

The Pros and Cons of Using Elderberry (*Sambucus nigra*) for Prevention and Treatment of COVID-19

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Abstract

Background: The novel severe acute respiratory syndrome coronavirus 2 emerged in 2019. Health-care systems around the world are looking for alternative prevention and treatment remedies. Herbal supplements are popular among consumers as a complementary method to prevent and treat illnesses. One of them is *Sambucus nigra*.

Materials and Methods: We searched for related articles in Scopus, Web of Science, PubMed, Google Scholar, and the Directory of Open Access Journals using the following keywords: elderberry, *S. nigra*, and COVID-19.

Results: Elderberry has antiviral properties due to its ability to modulate inflammatory cytokines. The current evidence suggests elderberry is appropriate for the prevention and initial treatment of viral disease. Concerns have been raised that elderberry may overstimulate the immune system, increasing the risk of a cytokine storm. There is not yet enough evidence to support this claim.

Conclusions: For COVID-19 patients, further research is required since elderberry may provoke a cytokine storm if administered therapeutically.

Keywords: COVID-19, elderberry, *Sambucus nigra*, severe acute respiratory syndrome coronavirus 2

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INTRODUCTION

On March 11, 2020, the novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) was categorized as a global pandemic.^[1] Health-care systems around the world are looking for alternative prevention and treatment remedies. Herbal supplements are popular among consumers as a complementary method to prevent and treat illnesses. According to Silveira *et al.*, five herbal medicines have a good effect as adjuvant therapy against COVID-19; one of them is *Sambucus nigra* fruit [Figure 1].^[2] The elderberry plant has been used for food or its health benefits for hundreds of years.^[3] In traditional medicine, dried elderberry fruit or flower is used to cure and prevent respiratory problems such as influenza or colds.^[4,5] The use of elderberry extract could be beneficial in reducing the duration of colds and influenza, according

to a systematic review.^[6] In the United States, elderberry supplements sales increased by 415% in the single-week period ending March 8, 2020.^[7] While elderberries and other herbal supplements can boost immunity, the Food and Drug Administration of the United States issued warning letters to corporations saying that products that state or indicate they are utilized in the prevention or treatment of COVID-19 are unapproved and unauthorized drugs.^[8]

IMMUNE RESPONSE TO SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

COV is an enveloped and RNA virus with a diameter of 60–140 nm. It features a concave surface containing spike

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Figure 1: *Sambucus nigra* var. *nigra*. Photograph courtesy of American Herbal Pharmacopoeia, Scotts Valley, CA (US)

proteins that increase its surface area, resulting in increased binding activity to angiotensin-converting enzyme 2 (ACE2) receptors.^[9] The virus is transmitted through respiratory droplets; the COV spike (S) glycoprotein attaches to the ACE2 receptor of the host cells and mediates viral entry.^[10] SARS-COV-2 causes an immunological response and the release of pro-inflammatory cytokines after it enters host cells in the lungs. If the infection progresses, this leads in macrophage and neutrophil infiltration into the lungs and causes a cytokine storm.^[11] The most critical pro-inflammatory cytokines are interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF- α). These three cytokines originate from macrophages, epithelial, endothelial, and mast cells. These three cytokines originate from macrophages, epithelial, endothelial, and mast cells that can inhibit the replication of DNA and RNA viruses. TNF- α has the potential to activate intracellular antiviral pathways. Furthermore, IL-1 and IL-6 can indirectly activate TNF- α upregulation through paracrine or autocrine activity.^[12]

COVID-19 has three progressive phases in some patients. The first phase is the early phase in which patients present with cough and fever. In this phase, innate immune system cells such as neutrophils, dendritic cells, and macrophages recognize virus particles. These immune cells activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathways. NF- κ B pathways produce several cytokines and have antiviral activity but appear to be inhibited by SARS-CoV-2.^[13] The second phase is the pulmonary phase which is presented with hypoxia. In this phase, the influx of neutrophils, monocytes, macrophages, and the production of transforming growth factor-beta, and nitric oxide leads to capillary leakage and oxidative injury. The third phase is the hyperinflammatory phase which appears 9–12 days after the onset of the disease.^[13] Older patients with other chronic diseases due to the deterioration of the immune system need more time to activate an effective adaptive immune response. This forced innate immunity to strengthen the response and production of uncontrolled inflammatory cytokines. The

cytokine storm is defined by the sudden increase in IL-1, IL-6, TNF- α , and interferon. This acute increase of cytokines results in the destruction of human tissues by the immune cells such as T cells, macrophages, and neutrophils.^[14]

ELDERBERRY

S. nigra Linnaeus is a tree that grows in Western and Central Asia, Europe, and North Africa. *Sambucus* is a generic Greek name that comes from an ancient musical instrument built with the wood of this tree. Taxonomically, the North American species is *S. nigra* var. *canadensis*, and the European is *S. nigra* var. *nigra* [Figure 2]. Other North American (*S. cearulea*) and European (*S. ebulus*) species exist. In traditional medicine, all parts of the tree have long been used; various factors, including as cultivar, location, ripening stage, and environmental circumstances, influence the chemical content of *S. nigra*. Elderberry contains a high concentration of bioactive compounds, especially polyphenols such as flavonols, phenolic acids, proanthocyanidins, and anthocyanins, which give the fruit its dark-purple hue.^[15] The anthocyanins in elderberries are cyanidin derivatives, with trace levels of other anthocyanins present.

The flowers of the elderberry tree contain sugar, cyanogenic glycosides, phenolic acids, flavonoids, and pectin. Flowers have antiviral properties, diuretic, and mild anti-inflammatory effects and are used to treat colds. The elderberry fruits have a high level of essential oils, flavonoids, and anthocyanin glycosides. They possess immunostimulatory, antiviral, and significant antioxidant activity to boost the immune system and act as a potent viral inhibitor to treat flu.^[16] *S. nigra* enhances the immune system in a nonspecific way and stimulates the generation of cytokines. Elderberry contains a unique protein that serves as a messenger, modulating the immune response.

ELDERBERRY AND ITS IMMUNOMODULATORY EFFECT

Part of the activity of elderberry is due to its anthocyanins, which are water-soluble pigments responsible for the colors of the many flowers, fruits, and vegetables that have an anti-inflammatory and immunomodulation effect.^[17] By attaching to viral glycoproteins that allow viruses to enter host cells, anthocyanins directly prevent viral infections. Caffeic acid derived from the plant has an anti-coronavirus activity by impairing the binding of COV spike proteins to ACE2 receptors.^[18]

The inhibitory effect of elderberry extracts against influenza A, influenza B, and H1N1 viruses has been shown in *in vitro* studies.^[19] The elderberry extract-treated group saw a substantial improvement in symptoms, including fever, in 93.3% of the cases within 2 days, whereas the control group saw an improvement in 91.7% of the patients within 6 days ($P = 0.001$). A complete cure was attained in over 90% of the SAM-treated group within 2–3 days, and in the placebo

group after at least 6 days ($P = 0.001$). A recent systematic review suggested that elderberries could be used to treat upper respiratory symptoms and shorten the duration of influenza or colds.^[20]

In addition to the direct virus inhibitory effect of elderberry, it may affect the host immune system through cytokines. Some evidence shows increases in inflammatory cytokines, whereas others suggest elderberry decreases cytokine production.^[21,22] *In vitro* studies show that elderberry flowers have an anti-inflammatory effect on cytokines' biosynthesis, such as TNF-alpha, IL-1-alpha, and IL-1-beta, with the concentration of 30 $\mu\text{g/mL}$.^[23] The inflammatory response is vital because in the initial stage of infection, cytokines have a potential antiviral role but in severe cases of COVID-19, releasing large amounts of pro-inflammatory cytokines leads to cytokine storm that can lead to multi-organ damage and death.^[24,25]

Plant-derived polysaccharides such as β -glucans and pectins are reported to have immunological activities.

Polysaccharides derived from elderflowers and elderberries have an immunomodulation effect on the complement system and macrophages. Immune modulators are the components that can be upregulated or downregulated by the host immune response [Figure 3].^[26-28]

DISCUSSION

Elderberry possesses antiviral effects as a result of its capacity to regulate pro-inflammatory cytokines^[3] and has been shown to be effective against a variety of viruses both *in vitro* and *in vivo*.^[29-33] There has been no published research on the usage of elderberry in COVID-19 patients as of this writing. Although the antiviral efficacy of phenolic acid components of elderberry against the human COV HCoV-NL63 was demonstrated *in vitro*, this could not be extended to COVID-19.^[30]

Elderberry lowers the duration of influenza symptoms, according to randomized, double-blind, placebo-controlled trials.^[6,17,34] A randomized controlled trial (RCT) suggests that elderberry reduces the duration and severity of cold symptoms

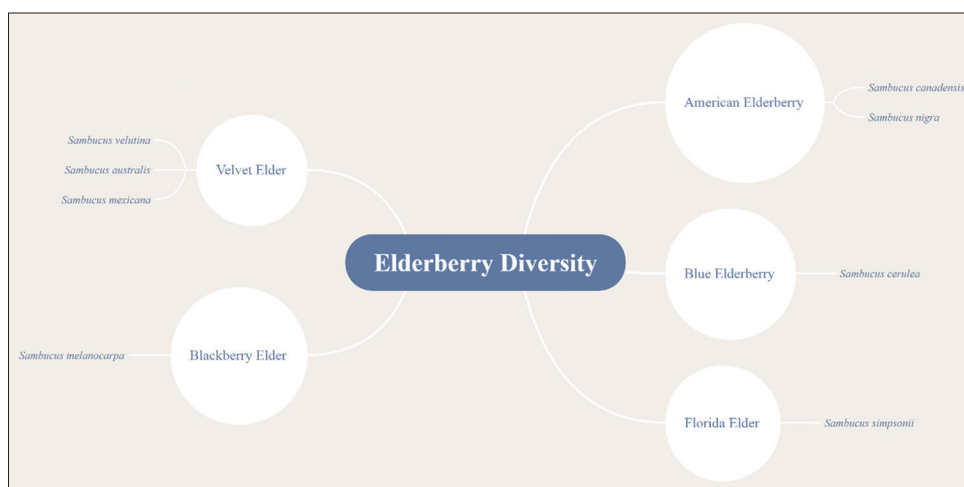


Figure 2: Elderberry diversity

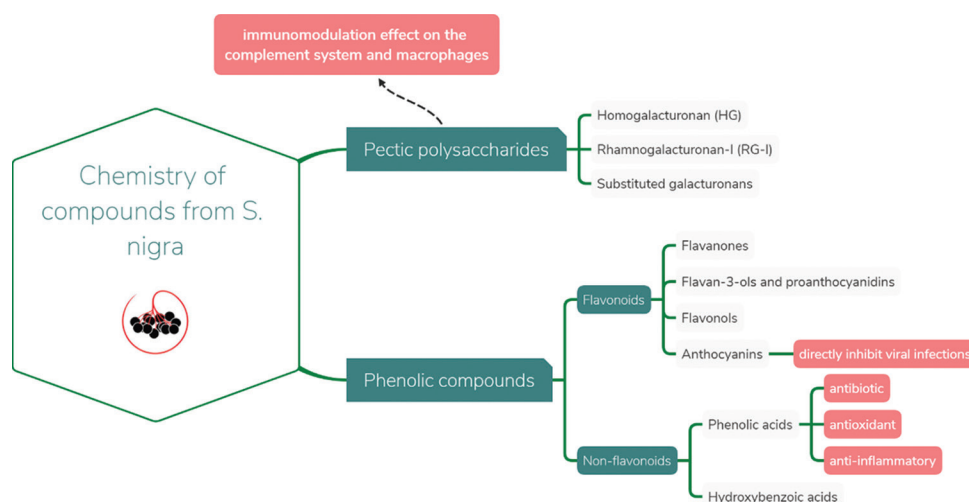


Figure 3: Chemistry of compounds from *Sambucus nigra*

by an average of 1.5 days. However, half of the patients in this study used additional medications.^[6]

Part of elderberry activity involves increasing cytokine production at the first stage of viral attachment and early viral replication. This helps kill the virus and stop replication. Once the cytokine storm begins, it theoretically would no longer be appropriate, but there is no data either way. The current evidence suggests elderberry is appropriate for the prevention and initial treatment.^[18] Some other botanicals, such as Echinacea, similarly initiate cytokine response during initial infection and downregulate cytokine storms later in progression.^[35] The recently published systematic review used RCTs to assess the effects of elderberry on preventing or treating viral respiratory infections. For studies examining cytokine storm and other outcomes such as cytokine production, they used three *ex vivo* studies that suggested elderberry may be safe for treating viral respiratory illness. It does not appear to overstimulate the immune system. There is still a lot of uncertainty about both the advantages and the dangers of this treatment; therefore, more recent and ongoing research is needed to draw definite conclusions.^[36] The concern regarding cytokine storms and the effects of elder needs to be addressed in future studies, and these studies that rely on limited *ex vivo* studies are insufficient.

CONCLUSIONS

Elderberry is effective for prevention in healthy individuals and stimulates immune system activity, but further studies are needed before it can be used therapeutically in COVID-19 patients because it may trigger cytokine storms.

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Conflicts of interest

There are no conflicts of interest.

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