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File: ■ Black Elderberry (*Sambucus nigra*, Adoxaceae)
■ Sambucol®
■ Influenza

HC 042138-677

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RE: Sambucol® Black Elderberry Syrup Did Not Improve Duration or Severity of Influenza Symptoms Compared with Placebo

Macknin M, Wolski K, Negrey J, Mace S. Elderberry extract outpatient influenza treatment for emergency room patients ages 5 and above: a randomized, double-blind, placebo-controlled trial. *J Gen Intern Med*. November 2020;35(11):3271-3277. doi: 10.1007/s11606-020-06170-w.

Black elderberry (*Sambucus nigra*, Adoxaceae), used historically for medicinal purposes, has been shown to relieve the symptoms of influenza. The sale of elderberry products in the United States more than doubled from 2017 to 2018. These authors conducted a randomized, double-blind, placebo-controlled trial to determine whether Sambucol® (PharmaCare Laboratories; San Diego, California) elderberry syrup reduces the duration and severity of influenza.

The study was conducted in three emergency rooms of a large health system in Cleveland, Ohio, between January 2018 and April 2019. Eligible patients reported influenza symptoms for 48 hours or less; had a positive rapid polymerase chain reaction influenza test; and had two of the following seven symptoms (moderate or severe): nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats. Only patients at high risk for influenza-related complications were included at the beginning of the study; however, all eligible patients were later enrolled.

Forty-four patients were randomized to the placebo group, and 43 patients were randomized to the elderberry group. The patients took the first 15 mL dose of the study medication in the emergency room and took the remaining doses at home. They were called daily until they had no symptoms and their temperature had remained lower than 100° F for a maximum of 21 days. All patients were given the opportunity to take oseltamivir, an antiviral medication used to treat influenza, because the authors did not want to deny patients a proven modestly effective drug if they were participating in a study of an unproven treatment.

Patients aged 13 years and older took 15 mL of Sambucol four times daily for five days, and those aged 5-12 years took 15 mL twice daily for five days. Each 15 mL dose of Sambucol contained the fruit juice equivalent to 5.7 g of black elderberry, glucose syrup, purified water, citric acid, and potassium sorbate. The placebo contained the same ingredients, except for the elderberry extract. At baseline, the patients in the elderberry

group were more likely to have received a flu vaccine for the current season, to have chosen to take oseltamivir, and to have a lower heart rate ($P < 0.05$ for all).

Two patients in each group were lost to follow-up. Two patients in the elderberry group and one patient in the placebo group were not symptom free for 24 hours after 21 days and were excluded from the analysis.

The primary outcome, the number of days until all symptoms were none or mild for at least 21.5 hours, was similar between the groups (5.3 ± 3.6 days in the elderberry group and 4.9 ± 2.8 days in the placebo group). The secondary outcome, the number of days to complete symptom resolution for 24 hours, was also similar between the groups (8.6 ± 3.9 days for the elderberry group and 8.7 ± 3.9 days for the placebo group).

The authors conducted a post hoc analysis to determine if the primary outcome was affected by the use of oseltamivir. In the patients not taking oseltamivir, those in the elderberry group experienced a longer time to symptom alleviation compared with the placebo group ($P = 0.02$). For the patients taking oseltamivir, the between-group difference was not significant. The duration of illness was significantly longer in the patients taking elderberry alone (7.3 ± 3.4 days) than in the patients taking elderberry plus oseltamivir (4.0 ± 3.1 days) ($P = 0.003$).

Patients in the elderberry group experienced aches and pains longer than the patients in the placebo group ($P = 0.02$). More patients in the placebo group took acetaminophen compared with the elderberry group ($P = 0.005$). Both groups reported dry mouth, constipation, rash, and bad taste.

The limitations of this study include the use of the patients' subjective reporting of their symptoms; the lack of subtyping of the influenza viruses detected in the study and checking for virus sensitivity to elderberry and oseltamivir; and the fact that the first 33 patients enrolled in the study were asked if they had felt ill for < 48 hours but not about the exact hour that their symptoms began. "Therefore, we have no evidence suggesting that elderberry treatment initiated within the first 24 h of treatment might have improved the results," write the authors.

"We found no evidence that elderberry benefits the duration or severity of influenza. … Our results contradict previous studies and demonstrate the need for further studies," the authors conclude.

Author M. Macknin reports that he looked into pursuing a patent for a drug combining oseltamivir and elderberry extract; however, the Innovations Department of the Cleveland Clinic, where he is employed, deemed the combination to not be patentable. Dr. Macknin encourages others to study this combination. The other authors declare no conflicts of interest.

—*Shari Henson*

The American Botanical Council has chosen not to reprint the original article.