UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Approval Date: 10/13/2021 Clinical Trial Numbers: NCT04667247 (1a), NCT04939415 (1b), and NCT04951336 (1c)

1. PROJECT TITLE

Multicenter Double Blind, Placebo Controlled RCT of modified Qing Fei Pai Du Tang (mQFPD) and Fomitopsis officinalis/Trametes versicolor for COVID-19

Working title:
Mushrooms and Chinese Herbs for COVID-19 (MACH-19)

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

UC San Diego (Study Coordinating site)
UC Irvine
UCLA
(Note: UC IRB Reliance Agreement has been completed)
La Jolla Institute for Immunology

4. ESTIMATED DURATION OF THE STUDY

It is anticipated that 12 months will be required for completion of study activities.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Despite biomedical advances, medical intervention for COVID-19 is largely limited to vaccination and supportive care during the later stages of disease. Integrative Medicine offers several promising antiviral and immunomodulatory therapeutics that are available today and warrant studying.

We propose to conduct two multi-center, randomized, double blind, placebo-controlled clinical Phase 1 trials (sub-studies 1a and 1b) to evaluate the safety of: (1) FoTv (a combination of two polypore mushrooms, Fomitopsis officinalis and Trametes versicolor, and (2) mQFPD as a modified form of Qing Fei Pai Du Tang, a Chinese herbal formula that has widely been used in China, Taiwan, and Korea to treat COVID-19 for COVID-19-positive outpatients with mild-to-moderate symptoms assigned to self-quarantined and home management.

Once safety and feasibility have been established in each of these first two sub-studies, we will move forward with a larger Phase 2 study comparing the efficacy of FoTv vs. mQFPD vs. Placebo.

We also herein propose a third, new sub-study, 1c, that will examine the effect of FoTv vs. placebo for use as an adjunct to vaccination for COVID-19 in a general population at the time of COVID-19 vaccination.

Fo and Tv have immunomodulatory properties which may increase antibody titers in response to vaccination more than vaccination alone. However, because they are also immunomodulatory – not purely immune stimulating - they may have the added benefit of simultaneously decreasing vaccine-related side effects following COVID-19 vaccination.

6. SPECIFIC AIMS

Sub-study 1a: FoTv vs. placebo in acute COVID-19 patients.

The primary objectives of this study are:

- Ascertainment of safety of FoTv and
- Assessment of feasibility of the intervention (with the primary outcomes focusing on determination of the rates of recruitment and completion)

A. Safety:

The following safety data will be collected and assessed during the study:

1) Incidence and severity of adverse events
2) Laboratory evaluations
3) Home glucometer measurements for diabetic participants
4) Home blood pressure measurements for hypertensive participants
5) Home daily weight measurements for patients with congestive heart failure or diuretic use

Safety data will be collected and assessed using the following methods:

1) Each participant will receive a paper copy and an emailed daily diary requesting information on symptoms (including duration and severity), vitals, and medication compliance. Participants who are unable to respond to emails will be asked to directly record this data into the provided paper study daily diary and then will be contacted daily to report this information to the study coordinator. All email exchanges among study personnel will be conducted within the UC intranet secure system. All communications with patients will be through virtual appointments using UC secure systems, UC San Diego encrypted emails or with password- protected study documents.

2) Study coordinators will collect and enter all safety data. All serious adverse events (SAEs) will, per UCSD IRB guidelines, be reported to the IRB and DSMB within 3 business days of learning of the event. Any adverse events, as well as any escalation of care, including urgent care, emergency room, or hospitalization, will be reported to the study team after appropriate medical care has been received, via a dedicated phone number or email address that is specific for urgent matters.

3) The UCSD site will implement a Data and Safety Monitoring Board (DSMB) to review data safety and monitoring as part of their responsibilities. The DSMB will include two senior researchers and a consumer representative. They will have conference calls bi-weekly (or more frequently, if needed).

4) The study biostatistician will send a tabulated symptom and adverse event report daily to all sites and to the study PI and weekly to the study DSMB and IRB.

5) The safety of the study medication will also be assessed through laboratory data collection at baseline, and at either the end of the treatments following end of quarantine (for non-hospitalized patients) or as part of hospital admission labs (for patients requiring hospitalization)
    a. Basic Metabolic Panel
    b. Complete Blood Count with Differential
    c. Liver Function Testing
    d. Prothrombin Time and Partial Thromboplastin Time

B. Feasibility:

The following feasibility data will be collected and assessed :

1) Recruitment:
    a. Recruitment sites (number, location, and method of their selection)
    b. Factors influencing recruitment rate
    c. Methods used for subject recruitment
    d. Number of subjects:
        i. Initially contacted
        ii. Initial interviewed

iii. Consented
iv. Baseline data collected

e. Reasons for non-participation:
   i. After initial contact and/or initial interview
   ii. After consent process
   iii. After initial data collection or throughout the study
   iv. Until end of study
f. Reasons for participating in and completing study

2) Randomization:
   a. Testing effect of randomization process on distribution of demographic, co-morbidity, and other
   b. background characteristics
   c. Testing randomization process on their baseline main outcomes
   d. Examining acceptability of the randomization process and its effect

3) Missing data:
   a. Differences in rates of missing data between medication and placebo groups and per time point
   b. Pattern of missing data

4) Retention rate:
   a. Differences in retention between medication and placebo groups
   b. Factors influencing these differences

5) Subjects' satisfaction with:
   a. Study procedures
   b. Study implementation and staffing
   c. Medication delivery methods
   d. Data collection timepoints and outcomes

6) Medication fidelity with:
   a. Delivery methods
   b. Number of successful and failed deliveries
   c. Assessment methods
   d. Timing and method of feedback

7) Study improvement procedures/maintaining documentation of:
   a. Study/protocol development, revision, and modification
   b. Issues and concerns with implementing recruitment strategies
   c. Issues and concerns with accessing, distributing, and tracking of medication and placebo
   d. Issues and concerns with measurements:
      i. Number of measurements
      ii. Time requirements of measurements
      iii. Redundancy among measurements
      iv. Positive or negative carryover

Sub-study 1b: mQFPD vs. placebo in acute COVID-19 patients.

The primary objectives of this study are:

- Ascertainment of safety of FoTv and
- Assessment of feasibility of the intervention (with the primary outcomes focusing on determination of the rates of recruitment and completion)

A. Safety:

The following safety data will be collected and assessed during the study:

1) Incidence and severity of adverse events
2) Laboratory evaluations
3) Home glucometer measurements for diabetic participants
4) Home blood pressure measurements for hypertensive participants
5) Home daily weight measurements for patients with congestive heart failure or diuretic use

Safety data will be collected and assessed using the following methods:

1) Each participant will receive a paper copy and an emailed daily diary requesting information on symptoms (including duration and severity), vitals, and medication compliance. Participants who are unable to respond to emails will be asked to directly record this data into the provided paper study daily diary and then will be contacted daily to report this information to the study coordinator. All email exchanges among study personnel will be conducted within the UC intranet secure system. All communications with patients will be through virtual appointments using UC secure systems, UC San Diego encrypted emails or with password- protected study documents.
2) Study coordinators will collect and enter all safety data. All serious adverse events (SAEs) will, per UCSD IRB guidelines, be reported to the IRB and DSMB within 3 business days of learning of the event. Any adverse events, as well as any escalation of care, including urgent care, emergency room, or hospitalization, will be reported to the study team after appropriate medical care has been received, via a dedicated phone number or email address that is specific for urgent matters.
3) The UCSD site will implement a Data and Safety Monitoring Board (DSMB) to review data safety and monitoring as part of their responsibilities. The DSMB will include two senior researchers and a consumer representative. They will have conference calls bi-weekly (or more frequently, if needed)
4) The study biostatistician will send a tabulated symptom and adverse event report daily to all sites and to the study PI and weekly to the study DSMB and IRB.
5) The safety of the study medication will also be assessed through laboratory data collection at baseline, and at either the end of the treatments following end of quarantine (for non-hospitalized patients) or as part of hospital admission labs (for patients requiring hospitalization)
    e. Basic Metabolic Panel
    f. Complete Blood Count with Differential
    g. Liver Function Testing
    h. Prothrombin Time and Partial Thromboplastin Time

B. <u>Feasibility</u>:

The following feasibility data will be collected and assessed :

1) Recruitment:
    a. Recruitment sites (number, location, and method of their selection)
    b. Factors influencing recruitment rate
    c. Methods used for subject recruitment
    d. Number of subjects:
        I. i. Initially contacted
        ii. Initial interviewed
        iii. Consented
        iv. Baseline data collected
    e. Reasons for non-participation:
        i. After initial contact and/or initial interview
        ii. After consent process
        iii. After initial data collection or throughout the study
        iv. Until end of study
    f. Reasons for participating in and completing study

2) Randomization:
   a. Testing effect of randomization process on distribution of demographic, co-morbidity, and other
   e. background characteristics
   f. Testing randomization process on their baseline main outcomes
   g. Examining acceptability of the randomization process and its effect

3) Missing data:
   a. Differences in rates of missing data between medication and placebo groups and per time point
   b. Pattern of missing data

4) Retention rate:
   a. Differences in retention between medication and placebo groups
   b. Factors influencing these differences

5) Subjects' satisfaction with:
   a. Study procedures
   b. Study implementation and staffing
   c. Medication delivery methods
   d. Data collection timepoints and outcomes

6) Medication fidelity with:
   a. Delivery methods
   b. Number of successful and failed deliveries
   c. Assessment methods
   d. Timing and method of feedback

7) Study improvement procedures/maintaining documentation of:
   a. Study/protocol development, revision, and modification
   b. Issues and concerns with implementing recruitment strategies
   c. Issues and concerns with accessing, distributing, and tracking of medication and placebo
   d. Issues and concerns with measurements:
      i. Number of measurements
      ii. Time requirements of measurements
      iii. Redundancy among measurements
      iv. Positive or negative carryover

Sub-study 1c: FoTv vs placebo for use as an adjunct to COVID-19 vaccination.

The primary objectives of this study are to determine whether FoTv, when taken for four consecutive days starting the day of COVID-19 vaccination, is safe and associated with:

- An enhanced peak COVID-19 antibody response
- A reduced rate of post-peak antibody decline
- Reduction in side effects from COVID-19 vaccination
- Other immunologic (e.g., T-cell mediated) responses

7. BACKGROUND AND SIGNIFICANCE

Despite biomedical advances, medical intervention for COVID-19 is largely limited to supportive care during the later stages of disease. While antiviral, anti-inflammatory, and antimalarial options have been explored for later stages of disease, fewer studies have been conducted on medications to reduce the risk of outpatient cases progressing to severe disease. Therefore, it is important that we broaden the search to include agents outside of our usual pharmacopeia. Integrative Medicine offers several promising therapeutics that are available today and warrant investigation.

Herbal medicines have been used for millennia in China, during which several therapeutic herb combinations have been developed and implemented using Chinese medicine principles. At this time, several of these Chinese Herbal Medicine (CHM) formulas are currently being recommended as part of the Chinese national guidelines to treat COVID-19. CHM

is traditionally prescribed and individualized for treatment following a history and physical examination by a practitioner. In this case, Chinese national guidelines recommend Qing Fei Pai Du Tang (QFPD) as a composite formula consisting of 21 total herbs which can be used broadly for all patients without individualization. As such, QFPD lends itself well to the double blinded RCT trial design. Early clinical trials are promising (Wang, R 2020), however the level of evidence is low. Given the discrepancy between usage and evidence, as well as the need for better therapeutics domestically, high quality trials are warranted. For the purposes of this study, one of the 21 herbs (Kuan Dong Hua) is known to contain potentially toxic pyrrolizidine alkaloids and is of relatively minor therapeutic value, so in an abundance of caution we have substituted a safe alternative, Pi Pa Ye which is known to have a similar clinical effect, to create a modified QFPD or mQFPD.

Some of the botanicals used for their possible immune modulating functions include polypore mushrooms. Among these, Turkey Tail (*Trametes versicolor*) has a long history of use for its immune supporting properties. An RCT examining the effects of *Trametes versicolor* in breast cancer patients detected increases in lymphocyte counts and natural killer cell functional activity (Torkelson et al, 2012 and Benson et al, 2019) both of which are key to host COVID-19 response. Further investigations into other relevant mushroom species demonstrated that Agarikon (*Fomitopsis officinalis*) can strongly induce an array of differential cytokine responses associated with both immune-activation and resolution of host defense- induced inflammatory reactions (unpublished). This homeostatic effect deserves attention for COVID-19 given the high mortality rate associated with cytokine storm.

COVID-19 Characteristics

Coronavirus Disease 2019 (COVID-19) is caused by serious acute respiratory syndrome coronavirus 2 or SARS-CoV-2. A betacoronavirus thought to have been transmitted from rhinophilus bats (Zhou et al., 2020) to humans in Wuhan China, SARS-CoV-2 is a positive-sense single stranded RNA virus. Spike-like surface proteins (coronas) extend from the RNA virus and bind to ACE2 receptors on epithelial cells of the upper respiratory tract and glandular cells in the gastrointestinal tract (Wong, Lui, & Sung, 2020). The effective reproductive number (R0 value) is estimated to be 3.86, (C. Wang et al., 2020) making it highly contagious and has led to a worldwide pandemic that has infected millions of confirmed individuals and caused countless deaths. Transmission can occur through large, virus-laden nuclei in air-borne droplets, physical touch, fomites, (van Doremalen et al., 2020) and possibly, though not confirmed, from fecal sources (Wong et al., 2020). The viral burden peaks early (<2 days) of symptoms based on culture and polymerase chain reaction testing and viral shedding can outlast symptoms and be detected for weeks after symptoms resolve.

Clinical characteristics of COVID-19 include fever, non-productive cough, dyspnea, myalgia, fatigue, nausea, diarrhea, normal or decreased leukocyte counts, and pneumonia confirmed with imaging (N. Chen et al., 2020; Huang et al., 2020; Rodriguez-Morales et al., 2020; C. Wang et al., 2020; D. Wang et al., 2020). In severe cases, patients can experience organ failure and even death in severe cases due to acute respiratory distress syndrome (ARDS) (Huang et al., 2020). Patients aged over 80 and older men are suspected to be at increased risk of experiencing more severe symptoms of COVID-19, especially with comorbidities such as smoking, diabetes, coronary and pulmonary diseases (N. Chen et al., 2020; Rodriguez-Morales et al., 2020). The World Health Organization estimated the unadjusted death rate was 4.0% in China and currently 4.7% worldwide (WHO, 2020).

There is no known cure for COVID-19, but it appears to be a self-limiting disease in 80% of patients (Yuen, Ye, Fung, Chan, & Jin, 2020). In 20% of acute cases requiring hospitalization, conventional treatment in the US is currently symptom management and SARS-CoV-2 viral load reduction in the early phase with the intent of preventing ARDS. COVID-19 prevention and symptom management during early onset of disease are essential to reduce acute care needs and protect hospital resource availability for critically ill cases.

Figure 1 shows the typical time course of COVID-19 patients who ultimately require hospitalization (Zhou et al, 2020). While data on the time course of mild to moderate cases of COVID-19 is more challenging to collect, this figure demonstrates the typical time course of patients that end up with hospitalization and survival (top) or death (bottom). Day 1 on these charts represents the first day that their SARS-CoV-2 RNA test was positive, suggesting several days of positive symptoms prior.

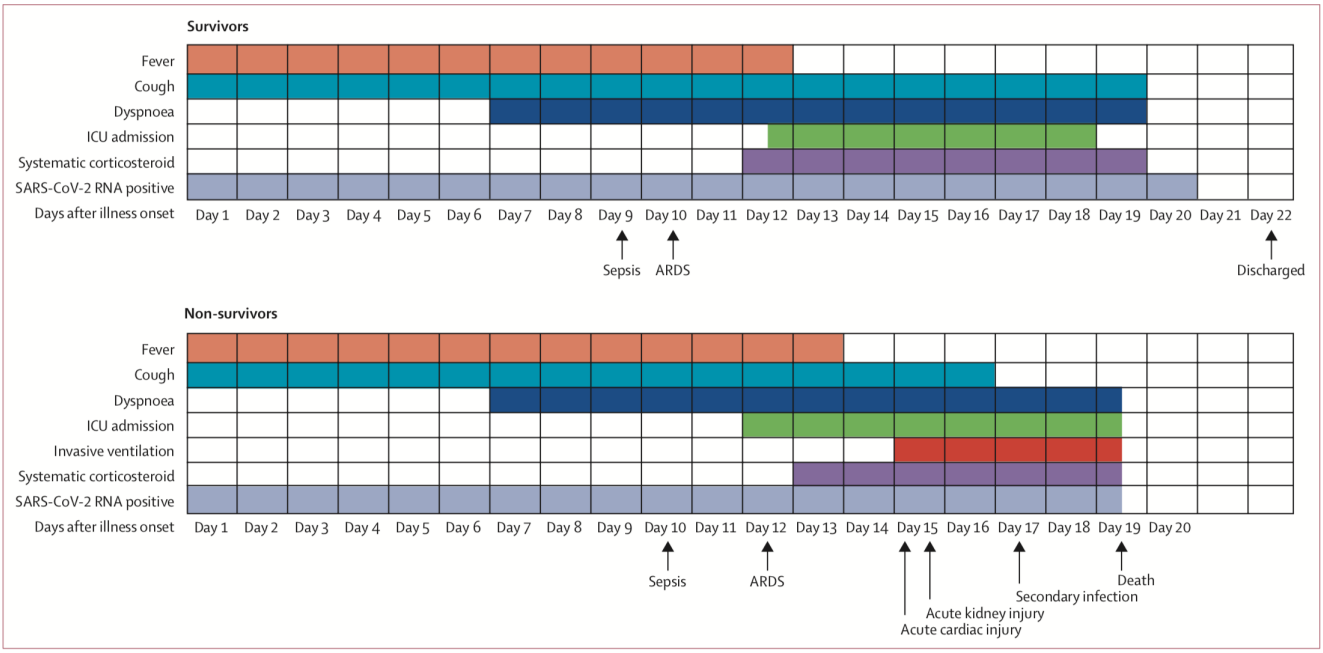

Figure 1: **Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19**
Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

As depicted, there is a 5-7 day window of disease burden during which patients have a confirmed COVID-19 diagnosis but they do not yet require inpatient management. In the US, these patients are assigned to strict home quarantine but no medical options are available aside from symptomatic treatment and supportive care. This represents an optimal population to target experimental therapies which have may modulate immune function and avert or delay the need for hospitalization.

Chinese Herbal Medicine (CHM)
Herbal medicines have been used for millennia in China, during which time several generations of practitioners have described systems of medicine to understand the pathophysiology of viral illness and suggest tools for treatment. The most revered of these works was compiled by Zhang Zhongjing sometime before 220 AD and is known as the "Shang Han Lun," known in English as the "Treatise on Cold Damage Disease." This remains one of the foundational texts in modern CHM, and informs the main formulas that are currently being used in combination with Western medicine for the treatment of COVID-19 in China. Unlike the United States, use of CHM is widely used along with Western medicine in the treatment of COVID-19.

CHM is largely well tolerated and adverse events (AEs) in trials tend to be mild when reported. In a narrative review, Jiang concluded CHM can be used in many conditions with minimum side effects (Jiang, 2005). In a cohort of 1,063 people who took CHM to prevent SARS infection, there were no serious adverse events (SAEs). Nineteen (1.8%) reported minor AEs of diarrhea, dizziness, and nausea, and nine participants stopped taking the formula altogether (Lau et al., 2005). Duan et al.'s RCT of patients with H1N1 reported 4 minor AEs in the CHM group. Another trial investigating Oseltamivir and CHM for H1N1 influenza reported two events of nausea and vomiting with CHM alone, but none in the group that combine CHM and oseltamivir (Wang et al., 2011). In a meta-analysis of 12 CHM and SARS trials, only two trials reported AEs. There were no serious adverse events (SAEs) or AEs in the CHM groups (Liu, Zhang, He, &Li, 2012). More details on the specific safety profiles are disclosed in the following section (Study Rationale/Risk / Benefit Assessment).

CHM constitutes common therapy and is used alongside conventional medicine in some Chinese and Taiwanese hospitals (M. C. Chen, Lai, Chen, & Wang, 2013; Ni, Zhou, Zhou, Zhao, & Wang, 2020). Yang et al reported 85% of SARS-CoV-2 infected patients used CHM (Yang, Islam, Wang, Li, & Chen, 2020). The number and overall quality of trials investigating CHM for any coronavirus type are generally low. Published pre-clinical and cohort studies suggest CHM could be a promising therapy

for prevention and adjuvant treatment, but rigorous investigation is needed to assess efficacy and safety. Du et al report that among 214 confirmed COVID-19 cases, 90% improved with Qingfei Paidu Decoction, but location and details of the cohort are not adequately described (Du, Hou, Miao, Huang, & Liu, 2020). No human trials evaluating CHM impact on COVID-19 symptoms are yet published, but at least 10 are registered on ClinicalTrials.gov. Still, the observations of providers in China are influencing CHM practice around the world.

The Office of the National Administration of Traditional Chinese Medicine disseminated guidance recommending Qing Fei Pai Du Decoction as "suitable for mild, moderate and severe COVID-19 cases" (China, 2020). Outcomes from other trials suggest CHM could play an important role in a viral pandemic. A recent review of 28 traditional medicine guidelines (26 Chinese and 2 Korean) that provide treatment measures for COVID-19 (Ang et al, 2020). In China specifically, 17 provinces, 4 municipalities and 4 autonomous regions in mainland China officially issued traditional medicine-related guidelines for the prevention and treatment of COVID-19.

The content of the recommended formulas varied by region and municipality. Among the various formulas recommended between the herbal formula of Qing Fei Pai Du Tang (QFPD), which is a combination of 4 different herbal formulae with 21 herbs, was recommended by the Chinese national diagnosis and treatment guidelines in the treatment of COVID-19 regardless of disease stage or regional status. According to Wang Wei, the vice president and professor of Beijing University of Chinese Medicine, "since February 5th, 390,000 bags [of QFPD] have been distributed to designated hospitals and isolation points in Wuhan, and 500,000 compound granules [of QFPD] have been distributed to the whole province" [reference available in Chinese at https://mp.weixin.qq.com/s/SNPWSecsuiyAwW8NI0nyaQ]. We can expect a thorough safety evaluation within a year, but the urgency of the pandemic demands more swift action. This herbal formula was also recommended for the treatment of severe stage disease in the Korean guidelines.

CHM prescriptions are usually considered after a detailed in-person examination with a skilled CM practitioner that almost always includes physical examination of the tongue and pulse, and considers multiple factors including regionality. Unfortunately, the isolation demanded in this pandemic makes this in-person evaluation impossible. Moreover, the nature of blinded randomized controlled trials generally requires that the same intervention is administered regardless of individual or regional study participant characteristics. For these reasons, QFPD stands out as the most versatile single-intervention herbal formula to study in this context.

Overview of Non-Clinical Studies

The main herbs of QFPD have antiviral effects via different mechanisms: 1) Direct effect on virus replication and autophagy, 2) Modulation of host pathways like TLRs, RGI, RLH, AMPK, P/13K/AKT, MAPK/ERK signal pathways, 3) Promotion of the human defense system via T and B cell functions, 4) Free radical scavenging activities by enhancing SOD, CAT and GPX (Zhong, 2020).

In silico studies identified over 210 possible targets of QFPD and 50 common targets with COVID-19. These targets are associated with several key immunological pathways including T helper (Th) 17 cell differentiation, T cell, B cell, tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), Vascular endothelial growth factor (VEGF), Hypoxia-inducible factor-1 (HIF-1) and Toll-like receptor (TLR) signalling with good affinity to ACE2 receptor (Wu et al., 2020; Xu et al., 2020; Zhao et al., 2020). Another primarily in silico study of QFPD validated the anti-inflammatory effects of glycyrrhizic acid and demonstrated its ability to attenuate IL-6 release by activated macrophages (Yang, 2020).

In studies of single herbs, Gan Cao/licorice root's active component, glycyrrhizin, was found to significantly inhibit SARS-CoV virus replication, adsorption, and penetration at high concentrations (4000mg/L) in isolates of coronavirus from hospitalized patients in Germany (Cinatl et al., 2003). The experiment compared glycyrrhizin with ribavirin, pyrazofurin, and mycophenolic acid. In a mouse model looking at lipopolysaccharide (LPS) induced rapid shock from platelet accumulation in the lung, glycyrrhizin was administered just before or at the same time as LPS. Glycyrrhizin significantly reduced the severity of rapid shock induced by LPS, and prevented death in both early and later periods (Yu et al., 2005).

Overview of Clinical Studies

Published human trials evaluating CHM impact on COVID-19 symptoms are limited, but at least 10 are registered on ClinicalTrials.gov. Still, the observations of providers in China are influencing CHM practice around the world. The Office of the National Administration of Traditional Chinese Medicine disseminated guidance recommending Qing Fei Pai Du Decoction (QFPD) as suitable for mild, moderate and severe COVID-19 cases (China, 2020). Outcomes from other trials suggest CHM could play an important role in a viral pandemic.

QFPD during COVID-19

As of June 6, 2020 only a single human trial has been published (Wang, R 2020) regarding QFPD for COVID-19. It is an uncontrolled prospective study of 98 cases tracked symptoms, laboratory data and CT scan findings every three days during a 9-day course of treatment. At 3 days, over 70% of patients had normalization of lymphocyte percentage, AST, ALT, and D-Dimer ($P < 0.01$). At day 6, 80% had normalization of laboratory indexes now including ESR and CRP ($P < 0.01$). At day 9 90% of patients had normal labs. CT scans at day 6 demonstrated improvement in 79 of 98 patients (80.6%).

Clinical improvement, as determined by "recovery" (>95% reduction in symptom scores), "significant effect" (70-95% reduction in symptom scores), "effective" (30-70% reduction in symptoms scores), or invalid, is as follows: At day 3, 21% recovered, 29% demonstrated significant efficacy, and 34% were deemed effective for a total "efficacy rate" (as defined by symptom scores improved by >30%) of 84%. At day 6, the numbers were 31% recovered, 30% significant efficacy, 29% effective for a total efficacy rate of 90%. At day 9, 41% recovered, 27% reached significant efficacy, and 24% were effective for a total efficacy rate of 92%.

Adverse reactions to QFPD

While this study's methodology including lack of a control group leaves much to be desired, their report on adverse reactions is important considering the complete 196g decoction was administered daily for 9 days, which is a substantially larger dose than that used in the present clinical trial. In the course of treatment of 98 patients, 4 patients developed symptoms of nausea and vomiting, 2 patients developed symptoms of dizziness, and 1 patient developed symptoms of rash. When reported as adverse reactions per total days of treatment, the incidence of adverse reactions was 0.07%.

Broader review of CHM for viral epidemics:

The history of use of these herbal medications throughout numerous prior epidemics suggests that the therapy is immune supporting and therefore virus agnostic. This makes it worthwhile to review the literature of CHM on other similar recent viral epidemics:

1. H1N1 Influenza

In a high-quality trial of 410 participants, CHM was an effective therapy during H1N1 pandemic. Wang et al. (2011) compared oseltamivir and CHM formula maxingshigan-yinqiaosan in hospitalized patients with uncomplicated H1N1 influenza. The oseltamivir and CHM group significantly reduced median time to fever resolution compared with control group (-47% 95% Confidence Interval (CI) -56 to -35, $p<0.001$) and when compared with oseltamivir alone (-19%, 95% CI -34 to -0.3, $p=0.047$). COVID-19 is not an influenza, but this study successfully integrated conventional medication with Chinese herbs. There were no adverse events reported in the oseltamivir and CHM group (Wang et al., 2011).

Duan et al. (2011) published a high quality trial of 256 participants investigating Lianhuaqingwen Capsule (LHC) compared with oseltamivir for H1N1. The median duration of illness was no different between groups, but the LHC group experienced significant symptom reduction compared with the oseltamivir (Duan et al, 2011).

2. SARS

The previous SARS pandemic of 2003 provides some insight on the role CHM could play in the current pandemic. In a meta-analysis of 12 trials investigating Chinese herbal treatment of SARS, there was no difference in mortality rates compared with controls (Liu, Zhang, He, & Li, 2012). The trials were assessed as having high risk for bias and no trials reported long-term follow-up (Liu et al., 2012). However, they did find three formulas (Kangfeidian No. 1, 2, 3) combined with conventional medicine improved the overall SARS symptom score (MD -5.43, 95% CI -7.17 to -3.69), reduced duration of fever (MD -2.50

days, 95% CI -4.10 to -0.90) (Zhang et al., 2003). But, Yi Qi Yang Ying recipe did not reduce the duration of fever compared with control (MD -1.13 days, 95% CI -.047 to 1.21) (L. S. Zhang et al., 2004). Four formulations improved more cases of absorption of pulmonary infiltration compared with conventional medicines alone (RR 1.95, 95% CI 1.16 to 3.26), (Liu et al., 2012) and one study did not find any difference between groups. Radiographic scores of lung infiltrate was greatly improved in three studies of Chinese herbal therapy compared with controls (Liu et al., 2012). Additionally, when Chinese herbs were combined with conventional medications, the total dosage of corticosteroids was significantly less at the end of the treatment period compared with a control in two studies (Liu et al., 2012).

Huoke granules were compared with penicillin and Xiaoer Shangfeng Zhike Tangjiang syrup in children with acute bronchitis. Huoke granules were superior to the control treatment to reduce duration of cough [mean difference (MD) -0.37 days, 95% Confidence Interval (95% CI) -0.57 to -0.05] and fever (MD -1.07 days, 95% CI -1.31 to -0.83) (Y. & Li, 2005). However, randomization quality and a conflict of interest (hospital produced the Huoke granules where study was performed) encourage caution.

Prevention is a central tenet of Chinese medicine practice (Huang Di Nei Jing Ling Shu, the Ancient Classic on Needle Therapy, The Complete Chinese Text with an Annotate English Translation, 2016; Ming, 2010). During the SARS outbreak of 2003, a cohort study of 16,437 participants in Hong Kong, hospital workers (n=1,063) took an herbal formula for two weeks and were compared with a control cohort (n=15,374) that did not take the formula. Study quality is difficult to assess as the methods do not clearly describe how the cohorts were recruited posing a significant risk of selection bias. Of those that took the CHM, none tested positive for SARS compared with 64 (0.4%) of the control cohort (Lau et al., 2005). The CHM formula used was modified Yu Ping Feng San (Jade Screen Powder) plus Sang Ju Yin (Mulberry Leaf and Chrysanthemum Drink).

In a narrative review, Luo et al. (2020) described two other single arm cohort studies (Xu, Jiang, Liu, & Zhang, 2006; L. Zhang, Chen, & Zeng, 2005) that followed hospital workers in Beijing and found staff who took CHM did not develop SARS. The first cohort of 3,561 doctors, nurses, and other staff took a modified Yu Ping Feng San (Jade Screen Powder) for <25 days (Xu et al., 2006). The second cohort of 163 medical staff directly treating SARS patients took the formula for six days. In both studies, the herbal intervention was intended to prevent SARS infections (L. Zhang et al., 2005). In both studies, there were no new cases of SARS amongst any of the staff that took CHM and study quality cannot be assessed due to publication in Chinese.

CHM is largely well tolerated and adverse events (AEs) in trials also tend to be mild when reported in these trials. In a narrative review, Jiang concluded CHM can be used in many conditions with minimum side effects (Jiang, 2005) In a cohort of 1,063 people who took CHM to prevent SARS infection, there were no serious adverse events (SAEs). Nineteen (1.8%) reported minor AEs of diarrhea, dizziness, and nausea, and nine participants stopped taking the formula altogether (Lau et al., 2005). Duan et al.'s (2011) RCT of patients with H1N1 reported 4 minor AEs in the CHM group. Another trial investigating oseltamivir and CHM for H1N1 influenza reported two events of nausea and vomiting with CHM alone, but none in the group that combine CHM and oseltamivir (Wang et al., 2011). In a meta-analysis of 12 CHM and SARS trials, only two trials reported AEs. There were no serious adverse events (SAEs) or AEs in the CHM groups (Liu et al., 2012).

In the current pandemic, Ni et al. reported a case report of a family (parents and one daughter) treated with both conventional medicine and CHM for COVID-19. Two family members failed to respond to other therapies, but did respond to Shuanghuanglian oral liquid with no AEs (Ni et al., 2020). Du et al. in their study reported 214 confirmed COVID-19 cases, 90% improved with Qing Fei Pai Du Decoction, but location and details of the cohort are not adequately described (Du, Hou, Miao, Huang, & Liu, 2020).

Herbal safety is a concern. Coghlan et al. (2015) evaluated 26 CHM patent formulas that were procured over the counter in Australia to verify ingredients, and analyze for toxicity and heavy metal contamination. Half of the samples contained pharmaceutical, plant or animal ingredients not included on the label and 92% had contamination or substitution (Coghlan et al., 2015). These concerns will be addressed through additional testing of the research product as described under mQFPD Risk in risk/benefit section below.

Novel compounds identified in immune modulating mushrooms

Some of the ingredients used in the traditional Chinese materia medica as well as in the U.S. and other countries include possibly immunologically supportive mushrooms such as turkey tail and reishi. Others, like agarikon (*Fomitopsis officinalis*, Fo), possess documented ethnomycological use for pulmonary conditions (Girometta, 2018).

Recently, these mushrooms along with many others have been studied to better characterize their biological activity. Prepared components of these fungi are widely used as dietary supplements by the lay public, including for the putative prevention and treatment of viral upper respiratory infections.

As a category, immune modulating mushrooms stimulate host defense and immunity due to their complex and varying polysaccharides. Some well-studied examples include (1,3;1,6)-β-glucans, proteoglycans, and heteroglycans that comprise the chitin-based fungal cell wall (Meng, Liang, & Luo, 2016). These polysaccharides exert immunological activity through the activation of natural killer cells, macrophages, and neutrophils, as well as induction of innate immune cytokines and interleukins (Ruthes, Smiderle, & Iacomini, 2016). Mushrooms are also the source of other pharmacologically relevant compounds, such as proteins like Ling zhi-8 in reishi (Kino et al., 1989) and lectins in several species (Singh et al., 2014), triterpenes (Akihisa et al., 2007), phenols (Durgo et al., 2013), and sterols (Akihisa et al., 2007). While nutraceutical mushrooms generally confer broad immune activity, individual species often possess unique immunological properties. Turkey tail (*Trametes versicolor*, "Tv") is known to enhance innate and adaptive immune responses (Ramberg, Nelson, & Sinnott, 2010). Recent clinical research involving Tv mycelium (Torkelson et al., 2012) suggests NK cell induction in women with breast cancer.

Other researchers cite antitumor effects (Lu et al., 2011), (Brown & Reetz, 2012), but this is generally considered to be a result of its underlying immunologic activity. Agarikon (*Fomitopsis officinalis,* "Fo"*)* is another mushroom of premier immunological importance. A polypore mushroom found in old-growth forests with an exceptionally long lifespan, and a species used for more than 2000 years in European pharmacopeia as an anti-inflammatory, Fo possesses several unique classes of compounds (such as chlorinated coumarins) which confer broad- spectrum antimicrobial and antiviral activity (Girometta, 2018; Hwang et al., 2013). Sections 1.1 details the antiviral and immunological activity observed with Agarikon.

The available data shows that immune modulating mushrooms are generally well tolerated. In the above-cited clinical study (Torkelson et al., 2012) in breast cancer patients (n=9), Tv was well tolerated for six weeks in the post-radiation treatment setting. Nine total adverse events were observed: "seven mild, one moderate, and only one grade 3 adverse event which was an anxiety attack in one participant that was likely unrelated to study medication" (page 3). Notably, the nausea and GI upset associated with previous clinical trials using Tv were not reported in this study. An expanded search of the literature allows an analysis of tolerability of different isolates, fractions, or parts of the Tv organism. In a clinical trial using a polysaccharopeptide (PSP) from Tv, one out of 8 participants in the PSP treatment arm reported increased gas and burping (Pallav et al., 2014). More details on mushroom risks and potential benefits are disclosed in the following section (Study Rationale/Risk / Benefit Assessment).

Rationale for FoTv as an Adjunct to Vaccination

COVID-19 vaccination has emerged as the primary tool for battling the COVID-19 pandemic. Successful rollout of vaccination among a population can rapidly and safely increase its progress towards herd immunity without the substantial morbidity of COVID-19 disease. Unfortunately, vaccine hesitancy remains high, especially in the United States, with a recent review reporting as low as a 56.9-75.4% vaccine acceptance rate among surveys (Malik 2021). One of these studies (Pogue 2020) reported the major reasons of concern being side effects and concerns about vaccine efficacy. Although these numbers are expected to improve with public health messaging and greater social acceptance, efforts at reducing side effects and improving efficacy are also required to maximize social acceptance to the COVID-19 vaccine. Data on the components of FoTv support a wide range of effects on both adaptive and innate immune mechanisms which are important for vaccine efficacy, and which may potentially reduce their side effect profiles.

Vaccine efficacy and variant evolution

Reports of mRNA vaccine efficacy are high, with the dual dose regimens of the Pfizer and Moderna vaccines approaching or breaching 95% after the second dose. However, the emergence of recent viral variants has raised the concern that a two-dose regimen may hasten the evolution of vaccine resistant variants. When people are infected after the first dose but before the second dose, the virus can replicate in the setting of a suboptimal level of neutralizing antibodies, a situation in which resistant variants may emerge (Saad-Roy, 2021). In addition to these, the storage infrastructure required for mRNA vaccines is a large barrier to wide scale adoption.

The newly released Johnson and Johnson adenovirus based vaccine is a single dose vaccination that comes at the cost of decreased efficacy. A single dose limits the time period of suboptimal neutralizing antibodies and limits the opportunity for resistant variant evolution. In addition to being delivered in a single dose, the vaccine itself requires much less storage infrastructure and so lends itself to greater distribution worldwide.

Depending on how efficacy is measured, rates are reported as between 66 and 74%. While this vaccine seems to offer excellent protection against severe COVID-19 disease and may potentially reduce evolution of resistant variants, its lower overall efficacy against infection than mRNA vaccines could impede public health efforts at implementing wide scale vaccine acceptance. As reported above, perceived lack of efficacy is an important source of vaccine hesitancy.

Vaccine side effects

Vaccine side effects are another major concern reported by those who are hesitant to receive the vaccine. Moderna's trial found that severe side effects included fatigue in 9.7% of participants, muscle pain in 8.9%, joint pain in 5.2%, and headache in 4.5%. In the Pfizer/BioNTech vaccine trial, the numbers were lower: Severe side effects included fatigue (3.8%) and headache (2%).

The Johnson and Johnson vaccine side effects were also notable, including 46-84% of participants who reported fatigue, myalgia or headache (Sadoff, 2021). This side effect profile is an additional challenge at battling vaccine hesitancy.

Effects of Trametes Versicolor as a vaccine adjunct

Turkey tail (Trametes versicolor, “Tv”) is known to enhance innate and adaptive immune responses (Ramberg, Nelson, & Sinnott, 2010). Recent clinical research involving Tv mycelium (Torkelson et al., 2012) suggests NK cell induction in women with breast cancer. Other researchers cite antitumor effects (Lu et al., 2011), (Brown & Reetz, 2012), but this is generally considered to be a result of its underlying immunologic activity. Agarikon (Fomitopsis officinalis, “Fo”) is another mushroom of premier immunological importance. A polypore mushroom found in old-growth forests with an exceptionally long lifespan, and a species used for more than 2000 years in European pharmacopeia as an anti-inflammatory, Fo possesses several unique classes of compounds (such as chlorinated coumarins) which confer broad- spectrum antimicrobial and antiviral activity (Girometta, 2018; Hwang et al., 2013). Sections 1.1 details the antiviral and immunological activity observed with Agarikon.

Protein-bound polysaccharide-K (PSK) is a hot water extract from Trametes versicolor, and has been studied for its vaccine adjuvant properties. In in-vitro and animal studies, PSK was found to activate Toll-like receptor 2 (TLR2), a protein expressed on dendritic cells (DC) that is a target for commonly used vaccine adjuvants (Engel, 2013). In vitro experiments using mouse bone marrow-derived DC (BMDC) demonstrated that PSK induces DC maturation as shown by dose-dependent increase in the expression of CD80, CD86, MHCII, and CD40. PSK also induces the production of multiple inflammatory cytokines by DC, including IL-12, TNF-α, and IL-6, at both mRNA and protein levels. In vivo experiments using PSK as an adjuvant to OVAp323–339 vaccine showed that PSK as adjuvant leads to enlarged draining lymph nodes with higher number of activated DC. PSK also stimulates proliferation of OVA-specific T cells, and induces T cells that produce multiple cytokines, IFN-γ, IL-2, and TNF-α. Altogether, these results demonstrate the ability of PSK to activate DC in vitro and in vivo and the potential of using PSK as a novel vaccine adjuvant, and support the exploration of Tv for its use alongside Fo as an adjunct to vaccination.

Overview of Non-Clinical Studies

There have been several preclinical studies demonstrating immune system and anti-viral impacts of Host Defense products in models including human peripheral blood mononuclear cells (PBMCs), bees, and in vitro assays. For instance, polypore products from Host Defense have demonstrated significant antiviral effects in bees. Notably, Ganoderma resinaceum mycelium- based extracts led to a 79-fold reduction in deformed wing virus (DWV) and a 45,000-fold reduction in Lake Sinai Virus (LSV). Additionally both the mycelial extracts of *Fomes fomentarius* (amadou conk) and *Ganoderma applanatum* (artist's conk) produced dose- dependent antiviral effects, while Tv also had antiviral activity, albeit to a lesser extent (P. E. Stamets et al., 2018).

A previous study by the U.S. Defense Department (DOD)'s Project BioShield program tested four Host Defense Fo strains for antiviral activity against Vaccinia virus (VV) and cowpox virus (CV). The 50% water/ethanol extracts of the mycelium grown on rice of Fo strains were diluted 100:1 with H_2O and then were tested for cytotoxicity, allowing for the calculation of a selectivity index (SI), the ratio of antiviral activity to toxicity. The Fo strains generally produced an SI index of at least "active" and some were also found to be "very active" against VV and CV (Stamets, 2005). A variety of influenza strains were also tested, with strong effects observed against influenza B in the viral yield reduction assay (SI >300), more active than ribavirin, the positive anti-viral drug control. Most notably Fo was very active against VV and CV with SIs exceeding 29 and 20 respectively, more active and/or nearly equivalent to cidofovir, the anti-pox drug control (P. Stamets, 2014, 2015).

Secondary bacterial infections are a significant risk to COVID-19 patients and others with viral pneumonia. Lung tissue histology of 74 deceased patients from 2009 HINI revealed 22 cases (29%) of bacterial co-infections. "The most common pathogen was *S. pneumoniae* (10 cases), followed by *Staphylococcus aureus* (seven cases), *Streptococcus pyogenes* (six cases), *Streptococcus mitis* (two cases), and *H. influenzae* (one case)" (CDC, 2009).

Staphylococcus aureus infections have been observed in this patient population. Fo demonstrated inhibitory activity against *S. aureus*, reducing CFU's of this bacterium ~ 10,000x within 72 hours *in vitro,* a different and complementary type of immune support (IEH Laboratories/Seattle, 2008, unpublished & Stamets, 2014).

Another third-party test on Host Defense products by NIS Labs investigated aqueous, ethanol, and solid fractions of Fo for their impact on pro- and anti-inflammatory cytokine and chemokine activity in PBMCs. Notably, the aqueous fraction of Fo produced a "robust upregulation" of 19 out of 22 cytokines assayed, while the solid fraction produced a nearly similar effect, inducing activity of all 22 tested cytokines. The strongest effects were observed on IL1-β, IL-6, MCP-1, MIP1α, MIP1β, ranging from approximately 8000 to 145,000-fold increases. Induction of the anti-inflammatory cytokines IL-1ra and IL-10 were observed as well. Interestingly, MCP-1, MIP-1α and MIP-1β are cytokines that are involved with antiviral activity. Testing at NIS also investigated the immune activation markers CD3, CD56, and CD69 to determine the impact of Fo extracts on natural killer (NK) cells, natural killer T (NKT) cells, and T lymphocytes. Aqueous-soluble fractions of Fo were able to activate these cell types in PBMCs (unpublished).

Polysaccharides extracted from agarikon fruiting bodies inhibited tumor growth and stimulated thymus and spleen growth in mice; as opposed to the positive control 5-fluorouracil that suppressed immune function, agarikon polysaccharide treatments both enhanced immune function and inhibited tumor growth (Hu, Zhang, Feng, Liu, & Guo, 2013).

Similar to the cytokine work on Fo, NIS labs also investigated the impact of Tv on 22 cytokines (Benson et al., 2019). This study investigated the impact of aqueous and solid fractions of initial substrate (IS), fermented substrate (FS), Tv mycelium (TvM), and a FS-TvM blend on immune system potentiation. The researchers focused on the early immune response marker CD69 in several subsets of immune cells. CD69 plays a major role in NK cytotoxicity of target cells and is rapidly induced in NK cells during immune cell activation. In human lymphocytes, TvM produced a robust increase in CD69 and natural killer T cells and also activated T cells and NK cells. Additionally, PBMCs were treated with Tv to determine the impact on inflammatory cytokines. Notably, Tv induced the production of two antiviral cytokines, interferon-gamma (IFN-γ) and macrophage inflammatory protein-1α (MIP-1α). Tv and Fo induced the expression of two key anti-inflammatory cytokines, interleukin-1-receptor antagonist (IL- 1ra) and interleukin-10 (IL-10) and induced strong expression of granulocyte colony-stimulating factor (G-CSF) and interleukin-8 (IL-8), two biomarkers that influence stem cell regeneration.

Ultimately, the data provide a basis for immune activity of TvM and FS through a multifaceted impact on NK cells, anti-inflammatory cytokines, and regenerative cytokines.

Overview of Clinical Studies

A phase I human clinical study from Bastyr University evaluated the impact of Host Defense TvM on post-chemotherapy recovery among breast cancer patients (Torkelson et al., 2012). Chemotherapy generally elicits reduced lymphocyte counts and a corresponding reduction in the activity of natural killer (NK) cells, cytotoxic CD8+ T cells, and B-lymphocyte antigen CD19+ cells. Investigations of patients with SARS-CoV-2 infection reveal reduced abundance of NK and CD8+ T cells, suggesting a similar pattern of immunodeficiency (Zheng et al., 2020).

Retrospective analysis of 522 patients in two Wuhan hospitals confirmed that low counts of T- cells (including CD8+) were associated with mortality (Diao et al., 2020). A case study of a non- severe COVID-19 patient revealed that immune cells including CD8+ T cells were recruited during the illness and persisted for at least a week after recovering from symptoms (Thevarajan et al., 2020). Functional exhaustion of these cytotoxic lymphocytes has been associated with severe SARS-CoV-2 virus infection, implying antiviral immunity may break down during early onset of COVID-19 in patients who become critically ill (Zheng et al., 2020). This phase I clinical study identified turkey tail mycelium (TvM) as a safe post-radiation immunotherapy that may help offset such immunodeficiencies. Oral doses of 6 and 9 g of TvM were found to increase recovery of lymphocyte counts and tumoricidal activity of NK cells. Further, TvM increased counts of CD19+ cells and CD8+T cells ($P = 0.0003$). In addition to influencing tumoricidal activity, cytotoxic T cells are also involved with cellular response to pathogens including viruses and bacteria. Cytotoxic T cells often recruit cytokines such as TNF-α and IFN- γ to combat pathogens, suggesting that Tv may potentially provide immune benefits beyond the context of post-radiotherapy recovery.

Tv ingredients have also been employed in microbiome research with beneficial results. A clinical trial tested PSP from turkey tail against amoxicillin for impacts to GI microbiota compared to controls. Tv PSP acted as a prebiotic in its alteration of the human GI microbiome (Pallav et al., 2014). PSP also modified human fecal microbiota in an earlier in vitro study (Yu, Liu, Mukherjee, & Newburg, 2013). While literature is available on mushroom isolates and derivatives like PSP, PSK, or B-glucans, there is evidence to support the role of other compounds in their absorption and distribution in the human body. One research group found that a structurally distinct lipid acts synergistically with the protein-bound B-glucan in its TLR-2 agonist activity (Quayle, Coy, Standish, & Lu, 2014).

To the best of our knowledge, there have been no human clinical trials of Fo products despite its nearly 2000 year history of use, with the first reports mentioned by the Greek physician Disocorides in 65 AD. Pre-clinical research conducted has utilized the fruiting body rather than mycelium and fermented substrate, assessing the effect of polysaccharide content. Studies assessing *in vitro* activity of Fo mycelial products support their safety and efficacy, with results indicating low cytotoxicity, significant antiviral and antibacterial activity, stimulation of innate immune function, and putative immunomodulatory effects (P. Stamets, 2015).

Since immune dysregulation and induced cytokine storms are associated with disease severity and mortality, antiviral agents may prove insufficient for treatment of respiratory distress in late- stage disease development; targeted immunomodulation may also be required to mitigate the harmful effects of pulmonary inflammation. Polypore mycelial products could constitute a valuable tool for combating COVID-19, given their potential to stimulate immune activity while concurrently modulating harmful inflammation.

Summary
Both mQFPD and FoTv represent potentially lifesaving avenue for the treatment of COVID-19. More specifically, these interventions are likely to be safe, inexpensive, and can be utilized during the early stages of disease when pharmacologic options are limited or unavailable. Further, FoTv may also constitute a means for enhancing the effectiveness of and duration of response to, standard COVID-19 vaccines, as well as for decreasing their side effects. If demonstrated, these properties of FoTv could also potentially contribute to reducing vaccine hesitancy, increasing vaccination rates, and helping to achieve herd immunity.

High quality investigation is urgently required to explore these preventive and therapeutic options for the control of COVID-19.

8. PROGRESS REPORT

Sub-study 1a was fully approved by IRB on April 7, 2021.

On April 8 2021, the FDA removed the partial clinical hold on mQFPD study and has granted full approval to proceed with the proposed study titled "Multicenter 3-Arm, Double Blind, Placebo Controlled RCT of modified Qing Fei Pai Du Tang and Trametes versicolor/Fomitopsis officinalis to Treat COVID-19". The corresponding letter has been attached to this amendment.

9. RESEARCH DESIGN AND METHODS

The following research design applies to each of the following studies:

Sub-study 1a: FoTv vs. placebo for acute COVID-19 patients
Sub-study 1b: QFPD vs. placebo for acute COVID-19 patients
Sub-study 1c: FoTv vs. placebo as an adjunct to COVID-19 vaccination

Sub-studies 1a and 1b of Phase 1 trial will each be 2-arm multicenter double blind randomized placebo controlled clinical trials.
Each of these safety/feasibility sub-studies will be conducted identically with the exception of additional exclusion criteria that will be required for sub-study 1b on account of the presence of herbal components including ephedrine that require these precautions for avoiding herb-drug interactions.

Sub-study 1c will be a single site double blind randomized placebo controlled clinical trial.
This will be a shorter intervention with broader inclusion criteria.

The research design and methods for the larger efficacy trial (Phase 2) will require analysis of these first two feasibility studies, and the final protocol will be submitted as a future amendment.

The primary objective of sub-studies 1a and 1b will be to assess the safety of FoTv or mQFPD, respectively, when used as therapies for acute COVID-19 infection and feasibility of the study protocol.
The primary objectives of sub-study 1c will be to ascertain the safety of FoTv when used as an adjunct to standard COVID vaccination as well as to evaluate its effects on post-vaccine COVID-19 antibody titers and on vaccination-related side effects.

A total of 66 subjects (33 FoTv or mQFPD and 33 placebo) will be enrolled in each of the 1a and 1b sub-studies.
A total of 266 subjects (133 FoTv and 133 placebo) will be enrolled in sub-study 1c.

The study protocol will be implemented and safety, feasibility, clinical, and laboratory data will be collected.

Interested participants will be asked to contact the study team, who will then conduct screening, consenting, and study enrollment. The study will be open to patients who are

a) Mildly-to-moderately symptomatic and have tested positive for COVID-19 (sub-studies 1a and 1b)
b) Scheduled for COVID-19 vaccination (sub-study 1c).
See section 11 for recruitment plan.

Once their eligibility has been confirmed, participants will be randomized to one of two groups by the study statistician:

- Group 1 – either Mycelium of Fomitopsis officinalis and Trametes versicolor (FoTv) for sub-studies 1a and 1c or modified Qing Fei Pai Du Tang (mQFPD) for sub-study 1b
- Group 2 - Inert placebo (encapsulated brown rice)

We anticipate screening approximately 90 or 75 potential candidates per sub-study in order to consent and enroll 66 or 48 participants to account for up to 20% drop-out rate.

Sub-studies 1a and 1b

Once enrolled, all study participants will be receive a package containing the following:

- 14 day supply of study medication (capsules containing either FoTv or mQFPD or placebo)
- Digital thermometer
- Urine pregnancy test (for women of child bearing potential)
- Written instructions on proper usage of study medication
- Paper study daily diary, to include daily medication diary, symptom scores, and temperature/BP measurement data
- A blood pressure cuff or glucometer will be provided to study subjects who require but do not possess one. The study participants are not responsible for lost, stolen, or damaged devices

The study package will be sent via local courier or phlebotomist who will coordinate directly with the study participant to complete delivery. Missed doses will be logged in the provided medication diary, remain unused, and be accounted for at the end of the study. Participants will continue to make every effort to maintain quarantine through vigorous hand washing and appropriate self-isolation measures. All study participants will also receive instruction to strictly avoid alcohol, cannabis, and dairy products during the study period.

During the trial period, participants will be verbally instructed on proper usage of study product, asked to take their temperature twice daily until they reach two consecutive afebrile readings. Participants with prior hypertension will also be required to take daily home measurements of their blood pressure and report any measurements of SBP <90 or >150, or DBP >90 directly to the study team. Any measurements of SBP below 80 or above 180 will be advised to seek immediate medical attention (as specified in Section 15). Participants with prior diabetes will take daily morning glucose measurements and report any blood glucose measurement >200 directly to the study team. Any measurements of blood glucose below 70 will be advised to eat a carbohydrate rich food and report to the study team, and measurements persistently below 70 will be advised to seek immediate medical attention as an immediate priority prior to reporting to the study team. Participants with congestive heart failure or using diuretics will take daily morning weight measurements using a home scale and report to the study team any weight change greater than 3 lbs (1.5 kg) during the study period.

Each participant will receive a paper copy and an emailed study daily diary requesting this information (temperature readings, blood pressure and/or glucometer readings) as well as symptom scores, and medication compliance. This survey (daily diary) will be generated directly through the study database and will interface directly with the secured study database. Participants who are unable to respond to emails will be allowed to record data into the provided paper diary and report the information at the completion of the study to a member of the study team by phone or photo at intervals specified below. Once this information has been reported, there will be no need for the study team to collect the diary.

Any adverse events, as well as any escalation of care, including urgent care, emergency room, or hospitalization, will be reported to the study team after appropriate medical care has been received, via a dedicated phone number or email address that is specific for urgent matters. A dedicated phone number will be available throughout the entire study period to call a physician member of the study team who is available 24 hours a day, 7 days per week, for urgent matters. Non-urgent messages will be routed to a dedicated email address or study coordinator.

If a study participant is hospitalized as a result of COVID-19, the participant will be instructed to discontinue study medication and the study team will follow up with either the patient or the emergency contact at the end of the trial period, or following the hospitalization, to determine final outcome and obtain laboratory records from the hospitalization.

At Day 14, a telephone call will be conducted among participants who have not been hospitalized to assess for COVID-19 symptoms, review any adverse events, review concomitant medications, drug accountability (participants will take pictures of

their empty bottles and send to the study team), and harmonize any data discrepancy between their daily diary and the study database. At this time, they will have completed the investigational product.

At the time of the Day 14 telephone call, participants who have not been hospitalized will be directed to obtain end-of-trial blood draw via outpatient laboratory or in-home phlebotomy.

A second follow up telephone call will be conducted among all participants, inclusive of hospitalized participants, on day 28 (14 days after completion of the medication) to ask about COVID-19 symptoms and adverse events. Participants who remain hospitalized during this time will be placed on a registry for members of the research team to contact every 4-7 days until they are discharged.

If a study participant is unable to participate in these phone conversations due to medical illness, emergency contacts will be allowed to supply this information. This will be explicit in the consenting process. If the subject's condition does not allow for these questions to be answered, hospital records will be reviewed to supply as much information as is possible.

A third follow-up telephone call will be conducted 1 month after their second telephone call (day 58, +/-5 days) to assess for residual symptoms including the need for prolonged physical or pulmonary rehabilitation.

Study participants will be followed (phone, text, or email) for 14 dosing days, and contacted 14 days and 44 days following their final dose. The total duration of each subject's participation in the study is expected to be 2 months.

Sub-study 1c

Once enrolled, all study participants will receive a package containing the following:

- Four day supply of study medication (capsules containing either FoTv or placebo)
-
- Written instructions on proper usage of study medication
- Paper study daily diary, to include daily medication diary, symptom scores, and temperature/BP measurement data

During the trial period, participants will be verbally instructed on proper usage of study product and to assess their symptoms. Each participant will receive a paper copy and an emailed study daily diary to record symptoms and symptom scores, medication compliance, and any other medication use.

Participants will be asked to report to the study team any adverse events, either of the study medication or of the vaccination itself, including urgent care, emergency room, or hospitalization.

Subjects will be contacted by phone by the study team 2 weeks after vaccination # 1, 4 weeks after vaccination # 1, 2 weeks after vaccination # 2 (if applicable), 4 weeks after vaccination # 2 (if applicable), 6 months after baseline, and 12 months after baseline to report any symptoms.

Clinical Assessments:

1. Demographics

Demographic information (name, age, gender, race/ethnicity, address, contact and emergency contact) will be recorded at Screening

2. Medical History

A targeted medical history, including history of current bleeding disorders, kidney disease, liver disease, immunocompromised status, and pregnancy/lactation status will be recorded at Screening. Updated medical history including medication reconciliation and adverse effects, will be recorded at:

- Baseline, Study Treatment Days 1 and 14, and at Study Days 28 and 58 for sub-studies 1a and 1b; or
- Baseline, 2 weeks after vaccination # 1, 4 weeks after vaccination # 1, 2 weeks after vaccination # 2 (if applicable), 4 weeks after vaccination # 2 (if applicable), 6 months after baseline, and 12 months after baseline (for sub-study 1c).

3. Concomitant Medications

All concomitant medication and concurrent therapies will be documented at

- Baseline/Screening Visit 1, Day 14 EOT visit, Day 28 Follow-up visit, and Day 58 EOS visit for sub-studies 1a and 1b; or
- Baseline, 2 weeks after vaccination # 1, 4 weeks after vaccination # 1, 2 weeks after vaccination # 2 (if applicable), 4 weeks after vaccination # 2 (if applicable), 6 months after baseline, and 12 months after baseline (for sub-study 1c)

Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

4. Symptoms

Study participant will report their COVID-19 symptoms and scores at the screening call and will receive a paper copy and an emailed daily diary requesting information on COVID-19 symptoms, symptoms' severity scores and potential medication side effects. Participants who are unable to respond to emails will be asked to directly record this data into the provided paper study daily diary and then will be contacted daily to report this information to the study coordinator.

5. Vital Signs (to be collected for participants of sub-studies 1a and 1b only):

- Body temperature will be self-reported at Study Treatment Day 1, daily throughout the treatment period until two consecutive afebrile results are seen, and again at the End of Study Treatment Day 14.
- Study participants with a baseline diagnosis of hypertension will be instructed to take daily blood pressure measurements using a home blood pressure cuff. If they do not have access to a home blood pressure cuff, members of the study team will purchase one online and have it sent next-day. They are to contact the study team with any measurement of systolic blood pressure above 150 or below 90, as well as diastolic measurements above 90. Any measurements of SBP below 80 or above 180 will be advised to seek immediate medical attention as specified in section 15.
- Study participants with a baseline diagnosis of diabetes mellitus who are on insulin or sulfonylureas will be instructed to take blood sugar measurements in the morning, as well as three times daily before meals. If they do not have access to a home glucometer, members of the study team will purchase one online and have it sent next-day. Any measurements of blood glucose below 70 will be advised to eat a carbohydrate rich food and report to the study team, and measurements persistently below 70 will be advised to seek immediate medical attention as an immediate priority prior to reporting to the study team.
- Study participants with a baseline diagnosis of congestive heart failure or diuretic use will be required to monitor their weight daily and notify the study team if their weight changes by greater than 3 lbs (or 1.5 kg) throughout the 14 day trial period. If they do not have access to a home scale, members of the study team will purchase one online and have it sent via next-day delivery.
- Study participants who are not hospitalized yet remain febrile and report ongoing symptoms at EOT visit (Day 14) will continue to take their temperature and be contacted every 2-3 days by members of the study team until they are no longer symptomatic and are afebrile.

6. Adverse Events

- Adverse events are being monitored in three formats: daily communication with study team to report symptoms and adverse event reporting as described elsewhere (see section 15), labs at the end of the 14-day treatment period, and urgent reporting of adverse events via a 24 hour physician staffed phone line (see below). The study team will have a daily communication with subjects where our study coordinators will review all subjects' symptoms and their severity. This information will be tallied daily and will be reported to each site's PI and study main PI and medical monitor. Furthermore, they will be reported to the study DSMB and IRB.
- Information regarding occurrence of adverse events will be captured on the IRB approved standard case report form (CRF) as follows: Duration (start and stop dates and times), severity/grade, outcome, and relation to study medication).

- Any deterioration in cardiac or pulmonary status will be immediately escalated to proper medical attention and that any study participant who is hospitalized for any reason will be required to stop study medication irrespective of the cause of this adverse event. These events will subsequently be reported to the DSMB and IRB for review.
- A list of anticipated side effects of FoTv or mQFPD will be available to study coordinators, as will a list of known symptoms of COVID-19. Any reported symptom on the COVID-19 list will be referred to the study participant's primary care provider.

Clinical Laboratory Measurements:

Sub-studies 1a and 1b:
Sample collection (nasal swab and approximately 25 mL of whole blood with an additional 50 mL whole blood optional) will occur at two time points: (1) screening/baseline and (2) end-of-study. The purpose of the time point (1) sample collection will be to obtain specimens for both screening and baseline clinical laboratory tests. The additional 50 mL of whole blood will allow for in-depth analysis of the peripheral mononuclear cell, including rare immune cell subsets. This collection is optional. The purpose of the time point (2) sample collection will be to obtain specimens for end-of-study clinical laboratory tests.

(1) Screening/Baseline:

Screening:

The following laboratory tests will be conducted and reviewed prior to study initiation to confirm that liver and renal failure (exclusion criteria) are not present:

- Basic Metabolic Panel
- Liver Function Testing
- Prothrombin Time and Partial Thromboplastin Time

Baseline:

The following laboratory assays will be conducted to establish baseline values for safety measures:

- Complete Blood Count with Differential
- Ferritin
- D-Dimer
- Lactate Dehydrogenase
- C-Reactive Protein
- Troponin
- T-cell differentiation panel
- Additionally, plasma, serum, and whole blood will be collected and banked for cytokine, immunological, and metabolomic assays.

Please note that nasal swab or salivary samples will be collected at day 0 (baseline) as well as at days 7 and 14 for all subjects.

A urine home pregnancy test will be delivered to women of childbearing potential and the results will be self-reported to the study team prior to starting study medication.

(2) End-of-Treatment:

For patients who are not hospitalized, the study phlebotomist will collect their specimens at Day 14 for the following laboratory tests:

- Basic Metabolic Panel
- Complete Blood Count with Differential
- Liver Function Testing

- Prothrombin Time and Partial Thromboplastin Time
- Ferritin
- D-Dimer
- Lactate Dehydrogenase
- C-Reactive Protein
- Troponin
- T-cell differentiation panel
- Salivary or nasal swab samples will be collected for SARS CoV-2 viral load assays
- Plasma, serum, and whole blood will be collected and banked for cytokine, immunological, and metabolomic assays

For subjects who require hospitalization by Day 14, results of the following laboratory tests will be obtained from their hospital records (please note that these tests are routinely conducted as part of COVID-19 treatment and results should be available within subjects' medical records):

- Admission Basic Metabolic Panel,
- Complete Blood Count with Differential, and
- Liver Function Testing.

Please note that medical records will also be reviewed for SARS-CoV-2 viral load, any inflammatory biomarkers (CRP, procalicitonin, IL-6, ferritin, D-dimer, lactate dehydrogenase) as well as markers of myocarditis (troponin, CK-MB) and further lymphocyte differentiation (T-Cell differentiation panel).

Sub-study 1c:
Sample collection will occur at the following time points:

- Single dose vaccine (such as J&J): baseline, day 14, day 28, and 6 months post vaccination
- Two-dose vaccine (such as Pfizer or Moderna): baseline, day 14, two weeks after your second dose, and 6 months post vaccination
- Vaccine booster: baseline, day 3, day 14, and 6 months

For all time points:

The following test will be run to establish values of immunogenicity against SARS CoV-2:

- SARS CoV-2 IgG antibody titer
- Cytokines and T-cell assays

For time points Baseline and Day 14:

The following laboratory assays will be conducted to ascertain FoTv safety:

- Basic Metabolic Panel
- Liver Function Tests

Test Product Dose and Route of Administration

Participants in sub-studies 1a and 1b: The dosage of FoTv or mQFPD is 8 capsules three times a day for 14 consecutive days. It does not need to be consumed with food. It is best taken at least 30 minutes before OR at least 60 minutes after meals, in the morning, noon and evening. Accidentally missed doses will not need to be taken at a later time, but will be recorded in a daily diary. Should swallowing capsules be an issue, they can be opened and dispensed into water or juice for easy ingestion.

Participants in sub-study 1c: The dosage of FoTv is 8 capsules three times a day for 4 consecutive days ((starting with the day of the first vaccination). It does not need to be consumed with food. It is best taken at least 30 minutes before OR at least 60 minutes after meals, in the morning, noon and evening. Accidentally missed doses will not need to be taken at a later time, but

will be recorded in a daily diary. Should swallowing capsules be an issue, they can be opened and dispensed into water or juice for easy ingestion

Control Product Dose and Route of Administration

The placebo control has been developed by the mycelium supplier and contains freeze-dried cooked organic brown rice. It has been encapsulated to a cGMP standard. It has been packaged identically to the test products and appears identical to the verum product (FoTv or mQFPD) by an untrained study participant. Subjects will be instructed to take 8 capsules three times with the same dosing instructions as the study medication for each respective sub-study (1a, 1b, or 1c) as described above.

Sample Size Justification:

We anticipate screening approximately 90 or 300 potential candidates for each sub-study in order to consent and enroll 66 or 266 participants per study 1a/b or 1c respectively.

The primary focus of sub-studies 1b and 1c, as with sub-study 1a, will be on ascertainment of the safety of the natural products under study. The study 1c will also examine efficacy of the mushroom blend.

Therefore, like sub-study 1a, sub-study 1b will also include 27 participants per arm as well as an additional 6 participants per arm to account for an anticipated 20% rate of study dropout. Thus, N = (33/arm x 2 arms) = 66.

Sub-study 1c:

This sub-study will include 266 subjects as well as an additional 53 participants to account for an anticipated 20% rate of study dropout. Number of subjects was adjusted due to recent introduction of the vaccination booster shot and availability of extra funding which allows us to expend study aims to further test of the treatment efficacy.

For other objectives of sub-study 1c, sample size was determined using the RMASS program (http://tigger.uic.edu/~hedeker/ml.html)

Based on our sample size estimation, we are confident that the enrollment of 66 (1a/1b) or 266 (1c) participants will provide a sufficient number of subjects to evaluate these outcomes with medium effect size while also ascertaining safety (Tubert-Bitter et al., 2000; Zhang P, 2003).

Statistical Methods And Considerations

For all sub-studies (1a, 1b, and 1c), data management and statistical analysis will be performed by the Krupp Biostatistical and Data Management Core and will employ the Krupp Data System (KDS). A computer-generated randomization list will be prepared by the study biostatistician and will be used to randomize subjects into one of the two treatment groups with equal probability. For sub-study 1c only, equal number of subjects based on age (18-55 and >55) and BMI (<30 and ≥ 30) will be randomized to the treatment groups. For all sub-studies, randomization tables will be prepared at the beginning of the study and will be maintained by the study biostatistician.

Within each of the sub-studies, the comparability of the two treatment groups in terms of baseline demographic and clinical features will be tested with analyses of variance (ANOVAs) for continuous variables and Chi-square analyses for dichotomous variables. Descriptive statistics and exploratory graphing will be used to assess the distribution, normality, and homogeneity of the data. If needed and applicable, the continuous outcome data will be transformed using an appropriate transformation such as a log transformation. Missing data will be examined to assess randomness and informativeness using methods developed by Diggle (1989). Similarly, we will test whether dropout is random or systematic by comparing the dropouts with the study completers in terms of the baseline data. An absence of significant differences would support the random nature of dropout.

The primary aims of our data analytic strategy will be directed toward assessing the safety of the interventions, antibody titers, vaccine side effects, adherence to treatment, and retention rate. This will help to provide guidance to inform any

required methodological modifications. The safety data will be summarized by treatment group and site. Adverse events will be tabulated. These will include the number of participants for whom the event occurred, the rate of occurrence, and the severity and relationship of adverse events to study treatment. Safety data will be analyzed using ANOVAs for continuous variables and Chi-square analyses for dichotomous variables at each time point. Wilcoxon-Mann-Whitney rank-sum test will be used to analyze treatment arm verses control arm across study visits and sites. We anticipate using non-parametric tests because the majority of the outcome measures used in our research may not be normally distributed. The Kruskal-Wallis test will be used to determine whether samples from each of the two arms originated from the same distribution. Since nonparametric tests are based on complete data and ignore missing follow-up data, general linear mixed regression modeling (Gibbons et al, 1988; Hedeker et al, 199; Laird et al, 1982) will be used to confirm the results of the nonparametric tests. The two arms will be compared over time with a focus on the treatment by Time interaction effect. Mixed regression modeling offers robust handling of missing data (Little, 1996) with an assumption that the data is missing at random. This method allows the inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. This method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction.

A detailed list of feasibility outcomes is provided in the previous section. Briefly, feasibility outcomes will be assessed by determining: 1) Numbers of potentially eligible and ineligible patients, number contacted, and consent rates. 2) Feasibility of recruiting sites in which staff are interested in participating in a future main trial. 3) Rate of retention in the trial, including response rates to questionnaires and individual measures. 4) Intervention fidelity and adherence using case report forms and patient-completed personal diaries. 5) Determining the primary outcome measure for the main trial by assessing and comparing sensitivity to change of the measures and other statistical properties, comparing follow-up rates of different methods of data capture and of individual measures, and evaluating which outcome measures best reflect the patients' recovery goals, as identified from the collected data.

As indicated above, the primary aims of our data analytic strategy for sub-studies 1a and 1b will be directed toward examining the safety and feasibility of the treatments. Although it is not our major focus, we also aim to estimate effect sizes to assist in future power calculations. However, recent work by Kraemer (2006) has highlighted important limitations of this aim due to the large standard error surrounding the pilot study effect size. As a result, the primary focus of our analyses will remain on safety and feasibility and we will report our findings with this limitation in mind. Our goal is to collect important data regarding our ability to implement recruitment strategies, and the safety and feasibility of the treatments and measurements. Information derived from this research will lead to better-designed full-scale studies and help inform decisions regarding whether it is worthwhile to commit additional resources to future treatment development. Due to our small sample size, our statistical analytical findings will be interpreted with caution. Sub-study 1c will include sufficient number of subjects to test for treatment efficacy.

Data will be analyzed from all randomized subjects. All statistical tests will be two-tailed. Differences will be considered statistically significant provided a p-value of 0.05 or less is obtained. The significance level for the tests will be adjusted with a Bonferroni correction for multiple comparisons, if needed. Data will be analyzed using SPSS version 27.

10. HUMAN SUBJECTS

Sub-study 1a Fo-Tv vs. placebo:
66 total patients (N=27 in each of two study arms: FoTv and placebo plus an additional 20% per arm to guard against dropout) who have tested positive for COVID-19 and are mildly-to-moderately symptomatic will be included in the study.

Inclusion Criteria

1. Positive COVID-19 diagnosis within the prior 72 hours or within 9 days of symptom onset
2. Age 18 and older

3. Women of childbearing potential must have a negative urine or serum hCG. Women of childbearing potential must have a negative serum pregnancy test at screening and agree to use contraception throughout the study period.
4. Capable of documenting vitals, symptoms, and study product intake daily and communicating this information to the study team
5. Willing to avoid alcohol, cannabis and dairy products during the study period.

Exclusion Criteria

1. Any of the following symptoms which, according to the CDC, require hospitalization:
    a. Trouble breathing
    b. Persistent pain or pressure in the chest
    c. New confusion or inability to arouse
    d. Bluish lips or face
2. Current use of investigational agents to prevent or treat COVID-19
3. Known liver disease (ALT/AST >3x ULN or diagnosis of cirrhosis)
4. Known renal disease (eGFR < 60 ml/min) or acute nephritis.
5. Uncontrolled hypertension (SBP>140 or DBP>90 while on medications)
6. Pregnant or breastfeeding women

Sub-study 1b mQFPD vs. placebo:

66 total patients (N=27 in each of two study arms: mQFPD and placebo plus an additional 20% per arm to guard against dropout) who have tested positive for COVID-19 and are mildly-to-moderately symptomatic will be included in the study.

Inclusion Criteria

1. Positive COVID-19 diagnosis within the prior 72 hours or within 9 days of symptom onset
2. Age 18 and older
3. Women of childbearing potential must have a negative urine or serum hCG. Women of childbearing potential must have a negative serum pregnancy test at screening and agree to use contraception throughout the study period.
4. Capable of documenting vitals, symptoms, and study product intake daily and communicating this information to the study team
5. Willing to minimize alcohol, cannabis and dairy products during the study period.

Exclusion Criteria

1. Any of the following symptoms which, according to the CDC, require hospitalization:
    a. Trouble breathing
    b. Persistent pain or pressure in the chest
    c. New confusion or inability to arouse
    d. Bluish lips or face
2. Current use of investigational agents to prevent or treat COVID-19
3. Prisoners
4. Known liver disease (ALT/AST >3x ULN or diagnosis of cirrhosis)
5. Known renal disease (eGFR < 60 ml/min) or acute nephritis.
6. Uncontrolled hypertension (SBP>140 or DBP>90 while on medications)
7. Pregnant or breastfeeding women
8. Allergy to tree nuts
9. Bleeding dyscrasia or on anticoagulation (aspirin and/or clopidogrel is allowed)
10. Use of Tolbutamide
11. Use of systemic corticosteroids (hydrocortisone, cortisone, prednisolone, betamethasone, methylprednisolone, prednisone, dexamethasone). Inhaled budesonide is to be allowed.
12. Use of digoxin
13. Use of Oxacillin
14. Use of Interferon

15. Use of Vincristine
16. Use of Cyclosporine
17. Use of Amiodarone
18. Patients with a past medical history of epilepsy
19. Use of monoamine oxidase inhibitors (MAOI)
20. Use of Methamphetamine within the prior 30 days
21. Use of Cocaine within the prior 30 days
22. Use of aminoglycosides, carbamazepine, flecainide, lithium, phenytoin, phenobarbital, rifampicin, theophylline and warfarin

Sub-study 1c Fo-Tv vs. placebo:
266 total patients who are receiving COVID-19 vaccination will be included in the study.

Inclusion Criteria

1. Scheduled to receive COVID-19 vaccination
2. Age 18 and older

Exclusion Criteria

1. Current use of investigational agents to prevent or treat COVID-19
2. Prisoners
3. Known liver disease
4. Known renal disease or acute nephritis.
5. Pregnant or breastfeeding women
6. Use of immunosuppressive medication

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Study participants will be recruited from COVID-19 testing sites, vaccination centers, UC, and other clinics. The 1a and 1b sub-studies will be open to patients who have received a positive COVID-19 diagnosis from CLIA certified and fully accredited COVID-19 testing laboratories and clinics. Sub-study 1c will be open to patients scheduled to receive vaccination at any vaccination centers or sites. Study participants will be asked to provide the contact information of their primary care physician so that the study team can contact them as needed.

The following methods may be used to recruit potential participants:

(1) Dissemination of IRB-approved recruitment materials throughout dedicated COVID-19 testing sites and clinics throughout California that are local to or affiliated with each of the participating UC study sites. Interested participants will be directed to contact a dedicated phone number or email address. Participation will be open to all members of the community.
(2) Review of medical charts for potential participant identification and selection. We will recruit participants from UC primary care patients who have screened positive for COVID-19 and meet other study eligibility criteria. Potential participants will be contacted via "MyChart" using the HRPP-approved recruitment flyer, or through their PCP using the same content. EPIC will be flagged and the physician will be notified via a secure email about their patient's participation in this study. The study consent form will be uploaded to Epic via Media Manager
(3) Use of the "ResearchMatch" platform
(4) Use of social media to advertise the study using text from the HRPP-approved materials.

Waiver of Documented Consent/HIPAA is requested for the purpose of aiding in research recruitment, identifying prospective research participants who meet the eligibility criteria for enrollment review

12. INFORMED CONSENT

A research coordinator will contact interested individuals to discuss the study details, answer any questions, and obtain informed consent orally. The consent document may also be emailed to the individual and then explained over the phone

In order to minimize the risk of transmitting infection during the COVID-19 pandemic and best comply with safety recommendations and regulations, personal contact, as well as the back-and-forth mailing of physical documents, with COVID-19 infected patients must be avoided. Therefore, the process for obtaining appropriate procedural informed consent from patients' needs to be revised. Signed informed consent from the sub-studies 1a and 1b subjects will be collected using the UCSD DocuSign part 11 certified service application.

The study team may also use an alternate form of consent (as indicated in FAQ12 of the FDA's Conduct of Clinical Trials of Medical Products During the Covid-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, dated 1/27/21):

The consent form may be sent to the trial participant or their legally authorized representative by facsimile or email, and the consent interview may then be conducted by telephone when the trial participant or their legally authorized representative can read the consent form during the discussion. After the consent discussion, the trial participant or their legally authorized representative can sign and date the consent form. Options for returning the document to the clinical investigator may include facsimile, a photographic image sent through electronic means, scanning the consent form and returning it through a secure email account, posting it to a secure Internet address, or having it picked by a study team member.

Prior to any investigation-related procedures, documented informed consent from sub-study 1c participants will be obtained by the study team, after explaining the objectives of and procedures involved in this investigation.

HIPAA Authorization waiver is requested for three reasons:

- To facilitate recruitment (as described above)
- The PHI will be used for three discrete purposes**:** To identify COVID-19 patients with confirmatory test and have a means for direct communication within this narrow time window. Note that for those individuals who decline to participate, any identifying information will be destroyed.
- To collect end-of-study data from any patients that are hospitalized during their involvement in the study, in order to 1) compare admission laboratory evaluations to baseline laboratory evaluations to determine safety, and 2) provide sufficient data for an endpoint adjudication committee to determine if primary and secondary endpoints were met. This component is minimal risk because the data analysis will be done retrospectively and will not impact the medical care of the study participant.

The data gathered as described above will explicitly be used only for the purposes of this study and will not be used for marketing, recruitment, or shared with anybody outside of the authorized members of the study team. Once collected, PHI will be removed and replaced with a unique patient identifier for analysis. The PHI will only be reviewed by properly trained and authorized study team members. Only eligibility criteria will be accessed/reviewed.

The measures described elsewhere in this document to protect the privacy of study participants will also be applied to these data. As with any digital technology, even the most secure data networks are at times subject to compromise. However, this small risk is outweighed by the direct benefit to the study participant of having accurate prior laboratory data to confirm their safety.

We plan to:

- Protect identifiers from improper use and disclosure. The data will not be used as a part of the research data. Only properly trained and delegated study team members will be authorized to perform the screening/chart review.
- Destroy identifiers at the earliest opportunity or provide justification for retaining the identifiers. All identifiers will be destroyed immediately after reviewing the daily list with the doctor. No PHI will be stored or utilized, unless a potential subject has agreed to participate, consented and signed a HIPAA authorization to do so.

The PHI data will not be re-used or disclosed for other purposes

Subjects will be granted a copy of the final study publication on request.

13. ALTERNATIVES TO STUDY PARTICIPATION

Sub-studies 1a and 1b:
The FDA has recently authorized co-administration of bamlanivimab and etesevimab for emergency use for the treatment of mild to moderate COVID-19 in adults who are at high risk for progressing to severe COVID-19 and/or hospitalization. Please be informed that this treatment option may be available to you, along with all other monoclonal antibody treatments authorized by FDA, as appropriate. Based on the totality of scientific evidence available, these therapies may be effective in reducing COVID-19 related hospitalization and/or deaths

Sub-study 1c: The alternative to participation in this study will be to not participate.

14. POTENTIAL RISKS

Risks from participation in this study may include the following:

Medicinal mushroom risk

Mushrooms have been widely consumed throughout the globe for hundreds of years. In China, the use of mushrooms extends back in time for millennia. Their overall tolerability in clinical settings has been documented by several research groups. Compared to most herbal products, safety research on mushroom products tends to be more robust, and many large-scale clinical trials of medicinal mushroom compounds have not revealed significant adverse events or drug-drug interactions (Sullivan, Smith, & Rowan, 2006). Eleven phase I, II, and III clinical trials in stomach, colorectal, esophageal, and breast cancer patients found immunomodulatory benefits with Tv treatment without significant adverse effects (Standish et al., 2008). The Host Defense product line (which will be providing the mushroom products to the study) launched in 2009 and has sold hundreds of millions of units of mushroom products. Consumer adverse event reports have been recorded in compliance with FDA regulations, and have been markedly low--0.003% for Fo and 0.002% for Tv.

In regard to purity of material, identity by HPTLC and microbiological testing is conducted on each batch of Host Defense finished products. Heavy metal (As, Pb, Hg, Cd) and pesticide (USP 561) testing is carried out on the raw material. The products are manufactured in full compliance with 21 CFR Part 111 Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements.

FoTv risk

Host Defense Tv mycelium has demonstrated immunological efficacy in preclinical and clinical research settings. A review of adverse data from Host Defense indicates that the primary adverse reaction recorded with Tv is gastrointestinal distress- typically nausea but also diarrhea, constipation, or bloating/gas (Torkelson et al., 2012). The lack of observed cytotoxicity in the neutral red and viral yield reduction assays conducted at the BioShield Biodefense project indicates tolerability on a basic cellular level (P. Stamets, 2014, 2015). In a separate research effort with Washington State University, agarikon has been well tolerated in honeybee populations (unpublished). No clinical safety data could be identified in the literature. Host Defense product adverse event records reveal extremely few complaints - the manufacturer has received two reports of nausea since 2016, with no other reported adverse events. From 2016 to present, more than 500,000 units of Host Defense Turkey Tail and 60,000 units of Host Defense Agarikon have been consumed, thus establishing a good safety profile for human consumption.

Effects of upregulation of IL-1-β and IL-6 on COVID-19 disease progression

Concern has been raised regarding isolated polysaccharide extracts and induction of IL-1B, an inflammatory cytokine that may exacerbate the runaway inflammatory presentations in later stages of the COVID-19 disease (Alschuler et al., 2020). Polysaccharides in mushrooms have been shown to initiate an immune response, sparking activity of TNF-a, IL-1B, IL-6, and other pro-inflammatory proteins involved in acute immune activation. However, other biologically active compounds in mushrooms and mycelium (such as the sterols, phenols, and other terpenoid compounds) are important for the resolution of this inflammatory response, inducing anti- inflammatory cytokines such as IL-10 and

IL-1ra (Davis et al., 2020, Davis et al. 2020 unpublished). Therefore, an unextracted whole mushroom mycelium complex impacts the immune system in a more balanced and modulatory manner.

Nevertheless, in its review of the IND application for this study, the FDA raised the following as a non-clinical hold issue regarding FoTv:

Because FoTv may stimulate immune function, we are concerned these products may accelerate the development or exacerbate the magnitude of COVID-19, a disease that is typically associated with excessive or aberrant host immune responses (i.e., cytokine storm). Specifically, we are concerned about the in vitro finding that Fo robustly upregulates cytokines IL-1-β and IL-6 ranging from 8,000- to 145,000-fold. Please further explain this finding and how it translates clinically, particularly in the context of COVID-19 and the risk of accelerating or exacerbating disease progression.

While IL-1-β and IL-6 upregulation effects have been observed with aqueous extracts of Fo in vitro, these findings warrant additional context and explanation for COVID-19 clinical studies. Firstly, these pro-inflammatory immune protective cytokines are being discussed in the context of monoclonal antibody treatment for COVID-19: IL- 1β, IL-6, and TNF-α. Secondly, the non-overlapping, post-aqueous ethanol extraction showed a decrease in IL-1-β and IL-6, demonstrating complex and differential effects on immune system functioning. While Fo aqueous fractions increased levels of pro-inflammatory and immune activating cytokines, it also triggered robust increases in the anti-inflammatory cytokines IL-10 and IL-1ra (as did Tv). These dual and opposing effects by different fractions of Fo may suggest a 'regulating' effect in vivo.

Fo has triggered the expression of cytokines relevant to other facets of viral pneumonic disease. Eotaxin is involved in the inflammatory recruitment and infiltration of eosinophils and other phagocytic cells to the lung tissue. The antiviral peptides IFN-γ, MIP-1α, and MIP-1β are currently being discussed in the context of SARS-Cov-2 infections, and whether high or low levels are beneficial or detrimental. IL-4, also upregulated by Fo, has protective effects in influenza, SARS, and pneumonia.

In terms of predicting potentially adverse clinical responses to FoTv, we are encouraged by the lack of reported adverse effects of these products pertaining to the exacerbation of viral infection during cold & flu season, which have sold hundreds of thousands of units over the past decade. While post market adverse effects reports are not considered to be high-quality evidence, they offer additional context into overall product safety and tolerability in a consumer population.

It is also worth mentioning that these effects were observed in PBMC cells from healthy donors. The clinical effects of FoTv in COVID-19 patients are unstudied and an adverse effect may present. We have relied on the Phase 1 safety study to monitor for any adverse effects that may result from FoTv administration.

mQFPD risk

The modified Qing Fei Bai Du preparation is a blend of 21 total herbs. Please refer to Appendix 1.pdf which provides a detailed safety profile of each of the herbs which was completed with the help of John K. Chen, Ph.D., Pharm.D., O.M.D., L.Ac. who is the author of "Chinese Medical Herbology and Pharmacology," a seminal textbook on Chinese herbal pharmacology. Each of the potentially negative herb-drug interactions listed in the document is reflected in the exclusion criteria and monitoring requirements.

As discussed above, a recent clinical trial of 98 patients using the complete 196g decoction dose of mQFPD daily for 9 days demonstrated the following adverse reactions: 4 patients developed symptoms of nausea and vomiting, 2 patients developed symptoms of dizziness, and 1 patient developed symptoms of rash. When reported as adverse reactions per total days of treatment, the incidence of adverse reactions was 0.07% (Wang 2020). By comparison, this trial will utilize an equivalent to 74.5g per day for 14 days.

1. Of note, three of the herbs in the original QFPD formulation have additional concerns that are addressed below. The herbs and concerns are addressed as follows.Ma Huang (Herba Ephedrae)
    - This herb has a long history of use in China as well as domestically for viral respiratory infection, part of which is attributed to the presence of ephedrine. Unfortunately, in the 1990s it became used in extracted forms as an OTC stimulant. Subsequently, the FDA restricted OTC sales to respond to

concerns of abuse potential, but it remains available to be prescribed domestically by licensed TCM practitioners.

- In consultation with the Study Team of TCM practitioners, this herb is of central medicinal value in the formula and cannot be replaced. The dosages of ephedrine used in this study will be far lower than they were in OTC extracted forms prevalent in the 1990s.

- To ensure safety, concerns regarding drug-drug interactions and adverse events are addressed in the exclusion criteria as well as our safety monitoring as described in the protocol, which includes daily blood pressure measurements for hypertensive study participants. In addition, a certificate of analysis (COA) will be produced demonstrating specific quantities of ephedrine in the Ma Huang BRM. If the total daily ephedrine contained within 12g of mQFPD capsules exceeds the recommended maximum of 150mg per 24 hours, we will notify the FDA and amend the quantity of Ma Huang in the formula as appropriate.

2. Xi Xin (Radix et Rhizoma Asari): This herb is of concern due to the possibility of improper preparations which have contained Aristolochic acid (AA). Consequently, this herb has been restricted from importation by the FDA.

    - In consultation with the study's panel of TCM practitioners, this herb is also of central medicinal value and cannot be replaced.

    - To ensure proper safety standards, a certificate of analysis (COA) is attached demonstrating non-detectable quantities of AA by HPLC with tandem mass spectroscopy LC/MS/MS. This analysis was conducted on the specific batch of botanical raw material to be used in final production of study material.

3. Kuan Dong Hua (Flos Farfarae) is present in the original QFPD formula being used in China. This has been substituted with Pi Pa Ye (Folium Eriobotryae) for the purpose below:

    - This herb (Flos Farfarae) contains pyrrolizidine alkaloids (PA) and may be linked to liver injuries. The FDA prohibits the use of herbs that contain PA.

    - In consultation with the study's panel of TCM practitioners, this herb is not of central medicinal value and can be replaced. To avoid this issue of PA, this herb has been substituted with Pi Pa Ye (Folium Eriobotryae) in the research formulation.

This substitution requires the formula be renamed with the moniker modified QFPD, or mQFPD, to reflect the substitution of Kuang Dong Hua with Pi Pa Ye.

In addition to these concerns regarding specific herbs, Chinese medicine formulations in general have had a history of containing inappropriate amounts of heavy metals in the final protocol. For this reason, both the raw herbs and the final investigational product will be extensively tested and analyzed for heavy metals, the results to be included in the COA as specified in section 8.3.

Lastly, concerns of herb identification are present in all herbal products. To address these concerns, each of the 21 herbs in the preparation will be traceable back to its original source by the supplier by chain of custody. Further, each of the 21 herbs will undergo identification verification testing to confirm herb identity, with information submitted to the FDA for final approval prior to the initiation of recruitment.

Brown Rice Placebo Risk

Over the past decade, we at the UCSD Centers for Integrative Health have worked with hundreds of patients with a wide range of disease states including various types of cancer, CAD/CHD, NIDDM, inflammatory bowel disease, and other digestive and autoimmune diseases. In our clinic and several clinical trials we are supporting, we have been offering Medical Nutrition counseling with RD's, diet-focused Integrative Medicine counseling with nutritionally-trained MD's, plant-based cooking classes, dietary coaching, and rigorous nutritional and anthropometric assessments. And on our Integrative Nutrition certificate program, we have been training healthcare professionals in basic nutrition science, clinical nutrition, and the advanced use of food as medicine. In our experience, we have found brown rice, a gluten-free whole grain, to be the single well-tolerated food among our patients. We specifically selected it for the placebo for this reason.

Some have raised hypothetical concerns about problems with grain consumption: (1) gluten exposure, (2) glycemic control in pre-diabetic and diabetic patients, and (3) arsenic contamination. Brown rice: (1) does not contain gluten, (2) tends to improve glycemic control in most individuals (the glycemic index of brown rice is 40% lower than the maltodextrin in a standard "sugar pill"), and (3) poses virtually no risk of arsenic toxicity unless grown in contaminated soils and consumed in large amounts for long periods of time. In the amounts that will be used in this study (24 capsules/day x 500 mg/capsule x 14 days), subjects will be asked to consume just under ½ oz of rice per day - or, to put it in context - the equivalent of one small (6 oz) bowl of brown rice over the course of the study. There is no known risk at this level of consumption.

Virulogic risk

According to the WHO, approximately 81% cases of COVID-19 are mild to moderate, and severe disease may require hospitalization in approximately 19% of cases. A total of approximately 5-10% of COVID-19 patients may ultimately require ICU level of care which may include intubation. The CDC estimates the case fatality rate among COVID-19 patients is expected to be between 0.25-3%, with a dramatic increase in death rate among older populations (10 to 27% among persons aged >84 years old). These statistics may change as we learn more about the disease.

Reproductive risk:

Given the unknown reproductive risks associated with FoTv, women of childbearing potential (WOCBP) must be willing to use a provided home urine pregnancy test at screening for study entry and excluded from participation if pregnant. All WOCBP must agree to use of contraception throughout the study period and up to 14 days after the last dose of the study medication. It should be noted that there is a current real concern of both teratogenicity from SARS CoV-2 infection itself, as well as increased risk of COVID-19 severe disease for pregnant women. Unfortunately, it is too early in the cycle of the pandemic to know the true risks. As such, pregnant and breastfeeding women will not be recruited for the study.

Obtaining blood samples:

Mild bruising and pain is possible

Obtaining nasal swabs:

The nasal swabs require the insertion of a swab inside the nose. This can be uncomfortable and can cause temporary runny nose and sneezing in some people.

Loss of confidentiality

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Subjects will be monitored throughout the study and their symptoms will be recorded and reviewed by the medical monitor on a daily basis during the active phase of treatment.

Safety of the study medication will also be assessed through laboratory data collection either at the end of the treatments (for non-hospitalized patients) or on hospital admission (utilizing labs on admission for hospitalized patients)

Study participants will be advised to report any skin eruptions to the study team and to stop medication immediately until they can be interviewed by our medical monitor who will make the assessment of allergy.

Respiratory allergies such as asthma exacerbations will be treated as COVID-19 exacerbations, where medication will be stopped and participants will be directed to immediate medical attention. An adverse event will be logged, and relation to the study medication will be determined per protocol.

In an event of participants requiring immediate medical attention, the study team will first refer the patient to contact their primary care physician if they are in close communication. If they are not, the study team will provide the participant with a short list of telephone numbers that patients can call to seek immediate medical attention. This will be specific to Southern California and will include 24-hour hotlines that are run by insurance companies, healthcare centers, and regional governments. If none are appropriate, they will be directed to dial 911.

All serious adverse events (SAEs) will, per UCSD IRB guidelines, be reported to the IRB and DSMB within 3 business days of learning of the event. The study biostatistician will send a tabulated symptom and adverse event report daily to all sites and to the study PI and weekly to the study DSMB and IRB

Any adverse events, as well as any escalation of care, including urgent care, emergency room, or hospitalization, will be reported to the study team after appropriate medical care has been received, via a dedicated phone number or email address that is specific for urgent matters.

The UCSD site will implement a Data and Safety Monitoring Board (DSMB) to review data safety and monitoring as part of their responsibilities. The DSMB will include two senior researchers, and a consumer representative. They will have a conference call bi-weekly (or more frequently, if needed).

To address loss of confidentiality and data security risks all data management tasks will be performed by the KCIR Data Core in compliances with all UCSD and Federal regulations. A comprehensive menu driven data management system is already developed for all KCIR funded studies using Microsoft Access software. This system is located within the UCSD Health Science computer network with limited access and DUO authentication system. This system provides a stable and secure platform for: a) study data input, validation, edit and query; b) subject tracking system for all subjects' study activities (screening and study visits); c) data storage, compilation, selection, and summary transfer to various statistical/graphical software. We are also planning on using UCSD REDCap forms to collect data from subjects. All subjects are assigned a unique ID number. Patient names are never used in conjunction with the unique clinic ID number. The single name-to-ID relational file is kept in an encrypted form electronically and in a locked filing cabinet physically. Statistical analysis will be conducted using SPSS software package. All statistical transfer routines are inherently secure via their operating platform and they contain no patient names or personal data.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified on the basis of a coded number only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA or IRB. The Principal Investigator will also comply with all applicable privacy regulations.

Email communication with patients will be conducted using encrypted email, or via MyChart.

Data will be entered into Microsoft Access or CTRI RedCap where it will be stored on the university server with access available to the Principal Investigator, data manager, and biostatistician. Only the research team will have access to the data. All communications will be conducted using UC secure systems with multiple identification checks.

The UCSD site will be responsible to provide data management support and will conduct all data analyses except for hospital record acquisition and adjudication of all study participants across all sites, which will be conducted at UCI and data sent to UCSD for analysis. We will establish a publication committee that includes among others each member, each study site PIs and the study statistician. It is the responsibility of this committee to approve and overseas all analyses, presentations and publications related to this project.

The majority of study consenting and conducting the study intervention will be done remotely by the study team at UCSD, although available staff at UCI and later UCLA sites may be asked to contribute to this effort. Otherwise, the UCI and later UCLA sites will be primarily responsible for recruitment of study participants.

17. POTENTIAL BENEFITS

For the study participant, FoTv and mQFPD may potentially provide direct benefit by reducing the severity of their illness as measured by duration of fever, risk of hospitalization, intubation or death.
Fo-Tv can potentially accelerate, prolong, or enhance the quality of immune responses to vaccine antigens and improve the efficacy of vaccines in individuals with reduced or weakened immune responses as measured by laboratory testing and/or reduce severity of vaccine side effect profile as measured by symptoms scoring.
It is also possible that there may not be any direct benefit for study participants.

18. RISK/BENEFIT RATIO

The most significant potential benefit of this study is to contribute to the possible future availability of safe and inexpensive agents for the treatment of COVID-19. This study will generate important safety data needed to subsequently evaluate the efficacy of FoTv and mQFPD in time to provide guidance for the use of these medicines during the current pandemic.

Furthermore, the collaborations formed as part of this study will provide a foundation for future studies evaluating the safety and efficacy of similar therapeutics for treatment of active COVID- 19, and the application of these therapeutics for more severe manifestations of disease.

For the study participant, FoTv or mQFPD may potentially provide direct benefit by potentially reducing the severity of their illness as measured by duration of fever, risk of hospitalization, intubation or death. Due to the high mortality associated with COVID-19, the benefits of participation in the trial outweigh the potential risks as outlined above in the background and risks sections.

The other most significant potential benefit of this study is to contribute to the possible future availability of safe and inexpensive agents for adjunctive therapy of COVID-19 vaccination.

For the study participant, FoTv may potentially provide direct benefit by potentially reducing the severity of their symptoms or improving vaccination response. Due to the high mortality associated with COVID-19 and the high concerns of vaccine hesitancy due to side effect burden, especially during upcoming public health campaigns for booster immunizations, the benefits of participation in the trial outweigh the potential risks as outlined above in the background and risks sections.

19. EXPENSE TO PARTICIPANT

There is no cost to the participant.

20. COMPENSATION FOR PARTICIPATION

In compensation for subject's time and efforts they might receive up to $250 for sub-studies 1a and 1 b, and up to $200 for sub-study 1c for entire study participation. It will be paid in gift cards as following:

Sub-studies 1a and 1b: will receive $50 at the beginning of the study and $100 after 14 days of taking study medication. They will also receive an additional $100 bonus at the study completion after second follow up at day 58. They will also receive a thermometer for their participation, which they will be allowed to keep.
Sub-study 1c: participants will receive $50 at the beginning for the study, $50 at each of the follow up at 2 and 4 weeks; and a final $50 at 12 months after the study baseline.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

All members of the research team have necessary privileges/certifications and licenses.

Gordon Saxe, MD, PhD, MPH, Director of the UCSD Center for Integrative Research and the UCSD Krupp Endowed Fund Research Executive Chair is the PI and will maintain overall oversight of the operation of the study at UCSD and affiliated sites.

Andrew Shubov, MD, Assistant Clinical Professor of Medicine, Co-PI, help oversee all recruitment and clinical aspects of the study, and assist with the evaluation of the feasibility and safety data during the first phase, and with the expansion of the study to the other sites (UCLA, UCSF, and UC Davis) during the second (efficacy) phase.

Shaista Malik, MD, PhD, Professor of Medicine, Co-PI, will oversee recruitment and clinical aspects of the study at the UCI site. She will maintain oversight for the operation of the study at the UCI site.

Daniel Slater, MD, Health Sciences Clinical Professor, will serve as study Medical Monitor

Shahrokh Golshan, PhD, Co-Investigator, will serve as the study biostatistician and data manager

Lan Kao, LAc, DAOM, Co-Investigator, Clinical Specialist in Chinese Medicine, will serve as safety monitor to assist the study team and Medical Monitor in evaluating adverse events that may be related to Fomitopsis officinalis and Trametes versicolor mycelium .

Eli Aranoff-Spencer, MD, Assistant Physician, UCSD, Lanny Hsieh, MD, UCI, and Debika Bhattacharya, MD, UCLA, are Infectious Disease specialists that will serve as Co-Investigators at each site.

Alpesh Amin, MD, Professor of Medicine, Chair of Dept of Medicine, UCI will serve as Co-Investigator.

Stephen Wilson, Ph.D, La Jolla Institute for Immunology, will oversee viral load and other basic science laboratory testing.

The following study team members will be involved with study coordination and administration; subject' data collection and data process:
Tatyana Shekhtman, MS (project manager), Renu Sugathan (data analyst/Epic specialist), Phoebe Senowitz (study coordinator) Monica Lopez, MS (study coordinator/health coach), Brianna Sercu, MS (study coordinator/health coach), Ashwini Erande (study coordinator)

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23. FUNDING SUPPORT FOR THIS STUDY

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24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

The FDA application has been reviewed and approved under the IND number 150080. The IND holder is Dr. Gordon Saxe. The “study may proceed” letter from April 8, 2021is attached. Please note that the IND submission is a larger research plan which includes two separate study stages (phases): safety/feasibility followed by a larger efficacy trial.

26. IMPACT ON STAFF

None

27. CONFLICT OF INTEREST

None

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

N/A

29. OTHER APPROVALS/REGULATED MATERIALS

N/A

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
N/A