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Sambucus (Elderberry), Echinacea, and Cytokine Storm in respiratory infection.

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The "cytokine" storm emerged into scientific literature and into popular consciousness between 1997 and 2003 when the Bird Flu (H5N1) (1997) and SARS Coronavirus (2003) infections killed a number of people in Asia. The cytokine storm is a phenomenon is an excessive immune response which may occur in late stage severe illness, as a drug side effect, or several other causes, typically occurring in conditions of a critical care unit. Subsequently it was speculated that the severity of the 1918 influenza pandemic in young adults was due to an excessive cytokine response. As with theH5N1 and SARS epidemics, young urban adults were dying, and it was proposed that because they were young and healthy, that the inflammatory response they produced was excessive. (See Review: Sino Biological) In 2009, The H5N1 flu pandemic emerged in North America, and the question arose among herbalists about whether the herbs *Echinacea* and *Sambucus* should be used for this flu or if it presented a problem of stimulating a cytokine storm. Now in 2020, the question about *Sambucus* is being raised again, and in social and other media it is stated positively on scanty evidence that *Sambucus* should not be used in COVID-19 infections. This has creates a viral phenomenon that is now appearing with authoritative proclamations in print media, blogs, and other sources.

Unfortunately, both medical professionals and herbalists after 2003 have taken a two-dimensional view of the cytokine storm phenomenon. Originally among professionals treating H5N1 in 1997, the heightened pro-inflammatory cytokines led clinicians to prescribe steroids to reduce the inflammation. All patients treated with this strategy died, until the WHO issued guidelines that steroids should not be used to treat these virally-induced storms. Steroids are now also being strictly avoided in critical care for COVID-19 infection, including in cytokine storm. Today's understanding of the cytokine storm is more nuanced, that it is not a simple on-off, inflammatory switch, but a complex orchestrated response of many cytokines. While some cytokines induce pathologies related to inflammation, others are not pathological but positive. Non-inflammatory portions of the cytokine storm facilitate viral clearance and promote tissue repair, and regulate the severity of the inflammatory cytokines (Guo XJ). This may explain why steroids, resulted in death in all the N5N1 patients they were given to. The beneficial and regulatory cytokines were suppressed along with the inflammatory, and anti-viral immunity was suppressed.

This is also why herbalists cannot take and isolate the effects of a substance on a single cytokine while ignoring its effects on others and especially in lab dish *in-vitro* studies. In the lab dish, both *Echinacea* and *Sambucus* have been shown to stimulate immuno-regulatory cytokines (making the inflammatory response more moderate), as well as inflammatory ones, with a *net non-inflammatory effect. Sambucus* extracts were shown to enhance both inflammatory and anti-inflammatory cytokines in human cells in lab dish experiments (Barak et al.). In another lab dish study, an extract of *Sambucus* flowers inhibited all pro-inflammatory cytokines measured (Harokopakis et al.) Another yet another showed regulation through partial inhibition of inflammatory cytokines (Yesilada et al). One trial of the use of a combination of *Echinacea* and *Eupatorium perfoliatum* found no net inflammatory effect produced by cytokines in humans at the dose tested (Elsasser-Beile et al.) Researchers at University of British Columbia who have studied *Echinacea* extensively concluded that the plant has a net anti-inflammatory effect, while maintaining "direct and selective" antiviral and antibacterial activity. In infected cell media, genes that code for pro-inflammatory cytokines, were stimulated by the pathogens, but *Echinacea* reversed the effects. A study showed that infection with virus or bacteria in cell arrays induced secretion of pro-inflammatory cytokines, but that this was also reversed by *Echinacea* (Hudson

et al).

The proponents of the *Sambucus*-stimulates-cytokine-storm theory make a more fundamental scientific error, that of tunneling on reports of a single cytokine while ignoring total effect of the plant on the whole spectrum of cytokines. They extrapolate the results of lab dish studies to human clinical reality. In bedrock scientific discipline, lab dish studies cannot be extrapolated to in-vivo animal studies, or to human clinical effects without actually testing a form and dose of the substance in a living system. Likewise animal trial results cannot be extrapolated to human clinical effects, they must be tested in a dose and form appropriate for a human. A substance that comes into direct contact with cells in one form in a lab dish cannot be delivered in that same form and concentration in a living system. There, if taken orally, it must encounter the digestive processes, and the liver detoxification pathways, and further be diluted by the entire blood volume of the body. Our information on the effects of *Sambucus* on cytokines comes *exclusively* from lab dish studies. Looking at the scientific literature we find no human trials of any oral *Sambucus* form that measure effects on cytokines in the living system of a human being. As such any extrapolation of that research to humans should be rejected out of hand.

This same error of extrapolating lab dish effects to human clinical reality lies at the root of the common misconception that *Sambucus* has a specific anti-influenza effect, as opposed to enhancing general host resistance against respiratory infection. The original source of this misconception is an early study of the *Sambucus* syrup product Sambucol. (Zakay-Rones et al). In the first part of this trial, the researchers tested the effect of the syrup on the ability of influenza virus to infect cells. They found that it impaired the ability of the virus to bind to or enter the lab dish cells they used. In the second, they did a clinical trial of the effect of the *Sambucus* syrup on duration of symptoms of influenza, and on production of anti-influenza antibodies. The clinical trial was very successful, with a remarkable reduction of the duration of fever and other symptoms in the *Sambucus*-treated group, a reduction which has been observed by professional herbalists clinically for the two decades since this research appeared. But interpretation is required for the lab-dish portion of the article. The authors state that the *Sambucus* preparation was not effective when applied to virus-infected cells, only when they applied it to the viral innoculum before applying the virus to the cells. The results cannot be extended to human oral use, because the product consumed orally has no way of actually reaching unchanged a free virion circulating in the system. This is not just a nit-picking argument. If *Sambucus* has no demonstrable specific effect against influenza virus in the living system, but does have a clinical effect, then it must be acting through enhancement of host resistance. Sambucus syrup appears from clinical experience to be equally effective against non-influenza viral respiratory pathogens. This is also consistent with the finding of increased antibody production in the Sakay-Rones trial, a sings of active immune response to the virus rather than virucidal effects of the product.

So while we find no human trials showing the effect of *Sambucus* on cytokines, or reasonable evidence of influenza-specific effects, We do find more well-designed human clinical trials of the effects of *Sambucus* on respiratory infections in general. A meta-analysis of these trials in 2018 shows that *Sambucus* products significantly and consistently reduce the symptoms of influenza when taken at first onset (Hawkins et al) without adverse consequences. If Sambucus is indeed acting through enhancement of the respiratory immunity, we would expect similar benefits in COVID-19 infection, as with other viral respiratory infections.

The timing of the development of cytokine storm is also important to understand the potential role of the herbalist in aggravating it. Cytokine storms are a phenomenon of the critical care unit or the ICU. Here patients with advanced respiratory disease are losing the battle against the viral infection, and have acquired pneumonia, or other complications such as multi-organ involvement or sepsis during the late stage of the disease. The intense cytokine reaction might be seen as a last-gasp desperate attempt by the body, in a apparently losing battle the equivalent of a military unit whose position has been overrun calling in an airstrike on its own position. This happens late in the disease process, in hospitalized patients. At this point, the herbalist will not be likely given access to the patient anyway, so

what to give or not give them will not be an issue. This is also consistent in the COVID-19 epidemic in China. In one of the first studies of COVID-19 patients, appearing in the Lancet on January 2, 2020, 41 hospitalized patients with confirmed infection were assessed. Of the 41 patients, 22 developed shortness of breath. This occurred after a median time of six days from the first appearance of symptoms. Thirteen were admitted to the ICU, and half of these died. The ICU patients had elevated plasma levels of cytokines relative to those not in the ICU (Huang et al). More recent observations of COVID-19 patients in critical care in New York City reported the cytokine storm starting "like clockwork" on day 10 of the disease. So the cytokine storm is not an issue for the medical herbalist working for prevention or for treatment of early symptomatic disease. In fact early treatment which may moderate symptoms and severity of the illness may prevent the progression to pneumonia and severe disease that leads to cytokine storm.

As for influenza and cytokine storm, despite speculation that a strong cytokine storm was responsible for excess mortality in the "healthy young people" in 1918, this has never gone beyond speculative papers. Cytokine storm is not a known issue with actual influenza patients today. Historical researchers have also pointed out factors in the general population, including young adults, indicating that "healthy young people" were probably rare in North American in 1918. Medical historian Mary Weick points out that the vitamin D deficiency disease Rickets was endemic in the United State in that era (Weick). Rates had been much lower in the 1890s, but with the mass migration of a large part of the US population from the countryside to the cities over the next thirty years, with people living in crowded tenements, smoke-clouded cities, and and working dawn-to-dusk in crowded factories, Rickets became endemic in the U.S. Weick described the statistics from the 1920's as “almost unbelievable.” (Weick) Nearly 100% of babies born in Boston, New York, Washington DC, Cincinnati, and New Orleans developed Rickets by the age of one year old in 1920. The statistics suggest a population-wide deficiency of this vitamin, especially in late Fall and Winter. One aspect of Rickets, and of vitamin D deficiency, is increased respiratory infection. At the serum level where Rickets begins to develop in some individuals, the frequency of respiratory infections double. This was the condition of the “healthy young” that the influenza pandemic encountered: near-universal vitamin D deficiency with accompanying respiratory immuno-deficiency, and the heightened likelihood of progression to pneumonia, and reduced likelihood of recovering from severe disease.

Other researchers of the 1918 pandemic cite other factors that promoted excess mortality. Researcher Karen Starko has pointed out that in the month before the mortality from the 1918 pandemic began to skyrocket, the Surgeon General of the Army and the head of the American Medical Association, advised that all influenza patients should receive between 9 and 30 grams a day of aspirin. This dose today is known to be toxic, and if given to critically ill patients could cause mortality on its own with symptoms of respiratory failure indistinguishable from influenza (Starko). Historian Karen Clay and her coauthors demonstrated that the general poor health of the population, as reflected in those areas with highest infant mortality rates, as well as areas high in poverty, and air pollution from coal smoke may have collectively accounted for 50% of the excess mortality of the pandemic (Clay et al). Instead of a cytokine storm killing the “healthy young” in 1918 here was a socio-economic-medical storm devastating the population. Today we are more likely to blame something on the pathogenicity of a virus than on the social ills of the society it has entered.

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References

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 Nov;4(11 Suppl):919-22.

Clay K, Lewis J, Severnini E. What explains cross-city variation in mortality during the 1918 influenza pandemic? Evidence from 438 U.S. cities. Econ Hum Biol. 2019 Dec;35:42-50.

Elsasser-Beile U, Willenbacher W, Bartsch HH, Gallati H, Schulte, Monting J, von Kleist S. Cytokine productionin leukocyte cultures during therapy with Echinacea extract. J Clin Lab Anal. 1996;10(6):441-5.

Guo XJ, Thomas PG. New fronts emerge in the influenza cytokine storm. Semin Immunopathol. 2017 Jul;39(5):541-550.

Harokopakis E, Albzreh MH, Haase EM, Scannapieco FA, Hajishengallis G. Inhibition of proinflammatory activities of ajor periodontal pathogens by aqueous extracts from elder flower (Sambucus nigra). J Periodontol. 2006 Feb;77(2):271-9.

Hawkins, J., Baker, C., Cherry, L., & Dunne, E. (2019). Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. Complementary Therapies in Medicine, 42, 361–365.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet.

Hudson J.B. et al. Echinacea: From folklore to scientific validation Department of Pathology & Lab Medicine, University of British Columbia

Sino Biological. “Cytokine Storm.” https://www.sinobiological.com/cytokine-storm-cytokine-storms-a-5800.html [downloaded 3/15/20 11:12 AM]

Starko KM. Salicylates and pandemic influenza mortality, 1918-1919 pharmacology, pathology, and historic evidence. Clin Infect Dis. 2009 Nov 1;49(9):1405-10.

Yesilada E, Ustün O, Sezik E, Takaishi Y, Ono Y, Honda G. Inhibitory effects of Turkish folk remedies on inflammatory cytokines: interleukin-1alpha, interleukin-1 beta and tumor necrosis factor alpha. J Ethnopharmacol. 1997 Sep;58(1):59-73.

Zakay-Rones, Z., Varsano, N., Zlotnik, M., Manor, O., Regev, L., Schlesinger, M., & Mumcuoglu, M. (1995). 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. The Journal of Alternative and Complementary Medicine, 1(4), 361–369.