

Plant power

How nature can help combat viral infections

Plants have been used as medicines by humans for thousands of years, yet we have only uncovered a tiny part of their potential. Dr Bruno Frank of CogniVerde GmbH in Germany, is exploring the use of plant-derived substances against viral infections such as SARS-CoV-2. Laboratory studies have shown that green tea and some plant juices, particularly chokeberry juice, can reduce the viral infectivity of several respiratory viruses. This highlights the need for further clinical trials to explore their potential to reduce virus transmission.

The importance of oral hygiene in infectious diseases is often overlooked. It has been suggested that inflammation and open wounds in the mouth (mouth ulcers, sores, gum disease) may increase susceptibility to viral infections by allowing the virus to multiply and move directly into the bloodstream, bypassing the oral mucosa barrier (Lloyd-Jones et al, 2021).

The involvement of the oral cavity in SARS-CoV-2 (the virus that causes COVID-19 disease) is less well understood. New research found that the oral cavity is not only an important site for SARS-CoV-2 infection, but the primary place of virus multiplication before affecting other organs, such as the lungs, the vascular system, and nerves.

Many substances derived from plants have been shown to have anti-viral activity. For example, sage, thyme, green tea, and some essential oils can have antibacterial, anti-viral, and anti-inflammatory effects. Some of these products have also been used to treat conditions in the oral cavity.

Dr Bruno Frank of CogniVerde GmbH has planned and organised a set of laboratory studies to find herbal agents against the transmission and infection of SARS-CoV-2 and other respiratory viruses, especially influenza viruses. He and his team hope that this will create a simple way to protect against all infectious diseases with only one product. CogniVerde GmbH already has several patents relating to the production and marketing of dietary supplements for health conditions, including

Alzheimer's disease, Parkinson's disease, and stress.

Their latest research, published in a not yet peer-reviewed article from 2020, suggests that plants used as foods and rich in tannins, such as green tea, chokeberry (also called Aronia), or pomegranate juice, and lozenges containing dedicated plant extracts, may be able to reduce the infectivity of some viruses. Tannins are a class of molecules that have a strong binding to proteins; therefore, they may help create an additional barrier in the oral cavity that keeps viruses at bay. Tannins are very good haemostatic agents (they stop bleeding) and are also anti-inflammatory, which is very relevant in gum inflammation.

Initially, this work was done in vitro, so it was not known whether this phenomenon would also occur in a real-life setting. Still, these plant-based products may be better tolerated than aggressive commercially available mouthwashes as they have very few adverse effects. In addition, plant-based products can be anti-inflammatory and form a protective film due to the tannin-protein reaction.

Pilot studies done by other research groups have already shown that patients infected with SARS-CoV-2 may clear the infections quickly if they gargle with commercially available mouthwashes, or use lozenges with plant extracts such as pomegranate. These studies only included a small number of patients and were observational, meaning that the participants were likely infected with SARS-CoV-2 at different time points, with different levels of increasing or waning infectivity, all of which can make the results difficult to interpret.

A scoping review (Ather et al, 2021) considered the results of multiple reliable studies and concluded that there is insufficient evidence to recommend mouth rinses for dental care providers and patients with SARS-CoV-2. However, they did find that the results of laboratory studies have been promising, highlighting a need for further research.

The recommendation of the German Society for Hospital Hygiene, which includes a more in-depth assessment of usable products for transmission prevention in a clinical setting and in the protection of the population, concluded that green tea and juices as tested in Dr Frank's study can be used for daily preventative measures, especially for children and school classes. Clinical settings, where only occasional disinfection is involved, need to be evaluated differently. In clinical settings, very comprehensive and strongly effective agents such as iodine preparations are indicated, whereas for daily preventative measures, agents that are less aggressive and do not damage the oral flora and oral mucosa during continuous use are recommended (Kramer et al, 2021).

PLANT JUICES REDUCE VIRUS INFECTIVITY

Dr Frank and his team analysed the virucidal (virus-killing) activity of black chokeberry, pomegranate, and elderberry juices, as well as green tea. Different respiratory viruses were tested, including influenza virus and SARS-CoV-2.

The plant preparation was added to the virus and the mixture was left for a certain incubation time, before being diluted for infectivity tests. Viral suspensions were incubated with either a plant preparation or a control buffer at room temperature for one, five or 20 minutes. The remaining infectivity of the viruses was then determined by the tissue culture infectious dose 50 (TCID 50) endpoint titration, which is a test to calculate how infectious the virus is after treatment.

The results showed that green tea and all juices inactivated influenza by as much as four log levels, meaning that after treatment, the amount of virus



Black chokeberry (left) and pomegranate (right) are rich in tannins.



Essential oils can have antibacterial, anti-viral, and anti-inflammatory effects.

Preventing any bleeding in the oral cavity by using plant tannins may inactivate viruses and prevent them from spreading to other parts of the body.

detected was reduced by 99.99%. Green tea and plant juices were most effective against influenza virus, showing a decrease in virus activity that is similar to typical disinfectants.

SARS-CoV-2 and vaccinia virus show a quite similar sensitivity against the tested products but were not affected as much as the influenza virus. The plant juices still reduced the infectivity by one to two orders of magnitude. In the case of SARS-CoV-2, after one minute, infectivity was reduced by 97% (chokeberry) and 80% (green tea and pomegranate). Elderberry had no effect.

Interestingly, there was very little difference when the virus was incubated with the plant extracts for different lengths of time, suggesting the anti-viral effect is very rapid.

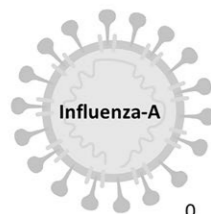
The researchers next hope to explore whether using plant juices or green tea as an oral rinse will lower viral loads in the oral cavity in human subjects.

UNDERLYING MECHANISMS?

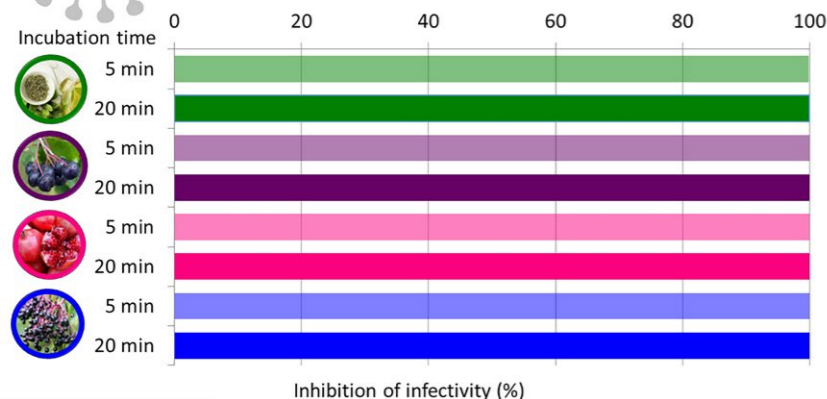
SARS-CoV-2 is spread mainly by aerosols and tiny droplets in the air that are breathed in through the nose or mouth. Once in the oral-nasal cavity, the SARS-CoV-2 viruses multiply and can then be transmitted via the respiratory tract to the lungs and other organs. In the case of inflammation or small wounds, including gum infection (periodontitis), the virus can also travel via the blood stream (Lloyd-Jones et al, 2021). There are a large number of ACE2 receptors in blood vessels; these receptors are recognised by spike proteins on the surface of coronaviruses. Once in the blood stream, the virus can bind to these



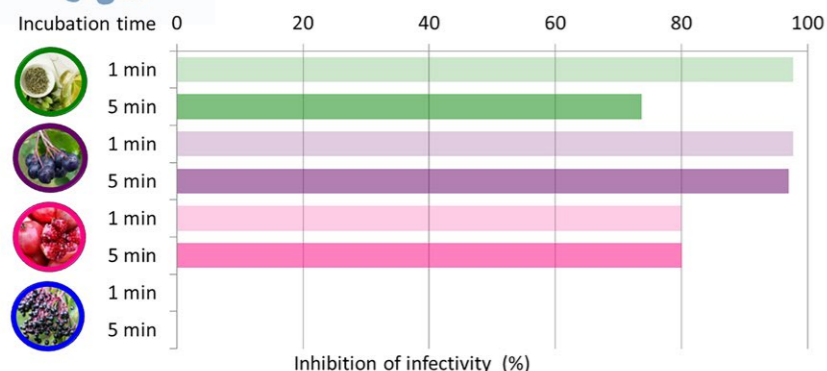
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All herbal preparations inhibit influenza A viruses almost 100%.



Green tea, chokeberry and pomegranate almost completely inhibit SARS-CoV-2.



Herbal preparations effectively inhibit various viruses, including Influenza-A (top) and SARS-CoV-2 (bottom).

The work done by Dr Frank and colleagues suggests that plant juices and teas may have some impact on viral infections.

receptors and thereby spread to other parts of the body.

Previous publications and studies have also suggested a link between periodontitis and COVID-19 severity, demonstrating that periodontitis was associated with a higher risk of admission to an intensive care unit, need for ventilation, and mortality.

The study demonstrated that green-tea tannins bind to the spike protein of SARS-CoV-2 and the ACE2 receptor of the host, as well as to some further viral proteins. A similar relationship was shown with a group of tannins called ellagitannins of pomegranate, that were found to be the most effective group against coronavirus proteins in pomegranate.

The underlying anti-viral mechanisms of juices and green tea in this particular study are likely to be very similar to these mechanisms. Therefore, Dr Frank also suggests that preventing any bleeding in the oral cavity by using plant tannins may inactivate viruses and prevent them from spreading to other parts of the body.

Furthermore, SARS-CoV-2 is inactivated by acidic pHs, such as that in the stomach, and this may help explain why they are reduced after being exposed to acidic juices.

Dr Frank highlights that there are a number of key properties that should be considered for an effective mouthwash. These include a broad spectrum of activity, good efficacy, no side effects, no adverse impact on the oral microbiome (the bacterial ecosystem in the mouth), and there should be no chance of viruses developing resistance against tannins. This could occur through mutations in viral proteins, but a recent publication has shown that green tea is effective against new and emerging strains of SARS-CoV-2 which confirms the non-specific effect of tannins on (mutated) proteins (Liu et al, 2021).

A NEED FOR CLINICAL TRIALS

Given the many existing medications that are derived from plant ingredients, there are likely many more opportunities to harness the power of nature. The work done by Dr Frank and colleagues suggests that plant juices and teas should have some impact on viral infections. They may have the potential to be used alongside existing, validated medications and vaccines to help stop transmission, improve symptoms, and reduce the length of illness.

As Dr Frank explains, further work is still highly desirable. Clinical trials in human subjects should be done to show the value of such procedures. However, there are many challenges to doing these studies, such as access to funding.

In the meantime, good oral hygiene remains an important factor in reducing risk of infectious disease and a preventive daily mouth rinse could be a helpful way to reduce viral transmission.



Behind the Research

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Research Objectives

CogniVerde GmbH has arranged laboratory studies to show that green tea, chokeberry juice, and pomegranate juice were able to reduce levels of flu and SARS-CoV-2 virus.

Detail

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Bio

Dr Frank is a pharmacist and PhD in pharmaceutical biology. He has industrial experience as head of various departments, such as analytical development, drug regulatory affairs, R&D pharmaceuticals, and pharmaceutical and medical science and research. In parallel, he is a member of scientific committees and expert commissions, as well as boards of scientific societies and associations. Dr Frank is active in numerous working committees of research projects, a book author, referent, and product developer.

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Personal Response

Are you planning any controlled in vivo studies to explore these findings further?

Yes, I have talked to some experienced doctors and researchers about this. They would like to get involved but see no real chance because of the too low case numbers in most European countries, especially Germany – and the lack of funding!