aldehydes, alcohols, and esters
- Minerals (8–9%), mainly potassium (6)
- Chlorogenic acid (3%), glucosides of caffeic and ferulic acids
- Tannin, mucilage, pectin, and sugar (7,8)

The highest amount of rutin (1.9%) is present in the buds together with pectin (0.8%) and sugars (2.5%) (9).

Elder leaves contain essential oils (0.02%), fats (4.8%), resins (4.3%), ketoses (3.5%), aldoses (0.9%), chlorophyll (0.8%), tannins (0.4%), pectins (0.2%), xanthophylls (0.1%), carotenes (0.05%), sambunigrin (0.04%),



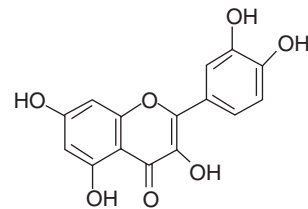
**Figure 1** Flowers of *Sambucus nigra* L.

and rutin (0.02%), as well as pentacyclic hydroxy triterpenoids—oleanoic and ursolic acids (9).

The fruits (Elderberries) are rich in flavonoids, thiamine, riboflavin, vitamins B6, C, and P-complex (10). Like the flowers, they contain flavonoid glycosides and anthocyanin glycosides (such as chrysanthemine, sambucinin, and sambucyanin). They also contain approximately 0.01% of



**Figure 2** Berries of *Sambucus nigra* L.



**Figure 3** Quercetin chemical structure.

essential oils. Present in the seeds are the cyanogenic glycosides including holocalin, prunasin, sambunigrin, and zierin (10).

**Quantitative Standards:** Total flavonoids: not less than 0.8% (calculated as isoquercetin). Foreign matter: not more than 10% pedicels and not more than 1% other foreign matter. Loss on drying: not more than 10%. Ash: not more than 10% (8).

### Preparations and Dosage

**Infusion:** 2 to 4 g of flowers in 150 mL of boiling water; strain after 10 minutes. Take three times daily. One teaspoon ~1.5 g. **Liquid Extract** (1:1 in 25% alcohol): 2 to 4 mL, three times daily.

**Tincture** (1:5, 25% alcohol): 10 to 25 mL per day (11–13). Another source (14) reports that the tincture is prepared in 45% alcohol and the dosage is 5 to 8 mL per day. According to WHO, the tincture should be prepared with 25% alcohol (11).

**Topical Use:** Infusion of the flowers is used as a wash or compress for improving oily skin or acne, or for treating injured tissues. Tincture of 3 to 5 mL diluted in 240 mL of water can be used for the same purpose (14). There are lotion and cream formulations of the flower extracts also.

**Use as Food:** The flowers are used as flavor in numerous food products, including alcoholic and non-alcoholic beverages, frozen dairy desserts, candy, baked goods, and gelatins and puddings. The highest concentrations of flowers are known to be in nonalcoholic beverages (0.05%) (15).

**Phytomedicines:** The flowers are added to a variety of tea mixtures. Flower extracts are also present in anti-tussives, for example, Sinupret for sinusitis (8).

**Branded Preparation:** Sambucol<sup>®</sup>, liquid formula contains 38% standardized liquid Elderberry extract 2:1 (10 mL, 1–4 times a day). Lozenge formula contains 130 mg standardized Elderberry dry extract (1–2 lozenges, 2–3 times a day).

### PRECLINICAL AND CLINICAL STUDIES

The extracts of the Elder have antiviral, anticatarrhal, diaphoretic, diuretic, and topical anti-inflammatory properties. Accordingly, Elderberry is used for colds, feverish catarrhal complaints, cough, and bronchitis, as well as an expectorant for treatment of mild inflammation of the upper respiratory tract (11).

## Pharmacokinetics

The pharmacokinetics and the bioavailability of Elder ingredients are not fully understood. One of the main controversies is whether the anthocyanins are absorbed intact or after they are metabolized in the gastrointestinal tract. Pharmacokinetic studies of Elderberry extract show that anthocyanins are absorbed and excreted in an intact form (16,17). In the first study, six healthy volunteers were given a single oral dose of 30 mL Elderberry extract (147.3 mg total anthocyanins) resulting in a fast urinary excretion of intact anthocyanins; the  $t(1/2)$  value was reported to be 1.74 hour (16). In another study, it was shown that Elderberry anthocyanins can be detected unchanged in the plasma, and most of them were excreted within four hours after consumption (17). A subsequent study with seven volunteers revealed similar results; however, it was concluded that the low urinary excretion of unchanged anthocyanins may indicate that a large portion of them are metabolized before entry into the circulation (18). All studies mentioned in this article (18) agree that oral administration of anthocyanins display first-order, one-compartment kinetics.

## Activities and Indications

As already mentioned, the different parts of the plant are used for the treatment of a variety of ailments. The following discussion is therefore divided according to the individual plant parts and their respective indications.

### Flowers

Human studies have not been documented for Elder flowers.

### Anti-inflammatory Effects

Elder flowers alleviate inflammation and pain in carrageenan-induced rat paw edema. An alcohol extract of the flowers was administered intragastrically one hour before the administration of carrageenan (100 mg/kg) (19). The control drug, indomethacin (5 mg/kg body weight) inhibited carrageenan-induced rat paw edema by 45%, while the extract of Elder flowers inhibited inflammation by 27% (19).

Elder flowers were found to inhibit the proinflammatory activity of major virulence factors from the periodontal pathogens, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* (20). Inhibitory effects on the biosynthesis of the inflammatory cytokines such as interleukin-1-alpha, interleukin-1-beta, and tumor necrosis factor alpha (TNF-alpha) were shown in vitro with an extract of flowers at a concentration of 30  $\mu\text{g}/\text{mL}$  (21).

### Antiviral Effects

An infusion made from flowers of *S. nigra*, aerial parts of *Hypericum perforatum*, and roots of *Saponaria officinalis* has shown antiviral activity against influenza types A and B both in mice and in vitro, as well as against herpes simplex virus type 1 (22).

### Diuretic Effects

Intragastric administration of an infusion of the flowers (20 mL/kg body weight) or a potassium- and flavonoid-rich extract of the flowers had a diuretic effect in rats. Their

diuretic effect exceeded that of theophylline. The greatest activity was exhibited by extracts rich in potassium and flavonoids (23). It has also been stated that flavonols could also contribute to the diuretic action (12).

### Diaphoretic Effects

Although the diaphoretic effect of the flowers is well known, the mode of action is not fully understood. It is possible that flavonoids and phenolic acids are involved (12). It has been suggested that Elder flowers increase the response of sweat glands to heat stimuli (diaphoresis) in healthy subjects (8,11).

## Fruits (berries)

### Antiviral Effects

Though there are far fewer studies on the berries than on the flowers, in recent years there has been an increase in the awareness of the benefits of the Elder fruit among scientists. Most of the scientific studies on Elderberries, including in vivo clinical studies, were performed using a standardized preparation called Sambucol. In vitro studies have shown a reduced hemagglutination and inhibition of replication of types A and B human influenza viruses including human H1N1 (Swine flu), as well as of animal strains including a type A turkey influenza virus (24). One study examined the effects of Sambucol against four strains of Herpes Simplex Virus-1 (HSV-1) (25), two of which were acyclovir-resistant. The viral replication was completely inhibited in all four strains, irrespective of whether the cells were preincubated with the extract, simultaneously incubated with extract, or the extract was added 30 minutes after viral adsorption to cells.

A direct binding assay established in vitro that flavonoids from the elderberry extract bind to H1N1 virions and, when bound, block the ability of the viruses to infect host cells. The flavonoids were identified as, 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. This work was performed in 2007 on the H1N1 strain obtained from the American Type Culture Center and not on the novel 2009 H1N1 strain (26).

It is interesting to note that elderberry concentrates have no antibacterial effect and exhibited even a slight stimulatory effect on the growth of *Staphylococcus aureus* and *Saccharomyces cerevisiae* (27).

The above-standardized extract (Sambucol) was also tested in two double blind, placebo-controlled clinical trials. The first consisted of individuals with confirmed influenza B experiencing flu symptoms. Patients were randomized to receive either Sambucol or placebo (a liquid of the same color and texture as the Sambucol) daily for three days. A significant improvement in symptoms, including fever was experienced by 93.3% of the Elderberry-treated group within two days. In contrast, 91.7% of the placebo group showed a similar improvement only after day six. Complete cure was achieved within two to three days in approximately 90% of the Elderberry-treated group, and within six days in the placebo group. Higher levels of influenza antibodies were detected in patients receiving Elderberry than those receiving the placebo, suggesting

an enhanced immune activity (24). A second clinical trial (conducted by scientists from the University of Oslo) with 60 adults also demonstrated the safety and efficacy of the standardized Elderberry syrup in the treatment of influenza and its symptoms (28). Patients with either influenza type A or type B were given 15 mL of Sambucol or a placebo four times per day. Treatment was initiated within 48 hours of the onset of symptoms and continued for five days. The global evaluation scores (symptoms and overall wellness scores combined) for the Elderberry-treated group showed a pronounced improvement after a mean of 3.1 days as compared to 7.1 days for the placebo group. A larger number of patients in the control group resorted to a "rescue medication" such as paracetamol as compared to the treatment group. Both studies concluded that patients exhibiting flu symptoms and treated with Elderberry standardized extract recovered significantly faster than patients in the control group. As the authors note in their report, these findings need to be confirmed in a larger study.

Another placebo-controlled study indicated that Sambucol given as prophylactic to a group of chimpanzees accumulated over a period of six months reduced the flu-like symptoms to 12 days as compared to 39 days in the control group (total of ten chimpanzees randomized into two equal groups) (29).

### Immune Enhancement

Results from two in vitro studies demonstrated that Sambucol upregulates cytokine release (30,31). Both studies used blood-derived monocytes and examined the concentration of four inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ ) and one anti-inflammatory cytokine (IL-10), in response to various Elderberry (Sambucol) formulations and control syrups (other branded preparations based on Echinacea and Propolis). A 1.3- to 6.2-fold increase in cytokine production was observed compared to control (31). It was concluded that the standardized Elderberry extract activates the healthy immune system and may possess immunoprotective or immunostimulatory effects when administered to patients with various diseases.

### Antioxidant Activity

The berries are rich in anthocyanins, which serve as natural antioxidants. Ginsburg et al. (32) suggested that the unique composition of the constituents results in antioxidants, which are more resistant to oxidation. Because it has been observed that anthocyanin glycosides are indeed absorbed in humans (see pharmacokinetics), it is possible that Elderberry extracts containing anthocyanins may be a significant source of antioxidants.

Plasma antioxidant capacity and total phenolics were significantly increased one hour after ingestion of 400 mL of Elderberry juice (33), while heating over six hours at 95°C caused a decline of the trolox equivalent antioxidant capacity due to colorless degradation following thermal exposure (34). Another in vitro study demonstrated that Elderberry derived anthocyanins could be incorporated into the membrane and cytosol of endothelial cells (human aortic) and thus increase protection against oxidative stress (35).

### Anticarcinogenic Activity

An aqueous acetone extract of the berries from cultivated *S. nigra* was fractionated and tested in a range of assays that gauge the anticarcinogenic potential. *S. nigra* fruits demonstrated significant chemopreventive potential through strong induction of quinone reductase and inhibition of cyclooxygenase-2, which is indicative of anti-initiation and antipromotion properties (36). Elderberry anthocyanins played a major role in chemoprotection and could inhibit the growth of a human colorectal adenocarcinoma (HT29) cell line (37).

### Leaves

While the flowers and leaves are the plant parts mainly used, intraperitoneal administration of the unsaponifiable fraction (the fraction not soluble in water after saponification of total extract in KOH) of the leaves to mice moderately enhanced phagocytosis at a dose of 0.5 mL/animal (38).

### Safety

The majority of safety issues refer to the presence of the cyanogenic glycoside sambunigrin, which may be hydrolyzed in various plant parts to free hydrogen cyanide. Various sources state that the ripe fruits are edible without causing harm and are frequently used as additives for various foods. The safety of the standardized Elderberry extract preparation, Sambucol was demonstrated in a clinical study (28), where it was concluded that this Elderberry extract is safe and can be administered to the whole population, including infants and children.

One study reported type I allergy to proteins of *S. nigra* (39) after inhalation of pollens, and the authors suggested that oral administration of flowers or berries could also induce allergies. On the contrary, Elderberry and Elder flowers were suggested to be beneficial for allergic symptoms and reduce nasal congestion and other upper respiratory discomforts.

### Contraindications

To the best of our knowledge there are no published data showing that there are contraindications in the use of Elderberry.

Use During Pregnancy and Lactation: There are no known restrictions for pregnant or lactating women (6). Some authors propose that the use of Elder flowers during pregnancy should be avoided due to lack of toxicity data. However, there is no information available on impairment of fertility or teratogenic effects (7,40).

### Drug/Herb Interactions

There are no reported drug/herb interactions with other plants or medications. Theoretically, since the Elderberry may exhibit a diuretic and a laxative effect, caution should be exercised when taken for a long time concomitantly with diuretics or with drugs that interact with diuretics and laxatives.

### Side Effects

There have been no reported side effects from Elder flower preparations. The most common side effect for Elderberries quoted in the literature is the diuretic and laxative

effect (41). Elder preparations from unripe berries (as well as from other plant parts) can induce toxic effects in humans due to poisonous cyanogenic glycosides. Effects of cyanide, also known as hydrocyanic acid, on humans include nausea, vomiting, and diarrhea as well as central nervous system and respiratory depression, and general lethargy.

## REGULATORY STATUS

Both flowers and berries are classified as GRAS (generally recognized as safe).

Elder is listed by the Council of Europe in Categories N1 (refers to the fruit and indicates that there are no restrictions on quantities used) and N2 (41). In the list of plants in the French official bulletin of drugs based on plants, instructions for the submission of registration (AMM allég), Elderberries belong to category one for which no toxicological studies are needed (42). The berries of Elder are rated by the American Herbal Products Association as Class 1, meaning "herbs which, when used appropriately, can be consumed safely without specific use restrictions" (43).

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