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File: ■ COVID-19
■ Severe Acute Respiratory Syndrome (SARS)-CoV-2
■ Antiviral Activity

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RE: COVID-19 and the Potential Usefulness of Botanicals with Antiviral Activity

Hensel A, Bauer R, Heinrich M, et al. Challenges at the time of COVID-19: Opportunities and innovations in antivirals from nature. [published online May 20, 2020]. *Planta Med.* doi: 10.1055/a-1177-4396.

Severe acute respiratory syndrome (SARS)-CoV-2 (also known as COVID-19), SARS-CoV-1, Middle East respiratory syndrome (MERS)-CoV, influenza viruses, rhinoviruses, adenoviruses, and respiratory syncytial virus (RSV) have plagued humans for many decades. Some antivirals are effective (i.e., against influenza), but there are currently no known specific, highly effective antivirals for viral pathogens in the throat and upper airways.

Coronavirus, influenza virus, and RSV have a lipid bilayer envelope derived from the cellular membrane of the host cell. The lipid layer of the host often contains (glyco)proteins, which protrude and are the target of the virus. For example, influenza viruses target and colonize epithelia in the bronchial area, and COVID-19 viral envelope proteins bind to structures in the throat. The question arises – How can the mouth and throat be protected against virus penetration? The envelopes of viruses can be attacked by many exogenous compounds (e.g., solvents, detergents, and lipophilic substances such as essential oils). The authors question whether it is possible to achieve protection against enveloped viruses via topical treatment of the oral mucosa.

Tannins have antimicrobial effects and also inhibit functionality of viral envelope proteins. Proanthocyanidin is a tannin and is present in many plants such as green tea (*Camellia sinensis*, Theaceae) leaf and sorrel (*Rumex acetosa*, Polygonaceae) leaf. Proanthocyanidin inhibits binding of influenza A virus, thereby preventing virus adhesion to the host cell. The authors hypothesize that lozenges, chewing gum, or mouthwash containing tannins could be used prophylactically to protect against infection. However, the benefits most likely would only occur while the tannins are in the mouth (i.e., while sucking a lozenge). The authors point out the possibility that the brief exposure may decrease the viral load or inhibit incoming viruses from adhering and causing an infection. These hypotheses need to be tested.

Podophyllotoxin, a lignan from mandrake (*Podophyllum* spp., Berberidaceae) root and rhizome is active against HIV and human papillomavirus (HPV). Lignans may inhibit reverse transcriptase activity, to inactivate HIV. Bicyclol (a novel synthetic) drug is a type of lignan and has antiviral activity against hepatitis B virus (HBV).

Essential oils may provide antiviral activity. Eucalyptus (*Eucalyptus globulus*, Eucalyptaceae) leaf essential oil may reduce docking or uptake of herpes simplex virus and influenza virus, but the main effect may be via a reduction in inflammatory reactions in the lungs. Essential oil from bay laurel (*Laurus nobilis*, Lauraceae) aerial part inhibited replication of SARS-CoV in vitro; however, it has allergenic potential. Sage (*Salvia officinalis*, Lamiaceae) leaf essential oil was also inhibitory against SARS-CoV but had a weaker effect compared with bay laurel essential oil. Sage also contains tannins, so the authors suggest its potential as a gargle solution in addition to an inhalant.

The authors propose that lozenges containing tannins or essential oils be produced as a food supplement, which would not need the same approval as a pharmaceutical preparation. There is an urgent need for protection strategies especially in high risk individuals, such as elderly, immunocompromised patients, and patients with respiratory disease, as well as for personnel in nursing homes, ambulatory care, and hospitals. The authors point out that although it would not be ethical to conduct a randomized, placebo-controlled study, the lozenges could be evaluated in a non-interventional observational study.

When the immune system is weakened, a person is more susceptible to infections. Advanced aging (> 60 years) is associated with a reduction in B-lymphocytes and T-lymphocytes, which are needed to fight infection. Stimulating the immune system sounds like a positive approach. However, SARS is associated with an overreaction of the immune system in which the immune system produces too many inflammatory signals (a cytokine storm) and can lead to organ failure and death. Echinacea (*Echinacea* spp., Asteraceae) can modulate the immune system and has antiviral effects in vitro.

During the SARS-CoV and SARS-CoV2 outbreak in Guangdong, China, traditional Chinese medicine (TCM) was used as a treatment in > 85% of patients. The TCM treatments were commonly used formulations of many herbs. A 2007 survey during the SARS-CoV outbreak in China, reported that 40-60% of patients received TCM plus Western treatments. The 10 most popularly used herbal medicines in China to treat COVID-19 were astragalus (*Astragalus membranaceus*, Fabaceae), Chinese licorice (*Glycyrrhizae uralensis*, Fabaceae), siler (*Saposhnikovia divaricata*, Apiaceae) root, large-headed atractylodes (bai-zhu atractylodes; *Atractylodes macrocephala*, Asteraceae) rhizome, Japanese honeysuckle (*Lonicera japonica*, Caprifoliaceae) flower, weeping forsythia (*Forsythia suspensa*, Oleaceae) fruit, cang-zhu atractylodes (*Atractylodes lancea*) rhizome, platycodon (*Platycodon grandiflorum*, Campanulaceae) root, Korean mint (Chinese giant hyssop; *Agastache rugosa*, Lamiaceae), and fortune's holly fern (*Cyrtomium fortunei*, Dryopteridaceae). The authors state that clinical trials are needed to support the TCM treatments, and standardized treatments rather than self-prepared formulations should be used.

As demand for herbal medicines increases, the existing supply chains may be insufficient. The challenge is having a supply of authentic high-quality finished products in addition to having well-designed studies to provide evidence of efficacy.

—Heather S. Oliff, PhD

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