



Sambucus nigra (Photo Biopix.dk)

Sambucus nigra (Elderberry)

Introduction

Sambucus nigra, or European elder, is a tall tree-like shrub, native to Europe, Asia, and North Africa, and naturalized in the United States. Various parts of the elder have long been used in traditional medicine as a diaphoretic, diuretic, astringent, laxative, and emetic. The berries were used traditionally as a food to make elderberry wine and pies, and as a flavoring or dye. Currently, extracts of the berries are used primarily as

antiviral agents for colds, influenza, and Herpes virus infection. Research has also demonstrated *Sambucus nigra* has immune-modulating, antioxidant, and insulin-stimulating properties.

Description

The *Sambucus nigra* plant is a member of the Caprifoliaceae or honeysuckle family, and can be found growing in shady, moist areas in Europe, Asia, North Africa, and North America. It tolerates relatively poor soil conditions and is often found growing as part of the underbrush in forests. The naturalized plant in North America is known as *Sambucus nigra* ssp *canadensis*, *Sambucus canadensis*, or North American elderberry. The tree-like shrub has light brown or gray stippled bark and narrow, dark green, serrated leaves. In early summer, *Sambucus nigra* blooms with large clusters of small, fragrant, creamy-white flowers that develop into shiny, purplish-black berries by late summer and early fall.^{1,2} Historically, the leaves, bark, flowers, and berries have all been used medicinally, but most of the clinical studies have been conducted on the therapeutic uses and properties of the elderberry.

Active Constituents

The fruit of *Sambucus nigra* (elderberries) contains several constituents responsible for pharmacological activity. Among these are the flavonoids quercetin and rutin, anthocyanins identified as cyanidin-3-glucoside and cyanidin-3-sambubioside,³ the hemagglutinin protein *Sambucus nigra* agglutinin III (SNA-III),⁴ cyanogenic glycosides including sambunigrin,^{5,6} viburnic acid, and vitamins A and C.²

Pharmacokinetics

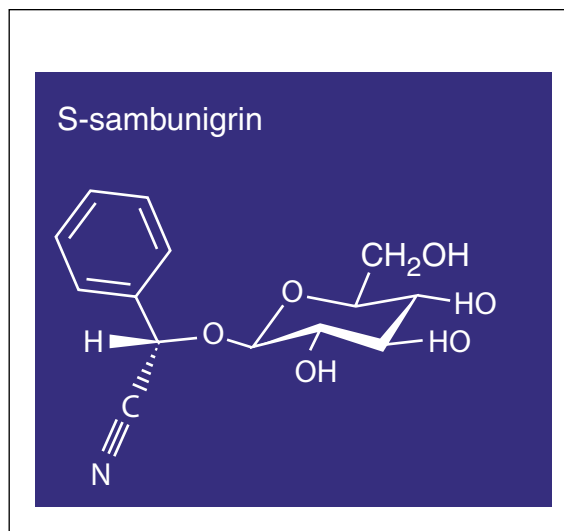
Due to limited research, the pharmacokinetics of many constituents of *Sambucus nigra* are not completely understood. Available research has focused on the absorption and urinary excretion of the anthocyanin constituents. Historically, researchers were uncertain whether anthocyanins were absorbed unless they were first hydrolyzed in the gastrointestinal tract. Recently, however, several small pharmacokinetic studies of elderberry extract in healthy volunteers demonstrated elderberry anthocyanins are indeed absorbed and excreted in an intact form.

Within four hours of consuming 12 g elderberry extract containing 720 mg total anthocyanins, the two major anthocyanins in elderberry extract were identified in the urine of four elderly women.³ A second similar study involving 16 healthy volunteers confirmed the presence of the same two anthocyanins in the urine of study subjects after oral administration of elderberry extract.⁷ In another study involving six healthy volunteers, a single oral dose of 30 mL elderberry extract (147.3 mg total anthocyanins) resulted in a rapid urinary excretion rate of intact anthocyanins with only 0.37 percent of the original dose being present in the urine at seven hours post-ingestion.⁸ One study investigated the absorption of elderberry anthocyanins in a single male subject given 25 g elderberry extract (1.5 g total anthocyanins); high-performance liquid chromatography (HPLC) analysis detected two anthocyanin peaks in plasma collected 30 minutes post-dose.⁹ Another study detected anthocyanins from elderberry in glycoside form in both plasma and urine four hours after dosing.¹⁰

Mechanisms of Action

Antiviral

While there are several mechanisms responsible for the beneficial effects of *Sambucus nigra* and extracts of its berries, perhaps the most important and best studied are the antiviral effects. Mumcuoglu, an Israeli virologist, was the first to discover elderberry constituents neutralize the activity of the hemagglutinin spikes found on the surface of several viruses. When these hemagglutinin spikes are deactivated the viruses can no longer pierce cell walls or enter the cell and replicate.¹¹ Based on these findings, Sambucol®, a syrup containing 38-percent standardized extract of black elderberry, was developed. Numerous studies using the Sambucol preparation have shown it to neutralize and reduce the infectivity of influenza viruses A and B,^{12,13} HIV strains and clinical isolates,¹⁴ and *Herpes simplex* virus type 1 (HSV-1) strains and clinical isolates.¹⁵ It probably does so in the same manner as with influenza viruses, via neutralization of the virus resulting in reduced infectivity.



Immune Modulation via Cytokine Production

Elderberry extracts also have immune-modulating activity in healthy individuals as well as in those with viral infections or other diseases characterized by immunosuppression. Production of certain cytokines leads to activation of phagocytes and facilitates their movement to inflamed tissues.¹⁶ Two studies using blood-derived monocytes from healthy donors demonstrated the ability of several Sambucol extracts to significantly increase cytokine production. Cytokines tested were tumor necrosis factor-alpha (TNF- α), and interleukins (IL) -1 β , -6, and -8.¹⁷ A second similar study also measured monocyte production of IL-10 when exposed to various Sambucol preparations and confirmed the results of the first study. A 1.3- to 6.2-fold increase in cytokine production was observed compared to control. A 2.3-fold increase in IL-10 was also observed.¹⁸

Antioxidant

Elderberries contain several anthocyanin flavonoids known to possess significant antioxidant properties. Research has demonstrated low-level concentrations (4 mcg/mL) of elderberry anthocyanins can efficiently regenerate alpha-tocopherol from alpha-tocopheroxyl radicals in models of copper-mediated LDL oxidation.¹⁹ Since it has been observed that anthocyanin glycosides are indeed absorbed in humans,^{3,7-10} it is likely that supplementing with elderberry extracts containing anthocyanins provides significant antioxidant benefit.

It has been established that endothelial cell dysfunction results in changes in the redox status of cells.²⁰ Based on this premise and previous research on elderberry's antioxidant potential, Youdin et al demonstrated elderberry anthocyanin incorporation into endothelial cells confers increased protection against oxidative stress. Human aortic endothelial cells incorporated elderberry anthocyanins into both the membrane and cytosol, affording significantly enhanced resistance to damage from reactive oxygen species. The most pronounced affect was seen with protection against H₂O₂-induced loss in cell viability.²¹

Clinical Indications

Viral Infections

Influenza

Two randomized, placebo-controlled, double-blind studies demonstrated the elderberry extract, Sambucol, effectively inhibited both influenza A and B strains when given orally to patients in the first 48 hours of influenza symptoms. In the earlier study, 27 individuals experiencing typical early flu symptoms were given Sambucol or placebo daily for three days – 2 tablespoons (children) or four tablespoons (adults). Patients were followed for six days and symptoms monitored. Serum from all subjects was analyzed for antibodies to influenza A and B at the initial dose and during the convalescent phase. In the treatment group, significant improvement in flu symptoms was observed in 93.3 percent of subjects within two days after initial dosing, while 91.7 percent of the control group demonstrated improvement after six days. A complete resolution was achieved in the treatment group in 90 percent of patients after 2-3 days, while the placebo group yielded similar results after six days. Of these 27 patients, 23 had laboratory confirmation of influenza B.¹²

In a second study, 60 patients (ages 18-54 years) experiencing early influenza symptoms were given 15 mL of Sambucol or placebo syrup four times daily for five days. Symptoms were monitored for eight days. In the treatment group, the majority of patients reported "pronounced improvement" after an average of 3-4 days, while the placebo group required 7-8 days to reach the same level.¹³

Herpes simplex

Mumcuoglu et al examined the effects of Sambucol against HSV-1 in human diploid fibroblasts. Four strains of HSV-1 were utilized – a reference strain, two acyclovir-resistant strains, and a strain isolated from a patient. Viral replication was completely inhibited in all four strains, whether the cells were pre-incubated with the extract, simultaneously incubated with extract, or the extract was added 30 minutes after viral adsorption to cells. The complete inhibition of four strains of HSV-1 *in vitro* by elderberry extract warrants further clinical trials in humans.¹⁵ A formula of *Sambucus nigra* (flower extract) in combination with *Hypericum perforatum* and *Saponaria officinalis* was also found to inhibit the replication of HSV-1 *in vitro*.²²

HIV

Sambucol was studied for the potential to inhibit the infectivity of HIV isolates in CD4+ cell lines, peripheral blood lymphocytes, and laboratory HIV strains. The elderberry extract at two different dilutions was pre-incubated with HIV virus prior to addition of the cells. A significant reduction was observed in the infectivity of all HIV strains. In patient isolates treated with the extract, no HIV antigen was detected at either five or nine days post-incubation.¹⁴

Anecdotal evidence (six case studies) reports a combination of elderberry extract and a thymus extract resulted in a reduction in viral load in people with HIV.²³

Conditions Associated with Oxidative Stress

Numerous disease states are characterized by oxidative stress, including cardiovascular disease, cancer, neurodegenerative disease, peripheral vascular disease, autoimmune diseases, and multiple sclerosis. The ability of elderberry extract to provide antioxidant protection via inhibition of LDL-oxidation and scavenging of free radicals makes it a potentially valuable tool in the treatment of disease resulting from oxidative stress.¹⁹ Elderberry's ability to incorporate into endothelial cells and potentially improve endothelial function may also indicate a role in prevention of vascular disease of various kinds.²¹

Effect on Blood Lipids

A randomized, placebo-controlled study of 34 healthy subjects examined the effectiveness of low-dose, powdered elderberry juice (10% anthocyanins) versus placebo on lipid parameters. Elderberry was dosed at 400 mg capsuled powder (equal to 5 mL elderberry juice) three times daily for two weeks; patients were instructed to follow a diet containing 35-percent fat. Serum was obtained at baseline and at the end of the two-week period. Analysis of results showed a slight, but statistically insignificant, decrease at two weeks in all lipid parameters of the low-dose elderberry extract group compared to baseline. Total cholesterol was 199 mg/dL at baseline versus 190 mg/dL at the end of the two-week period. Slight reductions were also reported in triglycerides, and HDL- and LDL-cholesterol.²⁴ Although improvements in lipid values were statistically insignificant, the dosage of elderberry extract was low and it is possible higher dosages might produce a more significant benefit. In addition, using subjects with normal lipid levels may not be as likely to produce significant results since the lipids are already within the normal range. Further study on patients with elevated lipid levels is warranted.

Diabetes

In folk medicine, *Sambucus nigra* flower was traditionally suggested as a remedy for diabetes.²⁵ Researchers in Northern Ireland conducted an *in vitro* study to evaluate the effect on blood sugar. In the two-armed study, aqueous extract of elder flower significantly increased glucose uptake, glucose oxidation, and glycogenesis in rat abdominal muscle. Elder flower extract incubated with rat pancreatic cells also had a dose-dependent stimulatory effect on insulin secretion. The researchers concluded elder flowers contain water-soluble constituents capable of direct stimulation of insulin secretion and glucose metabolism.²⁶ Further clinical study is warranted before *Sambucus* can be recommended for use in diabetes.

Drug-Botanical Interactions

There are no confirmed drug interactions with elderberry extract. However, due to the ability of *Sambucus* flower extracts to potentiate insulin release *in vitro*,²⁶ patients with diabetes should be advised to monitor blood sugar closely when using flower extracts.

Side Effects and Toxicity

Elderberry extracts are generally without side effects when taken in the suggested dosages.¹² Berries should be cooked, as the consumption of uncooked berries or juice can result in vomiting and diarrhea.¹ Certain constituents of the leaves, stems, flowers, and roots contain poisonous alkaloids.²⁷ It has also been reported that small percentages of the general population have a type-1 allergy to *Sambucus nigra* as evidenced by positive-skin prick or RAST test.²⁸

Dosage

Elderberry fruit syrups are often standardized to 30-38 percent elderberry. Powdered extracts are dosed at 500 mg (capsule) 2-3 times daily for 3-4 days, or if in liquid form, dosed at one tablespoonful (15 mL) three times daily. In the case of acute viral infections, course of treatment is generally at least three days.²⁹

Warnings and Contraindications

Currently there are no reported adverse effects in regard to fetal development, pregnancy, or lactation. However, as elderberry is not a well-researched botanical, health care practitioners should use caution in recommending it to women who are pregnant or nursing.

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