

Medical News & Perspectives

Trials Test Mushrooms and Herbs as Anti-COVID-19 Agents

Anita Slomski

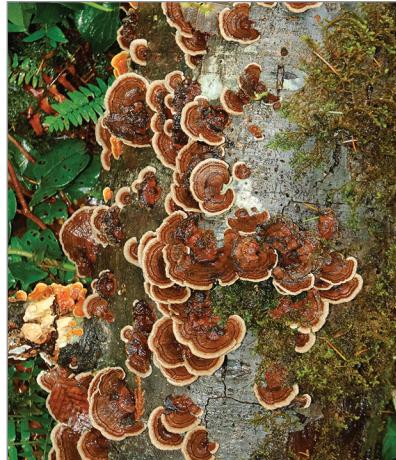
In the COVID-19 pandemic's early days, integrative medicine specialists Gordon Saxe, MD, PhD, MPH, and Andrew Shubov, MD, watched in frustration as desperate patients infected with the novel coronavirus tried one ineffective remedy after another. "People were taking increasingly toxic drugs, and nothing was working," Shubov said in an interview.

Missing from those early hit-or-miss therapeutics, however, were traditional medicines such as Chinese herbs and medicinal mushrooms. The omission was glaring to Saxe, an epidemiologist and executive director of the Krupp Center for Integrative Research at the University of California San Diego (UCSD), whose research focuses on using food as medicine. Shubov, director of Inpatient Integrative Medicine, Center for East-West Medicine, at the University of California Los Angeles (UCLA), also found it a stark oversight.

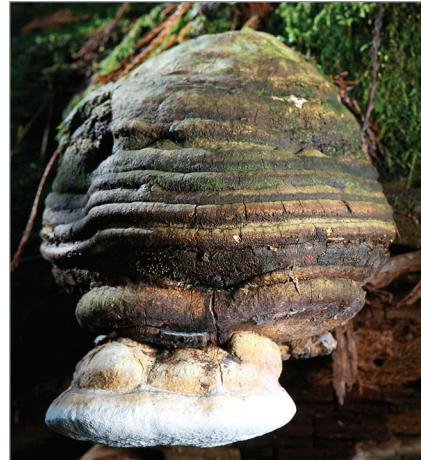
So in April 2020, they applied to the US Food and Drug Administration (FDA) for approval to conduct 2 randomized phase 1 trials. The double-blind, placebo-controlled studies would evaluate the safety and feasibility of treating mild to moderate COVID-19 with either [medicinal mushrooms](#), which have a long history as natural therapeutics for pulmonary disease, or a [Chinese herb formulation](#) from Taiwan that's widely used as a COVID-19 remedy in China.

The FDA ultimately sanctioned the MACH-19 (Mushrooms and Chinese Herbs for COVID-19) trials, which are now underway at UCLA and UCSD and are supported by the Krupp Endowed Fund. Meanwhile, a third MACH-19 trial is investigating the use of [medicinal mushrooms as an adjuvant to COVID-19 vaccines](#).

"Researchers are currently conducting *in vitro* and animal studies with natural products to evaluate direct antiviral activity or to address COVID-19 sequelae," D. Craig Hopp, PhD, deputy director of the Division of Extramural Research at the National Center for Complementary and Integrative Health (NCCIH), said in an interview. But the MACH-19 treatment trials are unique,



Paul Stamets/Fungi Perfecti



he noted, because they're evaluating natural products among humans with acute SARS-CoV-2 infection.

Medicinal Mushrooms Sprout Interest

The first trial is studying a combination of 2 mushrooms—turkey tail (*Trametes versicolor*) and agarikon (*Fomitopsis officinalis*)—both of which are available as over-the-counter supplements.

According to Saxe, the MACH-19 trials' principal investigator, it's biologically plausible that mushrooms may have immune-modulating properties against SARS-CoV-2. "The interactions of fungi as part of the gut microbiome include binding to receptors on immune cells," he explained in an interview. "There are receptors on T cells, for example, that bind mushroom polysaccharides. This is one mechanism by which mushrooms can modulate the behavior of our immune cells, which may have a potential effect against SARS-CoV-2."

Saxe noted that physicians in Greece treated pulmonary disease with agarikon about 2300 years ago. The traditional medicine practice has been documented in many other regions, as well. More recently, agarikon has been found to inhibit a number of viruses in [preclinical studies](#), including influenza A(H1N1), influenza A(H5N1), cowpox virus, and herpes viruses. Com-

pounds in agarikon have also been shown to have [antituberculosis](#) properties.

As for turkey tail, the mushroom was studied extensively as a chemotherapy adjuvant for a variety of cancers more than a decade ago, Hopp said. In 1 example, women with breast cancer who received the mushroom in a phase 1 trial appeared to have improved immunity following chemotherapy. A 2012 [meta-analysis](#) of 13 clinical trials, conducted by researchers in Hong Kong, found a 9% absolute reduction in 5-year mortality among patients with cancer who were treated with turkey tail in addition to chemotherapy.

"The mushrooms were being used to boost immune function that was suppressed by either the cancer or the chemotherapy," Hopp said. "The trials showed modest improvement in immune function, but nothing large and definitive that would affect clinical practice."

Consequently, cancer research involving mushrooms slowed considerably in the US, but their therapeutic use is still standard practice in Japan and China, according to Hopp.

Mushrooms have evolved a variety of antimicrobial properties against bacteria and viruses that colonize them, some of which also infect humans. The MACH-19 investigators said they believe the combination of

turkey tail and agarikon has the potential to impede COVID-19 by inhibiting viral replication, and they expect to test its antiviral effects in a phase 2 trial.

Testing Herbal Formulations

Their other treatment trial is testing an approach called modified Qing Fei Pai Du Tang (mQFPD)—a combination of 21 herbs from 4 Chinese herbal formulations that were developed to treat COVID-19 in Wuhan, China. "The experience with these herbs is very deep; the ones we are using are based on formulas that date to the third century," said Shubov, the trials' lead investigator.

In a large observational study in China, patients hospitalized with COVID-19 in early 2020 who used the herbs had a lower risk of death than those who didn't use them. Although individuals in both groups received antiviral medications, corticosteroids, and an immunomodulator, a higher percentage of the patients who used herbs also took antivirals, which could have skewed the results. However, after adjusting for patient characteristics and concurrent treatments, the risk of in-hospital mortality was 50% lower among those who received mQFPD for at least 3 days.

Shubov explained that in Chinese medicine, COVID-19 is understood to be an acute infection that causes a condition known as "cold dampness" to settle in the lungs. This triggers the production of mucus and phlegm which, if not expectorated, leads to "lung heat," or inflammation. "These terms sound unscientific, but they describe the

complex networks of physiology that match the clinical syndrome of coryza that can develop to ground glass opacities and an unchecked inflammatory response [in COVID-19]," he said.

In an email to *JAMA*, Chinese herbal medicine expert John Chen, PharmD, PhD, OMD, an unpaid consultant on the MACH-19 trials, described several possible mechanisms of action for the herbs. According to Chen, researchers recently found that herbs used to clear "lung heat," such as *Huang Qin* (*Radix scutellariae*), inhibit SARS-CoV-2 replication and block the virus from binding to angiotensin-converting enzyme 2 receptors on cells. *Ma Huang* (*Herba ephedrae*), an herb used to treat asthma, contains ephedrine alkaloids with potent α-adrenergic and β-adrenergic activity in the lungs. *Gan Cao* (*Radix et Rhizoma glycyrrhizea*) has anti-inflammatory effects. And *Ban Xia* (*Pipelite Rhizoma*) is known to thin mucus and promote its elimination, Chen noted.

A recent study in the *Chinese Journal of Natural Medicines* described 195 absorbed components and metabolites associated with mQFPD administration in mice. The data should provide "guidance for further investigation on the pharmacologically active substances and clinical applications" for the treatment, the study's authors wrote.

The Trials Commence

For each of the MACH-19 treatment trials, the investigators plan to recruit 66 patients who

have tested positive for SARS-CoV-2 and are quarantined at home with mild to moderate symptoms. The participants will be randomized to receive either the mushroom combination, the Chinese herb formulation, or a placebo for 2 weeks.

Patients who are being treated with monoclonal antibodies or the experimental oral antiviral medication molnupiravir won't be excluded. "As long as those therapies don't adversely interact with the mushrooms or Chinese herbs, there is no reason for participants not to take a known successful treatment for COVID-19" in addition to traditional medicine, Shubov said.

Aside from safety, the investigators will examine efficacy markers such as COVID-19 symptom severity and duration and hospitalization and ICU admission rates.

"The trials are not powered to evaluate those metrics, but we hope to have trends to evaluate," Shubov said. Down the line, the planned efficacy phase will have 3 groups, each with 240 participants who will receive the mushrooms, Chinese herbs, or placebo.

Enrolling participants for the treatment trials has been challenging, however. "The waning of the pandemic is making recruitment harder," Shubov said. And logically, only patients from the San Diego and Los Angeles areas are eligible to participate. "We have phlebotomists in personal protective equipment going to quarantining patients' homes to draw blood," Saxe said. "We have the resources to do that in Southern California, not in other parts of the country."

Conversely, recruiting participants for the trial evaluating mushrooms as a COVID-19 vaccine adjuvant has been relatively easy. "People perceive mushrooms to be completely safe and hope for a better response to their vaccine," Saxe said.

In this study, 66 participants in the general population will receive the mushroom mix or placebo for 4 days beginning on the day of their first vaccine dose. Individuals with previous SARS-CoV-2 infections can participate. "We are measuring participants' antibody levels at baseline and controlling for that," Saxe said. Besides safety, the trial will evaluate whether the mushroom combination increases antibody titers, reduces vaccine adverse effects, extends the vaccine's therapeutic duration, or affects other markers of immune function.



Thomas N. Leung, DACM/Kamwo Herbs

Too Much Immune Boosting?

The investigators recently launched a fourth trial comparing the mushrooms with placebo as an adjunct to a COVID-19 booster shot. The mushrooms may be safe as a vaccine adjuvant, but the NCCIH's Hopp said he is "mildly concerned" about using them to treat people with active SARS-CoV-2 infection.

"People with normal immune function should already be having a robust immune response to the viral challenge," he explained. "We know that a cytokine storm poses the greatest risk of COVID mortality, not the virus itself." The danger, he said, is that an immune-stimulating agent like mushrooms might supercharge an individual's immune response, leading to a cytokine storm.

Immunologist Stephen Wilson, PhD, who consulted on the MACH-19 trials when he was chief operating officer of the La Jolla Institute for Immunology, sees a different scenario. Mushrooms aren't likely to trigger a [cytokine storm](#) in people with mild or mod-

erate COVID-19 because their components don't mimic inflammatory cytokines, said Wilson, who is now chief innovations officer at Statera Biopharma Inc.

"Each dosing is thought to increase the level of cooperation between innate and adaptive cells that work together to recognize and seek out viral threats," he explained in an interview. "We think the mushrooms increase the number of immunologic opportunities to better see and respond to a specific threat. In the doses used, the mushrooms perturb the immune system in a good way but fall far short of driving hyper or sustained inflammation."

Chinese herbs appear to pose little or no threat, according to Hopp. He pointed to oseltamivir, sold as Tamiflu, which had its origins in Chinese medicine with star anise as an active ingredient. "There is plenty of potential there for various Chinese herbs to be useful in treating COVID," he said.

Initial safety data from the MACH-19 trials are expected by the end of this

year and efficacy data will be ready within a year. It's anyone's guess whether COVID-19 will still pose a major public health threat by then. But the lessons learned from the trials may be relevant for the next rogue virus.

"Western medicine generally doesn't need help treating infectious diseases until a pandemic like COVID hits," Shubov said. "That's when we realize we don't have good answers to treating viral respiratory diseases. We hope our trials will open the eyes of the Western world to a rich pharmacopeia of natural substances that we can draw from for many other diseases going forward." ■

Conflict of Interest Disclosures: Dr Shubov reported investment in the dietary supplement company Mycomedica Life Sciences, for which he also serves as an unpaid scientific advisor. Dr Chen is a medical consultant for Evergreen Herbs and Medical Supplies. Drs Hopp, Saxe, and Wilson reported no disclosures.

Note: Source references are available through embedded hyperlinks in the article text online.