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February 1, 2021

Black elderberry based syrups and other extracts have long been a core feature of a natural medicine chest. These berries have been used traditionally to address cold and flu symptoms and even demonstrate antiviral activity against winter viruses such as the common cold and influenza. With the advent of the 2019 pandemic spreading a deadly disease with respiratory symptoms, this dark berry has become the darling of the natural products industry.

Black elderberries contain anthocyanins (primarily cyanidin 3-glucoside and cyanidin 3-sambubioside), which have been shown to boost immune function and exhibit antiviral effects. Oral ingestion of elderberry results in detectable levels of these anthocyanins in blood plasma. These documented effects, combined with the COVID-19 pandemic, have resulted in a boom for the elderberry market, as the product has become the go-to for respiratory related conditions and remains a popular home remedy for winter illnesses.

The scientific substantiation of elderberry as a tool to reduce and shorten respiratory symptoms is promising. To date, four clinical trials have evaluated the effects of elderberry on routine cases of upper respiratory infections, and one clinical trial has evaluated black elderberry treatment in patients hospitalized with influenza.

In 1995, Zakay-Rones et al found that elderberry produces “inhibition of several strains of influenza virus in vitro and a reduction of symptoms of influenza B.” The same research team also found in 2004 that elderberry extracts are capable of reducing influenza symptoms in both flu type A and flu type B. In 2009, Kong, et al, replicated these findings, revealing that elderberry extracts substantially reduce upper respiratory symptoms during the flu, and in 2016, Tiralongo et al found that the supplement effectively reduces the duration and severity of symptoms from the common cold among air travelers.

This research was quantitatively analyzed in a 2018 meta-analysis which assessed the total impact of elderberry on all 180 trial participants. This study compared outcomes from flu symptoms with those attributed to cold symptoms and compared those who had been vaccinated with those who had not. Elderberry was found to have an extremely large reduction effect on cold and flu symptoms.

Collectively, the body of evidence demonstrating the beneficial effects of elderberry on upper respiratory symptoms is strong. The surge in elderberry sales during the COVID-19 pandemic can be explained through the strength of this body of evidence. As a dietary supplement to boost overall wellness, the effects of elderberry are clearly substantiated.

However, a recent study has looked at the potential for elderberry to become an authorized drug. Using an IND (investigational new drug) authorization from the FDA, clinicians from the Cleveland Clinic published a trial in 2020 evaluating the potential for elderberry to treat influenza in hospitalized patients.

Unlike previous studies which evaluated the effects of elderberry on routine winter respiratory infections, this trial included only patients who had been seen in the Emergency Room (ER) for severe influenza and the results showed no statistically significant benefits from elderberry in this population.

When a new study produces findings, which contradict the entire body of literature, it needs to be interpreted within the context of existing scientific evidence with the methods and outcomes of all studies considered. This requires further analysis of this new trial. What is different about this study and does it call into question previous conclusions regarding the benefits of elderberry?

When a study fails to find statistically significant results, the first area to assess is the study's power. The power of a study tells a researcher how many participants are required for them to find an effect of a certain size. Power refers to the risk of a false negative–the likelihood that the researchers only failed to achieve statistical significance because they failed to recruit sufficient participants. Because power is related to the risk of false negatives, a study must be powered not only for the primary endpoint, but for any endpoint that is to be statistically analyzed. Negative results can therefore mean that the study was underpowered, that the effect size is smaller than what the study was powered to detect, or concludes that the product actually does not work.

This study was initially powered to detect a 2-day reduction in flu symptoms. In theory this should be sufficient to detect a difference, as previous studies have found a substantial effect size of elderberry. However, the power analysis was based on two randomized groups. The study was forced to change its inclusion criteria mid-intervention and the resulting groups were unequal on many levels. Not only were age and sex potential confounders, the two groups differed in use of both acetaminophen and oseltamivir. When patients who opted to use oseltamivir were omitted from the analysis, only 43 patients remained, and only 17 of those were in the elderberry group. This resulted in a considerably underpowered analysis.

In other words, this initial study included a power analysis, but not for the trial that was ultimately completed. Underpowered trials have long been the debate of clinical research ethicists who question the appropriateness of recruiting human participants for studies which are unlikely to achieve statistical significance or offer any clinical value (Halpern, 2002). Because of these ethical concerns as well as the lack of scientific merit of underpowered analyses, many journals have policies against publishing negative results which were obtained from underpowered studies.

The next important factor to consider is the validity of the measurement instrument. In clinical trial design, the validity and reliability of a measurement instrument are among the most fundamental components to consider. A researcher must confirm that the measurement used in a study actually measures the outcome of interest. Metrics for clinical trials are studied through validity and reliability analysis. These metrics must also be directly related to the outcome of interest.

In the elderberry drug study, the outcome was measured as time from ER visit to recovery, with onset of symptoms determined through self-report at the start of the visit. Clinicians did not confirm stage of illness through any additional measures, nor did they validate the approach of self-reporting flu duration at admission. Furthermore, self-reported stage of illness was not controlled in the data analysis. Because stage of illness is a known indicator of remaining duration of illness, failure to control during randomization and data analysis can introduce significant bias in the study. While the elderberry drug study was well-intentioned given the overwhelming evidence of elderberry in the reduction of symptoms of flu, future studies should be sufficiently powered and include validated measurement instruments, precise inclusion/exclusion criteria, age and sex specific analyses, and successful randomization of patients, controlling for underlying disease severity and other confounders.

Until additional research is conducted, and replicated, the potential for elderberry to treat severe/advanced cases of influenza remains unknown. Given that elderberry is recommended for use early during an infection as its proposed mechanism of action is a reduction in viral replication, the potential for it to produce significant effects later in a course of illness would signal discovery of a new use for the supplement. The uncertainty surrounding elderberry's drug potential, however, does not negate the documented benefits of the substance as a dietary supplement in support of positive immune activity.

The totality of the scientific literature reveals that elderberry effectively prevents the onset of viral infections and substantially reduces both duration and severity of respiratory symptoms. While the outcome of the elderberry drug study has been recently cited as evidence that

elderberry is ineffective, such claims underscore the importance of understanding how to interpret the scientific literature. Clinical research must be interpreted within the context of the research question, relevant outcomes, research methodology, and the body of evidence as a whole.

The beneficial effects of elderberry on routine respiratory concerns have been confirmed through multiple clinical trials across three separate continents, as well as a meta-analysis with moderator variable analyses to identify factors which might affect the impact of elderberry. This dark berry, which has been used for centuries to boost wellness, has earned its place among the best-sellers in the natural product industry and, if community-based data is any indicator, shows no sign of slowing down.

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