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Compositions and Prevention and Intervention Methods for COVID-19 with Divine Ayats' "Fitra30 COVID-19 Protocol" consisting of Herbal Preparations of Milhu Shamsi "Sun Salt"™, Intermittent Fasting, Nutritional Therapy, and "Autophagy Jump Start" ™

By:

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"Fitra30 COVID-19 Protocol" is a method comprising;

- Identifying a human subject with COVID-19 and;
- Establishing a regime for administering a composition to the subject;
- The composition is formulated to restore stasis in all bodily systems and rid the body of COVID-19 compromising of Nigella sativa (Black Seed) and Sassurea lappa (Indian Costus) which are main active ingredients and;
- At least **one** supplemental herb selected from the group consisting of; **Astragalus membranaceus (Astragalus), Paeonia lactiflora (Peony Root), Nelumbo nucifera (Lotus Seed), Panax ginseng (Ginseng), Radix Bupleuri (Bupleuri Powder), Artemisia vulgaris (Mugwort), Angelica archangelica (Angelica Root Powder), Ocimum tenuiflorum (Holy Basil), Citrus sinensis (Orange Peel Powder), Zingiber officinale (Ginger Powder), Rosa canina (Rosehip Powder), and Glycyrrhiza glabra (Licorice Root Powder) collectively referred to as Milhu Shamsi Sun Salt.**
- **Intermittent fasting protocol based upon Islamic Medicine** designed to induce autophagy and increase antimicrobial peptides which includes a herbal formula entitled; **"Autophagy Jump Start"** consisting of the following herbs;
  - **Vaccinium angustifolium (Wild Blueberry Powder), Andrographis paniculata (Kalmegh Powder), Polygonum cuspidatum root (Japanese Knotweed Powder), and Glycyrrhiza glabra (Licorice Root Powder).**
- **Divine Ayats' Spiritual, Mental, and Emotional Rejuvenation (SMER) Program (Optional)**. This is an optional therapy using methods of Islamic Medicine which consists of a 30 Day Guided Meditation online program and Journaling.

Abstract:

Though young hosts have robust immune systems they are able to contract and spread COVID-19 due to their having an abundance of the bacteria Nontypeable Haemophilus influenzae in their nose and mouth while remaining asymptomatic. NTHI is present in the nasopharyngeal region about 50% of young children and 80% of all humans . This bacteria is usually not harmful until it moves into the lungs and middle ear. Due to food allergies, colds, flu, compromised immune function, an imbalance in the gut flora (namely Candida albicans infection), and a disrupted gut barrier, fluid containing high amounts of NTHI can get trapped inside of the middle ear which is part of the united airways concept. NTHI is the cause of chronic ear infections and chronic respiratory illness. Once in the middle ear NTHI increases susceptibility of airway epithelial cells to viral infections such as COVID-19. NTHI causes ICAM-1 Upregulation which can destroy the structural integrity of airway epithelial cells and spurr an exaggerated systemic inflammatory response and multisystem organ failure in some individuals with pre-existing conditions, specifically those with disrupted gut barrier integrity. Once COVID-19 attaches to ICAM-1 receptors a cytokine storm may occur due to enzyme action in glycoprotein synthesis. Unpredictability and unknown mechanisms of the new strain of COVID-19 makes it hard to determine the effectiveness of recently approved therapeutics (i.e., vaccines). The Fitra30 COVID-19 Protocol consists of treatments that stimulate healing mechanisms which are intrinsic to the host. This protocol consists of three features: 1) The Milhu Shamsi Herbal Formulation (MSHF). MSHF is designed to prevent and treat COVID-19 by targeting internal mechanisms which act as conduits for COVID-19 infection such as ICAM-1 and CCR5. 2) Induction of autophagy. The Fitra30 COVID-19 Protocol is holistic in the sense that it aids the body in inducing autophagy, an essential internal process for disease prevention and eradication. Interventions include Autophagy Jumpstart (AJ) and lifestyle modifications (i.e., proper diet, exercise, and sleep recommendations). 3) Divine Ayat's Spiritual, Mental, and Emotional Rejuvenation Program. The presence COVID-19 has caused stress, anxiety, and other mental health crises around the world therefore it is essential to address this disease via Physical, Spiritual, Emotional, and Mental mechanisms. RNA viruses, COVID-19 in particular, are highly mutagenic- up to a million times higher than that of their hosts. It is essential to build host resilience and defence mechanisms which is the core feature of The Fitra30 COVID-19 Protocol.

Specification:

Nontypeable Haemophilus Influenzae (NTHI), a catalyst for COVID-19?

According to research on emerging pathogens published by the National Institutes of Health in 2015, Nontypeable Haemophilus Influenzae (NTHI) is a major cause of invasive disease worldwide (1). It is believed that this emergence may be partly due to increased NTHi colonization in children which might contribute to increased transmission to persons susceptible to developing invasive NTHi disease. Over the last 25 years in the U.S., the elderly have accounted for 89% of all invasive NTHI infections. Much like SARS-CoV-2, pre-existing diseases such as COPD, cancer, chronic renal failure, and diabetes place people at greater risk for contracting invasive NTHI (10, 203). However, it has been found that NTHI infections are not just found in persons with immunocompromising conditions or co-existing conditions but in almost half the cases in persons who were otherwise in good health (203).

Viral infections in patients colonized with NTHI may be at risk for future exacerbations as specific viruses, like SAR-CoV-2, on top of a bacterial infection may significantly enhance the risk for excessive inflammation. In a 2015 study, it was found that Nontypeable Haemophilus influenzae (NTHI) can enhance expression of the cellular receptor intercellular adhesion molecule 1 (ICAM-1) on airway epithelial cells, which in turn increases the binding of major group human rhinoviruses (HRVs) for attachment (9).

Major group human rhinoviruses or HRVs are members of the Picornaviridae family. Like Coronaviruses or CoVs, they are a large family of single stranded RNA viruses. These viruses can cross species barriers and can cause, in humans, illness ranging from the common cold to more severe diseases such as MERS and SARS (8).

Many COVID-19 patients experience symptoms that are similar to symptoms presented by those who have COPD including frequent coughing, excess phlegm, shortness of breath, and trouble breathing (24). Recent studies have focused on the role of viral and bacterial coinfection in patients with COPD. This coinfection is associated with incidences of intensified respiratory disease and more inflammation (11). The most common co-infection is with rhinovirus (RV) and NTHI in COPD (12-13). NTHI also has significant and scientifically noted high morbidity risks for patients who smoke, or have Bronchiectasis, Cystic Fibrosis, Pneumonia, and Intestinal Lung Disease (14). These factors and diseases are also associated with increased risk of severe complications from COVID-19 (10).

NTHI is a very common gram-negative coccobacillus that colonizes the nasopharyngeal region in up to 80% of humans (5). It is present in the nose and throat of 50% of all children and is usually harmless until it moves to the middle ear or the lungs where it can cause the most damage. NTHI is a frequent cause of otitis media (chronic middle ear infections) (2) in children and acute bronchitis and pneumonia in patients with chronic obstructive pulmonary disease (3). Non-typeable Haemophilus influenzae (NTHI) has been associated with early pregnancy loss and in a 2020 report it was deemed an emerging neonatal and maternal pathogen (4).

This bacterium needs an iron rich environment to survive. Once NTHI has moved into the lungs and middle ear, heme iron is sequestered as part of the body's immune response. Instead of dying, the bacterium is kept alive by using clever hacks of the host's immune response (6).

Scientists Kevin M. Mason, PhD and Sheryl S. Justice, PhD, principal investigators in the Center for Microbial Pathogenesis figured out how NTHI was able to maintain a relatively low profile amongst clinicians with respiratory/pulmonary backgrounds and not be considered an important pathogenic bacterium. Their research shows that NTHI uses the body's own immune system to its advantage. Once the immune system is alerted of a bacterial invasion in the lungs, middle ear, and other parts of the body, the immune system cuts off access to nutrients the bacteria need to survive- including heme iron. This process is known as nutritional immunity. This immune response triggers a series of additional immune defenses to include inflammation, which involves the release of chemicals that are designed to find and sequester NTHI and bring in white blood cells to the site of infection to destroy the invading bacterium (6).

The scientist developed a lab experiment designed to imitate the immune response to NTHI infection in the middle ear and to further observe how NTHI responds to the body's immune responses. The research results showed that in the body's immune response a serum designed to carry disease fighting chemicals and white blood cells to the site of the infection includes heme-iron. They further observed that when NTHI was re-exposed to heme-iron the bacteria underwent structural changes that allowed it to divide much more slowly and become elongated and spaghetti-like in appearance. As a result, the NTHI was ignored by the disease fighting white blood cells as they usually target rapidly dividing shorter cells. Thus, NTHI was left alone to replicate and thrive. "This clearly shows that NTHI is changing to become more fit in the host," says Dr. Justice, who also is an assistant professor of pediatrics and urology at the Ohio State University College of Medicine (7).

Much like NTHI, SARS-Co-V-2 also has the ability to block the host innate immune response through its links to the function of structural and non-structural proteins (202) which makes co-infection with invasive NTHI and SARS-Co-V-2 a severe threat to host morbidity.

Could Upregulated ICAM-1 in COVID-19 Patients Come from NTHI + SARS-CoV-2 Co-Infections?

To date it is believed that SARS-CoV-2 via its surface spike glycoprotein interacts with Angiotensin-converting enzyme 2 (ACE2) and invades host cells. ACE2 is expressed in human vascular endothelium, respiratory epithelium, and other cell types (182). Endothelial cells play an important role in virtually every system in the body. These cells form the inner lining of the cardiovascular and lymphatic systems. They make up the inner layer of blood and lymphatic vessels and organs including the brain, lungs, skin and heart (22). Epithelial cells provide biochemical barriers by synthesizing and secreting substances meant to trap or destroy bacteria like NTHI (15). However, NTHI is able to allow its binding to epithelial cells. There is also evidence that NTHI may thrive in the respiratory tract by surviving inside of epithelial cells (16).

Though ACE2 is thought to be the main point of cellular entry for SARS-CoV-2, it is well known that viruses often use a variety of mechanisms for attachment. The most common cell adhesion molecules are CAMs which are routinely exploited by viruses to gain cellular entry (187). A retrospective study of COVID-19 patients in China found that serum levels of fractalkine, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion protein-1 (VAP-1) were elevated in patients with mild disease, dramatically elevated in severe cases, and decreased in the convalescence phase (188).

Much like Human herpesvirus 8 (HHV-8), HIV, and AIDS, NTHI can inhibit epithelial host defense proteins (18,19, 80,81). Once compromised, airway epithelial cells respond to the invasion of NTHI by secreting inflammatory acute-phase reactants such as IL-6, IL-8, and TNF-ą (18-19).
NTHI then increases the expression of ICAM-1 by airway epithelial cells which increases the susceptibility of viruses binding to the cells (20).

ICAM-1 or Intercellular Adhesion Molecule 1, also known as CD54 (Cluster of Differentiation) is a protein that in humans is encrypted by the ICAM-1 gene. The ICAM-1 gene is coded by a cell surface glycoprotein which is expressed on endothelial cells and cells of the immune system (21). An NTHI and SARS-CoV-2 co-infection that originates from the middle ear might allow these pathogens cellular access to the respiratory system as scientists have discovered that there is a similar allergic inflammation in the middle ear and the upper airway suggesting the middle ear may be a part of the united airways concept (17). The major leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome (ARDS) (204).

Can we compare Pathophysiology of COVID-19 to that of HIV/AIDS for better understanding of the disease and to develop treatments?

Many receptors for cytokines/chemokines have recently been identified by a group of scientists as upregulated in COVID-19 patients including; C-C chemokine receptor (CCR) 1 (CCR1), CCR2, and CCR5. These same scientists claim; “our work highlights opportunities for clinical trials with existing or under development CCR5 drugs to treat high risk or severe COVID-19 cases” (86). ICAM-1 and CCR5 upregulation are both implicated in the pathogenesis and progression of HIV (82, 189).

It has been previously established that HIV’s replication is facilitated by ICAM-1 which is believed to increase infection of CD4 T-cells (99). Plasma biomarkers of endothelial injury such as higher levels of cICAM-1, lower levels of cICAM2, an increase in cB2 microglobulin levels, and the decrease in CD4 T-cell counts are well established predictive biomarkers in HIV1-infected patients used to determine disease progression and prognosis for AIDS progression (82). These same markers may be useful in determining disease progression and prognosis in asymptomatic COVID-19 patients and further identifying potential therapeutic candidates.

Due to the similarities between COVID-19 and HIV disease infection and progression, a closer look at the mechanisms of HIV infection is warranted. HIV gains entry into the cells via gp120 and CD4. This allows for binding to the chemokine receptors CCR5 or CXCR4, which act as coreceptors for the virus for which CD4 antibodies have been identified as effective therapeutic targets (84). It is important to note

that a 2008 research study found that HIV transfer between CD4 T-cells did not require LFA-1 binding to ICAM-1 and is governed by the interaction of HIV envelope glycoprotein with CD4. The researchers discovered that HIV transmission between infected and uninfected primary CD4 T-cells was stopped by inhibitors of gp120 binding to CD4 by not blocking LFA-1 binding to ICAM-1 or ICAM-3. Further, it was noted that LFA-1 and ICAM-3 monoclonal antibodies (MoAb) actually enhanced HIV transfer (85). Recent research noted that CCR5 receptor and chromosome 3 gene clusters contribute to susceptibility to COVID-19 and the development of severe complications. Additionally, □32 allele , a polymorphism in CCR5 that regulates its expression has been identified as a partial to full protection against HIV infection and acts as a foundational basis for gene deletion studies aimed at achieving a permanent cure to HIV (88-89). It should be noted that a positive correlation between COVID-19 mortality rate and the □, 32 allele (n African population was found (86).

Further, there is a correlation between the progression of HIV and invasive NTHI infections. A study designed to evaluate increases in invasive NTHI infection from 2017-2018 among homosexual HIV infected men in Atlanta, Georgia found the incidence of invasive NTHI infection increased significantly from 2017-2018 compared with 2008-2016. Additionally, two unique but genetically connected strains were observed and associated with septic arthritis among homosexual black men who lived in geographic proximity (83).

Theoretical Proposition: COVID-19 Pathophysiology is much like HIV/AIDS

Like HIV, SARS-CoV-2 gains cellular entry via CD4 T-cells. However, different mechanisms lead to SARS-CoV-2 infection.

Asymptomatic people are super spreaders due to high levels of NTHI. SARS-CoV-2 not cause serious disease in these populations yet cause severe disease progression in others. This may be due to the condition of the innate immune system- several groups have found that the binding of IgM to the bacterial surface might play a role in the innate defense against NTHI infections. Another study found that patients with hyper-IgM syndrome were less susceptible to NTHI colonization, a finding that emphasizes the role of IgM in the immune system defense against NTHI. The percentages of IgM-producing CD27+ memory B cells in the peripheral blood of children are low but increases to almost 20% in adults and declines again in the elderly. This might address the question of whether a diminished protective immunoglobulin level in the elderly contributes to susceptibility to invasive NTHI disease.

The COVID-19 Model

1. A person with increased NTHI colonization becomes infected with SARS-CoV-2
2. Due to a weakened immune system (lower IgM levels) the body pushes harder against the co-infection through mounting an excessive inflammatory response.
3. ICAM-1 becomes upregulated
4. ICAM-1 acts as a ligand to LFA-1
5. LFA-1 becomes activated on CD4 T-cells
6. LFA-1 activation on target and infected CD4 T-cells enhance SARS-CoV-2 infectivity and transmission by promoting virus binding and cell to cell spread via the CCR5 coreceptor.

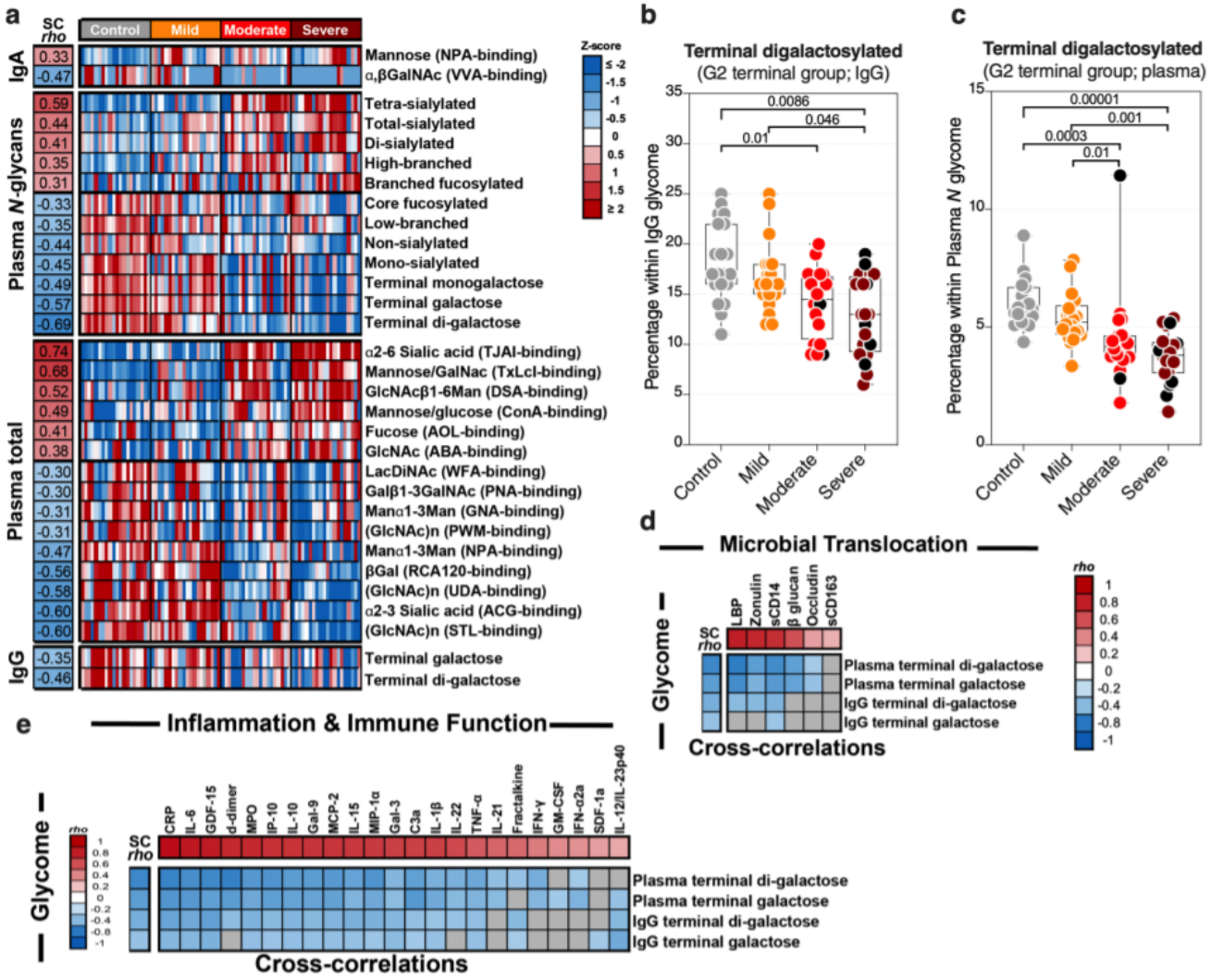
7. LFA-1also increases the cell susceptibility to bacterial toxin LtxA that preferentially targets active LFA-1 (238).
    a. Leukotoxin (LtxA; Leukothera), a protein toxin secreted by the oral bacterium Aggregatibacter actinomycetemcomitans, specifically kills white blood cells (WBCs). LtxA binds to the receptor known as lymphocyte function associated antigen-1 (LFA-1), a β2 integrin expressed only on the surface of WBCs (239).
    b. NTHI and Aggregatibacter actinomycetemcomitans are two species under genus Pasteurellaceae thus closely related (240).
    c. A. actinomycetemcomitans is associated with gum disease.
8. LtxA binds preferentially to the active form of LFA-1 and minimally affects cells that express resting-state LFA-1 (DiFranco et al., 2012; Hioe et al., 2011; Stenderup et al., 2011). The mechanism of cellular killing by LtxA has been studied in several cell types. Studies indicate that in HL-60 monocytes, LtxA causes necrosis at high doses by forming pores in the host cell membrane, while at low doses LtxA induces apoptosis (Korostoff et al., 1998, 2000).
9. Persons with increased NTHI colonization and Aggregatibacter actinomycetemcomitans colonization are at higher risk from severe complications of COVID-19 as NTHI increases the host's susceptibility to viral infections, while A. actinomycetemcomitans kill white blood cells designed to clear the body of the invading pathogens (NTHI and SARS-CoV-2) leaving the host completely vulnerable to COVID-19.

Intestinal Disease as a Marker for COVID-19 Disease Progression

Cytokine induced changes in mucin expression and O-glycosylation are likely involved in the pathogenesis and progression of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease. Disrupted gut barrier integrity is at the heart of all inflammatory bowel diseases (29,30).

A recent study performed by researchers Giron, Dweep and others revealed severe COVID-19 is fueled by disrupted gut barrier Integrity. These researchers found that hospitalized COVID-19 patients had higher plasma levels of zonulin, (the only known physiological conciliator of tight junction permeability in the digestive tract), and were more likely to die. This progression of disease was due to the ability of microbes to enter into the bloodstream causing systemic inflammation. The researchers also pointed that systemic inflammation caused by a lung infection can lead to a disruption of the gut barrier integrity leading to microbial translocation. Upon examining plasma glycomes, their research uncovered that translocation of glycan-degrading enzymes alter extraintestinal circulating high-mannose glycoform (HM-ICAM-1) (31). Further, in the inflamed gut of Crohn's Disease and Ulcerative Colitis patients, 1CAM-1 is enhanced. Research points to HM-ICAM-1, ICAM-1 as a key therapeutic target for controlling leukocyte trafficking and endothelial inflammation (32,144).

Figure 6



Some bacteria in the normal intestinal microbiome are opportunistic. Opportunistic bacteria like Candida albicans can overgrow due to prolonged treatment with broad-spectrum antibiotics (33). Broad-spectrum antibiotics are often prescribed to target pathogens sensitive to antimicrobial agents. However, other organisms such as Candida albicans that are resistant to the therapeutic intervention invade the unoccupied space and multiply rapidly. This occurrence is called Candidiasis or superinfection (34). In 2019 the CDC listed drug resistant Candida species in its Antimicrobial Resistance Threats Report, stating that many are resistant to antifungals used to treat them (35).

When Candida albicans overgrowth and the normal lining of the intestinal tract is damaged, the body can absorb yeast cells, particles of yeast, and various toxins (36). Candida accounts for 70-90% of all invasive fungal infections in hospitalized patients and is a leading cause for sepsis in critically ill patients. Additionally, administration of broad-spectrum antibiotics, central vascular catheters, diabetes mellitus, parenteral nutrition, mechanical ventilation, renal insufficiency, hemodialysis, colonization, antifungal prophylaxis, surgery, pancreatitis, and treatment with corticosteroids and chemotherapy were the most frequently identified risk factors for sepsis in patients with Candidiasis (37). Researchers have

increasingly become aware of COVID-19 fungal co-infections. The main fungal pathogens for fungal co-infections in severe COVID-19 patients are Aspergillus and Candida (225).

On April 24, 2020 a 67 year old COVID-19 patient presented oral mucosal lesions resembling late state herpetic recurrent oral lesions associated with candidiasis. He was admitted to the ICU for supplemental oxygen therapy. The patient's symptoms worsened and doctors suspected pneumonia. The patient was placed on antibiotic regimens. On the twenty fourth day of hospitalization, dentists discovered white patches on the patient's tongue. He was prescribed antifungal medications and the patches cleared up. The patient was released from ICU two weeks later and was discharged from the hospital after forty-four days.

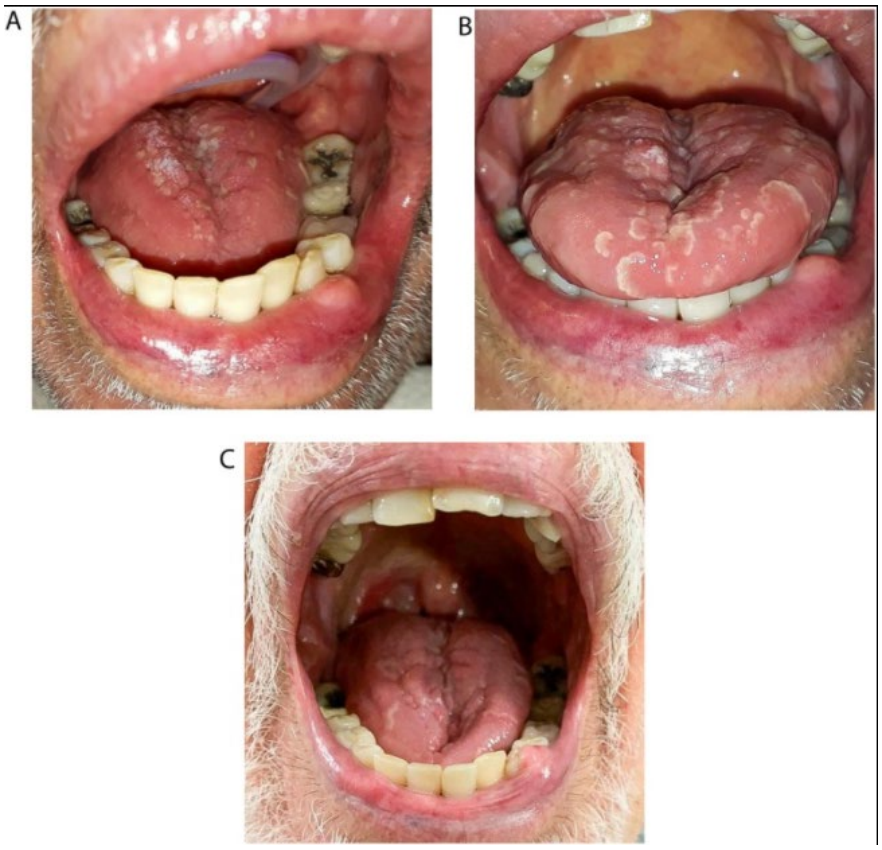


Figure 1

(A) April 24, 2020. COVID-19 patient presenting a white plaque on the tongue dorsum, centrally located, associated with several small, circle-shaped yellowish ulcers resembling the late stage of herpetic recurrent oral lesions associated with candidiasis. A nodule located in the lower lip was observed, measuring approximately 1 cm in its largest diameter, suggesting a reactive lesion (fibroma). (B) May 7, 2020. COVID-19 patient presenting atrophic areas surrounded by an elevated yellow-white halo classified as severe geographic tongue according to the severity index scoring system (Picciani et al., 2019) associated with fissured tongue. Also, the tongue's white lesions, suggestive of candidiasis, showed almost complete resolution. (C) May 25, 2020. The patient, recovered from COVID-19, showing atrophic areas surrounded by an elevated yellow-white halo classified as moderate geographic tongue according to the severity index scoring system (Picciani et al., 2020). We could observe a slightly erythematous area in the right palatine tonsil region; however, the patient reported being asymptomatic.

(38)

It should be noted that Acute Acquired Haemolytic Anaemia has been associated with Herpes Simplex Infection (39). Hemolytic anemia is a blood disorder that occurs when your red blood cells are destroyed faster than they can be replaced. Severe hemolytic anemia can cause fever, chills, back pain, shock, irregular heartbeat, and cardiomyopathy in which the heart grows larger than normal (40).

Intestinal Disease & Inflammation: Making Sense of MIS in Children

Inflammation can modify the glycosylation pattern of glycolipids and glycoproteins. It is well known that the glycosylation of acute-phase proteins is subjected to marked changes during acute and chronic inflammation (27). The inflammatory response caused by ICAM-1 Upregulation and COVID-19 can lead to increased levels of pro-inflammatory cytokines in response to pathogens lead to a constant NF-κB activation resulting in an increased synthesis of pro-inflammatory cytokines, which contributes the vicious inflammatory cycle seen in patients with Kawasaki disease and other systemic inflammation presentations (28-29).

NTHi strains cause mucosal infections, including otitis media, conjunctivitis, sinusitis, bronchitis, and pneumonia. Less commonly, these strains cause invasive disease in children but account for half of the invasive infections in adults which may explain why children are less likely to become severely ill from COVID-19 (41).

On August 7, 2020 a report on Multisystem Inflammatory Syndrome in Children (MIS-C) was released by the U.S. Department of Health and Human Services and the CDC. Clinical symptoms of patients included in this report included; fever, rash, conjunctivitis, peripheral edema, gastrointestinal symptoms, shock, and elevated markers of inflammation and cardiac damage.

This report found that of the 570 children with COVID-19 related MIS-C, 25% of them were obese. 90% of them experienced gastrointestinal symptoms including abdominal pain, vomiting, and diarrhea. About 71% of them experienced dermatologic and mucocutaneous presentations including rash (55.3%) and mucocutaneous lesions (35.3%). Furthermore, 60.4% of these children had Elevated D-dimer levels

indicating significant formation and breakdown of blood clots in the body. Researchers further found that it is often difficult to distinguish MIS-C from other conditions like severe COVID-19 and Kawasaki disease. Hispanic and Black children made up 73% of this study (29).

Discussions:

1. Male children who are more prone to chronic ear infections may be more likely to be the asymptomatic superspreaders of COVID-19.
2. High COVID-19 morbidity rates among men may be explained by a lifetime overuse of antibiotics (for chronic ear infections and other diseases) which may have led to imbalance in gut flora specifically candida albicans infection, and a disrupted gut barrier. Generally, Men are underdiagnosed for candida albicans infection. Men become more susceptible to this infection by using testosterone containing products as research strongly suggests that testosterone plays an important role in decreasing resistance to systemic C. albicans infection (42).
3. Published national and state data shows that persons of color might might be more likely to become infected with SARS-CoV-2, the virus that causes COVID-19, experience more severe COVID-19–associated illness, including that requiring hospitalization, and have higher risk for death from COVID-19 (43) and pre-existing anemia may be a contributing factor.

   In a 2013 study, it was found that Blacks have moderate to severe anemia almost 3 times more Than whites and hispanics (44).

   Pre-existing anemias, can worsen the symptoms of NTHI/COVID-19 Infections during the nutritional immunity stage. During this stage iron is sequestered as a first line defense strategy. However, iron is reintroduced to NTHI which causes sharp rises and falls in iron levels which can have severe clinical implications for those who suffer with iron deficient blood. Furthermore, acquired haemolytic anemia may develop after treatment with drugs such as quinine, sulphonamides, para-amino-salicylic acid, or it may follow infections caused by bacteria or viruses (39). In the case of a patient with pre-existing anemias getting infected with NTHI/COVID-19 could be deadly especially when the aforementioned treatments are used.

4. **Discussion of current therapies:**
   a. **Oxygen therapy.** Doctors have reported that after NIV respiratory therapy, there is a sudden, unexpected worsening of symptoms in some patients. This often leads to intubation and invasive mechanical ventilation (8).
      Nontypeable Haemophilus bacteria is an anaerobe. These pathogens die quickly when exposed to oxygen. The rapid decline in patients' health after NIV may be explained by the Herxheimer Reaction or “die off effect” of the NTHi bacteria dying quickly.
   b. **Antibiotics are not appropriate therapies.** Infections caused by NTHI are chronic and similar to other bacterial infections that are difficult to treat (7).
   c. **Antibiotics further strengthen bacterial resistant microbes which in turns further disrupts the gut barrier integrity.** “In essence, antibiotics progress COVID-19 disease

manifestations leaving moderate to severe patients open to re-infection. In severe patients, antibiotic therapies can lead to death as in the case of Penicillin. Penicillin is known to cause hemolytic anemia which can lead to hemorrhaging, blood clots, heart failure, and stroke" (45).

What Practitioners Can Do Now:

1. Consider Antiviral therapies using iminosugar derivatives. Since ADCC is thought to play a role in protecting against initial infection and controlling progression of infection in HIV, 2G12 dimmers may be a possible therapy (92). 2G12 is a neutralising human monoclonal antibody that has 3 possible combining sites. It has been identified as a possible antiviral therapy for various viruses (93). Studies also suggest that " 2G12 competitively inhibits interactions between gp120's V3 loop and the tyrosine sulfate-containing CCR5 amino terminus, thereby reducing assembly of complexes that catalyze entry (94).
2. Cleanse Patient Gut - consider using enema treatments with antisense oligonucleotides as a short term remedy to reduce intestinal inflammation and downregulate ICAM-1 (130,142,143). A holistic approach using herbs and lifestyle modifications will be necessary to prevent symptom relapse after therapy.
3. Consider Replenishing Gut Flora via exaggerated probiotic therapy.
4. Consider available therapies using iminosugar derivatives for Candida Albicans overgrowth;
5. Enlist Resident Nutritionists with backgrounds in Vitamin Therapy, microbiology, biochemistry etc to help formulate the appropriate (and available) therapies given the considerations outlined in this research.

Divine Ayat's Fitra30 COVID-19 Protocol

RNA viruses, COVID-19 in particular, are highly mutagenic- up to a million times higher than that of their hosts therefore, it is essential to build host resilience and defense mechanisms to ward off entry of this disease into the body. The Fitra30 COVID-19 Protocol consists of natural treatments that stimulate and strengthen defense and healing mechanisms which are intrinsic to the host. These treatments are designed to specifically target COVID-19 by 1) blocking of pathways to SARS-CoV2 cellular entry and 2) Riding the body of COVID-19. Divine Ayats' Fitra30 COVID-19 Protocol is useful for individuals who desire effective natural treatments to prevent and treat COVID-19 as opposed to (or in conjunction with) vaccines and standard treatments.

This protocol consists of three features:

1) The Milhu Shamsi Herbal Formulation (MSHF). MSHF is designed to prevent and treat COVID-19 by targeting internal mechanisms which act as conduits for COVID-19 infection such as ICAM-1 and CCR5.

2) Induction of autophagy. The Fitra30 COVID-19 Protocol is holistic in the sense that it aids the body in inducing autophagy, an essential internal process for disease prevention and eradication. Interventions include Autophagy Jumpstart Herbal Blend (AJHB) and lifestyle modifications (i.e., proper diet, exercise, and sleep recommendations).

3) Divine Ayat's Spiritual, Emotional, and Mental Rejuvenation Program (SEM-RP) . The presence COVID-19 has caused stress, anxiety, and other mental health crises with people around the world. Consequently, it is essential to address this disease via Physical, Spiritual, Emotional, and Mental mechanisms. SEM-RP is an optional therapy using methods of Islamic Medicine which consists of a 30 Day Guided Meditation program (online) and Journaling.

These components will now be discussed in detail as well as the specific therapeutic targets.

1) Divine Ayats' "Milhu Shamsi" Herbal Formulation

U.S. Patent Application No.: 63113935

Divine Ayats' Milhu Shamsi Herbal Formulation is a multi-compound herbal formulation inspired by Islamic Medicine (Tibb An-Nawawi or Medicine of The Prophet (صلى الله عليه و سلم), Traditional Chinese Medicine (TCM), and Traditional Japanese Medicine (Kampo). The composition is formulated to restore stasis in all bodily systems and rid the body of COVID-19. Milhu Shamsi was scientifically developed to act as an immunomodulator drug with exemplary additive and synergistic effects. Immunomodulators are effective treatments for inflammatory and immune system diseases (71). Specific therapeutic targets include of the Milhu Shamsi formulation include; 1) Downregulation of ICAM-1 2) Enhance the function/increase number of CD4 T-cells 3) Interference with SARS-CoV2/CD4 interaction, 4) Downregulation of CCR5 5) Preventing and treating Systemic Inflammation and Microbial Infection. A brief summary of scientific relevance is discussed below.

Downregulation of ICAM-1, CCR5, Interference with SARS-CoV2/CD4 Interaction:
Currently, ACE2 is believed to be the main glycoprotein utilized by SARS-CoV2 for cellular entry (182). However, many other receptors have been identified as facilitating SARS-CoV2 including; CD209L (L-SIGN), CD209 (DC-SIGN) (183), Neuropilin receptors (NRPs) which allows for viral entry into the central nervous system (184-185), and CD147/Basigin (186). It is well known that viruses may use a variety of mechanisms for attachment. The most common cell adhesion molecules are CAMs which are routinely exploited by viruses to gain cellular entry (187). A retrospective study of COVID-19 patients in China found Serum levels of fractalkine, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and vascular adhesion protein-1 (VAP-1) were elevated in patients with mild disease, dramatically elevated in severe cases, and decreased in the convalescence phase (188). Additionally, many receptors for cytokines/chemokines have recently been identified by a group of scientists as upregulated in COVID-19 patients including; C-C chemokine receptor (CCR) 1 (CCR1), CCR2, and CCR5. These same scientists claim; "our work highlights opportunities for clinical trials with existing or under development CCR5 drugs to treat high risk or severe COVID-19 cases" (86). ICAM-1 and CCR5 upregulation are both implicated in the pathogenesis and progression of HIV (82, 189).

Due to the similarities between COVID-19 and HIV disease contraction and progression, a look at the mechanisms of HIV infection is warranted. HIV gains entry into the cells via gp120 and CD4. This allows for binding to the chemokine receptors CCR5 or CXCR4, which act as coreceptors for the virus for which CD4 antibodies have been identified as effective therapeutic targets (84). It is important to note that a 2008 research study found that HIV transfer between CD4 T-cells did not require LFA-1 binding to ICAM-1 and is governed by the interaction of HIV envelope glycoprotein with CD4. The researchers discovered that HIV transmission between infected and uninfected primary CD4 T-cells was stopped by inhibitors of gp120 binding to CD4 by not blocking LFA-1 binding to ICAM-1 or ICAM-3. Further, it was noted that LFA-1 and ICAM-3 monoclonal antibodies (MoAb) actually enhanced HIV transfer (85). As aforementioned, recent research on chemokine receptor gene polymorphisms and COVID-19

identified CCR5 as a therapeutic target for COVID-19. The research noted that CCR5 receptor and chromosome 3 gene clusters contribute to susceptibility to COVID-19 and the development of severe complications. Additionally, □32 allele , a polymorphism in CCR5 that regulates its expression has been identified as a partial to full protection against HIV infection and acts as a foundational basis for gene deletion studies aimed at achieving a permanent cure to HIV (88-89). It should be noted that a positive correlation between COVID-19 mortality rate and the □, 32 allele (n African population was found (86).

Prevention and Treatment of Systemic Inflammation / Microbial Infection which can lead to Sepsis
A recent study performed by researchers Giron, Dweep and others revealed severe COVID-19 is fueled by disrupted gut barrier Integrity. These researchers found that hospitalized COVID-19 patients had higher plasma levels of zonulin, (the only known physiological conciliator of tight junction permeability in the digestive tract), and were more likely to die. This progression of disease was due to the ability of microbes such as Candida albicans and other bacteria to enter into the bloodstream causing systemic inflammation and sepsis. Bacteria can also enter the bloodstream as a complication of pneumonia and standard treatments to include; catheters, injections, and other medical devices used when treating COVID-19 patients. All these factors put the patient at increased risk for sepsis and death (31, 196). The researchers also pointed that systemic inflammation caused by a lung infection can lead to a disruption of the gut barrier integrity leading to microbial translocation. Upon examining plasma glycomes, their research uncovered that translocation of glycan-degrading enzymes alter extraintestinal circulating high-mannose glycoform (HM-ICAM-1) (31). Further, in the inflamed gut of Crohn's Disease and Ulcerative Colitis patients, 1CAM-1 is enhanced. Research points to HM-ICAM-1, ICAM-1 as a key therapeutic target for controlling leukocyte trafficking and endothelial inflammation (32,144).

Accordingly, primary therapeutic targets of Divine Ayat's Milhu Shamsi Herbal Formulation include; downregulation of ICAM-1 and CCR5, increasing the function and number of CD4 T-cells, and preventing and treating Systemic Inflammation and Microbial Infection.

Divine Ayats' Milhu Shamsi Herbal Formula consists of 14 herbs which include;

1. Nigella sativa (Black Seed),
2. Sassurea lappa (Indian Costus),
3. Astragalus membranaceus (Astragalus),
4. Panax ginseng (Ginseng),
5. Radix Bupleuri (Bupleuri Powder),
6. Angelica archangelica (Angelica Root Powder),
7. Citrus sinensis (Orange Peel Powder),
8. Zingiber officinale (Ginger Powder),
9. Glycyrrhiza glabra (Licorice Root Powder),
10. Paeonia lactiflora (Peony Root),
11. Nelumbo nucifera (Lotus Seed),
12. Artemisia vulgaris (Mugwort),
13. Ocimum sanctum (Tulsi) and;
14. Rosa canina (Rosehip Powder)

For Muslims, Islam is a complete way of life that promotes homeostasis in the Spiritual, Physical, Mental, and Emotional domains of wellness. COVID-19 has thrust this generation into a very precarious time where understanding and exploring Islamic pathways to wellness is obviously more relevant now than ever during our time. For example key principles to promote wellness during COVID-19 include social distancing; including refraining from handshaking, an emphasis on physical cleanliness through frequent handwashing, and covering the face and hands, are all fundamental acts performed daily by billions of Muslims worldwide as religious obligations.

Two main herbs in the Milhu Shamsi formulation are Nigella sativa and Sassurea lappa. Over 1400 years ago, Prophet Muhammad (peace and blessings of Allah be upon him) informed us about how to treat over 30 ailments and specifically 61 different herbs. Two of the most potent herbs he, (peace and blessings of Allaah be upon him), mentioned were Nigella sativa, commonly known as Black Seed and Sassurea lappa which is commonly known as Indian Costus (46-47). It was narrated by a nobel companion, Abu Hurairah رضى الله عنه, that Prophet Muhamamd (peace and blessings of Allah be upon him) said; "In black seed there is healing for every disease, except death." (50). It was also reported that The Prophet (peace and blessings of Allaah be upon him) also informed us to use Indian Costus as it contains "seven cures" including a cure for pleurisy (51).

Much scientific research has been done about the benefits of both herbs which has proved their efficacy in treating diseases including cancer, diabetes, hypertension, and more (48-49).

A concoction of 60% Nigella sativa and 40% honey induced sustained seroreversion in an adult HIV patient. The patient visited a Herbal Medicine Practitioner and was recommended the Nigella sativa concoction at a dose of 10mls twice daily for 6 months. The patient was monitored daily. The patient reported that fever, diarrhoea, and multiple pruritic lesions disappeared on day 5, 7, and 20 respectively. Although the patients CD4 counts decreased to 160 cells/mm3 there was a significant reduction in viral load by Day 30 (≤1000 copies/ml). It should be noted that the patient was not on highly active anti-retroviral therapy (HAART) before, during, or after the Nigella sativa concoction therapy (90).

Table 1

Monthly CD4 count, viral load and HIV tests of the patient

PERIOD	CD4 count (cells/mm3	Viral (HIV-RNA) load (copies/ml)	HIV tests (EIA & Western blot)
0th (pre-treatment)	250	27,000	Positive
1st month	160	≤1,000	Positive
2nd month	190	≤50	Positive
3rd month	270	≤50	Positive
4th month	420	≤50	Positive
5th month (Jan 2010)	540	≤50	Weakly positive
6th month (Feb 210)	650	≤50	Negative
8th month	830	≤50	Negative
12th month (a year)	840	≤50	Negative
18th month (Feb 2011)	820	≤50	Negative
24th month (2nd year)	880	≤50	Negative
30th month (3rd year)	790	≤50	Negative
36th month (Feb 2012)	850	≤50	Negative
44th month (Oct 2012)	870	≤50	Negative
47th month (Jan 2013)	880	≤50	Negative

There is growing evidence to support the effectiveness of treating COVID-19 with Nigella sativa. Bioactive constituents of Nigella sativa seed, in particular thymoquinone, a-hederin, and nigellidine, have been identified as alternative and promising herbal therapies to combat COVID-19 (90). Thymoquinone, thymohydroquinone, and nigellidine, all have proven antihistamine effects. Nigella sativa seeds have also shown significant immuno-potentiating effects in human T cells in vitro. Additionally, these constituents are believed to reduce inflammation, oxidative stress, cardiovascular disorder, hypertension, and induce autophagy (91).

TABLE 1

Pharmaceutical effects of *N. sativa* on various pathophysiological conditions

Models	Types and doses	Effects of *N. sativa* or its active components on mechanisms involved
Mouse (blood)	Hydroethanolic extract of *N. sativa* seed (200 mg/kg/day)	Increases concentration of IL-6, IL-10 and TNFα and balances Th1/Th2 lymphocytes ratio
Mouse (blood)	*N. sativa* oil (100 mg/100 ml/mouse for 7 days)	Increases the serum level of interferon-gamma, numbers of CD4+ helper T cells and macrophages against murine cytomegalovirus infection
Guinea-pigs (lung and trachea)	Hydroethanolic extract of *N. sativa* seed (0.125 mg/ml and 0.25 mg/ml)	Increases anti-inflammatory activity and decreases release of histamine with improved tracheal responsiveness
Mouse (lung and blood)	*N. sativa* oil (29. 5 ml kg^{-1} day^{-1} for 17 days)	Reduces the serum levels of IgG1, IgG2a, IL-2, IL-12, IL-10, IFN-γ, and inflammatory cells in lung tissue of mouse model of allergic asthma
Human (blood)	*N. sativa* seed powder (3 g/day for 8 weeks)	Oxidative stress: -decreases plasma MDA levels -increases activity in erythrocyte GSH-Px, GST, and SOD
Rat (blood)	Ethanolic extract of *N. sativa* (different doses for 5-week period)	Diabetes and hyperglycemia: -decreases plasma glucose, serum MDA, IL-6, immunoglobulin A, G, and M; -increases SOD, GST, and catalase expression -develops pancreatic β-cells degeneration, inflammation, and congestion
Rat (blood and urine)	*N. sativa* oil (0.6 ml kg^{-1} day^{-1})	Cardiovascular disorders and hypertension: -suppresses AA (arachidonic acid) induced platelet aggregation and blood coagulation by increasing discharge of chloride, sodium, potassium and urea followed by diuresis.
Rat (stomach and colon)	*N. sativa* oil (2.5 ml/kg, orally)	Protects stomach lining against the injurious effects of alcohol and other toxins and stress in colitis and gastritis
Rat (heart)	Thymoquinone (10 mg/100 µl/kg, i.p)	Converts LC3I to LC3II in autophagy
Staphylococcus aureus *S. epidermidis*	Thymoquinone (MICs values ranged from 8 to 32 µg/ml)	Promotes bacterial biofilm inhibition

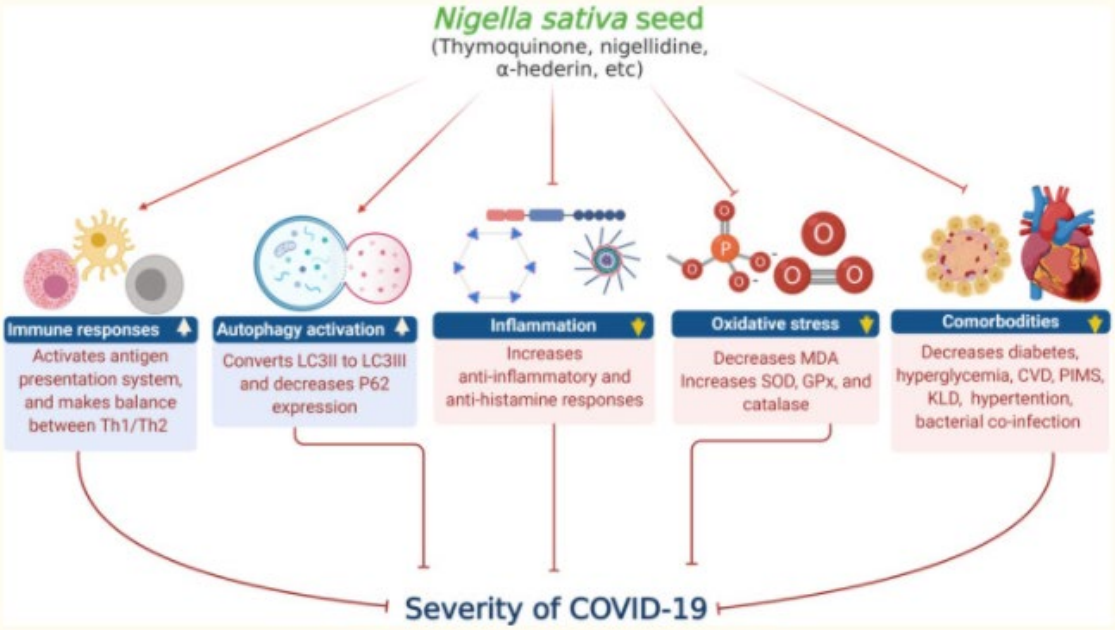


FIGURE 1

Mechanisms involved in pharmacological effects of *N. sativa* on COVID-19. Black cumin seed or its active compounds activate immune cells, initiate antigen presentation system, and make balance between Th1 and Th2 cytokines. The bioactive compounds of black cumin seed increase conversion of LC3II to LC3III, a marker of autophagy activation. Besides, black cumin decreases inflammation, oxidative stress (MDA) and increases anti-inflammation, ant-histamine responses, SOD, and GPx. Comorbodities increase the severity of SARS-CoV-2 infection. Black cumin may also be beneficial through improving comorbodity situation in SARS-CoV-2-infected patients. CVD, cardiovascular disease; KLD, Kawasaki-like diseases; PIMS, pediatric inflammatory multisystemic syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

The second main herb used in Divine Ayats' Milhu Shamsi formula is Sassurea lappa. This herb has been widely studied and documented for its anti-inflammatory, anticancer/tumor, hepatoprotective, immunomodulating, antimicrobial, and antiparasitic benefits (101). Costunolide is a sesquiterpene lactone isolated from Sassurea lappa which stops the endothelial cell proliferation instigated by vascular endothelial growth factor or VEGF. which increases expression of ICAM-1. Costunolide was also found to inhibit the VEGF induced movement of human umbilical vein endothelial cells (HUVECs) thus proving that Sassurea lappa might prevent angiogenesis (the formation of new blood vessels) by blocking the angiogenic factor signaling pathway. Further, costunolide and dehydrocostus lactones found in Saussurea lappa inhibit hepatocyte growth factor which in turn downregulates ICAM-1 (102, 103, 104). Molecules that reduce cholesterol or disrupt viral entry points is believed to reduce the severity of COVID-19 in obese patients (107). Sassurea lappa has hypolipidemic action which proves useful when treating obsese COVID-19 patients presenting high cholesterol levels (101). Additionally, the

significance of Sassurea lappa as a potential treatment of COVID-19 has risen in the medical community. Researchers are encouraging exploration of this beneficial herbal medicine through clinical trials (110).

Synergistic Herbs in the Milhu Shamsi Formulation:

Japanese herbal formulations date back more than 1500 years. The word "Kampo" which literally means "method from the Han period (206 BC to 220 AD) of ancient China", refers to its origin from ancient China (56). In fact, many Japanese herbal formulations are variations of formulations found in TCM with different names. Consequently,Traditional Chinese Medicine (TCM) has an even longer history dating 3000 years starting from the early Zhou Dynasty of China. According to researchers TCM could date back even earlier as the oldest medical writings on herbs were found in Classic of Changes (Yi Jing) and Classic of Poetry (Shi Jing) (57).

Along with Nigella sativa and Sassurea lappa, herbs in Divine Ayat's Milhu Shamsi formulation include some herbs that are used in a Kampo formulation entitled; "Hochuekkito". Herbs in the Hochuekkito consist of 10 component herbs;

1. Astragalus membranaceus (Astragalus)
2. Panax ginseng (Ginseng)
3. Atractylodis macrocephalae Rhizoma
4. Jujubae Fructus
5. Citri reticulatae Pericarpium
6. Bupleuri Radix
7. Angelicae sinensis Radix
8. Cimicifugae Rhizoma
9. Glycyrrhizae Radix
10. Zingiberis Rhizoma

Hochuekkito (HET) has been traditionally used by Kampo practitioners to treat fatigue, poor appetite, spontaneous sweating, loose stools, frequent colds and infections, hemorrhage, male infertility, and sexual dysfunction. Research points to Hochuekkito's effectiveness in clinical settings with strengthening the immune system, improving systemic inflammation in patients with COPD, modulating the immune function, in Intestinal Peyer's Patches and Epithelial cells (59-66). In a 2017 study, researchers discovered that Hochuekkito restores metabolic homeostasis between mitochondrial and glycolytic pathways impaired by Influenza A Virus Infection (68).

A 2010 research study found that orally administered Hochuekkito, may partly contribute to enhancement of IgA immune response against intestinal antigens and strengthen immune defense systems against various pathogens and food antigens in the intestinal tract. A spray-dried extract preparation of HET in the following composition was used; a mixture of Astragali Radix (4 g, roots of Astragalus membranaceus Bunge), Atractylodis lanceae Rhizoma (4 g, rhizomes of Atractylodes lancea DC.), Ginseng Radix (4 g, roots of Panax ginseng C.A. Meyer), Angelicae Radix (3 g, roots of Angelica acutiloba Kitagawa), Bupleuri Radix (2 g, roots of Bupleurum falcatum L.), Zizyphi Fructus (2 g, fruits of Zizyphus jujuba Miller var. inermis Rehder), Aurantii Bobilis Pericarpium (2 g, pericarps of ripe fruits of Citrus unshu Markovich), Glycyrrhizae Radix (1.5 g, roots of Glycyrrhiza uralensis Fisch et DC.),

Cimicifugae Rhizoma (1 g, rhizomes of Cimicifuga simplex Wormskjord) and Zingiberis Rhizoma (0.5 g, rhizomes of Zingiber officinale Roscoe) was added to water and extracted at 100°C for 1 h. The extracted solution was filtered and spray-dried to obtain dry extract powder (5 g) which was chosen to be the 1 day dosage. To investigate HET potentials on mucosal IgA immune response, mice were orally immunized with ovalbumin (OVA)-entrapped biodegradable microparticles (OVA-microparticles) as an antigen for 3 days. HET or water was then administered via gavage from through the 7th -27th day after the onset of immunization. Data showed that OVA-specific IgA titers in intestinal washes were greatly amplified by oral administration of HET. Further, upon investigating cytokine production in the lymphocytes from the spleen, peripheral blood, and Peyer's patch cells revealed that the IFN-y secretion from the lymphocytes was increased by the administration of HET (69).

In Traditional Chinese Medicine (TCM), "Hochuekkito" is called"Hochuekki". Hochuekki contains the exact same 10 component herbs as its Japanese successor. In 2009 a group of researchers reviewed 59 research studies of in vitro and in vivo models (both animals and humans) studying the effect of Traditional Chinese Medicine formulations on cytokine activity. There research showed that in vivo aqueous Hocheukki formulations administered at 1000mg/kg QD, PO for 2-21 days had an effect on cytokines; IL-1a↓, IL-6↓, GM-CSF, IL-4↓, IL-5↑, IFN-y↑ (70).

Table 2A
In vivo.

Formula name	Preparation used	Daily dose	Duration of exposure	Tissue	Model	Cytokines affected	T helper influence	Author/date
Antitumor-I	Capsule	800 mg/kg	8 days	NK spleen Murine	Tumor bearing	IL-2↑,6↑	Th0	Lei and Chu (1996)
Dang-gui-bu-xue-tang	Aqueous	360 mg	7 days	Lymphocytes Murine	None	IL-2↑	Th1	Chen (1994)
Food Allergy Herbal Formula-1	Aqueous	21 mg BID, Intragastric gavage	7 weeks	Splenocytes Murine	Peanut allergen	IL-4↓,5↓,13↓	Th1	Li et al. (2001)
Food Allergy Herbal Formula-2	Aqueous	20 mg BID, Intragastric gavage	7 weeks	Splenocytes Murine	Peanut allergen	IL4↓,5↓,13↓IFN-γ↑	Th1	Srivastava et al. (2005)
Hochuekki	Aqueous	1000 mg/kg PO	2 days before to 4 days after infection	Bronchioles Murine	Influenza	IL-1α↓,6↓ GM-CSF	Th0	Mori et al. (1999)
Hochuekki	Methanol	1000 mg/kg OD, Intragastric gavage	2 days before to 2 days after infection	Bronchioles Murine	Influenza	[a]IFN-α↓↑	–	Mori et al. (1999)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	OVA	IL-4↓,5↑ IFN-γ↑	Th0	Ishimitsu et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen and lung cells Murine	OVA	IL-4↓,5↑	–	Ishimitsu et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	*L. monocytogens*	IFN-γ↑	–	Yamaoka et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	7 days	Spleen cells Murine	Anti CD24 and/or anti CD3	IFN-γ↑	–	Yamaoka et al. (2001)
Hochuekki	Aqueous	1000 mg/kg QD, PO	21 days	Gastric mucosa Murine	*H. pylori*	IFN-γ↑	–	Yan et al. (2002)
Hochuekki	Aqueous	1000 mg/kg QD, PO	18 days	Ear Murine	Trinitro chlorobenzene	IL-4↓	–	Nakada et al. (2002)

OVA: ovalbumin.
[a]IFN-α was initially up-regulated and by the end of infection down-regulated as compared to the control group.

J.J. Burns et al. / Toxicology 278 (2010) 140–159

Divine Ayats' Milhu Shamsi Herbal formulation contains 6 of the 10 herbs in the Hochuekkito/Hochuekki formulations to include;

1. Astragalus membranaceus (Astragalus)
2. Panax ginseng (Ginseng)
3. Bupleuri Radix
4. Angelicae sinensis Radix

5. Glycyrrhizae Radix
6. Zingiberis Rhizoma

Recent research performed by David Lee from Bio-Organic and Natural Research Laboratory, McLean Hospital, Harvard Medical School, and Belmont has shown that herbs commonly used in TCM formulations along with cutting edge science and technology may be effective in treating COVID-19. The primary goal of this research was based upon their theory of treating COVID-19 by expelling toxic moisture from the upper respiratory system while improving intestinal obstruction. These researchers believe that the goal of TCM in the treatment of COVID-19 is to promote and restore balance between the lung and intestine. This study examined TCM relating to treating COVID-19 that is registered on www.ClinicalTrails.gov. The study found that trials in Wuhan showed 89% to 92% effectiveness of TCM therapies in the 692 studies registered. Further, an examination of the pharmacological basis of the Chinese herbs used the most frequently in the clinical trials was performed (67). Of those frequently used herbs, there are 3 that are used in the Milhu Shamsi formulation which include;

1. **Astragalus membranaceus (Astragalus)**- a 2020 study on the effects of this herb on cytokine storms producing systemic inflammatory was promising. Astragalus impeded the activation of MAPK/NF-B signaling pathway, promoted the down regulation of of IL-6, IL-8, TNF-a levels, activated the PI3K/Akt/mTOR signaling pathway, promoted the upregulation of superoxide dismutase (SOD), promoted the detoxification of free radicals (67).
2. **Glycyrrhizae Radix-** a 2014 study showed that this herb inhibited the replication of FFM-1 and FFM-2 viruses. A water extract also had anti-herpes simplex virus (HSV-1) activity possibly due to its anti-adhesion activity which disallowed the attachment process of the HSV-1 virus (67). Additionally, Glycyrrhizae Radix has been identified as a highly beneficial treatment for COVID-19 patients (111).
3. **Bupleuri Radix-** in a 2015 study this herb reduced fever in dry yeast-induced rats. It also increased arginine vasopressin in rat plasma (67).

Finally, six additional herbs were chosen to be a part of the Milhu Shamsi formulation. After careful study and research, it was determined that the follow herbs would add balance and synergistic effects to the overall formulation making it more effective in the treatment of COVID-19:

1. Citrus sinensis (Orange Peel Powder);
2. Paeonia lactiflora (Peony Root);
3. Nelumbo nucifera (Lotus Seeds);
4. Artemisia vulgaris (Mugwort);
5. Ocimum sanctum (Tulsi); and
6. Rosa canina (Rosehip Powder)

Below we will discuss in detail each herb in Divine Ayats; Milhu Shamsi formula to include; a description of the active ingredient, a description of its physical characteristics, indications, specific mechanisms of actions for treating COVID-19, pharmacokinetic, and toxicology data. Note: the dosage form for the Milhu Shamsi composition is an **aqueous extract which may be delivered by mouth or feeding tube. .** In true Islamic Medicine (Tibb an-Nawawi) alcohol extractions are not permissible;

In Saheeh Muslim it is narrated from Taariq ibn Suwayd al-Ju'fi that he asked the Prophet (peace and blessings of Allah be upon him) about alcohol and he forbade him or told him not to make it. He said: "But I make it as a remedy." He said: "It is not a remedy, it is a disease."

Further, some herbs in this formulation may not be suitable for every patient. The mix of synergistic herbs with corresponding functions is a build in measure that serves two purposes: 1) to enhance the therapeutic effectiveness of this drug and 2) ensure the overall therapeutic effect (preventing and eradicating COVID-19 from the body) if the main herbs; Nigella sativa and Sassurea lappa in addition to at least one synergistic herb is present in the formulation.

Claims:

Claim 1: A composition for preventing, treating, and curing COVID-19 compromising herbs: **Nigella sativa** and **Sassurea lappa**.

- ❑ **Nigella sativa**
  - ❑ Common Name: Black Seed
  - ❑ Forumulation Function: Main Herb
  - ❑ Main Active Constituent: Thymoquinone
    - ❑ Other constituents: n-Nonanea, Tricyclene, Camphene, β-Pinene, 2,4,(10)-Thujadiene, Sabinene, β-Myrcene. 1,8-Cineole, α-Terpinene, Limonene, γ-Terpinene, cis-Sabinene hydrate, allo-Ocimenola, Linalool 1087, Terpinolene, trans-Sabinene hydrate, STerpinen-1-ol, 1,5,8-p-Menthatrienea, Borneol, Pinocarvone, trans-Dihydrocarvone, Dihydrocarvonea, Ocimenone (E)a, Thymoquinone, Thymol, Carvacrol, 2-Undecanone, n-Octyl isobutyratea, α-Longipinene, Citronellyl acetatea, Thymohydroquinone methyl ethera, Cyclosativene, α-Longicyclene, α-Copaene, α-Longifolene, (Z)-Caryophyllenea, β-Caryophyllene, Thymohydroquinone dimethylethera, Aromadendrenea, Thymohydroquinone, Davanonea, 8-Heptadecenea, Dihydrofarnesyl acetatea, Pimaradienea, Palmitic acid, Pimara-8(14),15-diene, Octadecanoic acid, Quinones, Monoterpene hydrocarbons, Oxygenated monoterpenes, Sesquiterpene hydrocarbons, Oxygenated sesquiterpenes, Diterpenes, Alkane, Alkenes Fatty acids, Fatty acid esters (145).
  - ❑ Plant Part Used: Seed
  - ❑ Primary Target for COVID-19 & Clinical Outcomes: Suppress viral load of COVID-19. Increase the number and improve function of CD4 T-cells, and increase in the production of interferon (INF) gamma (74-76, 98), decreases in plasma MDA levels (95)
  - ❑ Herbal Actions: Antibacterial, Antifungal, Antiviral, Antiparasitic, Anticancer, Antioxidant, Antihypertensive, Anti-Inflammatory, Antimicrobial (72)
  - ❑ Daily Recommended Dosage: 80mg/kg/day
    - ❑ Dosage Rationale:
      - ❑ A recent multi-center placebo-controlled randomized clinical trial conducted in Pakistan tested Honey and Nigella sativa against COVID-19. The study included adults showing moderate or severe COVID-19 disease. The patients were randomly assigned to receive the following dosage: honey (1 gm/Kg/day) and encapsulated Nigella sativa seeds (80 mg/Kg/day) or a placebo up to 13 days along with receiving standard care. The formulation was administered in 2-3 divided doses each day. The results showed that the Honey & Nigella sativa (HNS) medication groups symptoms were alleviated 50% more than the placebo group. Additionally, HNS cleared COVID-19 4 days earlier than the placebo groups in both the moderate and severe groups. Participants reported feeling better and resuming normal activities by day 6 (63.6% verses 10.9% in moderate cases). The HNS group also saw higher hospital

discharge rates in severe cases (50% versus 2.8% in the placebo group). Lastly, in severe cases, the mortality rate was 4 times lower than the placebo group. Notably, no HNS related adverse effects were noted (73). https://www.medrxiv.org/content/10.1101/2020.10.30.20217364v4.full.pdf

- ❑ A 2006-2007 double blind trial was conducted at Aga Khan University Hospital, Karachi to gauge the safety, tolerance, and effectiveness of powdered Nigella sativa seed capsules on serum lipid levels, blood sugar, blood pressure, and body weight in adults. 123 participants were recruited for this study-64 was placed in the intervention group and 59 were placed in the control group. Due to high dropout rate only 39 participants from the intervention group and 34 participants from the control group completed the study. The intervention group received 2capsules daily. Each capsule contained 500mg of crushed powdered Nigella sativa seed for 6 weeks. The control group received dietary recommendations and calcium lactate powder placebos. The results yielded positive trends across all variables studied with no adverse effects noted. The study proved the safety and tolerability of Nigella sativa (78).
- ❑ In vivo study of the activity of Nigella sativa seed powder- human participants were given 3g/day for 8 weeks. Conclusions: reduction in oxidative stress as evidenced by a decrease in plasma MDA levels and increases in activity in erythrocyte GSH-Px, GST, and SOD (96, 97)
- ❑ In vivo study of antifungal activity of Nigella sativa water extract. Mice were treated with 6.6ml/kg equal to 5mg of estimated protein once daily for 3 days. A 5 fold decrease of Candida albicans bacteria was observed in the kidneys, an 8 fold decrease in the liver, and an 11 fold decrease in the spleen in mice treated with extract. Results proved that Nigella sativa aqueous extracts are effective in inhibiting Candida albicans infections.

- ❑ Toxicology & Safety:
  - ❑ Daily dosing of thirty (30) six-to-eight week old non-pregnant female mice for 6 weeks with an aqueous extract of Nigella sativa via gavage using an esophageal probe. The water extraction was performed by macerating 150 g of black seed powder in 500ml of water for 12 hours at 203°F. The mixture was then filtered with a muslim cloth into a glass Petri dish where it was left for 8 hours at 194°F. The mice were kept under fasting conditions 12 hours prior to the gavage. The mice were split into 6 groups- a control group that received distilled water and 5 groups each receiving one of the following dosages: 2g/kg/day, 6.4g/kg/day, 21g/kg/day, 33g/kg/day, and 6g/kg/day. One mouse died after 2 weeks of treatment with 6.4g/kg/day. Two mice died after the 3rd week of treatment with 21g/kg/day. Three mice died after the 5th week of treatment with 60g/kg/day. No other deaths were reported (77).

- An in vivo study testing the effect of an alcohol based Nigella sativa extract on pregnant mice. Mice were injected with human serum to achieve the symptoms of preeclampsia. Results showed that a dose of 1500mg/kg/day was optimal for lowering IL-8 and TNF-a levels in models of preeclampsia. It should be noted that IL-6 levels increased at 2000mg/kg/day doses (79). It should be noted that the Milhu Shamsi formulation is non-alcoholic and thus substantially less potent than alcoholic extracts.
- Powdered and Aqueous extracts of Nigella sativa are safe for pregnant and breastfeeding women (100)

- **Sassurea lappa**
  - Common Name: Indian Costus
  - Formulation Function: Specific
  - Main Active Constituent: Sesquiterpene lactones
    - Other constituents: 1beta-hydroxycolartin, 5alpha-hydroxy-beta-costic acid, 11alpha,13-dihydroxydehidrocostuslactone ,11,13-dihydro-7,11-dehydro-13-hydroxy-3-desoxyzaluzanin C, 8alpha-hydroxyl-11betaH-11,13-dihydrodehydrocostuslactone, Soulangianolide A, Syringaresinol , Scopoletin among many other constituents (146).
  - Plant Part Used: Root
  - Primary Target for COVID-19 + Clinical Outcomes: Inhibition of ICAM1 Upregulation, Inhibition of angiogenesis, Inhibition of Hepatocyte growth factor (which causes ICAM1 Upregulation) (101) Sassurea lappa has been found to inhibit the Vascular Endothelial Growth Factor expression of ICAM1, induced chemotaxis (movement of somatic cells), bacteria, and other single celled or multicellular organisms of human umbilical vein endothelial cells (HUVECs) in a dose dependent manner (101, 105).
  - Herbal Actions: Anti-Inflammatory, Anticancer, Hepatoprotective, Anti-ulcer, Cholagogic, Immunomodulator.
  - Daily Recommended Dosage: .5-600mg/kg/day though 100mg/kg/day has proven to be ideal for ICAM1 downregulation.
    - Dosage Rationale:
      - An alcohol extract of Sassurea lappa at doses of 50, 100, and 200 mg/kg/, p.o., was used to evaluate its effectiveness against acute and chronic inflammation in symptomatic mice and rats. Sassurea lappa proved an effective treatment for acute and chronic inflammation at doses of 50-200 mg/kg (106)
      - An in vivo study designed to evaluate the cardioprotective effect of aqueous extract of root Sassurea lappa (AESL) against induced myocardial injury in rats. The rats were given the aqueous extract of Sassurea lappa in three different doses: (100, 200, and 300 mg/kg, p.o. orally). Consistent oral administration of AESL greatly improved the level of myocardial LDH, CK, AST, TBARS, and GSH. The extract was

compared with standard treatment a-tocopherol. 200mg/kg proved the most beneficial dosage to protect against isoproterenol induced myocardial injury. Additionally, AESL up to a dose of 2000 mg/kg did not produce any signs of toxicity and mortality (108).

- ❑ "By in vivo method the neovascularization of mouse corneal stimulated by vascular endothelial growth factor is reported to be inhibited at a dosage of 100 mg/kg/day. Inhibition of of vascular endothelial growth factor on VEGFR KDR/Flk-1 was also proved through signaling pathways (109)
- ❑ Herbal Composition of Saussurea lappa for the Treatment of a Subject infected with HIV. Clinical research revealed HIV "undetectable" and CD4 T-cells increased after participants were administered either an aqueous extract or capsulated extract of 0.4g/kg - 0.6g/kg, three times per day for 6 months. Only one patient had adverse effects during the study which included diarrhea. 36 participants were involved in this study. WIPO Patent # WO 201 1/039574 AI (124).

- ❑ Contraindications: Not a lot of research on pregnant/breastfeeding women.
- ❑ Toxicology & Safety: Sassureal lappa has proved to be safe in in vivo studies of humans, rabbits, and pigs at dosage of up to 16g/day for the treatment and eradication of HIV (124).
- ❑ Rabbits and guinea pigs were used in a toxicity study of Sassurea lappa which was conducted at the School of Medical Sciences, Pharmacology Department, University of Science and Technology, Sana'a Republic, Yemen. Each was given an oral, aqueous dosage of 16g (the maximum recommended dose) then observed for a period of 2 weeks. All of the animals were alive two weeks after receiving the maximum dosage and no abnormalities were observed. At the end of the observation the animals were sacrificed and dissected. Upon examination of the eyes, liver, lung, and spleen it was determined that there were no extraordinary syndromes and no acute toxicity (124).

Claim 2: A composition of claim 1, wherein the composition further comprises **Astragalus membranaceus.**

- ❑ Common Name: Astragalus
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituents: Triterpene saponins (astragalosides I-X and isoastragalosides I-IV), and polysaccharides (e.g. astragalan, astraglucan AMem-P) (125-126)
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Immunopotentiating (112-116), Induction of Phagocytosis - the removal of pathogens and cellular debris i.e. bacteria and viruses from the middle ear in non-infected and asymptomatic persons. Performs the same function after COVID-19 has spread through the body through promotion of Phagocytosis via the reticular endocrine system or RES thus clearing pathogens on a cellular level (117-118) by facilitating the antibody response to a T-dependent antigen. Enhancement of this response is correlated with an increase

in T-helper cells in normal and immunosuppressed mice (120). Astragalus also acts as an effective anti-inflammatory and antioxidant agent for intestinal diseases such as Candida albicans infection (119)

- ❑ Herbal Actions: Immunomodulator (112-116)
- ❑ Daily Recommended Dosage: **16,000 mg per day.** 9-30g dried root. Immunostimulant effect seen at a dose of 16g/day for adults for 20 days as evidenced by increased serum IgM, IgE, and cyclic AMP concentrations (121). ¼ of this dosage for children.
    - ❑ Dosage Rationale, Toxicity, and Safety: According to the National Institutes of Health there are no high-quality studies in people of astragalus for any health condition. However, they do report that Astragalus may be safe when used by mouth at appropriate dosages. Further, it is reported that doses up to 60 grams daily for up to 4 months have been reported without any adverse effects (123).
    - ❑ 12 month old male mice were used in a study to assess the effects of Astragalus on learning and memory impairments and neuron apoptosis induced by glucocorticoids. In this study the mice were chronically treated with stress-level dexamethasone (DEX 5mg/kg) and an aqueous extract of Astragalus in doses of either 10, 20, and 40 mg/kg or Ginsenoside Rg1 (6.5 mg/kg) for 21 days. Findings showed that Astragalus has a positive effect on learning and memory and most importantly no adverse effects were observed (147).
- ❑ Contraindications: No data for pregnant or breastfeeding population and consequently not suggested for use in these populations. No herb/drug interaction or pediatric use studied-no generally recommended. No adverse reactions (122).
- ❑ Inclusion Rationale: Theoretically, Sassurea lappa and Astragalus membranaceus seem to complement one another well. This is due to Sassurea lappa's possible inhibition of ICAM-1 upregulation rendering the COVID-19 virus unable to attach making way for Astragalus membranaceus to "sweep" away pathogens from the body specific to where they are most concentrated (endothelial cells).

Claim 3: A composition of claim 1, wherein the composition further comprises **Paeonia lactiflora.**

- ❑ Common Name: Peony Root
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent: Paeoniflorin, a monoterpene glycoside (127-128).
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Decrease pain, depression, and anxiety in COVID-19 patients via increasing hippocampal glucocorticoid receptor messenger RNA (mRNA) expression. Down Regulation of ICAM-1 and CCR5 expression. Paeonia lactiflora is a potent herb that has been scientifically proven to suppress the expression of ICAM-1 and CCR5 due to endotoxins. In patients with disrupted gut barriers this Paeonia lactiflora aids in tapping into the gut-brain axis guiding interactions between enteric microbiota and the central and enteric nervous systems. The gut brain axis (GBA) is a bidirectional communication signaling from gut-microbiota to the brain and from the brain to gut-microbiota through neural, endocrine, immune, and humoral links (131). Enhancement of the hippocampal glucocorticoid receptor messenger RNA (mRNA) expression may allow the messenger RNA to pick up cues from antisense oligonucleotides. Antisense oligonucleotides are short, single stranded DNA molecules that

interact with messenger RNA to prevent translation of a targeted gene. They have proven effective treatments in bowel diseases (135). Their DNA sequence is complementary to the specific mRNA target. Binding leads to the degradation of the DNA sequences with failure of production essentially acting as an enzyme inhibitor for ICAM-1 and CCR5 (induced by endotoxin-induced pneumonia) in conjunction with Peony Root (130-134).

- ❑ Herbal Actions: Targets the hypothalamic-pituitary-adrenal axis (HPA), wide applications for stagnated blood conditions, Analgesic, Antiallergic, Anti-Inflammatory, Anticancer, Antioxidant, Immunomodulatory, Neuroprotective, Anti-depressant, Adaptogen (130,140).
- ❑ Daily Recommended Dosage: 80 mg/kg/day (130) maximum daily oral dose of crude herb 15,000 mg (139)
    - ❑ Dosage Rationale/Toxicity:
        - ❑ In vivo study testing the antidepressant-like effect of ethanol extract from Paeonia lactiflora in mice via intragastric administration revealed that beneficial effects were seen at 80-160mg/kg/day for 6 weeks-indications: inhibition of the serum corticosterone level and increasing hippocampal glucocorticoid receptor messenger (RNA) mRNA expression. Administration at this dosage did not reveal toxicity (136).
- ❑ Treatment Duration: 6 weeks max.
- ❑ Inclusion Rationale: Down regulates ICAM-1 expression elevated in LPS-induced U937 cells and TNFa stimulated HUVECs. Paeonia lactiflora suppresses the activation of the NF-KB pathway, which regulates the expression of ICAM-1 (129). Due to its effect on HUVECs it is a reinforcing synergistic herb that will further support Sassurea lappa in inhibiting abnormal vascular endothelial growth. Further, Paeoniflorin has been shown (in conjunction with other natural herbs) to increase NFG and BDNF production which effectively suppresses CCR5 gene expression (133).
- ❑ Contraindications and Precautions: Paeonia lactiflora may have abortifacient activity, therefore it is not recommended for use during pregnancy (137). There is no information on the use of this herb with children or breastfeeding mothers. Further, peony root might slow blood clotting and should not be used at least 2 weeks before surgery.
    - ❑ Drug Interactions: Paeonia lactiflora should not be combined with Fritillaria verticillata, Cuscuta japonica, and Rheum officinale (138). May also interact with medications that slow blood clotting. Phenytoin (Dilantin) interacts with Paeonia lactiflora.

Claim 4: A composition of claim 1, wherein the composition further comprises **Nelumbo nucifera.**

- ❑ Common Name: Lotus Seed
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituents: Dauricine, Pronuciferine, Dauricine, Lotusine, Liensinine, Isoliesinine, Neferine, Nuciferine, N-Nornuciferine, O-Nornuciferine, Roemerine, Armepavine, D(-)-3'bromo-O-methyl-armepavine, Procyanidin, D-1,2,3,4-tetrahydro-6-methoxy-1-(p-methoxybenzly)-2-methyl-7-isoquinolinol, and Gallic acid. Rich in protein, amino acids, unsaturated fatty acids, and minerals. Chromium (0.0042%), sodium (1.00%), potassium (28.5%), calcium (22.10%), magnesium (9.20%), copper (0.0463%), zinc (0.0840%), manganese (0.356%)), and iron (0.1990%) (141).

- ❑ Plant Part Used: Seeds
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Antioxidant- increase in levels of superoxide dismutase (SOD) and catalase / decreases in the levels of thiobarbituric acid reactive substances (TBARS). Anti-Inflammatory- inhibits the production of pro-inflammatory cytokine tumor necrosis factor-a (TNF-a), increases anti-inflammatory cytokine IL-10 (149).
- ❑ Herbal Actions: Anti-ischaemic, Antioxidant, Hepatoprotective, Antiproliferative, Anti-inflammatory, Anti-Arrhythmic, Anti-Fibrosis, Anti-Viral (141)
- ❑ Daily Recommended Dosage: 100 mg/kg/day (148)
    - ❑ Dosage Rationale/Toxicity:
        - ❑ In vivo study to assess the antioxidant activity of a hydro alcoholic extract of Nelumbo nucifera (HANN) using Swiss Albino mice. Mice were given an oral dose of HANN at 100 and 200 mg/kg body weight for 4 days prior to carbon tetrachloride (CCI (4)) treatment. Results showed that the HANN treatment produced a significant dose-dependent increase in the level of superoxide dismutase (SOD) and catalase and a significant decrease in the level of thiobarbituric acid reactive substances (TBARS) when compared to CCI (4) treated control in the kidney and liver. Changes observed at 100 mg/kg body weight HANN treatment comparable to those observed for a standard vitamin E treatment at 50 mg/kg. No observation of toxicity up to the oral dose of 1,000 mg/kg body weight noted (148).
- ❑ Inclusion Rationale: Due to Nulembo nuciferas' potent free radical scavenging effects at the recommended dosage, it will reinforce Astragalus in the process of Phagocytosis.
- ❑ Safety: Not enough reliable information on the safety of using Nelumbo nucifera for pregnant or breastfeeding mothers. Nelumbo nucifera has a Anti-fertility activity at 3 mg/kg. Additionally, it may lower blood sugar (150).

Claim 5: A composition of claim 1, wherein the composition further comprises **Panax ginseng.**

- ❑ Common Name: Ginseng
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent: Ginsenosides (Rg1)
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: To assist the body in adapting to the physiological stresses of COVID-19 infection, increase the production of white blood cells via an increase in chemotaxis of polymorphonuclear leukocytes and improve oxygen utilization.
- ❑ Herbal Actions: Adaptogen, Anti-fatigue, Immunomodulator, Antioxidant, Anti-Diabetic, Anti-inflammatory, Hepatoprotective (151)
- ❑ Daily Recommended Dosage: 100 mg daily
    - ❑ Dosage Rationale:
        - ❑ A double blind in vivo study designed to assess the immunomodulating effects of Panax ginseng- Three groups of 20 healthy human volunteers were either given 1) an aqueous extract of 100 mg Panax ginseng, 2) a

standard extract of 100 mg Panax ginseng, or 3) a capsule containing lactose (control groups). Patients took 1 capsule every 12 hours for 8 weeks. Blood tests revealed an increase in chemotaxis of polymorphonuclear leukocytes, the phagocytic index, and the total number of T3 and T4 lymphocytes after 4 and 8 weeks of Ginseng therapy as compared to the control group. No toxicity reported (152).

- ❑ Drug interactions: Panax ginseng may interact with phenelzine, a monoamine oxidase inhibitor (154-155)
- ❑ Toxicology & Safety:
  - ❑ In vivo: The safety and tolerance of Panax ginseng was assessed through a randomized, double blind, placebo controlled study. 170 healthy Korean volunteers were randomly assigned to take a 20% ethanol extract of Panax ginseng root by mouth at dosages of either 1) 500 mg twice a day or 2) 1000 mg twice per day. The 3rd group received a placebo. There were no adverse events, deaths, or otherwise toxic effects reported (153).
- ❑ Inclusion Rationale: Lethargy and fatigue are common symptoms in COVID-19 patients. There are three sedative herbs in the Milhu Shamsi formulation; Peony Root, Tulsi and Bupleurum. Ginseng as a therapeutic agent will offset the sedative effects of this formulation by making the patient feel more productive, alert, yet calm in the face of tremendous difficulty. Ginseng also provides beneficial synergistic effects when paired with Sassurea lappa and Peony Root. The two latter herbs inhibit chemotaxis of HUVECs while Ginseng increases chemotaxis of immune cells.

Claim 6: A composition of claim 1, wherein the composition further comprises **Radix Bupleuri.**

- ❑ Common Name: Bupleurum Root
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituents: Triterpene saponins, including saikosaponin A, B 1-4), D, E, F, and H and related compounds including saikogenins A-G and polysaccharides, bupleurans 2IIb and 2IIc (156-159).
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Reduction of fever, pain and inflammation (160, 163).
- ❑ Herbal Actions: Immunomodulator, Anti-Inflammatory, Anti-Ulcer, Antipyretic, Analgesic, Sedative, Hepatoprotective (160) act in synergy with the "Autophagy Jump Start" Blend by assisting with the induction of autophagy (161).
- ❑ Daily Recommended Dosage: 200-800 mg/kg per day, up to 9g / day (160)
  - ❑ Dosage Rationale:
    - ❑ Oral administration of 200-800 mg/kg of Bupleurum extract given to mice produced sedative, analgesic, and antipyretic effects. No toxic effects documented (160).
- ❑ Toxicity:
  - ❑ In vitro study to determine the effects of Bupleurum root on anti-inflammatory activity on adipocytes using 3T3-LI cells revealed that the saikosaponins in Radix Bupleurum inhibits the expression of inflammatory associated genes and it

is a viable inhibitor of NF-xB activation. 3T3-LI cells were treated with 200 ul of various concentrations of the Bupleurum extract for 24 hours. The MTT assay revealed that the extract of Bupleurum did not affect cytotoxicity of the 3T3-L1 cells (163).

- ❑ Contraindications: Radix Bupleuri causes sedation, caution should be taken in large doses. Possible synergistic effects with other sedative herbs. No data on the safety of this herb for use by pregnant and breastfeeding mothers (160).
- ❑ Inclusion Rationale: Radix Bupleuri has been identified as a potential natural treatment for COVID-19 (162) the potency of its anti-inflammatory activity due to its saikosaponins is similar to the steroid prednisolone (160).

Claim 7: A composition of claim 1, wherein the composition further comprises **Artemisia vulgaris.**

- ❑ Common Name: Mugwort
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituents: Sesquiterpenoid lactones including artemisinin, psilostachyin, psilostachyin C, and vulgarin. Flavonoids include kaempferol and quercetin, coumarin compounds (esculin, umbelliferone, and scopoletin) and essential oil (164).
- ❑ Plant Part Used: Leaf
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Induce autophagy as evidenced by increasing intracellular ROS and reduction MMP reduction. Inhibition of migration of colon cancer cells (165).
- ❑ Inclusion Rationale: Those with diagnosed cancers are at high risk of developing severe complications from COVID-19 infection. In some cases a cytokine storm which causes severe tissue damage occurs in COVID-19 patients. This storm is instigated by interleukin 6 (IL-6) which acts on a large number of cells and tissues. IL-6 increases during colonic cancer, inflammatory bowel disorders, and infections due to viruses and bacteria (8).

  A retrospective controlled study conducted in Italy to compare data of the colorectal cancer screening (CRCS) during the COVID-19 lockdown period (March 9-May 4, 2020) with those of the same period of 2019 (control group). In the lockdown group 60 endoscopies were performed whereas in the control group 238 CRCS colonoscopies were done. The results of this study revealed that despite the lower number of exams performed in the lockdown group there were more colorectal cancers than in the control group. Furthermore, the high-risk adenomas detection rate was significantly higher in the lockdown group than in the control group (166). A recent study also conducted in Italy, sought to understand the psychological aspects of eating habits during COVID-19 home confinement from April 24-May 18, 2020. 602 people participated in an online survey. The results showed that 63.3% of respondents experienced a depressed mood, 70.4% had anxious feelings, 46.2% were hypochondrial, and 52.2% experienced insomnia. Almost half of the respondents reported feelings of anxiousness due to their increase of food intake, "comfort food" in particular. The results also indicated that women were more likely to be more anxious and inclined to comfort food than men (167).

It is well documented that poor lifestyle and dietary habits including lack of exercise, sleep deprivation, and irregular eating increase the incidence of inflammatory bowel disorders (168). Further, it has been established that inflammatory bowel disorders lead to increased risk for colorectal neoplasia (169).
Artemisia vulgaris extracts have been proven have an antifungal effect against Candida albicans and similar pathogens (170). Additionally, a methanolic extract prepared from arial parts of Artemisia vulgaris showed inhibitory effects against MCF7 and HeLa cancer cell lines (171) and colon cancer cells by inducing autophagy and inhibiting cell migration (165).

The use of Artemisia vulgaris, as well as other herbs in this formulation, makes Milhu Shamsi an appropriate drug for prevention of COVID-19 and its complications as it relates to inflammatory bowel disorders and colon cancer and as an appropriate drug intervention COVID-19 patients. Further, Artemisia vulgaris has been included in this formulation to aid in inducing autophagy, a key component in The Fitra30 COVID-19 Protocol.

- ❑ Herbal Actions: Antioxidant, Hypolipemic, Hepatoprotective, Antispasmolytic, Bronchodilatory, Analgesic, MAO inhibition, Antihypertensive, Estrogenic, Cytotoxic, Antifungal, Antibacterial, Anti-inflammatory, Antialergenic, Antimalarial, Anthelmintic (164).
- ❑ Daily Recommended Dosage: 25-100 mg/kg/day
    - ❑ Dosage Rationale / Toxicity:
        - ❑ An in vivo study was conducted by scientists in Egypt to assess the antioxidant capacity of Artemisia vulgaris. 15 healthy male rats weighing 150-200g each were used in the study. The rats were divided into 3 groups of 5. The first group (control group) enjoyed an unrestricted diet and water. They were treated with distilled water (2 ml/kg/p.o. only). The second group was treated orally with an aqueous extract of Artemisia vulgaris at a dose of 100 mg/kg. The third group was treated with Silymarin at a dose of 100 mg/kg. All animals were administered their respective interventions by orogastric catheter once daily for 42 days. The results showed that Artemisia vulgaris has strong antioxidant activity. There were no reported adverse effects or toxicity (172).
        - ❑ In vivo study to assess the effects of Artemisia vulgaris extract in hycholestoromic rats. 24 male Wistar albino rats weighing 120-140g were used for this experiment. The animals were divided into 4 groups of 6 each. Group 1 was kept on a standard pellet diet. Group two-these rats were fed a high fat diet (HFD) consisting of 3% cholesterol, 9% cotton seed oil, 10% olein oil, and 0.5% cholic acid for 8 weeks. Group three- were fed a HFD given an aqueous dose of Artemisia vulgaris (100 mg/kg per day) via stomach tube once daily for 4 weeks. The fourth group were fed a HFD and orally administered Atorvastatin by stomach

tube once daily for a period of 4 weeks. The study concluded Artemisia vulgaris has hypolipidemic, anti-inflammatory, and antioxidant properties due to the polyphenols and saponins present in the herb. Further, no reported adverse effects were observed or toxicity noted (173).

- ❑ Safety: The use of Artemisia vulgaris aqueous extracts in therapeutic doses is likely safe. However, persons allergic to Artemisia vulgaris or any plant in the Asteraceae family should avoid as there have been reported adverse effects after swallowing the plants pollen including; anaphylactic shock, breathing difficulties, bronchospasm, airway hypersensitivity, asthma attack, seasonal rhinitis, and conjunctivitis. Allergic skin reactions may also occur. In large doses Artemisia vulgaris may cause miscarriage, nausea, vomiting, and nervous system damage. Hypertension has also been reported. Artemisia vulgaris must be used with caution in patients with diabetes as it may cause blood glucose levels to rise (164).

Claim 8: A composition of claim 1, wherein the composition further comprises **Angelica archangelica.**

- ❑ Common Name: Angelica Root
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent:
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: To act as a natural antimutagen against COVID-19 (175). Radioprotective: provide protection against the harming of normal tissues and impeding immune functions through exposure to moderate to high levels radiation stemming from hospital treatments (radiation therapy) (177).
- ❑ Inclusion Rationale: Angelica root exhibits strong Antioxidant activity which will strengthen the free radical scavenging potential of the overall formulation. Additionally, as a Antimicrobial agent, the essential oil content of Angelica root has proved effective against bacteria and fungus to include; Fusarium genus, Botrytis cinerea, Alternaria solani, Clostridium difficile, Clostridium perfringens, Enterococcus faecalis, Eubacterium limosum, Peptostreptococcus anaerobius, and Candida albicans (179-180).
- ❑ Herbal Actions: Antitumor, Anti-anxiety, Cytotoxic Effect, Hepatoprotective, Antimutagenic, Butyrylcholinesterase Inhibitory Activity, Inhibition of Acetylcholinesterase, Antimicrobial, Antiseizure (176).
- ❑ Daily Recommended Dosage: 100 mg/kg/day
    - ❑ Dosage Rationale:
        - ❑ Antimutagenic activity of an aqueous solution of Angelica archangelica and alcohol extracts of thio-TEPA against mutagenicity was studied by micronucleus tests in murine bone marrow cells. It was found that the reduction of Thio-TEPA's mutagenic activity was enhanced when the Angelica root extracts were injected two hours before thio-TEPA treatment. The reduction of micronuclear frequencies were as high as 77%. Aqueous extract dosages were tested at 50, 100, 500, and 1000 mg/kg (175).
- ❑ Toxicology & Safety:

- ❑ An in vivo study designed to evaluate the anti-anxiety effects of Angelica archangelica linn. using Albino rats. An acute toxicity study was conducted. Overnight healthy rats received successive extracts of Angelica archangelica (petroleum ether, chloroform, ethyl acetate, methanol and water) at doses of 100, 200, 400, 800, 1600, and 3200 mg/kg body weight and observed for 4 hours and again after 24 hours for abnormalities and mortality. Extracts at 3200 mg/kg were found to be safe. Further, it was concluded that Angelica archangelica exhibited strong anti-anxiety effects (178).
- ❑ The Food and Drug Administration includes angelica in its list of herbs and spices that are generally regarded as safe (GRAS).
- ❑ Not recommended for pregnant and breastfeeding women (181).

Claim 9: A composition of claim 1, wherein the composition further comprises **Ocimum sanctum (Krishna).**

- ❑ Common Name: Tulsi
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent: Eugenol (1-hydroxy-2-methoxy-4-allylbenzene) (191), orientin and vicenin (194)
- ❑ Plant Part Used: Leaf
- ❑ Primary Targets for COVID-19 + Clinical Outcomes: Interference of SARS-CoV-2/CD4 interaction (192, 193). Decrease inflammation as evidenced by inflammation markers which may include; including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and plasma viscosity (PV) (197). Increase lung vital capacity and relieve laboured breathing (201).
- ❑ Inclusion Rationale: In a previous study, the combination of aqueous extracts of Ocimum sanctum (Tulsi) and Withania somnifera (Ashwagandha) have showed significant inhibition of RNA Dependant DNA Polymerase (RDDP) function of HIV-reverse transcriptase (190). Additionally, this herbal combination is thought to inhibit gp120/CD4 interaction by binding to CD4 but not to gp120 (192) which shows the potentiality of this combination interfering with SARS-CoV2/CD4 interaction.
- ❑ Herbal Actions: Antibacterial, Antifungal, Antiviral, Anti-HIV, Radioprotective, Antifertility, Anticancer, Antidiabetic, Antimicrobial, Hepatoprotective, Cardioprotective, Antiemetic, Antispasmodic, Analgesic, Adaptogenic and Diaphoretic (191).
- ❑ Daily Recommended Dosage: 100 mg/kg/day
    - ❑ Dosage Rationale / Toxicology:
        - ❑ An in-vitro testing of anti-HIV activity of an aqueous extract of Ocimum sanctum using two Anti-HIV assays: 1) Reverse Transcriptase (RT) Inhibition Assay and 2) Gp120 Binding Inhibition Assay. Results showed that aqueous extracts of Ocimum sanctum interfered with gp120/CD4 interaction and inhibited viral Reverse Transcriptase (RT). The aqueous extracts were made using the decoction method using 3-20g of plant material to 50-200 ml. Distilled water (192).

- In-vivo study designed to test the radioprotective effect of an alcoholic and aqueous extract of Ocimum sanctum using albino mice. Mice were given either single or multiple doses of the extracts before whole-body exposure to 11 Gy(LD100/30) of 60Co gamma radiation for 5 consecutive days. The study found that the water extract was more effective and less toxic than the alcohol extract. The maximum dose of the aqueous extract was 50 mg/kg/day however, a dose of 10 mg/kg/day for 5 days gave the maximum survival. Routes of administration included im, iv, po, and intraperitoneal. The intraperitoneal route gave the best protection for survival (70%) while the other routes produced 37-47% survival rates (195).
- An in-vivo study to test the anti-inflammatory and analgesic properties of an aqueous extract Ocimum sanctum was conducted using Wistar albino rats weighing (150-200g). The rats were split into 4 groups of 6 each. To test the anti-inflammatory activity of the herb the first group was given 0.9% normal saline (control group). The second group was given the aqueous extract of Ocimum sanctum at a dosage of 100 mg/kg. The third group was given Aspirin at a dosage of 150 mg/kg. The fourth group was given Celecoxib at a dosage of 20 mg/kg. All dosages were administered orally for 7 days. Raw paw edema induced by carrageenan and cotton pellet induced granuloma were the models used to screen the anti-inflammatory activity of Ocimum sanctum. The results showed that in the Carrageenan induced enema model, the aqueous extract of Ocimum sanctum (100 mg/kg) showed significant anti-inflammatory activity (13.43% inhibition at 2 hours). In the cotton pellet granuloma model 100 mg/kg the aqueous extract of Ocimum sanctum showed extremely significant inhibition of granuloma formation with a PI of 23.85% (197).
- "The present study was aimed to study the acute and subacute toxicity studies with orally administered 50% ethanolic leaves extract of Ocimum sanctum Linn (OSE). In acute toxicity tests, four groups of mice (n = 6/group/sex) were orally treated with doses of 200, 600, and 2000 mg/kg, and general behavior, adverse effects, and mortality were recorded for up to 14 days. In subacute toxicity study, rats received OSE by gavage at the doses of 200, 400, and 800 mg/kg/day (n = 6/group/sex) for 28 days, and biochemical, hematological, and histopathological changes in tissues (liver, kidney, spleen, heart, and testis/ovary) were determined. OSE did not produce any hazardous symptoms or death and CNS and ANS toxicities in the acute toxicity test. Subacute treatment with OSE did not show any change in body weight, food and water consumption, and hematological and biochemical profiles. In addition, no change was observed both in macroscopic and microscopic aspects of vital organs in rats." (200)

- ❑ Contraindications / Safety: Ocimum sanctum is contraindicated during pregnancy and lactation (198). Ocimum sanctum should be used with caution in patients taking drugs such as paracetamol (acetaminophen) that deplete glutathione (199).

Claim 10: A composition of claim 1, wherein the composition further comprises **Citrus sinensis.**

- ❑ Common Name: Orange Peels
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent: Nobiletin is responsible for its anti-inflammatory effects (205). Also includes flavonoids, steroids, hydroxyamides, alkanes, fatty acids, coumarins, peptides, carbohydrates, carbamates, alkylamines, carotenoids, volatile compounds, and nutritional elements to include potassium, magnesium, calcium, and sodium (206).
- ❑ Plant Part Used: Peels
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Citrus sinensis is rich with Vitamin C which makes it potent source antioxidant- will help to protect cells from damage caused by free radicals (206).
- ❑ Inclusion Rationale: To provide Vitamin C and support other herbs in the formulation that have antioxidant properties.
- ❑ Herbal Actions: Antioxidant, Antifungal, Antiparasitic, Antiproliferative, Hypocholesterolemic, Antidiabetic (206).
- ❑ Daily Recommended Dosage: 250 mg/kg
    - ❑ Dosage Rationale / Toxicity:
        - ❑ In vivo study to test antidiabetic and antihypercholesteroleic activities of citrus sinensis in rats. 25 rats were divided into groups of 5. Group 1 was given a negative control (0.5% cMC-Na), Group 2 was given a positive control (glibenclamide and simvastatin). Groups 3-5 were given alcoholic doses of Citrus sinensis at 125, 250, and 500 mg/kg body weight respectively. The extract of Citrus sinensis peels at a dose of 500 mg/kg showed the highest antidiabetic activity in the rat models. No acute toxicity was reported (207).

Claim 11: A composition of claim 1, wherein the composition further comprises **Zingiber officinale.**

- ❑ Common Name: Ginger
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent (s): Gingerols, Shogaols, and Zingiberene (208).
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Reduce inflammation, nausea, and vomiting (209).
- ❑ Inclusion Rationale: Zingiberene, one of the main constituents of Zingiber officinale has proven to inhibit in vitro and in vivo human colon cancer cell growth via autophagy induction, suppression of PI3K/AKT/mTOR Pathway and caspase 2 deactivation (209). Therefore, this herb will provide synergistic effects with other anticancer herbs in this formulation. Further, due to its ability to induce autophagy, it will also enhance the effectiveness of The Autophagy Jump Start Blend. Lastly, Zingiber officinale will

enhance the anti-inflammatory effect of the formulation due to its anti-inflammatory activity (209).

- ❑ Herbal Actions: Cholagogic, Antiemetic, Anti-inflammatory (209), Antihepatotoxic (210).
- ❑ Daily Recommended Dosage: 1000 mg per day
  - ❑ Dosage Rationale / Toxicity: In vivo, double blind randomized cross over clinical trial found that ginger (25 mg by mouth, 4 times per day) effectively treated harmful vomiting in pregnancy. No adverse effects were reported (211).

- ❑ Contraindications / Safety:
  - ❑ The Food and Drug Administration includes ginger in its list of herbs and spices that are generally regarded as safe (GRAS).
  - ❑ Ginger should be used with caution in patients taking anticoagulant drugs or those with blood coagulation disorders.
  - ❑ A hot water extract was found to be mutagenic in B2911 cells and Salmonella typhimurium strain TA 100 but not strain TA 98 (212).
  - ❑ Not recommended for children under 6 years of age.

Claim 12: A composition of claim 1, wherein the composition further comprises **Rosa canina.**

- ❑ Common Name: Rose Hips
- ❑ Formulation Function: Synergistic Herb
- ❑ Main Active Constituent: Vitamin C
- ❑ Plant Part Used: Fruit
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Reduction of cough, fever, and congestion by increasing Vitamin C intake (220). Prevent and treat oxidative stress by decreasing Reactive Oxygen Species (221).
- ❑ Inclusion Rationale: Rosa canina has been added to this formulation to synergize with Citrus sinensis thereby increasing the Vitamin C content. Vitamin C has proven effective in preventing and relieving the symptoms of virus-induced respiratory infections (220).
- ❑ Herbal Actions: Anti-inflammatory, Antioxidant, Anti-mutagen (217), Vitaminisant, Astringent, Cholagogue, Choleretic, Diuretic, Anti-diarrhoea (218), and Anti-diabetic (219).
- ❑ Daily Recommended Dosage: 1000 mg per day
  - ❑ Dosage Rationale / Toxicity:
    - ❑ The aqueous and ethanol extracts of Rosa canina L. (Rosaceae) fruits and the fractions prepared from the latter were investigated for their anti-inflammatory and antinociceptive activities in several in vivo experimental models. Extracts displayed potent anti-inflammatory and antinociceptive activities at a dose of 919 mg/kg without inducing acute toxicity. (222).
- ❑ Contraindications / Safety:
  - ❑ Rosa canina may have serious drug interactions with; demeclocycline, doxycycline, eltrombopag, fleroxacin, gemifloxacin, levofloxacin, minocycline, moxifloxacin, mycophenolate, ofloxacin, oxytetracycline, and tetracycline (223).

- ❑ Patients taking Rosa canina should be monitored closely when taking;
  - ❑ aluminum hydroxide
  - ❑ Amoxicillin
  - ❑ Ampicillin
  - ❑ calcium carbonate
  - ❑ Cimetidine
  - ❑ Deferoxamine
  - ❑ Dexlansoprazole
  - ❑ Enalapril
  - ❑ Esomeprazole
  - ❑ Famotidine
  - ❑ Flucloxacillin
  - ❑ Ibandronate
  - ❑ ibuprofen/famotidine
  - ❑ Lansoprazole
  - ❑ Levothyroxine
  - ❑ Liothyronine
  - ❑ Methotrexate
  - ❑ Methyldopa
  - ❑ Mycophenolate
  - ❑ Nafcillin
  - ❑ Nizatidine
  - ❑ Omeprazole
  - ❑ Oxacillin
  - ❑ Pantoprazole
  - ❑ Penicillamine
  - ❑ penicillin G aqueous
  - ❑ penicillin VK
  - ❑ Pivmecillinam
  - ❑ Probenecid
  - ❑ Rabeprazole
  - ❑ sodium bicarbonate
  - ❑ sodium citrate/citric acid
  - ❑ Temocillin
  - ❑ thyroid desiccated
  - ❑ Ticarcillin
  - ❑ Trientine
  - ❑ wheat germ extract (223)
- ❑ Contraindicated in patients with Sickle Cell Anemia (224)
- ❑ Unknown if safe for pregnant or breastfeeding women (224)

Claim 13: A composition of claim 1, wherein the composition further comprises **Glycyrrhiza glabra.**

- ❑ Common Name: Licorice Root
- ❑ Formulation Function: Synergistic Herb

- ❑ Main Active Constituent: Glycyrrhizin (GL) (210)
- ❑ Plant Part Used: Root
- ❑ Primary Target for COVID-19 + Clinical Outcomes: Interference with virus to cell binding via inhibition of ICAM-1 expression by blocking JNK and NF-xB pathways (213).
- ❑ Inclusion Rationale: This herb will work to offset any mutagenic effects of Zingiber officinale as Glycyrrhiza glabra has an antimutagenic effect against Salmonella typhimurium strains TA100 and TA98 (210). Glycyrrhiza glabra also inhibits the overgrowth of intestinal bacteria including Candida albicans (214).
- ❑ Herbal Actions: Antimutagenic, Anticarcinogenesis, Detoxification, Antiulcer, Anti-inflammatory, Antihepatitis, Antiviral, Anti-AIDS, Antiatherogenic, Antioxidant (210).
- ❑ Daily Recommended Dosage: 1000 mg per day
    - ❑ Dosage Rationale / Toxicity:
        - ❑ In vivo study to test the effectiveness of Hochuekkito a Kampo (traditional Japanese herbal) Medicine on mucosal IgA immune response using mice. The mice were given the aqueous Hochuekkito formulation which consisted of 1.5g of Glycyrrhizae Radix for 27 days orally via the intragastric route. Results showed that Hochuekkito enhances mucosal IgA Antibody response in mice immunized with antigen-entrapped biodegradable microparticles. No adverse effects were observed (69).
        - ❑ In vivo study to test the effects of Glycyrrhiza glabra on learning and memory impairment in 1 month old Wistar albino rats. Four doses 75, 150, 225, and 300 mg/kg of an aqueous extract of Glycyrrhiza glabra root was administered to the rats orally for six weeks. Results showed that all doses enhanced memory however, doses of 150 and 225 mg/kg had the most significant effect. Memory impairment is thought to be brought on by age, oxidative stress, harmful free radicals, and inflammation. No adverse effects were observed (215).
- ❑ Contraindications / Safety:
    - ❑ Contraindicated in patients with hypertension, cholestatic disorders, or cirrhosis of the liver, hypokalaemia, or chronic renal insufficiency during pregnancy (216).
    - ❑ Prolonged use of large doses (more than 50g per day) for extended periods (more than 6 weeks) may increase the risk of water accumulation. Sodium excretion is reduced and potassium excretion is increased. Blood pressure may rise (216).
    - ❑ Glycyrrhiza glabra should not be taken concurrently with corticosteroid treatment (216).
    - ❑ Because it increases potassium loss, Glycyrrhiza glabra should not be administered for prolonged periods with thiazide and loop diuretics or cardiac glycosides. Because it reduces sodium excretion the effectiveness of drugs used in the treatment of hypertension could be reduced. Glycyrrhiza glabra should not be given in conjunction with spironolactone or amiloride (216).
    - ❑ The safety of using Glycyrrhiza glabra in women who are pregnant and nursing as well as in children has not been established (216).

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PTO/SB/452 (09-20)

CERTIFICATION AND REQUEST FOR COVID-19 PROVISIONAL PATENT APPLICATION PROGRAM

(Page 1 of 1)

First Named Inventor:	Taliah Safah Muhammad
Title of Invention:	Compositions and Prevention and Intervention Methods for COVID-19 with Divine Ayats' Fitra30 COVID-19 Protocol
Contact information to include in database (optional)	(301) 549-6396 ummnadia@divineayat.com www.DivineAyat.com

APPLICANT HEREBY MAKES THE FOLLOWING CERTIFICATIONS AND REQUESTS THAT THE USPTO INCLUDE THE DESCRIPTION OF THE ACCOMPANYING PROVISIONAL PATENT APPLICATION IN A PUBLIC DATABASE.

1. The description of the accompanying provisional patent application concerns a product or process relating to COVID-19 and such product or process is subject to an applicable FDA approval for COVID-19 use.

2. The accompanying application is in the English language.

3. The accompanying application is being filed in DOCX format via the USPTO's Patent Center filing system, together with this form.

4. The applicant understands that while the required filing fee for the accompanying provisional application may be deferred by acceptance into this program, the appropriate filing fee must be paid in order for a subsequent U.S. nonprovisional application to claim the benefit of the filing date of the accompanying provisional application. Applicant recognizes that the filing fee due in the future may be more than the current fee due and that by deferring payment of the filing fee, there may be an increase in the total fee due.

5. Applicant authorizes and requests that the description, including the specification and any drawings, claims and/or abstract of the accompanying provisional patent application, as well as this form, be included in a searchable online public database.

6. Applicant understands that inclusion in the public database is a publication of the description and this form.

Signature Taliah Safah Muhammad Verified by PatentCenter 12/30/2020	Date 12/30/2020
Name (Print/Typed) Taliah Safah Muhammad	Practitioner Registration Number

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☒ *Total of 1 forms are submitted.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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