Article Type: Original Investigation

Title: Polypore Mushroom Mycelia for Treatment of Active COVID-19 Infection: A Randomized Clinical Trial

Running Title: Mushroom Mycelium for COVID Treatment

Authors: Gordon Saxe, MD/PhD,[1,2*] Andrew Shubov, MD,[3] Christine N. Smith, PHD,[4,5,2,6] Shahrokh Golshan, PhD,[1,2,4,5] Tatyana Shekhtman, MS,[1,2] Stephen Wilson, PhD,[6] Daniel Slater, MD/FAAFP,[1] Zolton J. Bair, PhD,[8] Chase Beathard, PhD,[8] Renee A. Davis, MA,[8,9] Lauray MacElhern, MBA,[1,2] Lan K. Kao, DACM,[3] Phoebe Senowitz, MEd,[1,2] Natalie Gosnell, BS,[10] David Buchholz, PhD,[11] Hector Aguilar-Carreno, PhD[11]

[1] Department of Family Medicine, University of California San Diego, California, U.S.A.

[2] Krupp Center for Integrative Research, Centers for Integrative Health, University of California San Diego, California, U.S.A.

[3] Center for East-West Medicine, Department of Medicine, University of California Los Angeles, California, U.S.A.

[4] Veterans Affairs San Diego Healthcare System, San Diego, California, U.S.A.

[5] Department of Psychiatry, University of California San Diego, California, U.S.A.

[6] Center for the Neurobiology of Learning and Memory, University of California Irvine, California, U.S.A.

[7] Botnar Institute of Immune Engineering, Basel, Switzerland

[8] Department of Research and Development, Fungi Perfecti, LLC, Olympia, Washington, U.S.A.

[9] Department of Civil and Environmental Engineering, University of Washington, Seattle, Washington, U.S.A.

[10] Department of Microbiology and Immunology, Cornell University, Ithaca, New York, U.S.A.

[11] Microbiology Immunology & Molecular Genetics, University of California Los Angeles, Los Angeles, California, U.S.A

* Corresponding author:

Gordon Saxe, M.D./Ph.D.

University of California, San Diego

9500 Gilman Drive MC8998

La Jolla, California, 92093, U.S.A.

Email: gsaxe@health.ucsd.edu

Telephone: (844) 747-0474

Keywords: SARS-CoV-2, FDA, fungi, symptoms, antiviral, H5N1, influenza A, Bird Flu

ABSTRACT

Use of fungal mycelia, which has antiviral properties, constitutes a novel strategy for addressing existing and newly emerging viral diseases. We evaluated safety and feasibility of fungal mycelia (*Fomitopsis officinalis* and *Trametes versicolor*, FoTv) for treatment of COVID-19 and assessed its antiviral effects and potential to reduce symptoms. In a randomized, double-blind, placebo-controlled, dual site (UCSD/UCLA medical centers) clinical trial we examined non-hospitalized patients who contracted mild-to-moderate COVID-19 ≤ 96 hours, and experienced symptom onset ≤ nine days, before enrollment. FoTv was safe, well-tolerated, and feasible for COVID-19 treatment. Minor differences in biochemical markers were observed between groups (26 FoTv, 24 Placebo). FoTv significantly reduced the number and severity of symptoms, particularly sore throat/cough, and *in vitro* SARS-CoV-2 (pseudovirus) cellular infection. In conclusion, FoTv was safe and reduced COVID-19 symptoms and cellular viral infection. Future studies should investigate therapeutic benefits of fungal mycelia for SARS-CoV-2 and other viruses. Clinicaltrials.gov registration:NCT04667247.

INTRODUCTION

COVID-19: Lessons and guidance for future pandemics

The COVID-19 pandemic underscored the need for effective medical strategies to reduce morbidity, mortality, and global disruption in both current and future public health emergencies. Although effective strategies now exist for managing SARS-CoV-2, emerging variants and other infectious viral diseases (e.g., bird flu, Zika virus, Hantavirus, dengue fever, etc.) continue to pose significant risks to global public health. Numerous primary prevention and treatment strategies, as well as diet and natural therapeutics, may all help reduce these risks.

During the COVID-19 pandemic, vaccines and antiviral medications constituted the first lines of defense. However, this approach may not be fully reliable in the future because development of relevant vaccines and antivirals may not be able to keep pace with the emergence of new viral variants and diseases. In addition, vaccines are usually only effective if taken prior to disease exposure. Similarly, antivirals may be less effective unless they are taken during a limited time window (prior to or shortly after exposure or symptom onset) and may encounter drug resistance because of misuse or overuse. Furthermore, vaccines and antiviral interventions may be limited by cost, supply constraints, or distribution challenges.

Although COVID-19-related morbidity and mortality have declined far below pandemic levels, other emerging infectious diseases continue to warrant close attention. Among these, highly-pathogenic avian influenza A (HPAI) is of particular and growing concern.

HPAI, caused by a viral subtype of H5N1, has led to a serious form of bird flu with symptoms in humans ranging from mild (e.g., conjunctivitis, flu-like symptoms) to severe or fatal outcomes (e.g., respiratory failure). Between January 2003 and April 2024, there were 896 reported cases of HPAI caused by H5N1 across 24 countries, resulting in a case-fatality rate of approximately 52%[1]. One particularly concerning novel H5N1 clade (2.3.4.4b) has been detected in more than 500 avian and mammalian species worldwide, including poultry, swine, cats, seals, sea lions, sea otters, ferrets, minks, cattle and dairy products[2,3] with sporadic transmission to humans[4]. While most human cases have been mild thus far, the expanding host range and increasing evidence of cross-species transmission (avian to mammal, mammal to mammal, avian to human, and mammal to human) raise concerns about the potential for sustained human-to-human transmission. This, combined with ongoing outbreaks of this clade in animals and the high case-fatality rate observed in earlier H5N1 clades, has raised concern that a future pandemic virus could emerge with greater lethality and societal impact than SARS-CoV-2.

Antiviral and disease modifying properties of polypore fungi

A recent randomized clinical trial of *Fomitopsis officinalis* and *Trametes versicolor* (FoTv) mycelium demonstrated that it is a safe, well-tolerated, and feasible adjunct to COVID-19 vaccination. In previously unvaccinated individuals without previous COVID-19 infection, FoTv in conjunction with COVID-19 vaccination was associated with significantly reduced vaccine side effects while preserving, or potentially enhancing,

Spike and receptor-binding domain (RBD) antibody titers over a six-month period[5]. Although FoTv is a relatively new therapeutic formulation, it comprises two fungal species that are well-characterized with established bioefficacy profiles which highlight the unique and potentially complementary benefits of each component.

Turkey tail *(Trametes versicolor,* Tv [syn. *Coriolus versicolor*]) is a widely studied polypore fungus with a long history of use in traditional medicine along with numerous clinical trials supporting the bioefficacy of its mycelium[6]. Interest in Tv has been growing because of its antiviral[7,8] and immunomodulatory[9–11] effects. Flow cytometry and cytokine profiling demonstrated that treatment with Tv mycelium resulted in notable changes in activation markers on human monocytes and lymphocytes and influenced the profile of pro-inflammatory, anti-inflammatory, and antiviral cytokines[10]. Tv has consistently exhibited wide-ranging antiviral activity in numerous studies, including potent anti-influenza effects[12–14]. In comparative analyses across multiple mushroom species, Tv mycelium emerged as the most promising candidate for both anti-influenza and anti-herpetic applications, likely due to its strong therapeutic efficacy and low toxicity [15,16]. More broadly, in vivo treatment of honeybees with Tv mycelium resulted in a substantial reduction in viral titers, including a 75-fold decrease in Lake Sinai virus, indicating cross-species antiviral activity in a real-world animal model[8].

Agarikon (*Fomitopsis officinalis,* Fo [syn. *Laricifomes officinalis*]) is another polypore fungus with broad-spectrum antiviral, antibacterial, and immunomodulatory effects attributed to both mycelium and fruit bodies[17–19], demonstrating its medicinal potential[20].

Mycelial extracts of Fo neutralized influenza A viruses, including H5N1, *in vitro* and significantly reduced infectious viral titers at non-cytotoxic concentrations[21]. *In vitro* activity of Fo has been shown against a range of pathogens, including viruses such as HSV, H5N1, H3N2, and Orthopoxviruses[21–24], as well as bacteria such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*[23,25]. Complementing its antimicrobial and antiviral properties, triterpenoids from Fo also showed anti-inflammatory effects in RAW 264.7 murine macrophages and have elicited NF-κB mediated immune-engaging effects *in vivo* in a zebrafish cancer model[26–28].

Polypore fungi in the management of COVID-19

In the early stages of the COVID-19 pandemic, we explored ways to employ integrative medicine, particularly the use of fungi, as part of the management of COVID-19. One concept was to use mushroom mycelium as a vaccine adjunct to prevent the likelihood of contracting COVID-19[5], an approach that had been previously explored in humans for influenza B[29], and in the veterinary literature for other diseases[30–32]. Another was to employ fungi as a therapy to reduce the morbidity and mortality in individuals who contract COVID-19. Both approaches (prevention and therapy) would help society achieve herd immunity more quickly and with less harm. Given the early effectiveness of vaccines and the unprecedented pace (e.g., “Operation Warp Speed”) with which they were deployed, it quickly became apparent that vaccines rather than fungi would be become the primary focus of societal prevention efforts. Rather than study fungi as a preventive, we investigated the effects of fungi on active disease, focusing on the real-world need for effective treatments in infected individuals.

The primary objective of the current study was to examine, in patients with mild-moderate COVID-19 undergoing routine care, the effects of adjunctive oral treatment with FoTv versus Placebo. We hypothesized that treatment with FoTv would be:

H1: (a) safe and (b) feasible.

H2: associated with significantly fewer COVID-related symptoms and reduced symptom severity.

A secondary objective was to characterize the effects of FoTv (versus control) on inhibition of *in vitro* SARS-CoV-2 viral entry into cells. We further hypothesized:

H3: FoTv would inhibit viral entry into Vero-TMPRSS2 (mammalian epithelial) cells.

METHODS

Study Design

This was a 14-day, double-blind, placebo-controlled, dual-site randomized clinical trial. Food and Drug Administration (FDA) approval was obtained prior to recruitment and enrollment. Participants were recruited from University of California San Diego (UCSD) or University of California Los Angeles medical centers and their local communities and consented at UCSD. The trial protocol can be accessed at ClinicalTrials.gov, Identifier: NCT04667247[33] and this study adheres to CONSORT guidelines (see CONSORT Checklist).

Participants

Originally, a planned recruitment of 66 in total (53 complete cases) was estimated based on the number needed to assess safety and feasibility, which included a 20% dropout rate (estimated using RMASS)[34] for a model with one between and one within factor to provide minimum power of 80% to detect a medium effect size. Due to our low observed dropout rate (2%, see Results section) we were able to obtain a similar power with a total sample size of 50 participants. Sex was self-reported in response to an open-ended query.

Eligibility Criteria

Inclusion: (1) Diagnosed with COVID-19 within the prior 96 hours; (2) onset of symptoms within the prior 9 days; (3) 18 years or older.

Exclusion: (1) Known renal or liver failure; (2) acute symptoms that required hospitalization (3) current use of investigational agents to prevent or treat COVID-19; (4) prisoners; or (5) pregnant or breastfeeding women.

Participants were asked to minimize alcohol and cannabis use during the study period. Use of monoclonal antibodies, supplements, hydroxychloroquine, ivermectin, and vaccines were permitted throughout the study.

Randomization and Masking

After enrollment (Day 0), participants were randomly assigned in a 1:1 ratio to receive FoTv or Placebo starting on Day 1 (Figure 1). Prior to recruitment, the statistician (S.G.) created a randomization table using block sizes of 4 and 6 (SPSS software) and then randomization status was directly communicated to the pharmacist, who shipped the capsules to participants without direct communication. Only the statistician and pharmacist were unblinded to participant randomization. FoTv and Placebo capsules were visually identical and distributed in unlabeled containers.

Materials

FoTv consisted of dried FoTv mycelium and the fermented brown rice substrate on which it was cultivated, and inert Placebo of dried cooked organic brown rice. Fo and Tv mycelia were independently cultivated through solid state fermentation on an organic brown rice substrate. Each myceliated fermented substrate ingredient was frozen, dried, and milled into a powder before being combined evenly and encapsulated in 500-mg pullulan capsules to produce the FoTv formulation. FoTv and Placebo were developed, encapsulated to a cGMP standard, and provided by Fungi Perfecti, LLC, which was granted Investigational New Drug (IND) status and approved for study in a Phase I clinical trial by the FDA. As required by the FDA, certificates of analysis were obtained for Fo, Tv, and Placebo. Capsules were packaged and appeared identical to untrained study participants. FoTv/Placebo dosage was eight capsules three times daily (TID) for

14 consecutive days. The dosage was based on a prior study of effects of Tv on immune response[11] and was the regimen employed in a clinical trial of individuals who received FoTv as an adjunct to COVID-19 vaccination (Saxe et al. 2026). A treatment duration of 14 days was selected to minimize subject burden and maximize adherence, while timing delivery to the typical 1-2 week duration of COVID-19 symptoms at the time of study design[36].

Procedure

Participants in both groups received mobile phlebotomy services to collect blood samples on Day 0 and Day 14, provided mid-turbinate nasal swabs on Days 0, 7 and 14 (to assess viral load), and completed a daily symptom diary from Day 0-14 (Figure 1). Following the 14-day treatment period, follow-up phone calls were conducted on Days 28 and 58 to review symptoms and identify any emergency department or hospital visits. Compliance with study medication was monitored by a combination of daily diary, routine phone calls by the study team, and photo evidence of empty bottles at study completion.

Viral entry assay using SARS-CoV-2 spike-pseudotyped VSV

Viral entry was measured using a modified VSV that carried the SARS-CoV-2 spike (S) protein on its surface. This type of virus, a “pseudovirus”, is useful for studying viral entry because it can enter cells but is not able to complete a full round of virus

production on its own[37–39]. The virus also contained a *Renilla* luciferase (Rluc) reporter gene, which generated a light signal after the virus entered cells. This allowed viral entry to be measured by luminescence. Because the normal VSV glycoprotein gene was removed, the virus could undergo only a single round of infection and could not produce new infectious virus unless a glycoprotein (SARS-CoV-2 Spike) was provided in trans (i.e., externally sourced to create the pseudovirus).

For assay optimization, a range of pseudovirus input doses was tested to identify conditions that produced a reporter signal within the linear range of detection. For inhibition experiments, the selected amount of pseudovirus was incubated with FoTv at a final concentration of 0.01 mg/mL for 1 hour before infection. Because FoTv was dissolved in dimethyl sulfoxide (DMSO), an equivalent volume of DMSO alone was included as a vehicle control. As a validation control, we also included an uninfected control condition in which cells were incubated with plain media. The resulting pseudovirus mixtures were added to Vero-TMPRSS2 (mammalian epithelial) cells and incubated for 24 hours under standard culture conditions. After incubation, the cells were lysed and Rluc activity was measured according to the manufacturer's protocol (Promega Rluc Assay System). Luminescence was then read on a Tecan plate reader as an indicator of pseudovirus entry. Three independent replicates of each condition were performed.

Outcome Variables

Primary Objective: Randomized Clinical Trial

Safety: (1) Adverse event (hospitalizations; ER or urgent care visits) frequency across Days 1-14; and (2) markers of serum renal and hepatic function and of coagulation on Days 0 and 14. Participants were classified as having normal vs. abnormal renal function using markers including adjusted estimated glomerular filtration (eGFR)[40], as well as sodium, chloride, and blood urea nitrogen (BUN). Classification of normal vs. abnormal hepatic function was based on serum total protein, albumin, alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), and total bilirubin. Classification of normal vs. abnormal coagulation was based on prothrombin time, activated partial thromboplastin time (APTT), and international normalized ratio. Cutoff scores for normal vs. abnormal classifications appear in Supplemental Table 1.

Feasibility: (1) Completion rate at Day 14 (end of safety assessment period); and (2) Treatment Adherence= (capsules taken/assigned) * 100%.

Efficacy: (1) Primary serum inflammatory markers examined Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), as well as secondary COVID-19 disease markers troponin-T, lactate dehydrogenase (LDH), ferritin, and D-dimer, (2) SARS-CoV-2 viral load (polymerase chain reaction [PCR] cycle threshold value--a measure of detectable viral genetic material), and the (3) duration and severity of COVID-19 symptoms as assessed by daily questionnaires, were examined.

Participants were asked to rate their symptoms on a scale of 0 (none or absent) to 4 (very severe) across 12 symptoms commonly associated with COVID-19: fever, fatigue, muscle aches, shortness of breath, shortness of breath upon exertion, cough, sore throat, stuffy nose, runny nose, loss of taste, loss of smell, and headache. Symptom summary outcome measures were also computed for each day by (1) counting the total number of symptoms reported (Symptom Count), and (2) summing the severity ratings of all symptoms reported (Symptom Severity). Results for individual symptoms and symptom summary outcome measures are reported in Table 3 and Supplemental Table 2.

Secondary Objective: *In Vitro* Experiment

Vero-TMPRSS2 cells were lysed and *Renilla* luciferase activity was measured according to the manufacturer's instructions as a readout of viral entry. Luminescence values were used to quantify relative pseudovirus entry into cells.

Data Management and Analysis

Data were managed and statistical analyses performed by Krupp Center for Integrative Research (KCIR) biostatistics and data management core, using the KCIR Data System. Each participant was assigned a sequential participant number. Baseline group

demographic and clinical feature comparability was tested using Analysis of Variance and Chi-square analyses. Descriptive analyses assessed data distribution, normality, and homogeneity. Missing data and group dropout rate were examined for randomness. Data were analyzed in SPSS (v.28) using two-tailed statistical tests (differences considered statistically significant for p values <0.05).

Feasibility. Feasibility was determined by obtaining a minimum of 80% completion/adherence rates.

Safety. Linear mixed-effects (LME) analyses compared serum levels between one grouping factor (Treatment Group: FoTv vs. Placebo) across two timepoints (Days: 0 and 14). Differences between groups across days were examined using in terms of the percentage (±95% CI) of participants transitioning from a normal serum level of each marker on Day 0 to an abnormal level on Day 14.

Efficacy. Efficacy analysis used linear mixed-effects (LME) analyses. The first set of efficacy analyses compared serum levels of inflammatory markers between one grouping factor Treatment Group (FoTv vs. Placebo) across two timepoints (Days: 0 and 14). The second efficacy analysis compared SARS CoV-2 Viral Load between one grouping factor Treatment Group (FoTv vs. Placebo) across three timepoints (Days: 0, 7, and 14). The third set of efficacy analyses compared symptoms between one grouping factor (Treatment Group: FoTv vs. Placebo) across 15 timepoints (Days: 0-

14). The main effects of Group, Day, and the Group by Day interaction were examined for each analysis.

The standards for serum levels for five serum outcomes (total protein, sodium, BUN, ferritin, and D-dimer) were different across the two recruitment sites. For these outcomes, data were z-transformed prior to mixed-effects analyses.

Exploratory analyses were carried out to examine whether vaccination status (vaccinated vs unvaccinated) was associated with symptom outcomes. We first examined whether there was a significant Group (FoTv/Placebo) by Vaccination Status (vaccinated/unvaccinated) by Day (Days 0-14) interaction. Because of the small sample size of the unvaccinated group (5 FoTv, 7 Placebo) no mixed-model follow-up analyses were conducted. Instead, we carried out descriptive follow-up analyses that examined the Symptom Count (and Severity) averaged across Days 0-14, and also identified the study day (Days 1-14) on which Symptom Count (and Severity) had decreased by 50% compared to Day 0.

In vitro luminescence data were analyzed using Analysis of Variance comparing FoTv to DMSO on three independent biological samples. Data from the uninfected condition are also shown.

RESULTS

Sample Characteristics

Participants were enrolled between December 2020 and March 2022, with the last follow-up visit in August 2022. Fifty participants were enrolled, 26 receiving FoTv and 24 Placebo (Figure 1, Figure 2). Mean participant age was 45.4 ± 14.4 years. Participants were: 64% female, 84% Caucasian, 6% Asian, 8% other race; 26.5% reported Hispanic ethnicity.

At baseline (Day 0), there were no significant differences between FoTv and Placebo groups in demographic or clinical characteristics, presence of cardiovascular disease, hypertension, or diabetes, or the number of days between symptom onset and start of treatment (Day 1), indicating effectiveness of the randomization procedure (Table 1).

The means of the two groups were not significantly different at baseline with regard to any laboratory data, except for BUN ($F_{(1,49)} = 4.222$, $p = 0.045$), which was significantly higher in the Placebo than the FoTv group (Table 2).

Nevertheless, some participants had abnormal baseline markers of hepatic (Total Protein [four FoTv participants, one Placebo participant]; Albumin [one FoTv, two Placebo], ALP [three FoTv and one Placebo], AST [two FoTv, zero Placebo], and ALT [one FoTv, three Placebo]) or renal function (eGFR [two FoTv, 11 Placebo], Sodium [three FoTv, zero Placebo], Chloride [three FoTv, one Placebo], BUN [four FoTv, two

Placebo]). Additionally, some participants had abnormal markers for coagulation (Prothrombin Time [two FoTv and two Placebo] and APTT [four FoTv and four Placebo]).

At baseline, mean viral load was 15.3 cycle threshold in the FoTv group and 14.9 cycle threshold in the Placebo group, demonstrating a high viral load in the population, as well as matched viral load across groups ($F_{(1,41)} = 0.056$, $p = 0.814$) (Table 3).

Feasibility

Feasibility analyses examined 186 participants for eligibility, of whom 132 were excluded and 54 enrolled with 28 originally randomized to FoTv and 26 to Placebo (Figure 2). In the Placebo group, one participant was lost to follow-up (on Day 1). In the FoTv group, none were lost to follow-up. Analysis of SARS-CoV-2 viral levels indicated that three participants did not have, or had already recovered from, COVID-19 upon enrollment (2 FoTv; 1 Placebo), so these participants were excluded from analysis. From the 51 (26 FoTv, 25 Placebo) remaining participants, 98.8% completed Days 0-14 (26 FoTv [100%], 24 Placebo [96%]). All participants who completed Day 14 also completed the Day 58 follow-up (Figure 1). Treatment Adherence was high (96.1% ± 5.1%, CI: 94.7-97.6%); and similar for FoTv (96.9% ± 4.7%, CI: 95.0-98.8%) and Placebo (95.3% ± 5.6%, CI: 93.0-97.7%).

Safety

Sentinel Study Required by FDA

The FDA required close monitoring of the first six participants due to concern that polypore fungi (known to modify immune response) might inadvertently trigger cytokine storm, a sudden, inexplicable, severe, and potentially life-threatening immune response to infection that had been observed early in the course of the COVID-19 pandemic[41]. No indications of cytokine storm were observed in these participants.

Adverse Events

No hospitalizations were reported in either group during the 14-day study period or across the 28- and 58-day follow-ups.

Out of the four participants with hypertension in the Placebo group, one reported abnormal blood pressure on Days 7 and 12. The one individual with hypertension in the FoTv group reported abnormal hypertension on Days 2 to 6 and 8 to 14. Four participants had hyperglycemia; the single participant in the FoTv group experienced no deviations outside of the normal range, whereas one of the three participants in the Placebo group had abnormal glucose at the baseline visit.

Renal Function, Hepatic Function, and Coagulation

There were no statistically significant differences between FoTv and Placebo groups from Day 0 to Day 14 for measures of hepatic or renal function or coagulation, except for adjusted eGFR ($F_{(1,45)} = 7.186$, $p = 0.010$), which exhibited a significant Group by

Day interaction (Table 2). Follow-up tests revealed that eGFR significantly decreased across days in the FoTv group ($F_{(1,22)}$ = 5.327, p = 0.031), but not in the Placebo group ($F_{(1,23)}$ = 1.697, p = 0.206). Notably, there were no group differences in these eGFR levels at Day 0 or Day 14 (p values > 0.114).

We also examined whether the groups differed in the proportion of participants that transitioned from normal to abnormal from Day 0 to Day 14 (versus those that remained normal on both days). Importantly, there were overlapping CIs for the percentage of participants in each group transitioning from normal to abnormal function across this timeframe for both hepatic and renal function, as well as for coagulation (Table 2).

Efficacy

Inflammatory Markers

Considering the primary inflammatory markers, CRP, but not ESR, exhibited a significant difference between FoTv and Placebo groups across Days (Table 3). Follow-up tests revealed that CRP levels significantly decreased across days for the FoTv group ($F_{(1,25)}$ = 11.735, p = 0.002), but not the Placebo group ($F_{(1,23)}$ = 3.831, p = 0.063). The levels were similar across the groups at both Day 0 and Day 14 (p values > 0.115). Among inflammatory markers associated with COVID-19 risk, both Troponin-T and Ferritin exhibited a significant difference between FoTv and Placebo groups across Days (Table 3). Troponin-T levels significantly increased across days for the FoTv group ($F_{(1,28)}$ = 7.216, p = 0.012), but not the Placebo group ($F_{(1,31)}$ = 0.508, p = 0.482).

Ferritin levels significantly decreased across days for the Placebo group ($F_{(1,23)}$ = 8.750, p = 0.007), but not the FoTv group ($F_{(1,27)}$ = 0.000, p = 0.993). The levels were similar across the groups at both Day 0 and Day 14 (p values > 0.080).

SARS-CoV-2 Viral Load

There were no statistically significant differences between FoTv and Placebo groups across days for SARS-CoV-2 viral load (Days 0, 7, and 14) (see Group by Day Effect in Table 3). SARS-CoV-2 viral loads consistently declined across the study period (Day Effect: $F_{(1,89)}$ = 270.303, p < 0.001) and there were no significant differences between the groups (Group main effect, $F_{(1,116)}$ = 0.468, p=0.495; Table 3, Figure 3B). There were also no significant differences between the groups at Day 0, 7, or 14 (all p values > 0.088; Figure 3B).

COVID-19 Symptom Scores

There were significant Group by Day (Days 0-14) interactions for Symptom Severity and Symptom Count (Table 3, Supplemental Table 2). In both cases, lower symptom severities ($F_{(1,697)}$=16.560, p < 0.001), and counts ($F_{(1,697)}$=7.835, p = 0.005), were observed in the FoTv relative to the Placebo group (see Figure 3A for Symptom Count). Among the 12 COVID-19 symptoms, the severity of the following symptoms exhibited reductions evidenced by significant effects of Group or Group by Day interactions: sore throat, cough, muscle aches, headache, stuffy nose, and runny nose (Table 3 and Supplemental Table 2). Among these, particularly strong effects were observed for sore

throat ($F_{(1,697)}$=46.928, p < 0.001), cough ($F_{(1,697)}$=18.931, p < 0.001), and muscle aches ($F_{(1,697)}$=10.826, p = 0.001).

Exploratory analyses examining the Group (FoTv/Placebo) by Vaccination Status (vaccinated/unvaccinated) by Day (Days 0-14) interaction revealed a strong trend for both Symptom Count ($F_{(2,695)}$ = 2.917, p = 0.055) and Symptom Severity ($F_{(2,695)}$ = 2.829, p = 0.060)(Supplemental Figure 1). These findings should be interpreted with caution because of the small sample size of the unvaccinated group (5 FoTv, 7 Placebo). Thus, instead of mixed-model follow-up analyses, we carried out descriptive follow-up analyses. For Symptom Count, the vaccinated FoTv group exhibited 0.79 fewer symptoms than Placebo, and the unvaccinated FoTv group exhibited 0.92 fewer symptoms than Placebo. The findings were similar for Symptom Severity (0.84 and 0.93, respectively). For Symptom Count, the vaccinated FoTv group reached ≥50% reduction 0.9 days earlier than Placebo, whereas the unvaccinated FoTv group reached ≥50% reduction 5.1 days earlier than Placebo. The findings were similar for Symptom Severity (0.7 and 3.1 days, respectively).

In Vitro Experiment

We observed that Vero-TMPRSS2 cells bathed in media containing FoTv in DMSO (N=3, 91002±7451 relative light units; RLU) exhibited significantly reduced relative luminescence units ($F_{(1,4)}$ = 22.395, p = 0.009), compared to cells bathed in media containing the same concentration of DMSO, as a negative control (N=3,161933±24868 RLU), suggesting that FoTv reduced viral entry into the cells (see Figure 3C).

DISCUSSION

This study addressed whether FoTv, a natural fungal product composed of polypore mushroom mycelia on a fermented brown rice substrate, could serve as a safe and effective therapeutic as an adjunct to standard COVID-19 care. Use of FoTv during active COVID-19 infection was safe and feasible. Aside from modest between-group mean differences in serum levels of adjusted eGFR (renal function), FoTv and Placebo serum levels of hepatic function, renal function, and coagulation were equally likely to transition from normal to abnormal levels across the treatment period (Table 2). Viral loads were similar for the FoTv and Placebo groups across the treatment period, although analyses could not distinguish between active and inactive viral genetic material (Table 3, Figure 3B). Notably, several inflammatory markers significantly changed across this period for the FoTv group, but not the Placebo group (Table 3). Finally, symptom severity and burden were significantly lower in the FoTv group than in the Placebo group (Table 3, Figure 3A), with exploratory analyses suggesting that FoTv reduced symptom count and severity for both vaccinated and unvaccinated participants. In parallel, we found that FoTv inhibited pseudotyped SARS-CoV-2 entry into cells, suggesting that direct antiviral activity may have contributed to the observed clinical benefits.

Although adjusted eGFR significantly decreased in the FoTv group from Day 0 to Day 14, mean values for both groups at both time points were well within the normal range

for renal function (> 60 mL/min; Supplemental Table 1), with Day 14 mean adjusted eGFRs of 104.28 and 103.87 for FoTv and Placebo groups, respectively (Table 2). Across the treatment period, participants in the FoTv group were no more likely to transition from normal to abnormal eGFR than were participants in the Placebo group (see overlapping confidence intervals in Table 2). Finally, concordant findings of FoTv's safety were reported in a study of healthy individuals who took FoTv over a 4-day treatment period as an adjunct to COVID-19 vaccination[5]. Nevertheless, for participants with an active infection, caution should be employed when using FoTv at this dosage for a timeframe longer than 14 days. Future studies with longer treatment periods (and possibly lower dosage regimens) and in other patient populations and disease settings may be warranted.

In the early days of the COVID-19 pandemic, it was observed that SARS-CoV-2 infection could suddenly and inexplicably trigger cytokine storm (signal event). Cytokine storm is a severe and potentially life-threatening immune overreaction to infection. While intended to clear the virus, it may cause a hyper-inflammatory state, marked by a failure to switch from innate to adaptive immunity, resulting in damage to tissue, hampered viral clearance, and higher and more persistent viral loads[42]. Given that the risk for cytokine storm may be higher in those with a seemingly more robust (but arguably hyperactive or dysregulated) immune response, the known immune-enhancing effects of fungal polysaccharides raised the concern that the possible therapeutic use of fungi might inadvertently trigger this event[41]. For this reason, the FDA requested that a sentinel study of the first six participants be conducted to rule out this possibility before

continuing enrollment. No indication of cytokine storm was observed in these six individuals nor in any subsequently enrolled individuals. We also did not find any significant group differences in viral levels across the treatment period, and viral levels significantly and continuously declined for both groups. Moreover, a clinical trial of COVID-19 patients found a fungal-derived treatment could actually decrease inflammatory markers IL-6 and D-dimer[43]. This idea is reinforced by the fact that polypore fungi contain various bioactive peptides[44] which can regulate cytokine responses, enhancing the shift from innate to adaptive immunity, thereby optimizing the overall immune response[45]. In further contrast to this earlier speculative concern about fungal treatments inducing an inflammatory cytokine storm, the FoTv group exhibited a significant reduction in CRP, a general inflammatory marker, as well as a numerical decrease in ESR. Because the Placebo group did not exhibit a significant decrease in CRP, it appears that FoTv may in fact have decreased inflammation (a hallmark of immune dysregulation) rather than triggered it.

The FoTv group exhibited significantly fewer (and less severe) COVID-19 symptoms across the study period versus Placebo. The symptoms most significantly reduced in severity were cough, sore throat, runny nose, stuffy nose, muscle aches, and headache (which all have an inflammatory component). Among symptoms of COVID-19, FoTv's effect on cough was one of the most statistically significant. This is notable because cough is the primary driver of person-to-person viral transmission, due to its unique ability to forcefully expel viral particles in high concentrations, with particles travelling further and remaining in the air longer (vs. breathing or talking)[46,47].

Although the study was not designed to examine symptom effects according to vaccination status, we observed that both vaccinated and unvaccinated participants who received FoTv (vs. Placebo) exhibited a reduction in symptoms, with a strong trend suggesting a more robust effect of FoTv in the unvaccinated group. Moreover, the unvaccinated FoTv group (vs. Placebo) exhibited a faster, though not statistically significant, reduction in symptoms compared with the vaccinated FoTv group, although the small subsample sizes prevented formal statistical analysis of these effects. These findings may have public health significance as they suggest FoTv might serve both as a suitable treatment for viral infection and method for reducing person-to-person transmission, at a time when vaccines may not yet be broadly available or may not be accepted by some individuals.

Given that FoTv also appears to reduce vaccine-related side effects when used as an adjunct to COVID-19 vaccines (Pfizer, Moderna, Johnson & Johnson[5], FoTv appears to have the ability to reduce symptoms of immune response to active viral infection as well as induced viral challenge. If these effects are not specific to SARS-CoV-2 and COVID-19 vaccination and were to be applied generally to other infectious diseases and vaccinations, FoTv might potentially have even broader public health impact. Given the increased concerns about the H5N1 bird flu contagion, more research is warranted to explore these possible benefits.

In contrast with the significant differences in symptoms between the FoTv and Placebo groups, these groups did not exhibit any differences over time in SARS-CoV-2 viral RNA levels according to nasal swab PCR. However, because PCR only measures total viral RNA, it cannot distinguish infectious from noninfectious viral material, making it difficult to determine whether FoTv may have reduced viral infectivity without substantially altering RNA levels. This distinction is particularly relevant because the FoTv group showed reduced clinical burden (Figure 3A) despite no apparent difference in nasal swab viral RNA levels (Figure 3B). It is also consistent with prior reports that both Fo and Tv exhibit antiviral activity against other live viruses, including influenza A subtypes H5N1 and H3N2[8,15,16,21,22]. We therefore tested FoTv in an *in vitro* assay, where it significantly reduced infection by SARS-CoV-2 pseudovirus in cells (Figure 3C). In contrast to the similar viral RNA measurements observed in nasal swabs for FoTv and Placebo groups, the *in vitro* results support antiviral activity of FoTv and raise the possibility that some of its clinical effects may have involved reduction of infectious virus not detected by PCR testing alone. Future clinical trials incorporating plaque assays or other infectivity-based methods will likely be needed to determine whether FoTv reduces infectious SARS-CoV-2 or other viruses in humans.

There are numerous reasons why fungal mycelial products like FoTv may be practical for widespread, standardized use as adjuncts to standard care COVID-19 and other viral diseases fungi: [1] are chemically complex and biosynthesize numerous compounds and may work synergistically to address several elements of viral infection through both innate and adaptive immune responses; [2] may constitute a safe, natural,

sustainable, scalable, low-cost, and feasible treatment to mitigate symptoms; and [3] allow for rapid and high-volume production because the technology employs existing infrastructure for aseptic cultivation using solid-state fermentation. Population-scale medical use of mushroom fruit bodies is likely infeasible due to impracticality of controlled cultivation, potential for contamination with insects and microorganisms[48], and concerns about overharvesting, particularly of agarikon, which has been listed as Endangered by the International Union for Conservation of Nature[49]. In contrast, industrial production of mycelia from fungi, such as Fo and Tv, is a realizable, standardizable, and scalable strategy for population-level treatment of viral diseases with pandemic potential.

This study had several limitations warranting discussion. First, while we selected a particular dosage and duration, alternate regimens might have resulted in different effects on symptoms and other outcomes. Second, the rapidly changing nature of the COVID-19 pandemic and administrative delays that followed delayed the start of the study to a time that was less advantageous for identifying FoTv's effect on morbidity from COVID-19. Specifically, the protocol was designed in March 2020, when COVID-19 hospitalization rates up to 26% were reported[50]; however, recruitment only began after the winter 2020/2021 COVID-19 peak and initial vaccine deployment, preventing in-depth examination of the effects of FoTv on COVID-19 illness itself, including important outcomes such as hospitalization rate and ER visits. Had the study been launched earlier, more unvaccinated patients infected with the higher-morbidity SARS-CoV-2 Alpha variant may have been recruited, and thus FoTv treatment might have

demonstrated even greater reductions in symptom count and severity, as well as ER visits and hospitalizations. Finally, even though we employed *in vitro* methods that are standard in the field, we tested FoTv on cells infected with a SARS-CoV-2/vesicular stomatitis virus (VSV) pseudotyped virus (rather than SARS-CoV-2 itself) and this test was conducted on non-human mammalian cells. And, as is the case with all cell culture research, our *in vitro* findings may not generalize to humans.

Conclusions

In this FDA-approved double-blind, placebo-controlled, randomized clinical trial, treatment with polypore mushroom mycelia significantly reduced the number and severity of symptoms of acute COVID-19. FoTv, a combination of agarikon and turkey tail mycelia, was shown to be a safe, well-tolerated, feasible, and practical means of mitigating symptoms associated with SARS-CoV-2 viral infection. The same degree of symptom reduction was observed regardless of vaccination status (perhaps with a greater and more rapid reduction in unvaccinated participants), possibly reducing the need for ER/hospital visits, and specifically in symptoms that typically contribute to the spread of virus (cough, sore throat, and runny nose). These findings suggest that, in the event of a future viral pandemic, FoTv might both provide an effective therapeutic in the absence of any proven pharmaceutical or other treatments and help break the chain of transmission by reducing the spread of viral particles through coughing. Moreover, polypore or polypore-like fungi also appear to be effective adjuncts to COVID-19 vaccination in humans[5] and influenza A/H5N1 vaccination in mice[30]. Therefore, FoTv's

potential as a therapeutic for active COVID-19 infection adds to these prior vaccination findings and raises the intriguing possibility that FoTv or other polypore (or polypore-like) fungi could also serve as adjuncts to vaccines for viruses beyond SARS-CoV-2. These could potentially include influenza A viruses such as human H3N2 and avian H5N1. Future studies of FoTv may explore different dosing regimens and durations in the treatment of COVID-19 or other viral diseases with pandemic potential where vaccinations may not be available or acceptable by significant portions of the population.

ARTICLE INFORMATION

Conflict of Interest Disclosures: None.

Funding/Support: Funding: This work was supported by a grant from the University of California San Diego (UCSD) Krupp Endowed Fund to Dr. Saxe for the MACH-19 (Mushrooms and Chinese Herbs for COVID-19) studies[33]. Dr. Saxe serves on the board of the Krupp Endowed Fund but was recused from decision-making regarding this grant award. We would also like to acknowledge the generous support provided by the following donors: Jonathan and Kathleen Altman Foundation (financial support), Fungi Perfecti, LLC (financial and material [encapsulated FoTv and Placebo for the MACH-19 studies] support), Sacharuna Foundation (financial support), Jesy Foundation (financial support), and Texas Instruments Foundation (financial support).

Role of the Funder/Sponsor: None of the funders listed above were involved with design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Authors from Fungi Perfecti, LLC assisted only with mycology-related literature review and writing.

Disclaimer: None.

Data Sharing Statement: Data are available upon request from the corresponding author.

Authors' Contributions: GS, AS, SG, SW, and HAC contributed to conceptualization; SG, TS, PS, NG, and DB contributed to data curation; SG and CNS carried out the formal analysis; GS and LM contributed to funding acquisition; TS, PS, and SG

contributed to investigation; GS, SG, AS, LK, DB, and HAC contributed to methodology; TS, AS, PS, LM, and GS contributed project administration; TS, SG, PS, and RD contributed resources; SG contributed software; GS, TS, AS, LM, and DS supervised the work; SG and CNS validated the data; CNS, GS, and DB contributed to visualization; GS, CNS, AS, ZB, CB, DB, and HAC wrote the original draft; and all authors contributed to reviewing and editing the final draft.

Acknowledgements: We are thankful for the visionary and pioneering work of Paul Stamets, whose contributions were critical to the development of the MACH-19 studies. We would also like to acknowledge Lee Stein, Esq., whose advocacy and encouragement made the MACH-19 studies possible.

Ethics approval and consent to participate: Written informed consent was obtained for all patients included in this clinical trial. This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the UCSD Institutional Review Board: 200633-1a.

Consent for publication: Not applicable.

Competing Interests: The authors declare no competing interests.

References

1. Xie, Z. *et al.* Clade 2.3.4.4b highly pathogenic avian influenza H5N1 viruses: knowns, unknowns, and challenges. *J Virol* **99**, e00424-25 (2025).
2. DeWeerdt, S. Could tracking animals' health help to avert the next pandemic? *Nature* d41586-025-03602–7 (2025) doi:10.1038/d41586-025-03602-7.
3. Capelastegui, F. & Goldhill, D. H. H5N1 2.3.4.4b: a review of mammalian adaptations and risk of pandemic emergence. *Journal of General Virology* **106**, (2025).
4. Webby, R. J. & Uyeki, T. M. An Update on Highly Pathogenic Avian Influenza A(H5N1) Virus, Clade 2.3.4.4b. *The Journal of Infectious Diseases* **230**, 533–542 (2024).
5. Saxe, G. *et al.* Polypore mushroom mycelia as an adjunct to COVID-19 vaccination: a randomized clinical trial. *BMC Immunol* **27**, 24 (2026).
6. Eliza, W. L. Y., Fai, C. K. & Chung, L. P. Efficacy of yun zhi (*Coriolus versicolor*) on survival in cancer patients: Systematic review and meta-analysis. *Recent Pat Inflamm Allergy Drug Discov* **6**, 78–87 (2012).
7. Arunachalam, K., Sasidharan, S. P. & Yang, X. A concise review of mushrooms antiviral and immunomodulatory properties that may combat against COVID-19. *Food Chem Adv* **1**, 100023 (2022).
8. Stamets, P. E. *et al.* Extracts of Polypore Mushroom Mycelia Reduce Viruses in Honey Bees. *Sci Rep* **8**, 13936 (2018).

9. Davis, R. *et al.* Differential immune activating, anti-inflammatory, and regenerative properties of the aqueous, ethanol, and solid fractions of a medicinal mushroom blend. *J Inflamm Res* **13**, 117–131 (2020).
10. Benson, K. F. *et al.* The mycelium of the *Trametes versicolor* (turkey tail) mushroom and its fermented substrate each show potent and complementary immune activating properties in vitro. *BMC Complement Altern Med* **19**, (2019).
11. Torkelson, C. J. *et al.* Phase 1 clinical trial of *Trametes versicolor* in women with breast cancer. *ISRN Oncol* **2012**, (2012).
12. Ng, T. B., Wang, H. & Wan, D. C. C. Polysaccharopeptide from the Turkey Tail Fungus Trametes versicolor (L.:Fr.) Pilát Inhibits Human Immunodeficiency Virus Type 1 Reverse Transciptase and Protease. *Int J Med Mushr* **8**, 39–43 (2006).
13. Shi, Z. T., Bao, H. Y. & Feng, S. [Antitumor activity and structure-activity relationship of seven lanostane-type triterpenes from Fomitopsis pinicola and F. officinalis]. *Zhongguo Zhong Yao Za Zhi* **42**, 915–922 (2017).
14. Camilleri, E. *et al.* A comprehensive review on the health benefits, phytochemicals, and enzymatic constituents for potential therapeutic and industrial applications of Turkey tail mushrooms. *Discov Appl Sci* **6**, 257 (2024).
15. Shi, S. *et al.* β-Glucans from Trametes versicolor (L.) Lloyd Is Effective for Prevention of Influenza Virus Infection. *Viruses* **14**, 237 (2022).
16. Krupodorova, T., Rybalko, S. & Barshteyn, V. Antiviral activity of Basidiomycete mycelia against influenza type A (serotype H1N1) and herpes simplex virus type 2 in cell culture. *Virol. Sin.* **29**, 284–290 (2014).

17. Altannavch, N. *et al.* Anti-oxidant and Anticancerous Effect of Fomitopsis officinalis (Vill. ex Fr. Bond. et Sing) Mushroom on Hepatocellular Carcinoma Cells In Vitro through NF-kB Pathway. *Anticancer Agents Med Chem* **22**, 1561–1570 (2022).
18. Elkhateeb, W. A., Daba, G. M., Elnahas, M. O. & Thomas, P. W. *Fomitopsis officinalis* mushroom: Ancient gold mine of functional components and biological activities for modern medicine. *Egypt Pharmaceut J* **18**, 285 (2019).
19. Karunarathna, S. C., Patabendige, N. M., Kumla, J., Hapuarachchi, K. K. & Suwannarach, N. The bioactive compounds, beneficial medicinal properties, and biotechnological prospects of Fomitopsis: a comprehensive overview. *Front. Cell. Infect. Microbiol.* **15**, 1534617 (2025).
20. Fijałkowska, A. *et al.* Medicinal potential of mycelium and fruiting bodies of an arboreal mushroom Fomitopsis officinalis in therapy of lifestyle diseases. *Sci Rep* **10**, 20081 (2020).
21. Teplyakova, T. V. *et al.* Antiviral activity of polyporoid mushrooms (higher basidiomycetes) from Altai Mountains (Russia). *Int J Med Mushrooms* **14**, 37–45 (2012).
22. Stamets, P. Antipox properties of *Fomitopsis officinalis* (Vill.: Fr.) Bond. et Singer (agarikon) from the Pacific Northwest of North America. *Int J Med Mushrooms* **7**, 495–506 (2005).
23. Girometta, C. Antimicrobial properties of *Fomitopsis officinalis* in the light of its bioactive metabolites: a review. *Mycology* **10**, 32–39 (2019).
24. Teplyakova, T. & Kosogova, T. Fungal bioactive compounds with antiviral effect. *J Pharm Pharmacol* **3**, 357–371 (2015).

25. Hwang, C. H. *et al.* Chlorinated coumarins from the polypore mushroom *Fomitopsis officinalis* and their activity against *Mycobacterium tuberculosis*. *J Nat Prod* **76**, 1916–1922 (2013).
26. Liu, W. *et al.* A fungal polysaccharide from Fomitopsis officinalis as a multi-target molecule to combat cancer. *International Journal of Biological Macromolecules* **272**, 132543 (2024).
27. Shen, Y. *et al.* An antitumor fungal polysaccharide from Fomitopsis officinalis by activating immunity and inhibiting angiogenesis. *Int J Biol Macromol* **267**, 131320 (2024).
28. Han, J. *et al.* Lanostane triterpenoids from the fruiting bodies of *Fomes officinalis* and their anti-inflammatory activities. *Molecules* **25**, 4807 (2020).
29. Roman, B. E., Beli, E., Duriancik, D. M. & Gardner, E. M. Short-term supplementation with active hexose correlated compound improves the antibody response to influenza B vaccine. *Nutrition Research* **33**, 12–17 (2013).
30. Ichinohe, T. *et al.* Induction of cross-protective immunity against influenza A virus H5N1 by an intranasal vaccine with extracts of mushroom mycelia. *Journal of Medical Virology* **82**, 128–137 (2010).
31. Engel, A. L. *et al.* Protein-bound polysaccharide activates dendritic cells and enhances OVA-specific T cell response as vaccine adjuvant. *Immunobiology* **218**, 1468–1476 (2013).
32. Gao, W. *et al.* Mushroom lectin enhanced immunogenicity of HBV DNA vaccine in C57BL/6 and HBsAg-transgenic mice. *Vaccine* **31**, 2273–2280 (2013).

33. Saxe, G. *Multicenter Double Blind, Placebo Controlled RCT of Fomitopsis Officinalis and Trametes Versicolor to Treat COVID-19*. https://clinicaltrials.gov/study/NCT04667247 (2024).
34. Hedeker, D., Gibbons, R. D. & Waternaux, C. Sample Size Estimation for Longitudinal Designs with Attrition: Comparing Time-Related Contrasts Between Two Groups. *Journal of Educational and Behavioral Statistics* **24**, 70–93 (1999).
35. Saxe, G. *et al.* Polypore Mushroom Mycelia as an Adjunct to COVID-19 Vaccination: A Randomized Clinical Trial. Preprint at https://doi.org/10.1101/2025.06.06.25327723 (2025).
36. Wang, D. *et al.* Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. *Crit Care* **24**, 188 (2020).
37. Aguilar, H. C. *et al.* N-Glycans on Nipah Virus Fusion Protein Protect against Neutralization but Reduce Membrane Fusion and Viral Entry. *J Virol* **80**, 4878–4889 (2006).
38. Aguilar, H. C. *et al.* Polybasic KKR Motif in the Cytoplasmic Tail of Nipah Virus Fusion Protein Modulates Membrane Fusion by Inside-Out Signaling. *J Virol* **81**, 4520–4532 (2007).
39. Ezzatpour, S. *et al.* Broad-spectrum synthetic carbohydrate receptors (SCRs) inhibit viral entry across multiple virus families. *Sci. Adv.* **11**, eady3554 (2025).
40. National Kidney Foundation. National Kidney Foundation. https://www.kidney.org/ckd-epi-creatinine-equation-2021-0 (2024).

41. Alschuler, L. *et al.* Integrative considerations during the COVID-19 pandemic. *Explore (NY)* **16**, 354–356 (2020).
42. Hiti, L. *et al.* The immunopathogenesis of a cytokine storm: The key mechanisms underlying severe COVID-19. *Cytokine & Growth Factor Reviews* **82**, 1–17 (2025).
43. Raghavan, K. *et al.* Beneficial effects of novel *Aureobasidium pullulans* strains produced beta-1,3-1,6 glucans on interleukin-6 and D-dimer levels in COVID-19 patients; results of a randomized multiple-arm pilot clinical study. *Biomed Pharmacother* **145**, 112243 (2022).
44. Li, H., Gao, J., Zhao, F., Liu, X. & Ma, B. Bioactive peptides from edible mushrooms-the preparation, mechanisms, structure-activity relationships and prospects. *Foods* **12**, 2935 (2023).
45. Nicholls, E. F., Madera, L. & Hancock, R. E. W. Immunomodulators as adjuvants for vaccines and antimicrobial therapy. *Annals of the New York Academy of Sciences* **1213**, 46–61 (2010).
46. Schijven, J. *et al.* Quantitative Microbial Risk Assessment for Airborne Transmission of SARS-CoV-2 via Breathing, Speaking, Singing, Coughing, and Sneezing. *Environ Health Perspect* **129**, 047002 (2021).
47. Reyes, J., Stiehl, B., Delgado, J., Kinzel, M. & Ahmed, K. Human Research Study of Particulate Propagation Distance From Human Respiratory Function. *The Journal of Infectious Diseases* **225**, 1321–1329 (2022).
48. Videv, P. V., Gartner, G., Uzunov, B. A., Dimitrova, P. H. & P.Stoyneva-Gartner, M. Epimycotic Algae on the Medicinal Fungus Trametes Versicolor(L.) Lloyd. *International Journal of Advanced Research in Botany* **3**, 18–26 (2017).

49. Kałucka, I. L. & Svetasheva. *Fomitopsis Officinalis (Vill.) Bondartsev & Singer. The IUCN Red List of Threatened Species 2019*. (2019).

50. Thompson, C. N. COVID-19 Outbreak — New York City, February 29–June 1, 2020. *MMWR Morb Mortal Wkly Rep* **69**, (2020).

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	FoTv	Placebo			
	Mean/Count (SD/%)		Statistic	df	p value
Number of Participants	26	24			
Age	43.3 (11.1)	47.7 (17.3)	1.188	1,48	0.281
Body Mass Index	25.8 (5.1)	25.7 (5.3)	0.002	1,45	0.964
Sex (female)	16 (61.5%)	16 (66.7%)	0.142	1	0.706
Race			2.352	3	0.503
Asian	3 (11.5%)	1 (4.2%)			
Caucasian	20 (76.9%)	22 (91.7%)			
African	1 (3.8%)	0 (0.0%)			
Other	2 (7.7%)	1 (4.2%)			
Ethnicity					
Hispanic	7 (28.0%)	6 (25.0%)	0.057	1	0.812
Past Medical History					
Cardiovascular Illness	1 (4.0%)	1 (5.0%)	0.026	1	1.000
Diabetes Mellitus	0 (0%)	3 (15.0%)	4.018	1	0.080
Hypertension	1 (4.0%)	4 (20.0%)	2.880	1	0.155*
COVID-19 status					
Vaccinated	23 (88.5%)	17 (70.8%)	2.424	1	0.164*
Use of MAT	2 (7.7%)	1 (4.2%)	0.297	1	0.862*
Days to enrollment	5.5 (1.7)	5.8 (1.8)	0.428	1,48	0.516

Note. Statistic refers to χ^2 for categorical variables and F value (ANOVA) for continuous variables. *Due to the small sample size for cells in these analyses, probability values for Fischer's exact tests are reported in lieu of chi-squared tests. MAT, monoclonal antibody treatment.

Table 2. Serum Safety Findings at Day 0 (baseline) and at Day 14

	Comparison of Laboratory Data across Groups and Days					Percentage Transitioning from Normal to Abnormal Function from Day 0 to Day 14			
	Day 0		Day 14		Group by Day Effect	FoTv		Placebo	
	FoTv	Placebo	FoTv	Placebo					
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value	%	95% CI	%	95% CI
Hepatic Function									
Total Protein[1]	0.24 (0.90)	-0.03 (1.07)	0.06 (0.82)	-0.29 (0.87)	0.417	0	0.0-15.4	0	0.0-14.8
Albumin	4.57 (0.36)	4.52 (0.27)	4.64 (0.29)	4.56 (0.29)	0.690	4.0	0.1-20.4	0	0.0-14.8
Alkaline Phosphatase	75.64 (38.58)	76.29 (22.89)	68.50 (20.09)	77.54 (19.80)	0.109	0	0.0-14.2	0	0.0-14.8
AST	23.50 (7.81)	22.92 (6.41)	20.73 (4.94)	20.54 (4.40)	0.841	0	0.0-13.7	0	0.0-14.2
ALT	28.15 (21.75)	22.92 (10.90)	22.62 (11.88)	19.79 (7.16)	0.612	4.3	0.1-21.9	0	0.0-14.8
Total Bilirubin	0.42 (0.19)	0.37 (0.13)	0.55 (0.24)	0.42 (0.19	0.174	0	N/A	0	N/A
Renal Function									
Adjusted eGFR	111.94 (20.47)	101.73 (22.89)	104.28 (20.42)	103.87 (21.26)	0.010	28.6	11.3-52.2	0	0.0-23.2
Sodium[1]	-0.11 (1.19)	-0.06 (1.02)	-0.26 (0.91)	0.46 (0.68)	0.063	4.3	0.1-21.9	0	0.0-14.2
Chloride	101.77 (2.96)	101.63 (2.57)	102.35 (1.77)	102.63 (1.69)	0.625	4.3	0.1-21.9	0	0.0-14.8
BUN[1]	-0.46 (0.90)	0.11 (1.06)	-0.06 (0.72)	0.46 (1.10)	0.607	0	0.0-15.4	0	0.0-15.4
Coagulation									
Prothrombin Time	11.52 (0.77)	11.45 (0.93)	11.34 (0.57)	11.34 (1.15)	0.846	0	0.0-14.8	14.3	3.0-36.3
APTT	32.38 (3.10)	32.23 (2.98)	32.11 (2.87)	31.51 (3.08)	0.560	4.5	0.1-22.8	5.0	0.1-24.9
INR	1.07 (0.06)	1.05 (0.06)	1.05 (0.06)	1.03 (0.06)	0.707	--	--	--	--

Note. Linear Mixed Effects models (2X2) were used to test the Group by Day interactions. For safety, the Normal to Abnormal transition analysis reflects the percentage of participants with normal function at Day 0 that transitioned to abnormal at Day 14 compared to participants with normal function at both Days. [1]Recruitment site laboratories used different standards, therefore z scores were used. -- normal range not provided by laboratories. N/A = the 95% confidence intervals could not be computed for Total Bilirubin because all participants were normal at both Day 0 and Day 14. AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; APTT, activated partial thromboplastin time; BUN, Blood Urea Nitrogen; CI, Confidence Interval; eGFR, estimated glomerular filtration rate; INR, International Normalized Ratio.

Table 3. Serum, Viral Load, and Symptom Efficacy Findings at Day 0 (baseline) and at Day 14

	Comparison of Groups across Day 0 and Day 14				
	Day 0		Day 14		Group by Day Effect
	FoTv	Placebo	FoTv	Placebo	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p value
Inflammatory Markers					
troponin-T[1]	5.88 (1.92)	8.13 (6.11)	7.32 (3.77)	7.48 (5.77)	0.029
Ferritin[2]	0.09 (0.99)	0.05 (0.98)	0.08 (1.18)	-0.23 (0.80)	0.035
C-reactive protein	0.94 (1.16)	0.55 (0.38)	0.33 (0.48)	0.37 (0.44)	0.044
D-dimer[2]	0.24 (1.78)	0.03 (0.46)	-0.20 (0.20)	-0.10 (0.52)	0.283
ESR	12.54 (9.29)	14.89 (13.78)	11.13 (13.77)	12.68 (10.41)	0.765
LDH	186.08 (29.02)	195.38 (41.48)	195.77 (33.45)	207.70 (37.92)	0.884
SARS-CoV-2 Viral Load	15.29 (4.93)	14.94 (4.66)	37.72 (5.15)	37.41 (4.78)	0.994
COVID-19 Symptoms					
Summary Measures					
Symptom Count	7.23 (2.30)	6.88 (1.99)	1.11 (1.66)	2.17 (2.24)	0.005
Symptom Severity	13.65 (6.62)	11.08 (4.26)	1.61 (2.78)	2.92 (3.54)	<0.001
Individual COVID Symptoms					
Sore throat	1.57 (1.20)	0.59 (0.67)	0.00 (0.00)	0.00 (0.00)	<0.001
Cough	1.77 (0.99)	1.37 (0.76)	0.23 (0.51)	0.42 (0.65)	<0.001
Muscle aches	1.39 (0.99)	0.86 (0.90)	0.13 (0.34)	0.40 (1.00)	0.001
Headache	10.9 (1.00)	1.05 (0.84)	0.00 (0.00)	0.35 (0.67)	0.003
Runny nose	1.35 (1.03)	1.09 (0.97)	0.09 (0.29)	0.15 (0.37)	0.022
Stuffy nose	1.87 (1.10)	1.36 (1.14)	0.22 (0.42)	0.20 (0.41)	0.038
Fatigue	1.70 (0.97)	1.14 (0.80)	0.30 (0.77)	0.50 (0.95)	0.084
Loss of taste	0.74 (1.29)	0.73 (1.20)	0.17 (0.49)	0.45 (0.90)	0.155
Fever	0.73 (0.96)	0.58 (0.83)	0.00 (0.00)	0.00 (0.00)	0.168
Loss of smell	0.70 (1.26)	0.73 (1.20)	0.48 (1.12)	0.25 (0.72)	0.189
Shortness of breath upon exertion	0.70 (1.06)	0.73 (0.94)	0.13 (0.46)	0.20 (0.41)	0.591
Shortness of breath	0.30 (0.64)	0.23 (0.43)	0.00 (0.00)	0.15 (0.49)	0.919

Note. Linear Mixed Effects models were used to test the Group by Day interactions for Inflammatory Markers (FoTv/Placebo X Days 0,14) and Symptoms (FoTv/Placebo X Days 0-14). Data for individual COVID-19 symptoms reflect severity ratings on a scale of 0 (none or absent) to 4 (very severe). [1]Data available only from UCSD site. [2]Recruitment site laboratories used different standards, therefore z scores were used. [3]Viral load is reported as cycle threshold values, which are inversely proportional to viral load. Full statistical reporting for symptoms appears in Supplemental Table 2. ESR, Erythrocyte Sedimentation Rate; LDH, lactate dehydrogenase.

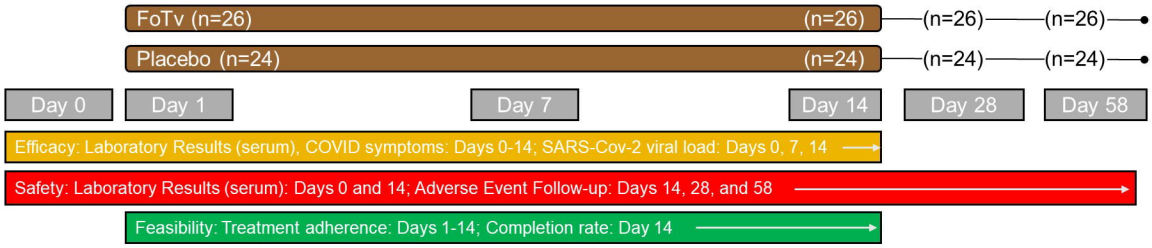
Figure Captions

Figure 1. Design of Clinical Trial. Participants with COVID-19 were randomized to receive either a 14-day regimen of FoTv or Placebo on Day 0 (baseline). COVID-19 symptoms were assessed daily across Days 0-14. Laboratory results (serum) were examined for safety on Days 0 and 14 and adverse events were assessed at follow-up visits on Days 14, 28, and 58. Feasibility analyses examined treatment adherence (Days 1-14) and completion rate at Day 14. Efficacy analyses examined laboratory results (serum) on Days 0 and 14 and SARS-CoV-2 viral load on Days 0, 7, and 14.

Figure 2. CONSORT Diagram.

Figure 3. Efficacy Results for Symptoms, Viral Load in Humans, and *In Vitro* Viral Infection. **a.** Mean Symptom Count for the 12 COVID-19 symptoms assessed for FoTv (red, n=26) and Placebo (black, n=24) groups from Day 0 through Day 14. The FoTv group exhibited significantly fewer symptoms than the Placebo group across days (F-test, $p = 0.005$). Error bars show SEM. **b.** Mean nasal swab viral load at days 0 and 14 via PCR. Viral load (i.e., detectable SARS-CoV-2 genetic material) significantly decreased across days (F-test, $p < 0.001$) and did so similarly for both groups (F-test, $p = 0.994$). Error bars show SEM. **c.** Mean viral infection of TMPRSS2 cells with FoTv or control (DMSO) after 1-hour of incubation showed significant inhibition (F-test, $^*p = 0.009$) of pseudotyped SARS-CoV-2 entry into TMPRSS2 cells (black circles show the three independent biological samples for each condition). Relative Light Units are non-

standardized units that measure Renilla luciferase luminescence values as a quantification of relative pseudovirus entry into cells. Error bars show SD.


FoTv (n=26)
(n=26)
(n=26)
(n=26)
Placebo (n=24)
(n=24)
(n=24)
(n=24)
Day 0
Day 1
Day 7
Day 14
Day 28
Day 58
Efficacy: Laboratory Results (serum), COVID symptoms: Days 0-14; SARS-Cov-2 viral load: Days 0, 7, 14
Safety: Laboratory Results (serum): Days 0 and 14; Adverse Event Follow-up: Days 14, 28, and 58
Feasibility: Treatment adherence: Days 1-14; Completion rate: Day 14

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

Enrollment

Assessed for eligibility (**n=186**)

Excluded (**n=132**)
- Not meeting inclusion criteria **(n=66)**
- Declined to participate **(n=60)**
- Other reasons **(n=6)**

Randomized (**n=54**)

Allocation

Allocated to FoTv intervention **(n=28)**
- Received allocated intervention **(n=28)**
- Did not receive allocated intervention **(n=0)**

Allocated to Placebo intervention **(n= 26)**
- Received allocated intervention **(n=26)**
- Did not receive allocated intervention **(n=0)**

Follow-Up

Lost to follow-up **(n=0)**
Discontinued intervention **(n=0)**

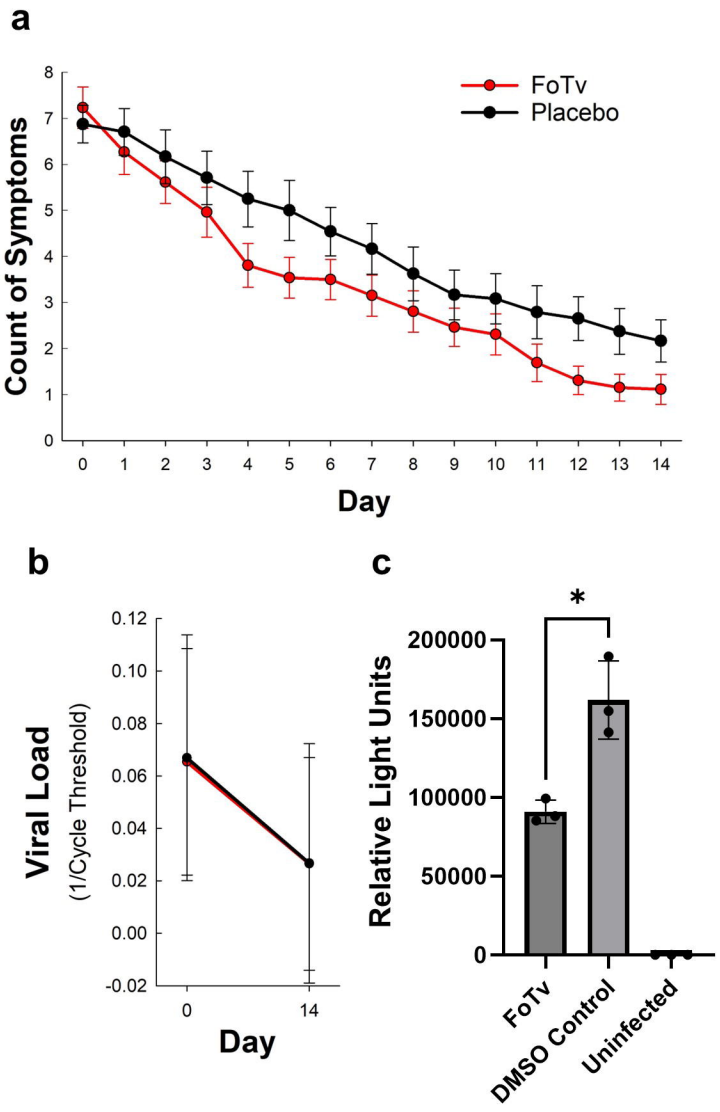
Lost to follow-up (**n=1**)
- 1 dropped out on Day 1 (too busy)

Discontinued intervention **(n=0)**

Analysis

Analysed (**n=26**)
- Excluded from analysis (**n=2**) from n=28
  - No COVID-19 (**n=2**)
  - Insufficient data (**n=0**)

Analysed (**n=24**)
- Excluded from analysis (**n=2**) from n=26
  - No COVID-19 (**n=1**)
  - Insufficient data (**n=1**)


a
FoTv
Placebo
Count of Symptoms
Day
b
Viral Load
(1/Cycle Threshold)
Day
c
Relative Light Units
*
FoTv
DMSO Control
Uninfected