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

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.¹ The elderberry plant has been used for food or its health benefits for hundreds of years.² In traditional medicine, dried elderberry fruit or flower is used to cure and prevent respiratory problems such as influenza or colds.³ The use of elderberry extract could be beneficial in reducing the duration of colds and influenza, according to a systematic review.⁴ In the United States, elderberry supplements sales increased by 415% in the single-week period ending March 8, 2020.⁵ 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.⁶

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 proteins. This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms. For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

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proteins that increase its surface area, resulting in increased binding activity to angiotensin-converting enzyme 2 (ACE2) receptors. 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. 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. 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.

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-κβ) pathways. NF-κβ pathways produce several cytokines and have antiviral activity but appear to be inhibited by SARS-CoV-2. 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. 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.

**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. 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. *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. 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.

The inhibitory effect of elderberry extracts against influenza A, influenza B, and H1N1 viruses has been shown in *in vitro* studies. 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.\cite{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.\cite{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 ug/mL.\cite{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.\cite{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].\cite{26-28}

**DISCUSSION**

Elderberry possesses antiviral effects as a result of its capacity to regulate pro-inflammatory cytokines\cite{3} and has been shown to be effective against a variety of viruses both *in vitro* and *in vivo*.\cite{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.\cite{30}

Elderberry lowers the duration of influenza symptoms, according to randomized, double-blind, placebo-controlled trials.\cite{6,17,34} A randomized controlled trial (RCT) suggests that elderberry reduces the duration and severity of cold symptoms.
by an average of 1.5 days. However, half of the patients in this study used additional medications.[10]

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.[19] 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.[19,20] 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.

**References**

1. Bedford J, Enria D, Giesecke J, Heymann DL, Ihekweazu C, Kobinger G, et al. COVID-19: Towards controlling of a pandemic. Lancet 2020;395:1015-8.
2. Silveira D, Prieto-Garcia JM, Boylan F, Estrada O, Fonseca-Basso YM, Jamal CM, et al. COVID-19: Is there evidence for the use of herbal medicines as adjuvant symptomatic therapy? Front Pharmacol 2020;11:581840.
3. Ulbricht C, Basch E, Cheung L, Goldberg H, Hammerness P, Isaac R, et al. An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the Natural Standard Research Collaboration. J Diet Suppl 2014;11:80-120.
4. Knudsen BF, Kaack KV. A review of traditional herbal medicinal products with disease claims for elder (Sambucus nigra) flower. Acta Hortic 2015;1061:109-20.
5. Knudsen BF, Kaack KV. Review of human health and disease claims for elderberry (Sambucus nigra) fruit. Acta Hortic 2015;1061:121-31.
6. Tiralongo E, Wee SS, Lea RA. Elderberry supplementation reduces cold duration and symptoms in air-travellers: A randomized, double-blind placebo-controlled clinical trial. Nutrients 2016;8:182.
7. Dietary Supplement Sales Skyrocket during Coronavirus Pandemic. Available from: https://www.nutritionaloutlook.com/view/dietary-supplement-sales-skyrocket-during-coronavirus-pandemic. [Last accessed on 2021 May 03].
8. Center for New Medicine/Perfectly Healthy by Connealy MD – 605804 – 05/11/2020. FDA. Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/center-new-medicineperfectly-healthy-connealy-md-605804-05112020. [Last accessed on 2021 May 03].
9. Shang J, Ye G, Shi K, Wan Y, Luo C, Alhara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020;581:221-4.
10. Zhu Z, Zhang Z, Chen W, Cai Z, Ge X, Zhu H, et al. Predicting the receptor-binding domain usage of the coronavirus based on kmer frequency on spike protein. Infect Genet Evol 2018;61:183-4.
11. Hussman JP. Cellular and molecular pathways of COVID-19 and potential points of therapeutic intervention. Front Pharmacol 2020;11:1169.
12. Thomson AW, Lotze MT, editors. The Cytokine Handbook, Two-Volume Set. Elsevier; 2003 Apr 22.
13. Khadke S, Ahmed N, Ahmed N, Ratts R, Raju S, Gallogly M, et al. Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: A review of the phases of illness and therapeutic agents. Virol J 2020;17:154.
14. Shimizu M. Clinical features of cytokine storm syndrome. In: Cytokine storm syndrome 2019 (pp. 31-41). Springer, Cham.
15. Anton AM, Pintea AM, Rugină DO, Sconța ZM, Hanganu D, Vlase L, et al. Preliminary studies on the chemical characterization and antioxidant capacity of polyphenols from Sambucus SP. Dig J Nanomater Biostructures 2013;8:973-80.
16. Elderberry. Madeleine Mumcuoglu, Daniel Safirman, and Mina Ferne – PDF Free Download. Available from: http://docplayer.net/63345886-Elderberry-madeleine-mumcuoglu-daniel-safirman-and-mina-ferne.html. [Last accessed on 2021 May 03].
17. Zakay-Rones Z, Thorn E, Wollan T, Wadstein J. 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 2004;32:132-40.
18. Chioiu SY, Sung JM, Huang PW, Lin SD. Antioxidant, antiadipetic, and antihypertensive properties of echinacea purpurea flower extract and caffeic acid derivatives using in vitro models. J Med Food 2017;20:171-9.
19. The Effect of Sambucol, a Black Elderberry-Based, Natural Product, on the Production Of Human Cytokines: I. Inflammatory Cytokines – PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/11399518/. [Last accessed on 2021 May 03].
20. Hawkins J, Baker C, Cherry L, Dunne E. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complement Ther Med 2019;42:361-5.
21. Barak V, Birkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. Isr Med Assoc J 2002;4:919-22.
22. Badescu M, Badulescu O, Badescu L, Ciocoiu M. Effects of Sambucus nigra and Aronia melanocarpa extracts on immune system disorders within diabetes mellitus. Pharm Biol 2015;53:533-9.
23. Yesilada E, Ustün O, Sezik E, Takaishi Y, Ono Y, Honda G. Inhibitory effects of Turkish folk remedies on inflammatory cytokines: Interleukin-1alpha, interleukin-1beta and tumor necrosis factor alpha. J Ethnopharmacol 1997;58:59-73.
24. Jose RJ, Manuel A. COVID-19 cytokine storm: The interplay between inflammation and coagulation. Lancet Respir Med 2020;8:e46-7.
25. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev 2012;76:16-32.
26. Ho GT, Ahmed A, Zou YF, Aslaksen T, Wingsteen H, Barsett H. Structure-activity relationship of immunomodulating pectins from elderberries. Carbohydr Polym 2015;125:314-22.
27. Ho GT, Zou YF, Aslaksen TH, Wingsteen H, Barsett H. Structural characterization of bioactive pectic polysaccharides from elderflowers (Sambuci flos). Carbohydr Polym 2016;135:128-37.
28. Ho GT, Zou YF, Wingsteen H, Barsett HG. RI regions from elderflower pectins substituted on GalA are strong immunomodulators. Nanomater Biostructures 2013;8:973‑80.
29. Roschek B Jr, Fink RC, McMichael MD, Li D, Albette RS. Elderberry
flavonoids bind to and prevent H1N1 infection in vitro. Phytochemistry 2009;70:1255-61.

30. Weng JR, Lin CS, Lai HC, Lin YP, Wang CY, Tsai YC, et al. Antiviral activity of *Sambucus* FormosanaNakai ethanol extract and related phenolic acid constituents against human coronavirus NL63. Virus Res 2019;273:197767.

31. Krawitz C, Mraheil MA, Stein M, Imirzalioglu C, Domann E, Pleschka S, et al. 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 2011;11:16.

32. Uncini Manganelli RE, Zaccaro L, Tomei PE. Antiviral activity *in vitro* of *Urtica dioica* L., *Parietaria diffusa* M. et K. and *Sambucus nigra* L. J Ethnopharmacol 2005;98:323-7.

33. Chen C, Zuckerman DM, Brantley S, Sharpe M, Childress K, Hoiczyk E, et al. *Sambucus nigra* extracts inhibit infectious bronchitis virus at an early point during replication. BMC Vet Res 2014;10:24.

34. Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, et al. 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 1995;1:361-9.

35. Aucoin M, Cooley K, Saunders PR, Carë J, Anheyer D, Medina DN, et al. The effect of *Echinacea* spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. Adv Integr Med 2020;7:203-17.

36. Wieland LS, Piechotta V, Feinberg T, Ludeman E, Hutton B, Kanji S, et al. Elderberry for prevention and treatment of viral respiratory illnesses: A systematic review. BMC Complement Med Ther 2021;21:112.