Neem Bark Extract Has Potential to Treat COVID-19

By Alexandra Brodin
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Azadirachta indica (neem) is a type of tree whose bark, leaves, and seeds have long been used in India as traditional phytomedicine. Jayasri Das Sarma, PhD, a Neurovirologist/Neuroimmunologist at the Indian Institute of Science Education and Research (IISER)-Kolkata and an Adjunct Professor in the Department of Ophthalmology at the University of Pennsylvania (UPenn), is leading a large multicenter, cross-disciplinary study on the potential of neem bark extract (NBE) as a therapy for COVID-19. Dr. Das Sarma is collaborating on this study with Ken Shindler, MD, PhD, specialist in neuro-ophthalmology in the UPenn Department of Ophthalmology.

The project, titled 'Leveraging reverse genetics strategies to study structure-function interplay of virus-host attachment spike protein to design therapies for COVID-19,' is funded by the Indo-U.S. Science and Technology Forum (IUSSTF). The award period began in October 2020.

Although neem is widely used for its antifungal and antibacterial properties, its antiviral and anti-inflammatory activities are less well-known. Dr. Das Sarma recently published a study in *Frontiers in Cellular Neuroscience* showing that NBE binds to the Spike protein found in mouse hepatitis virus (MHV), a group 2 coronavirus that serves as a model for neuroinflammatory diseases in humans. In this study, NBE binding to the Spike protein inhibited cell-to-cell fusion and viral replication, effectively reducing neuroinflammation.

The novel coronavirus (SARS-CoV-2) that causes the respiratory disease COVID-19 (as well as SARS, OC43, and other human coronaviruses) also contains the Spike protein, composed of two subunits known as S1 and S2. The spike protein gives SARS-CoV-2 its characteristic jagged shape and mediates viral entry into host cells. The S1 subunit first binds to a receptor located on the surface of the host cell, and then the S2 subunit fuses the viral and host cell membranes. This way, genetic material from the novel coronavirus enters the host cell and uses the cellular machinery to replicate the virus and spread to other host cells.

However, if another compound binds to the coronavirus Spike protein, the virus is unable to bind to a host cell. Similar to its antiviral activity against MHV, NBE may reduce viral entry and spread of SARS-CoV-2 by targeting the coronavirus Spike protein.

"The theory that Dr. Das Sarma and her group of collaborators from around the globe are looking at is whether NBE can block the Spike protein from the SARS-Cov-2 virus that causes COVID-19," explained Dr. Shindler.

Dr. Debnath Pal, a collaborator at the Indian Institute of Science, is using an in silico approach to investigate which compounds in the NBE bind most effectively to the Spike protein.

“It’s a big protein, so we want to see the minimum that is required to mitigate the pathogenicity of the virus,” Dr. Das Sarma said. Additional collaborators at University of Colorado, University of Florida, and Emory University are examining the ability of NBE to block viral entry into a variety of different cell types.

Dr. Das Sarma’s group is also creating a recombinant murine coronavirus containing the Spike gene from SARS-CoV-2. With this recombinant virus, her team can use murine models to study the effect of NBE on viral spread and pathogenicity of SARS-CoV-2.

Dr. Shindler’s lab has shown that the murine coronavirus MHV causes optic neuritis, or inflammation of the optic nerve. The ability of this virus to move up and down the optic nerve, as well as the isolated nature of the optic nerve, provides an excellent model for evaluating the role of the Spike protein in viral spread. Dr. Shindler plans to use the recombinant murine coronavirus to investigate the effect of COVID-19 on the optic nerve, as well as the potential for NBE to prevent damage to the optic nerve.

Although Dr. Das Sarma’s team is making tremendous progress, the COVID-19 pandemic has presented challenges in carrying out this research. For example, shipping physical materials and reagents between labs all over the world, which was a complicated process before the pandemic, has become even more difficult. International travel is also much more restricted, which poses limitations on researchers, trainees, and students who are involved in the research. Moreover, the use of a high-biosafety level (BSL) facility is often required to conduct research on viruses. Although a BSL-3 facility is available to collaborators at UPenn, use of the facility is in very high demand due to the increasing volume of studies on SARS-CoV-2.

However, videoconferencing has allowed collaborators to stay in contact, share data, and continue the investigation. “One good thing is that these online platforms are helping us a lot. We can still keep our work going. At least we have the opportunity to meet with people overseas without any barriers,” said Dr. Das Sarma.

Studying the therapeutic benefit of NBE with respect to the novel coronavirus has several potential exciting outcomes. One is that NBE may offer a treatment for not only the SARS-CoV-2 virus, but also other types of coronaviruses that may lead to outbreaks in the future. In addition, Dr. Das Sarma’s team is learning much about the antiviral activities of neem, which may lead to future studies and therapeutic applications beyond the immediate need to treat COVID-19.

“It’s also exciting to just work in the network that Dr. Das Sarma has put together to show how this work in virology can advance science and get people to collaborate across different fields,” said Dr. Shindler. “For me, it’s exciting to have ophthalmology play a small role in something so broad, involving multiple systems in the body.”

Dr. Das Sarma and Dr. Shindler are currently coordinating on plans to test the effect of NBE on the pathogenicity of the recombinant murine coronavirus in summer 2021.

References:

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