

Will Elderberry Induce a Cytokine Storm?

Elderberry is one of the most used, and most trusted immune support botanicals in the integrative medicine repertoire. But there has been a lot of discussion within online clinician forums on whether elderberry could or would induce a cytokine storm if used during an infection where that is the risk. I'd like to share my perspective based on the research I can pull.

Cytokine Release Syndrome (CRS) and its extreme form, cytokine storm, can occur in advanced infection states like Acute Respiratory Distress Syndrome (ARDS), sepsis, or with specific immunologic medications. It is relatively rare, very serious, and is an ICU-level intervention required if it occurs. This is a serious condition, and if a patient is experiencing cytokine storm or ARDS, herbal medicine is not the go-to. Emergency medicine is. So, I'd like to frame this conversation very much in the space of academic discussion, and in the space where we are talking about elderberry use in the healthy population for immune supportive purposes. Not as a treatment for severe disease or even mild disease!

Pro- and anti-inflammatory cytokines are a big part of the pathology of CRS and of ARDS. Studies looking in the bronchoalveolar lavage (BAL) of patients with ARDS have shown elevation in cytokines like TNF-alpha, IL-1 beta, IL-6, and IL-8 levels, with a more rapid rise and more persistent elevation in non-survivors compared to survivors.

The study I have seen cited over and over again to back up a claim that elderberry could trigger a cytokine storm is a study published in *European Cytokine Networks* in 2001 by Barak, et al. This study was done in monocytes collected from 12 healthy human donors. This study showed that there was an increase in IL-1 beta, TNF-alpha, IL-6, and IL-8 after exposure of the monocytes to a commercially available elderberry extract, with a particularly noted increase in TNF-alpha release by the monocytes. The study concluded that elderberry extract could "activate the healthy immune system by increasing inflammatory cytokine production."

A similar study in 2002 by the same researcher found that the same elderberry extract increased the production of the 5 cytokines tested (including 4 inflammatory (IL-1 beta, TNF-alpha, IL-6 and IL-8) and one anti-inflammatory cytokine, IL-10) from 1.3-6.2 fold. To compare, stimulation with LPS (lipopolysaccharide, a known monocyte stimulator) increased cytokines 3.6-10.7 fold). Let's put this into perspective- running in a marathon has been shown to increase IL-6 about 100-fold, and another study in *PLOS One* on the dynamics of cytokine storm (in a drug-induced model in healthy adults) measured (or estimated, when levels exceeded measurable limits) many cytokine levels (including inflammatory cytokines mentioned like IL-6, etc) to be up 4,000-5,000 fold in a cytokine storm.

¹ <https://www.ncbi.nlm.nih.gov/pubmed/7587434>

² <https://www.ncbi.nlm.nih.gov/pubmed/11399518>

³ <https://www.ncbi.nlm.nih.gov/pubmed/12455180>

⁴ <https://www.ncbi.nlm.nih.gov/pubmed/11579746>

⁵ <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0045027>

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So, weaving these studies into a story that “elderberry could cause cytokine storm” is a far leap, in my opinion. There is no evidence to suggest that the small elevation in cytokine release by monocytes after high-dose elderberry exposure is enough to trigger a cytokine storm in a human.

In addition, remember that IL-6 and other cytokines are not produced only by monocytes, but by a range of cells- T-cells, B-cells, monocytes, fibroblasts, osteoclasts, keratinocytes, skeletal muscle cells, and many others. You cannot extract data from monocytes and apply it to the whole human, or to the local cellular environment in the lungs. We just don't have that data.

Sambucus nigra has also been studied in humans with influenza, an infection with a known risk of cytokine storm and ARDS, and there are no studies reporting an increased risk of respiratory distress, cytokine storm, or ARDS. (To be clear, we make no claims about *Sambucus* to prevent or treat influenza or any other condition, we cite these for safety purposes only). Here are a few examples:

1) A 2004 study in Norway followed 60 patients (aged 18-54) suffering from influenza-like symptoms for 48 hours or less. They were given 15 mL of elderberry extract 5 times daily or placebo for 5 days. Among reported outcomes, the patient use of respiratory rescue medication was reduced, suggesting fewer respiratory complications in the elderberry group.

2) A 2019 meta-analysis of *Sambucus* supplementation for upper respiratory symptoms (including influenza) reported no increase in respiratory risk or side effects and determined elderberry to be safe in this population.

Again, these studies do not report an increased risk of respiratory complications and continue to represent elderberry as a safe therapeutic.

It is my conclusion that a risk of elderberry extract triggering a cytokine storm is implausible, and that elderberry still appears to be one of the safest botanicals we have in our toolkit.