

Black Elderberry Supplementation for Upper Respiratory Infection Symptoms

Dr. Selfridge reports no financial relationships relevant to this field of study.

By Nancy J. Selfridge, MD

Professor, Clinical Foundations Department, Ross University School of Medicine, Barbados, West Indies

SUMMARY POINTS

- Black elderberry supplementation appears to have a significant effect in reducing duration and severity of the common cold and influenza symptoms.
- The symptom-mitigating effect appears to be most significant for influenza infections, and influenza vaccine status does not seem to moderate the beneficial effect.
- Black elderberry immune-modulating effects may include increasing inflammatory cytokine levels; therefore, generalizing its use for all viral respiratory infections, including COVID-19, is not recommended and may be harmful.

SYNOPSIS: A meta-analysis of results from four randomized, controlled clinical studies evaluating the effect of black elderberry supplementation suggests that the botanical significantly reduces upper respiratory symptoms due to common cold and influenza viruses.

SOURCE: 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;42:361-365. doi.org/10.116/j.ctim2018.12.004

Extract from the berries of the black elder bush have been used in traditional pharmacopeia to treat viral upper respiratory symptoms. Although black elderberry has demonstrated antiviral activity in both in vitro and in vivo murine studies,¹ no large-scale human trials have been conducted. Nonetheless, in this time of the COVID-19 pandemic, the putative antiviral benefit of elderberry has been sufficiently prominent in news and social media that U.S. outlets for the products are struggling to meet demands. Although no studies to date specifically have studied SARS-CoV-2, the virus that causes COVID-19, Hawkins et al offer a meta-analysis in 2019 of existing randomized, placebo-controlled trials of black elderberry for influenza and cold symptoms to determine effectiveness and effect size.

A literature search yielded 137 studies, four of which met inclusion criteria and were selected for meta-analysis. Inclusion characteristics limited selected studies to randomized controlled trials, human subjects, elderberry supplementation as the primary intervention, and respiratory symptoms as the primary outcome. All studies used black elderberry supplement products that were commercially prepared. Self-reporting of symptoms occurred in all four studies and were measured at baseline and at least once daily for the duration of symptoms. A visual analog scale

was used in three studies. One study (Tiralongo) employed the Jackson scale, a decades-old index used to determine the presence and severity of upper respiratory infection (URI) common cold symptoms that has been compared to laboratory studies but has not been assessed psychometrically.²

The Tiralongo study was constructed to evaluate the preventive effects of elderberry supplementation on URI. Of 312 participants, 29 developed URI symptoms during the study and only these subjects were included in this meta-analysis. The other three studies evaluated the effects of elderberry supplementation on patients with influenza, either laboratory-verified or manifesting symptoms consistent with influenza infection. Two studies by Zackay-Rones excluded patients who had received the influenza vaccine. The other two studies only excluded patients who had been recently vaccinated, and the baseline vaccine status of the subjects was otherwise unknown. (See Table 1.) The main outcomes compared in all studies — duration and severity of symptoms — were used to calculate effect sizes. Data from the studies were analyzed using Comprehensive Meta-Analysis (CMA) version 3 software.

Table 1. Characteristics of Black Elderberry Studies

Study Principal Investigator/Year	Influenza Vaccine Status	# of Patients	Cause of Symptoms
		Treatment/Control	
Zackay-Rones, 1995	no	15/12	influenza
Zackay-Rones, 2004	no	30/30	influenza
Kong, 2009	unknown	30/30	influenza
Tiralongo, 2016	unknown	12/17	common cold

Analysis of the study results is shown in Table 2. The effect size for each study is represented as standard difference in outcome means between treatment and control groups. Overall synthesis of effect size for all studies is bolded and shown in the last line of the table.

Table 2. Black Elderberry: Results Summary

Study Principal Investigator/Year	Effect Size (Std diff in means)	Standard Error	95% Confidence Interval	P Value
Zackay-Rones, 1995	1.360	0.429	0.519 - 2.201	0.002
Zackay-Rones, 2004	2.009	0.317	1.387 - 2.628	< 0.001
Kong, 2009	2.767	0.350	2.082 - 3.453	< 0.001
Tiralongo, 2016	0.662	0.387	-0.096 - 1.421	0.087
All Studies	1.717	0.447	0.840 - 2.593	< 0.001

Because elderberry supplementation appeared to have a greater effect in the studies focusing on influenza illness, the authors calculated a separate weighted effect size for these studies of 2.074 (standard error, 0.383; 95% confidence interval [CI], 1.323-2.824; $P < 0.001$). Of note is that moderator analysis of influenza vaccine status did not influence elderberry supplementation effect size.

Limitations hindering this meta-analysis include the small number of studies and total patients and a lack of age group-specific and sex-specific analysis. Bias within studies was judged to be low risk; a failure to report justification of sample size and failure to identify analyses as intention-to-treat or actual treatment were noted most commonly. The greatest risk of bias came from funding sources. Zackey-Rones 2004, Kong 2009, and Tirolongo 2015 were funded by proprietary elderberry supplement manufacturers. The 1995 Zackey-Rones study did not disclose funding but used a proprietary product from the same company that funded their later study.

COMMENTARY

The results of this meta-analysis, taking into account the limitations detailed earlier, appear to support the effectiveness of black elderberry for reducing duration and severity of symptoms due to influenza and the common cold. The effects appear more clinically significant for influenza symptoms. In light of the current COVID-19 pandemic, it is tempting to generalize these results and consider recommending or using black elderberry supplementation to mitigate the clinical impact of this novel coronavirus infection. However, there are compelling reasons not to generalize the application of this evidence to the use of black elderberry in the treatment of COVID-19. Black elderberry has immune-modulating effects in vitro and in vivo, and these are likely linked to its ability to affect URI and influenza symptoms.^{1,3} Barak et al¹ and Torabian et al³ specifically identified that a key mechanism of action of black elderberry is to increase circulating inflammatory cytokines, including IL-6, IL-8, and TNF- α . In addition to black elderberry's ability to inhibit influenza virus entry into cells, its ability to augment the innate immune response appears to help mitigate influenza symptoms and infection duration.

However, COVID-19 is caused by a different virus that exerts its main, and potentially deadly, pathophysiologic effects by increasing inflammatory cytokine levels. It is this "cytokine storm" that causes the acute respiratory distress syndrome (ARDS) in vulnerable infected patients, leading to respiratory failure and death. Inflammatory cytokine increase is a "double-edged sword," forming an essential antimicrobial defense mechanism, but having the potential to "run amok," creating an endotheliopathy in lungs and other vulnerable tissues. The result in the lungs includes increased alveolar capillary permeability, injury to type 2 pneumocytes with resultant loss of pulmonary surfactant production, and widespread pulmonary edema manifesting in diminished gas exchange.⁴ A preprint report of lab data analysis from 21 hospitalized COVID-19 patients in Wuhan, China, indicates that significantly higher levels on admission of TNF- α and other inflammatory cytokines (IL-2R and IL-10) were associated with more severe clinical disease.⁵ Thus, inflammatory cytokines, so helpful in normal innate immune function, may be a significant and potentially lethal factor in the pathophysiology of COVID-19.

Although it is not known if black elderberry helps or hurts in COVID-19 illness, at least some of the documented immune-modulating effects of black elderberry actually might augment the pathological impact of the virus. Until more is known about both the virus and the specific pharmacologic effects of black elderberry, it is wisest to err on the side of caution and refrain from using the supplement in this current pandemic.

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