

I-RECOVERSM

POST-VACCINE TREATMENT

**An approach to managing
post-vaccine syndrome**

July 2023

FLCCC[®]
ALLIANCE

Table of Contents

Summary of Suggested Therapies	3
Disclaimer	4
Contributors	4
Definition	4
Epidemiology.....	4
Pathogenesis	5
Complications/ injuries caused by COVID injections.	7
Treatment Approach	10
Baseline Testing.....	11
Anticoagulation post-vaccination and the three clinical phenotypes of the vaccine injured ..	13
Provisional approach to anticoagulation in the post-vaccine phenotypes	15
First-Line Therapies	17
Intermittent daily fasting or periodic daily fasts	17
Ivermectin (IVM)	17
Moderating physical activity	19
Low-dose naltrexone (LDN)	19
Nattokinase	19
Melatonin	19
Magnesium	20
Methylene blue.....	20
Sunlight and Photobiomodulation (PBM)	21
Resveratrol or a combination flavonoid.....	23
Probiotics/prebiotics.....	24
Adjunctive/Second-Line Therapies	24
Third Line Therapies	27
Patients with elevated homocysteine levels	28
Other Potential Treatments.....	28
Disease-Specific Therapeutic Adjuncts.....	31
Small fiber neuropathy (SFN)/autonomic neuropathy	31
Generalized neurologic symptoms/“brain fog”/fatigue/visual symptoms.....	32
Depression	33
Patients with elevated DIC and those with evidence of thrombosis	34
Vaccine-induced myocarditis/pericarditis.....	34
Herpes virus reactivation syndrome	34
Tinnitus.....	34
Ageusia and anosmia (Loss of taste and smell)	35
Bell’s palsy/facial paresthesia/visual issues.....	35
Patients with new onset allergic diathesis/features of Mast Cell Activation Syndrome (MCAS)	36
Alopecia (hair loss).....	36
References.....	37

Summary of Suggested Therapies

First-Line Therapies <i>(Not symptom specific; listed in order of importance)</i>	Adjunctive/Second-Line Therapies <i>(Listed in order of importance)</i>	Third Line Therapies
Intermittent daily fasting or periodic daily fasts	Vitamin D (4000-5000 units/day) and Vitamin K2 (100 mcg/day)	Hyperbaric oxygen therapy
Ivermectin; 0.2-0.3 mg/kg daily	Omega-3 fatty acids; we suggest a combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids)	Low Magnitude Mechanical Stimulation (LMMS or Whole-Body Vibration)
Moderating physical activity	N-acetyl cysteine (NAC); 600-1500 mg/day	“Mitochondrial energy optimizer”
Low-dose naltrexone (LDN); 1-4.5 mg daily	Cardio Miracle™ and L-arginine/L-citrulline supplements	Hydroxychloroquine (HCQ); 200 mg twice daily for 1-2 weeks, then reduce as tolerated to 200 mg/day
Nattokinase 100-200 mg (2000- 4000 Fibrinolytic Units) twice daily. ? Low dose ASA 81 mg daily	<i>Nigella sativa</i> ; 200-500 mg encapsulated oil twice daily	Low dose corticosteroid; 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day, as tolerated
Melatonin; 2-6 mg <i>slow release/extended release</i> prior to bedtime	Sildenafil with or without L-arginine-L-Citrulline	
Magnesium; 100-400 mg daily	Bromelain 500 mg twice daily +/- N-acetyl cysteine (NAC)	
Methylene blue; 10-30 mg daily	Vitamin C; 1000 mg orally two to three times a day	
Sunlight and Photobiomodulation (PBM)	Spermidine; 1000-2000 mg (wheat germ extract) daily	
Resveratrol; 400-500 mg daily	Non-invasive brain stimulation (NIBS)	
Probiotics/prebiotics	Intravenous Vitamin C; 25 g weekly, together with oral Vitamin C 1000 mg (1 gram) 2-3 times per day	
	Behavioral modification, relaxation therapy, mindfulness therapy, and psychological support	

Disclaimer

This document is primarily intended to assist healthcare professionals in providing appropriate medical care for vaccine-injured patients. Patients should always consult a trusted healthcare provider before embarking on any new treatment.

Definition

Although no official definition exists for ‘post-COVID-vaccine syndrome,’ a temporal correlation between receiving a COVID-19 vaccine and the beginning or worsening of a patient’s clinical manifestations is sufficient to diagnose as a COVID-19 vaccine-induced injury when the symptoms are unexplained by other concurrent causes.

Since Phase 3 and Phase 4 clinical trials are still ongoing, the full safety and toxicity profile for COVID-19 vaccines cannot be fully determined. From a bioethical perspective, cases of any new-onset or worsened signs, symptoms, or abnormalities following any dose of COVID-19 vaccine must be considered as an injury caused by the vaccine, until proven otherwise.

Note that there are significant overlaps between the symptoms and features of long COVID/long-hauler syndrome and post-vaccine syndrome. However, a number of clinical features appear to be characteristic of post-vaccine syndrome; most notably, severe neurological symptoms appear to be more common following vaccination. To complicate matters further, patients with long COVID are often also vaccinated, making the issue of definition more difficult.

Epidemiology

The Centers for Disease Control (CDC), National Institutes for Health (NIH), Food and Drug Administration (FDA), and World Health Organization (WHO) do not recognize post-COVID-19 vaccine injuries as a specific medical condition, (1) even though there is a specific ICD-10 code. Curiously, the code U12.9 is recognized in Europe but not in the United States. There have been no prospective studies that have *accurately classified and logged* the incidence of this complication; therefore, the true magnitude of post-vaccine syndrome is unknown.

However, as of December 2nd, 2022, nearly 1.5 million adverse events had been reported. This includes over 30,000 deaths, 185,000 hospitalizations, 15,000 heart attacks, 35,000 cases of myocarditis, and 60,000 cases of permanent disability according to [OPEN VAERS](#), which tracks data recorded in the U.S. [Vaccine Adverse Event Reporting System](#) (VAERS). Note that VAERS data is limited by underreporting, by a factor of at least 30-fold. (2)

The true incidence of adverse events following COVID-19 injections, including deaths and serious vaccine injuries, is unknown; this is complicated by the deliberate and willful manipulation of data (underreporting) by governmental agencies in the United States, United Kingdom, Israel, and many other countries. (2, 3).

Contributors

This protocol was a collaborative effort drawing on the expertise of a dozen world-renowned physicians. Dr. Pierre Kory and Dr. Paul Marik are thankful for the contributions of: Dr. Keith Berkowitz; Dr. Flavio Cadegiani; Dr. Suzanne Gazda; Dr. Meryl Nass; Dr. Tina Peers; Dr. Robin Rose; Dr. Yusuf (JP) Saleeby; Dr. Eugene Shippen; Dr. Mobeen Syed; and Dr. Fred Wagshul.

We are also extremely grateful to the many vaccine-injured people who shared their feedback and experiences with us.

However, available data consistently and reproducibly demonstrates a rate of serious adverse events (SAE) of about 8%. (2, 3) Most importantly, the V-SAFE database administered by the CDC demonstrates an 8% rate of SAE (<https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/vsafe.html>, <https://icandecide.org/v-safe-data/>). Translated to the U.S. vaccinated population, this would mean approximately 18 million vaccine injuries. A Pollfish survey released on July 4, 2022 reported that 8.64% of adult respondents who had received a COVID-19 vaccine in the U.S. developed a vaccine injury. A Rasmussen report published in December 2022 reported a 7% rate of SAE those jabbed. In a nationwide cohort of U.S. veterans, an adverse reaction was reported in 8.5% of recipients of the Pfizer vaccine and 7.9% of those receiving the Moderna vaccine. (4)

As the mainstream medical community does not recognize this serious humanitarian disaster, these patients have been shunned and denied access to the care they need and deserve. Furthermore, there is limited clinical, molecular, and pathological data on these patients to inform an approach to treating the condition. Consequently, our approach to the management of vaccine-injured patients is based on the presumed pathogenetic mechanism, pharmacologic principles, as well as the clinical observations of physicians and patients themselves.

Pathogenesis

The spike protein, notably the S1 segment, is likely the major pathogenetic factor leading to post-vaccine syndrome (see figure 1). (4-6) The S1 protein is profoundly toxic. Multiple intersecting and overlapping pathophysiologic processes likely contribute to the vast spectrum of vaccine injuries: (1, 7)

- The acute, immediate reaction (within minutes to hours) is likely the result of an acute type I IgE-mediated hypersensitivity reaction. The type I response may be due to preformed antibodies against mRNA, polyethylene glycol (PEG) (8, 9), or other components of the nano-lipid particle. In addition, PEG activates multiple ‘complement components,’ the activation of which may be responsible for both anaphylaxis and cardiovascular collapse. (9-11) A prospective study on 64,900 medical employees, in which reactions to their first mRNA vaccination were carefully monitored, found that 2.1% of subjects reported acute allergic reactions. (12)
- The acute myocarditis/sudden cardiac death syndrome that occurs post-vaccination (within hours to 48 hours), noted particularly in young athletes, may be caused by a “stress cardiomyopathy” due to excessive catecholamines produced by the adrenal medulla in response to spike protein-induced metabolic aberrations. (13)
- The subacute and chronic myocarditis is likely the result of a spike protein-induced inflammatory response mediated by pericytes and macrophages. (14, 15)
- The subacute (days) and chronic (weeks to years) vaccine-related injuries likely result from the overlapping effects of an S1-induced inflammatory response, the production of autoantibodies, activation of the clotting cascade, and secondary viral reactivation.
- The inflammatory response is mediated by spike protein-induced mononuclear cell activation in almost every organ in the body but most notably involving the brain, heart, and endocrine organs.
- Patients with long COVID and those post-vaccination may have spike protein circulating in the blood for as long as 15 months. (16-18) Spike protein inhibits natural killer (NK) cell activity, (19-22) cytotoxic T-cells, and inhibits autophagy (23); this may account for the persistence of the spike protein.

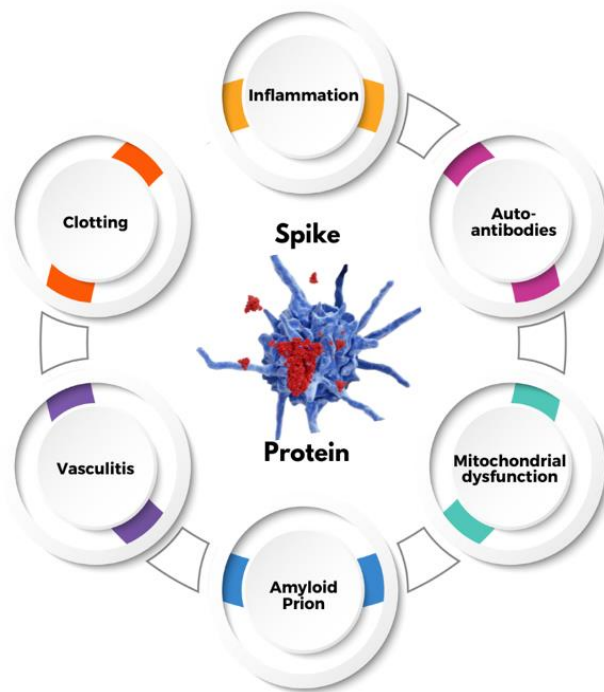
- The lipid nanoparticles (LNP) themselves are highly pro-inflammatory, as evidenced by excessive neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines. (24-26)
- Neuro-COVID, the neurological manifestations related to the spike protein, are related to the complex interplay of neuroinflammation, (27) production of amyloid and prion protein, [28-34] autoantibodies, microvascular thrombosis, and mitochondrial dysfunction. [35]

The spike protein of SARS-CoV-2 has extensive sequence homology with multiple endogenous human proteins and could prime the immune system toward development of both auto-inflammatory and autoimmune disease. (11) As a consequence of molecular mimicry with the spike protein, a diverse spectrum of autoantibodies has been reported. [36-46] These autoantibodies are the likely cause of Guillain-Barré Syndrome (GBS), transverse myelitis, immune thrombocytopenia, and Small Fiber Neuropathy (SFN)/Autonomic neuropathy. (28-35)

Many of these antibodies are directed against G-protein-coupled cell membrane receptors. [43,45] Anti-neuronal antibodies likely contribute to the myriad of neurological findings. SFN/autonomic neuropathy appears to be a characteristic disorder following vaccination and is strongly associated with a vast array of autoantibodies. Further, autoantibodies may result in a number of specific syndromes, including anti-phospholipid syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, etc.

The spike protein is highly thrombogenic, directly activating the clotting cascade; in addition, the clotting pathway is initiated via inflammatory mediators produced by mononuclear cells and platelets. (6) Activation of the clotting cascade leads to both large clots (causing strokes and pulmonary emboli) as well as micro clots (causing microinfarcts in many organs, but most notably the brain). Emerging data suggest that the vaccines can induce an allergic diathesis (eczema, skin rashes, asthma, skin and eye itching, food allergies, etc.) This appears to be due to a unique immune dysregulation with antibody class switching (by B cells) and the production of IgE antibodies. There is an overlap with Mast Cell Activation Syndrome (MCAS) and the distinction between the two disorders is not clear. (36, 37) However, by definition MCAS has no identifiable causes, is not caused by allergen-specific IgE, and has no detectable clonal expansion of mast cells. (36)

Figure 1. Complex pathophysiology of spike-related vaccine-induced disease



And finally, due to altered immune function, the activation of dormant viruses and bacterial pathogens may occur, resulting in reactivated Herpes Simplex, Herpes Zoster, Epstein Barr Virus (EBV), and cytomegalovirus (CMV) infection, as well as reactivation of Lyme disease and mycoplasma. (38-41)

The common factor underlying the pathogenic mechanism in the vaccine-injured patient is “immune dysregulation.” The development of immune dysfunction and the severity of dysfunction likely result from several intersecting factors, including:

- **Genetics:** First-degree relatives of patients who have suffered a vaccine injury appear to be at a very high risk of vaccine injury. Those patients with a methylenetetrahydrofolate reductase (MTHFR) gene mutation (42) and those with Ehlers-Danlos type syndromes may be at an increased risk of injury. MTHFR C677T polymorphism is the most common MTHFR single nucleotide polymorphism (SNP) and the most common genetic cause of hyper-homocysteinemia. (43) Increased homocysteine levels have been linked to worse outcomes in patients with COVID-19. (44, 45) Increased homocysteine levels may potentiate the microvascular injury and thrombotic complications associated with the “spikopathy”. (43, 46)
- **mRNA load and quantity of spike protein produced:** This may be linked to specific vaccine lots that contain a higher concentration of mRNA. (1) The Moderna vaccine is reported to contain 100 ug of mRNA as compared to 30 ug mRNA for the Pfizer vaccine (10 ug in children 5-11 years of age), however, it is likely that the true concentration varies widely.
- **Sex:** It appears that about 80% of vaccine-injured patients are female. Furthermore, treatment with estrogens has been reported to worsen or precipitate an event/relapse. Women are known to be at a much higher risk of autoimmune diseases (especially SLE) and this likely explains this finding. Estrogens interfere with glucocorticoid receptor signaling. (47) In addition, estrogens modulate B and T cell function.
- **Underlying nutritional status and comorbidities:** Certain preexisting conditions may likely have primed the immune system to be more reactive after vaccination. This includes those with preexisting autoimmune disorders and chronic inflammatory diseases such as Lyme disease. Those patients with a poor nutritional status including those with deficiencies of nutrients such as Vitamin D, Vitamin B12, folate, and magnesium may be at an increased risk of injury.

Complications/ injuries caused by COVID injections

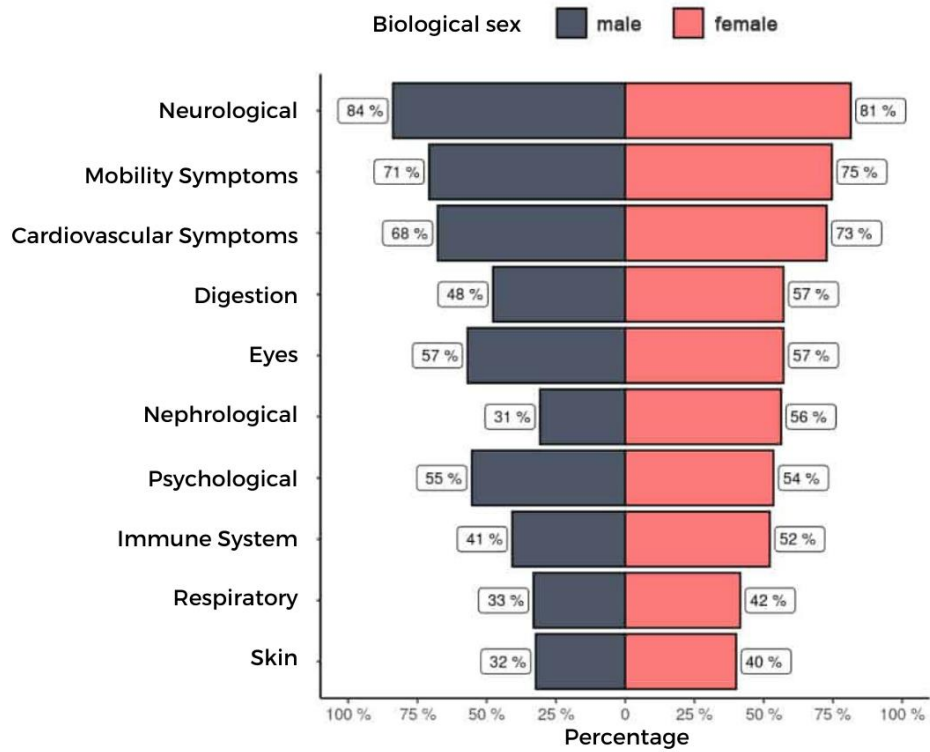
Over 3,000 peer-reviewed articles have been published on COVID vaccine injuries. Find links to these studies at [COVID Vaccine Injuries](#), [REACT19](#), and on [Substack](#). A selection of symptoms is listed below:

- Myocarditis, pericarditis, stress cardiomyopathy (contraction band necrosis)
- Takotsubo cardiomyopathy
- Acute coronary syndrome
- Hypertension
- MIS-V, Multisystem Inflammatory Syndrome
- Thrombosis, including pulmonary emboli and stroke (prothrombotic state)
- Cerebral venous thrombosis
- Thrombocytopenia
- Thrombotic thrombocytopenic purpura
- Idiopathic thrombocytopenic purpura
- Henoch Schönlein Purpura
- Immune-mediated hemolysis
- Reactivation and exacerbation of chronic underlying diseases/disorders
- Immune dysregulation
- Metabolic dysregulation (diabetes)
- Menstrual irregularities
- Menorrhagia

- Amenorrhea
- Spontaneous abortion
- Vulval and vaginal ulcers
- Vasculitis, including Leukocytoclastic vasculitis, Granulomatous vasculitis, microscopic polyangiitis.
- Guillain-Barre Syndrome
- Acute Myelitis
- Systemic lupus erythematosus
- Bell's Palsy
- Stills disease.
- Sweets syndrome
- Facial nerve palsy
- Multiple sclerosis
- Polyarthralgia/polyarthritits
- Cryoglobulinemia
- Lymphadenopathy, local and generalized.
- Anaphylaxis
- Allergic reactions
- Intracerebral hemorrhage
- Strokes (thrombotic strokes)
- Generalized neurological symptoms including "brain fog", cognitive decline, memory loss.
- Alzheimer's Disease like syndrome
- Acute hyperactive encephalopathy
- Acute disseminated encephalomyelitis
- Neuromyelitis Optica
- Ageusia and anosmia
- Aphasia
- Depression
- New onset panic disorders
- New onset psychosis and delirium
- Small fiber neuropathy
- Autonomic neuropathy
- POTS syndrome (postural Orthostatic Tachycardia syndrome)
- Mononeuritis multiplex, polyneuropathy
- Acute inflammatory neuropathies
- Tinnitus (severe and persistent)
- Sensorineural hearing loss
- Vestibulitis
- Severe headaches and migraines
- Seizures and status epilepticus
- Prion disease i.e., Mad Cow Disease
- Acute macular retinopathy
- Uveitis
- Acute Optic Neuropathy
- Rhabdomyolysis
- Keratolysis
- Herpes Keratitis
- Inflammatory myositis
- Immune mediate hepatitis
- Pancreatitis
- Acute kidney injury
- Nephrotic syndrome
- ANCA glomerulonephritis
- Skin reactions including rashes, urticaria, Pityriasis rosea
- Pemphigus vulgaris
- Hemorrhagic bullous pyoderma gangrenosum
- Eosinophilic dermatosis
- Alopecia, including alopecia areata
- Psoriasis
- Toxic epidermal necrolysis
- Erythema multiforme
- Hemophagocytic histiocytosis
- Varicella Zoster infection
- Epstein-Barr viral reactivation
- CMV reactivation
- Herpes Simplex reactivation
- Zoster meningitis
- Ramsay Hunt syndrome
- Thyroiditis
- Tolosa-Hunt syndrome
- Acute eosinophilic pneumonia
- Cancer recurrences
- New and unusual malignancies, including Angioimmunoblastic T Cell Lymphoma

The most common symptoms recorded in post-vaccine syndrome are presented in Figure 2. On average, patients reported 23 distinct symptoms. (Results from PVS Germany Survey; Reproduced with permission from React19/PVS Germany <https://react19.org/post-vaccine-syndrome-survey-results/>)

Figure 2. Vaccine injury is a multi-symptomatic disease*



Treatment Approach

A number of principles are essential for the optimal management of post-vaccine syndrome:

It is important to emphasize that there are no published reports detailing the management of vaccine-injured patients. Our treatment approach is, therefore, based on the postulated pathogenetic mechanism, pharmacologic principles, clinical observation, and feedback from vaccine-injured patients.

The core problem in post-vaccine syndrome is chronic “immune dysregulation.” The primary treatment goal is to help the body to restore and normalize the immune system—in other words, to let the body heal itself. We recommend the use of immune-modulating agents and interventions to dampen and normalize the immune system rather than the use of immunosuppressant drugs, which may make the condition worse. However, the concomitant use of a controlled course of an immunosuppressant drug may be appropriate in patients with specific autoimmune conditions.

The treatment strategy involves two major approaches i) promote autophagy to help rid the cell of the spike protein and ii) interventions that limit the toxicity/pathogenicity of the spike protein.

Treatment must be individualized according to each patient’s presenting symptoms and disease syndromes. Not all patients respond equally to the same intervention; this suggests that the treatment must be individualized according to each patient’s specific response. A peculiar finding is that a particular intervention (e.g., Hyperbaric oxygen therapy) may be lifesaving for one patient and totally ineffective for another.

Patients should serve as their own controls and the response to treatment should dictate the modification of the treatment plan. One (or at most two) new interventions should be added at a time in order to evaluate what helps the patient and those interventions that are not helpful.

Early treatment is essential; the response to treatment will likely be attenuated when treatment is delayed.

Patients should be started on the primary treatment protocol; this should, however, be individualized according to the patient’s particular clinical features. The response to the primary treatment protocol should dictate the addition or subtraction of additional therapeutic interventions. Second-line therapies should be started in those who have responded poorly to the core therapies and in patients with severe incapacitating disease.

Patients with post-vaccine syndrome must not receive further COVID-19 vaccines of any type. Likewise, patients with long COVID should avoid all COVID vaccinations.

A note about anesthesia and surgery:

Patients should notify their anesthesia team if using the following medications and/or nutraceuticals, as they can increase the risk of Serotonin syndrome (SS) with opioid administration:

- Methylene blue
- Curcumin
- Nigella Sativa
- Selective Serotonin Reuptake Inhibitors (SSRIs)

Patients with post-vaccine syndrome should do whatever they can to prevent themselves from getting COVID-19. This may include a preventative protocol (see FLCCC protocols).

In the event they do contract the virus or suspect infection, early treatment is essential (see FLCCC protocols). COVID-19 will likely exacerbate the symptoms of vaccine injury.

Vaccine-injured patients are frequently desperate to try any medication or intervention they believe may help them. Unfortunately, unscrupulous providers will take advantage of these very vulnerable patients and sell them expensive and unproven remedies.

Patients should avoid unscientific and poorly validated “Spike Protein Detox” programs.

Hyperbaric oxygen therapy (HBOT) should be considered in cases of severe neurological injury and in patients showing a rapid downhill course (see below).

Once a patient has shown a clinical improvement the various interventions should be reduced or stopped one at a time. A less intensive maintenance approach is then suggested.

Baseline Testing

Post-vaccine patients are often subjected to an extensive battery of diagnostic tests. These tests are rarely helpful, usually confusing the situation and leading to inappropriate therapeutic interventions. Patients frequently undergo diagnostic tests that are “experimental,” unvalidated, and clinically meaningless; patients should avoid getting such tests. **Remember the dictum: Only do a test if the result will change your treatment plan.** We recommend a number of simple, basic screening tests that should be repeated, as clinically indicated, every 4 to 6 months.

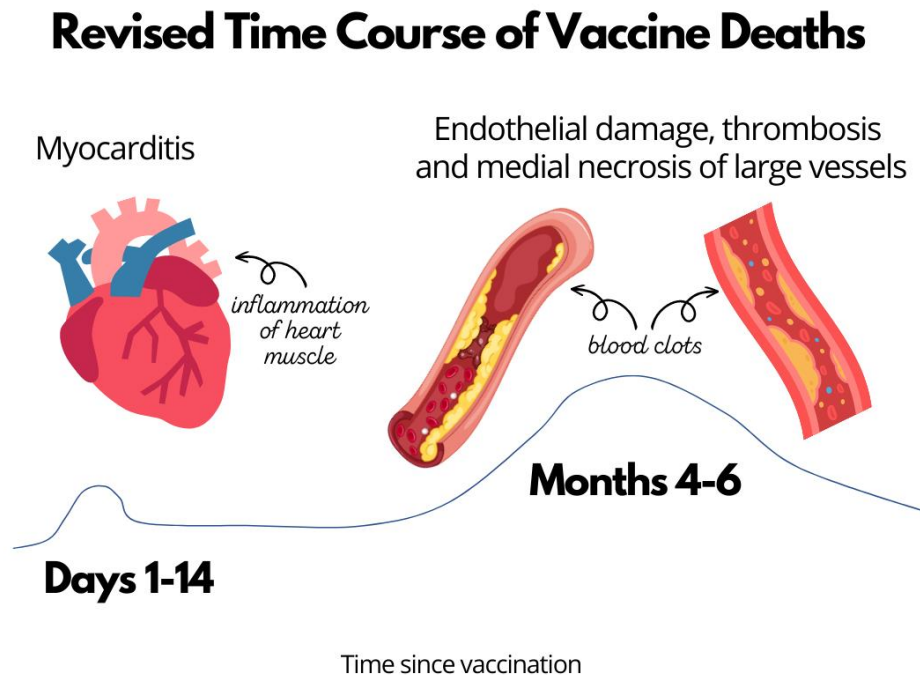
- CBC with differential and platelet count
- Standard blood chemistries, including liver function tests
- D-Dimer—as a marker of clotting activation. Those with a markedly elevated D-dimer should probably undergo screening for an inherited thrombophilia.
- CRP—as a marker of ongoing inflammation (A comprehensive extensive cytokine/chemokine panel is unnecessary and very costly, and the results will not change the treatment approach.)
- Early morning cortisol—some patients develop autoimmune adrenal failure)
- TSH—to exclude thyroid disease
- Homocysteine level (normal 5-15 $\mu\text{mol/l}$)
- HbA1C—Vaccine-injured patients are at an increased risk of developing diabetes
- Troponin and pro-BNP to exclude cardiac disease.

Patients with post-vaccine syndrome should do whatever they can to prevent themselves from getting COVID-19. In the event they do contract the virus or suspect infection, early treatment is essential



- CMV, EBV (early antigen-D IgG or nuclear antigen IgG), Herpes simplex, HHV6 and mycoplasma serology/PCR—to exclude viral/bacterial reactivation (In patients who respond poorly to therapy, it may be helpful to check for Lyme (Bb), Bartonella and Babesia tick-borne diseases—e.g., <https://igenex.com/> and <https://www.mdlab.com/>). (41)
- Vitamin D level (25OH Vitamin D)
- In patients with allergic features and those who experienced an acute reaction to the vaccine, the following tests may be helpful: eosinophil count; IgE levels, RAST testing, and/or skin testing. Serum tryptase, serum histamine, and/or 24-h urine N-methylhistamine should be considered in MCAS. (36)
- In patients who present with deep venous thrombosis (DVT) and/or pulmonary embolism soon after vaccination screening for an inherited thrombophilia is suggested. (48)
- Limited screening autoantibodies. Lupus anticoagulant (if positive B2 microglobulin etc.) and ANA. Vaccine-injured patients, particularly those with autonomic dysfunction/SFN frequently have an extensive array of autoantibodies directed against G-protein coupled cell surface receptors, [43,45] ACE-2, (49) neurons, myelin, and other self-epitopes. The presence or absence of these antibodies has little impact on the management of these patients.

Figure 3. Time course of sudden cardiac deaths following COVID-19 vaccination



Anticoagulation post-vaccination and the three clinical phenotypes of the vaccine injured

The need for anticoagulation in post-vaccination patients is a very complex and controversial issue. Three distinct clinical phenotypes with differing pathophysiological and clinical presentations exist (see Figure 3).

- The first is the “typical” post-vaccine, multi-symptomatic syndrome characterized typically by fatigue, brain fog, and other multiple complex symptoms (see figure 2). This syndrome is characterized by microvascular inflammation and microvascular thrombosis as part of the complex pathophysiology of post-vaccine spike related disease (see Figure 1).
- The second is that of sudden cardiac death within the first 2 weeks (usually first 7 days) following the last dose of vaccination. The early sudden deaths are likely arrhythmogenic deaths related to catecholamine-induced contraction band necrosis and spike-induced inflammatory myocarditis (often focal myocarditis).
- The third phenotype includes those otherwise healthy patients who “die suddenly” 4 to 6 months after the last dose of the COVID vaccine. Patients with this phenotype typically lack the typical symptoms characteristic of post-vaccine syndrome. While the pathology of this syndrome has not been studied (as it has been dismissed by governmental agencies), it is likely the result of a progressive spike-induced endothelialitis complicated by thrombosis.

Dr. Steven R. Gundry, a cardiac surgeon, performed a biomarker-based cardiac risk assessment score (the PULS Cardiac Test now available as the SMARTVascular Dx provided by SmartHealth Dx <https://www.smarthealthdx.com>) in 566 patients 2 to 10 weeks following the 2nd mRNA COVID shot and compared this score to the PULS score drawn 3 to 5 months prior to the jab. (50) The PULS score is a marker of endothelial inflammation. In this study, the 5-year Acute Coronary Risk Score (ACS) increased from a baseline of 11% to 25% after the jab. This study clearly demonstrates that the mRNA ‘jabs’ lead to progressive endothelial inflammation.

To complicate matters further, the clots (micro-clots and macro-clots) that develop in patients with spike-related disease are distinctly different from “usual clots” and have a number of unique characteristics. These clots are rich in fibrin with amyloid-like fibrils and are more resistant to fibrinolysis. Immunohistochemical staining demonstrates a high concentration of spike protein within the clots; this is important as spike protein via multiple mechanisms activates clotting as well as altering the structure of fibrin resulting in amyloid-like fibrils.

Based on this information, it would seem intuitive that the use of anti-coagulants and the approach to treatment would be different for these three phenotypes; however, the ideal approach has yet to be determined. A provisional approach to anticoagulation is provided below. A review of the pharmacological properties of the various anticoagulants available to the healthcare provider is provided. The general approach to the management of the multi-symptom vaccine syndrome is then reviewed.

The greatest risk with the use of anticoagulant drugs is clinically significant bleeding. A number of factors increase the risk of bleeding; (51-53) these include age > 65 years (advanced age is a major risk factor for bleeding), hypertension, renal impairment, diabetes, previous stroke, a previous bleed, and

male sex. Furthermore, the risk of bleeding increases exponentially as the number of anticoagulant/antiplatelet drugs is increased. (52, 54)

Antiplatelet drugs:

Aspirin (ASA): ASA produces a clinically relevant antiplatelet effect by irreversibly acetylating the active site of cyclooxygenase-1 (COX-1), which is required for the production of thromboxane A₂, a powerful promoter of platelet aggregation. These effects are achieved by daily doses of 75 mg (and higher). The major adverse effect is bleeding. Bleeding most commonly occurs in the gastrointestinal tract and is rarely fatal. Bleeding also occurs at other sites, with intracranial bleeding being the rarest (approximately 4 per 10,000) but the most serious (with a 50% case fatality rate).

Clopidogrel (Plavix): Clopidogrel requires *in vivo* biotransformation to an active thiol metabolite. The active metabolite irreversibly blocks the ADP receptors on the platelet surface, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Similar to ASA, platelets blocked by clopidogrel are affected for the remainder of their lifespan (~7 to 10 days). The usual dose is 75mg daily.

Direct oral anticoagulants (DOAC):

Apixaban (Eliquis): Inhibits platelet activation and fibrin clot formation via direct, selective, and reversible inhibition of free and clot-bound factor Xa (FXa). FXa, as part of the prothrombinase complex consisting also of factor Va, calcium ions, and phospholipid, catalyzes the conversion of prothrombin to thrombin. Thrombin both activates platelets and catalyzes the conversion of fibrinogen to fibrin. Typical dose is 2.5 to 5mg twice daily.

Rivaroxaban (Xarelto): Mechanism of action similar to apixaban. Typical dosage is 10–20 mg once daily with the evening meal.

Oral Fibrinolytic agents:

Nattokinase: Nattokinase (NK) is a serine protease purified and extracted from natto, a traditional Japanese (cheese like) food produced from the fermentation of soybeans with the bacterium, *Bacillus subtilis*. (55-57) Recent studies demonstrated that a high natto intake was associated with decreased risk of total cardiovascular disease mortality and, in particular, a decreased risk of mortality from ischemic heart diseases. (58)

Nattokinase has potent fibrinolytic, antithrombotic, and antiplatelet activity. (55, 56, 59-62) NK degrades fibrin directly and also increases the release of tPA with a subsequent increase in the formation of plasmin. (63) Furthermore, NK enhances fibrinolysis through cleavage and inactivation of PAI-1. (57, 62) In a study comparing the antiplatelet effects of NK and aspirin, NK was shown to display excellent antiplatelet aggregation and antithrombotic activities *in vitro* and *in vivo*, inhibiting thromboxane B₂ formation from collagen-activated platelets. (64) In addition, in both animal and human studies, NK also has antihypertensive, anti-atherosclerotic, lipid-lowering, and neuroprotective actions. (56, 62, 65) Of particular relevance to patients with spike-related clotting, nattokinase causes the proteolytic cleavage of both spike protein and amyloid proteins. (66) In a randomized study, NK proved to be more effective than statins (simvastatin) in reducing carotid artery atherosclerosis. (67)

Chen et al demonstrated that high dose NK (10 800 Fibrinolytic Units [FU]/day; ~ 500 mg/day) reduced the thickness of the carotid artery intima-media and the size of the carotid plaque. (68) The authors reported a synergistic effect between NK and ASA.

Studies indicate that an oral administration of NK can be absorbed by the intestinal tract. (65, 69) NK, unlike most proteins, is more resistant to the highly acidic gastric fluids in the stomach and can be absorbed in the later sections of the digestive tract.

The optimal dose of nattokinase is unclear, however, a dose of 100-200 mg (2000- 4000 FU/day) twice daily has been suggested.

While NK appears to have an excellent safety profile, (68, 70) bleeding has rarely been reported in patients with risk factors for bleeding (advanced age, renal failure, hypertension, concomitant ASA, etc). (71, 72) High concentrations of vitamin K₂ in natto can reduce the INR when coadministered with warfarin; this may also occur with nattokinase supplements if vitamin K₂ is not removed during the production process. Information regarding safety and efficacy in pregnancy and lactation is lacking.

Lumbrokinase: Lumbrokinase derives from a group of enzymes extracted from earthworms. The enzymes are sourced mostly from the earthworm *Lumbricus rubellus*. Lumbrokinase has very similar pharmacodynamic properties to Nattokinase, i.e., it directly breaks down fibrin clots, inhibits PAI-1 activity, enhances t-PA activity, has antiplatelet activity, and proteolytically cleaves amyloid. (73-75) The recommended dose is 300,000 to 600,000 IU/day (20-40 mg). Lumbrokinase has been widely used for patients with acute ischemic stroke in China; however, because rigorously designed studies are lacking, the safety and efficacy of lumbrokinase remains largely unknown. (76) As the pharmacology, clinical effectiveness, and safety of nattokinase has been assessed in a number of experimental and clinical studies, this agent is preferred over lumbrokinase.

Provisional approach to anticoagulation in the post-vaccine phenotypes

For more information see [I-PREVENT: Vaccine Injury](#)

- “Typical” post-vaccine syndrome. Nattokinase 100-200mg (2000 – 4000FU) twice daily is recommended. Low-dose aspirin (ASA) (81mg daily) can be added in patients at a low risk of bleeding complications (see risk factors). Pretorius et al reported on the use of “triple therapy” in 24 patients with long COVID and the presence of fibrin amyloid microclots on live blood analysis. (77) Patients were treated with one month of dual antiplatelet therapy (Clopidogrel 75mg/Aspirin 75mg) once a day, as well as Apixaban 5 mg twice a day. This was followed by ASA and nattokinase alone. These authors reported that “each of the 24 treated cases reported that their main symptoms were resolved, and this was also reflected in a decrease of both the fibrin amyloid microclots and platelet pathology scores.” Triple therapy can be considered in patients at low risk of bleeding (see risk factors) who have responded poorly to the combination of ASA and nattokinase alone; however, triple therapy should only be instituted under the direct supervision and monitoring of a clinician with expertise in the management of anti-coagulation.
- Early sudden death. Early post-vaccination sudden cardiac death is a condition of young patients, especially men. This is the most problematic phenotype with no clear guidance on the prevention of this fatal condition (except to stop vaccination in this high-risk group). Many of the deaths occur during physical activity (sudden death in soccer players); consequently, vigorous physical activity should be avoided for at least 3 weeks following vaccination.

Magnesium supplementation (see section on magnesium) may reduce the risk of arrhythmic deaths. The role of anti-inflammatory agents (e.g., curcumin, resveratrol, Nigella sativa, Omega-3 fatty acids) is unclear.

- Late cardiac deaths (4-6 months after “jab”). Ideally, these asymptomatic patients should be risk stratified with the initiation of prophylactic measures in the moderate to high-risk groups. Unfortunately, as this catastrophic disorder is not generally recognized and has therefore not been studied, there is no data to allow for risk stratification. Serial cardiac risk biomarker analysis may be helpful; (50) however, this test is expensive and not widely available. In the absence of a risk-stratified approach, the following interventions may reduce the risk of acute myocardial infarction and sudden death: (78)
 - Nattokinase 100-200 mg twice daily
 - ASA 81 mg daily (in those with low risk of bleeding)
 - Omega-3 fatty acids 2-4 g daily
 - Resveratrol or flavonoid combination supplement
 - Co-enzyme Q (CoQ) 200-400 mg/day.
 - Melatonin 3-10 mg at night (slow release/extended release).
 - Bromelain 500 mg twice daily +/- N-acetyl cysteine (NAC) 600 mg twice daily.
 - Berberine 500-600 mg twice daily.
 - “Green based diet”- Low carbohydrate, high fat diet (low in omega-6 vegetable oils)

First-Line Therapies

(Not symptom specific; listed in order of importance)

Intermittent daily fasting or periodic daily fasts

Fasting has a profound effect on promoting immune system homeostasis, improving mitochondrial health, and increasing stem cell production. [98-104] Fasting stimulates the clearing of damaged mitochondria (mitophagy), misfolded and foreign proteins, and damaged cells (autophagy). Autophagy likely removes spike protein and misfolded proteins induced by the spike protein. Autophagy may therefore play a critical role in reversing the “spikopathy” induced by COVID injections. Indeed, activation of autophagy may be the only mechanism to remove intracellular spike protein.

“A little starvation can really do more for the average sick man than can the best medicines and the best doctors.”

—Mark Twain
(1835-1910)

The reader is referred to the FLCCC Guide on intermittent Fasting and Healthy Eating Habits for more detailed information.

<https://covid19criticalcare.com/tools-and-guides/guide-to-intermittent-fasting/>

Ivermectin (IVM)

It is likely that ivermectin and intermittent fasting act synergistically to rid the body of the spike protein. Ivermectin binds to the spike protein, aiding in the elimination by the host. (79-81) A trial of ivermectin should be included in the first-line treatment approach. Ivermectin has potent anti-inflammatory properties. (82-84)

Dosing and administration

Ivermectin is best taken with or just following a meal for greater absorption.

It appears that vaccine-injured patients can be grouped into two categories: i) ivermectin responders and ii) ivermectin non-responders. This distinction is important, as the latter group is more difficult to treat and requires more aggressive therapy.

Based on the most updated clinical experiences in our collaborative network, we propose the following treatment approach:

- Initiate therapy with 0.3 mg/kg daily. Reassess for improvements in 2-3 weeks.
 - If no improvement is noted, a trial of discontinuation should be initiated. Be aware that in a minority of cases, patients who did not initially sense a benefit with use will report worsening of symptoms when IVM is discontinued. These patients should be restarted on daily ivermectin.
 - If improvements or a reduction in symptoms are noted, a 10-day trial of a higher dose should be initiated, typically by doubling the dose (0.6mg/kg day), given that a significant proportion of ivermectin-responsive patients report even greater benefits at higher doses.

- If the patient reports additional benefit with doubling the initial dose, continue patient on 0.6mg/kg daily.
- If the patient does not report additional benefit at the higher dose, reduce ivermectin to the initial dose of 0.3mg/kg daily.
- For ivermectin responders, prolonged and chronic daily treatment is often necessary to support their recovery. In many, if the daily ivermectin is discontinued worsening symptoms often recur within days.
- Weaning/discontinuation – once patients have clinically improved to a desirable extent on a treatment regimen that includes daily ivermectin, we maintain the treatment regimen for at least 2 months before trying to decrease dose and/or reduce the frequency of ivermectin. Weaning and/or discontinuing is not possible in many patients due to recurrence of symptoms.

Cautions and contraindications.

Due to the possible drug interaction between quercetin and ivermectin, these drugs should not be taken simultaneously (i.e., should be staggered morning and night). The safety of ivermectin in pregnancy is uncertain and this drug should therefore be avoided in the first trimester of pregnancy. (85)

Table 1. How to Calculate Ivermectin Dose

Use the table below to help determine how much ivermectin you should take, based on your body weight and the specific recommendation in the protocol or guide you are following. Based on the dosage, you can then determine how many pills or capsules you need to take, bearing in mind that ivermectin is available in different strengths (e.g., 3, 6, or 12 mg) and administration forms (tablets, capsules, drops, etc.). Remember that tablets can be halved for more accurate dosing, while capsules cannot.

For example: A 160 lb. person needs to take a daily dose of 0.3 mg/kg. Her doctor has provided her with 3 mg tablets. Based on this table, her daily dose should be 21-23 mg, so she should take 7 tablets.

How much do I weigh?		The protocol says...			
In pounds	In kilos	"0.2 mg/kg"	"0.3 mg/kg"	"0.4 mg/kg"	"0.6 mg/kg"
		So my dose is...			
70–90	32–41	6-8 mg	10-12 mg	13-16 mg	19-25 mg
91–110	41–50	8-10 mg	12-15 mg	17-20 mg	25-30 mg
111–130	50–59	10-12 mg	15-18 mg	20-24 mg	30-35 mg
131–150	60–68	12-14 mg	18-20 mg	24-27 mg	36-41 mg
151–170	69–77	14-15 mg	21-23 mg	27-31 mg	41-46 mg
171–190	78–86	16-17 mg	23-26 mg	31-35 mg	47-52 mg
191–210	87–95	17-19 mg	26-29 mg	35-38 mg	52-57 mg
211–230	96–105	19-21 mg	29-31 mg	38-42 mg	58-63 mg
231–250	105–114	21-23 mg	32-34 mg	42-45 mg	63-68 mg
251–270	114–123	23-25 mg	34-37 mg	46-49 mg	68-74 mg
271–290	123–132	25-26 mg	37-40 mg	49-53 mg	74-79 mg
291–310	132–141	26-28 mg	40-42 mg	53-56 mg	79-85 mg

Moderating physical activity

Patients with long COVID and post-vaccine symptoms frequently suffer from severe post-exertional fatigue and/or worsening of symptoms with exercise. (86, 87) Aerobic exercise is reported to be one of the worst therapeutic interventions for these patients.

Dosing and administration

We recommend moderating activity to tolerable levels that do not worsen symptoms, keeping the patient's heart rate under 110 BPM. Furthermore, patients need to identify the activity level beyond which their symptoms worsen, and then aim to stay below that level of activity. Stretching and low-level resistance exercises are preferred over aerobic exercises.

Mechanisms

Similar to patients with chronic fatigue syndrome, post-exertional fatigue may be related to mitochondrial dysfunction and the inability to augment production of ATP. (86, 88, 89) Magnetic resonance-augmented cardiopulmonary exercise testing suggests failure to augment stroke volume as a potential mechanism of exercise intolerance in patients with long COVID. (90)

Low-dose naltrexone (LDN)

LDN has been demonstrated to have anti-inflammatory, analgesic, and neuromodulating properties. (91, 92)

Dosing and administration

1-4.5 mg daily. Begin with 1 mg/day and increase to 4.5 mg/day, as required. May take 2 to 3 months to see the full effect.

Nattokinase

Dosing and administration

100-200 mg (2000-4000 FU) twice daily. Aspirin/ASA 81 mg daily can be added in low-risk patients.

Mechanisms

Nattokinase is a highly effective fibrinolytic and antiplatelet agent which targets the abnormal clotting in the spike injured patient. In addition, nattokinase has been demonstrated to lyse extracellular spike protein; this may further enhance the anti-clotting action of nattokinase.

Melatonin

Melatonin has anti-inflammatory and antioxidant properties and is a powerful regulator of mitochondrial function. (93-97)

Dosing and administration

2-6 mg *slow release/extended release* prior to bedtime. The dose should be started at 750 mcg (μg) to 1 mg at night and increased as tolerated.

Cautions and contraindications

Patients who are slow metabolizers may have very unpleasant and vivid dreams with higher doses.

Magnesium

Dosing and administration

A starting dose of 100 to 200 mg daily is suggested, increasing the dose as tolerated up to 300 mg (females) to 400 mg daily. Endpoints of treatment include an RBC-Mag at the higher end of the normal range (between 4.2 and 6.8 mg/dL to be about 6.0 ng/dL).

Mechanisms

There are at least 11 different types of magnesium that can be taken in supplement form with varying bioavailability. Generally, organic salts of Mg have a higher solubility than inorganic salts and have greater bioavailability. (98) Magnesium citrate is a widely used type of magnesium in salt form and is often recommended to treat constipation; high doses may cause diarrhea and prolonged use should be avoided. Magnesium oxide and magnesium citrate compounds, commonly prescribed by physicians, have poor bioavailability. (99) Magnesium Malate, Taurate, Glycinate, and L-threonate have good bioavailability and will readily increase RBC magnesium levels. Magnesium taurate and magnesium L-threonate significantly increase magnesium levels in brain cells; hence they are used in the treatment of depression and Alzheimer's disease. (99, 100)

Cautions and contraindications

High intakes of magnesium from dietary supplements and medications can cause diarrhea, nausea, and abdominal cramping.

Methylene blue

Low Dose Methylene Blue (LDMB) is a therapeutic option in patients with brain fog and other neurological symptoms; this can be combined with transcranial photobiomodulation.

Dosing and administration

10-30 mg daily. The optimal dose is highly individualized and each patient needs to find the right dose for them.

It is important that patients and/or their healthcare providers purchase high-quality, impurity-free, pharmaceutical-grade methylene blue. Patients may purchase a 1% methylene blue solution (e.g. <https://www.bphchem.com/product/methylene-blue-1-usp-grade-50-ml-1-drop-contains-0-5-mg-of-methylene-blue/>), MB in a powder form requiring reconstitution into a 1% solution (e.g. from CZTL at <https://czt1.bz/?ref=Lwr85>) or MB Buccal Troughes (<https://trocriptions.com/products/>) (will cause blue staining of mouth and teeth; troughes can be swallowed to avoid this effect).

A 1% methylene blue solution contains 10 mg MB in 1 ml solution (and 0.5 mg/drop). A 1% MB solution is formulated by mixing 1 gram of methylene blue with 100 ml of water. Use a dropper bottle to administer — 1 drop of 1% solution is approximately 0.5 mg of methylene blue).

Dosing of LDMB:

- Start with 5 mg (.5 ml) twice daily for the first week.
- Gradually increase the dosage every 2-3 days (guided by symptoms - i.e., improvement in fatigue and/or cognitive improvement) until you reach a maximum of 30 mg (3 ml) per day.
- Take the 7th day off every week to allow the body to “reset”.

Mechanisms

Methylene blue (MB) has a number of biological properties that may be potentially beneficial in vaccine-injured patients. MB induces mitophagy (mitochondrial autophagy) and has anti-inflammatory, antioxidant, neuroprotective, and antiviral properties. (101, 102) A study in 2013 found that methylene blue-induced neuroprotection is mediated, at least in part, by macroautophagy through activation of AMPK signaling. (103)

MB easily crosses the BBB and preferentially enters neuronal mitochondria. MB has high bioavailability to the brain with brain tissue levels tenfold higher than serum levels. (104, 105) Low-dose methylene blue (LDMB) stimulates mitochondrial respiration by donating electrons to the electron transport chain. MB can reroute electrons directly from complex I to complex III, avoiding electron leakage and subsequent ROS production.

MB and photobiomodulation (PBM) have similar beneficial effects on mitochondrial function, oxidative damage, and inflammation. Treatment with MB is therefore often combined with PBM therapy. (106, 107). However, because PBM and MB exert beneficial effects through distinct mechanisms, combining the use of these two therapies is expected to improve therapeutic outcomes synergistically. Numerous studies indicate an improvement in brain mitochondrial function and neurological function following treatment with MB and PBM for a spectrum of neurological diseases. (105, 106, 108)

Cautions and contraindications

LDMB will cause your urine to be blue or blue-green. Some patients may experience a Herx reaction. A Herx reaction may cause fatigue, nausea, headache, or muscle pain. If you experience a Herx reaction, stop the protocol for 48 hours and then resume again slowly.

DO NOT take MB if you are pregnant or breastfeeding.

MB is a potent monoamine oxidase inhibitor (MAOI) that, in conjunction with an SSRI, can potentiate serotonin syndrome, a life-threatening medical emergency. This combination of medications is to be strongly avoided. **Do not take FLUVOXAMINE, FLUOXETINE or BUPROPION or any other SSRI -NDRI (norepinephrine-Dopamine Reuptake Inhibitor) with MB.**

MB increases toxicity of hydrocodone bitartrate by increasing serotonin levels in the blood. This combination should be avoided.

Individuals with glucose-6-phosphate dehydrogenase deficiency (G6PD) should not be treated with MB as it can cause hemolytic anemia.

Sunlight and Photobiomodulation (PBM)

Sunlight has great therapeutic powers. Our forefathers roamed the earth and were exposed to sunlight on a daily basis, likely with profoundly important health benefits. (109)

Dosing and administration

We suggest that patients expose themselves to about 30 mins of midday sunshine whenever possible (at least 3 times a week). A brisk midday walk is a viable alternative. When neither of these interventions is

feasible or practical, and in those who wish to avoid ultraviolet radiation exposure, patients can expose themselves to red and NIR radiation emitted from LED panels.

Those interested in this therapy are recommended to read the book by Ari Whitten entitled “The Ultimate Guide to Red Light Therapy.” (110)

A number of LED panels with multiple red and IR lights are commercially available (e.g. <https://mitoredlight.com/>, <https://hoogahealth.com/>, <https://platinumtherapylights.com/>). The disadvantage of LED panels is they do not mimic that of solar radiation as they deliver 1-10 nm wide spiked emissions of red light at 660 nm and NIR-A at 830 nm. In contrast, ThermaLight® bulbs (SaunaSpace® Saunas™) have a radiation spectrum closely resembling that of solar radiation, but without UV radiation. About 39% of the emitted spectrum of the ThermaLight® bulb is NIR-A (the solar spectrum has 41% IR-A) and about 41% of the radiation is in the IR-B range; part of IR-A and IR-B (1000-3000 nm) contributes to the thermal effects of emitted radiation, which promotes induced hyperthermia (sauna therapy) and is discussed below under “Other Potential Therapies”.

Mechanisms

PBM is referred to in the literature as low-level light therapy, red light therapy, and near-infrared light therapy. The spectral radiance of solar radiation extends from 10 nm to about 3000 nm i.e., the spectrum from ultraviolet (10-400 nm), visible (400-700 nm with red light 600-700 nm), near-infrared radiation (750-1500 nm (NIR-A)) and mid-infrared radiation (1500- 3000 nm (NIR-B)).

Of all the wavelengths of sunlight, NIR-A radiation has the deepest penetration into tissues, being up to 23cm. NIR-A in the range of 1000 to 1500 nm is optimal for heating tissues. Indeed, during the 1918 influenza pandemic, “open-air treatment of influenzae” appeared to be the most effective treatment for seriously ill patients. (111) The Surgeon-General of Massachusetts reported that “*plenty of air and sunshine*” was highly effective for the treatment of influenzae pneumonia. He reported that “*very little medicine was given after the value of plenty of air and sunshine had been demonstrated.*” Further, he comments “*from being discouraged, the medical staff became enthusiastic, and the patients were treated with the confidence that at last something had been found which would give good results.*”

A more recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality. (112) In this study, the mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group. Apart from UV radiation stimulating vitamin D synthesis, red and near-infrared (NIR) radiation have a profound effect on human physiology, notably acting as a mitochondrial stimulant and increasing ATP production. (113)

The most well-studied mechanism of action of PBM centers around enhancing the activity of cytochrome c oxidase, which is unit four of the mitochondrial respiratory chain, responsible for the final reduction of oxygen to water. In addition, one of the most reproducible effects of PBM is an overall reduction in inflammation. PBM has been shown to reduce markers of M1 phenotype in activated macrophages. (113) Many reports have shown reductions in reactive nitrogen species and prostaglandins in various animal models. In addition, PBM activates a wide range of transcription factors leading to improved cell survival. It has also been suggested that NIR light increases the production of melatonin in mitochondria. (114)

In an outstanding *in vitro* study, Aguida et al demonstrated that infrared light caused a marked reduction in the TLR-4-dependent inflammatory response pathway in a human cell culture line. (115) In

this study, infrared light exposure resulted in a significant decline in NFkB and AP1 activity as well as a marked decrease in the expression of proinflammatory genes. The increased body temperature induced by NIR-A and NIR-B activates the production of heat shock proteins (which increase autophagy) as well as essential cell stress survival pathways.

Emerging data suggest that transcranial PBM has beneficial effects in a range of neuro-psychiatric diseases including stroke, traumatic brain injury, Alzheimer's disease, Parkinson's disease, and depression. (116-119) PBM has been suggested to have a role in the prevention and treatment of COVID-19. (120) A recent double-blind, sham-controlled study using an LED device demonstrated a marked improvement in the condition of hospitalized patients with acute COVID-19 infection. (121)

Resveratrol or a combination flavonoid

Resveratrol is a plant phytochemical (flavonoid) that has remarkable biological properties. (122-124) Most importantly it activates autophagy. (125, 126)

Dosing and administration

400-500 mg daily. Resveratrol may potentiate the effect of time restricted feeding (intermittent fasting) in activating autophagy. Resveratrol should therefore be taken during fasting and not with a meal. For acutely symptomatic patients, resveratrol in a dose of 500 mg twice daily is suggested. In recovered patients and those on preventative/maintenance therapy, a dose of 400-500 mg/day should suffice.

Mechanisms

Resveratrol has anti-inflammatory, antiviral (SARS-CoV-2), antioxidant, and anticoagulant properties and has beneficial effects on the microbiome. Resveratrol also binds to spike protein helping to promote autophagy.

Quercetin, a plant flavonoid with many of the biological properties of resveratrol, acts synergistically with resveratrol and increases the bioavailability of resveratrol. (127-129) Pterostilbene, is another plant flavonoid similar to resveratrol in structure with similar biological properties. (130-132) However, pterostilbene's unique structure makes it more oil-soluble than resveratrol, which increases its absorption and cellular uptake while reducing the rate of elimination from the body. Research has shown that pterostilbene has seven times the half-life of resveratrol and has greater bioactivity in reducing the effects of oxidative stress. We, therefore, suggest a "high quality" combination supplement with resveratrol and quercetin and ideally also containing pterostilbene.

Cautions and contraindications

Generally, the oral bioavailability of resveratrol is poor. (133) However, a bio-enhanced formulation containing trans-resveratrol from Japanese Knotweed Root appears to have improved bioavailability.

The safety of these phytochemicals has not been determined in pregnancy and they should therefore be avoided.

Due to the possible drug interaction between quercetin and ivermectin these drugs should not be taken simultaneously (i.e., should be staggered morning and night).

The use of quercetin has rarely been associated with hypothyroidism. (134) The clinical impact of this association may be limited to those individuals with pre-existent thyroid disease or those with

subclinical thyroidism. Quercetin should be used with caution in patients with hypothyroidism and TSH levels should be monitored.

Probiotics/prebiotics

Patients with post-vaccine syndrome classically have a severe dysbiosis with loss of Bifidobacterium. (135-137)

Dosing and administration

A no-sugar-added, Greek yogurt with both pre- and probiotics is recommended. Suggested probiotics include Megasporebiotic (Microbiome labs), TrueBifidoPro (US Enzymes), and yourgutplus+. (138) In addition, the use of Glucomannan (from Konjac root) and/or Chia seeds provide soluble and insoluble fiber (prebiotic) required for the normalization of the microbiome. [297-299]

Cautions and contraindications

If patients have moderate to severe dysbiosis and/or small bowel bacterial overgrowth (SBIO) then prebiotics may have the unwanted effect of "feeding the bad bacteria" and contributing to worsening of the dysbiosis. Probiotics alone and/or fermented foods are less likely to harbor and nourish commensal and abnormal gut microbes. Depending on the brand, some pro/prebiotic products can be very high in sugar, which promotes inflammation. Look for brands without added sugar and try to choose products that are also gluten-free, casein-free, and soy free.

Adjunctive/Second-Line Therapies

(Listed in order of importance)

- **Vitamin D** (4000-5000 units/day) and **Vitamin K2** (100 mcg/day); The dose of Vitamin D should be adjusted according to the baseline Vitamin D level. However, a dose of 4000-5000 units/day of Vitamin D, together with Vitamin K2 100 mcg/day is a reasonable starting dose.
- **Omega-3 fatty acids**; we suggest a combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids). The omega-3 fatty acids have anti-inflammatory and cardioprotective effects and play an important role in the resolution of inflammation by inducing resolvins production. (139, 140) Furthermore, omega-3 fatty acids are believed to afford potent vasculoprotective effects, by improving endothelial function, limiting vascular inflammation, reducing thrombosis, and limiting reactive oxygen species production. (141) Fish, particularly wild Atlantic (or Alaskan) salmon, are a good source of omega-3 fatty acids. Omega-3 supplements include Vascepa™ (icosapent ethyl; an ethyl ester of eicosapentaenoic acid [EPA]), Lovaza™ (a combination of ethyl esters of EPA and docosahexaenoic acid [DHA]) as well as "regular fish oil supplements" containing a combination of EPA/DHA. It is unclear if the reported cardiovascular and anti-inflammatory benefits of omega-3 fatty acids are predominantly due to EPA (i.e., Pharma marketing) or the combination of EPA and DHA. (142-149) However, it is now widely appreciated that "*EPA and DHA are metabolized to different mediators and are equally important with respect to cardiovascular protection (and inflammation).*" (146) Based on this data we suggest a combination of EPA/DHA with an initial dose of 1 g/day (combined EPA and DHA) and increasing up to 4 g/day (of the active omega-3 fatty acids).

- **N-acetyl cysteine (NAC);** 600-1500 mg/day (150-152) NAC is the precursor of reduced glutathione. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis. (152) Based on a broad range of antioxidant, anti-inflammatory, and immunomodulating mechanisms, the oral administration of NAC likely plays an adjuvant role in the treatment of the vaccine injured. Several studies showed that NAC is well absorbed by the intestine and that a supplementation with NAC is effective for increasing GSH levels. Oral glutathione is poorly absorbed and is generally not recommended. (153, 154) However, acetyl glutathione is more lipophilic than glutathione, sufficiently so to be taken up intact by cells, and has been shown to rapidly raise intracellular GSH levels. A combination supplement that contains acetyl glutathione, NAC and Vitamin C may enhance the bioavailability of glutathione. In addition, liposomal glutathione has been demonstrated to increase tissue levels, antioxidant capacity and immune function. (155)
- **Cardio Miracle™ and L-arginine/L-citrulline supplements.** Cardio Miracle is a supplement with over 50 ingredients formulated to increase nitric oxide (NO) production. The supplement contains L-arginine, L-citrulline, Beetroot (high in dietary nitrates), L-Ornithine, CoQ10, as well as a blend of fruit and vegetable phytonutrients. L-Arginine is the substrate used for NO production by nitric oxide synthetase (NOS). [257] Patients with acute COVID-19 infection have been demonstrated to have low plasma L-arginine levels. [258] In addition, COVID-19 syndromes are characterized by suppressed endothelial nitric oxide synthase (eNOS) activity compounding the deficiency of NO. [259;260] The spike protein itself may play a major role in inhibiting eNOS activity. The NO deficiency is a major factor causing endothelial dysfunction and thrombotic events. Furthermore, activation of the NO-cyclic GMP pathway has anti-inflammatory effects modulating activated T cells, reducing cytokine release, and stimulating vascular repair. [261] In addition, L-arginine itself is important for normal T cell function and macrophage M1-to-M2 switch. [257] It is likely that an L-arginine/L-citrulline supplement will have additive or synergistic effects when combined with a phosphodiesterase-5 inhibitor. (see below). L-arginine should likely be avoided in patients with active malignancies. (156, 157)
- ***Nigella sativa*;** 200-500 mg encapsulated oil twice daily. *Nigella sativa* is a small shrub native to Southern Europe, North Africa, and Southeast Asia. The seeds and oil of *Nigella sativa* have been used as a medical agent for thousands of years. The most important active component is thymohydroquinone. *Nigella sativa* has antibacterial, antifungal, antiviral (SARS-CoV-2), anti-inflammatory, antioxidant, and immunomodulatory properties. (158, 159) A dose of 200-500 mg twice daily of the encapsulated oil is suggested. (158-161) It should be noted that thymohydroquinone decreases the absorption of cyclosporine and phenytoin. Patients taking these drugs should, therefore, avoid taking *Nigella sativa*. (162) Furthermore, two cases of serotonin syndrome have been reported in patients taking *Nigella sativa* who underwent general anesthesia (probable interaction with opiates). (163)
- **Sildenafil** with or without L-arginine-L-Citrulline (164-169); Sildenafil doses titrated up from 25 to 100 mg 2-3 times daily with L-arginine/L-citrulline powder twice daily. May be helpful for brain fog as well as microvascular disease with clotting and poor perfusion. It is noteworthy that curcumin, resveratrol, EGCG, and valproic acid all potentiate phosphodiesterase 5 (PDE5) inhibitors.

- **Bromelain 500 mg twice daily +/- N-acetyl cysteine (NAC) 600 mg twice daily.** *In Vitro* studies have demonstrated that bromelain cleaves the spike protein. (170, 171) This effect appears to be enhanced by the addition of NAC (see below). (172)
- **Vitamin C;** 1000 mg orally two to three times a day. Vitamin C has important anti-inflammatory, antioxidant, and immune-enhancing properties, including increased synthesis of type I interferons. (173-177) Avoid in patients with a history of kidney stones. Oral Vitamin C helps promote the growth of protective bacterial populations in the microbiome.
- **Spermidine;** 1000-2000 mg (wheat germ extract) daily. Spermidine is a naturally occurring polyamine that, like resveratrol, has anti-inflammatory and antioxidant properties. It preserves mitochondrial function and has been shown to reduce cardiovascular disease and all-cause mortality and prolong lifespan. (178, 179) Furthermore, like resveratrol, spermidine promotes autophagy. However, resveratrol and spermidine activate autophagy via different metabolic pathways and are therefore likely to have additive or synergistic effects. (180) Wheatgerm, mushrooms, grapefruit, apples, and mango are high natural sources of spermidine. (181) Wheatgerm supplements contain high amounts of spermidine with good bioavailability. A dose of 1000-2000 mg wheat germ extract daily is suggested. Cancer cells are reported to have dysregulated polyamine metabolism and spermidine is therefore best avoided in patients with a known malignancy. (182) In addition, spermidine should be avoided in men over the age of 60 who are at high risk of an ischemic stroke. (183)
- **Non-invasive brain stimulation (NIBS),** using transcranial direct current stimulation or transcranial magnetic stimulation, has been demonstrated to improve cognitive function in patients with long COVID as well as other neurological diseases. (184-191) NIBS is painless, extremely safe, and easy to administer. NIBS is a recognized therapy offered by many Physical Medicine and Rehabilitation Centers (e.g., see https://www.hopkinsmedicine.org/physical_medicine_rehabilitation/services/programs/brain-stimulation/treatment.html). Patients may also purchase an FDA-approved device for home use (e.g., <https://www.fisherwallace.com>)
- **Intravenous Vitamin C;** 25 g weekly, together with oral Vitamin C 1000 mg (1 gram) 2-3 times per day. High-dose IV vitamin C is “caustic” to the veins and should be given slowly over 2-4 hours. Furthermore, to assess patient tolerability the initial dose should be between 7.5-15 g. Total daily doses of 8-12 g have been well-tolerated, however, chronic high doses have been associated with the development of kidney stones, so the duration of therapy should be limited. Wean IV Vitamin C as tolerated.
- **Behavioral modification, relaxation therapy, mindfulness therapy (192), and psychological support** may help improve patients’ overall well-being and mental health. (193) Suicide is a real problem in the vaccine-injured patient. Support groups and consultation with mental health professionals are important. Tai Chi, a health-promoting form of traditional Chinese martial art, has been shown to be beneficial for preventing and treating diseases including long COVID. (194, 195) Yoga has immunomodulating properties that may be beneficial in vaccine-injured patients. (196)

Third Line Therapies

- **Hyperbaric oxygen therapy (HBOT)** (197-205); HBOT has potent anti-inflammatory properties, decreasing pro-inflammatory cytokines while increasing IL-10. Furthermore, HBOT polarizes macrophages toward the M2 phenotype and improves mitochondrial function. Surprisingly, it is the increased pressure, rather than the increase in the concentration of dissolved oxygen, that appears to mediate these effects. HBOT is delivered at varying pressures, both with and without oxygen. The addition of oxygen increases the clinical response. Maximal clinical response is achieved via the use of high-pressure chambers (typically reaching 2.4 ATM) with 100% oxygen for 60-90 minutes. If HBOT is delivered using lower pressure chambers (less than 1.5 ATM) without supplemental oxygen, the clinical response, although present, is significantly less such that a higher number of sessions will be needed to reach a clinical plateau.

Zilberman-Itskovich et al performed a randomized, sham-controlled, double-blind trial that evaluated the effect of HBOT in 73 patients with long COVID. (206) Both HBOT and sham patients received 40 daily sessions (five times a week) in a multi-place chamber. The HBOT protocol included breathing 100% oxygen by mask at 2 ATM for 90 minutes. In the HBOT group, there was a significant improvement in global cognitive function, attention, and executive function as well as an improvement in the energy domain, psychiatric symptoms, and pain level. Clinical outcomes were associated with significant improvement in brain MRI perfusion and microstructural changes. In general, the duration of treatment of HBOT should be based on clinical response and continued for at least 40 sessions and until the benefit has plateaued. If no benefit is evident clinically after 10 sessions, then HBOT should be considered a therapeutic failure. This therapy is limited by logistical issues and cost. A number of companies offer to rent portable, low-pressure chambers with the option to purchase (<https://www.oxyhealth.com/vitaeris-320.html>, <https://summit-to-sea.com/>, <https://www.aha-hyperbarics.com/>)

- **Low Magnitude Mechanical Stimulation (LMMS or Whole-Body Vibration)**. Low-magnitude (0.3-0.4G), high-frequency (32-40 Hz) mechanical stimulation has been demonstrated to increase bone density as well as indices of general well-being in patients with a variety of medical disorders. (207) It is postulated that this intervention recruits bone marrow stem cells in addition to having metabolic and immunologic effects. In humans, low-magnitude acceleration is applied through the feet by standing on a platform oscillating at relatively high resonant frequency. These parameters are very safe, painless, and easy to administer. This therapy is offered by Physical Medicine and Rehabilitation Centers, or a device may be purchased for home use <https://www.juvent.com/health/>) similarly with noninvasive brain stimulation (NIBS).
- **“Mitochondrial energy optimizer”** with pyrroloquinoline quinone, glycerophospholipids, CoQ10, NADH, and other nutrients (e.g., Life Extension Energy Optimizer, Restorative Solutions Mitochondrial Nutrition PQQ, Researched Nutritionals ATP 360® and ATP Fuel® and Pure Encapsulations Mitochondria-ATP) (208-214)
- **Hydroxychloroquine (HCQ)**; 200 mg twice daily for 1-2 weeks, then reduce as tolerated to 200 mg/day. HCQ is a potent immunomodulating agent and is considered the drug of choice for systemic lupus erythematosus (SLE), where it has been demonstrated to reduce mortality from this disease. Thus, in patients with positive autoantibodies or where autoimmunity is suspected

to be a prominent underlying mechanism, HCQ should be considered earlier. Further, it should be noted that SLE and post-vaccine syndrome have many features in common. HCQ is safe in pregnancy; indeed, this drug has been used to treat preeclampsia. (215-219) With long-term usage, the dose should be reduced (100 or 150mg/day) in patients weighing less than 61 kg (135 lbs.). It should be noted that HCQ will limit the effectiveness of intermittent fasting.

- **Low dose corticosteroid;** 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day, as tolerated.

Patients with elevated homocysteine levels

Patients with elevated homocysteine levels may benefit from treatment with 800 ug of 5-methyl tetrahydrofolate (5-MTHF), the most biologically active form of folic acid. (220) Supplementation with folic acid alone will paradoxically increase homocysteine levels, particularly in patients with MTHFR polymorphism. (220) In addition, B complex vitamins containing B2 (riboflavin) and Vitamin B6, magnesium, and Vitamin D should be added. (43)

Other Potential Treatments

(Require further evaluation)

- **Plasmapheresis.** Plasmapheresis improves systemic cytokine levels, coagulopathy, and immune responsiveness in patients with severe COVID with a potential mortality benefit. (221-228) Kiprof, et. al. have published a case report of a dramatic clinical improvement in a patient with long COVID. (229) In this report, the patient's markers of inflammatory macrophages diminished, and markers of lymphocytes, including natural killer cells and cytotoxic CD8 T-cells, increased; in addition, circulating inflammatory proteins diminished. Furthermore, it is likely that plasmapheresis removes autoantibodies and improves the coagulopathy of these patients. We are aware of anecdotal reports of marked improvement in neurological symptoms, especially SFN and brain fog in vaccine-injured patients treated with this therapeutic modality. However, this is a limited and expensive resource that, in itself, is not without complications. Furthermore, the durability of the clinical response needs to be determined. While plasmapheresis/plasma exchange is a therapeutic option for the severely neurologically impaired patient following vaccination, additional data is required before this modality can be widely recommended.
- **Valproic acid** (230, 231); Depakote, 250mg 2-3 times daily. Valproic acid has anti-inflammatory effects and polarizes macrophages towards an M2 phenotype. (232) Histone deacetylase (HDAC) inhibitors are being studied for neural regeneration. In addition, valproic acid has important anticoagulant and anti-platelet effects (233) and is an inducer of heat shock proteins. (234) Valproic acid may be helpful for neurological symptoms. Treatment should be limited to less than 6 to 9 months due to the concern for the loss of brain volume particularly in those patients with cognitive dysfunction. (235) In a cerebral ischemia/hypoxia model resveratrol markedly enhanced the neuroprotective effects of valproic acid. (236) Furthermore, resveratrol has been reported to reverse the toxicity of valproic acid, (237, 238). These data suggest that resveratrol (in a dose of 500 mg – 1000 mg twice daily) should be recommended in patients prescribed valproic acid.

- **Induced hyperthermia and Cold Hydrotherapy.** The role of sauna bathing and cold therapy (cold showers, cold baths) in patients with long COVID and the vaccine-injured is unknown. (239, 240) Regular sauna bathing has been proven to reduce all-cause and cardiovascular mortality, prolong the lifespan, improve exercise performance, and improve the outcome of patients with neuropsychiatric disease. (241-245) Induced hyperthermia increases the expression of heat shock proteins, which activates autophagy. In addition, heat therapy increases the expression of cell stress pathways, has antioxidant and anti-inflammatory effects, and improves mitochondrial function. (239) Sauna bathing has very similar physiologic effects to that of aerobic exercise (increase heart rate, stroke volume, and cardiac output). (246, 247) As patients with long COVID and the vaccine-injured are exercise intolerant (they cannot increase cardiac output) (90) sauna bathing may be poorly tolerated. However, sauna bathing and induced hyperthermia have been shown to improve endothelial and cardiac function in patients with chronic heart failure. (248) Furthermore a recent meta-analysis reported that sauna bathing improved cardiac function in patients with chronic heart failure. (249) Waon therapy (infrared dry sauna) has shown promising results in patients with chronic fatigue syndrome. (250, 251) Patients interested in sauna bathing should determine their tolerance to short sessions (5-10 mins) and increase the duration as tolerated (up to 20 minutes) three to four times a week. Similarly, the role of cold therapy in the vaccine-injured is unknown; patients should similarly determine their tolerance to this treatment approach. (252, 253)
- **Pentoxifylline (PTX);** PTX ER, 400 mg three times daily, should be considered in those patients with severe microcirculatory disturbances. PTX is a non-selective phosphodiesterase drug that has anti-inflammatory and antioxidant effects. [224] In addition, PTX improves red blood cell deformability and reduces blood viscosity, so can mitigate the hyper-viscosity and RBCs hyper-aggregation, which is linked with the development of coagulopathy in the vaccine injured.
- **Maraviroc;** 300 mg orally twice daily. If 6 to 8 weeks have elapsed and significant symptoms persist despite the above therapies, this drug can be considered. Note Maraviroc can be expensive and has a risk of significant side effects and drug interactions. Maraviroc is a C-C chemokine receptor type 5 (CCR5) antagonist. While many long COVID and post-vaccine patients have been treated with Maraviroc, the role of this drug requires further evaluation. (254)
- **Sulforaphane (broccoli sprout powder)** 500 mcg – 1g twice a day. While sulforaphane has many potential benefits in patients with COVID, (255-257) long COVID, and post-vaccine syndrome, there is limited clinical data to support this intervention. Sulforaphane has immunomodulatory effects by targeting monocytes/macrophages, suggesting a benefit in chronic inflammatory conditions. (255-257) Sulforaphane is a beneficial supplement that may be useful for reducing microglial-mediated neuroinflammation and oxidative stress. In addition, as has been well-popularized, sulforaphane has an important role in cancer prophylaxis. The pharmacology and optimal dosing of sulforaphane are complex. Sulforaphane itself is unstable. The supplement should contain the two precursors, *glucoraphanin* and *myrosinase*, which react when the supplement is consumed. Broccoli “extracts” are produced in a way that completely destroys the activity of the myrosinase enzyme. As such, these extracts are incapable of producing sulforaphane when consumed in a supplement or food. (258, 259) We recommend a 100% whole broccoli sprout powder, which maximally retains both glucoraphanin and myrosinase whilst, at the same time, deactivating the inhibitors.

- **Dandelion** (*Taraxacum officinale*). The root, flower, and leaves of dandelion contain an array of phytochemicals that have anti-inflammatory, antioxidant, hypolipidemic, antimicrobial, and anticoagulant properties. (260, 261) It is widely reported that dandelion is effective for ‘detoxifying’ spike protein. An *in vitro* study demonstrated that a dandelion leaf extract altered the binding of SARS-CoV-2 spike protein to the ACE receptor. (262) It would appear that this effect was due to alterations (binding) of the ACE-2 receptor rather than binding to the spike protein. It, therefore, remains unclear whether dandelion extract actually binds to the spike protein and would potentiate clearance of this protein. The European Scientific Cooperative on Phytotherapy recommends a dose of 4-10 g TID (20-30mg/ml in hot water). (263) It should be noted that Dandelion extract is considered contraindicated in those with liver and biliary disease, bile duct obstruction, gallstones, cholangitis, and active peptic ulcer. (263) Furthermore dandelion is rich in potassium and should be used cautiously in patients with kidney failure.
- **VEDICINALS® 9**; a unique phytopharmaceutical-based therapeutic suspension that consists of nine bioactive compounds with antiviral, anti-inflammatory, immune-modulatory, antipyretic, and analgesic properties. The compounds include Baicalin, Quercetin, Luteolin, Rutin, Hesperidin, Curcumin, Epigallocatechin Gallate, Piperine, and Glycyrrhizin. (<https://www.vedicinals.com/vedicinals-9/>). A number of these compounds are included in our protocol and the additional benefit of this 9 phytopharmaceutical combination over more widely available flavonoid combinations is unknown. (264)
- **C60 or C60 fullerenes** (265, 266); C60, short for Carbon 60, is composed of 60 carbon atoms forming something that looks like a hollow soccer ball and is considered as a “free radical sponge.” C60 is considered the single most powerful antioxidant ever discovered. Robert Curl, Harold Kroto, and Richard Smalley were awarded the Nobel Prize for chemistry in 1996 for its discovery.
- **Intravenous immunoglobulin (IVIG) treatment**; The role of IVIG in the treatment of the vaccine injured is unclear. The response to IVIG in the general population of vaccine-injured patients is mixed, with very few showing long-term improvement. Many patients who report an initial improvement will relapse in 2 to 3 weeks. Other patients report no benefit, while some appear worsened. Due to the presence of non-neutralizing anti-SARS-CoV-2 antibodies and anti-ACE-2 antibodies, etc., the real possibility exists that IVIG will cause antibody-dependent immune enhancement (ADE) with a severe exacerbation of symptoms.

IVIG is, however, recommended in specific autoimmune syndromes, which include Guillain Barré Syndrome, transverse myelitis, and immune thrombocytopenia. These patients should concomitantly be treated with the core immune-modulating therapies. IVIG proved to be ineffective in an RCT that enrolled patients with small fiber neuropathy. (267)

The fact that many patients report an initial response to IVIG supports the notion that many aspects of this disease are due to autoantibodies. IVIG will remove preformed antibodies, but they do not prevent the B cells from ongoing antibody production; hence the response is likely to be short-lived, and interventions that limit the production of autoantibodies are therefore required (core immune-modulating therapies).

- **Immunosuppressive therapies**; As a rule, immunosuppressive therapy should be avoided, as these drugs may exacerbate the immune dysfunction in vaccine-injured patients and prevent the restoration of immune homeostasis. A trial of immunosuppressive therapy may be indicated

in patients with an established autoimmune syndrome who have failed other therapeutic interventions.

Disease-Specific Therapeutic Adjuncts

Small fiber neuropathy (SFN)/autonomic neuropathy

SFN is one of the commonest, most enduring, and most disabling complications in the vaccine injured. As symptoms appear once the nerve is already injured and inflamed it may be difficult to treat and reverse. It is likely that there is no single magic bullet to treat this disease and that a combination of therapies should be sequentially attempted in order to find a personalized therapy that has some benefit.

- Low-dose naltrexone (LDN) appears to play a pivotal role in the treatment of SFN.
- Tricyclic antidepressants (start at a low dose and increase as tolerated)
- Gabapentin: 300 mg twice daily and increase as tolerated
- Alpha lipoic acid; 600 mg/day (alpha-lipoic acid is an inducer of heat shock proteins). (268, 269)
- Zinc; 25 mg daily (elemental zinc) together with the zinc ionophore quercetin. SFN is an autoimmune disease; zinc deficiency has been associated with the development of autoimmune diseases. (270)
- Magnesium; 100-400 mg daily. Magnesium is an important nerve stabilizer.
- Resveratrol 500 mg twice a day. Resveratrol has important anti-inflammatory and immunomodulating properties. In addition, resveratrol activates autophagy.
- Cardio Miracle™ and L-arginine/L-citrulline supplements. Cardio Miracle is a supplement with over 50 ingredients formulated to increase nitric oxide (NO) production. Nitric oxide releasing lozenges or tablets are an alternative. NO likely improves microvascular flow and nerve repair. Sildenafil with or without L-arginine-L-Citrulline (164-169); Sildenafil doses titrated up from 25 to 100 mg 2-3 times daily with L-arginine/L-citrulline powder twice daily.
- Omega-3 fatty acids 2-4g/day. Omega-3 fatty acids have important anti-inflammatory and immunomodulating properties.
- Near infra-red photobiomodulation. PBM likely improves neuropathy via NO pathways and improving axonal and Schwann cell mitochondrial function. (271, 272)
- Whole-body vibration therapy has been shown to improve symptoms of small fiber neuropathy. (273, 274)
- POTS – ensure sufficient hydration and consider the use of compression stockings or abdominal binders.
- POTS – Clonidine; 0.1 mg twice daily as tolerated.
- POTS – Fludrocortisone; 0.1 to 0.2 mg/day or licorice root (has glycyrrhizinic acid, an aldosterone-like compound).
- POTS – midodrine; 5-10 mg three times daily
- A trial of hyperbaric oxygen therapy (HBOT)
- It should be noted that the diagnosis of small fiber neuropathy/autonomic neuropathy is a clinical diagnosis. (28-35) Complex and expensive tests are NOT required to make this diagnosis. It should be noted that SFN is closely associated with multiple autoantibodies. Testing for these autoantibodies serves no useful clinical purpose as it does not change the treatment plan.

Generalized neurologic symptoms/“brain fog”/fatigue/visual symptoms

- LDN appears to play a pivotal role in the treatment of many neurological symptoms.
- Methylene blue (as indicated above) and photobiomodulation
- Nigella Sativa; 200-500 mg twice daily.
- Non-invasive brain stimulation (NIBS) should be considered in patients with “brain fog,” memory disturbances, and as well as other cognitive issues.
- Bupropion, a norepinephrine-dopamine reuptake inhibitor has been demonstrated to improve fatigue and “brain fog” in patients with both cancer and non-cancer related fatigue.[316;317] The suggested dose is 150 mg extended-release tablet daily. After a month the dose can be cautiously increased to 300 mg daily. **Bupropion is CONTRAINDICATED in combination with methylene blue.**
- Intranasal oxytocin. Oxytocin is a nonapeptide produced in the hypothalamus, acting as a neuropeptide in different brain areas (most notably the amygdala and hippocampus) and as a hormone and paracrine substance in peripheral organs. (275-277) Oxytocin has colloquially been referred to as the “love hormone”, given its role in social interaction and bonding. (278) Oxytocin has powerful anti-inflammatory and immunomodulating properties and may play an important role in minimizing neuro-inflammation. [184-186] In addition, oxytocin has been demonstrated to stimulate neuronal growth (276) Oxytocin plays an important role in modulating the stress response. (279) Oxytocin has also been reported to have a role in the prevention and treatment of migraine. (280, 281) The nasal route appears to be the preferred mode of administration. Martins et al performed a dose-finding study in healthy human volunteers. [187] These authors measured changes in amygdala blood flow and demonstrated an inverse dose-response curve, with lower doses resulting in a greater increase in blood flow. They report the optimal dose as being between 9-18 IU. This suggests that one to two puffs to each nostril (4 IU per puff) two times a day may be optimal (total dosage of 16-32 IU per day). Oxytocin must be avoided in pregnancy. Oxytocin nasal spray should be compounded at 12 to 15 units/0.1ml (spray) and administered at onset aggressively to upregulate receptors at 2 sprays each nostril BID (8-sprays per day) for the first week and then maintenance at 2 sprays ea. nostril (4/d) once daily. (282) Oxytocin can also be delivered via SL liquid or via lozenge.
- Spermidine and Resveratrol. Experimental studies have demonstrated that spermidine reduces neuroinflammation, reduces accumulation of amyloid protein, and improves cognitive function. (283, 284) Similarly, resveratrol has been shown to be useful in the prevention and treatment of Alzheimer’s disease. (126)
- Valproic acid and pentoxifylline may be of value in these patients.
- Fluvoxamine: Start on a low dose of 12.5 mg/day and increase slowly as tolerated. Some patients report a significant improvement with fluvoxamine while other patients appear to tolerate this drug poorly. Fluoxetine 20 mg/day is an alternative, as are tricyclic anti-depressants (see section on Depression below).
- These symptoms may be mediated by Mast Cell Activation Syndrome (MCAS); see specific treatment below.

Depression

- Depression is a serious problem in long COVID and post-vaccine patients and, unfortunately, suicide is not uncommon. (285-287) Patients with a history of depression and/or those taking SSRI medications appear to be at particular risk of severe depression.
- Patients with depression are best managed by mental health providers with expertise in this area. Long-term SSRI medications are generally not recommended due to the long-term effects of these drugs on serotonin receptors, intracellular messenger pathways as well as genetic and epigenetic effects. (288, 289) It should be noted that most SSRI/SNRI agents, but notably sertraline, fluvoxamine, paroxetine, venlafaxine, and duloxetine are associated with severe anxiety which may progress to mania, self-inflicted harm, suicide, anger outbursts, physical violence, homicidal thoughts, and homicide. (290-293) Patients who are treated with antidepressant agents, therefore, require close monitoring for the development of these serious adverse reactions.
- There appears to be an interaction between vaccination, COVID-19, zinc levels, and depression. (294-297) COVID-19 infection and COVID vaccines may lead to low zinc levels. Zinc deficiency is associated with an increased risk of depression. Treatment with zinc has been shown to have antidepressant effects and to act synergistically with SSRI medication. (298) 25 mg zinc daily (elemental), together with the zinc ionophore quercetin is therefore suggested. (297)
- Non-invasive brain stimulation (NIBS) using transcranial direct current stimulation or transcranial magnetic stimulation has been demonstrated to be highly effective in the treatment of depression. (299-303) Indeed, The Fisher Wallace Stimulator® is FDA approved for the treatment of depression, anxiety, and insomnia. NIBS is painless, extremely safe, and easy to administer. NIBS is a recognized therapy offered by many Physical Medicine and Rehabilitation Centers. Patients may also purchase an FDA-approved device for home use (<https://www.fisherwallace.com/>).
- Methylene blue (dose as indicated above) has been proven to be beneficial in patients with depression. (304, 305) **Do NOT TAKE FLUVOXAMINE, FLUOXETINE, BUPROPION or any other SSRI-NDRI with MB.**
- Photobiomodulation and sauna bathing have been shown to be highly effective for the treatment of depression. (244, 306-308)
- In experimental models, *Nigella sativa* has been shown to have a role in the treatment of depression. (309)
- Altered gut flora/dysbiosis has been linked to anxiety and depression and the use of probiotics has been associated with an improvement in mood. (310-314) Since infection with SARS-CoV-2 and those who have been vaccinated have dysbiosis the use of pre- and probiotics are suggested. (136, 137, 315, 316) Unsweetened Greek yogurt with pre and probiotics is recommended. Suggested probiotics include Megasporebiotic (Microbiome labs) and TrueBifidoPro (US Enzymes) and yourgutplus+. (138) In addition, the use of Glucomannan (from Konjac root) and/or Chia seeds provide soluble and insoluble fiber required for the normalization of the microbiome. (317-319) If patients have moderate to severe dysbiosis and/or small bowel bacterial overgrowth (SBIO) then prebiotics may have the unwanted effect of "feeding the bad bacteria" and contributing to worsening of the dysbiosis. Probiotics alone and/or fermented foods are less likely to harbor and nourish commensal and abnormal gut microbes.

Patients with elevated DIC and those with evidence of thrombosis

- See section on anticoagulation. The patient's risk of bleeding needs to be assessed as this will determine the aggressiveness of anticoagulation.
- These patients should be treated with a DOAC or coumadin for at least three months and then reevaluated for ongoing anticoagulation.
- Patients should continue ASA 81 mg/day unless at high risk of bleeding.
- Nattokinase 100-200mg twice daily is suggested unless at high risk of bleeding.
- Triple anticoagulation should be considered in select patients. (77) Treat no longer than one month. Triple anticoagulation increases the risk of serious bleeding; patients should be counseled regarding this complication.
- In those patients with marked microvascular disease/thrombosis, the combination of pentoxifylline and sildenafil should be given a therapeutic trial. (320, 321)

Vaccine-induced myocarditis/pericarditis

- ACE inhibitor/ARB, together with carvedilol as tolerated to prevent/limit progressive decline in cardiac function.
- Colchicine in patients with pericarditis – 0.6 mg/day orally; increase to 0.6 mg twice daily if required. Reduce dose if patients develop diarrhea. Monitor white blood cell count. Decrease dose with renal impairment.
- Magnesium to reduce the risk of serious arrhythmias (see dosing above).
- Coenzyme Q (CoQ) 200-400mg/day. (322-325)
- Omega-3 fatty acids – EPA/DHA 2-4 g/day (326-328) Increase dose slowly as tolerated.
- Resveratrol/flavanoid combination for its anti-inflammatory and antioxidant properties.
- Referral to a cardiologist or ER in case of persistent chest pain or other signs and symptoms of cardiac events are observed.

Herpes virus reactivation syndrome

- Valtrex; 500-1000 mg twice daily for 7-10 days (acyclovir is an alternative). (329)
- Spironolactone 50-100 mg daily (330). Spironolactone has antiviral properties against Epstein Barr Virus by inhibiting viral capsid antigen synthesis and capsid formation. Spironolactone likely has antiviral effects against other Herpes viruses.
- L-Lysine; 1000 mg twice daily (331, 332)
- Valproic acid; Depakote, 250 mg 2-3 times daily. Valproic acid has activity against HSV-1, HSV-2, HZV, CMV, and EBV. (333-335)
- Zinc 40 mg daily (336, 337)
- Quercetin "Phytosome" 500 mg twice daily (antiviral properties and a Zinc ionophore) (338)

Tinnitus

- This a frequent and disabling complication reported in post-vaccine syndrome.
- Tinnitus refers to the sensation of sound in the absence of a corresponding external acoustic stimulus and can, therefore, be classified as a phantom phenomenon. Tinnitus sensations are usually of an unformed acoustic nature such as buzzing, hissing, or ringing. Tinnitus can be localized unilaterally or bilaterally, but it can also be described to emerge within the head. (339)
- Ideally, patients should be evaluated by an ENT specialist or audiologist to exclude underlying disorders.

- A number of treatment approaches exist to manage this disabling disease including: (339-341)
 - Cognitive behavioral therapy (342)
 - Specialized therapy including tinnitus retraining therapy, hearing aids, sound therapy, auditory perceptual training, and repetitive transcranial magnetic stimulation. (339)
 - A number of pharmacologic agents have been used to treat tinnitus. Anticonvulsants including carbamazepine have generally been disappointing. The following drugs have shown some clinical benefit.
 - Tricyclic antidepressant agents particularly nortriptyline and amitriptyline. (343, 344) In addition, the SSRI sertraline has shown some efficacy. (345)
 - Clonazepam and other benzodiazepines. These drugs may provide temporary relief, however, due to issues of dependence, long-term use is not recommended. (346)
 - Melatonin slow release 2-6 mg at bedtime. (347)
- Oxytocin nasal spray. Oxytocin acts as a neurotransmitter affecting several neural circuits, particularly in the hypothalamus and amygdala. (277) Oxytocin nasal spray has shown promising results for the treatment of tinnitus (one puff to each nostril two times a day; a total dosage of 16 IU per day). (348) Oxytocin must be avoided in pregnancy. Oxytocin nasal spray should be compounded at 12 to 15 units/0.1ml (spray) and administered at onset aggressively to upregulate receptors at 2 sprays each nostril BID (8-sprays per day) for the first week and then maintenance at 2 sprays ea. nostril (4/d) once daily. (282) Oxytocin can also be delivered via SL liquid or via lozenge.
- Non-invasive brain stimulation (NIBS) has proven to be effective in controlling treatment-resistant tinnitus. (190, 191)

Ageusia and anosmia (Loss of taste and smell)

- Loss of smell and taste is a troubling symptom in post-COVID patients and in the vaccine injured. The loss of taste usually follows the loss of smell. Multiple mechanisms may explain the loss of smell including direct injury to the olfactory bulb. (349) Anosmia is a particularly difficult condition to treat. (350)
- Oxytocin nasal spray. Oxytocin receptors are highly expressed on olfactory neurons as well as limbic structures. Oxytocin nasal spray has been demonstrated to improve the sense of smell in patients with schizophrenia. A dose of one puff in each nostril two times a day for a total dosage of 16 IU per day is suggested. (351) Oxytocin must be avoided in pregnancy.
- Olfactory training appears to be a promising therapy for patients with post viral olfactory loss to partly regain their sense of smell. (352)
- Nasal corticosteroids appear ineffective and are not recommended for the use of anosmia. (353)

Bell's palsy/facial paresthesia/visual issues

- Low-dose naltrexone. Begin with 1 mg/day and increase to 4.5 mg/day as required. May take 2-3 months for full effect.
- Low dose corticosteroid: 10-15 mg/day prednisone for 3 weeks. Taper to 10 mg/day and then 5 mg/day as tolerated.
- Reduced workload, stress, and light exercises for a couple of months.

Patients with new onset allergic diathesis/features of Mast Cell Activation Syndrome (MCAS)

- The novel flavonoid luteolin is reported to be a potent mast cell inhibitor. (354-357) Luteolin 20-100 mg/day is suggested.
- Turmeric (curcumin); 500 mg/day. Curcumin has been reported to block H1 and H2 receptors and to limit mast cell degranulation. (358, 359) Curcumin has low solubility in water and is poorly absorbed by the body; (360) consequently, it is traditionally taken with full-fat milk and black pepper, which enhance its absorption. Nano-curcumin preparations or formulations designed to enhance absorption are encouraged. (361-364)
- H1 receptor blockers. Loratadine 10 mg/day, Cetirizine 5-10 mg/day, Fexofenadine 180 mg/day.
- H2 receptor blockers. Famotidine 20 mg twice daily as tolerated. [391]
- Montelukast 10 mg/day. Caution as may cause depression in some patients. The efficacy of montelukast as a “mast cell stabilizer” has been questioned. (36)
- Ketotifen. 1 mg in 5 ml. Start with 0.5 ml at night. Once they get used to it, as it has a strong hypnotic effect, increase by 0.5ml increments up to 5ml. Some patients can increase up to 10 ml daily (1 mg BID). Ketotifen has antihistamine effects and is a mast cell stabilizer. Ketotifen may be particularly useful in patients with GI hypersensitivity. (365, 366)
- Vitamin C; 1000 mg twice daily. Vitamin C is strongly recommended for allergic conditions and MCAS. Vitamin C modulates immune cell function and is a potent histamine inhibitor.
- Low histamine diet.

Alopecia (hair loss)

Three types of alopecia have been described in connection with COVID-19 infection, long COVID, and post-vaccine syndrome. (367)

- Androgenetic alopecia (worsening of male pattern baldness)
- Alopecia areata, an autoimmune disorder that usually results in unpredictable, patchy hair loss. In most cases, hair falls out in small patches around the size of a quarter. There is currently no cure for alopecia areata; referral to a dermatologist is suggested. Preliminary research in animals has found that quercetin can protect against the progression of alopecia areata and may promote hair regrowth. (368, 369)
- Telogen effluvium, which results in temporary thinning of the hair, particularly on the scalp. Telogen effluvium is a reversible condition in which hair falls out after a stressful experience. The stress pushes large numbers of hair follicles into a resting phase. Within a few months, those hairs can fall out. This condition occurs predominantly in females and may be related to increased expression of pro-inflammatory mediators. No specific treatment is required, as the hair will usually grow back.
- Photobiomodulation treatments appear to be very effective in inducing hair regrowth. (370, 371)
- Nutritional supplements containing omega-3 fatty acids (Vascepa), vitamin D, vitamin C, and zinc are useful adjuncts to promote hair regrowth. (372-374)
- Topical minoxidil may promote hair regrowth. (375) Finasteride 2.5 mg daily is an option in both men and women; (376) consult with a dermatologist and treatment for less than 1 year is generally recommended.
- Topical valproic acid has been shown to stimulate hair regrowth. (377, 378)

References

1. Blaylock RL. COVID Update: What is the truth? *Surgical Neurology International*. 2022;13:167.
2. Rose J. A report on the U.S. Vaccine Adverse Events Reporting System (VAERS) of the COVID-19 messenger ribonucleic acid (mRNA) biologicals. *Science, Public Health Policy, and Law*. 2021;2:59-80.
3. Neil M, Fenton N, Smalley J, Craig C, Guetzkow J, Rose J. Latest statistics on England mortality data suggest systematic mis-categorisation of vaccine status and uncertain effectiveness of Covid-19 vaccination. *Research Gate*. 2021.
4. Dickerman BA, Madenci AL, Gerlovin H, Kurgansky KE, Wise JK, Muniz MJ, et al. Comparative safety of BNT162b2 and mRNA-1273 vaccines in a Nationwide Cohort of US veterans. *JAMA Intern. Med*. 2022;182:739-46.
5. Colunga Biancatelli RM, Solopov P, Sharlow E, Lazo J, Marik PE, Catravas J. The SARS-CoV-2 spike protein subunit 1 induces COVID-19 like acute lung injury in K18-hACE2 transgenic mice and barrier dysfunction in human endothelial cells. *Am. J. Physiol. Lung. Cell. Mol. Physiol*. 2021;321:L477-L84.
6. Marik P, Iglesias J, Varon J, Kory P. A Scoping Review of the pathophysiology of COVID-19. *International Journal of Immunopathology and Pharmacology*. 2021.
7. Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-C-V-2 mRNA vaccinations: The role of G-quadruplexes, exosomes and microRNAs. *Food & Chemical Toxicology*. 2022;164:113008.
8. Chen BM, Cheng TL, Roffler SR. Polyethylene glycol immunogenicity: Theoretical, clinical and practical aspects of anti-polyethylene glycol antibodies. *ASC Nano*. 2021;15:14022-48.
9. Mohamed M, Lila AS, Shimizu T, Alaaeldin E, Hussein A, Sarhan HA, et al. PEGylated liposomes: immunological responses. *Science and Technology of Advanced Materials*. 2019;20:710-24.
10. Hamad I, Hunter AC, Szebeni J, Moghimi SM. Poly (ethylene glycol)s generate complement activation products in human serum through increased alternative pathway turnover and a MASP-2 dependent process. *Molecular Immunology*. 2008;46:225-32.
11. Seneff S, Nigh G. Worse than the disease? Reviewing some possible unintended consequences of the mRNA vaccines against COVID-19. *International Journal of Vaccine Theory, Practice, and Research*. 2021;2:38-79.
12. Blumenthal KG, Robinson LB, Camargo CA, Shenoy ES, Banerji A, Landman AB. Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA*. 2022;325:1562-4.
13. Cadegiani FA. Catecholamines are the key trigger of mRNA SARS-CoV-2 and mRNA COVID-19 vaccine-induced myocarditis: a compelling hypothesis supported by epidemiological, anatomopathological, molecular and physiological findings. *Cureus*. 2022;14:e27883.
14. Schauer J, Buddhe S, Gulhane A, Sagiv E. Persistent cardiac MRI findings in a cohort of adolescents with post COVID-19 mRNA vaccine myocarditis. *J. Pediatr*. 2022.
15. Verma AK, Lavine KJ, Lin CY. Myocarditis after COVID-19 mRNA vaccination. *N. Engl. J. Med*. 2022;385:1332-4.
16. Roltgen K, Nielsen SC, Silva O, Younes SF, Yang F, Wirz OF. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell*. 2022;185:1-16.
17. Swank Z, Senussi Y, Alter G, Walt DR. Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae. *medRxiv*. 2022.

18. Patterson BK, Francisco EB, Yogendra R, Long E, Pise A, Hall E, et al. Persistence of SARS CoV-2 S1 protein in CD16+ monocytes in post-acute sequelae of COVID-19 (PASC) up to 15 months post-infection. *Front. Immunol.* 2022;12:746021.
19. Bortolotti D, Gentili V, Rizzo S, Rotola A, Rizzo R. SARS-CoV-2 Spike 1 protein controls natural killer cell activation via the HLA-E/NKG2A pathway. *Cell.* 2020;9:1975.
20. Gallardo-Zapata J, Maldonado-Bernal C. Natural killer cell exhaustion in SARS-CoV-2 infection. *Innate Immunity.* 2022;28:1-10.
21. Lee MJ, Leong MW, Rustagi A, Beck A, Zeng L, Holmes S. SARS-CoV-2 escapes direct NK cell killing through Nsp1-mediated downregulation of ligands NKG2D. *bioRxiv.* 2022.
22. van Eeden C, Khqn L, Osman MS, Tevaert JW. Natural killer cell dysfunction and its role in COVID-19. *Int. J. Mol. Sci.* 2020;21:6351.
23. Gassen NC, Papiés J, Bajaj T, Dethloff F, Emanuel J, Weckmann K, et al. Analysis of SARS-CoV-2 controlled autophagy reveals spermidine, MK-2206 and niclosamide as putative antiviral therapeutics. *bioRxiv.* 2020.
24. Verbeke R, Lentacker I, Smedt SC, DeWitte H. Three decades of messenger RNA vaccine development. *Nanotoday.* 2019;28:100766.
25. Parhiz H, Brenner JS, Patel PN, Papp TE, Li Q, Shi R. Added to pre-existing inflammation, mRNA-lipid nanoparticles induce inflammation exacerbations (IE). *Journal of Controlled Release.* 2022; 344:50-61.
26. Ndeupen S, Qin Z, Jacobsen S, Bouteau A, Estambouli H, Igyarto BZ. The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. *iScience.* 2021;24:103479.
27. Olajide O, Iwuanyanwu VU, Adegbola OD, Al-Hindawi AA. SARS-CoV-2 spike glycoprotein S1 induces neuroinflammation in BV-2 microglia. *Molecular Neurobiology.* 2022;59:45-458.
28. Oaklander AL, Mills AJ, Kelley M, Toran MK. Peripheral neuropathy evaluations of patients with prolonged long COVID. *Neurol. Neuroimmunol. Neuroinflamm.* 2022;9:e1146.
29. Burakgazi AZ. Small-fiber neuropathy possibly associated with COVID-19. *Case Rep. Neurol.* 2022;14:208-12.
30. Shouman K, Vanichkachorn G, Chesire WP, Suarez MD, Shelly S. Autonomic dysfunction following COVID-19 infection: an early experience. *Clinical Autonomic Research.* 2021;31:385-94.
31. Hinduja A, Moutairou A, Calvet JH. Sudomotor dysfunction in patients recovered from COVID-19. *Clinical Neurophysiology.* 2021;51:193-6.
32. Abdelnour L, Abdalla ME, Babiker S. COVID 19 infection presenting as motor peripheral neuropathy. *Journal of the Formosan Medical Association.* 2020;119:1119-20.
33. Abrams RM, Simpson DM, Navis A, Jette N, Zhou L. Small fiber neuropathy associated with SARS-CoV-2 infection. *Muscle & Nerve.* 2021.
34. Zhou L, Shin S. Small fiber neuropathy. *Practical Neurology.* 2021:36.
35. Bednarik J, Bursova S, Dusek L, Sommer C. Etiology of small-fiber neuropathy. *Journal of the Peripheral Nervous System.* 2009;14:177-83.
36. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation- or should it be mast cell mediator disorders? *Expert Rev. Clin. Immunol.* 2019;15:639-56.
37. Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ. Mast cell activation symptoms are prevalent in Long-COVID. *International Journal of Infectious Diseases.* 2021;112:217-26.
38. Gold JE, Okyay R, Licht WE, Hurley DJ. Investigation of Long COVID prevalence and its relationship to Epstein-Barr Virus reactivation. *Pathogens.* 2021;10:763.

39. Chen T, Song J, Liu H, Zheng H, Chen C. Positive Epstein-Barr virus detection in coronavirus disease 2019 (COVID-19) patients. *Scientific Reports*. 2021;11:10902.
40. Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Crit. Care*. 2020;24:530.
41. Peluso MJ, Deveau TM, Munter SE, Ryder D, Buck A, Lu S, et al. Evidence of recent Epstein-Barr virus reactivation in individuals experiencing Long Covid. *medRxiv*. 2022.
42. Pont G, Pastorino L, Manfredini M, Ozben T, Oliva G, Kaleci S. COVID-19 spreading across world correlates with C677T allele of the methylenetetrahydrofolate reductase (MTHFR) gene prevalence. *J. Clin. Lab. Anal.* 2021;35:e23798.
43. Karst M, Hollenhorst J, Achenbach J. Life-threatening course in coronavirus disease 2019 (COVID-19): Is there a link to methylenetetrahydrofolic acid reductase (MTHFR) polymorphism and hyperhomocysteinemia? *Medical Hypotheses*. 2020;114:110234.
44. Carpena G, Negrini D, Henry BM, Montagnana L, Lippi G. Homocysteine in coronavirus disease (COVID-19): a systematic literature review. *Diagnosis*. 2022.
45. Ponti G, Roli L, Oliva G, Manfredini M, Trenti T, Kaleci S, et al. Homocysteine (Hcy) assessment to predict outcomes of hospitalized COVID-19 patients: a multicenter study on 313 Covid-19 patients. *Clin. Chem. Lab. Med.* 2021;59:e354-e7.
46. Abu-Farha M, Al-Sabah S, Hammad MM, Hebbar P, John SE, Taher I, et al. Prognostic genetic markers for thrombosis in COVID-19 patients: A focused analysis on D-Dimer, homocysteine and thromboembolism. *Frontiers in Pharmacology*. 2020;11:587451.
47. Duma D, Collins JB, Chou JW, Cidlowski JA. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Science Signaling*. 2010;3(143):ra74.
48. Atoui A, Jarrah K, Al Mahmassani L, Bou-Fakhredin R, Taher AT. Deep venous thrombosis and pulmonary embolism after COVID-19 mRNA vaccination. *Ann. Hematol.* 2022;101:1111-3.
49. Tomassetti F, Nuccetelli M, Sarubbi S, Gisone F, Ciotti M. Evaluation of S-RBD and high specificity ACE-2 binding antibodies on SARS-CoV-2 patients after six months from infection. *International Immunopharmacology*. 2021;99:108013.
50. Gundry SR. Observational findings of PULS cardiac test findings for inflammatory markers in patients receiving mRNA vaccines. *Circulation*. 2021;144 (suppl. 1):A10712.
51. Decousus H, Tapson VF, Bergmann JF, Chong BH, Froehlich JB, Kakkar AK, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest*. 2011;139(1):69-79.
52. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-100.
53. Whitlock EP, Burda BU, Williams SB, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: A systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 2016;164:826-35.
54. Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127(5):634-40.
55. Sumi H, Hamada H, Tsushima H, Mihara H, Muraki H. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese Natto; a typical and popular food in Japanese diet. *Experientia*. 1987;43:1110-1.
56. Weng Y, Yao J, Sparks S, Wang KY. Nattokinase: An oral antitrombotic agent for the prevention of cardiovascular disease. *Int. J. Mol. Sci.* 2017;18:523.

57. Dabbagh F, Negahdaripour M, Berenjian A, Behfar A, Mohammadi F, Zamani M. Nattokinase: production and application. *Applied Microbiology and Biotechnology*. 2014;98:9199-206.
58. Nagata C, Wada K, Tamura T, Konishi K, Goto Y, Koda S, et al. Dietary soy and natto intake and cardiovascular disease mortality in Japanese adults: the Takayama study. *Am. J. Clin. Nutr.* 2017;105:426-631.
59. Sumi H, Hamada H, Nakanishi K, Hiratani H. Enhancement of the fibrinolytic activity in plasma by oral administration of nattokinase. *Acta. Haematol.* 1990;84:139-43.
60. Hsia CH, Shen MC, Lin JS, Wen YK, Hwang KL, Cham TM. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. *Nutrition Research*. 2009;29:190-6.
61. Kurosawa Y, Nirengi S, Homma T, Esaki K, Ohta M. A single-dose of oral nattokinase potentiates thrombolysis and anti-coagulation profiles. *Scientific Reports*. 2015;5:11601.
62. Chen H, McGowan EM, Ren N, Lal S, Nassif N, Qu X, et al. Nattokinase: A promising alternative in prevention and treatment of cardiovascular diseases. *Biomarker Insights*. 2018;13:1-8.
63. Yatagai C, Maruyama M, Kawahara T, Sumi H. Nattokinase-promoted tissue plasminogen activator release from human cells. *Pathophysiol. Haemost. Thromb.* 2009;36:227-32.
64. Jang JY, Kim TS, Cai J, Kim J, Kim Y, Shin K. Nattokinase improves blood flow by inhibiting platelet aggregation and thrombus formation. *Lab. Anim. Res.* 2013;29:221-5.
65. Fujita M, Ohnishi K, Takaoka S, Ogaswara K, Fukuyama R, Nakamuta H. Antihypertensive effects of continuous oral administration of nattokinase and its fragment in spontaneously hypertensive rats. *Biol. Pharm. Bull.* 2011;34:1696-701.
66. Tanikawa T, Kiba Y, Yu J, Hsu K, Chen S, Ishii A, et al. Degradative effect of Nattokinase on spike protein of SARS-CoV-2. *Molecules*. 2022;27:5405.
67. Ren NN, Chen HJ, Li Y, Megowan GW, Lin YG. A clinical study on the effect of nattokinase on carotid artery atherosclerosis and hyperlipidemia [Chinese, Abstract in English]. *Zhonghua Yi Xue Za Zhi*. 2017;97:2038-42.
68. Chen H, Chen J, Zhang F, Li Y, Wang R, Zheng Q. Effective management of atherosclerosis progress and hyperlipidemia with nattokinase: A clinical study with 1,1062 participants. *Front. Cardiovasc. Med.* 2022;9:964977.
69. Fujita M, Hong K, Ito Y, Misawa S, Takeuchi N, Kariya K, et al. Transport of nattokinase across the rat intestinal tract. *Biol. Pharm. Bull.* 1995;18:1194-6.
70. Gallelli G, Di Mizio G, Palleria C, Siniscalchi A, Rubino P. Data recorded in real life support the safety of Nattokinase in patients with vascular diseases. *Nutrients*. 2021;13:2031.
71. Ramachandran L, Aqeel A, Jafri A, Sidhu Y, Djirdeh TM. Nattokinase-associated hemoperitoneum in an elderly woman. *Cureus*. 2022;13:e20074.
72. Chnag YY, Liu JS, Lai SL, Wu HS, Lan MY. Cerebellar hemorrhage provoked by combined use of nattokinase and aspirin in a patient with cerebral microbleeds. *Inter. Med.* 2008;47:467-9.
73. Metkar SK, Girigoswami A, Vijayashree R, Girigoswami K. Attenuation of subcutaneous insulin induced amyloid mass in vivo using lumbrokinase and serratiopeptidase. *International Journal of Biological Macromolecules*. 2020;163:128-34.
74. Metkar SK, Girigoswami A, Murugesan R, Girigoswami K. Lumbrokinase for degradation and reduction of amyloid fibrils associated with amyloidosis. *Journal of Applied Biomedicine*. 2017;15:96-104.
75. Metkar SK, Girigoswami A, Bondage DD, Shinde UG, Girigoswami K. The potential of lumbrokinase and serratiopeptidase for the degradation of AB 1-42 peptide - an invitro and insilico approach. *International Journal of Neuroscience*. 2022.
76. Chen Y, Liu Y, Zhang J, Zhou K, Zhang X, Dai H. Efficacy and safety of lumbrokinase plus aspirin versus aspirin alone for acute ischemic stroke (LUCENT): study protocol for a multicenter randomized controlled trial. *Trials*. 2022;23:285.

77. Pretorius E, Venter C, Laubshder G, Kotze M, Moremi K. Combined triple treatment of fibrin amyloid microclots and platelet pathology in individuals with long COVID/Post -acute sequelae of COVID-19 (PASC) can resolve their persistent symptoms. Research Square. 2021.
78. Gundry SR, Epstein J. Improvement in vascular reactivity by institution of a "green-Based" diet with supplemental fish oil and polyphenolic compounds, grape seed extract and Pycnogenol. *Arteriosclerosis, Thrombosis and Vascular Biology*. 2012;32:A310.
79. Saha JK, Raihan J. The binding mechanism of ivermectin and levosalbutamol with spike protein of SARS-CoV-2. Research Square. 2021.
80. Bello M. Elucidation of the inhibitory activity of ivermectin with host nuclear importin alpha and several SARS-CoV-2 targets. *Journal of Biomolecular Structure and Dynamics*. 2021.
81. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. *In Vivo*. 2020;34:3023-6.
82. Ci X, Li H, Yu Q, Zhang X, Yu L, Chen N, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen activated protein kinase pathway. *Fundamental & Clinical Pharmacology*. 2009;23:449-55.
83. DiNicolantonio JJ, Barroso-Arranda J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. *Open Heart*. 2020;7:e001350.
84. Yan S, Ci X, Chen N, Chen C, Li X, Chu X, et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. *Inflamm. Res*. 2011;60:589-96.
85. Nicolas P, Maia MF, Bassat Q, Kobylinski KC, Monteiro W. Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob. Health*. 2020;8:e92-e100.
86. Poenaru S, Abdallah SJ, Corrales-Medina V, Cowan J. COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. *Ther. Adv. Infectious Dis*. 2021;8:1-16.
87. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Okell T, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post hospital discharge. *EclinicalMedicine*. 2022;31:100683.
88. Booth NE, Myhill S, McLaren-Howard J. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Int. J. Clin. Exp. Med*. 2012;5:208-20.
89. Wood E, Hall KH, Tate W. Role of mitochondria, oxidative stress and the response to antioxidants in myalgic encephalomyelitis/Chronic fatigue syndrome: A possible approach to SARS-CoV-2 'long-haulers'? *Chronic Diseases and Translational Medicine*. 2021;7:14-26.
90. Brown JT, Saigal A, Karia N, Patel RK, Razvi Y, Steeden JA. Ongoing exercise intolerance following COVID-19: A magnetic resonance-Augmented Cardiopulmonary exercise Test Study. *J. Am. Heart Assoc*. 2022;11:e024207.
91. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin. Rheumatol*. 2014;33:451-9.
92. Toljan K, Vrooman B. Low-dose naltrexone (LDN) - Review of therapeutic utilization. *Med. Sci*. 2018;6:82.
93. Molina-Carballo A, Palacios-Lopez R, Jerez-Calero A, Agil A. Protective effect of melatonin administration against SARS-CoV-2 infection: A systematic review. *Current Issues in Molecular Biology*. 2022;44:31-45.
94. Hasan ZT, AlAtrakji MQ, Mehuaiden AK. The effect of melatonin on thrombosis, sepsis and mortality rate in COVID-19 patients. *International Journal of Infectious Diseases*. 2022;114:79-84.

95. Reiter RJ, Sharma R, Ma Q, Liu C, Manucha W, Abreu-Gonzalez P. Plasticity of glucose metabolism in activated immune cells: advantages for melatonin inhibition of COVID-19 disease. *Melatonin Res.* 2020;3:362-79.
96. Reiter RR, Sharma R, Castillo R, Marik PE, Rodriguez AD, Cardinali DP. Coronavirus-19, Monocyte/Macrophage glycolysis and inhibition by melatonin. *J. SARS-CoV2 COVID.* 2021;2:29-31.
97. Colunga Biancatelli RM, Berrill M, Mohammed YH, Marik PE. Melatonin for the treatment of sepsis: the scientific rationale. *J. Thorac. Dis.* 2020;12 (Suppl 1):S54-S65.
98. Rylander R. Bioavailability of magnesium salts - A review. *Journal of Pharmacy and Nutrition Sciences.* 2014;4:57-9.
99. Uysal N, Kizildag S, Yuce Z, Guvendi G, Kandis S, Koc B, et al. Timeline (Bioavailability) of magnesium compounds in hours: Which magnesium compound works best? *Biological Trace Element Research.* 2018.
100. Li W, Yu J, Liu Y, Huang X, Abumaria N, Zhu Y, et al. Elevation of brain magnesium prevents synaptic loss and reverses cognitive deficits in Alzheimer's disease mouse model. *Molecular Brain.* 2014;7:65.
101. Di Y, He YL, Zhao T, Huang X, Wu KW, liu SH, et al. Methylene blue reduces acute cerebral ischemic injury via the induction of mitophagy. *Mol. Med.* 2015;21:420-9.
102. Jiang Z, Watts LT, Huang S, Shen Q, Rodriguez P, Chen C. The effects of methylene blue on autophagy and apoptosis in MRI-defined normal tissue, ischemic penumbra and ischemic core. *PLoS ONE.* 2015;10:e0131929.
103. Xie L, Li W, Winters A, Yuan F, Jin K, Yang S. Methylene blue induces macroautophagy through 5' adenosine monophosphate-activated protein kinase pathway to protect neurons from serum deprivation. *Frontiers in Cellular Neuroscience.* 2013;7:56.
104. Peter C, Hongwan D, Kupfer A, Lauterburg BH. Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur. J. Clin. Pharmacol.* 2000;56:247-50.
105. Tucker D, Lu Y, Zhang Q. From mitochondrial function to neuroprotection - An emerging role for methylene blue. *Mol. Neurobiol.* 2018;55:5137-53.
106. Yang L, Youngblood H, Wu C, Zhang Q. Mitochondria as a target for neuroprotection: role of methylene blue and photobiomodulation. *Translational Neurodegeneration.* 2020;9:19.
107. Gonzalez-Lima F, Auchter A. Protection against neurodegeneration with low-dose methylene blue and near-infrared light. *Frontiers in Cellular Neuroscience.* 2015;9:179.
108. Rojas JC, Bruchey AK, Gonzalez-Lima F. Neurometabolic mechanisms for memory enhancement and neuroprotection of methylene blue. *Prog. Neurobiol.* 2012;96:32-45.
109. Heiskanen V, Pfiffner M, Partonen T. Sunlight and health; shifting the focus from vitamin D3 to photobiomodulation by red and near-infrared light. *Ageing Research Reviews.* 2022;61:101089.
110. Whitten A. *The Ultimate guide to red light therapy:* Archangel Ink; 2018.
111. Hobday RA, Cason JW. The open-air treatment of pandemic influenza. *Am. J. Public Health.* 2022;99 Suppl.2:S236-S42.
112. Lindqvist PG, Epstein E, Landin-Olsson M, Ingvar C, Nielsen K, stenbeck M, et al. Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort. *Journal of Internal Medicine.* 2014;276:77-86.
113. Hamblin MR. Mechanisms and application of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys.* 2017;4:337-61.
114. Yeager RL, Oleske DA, Sanders RA, Eells JT, Henshel DS. Melatonin as a principal component of red light therapy. *Medical Hypotheses.* 2007;69:372-6.

115. Aguida B, Pooam M, Ahmad M, Jourdan N. Infrared light therapy relieves TLR-4 dependent hyper-inflammation of the type induced by COVID-19. *Communicative & Integrative Biology*. 2021;14(1):200.
116. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. *BBA Clinical*. 2016;6:113-24.
117. Hamblin MR. Photobiomodulation for Alzheimer's disease: Has the light dawned? *Photonics*. 2019;6:77.
118. Cassano P, Petrie SR, Cusin C, Yeung A, Bui E, Baer L, et al. Transcranial photobiomodulation for the treatment of major depressive disorder. The ELATED-2 pilot trial. *Photomedicine and Laser Surgery*. 2018;36:634-46.
119. Nizamutdinov D, Qi X, Berman MH, Dougal G, Wu E, Yi SS, et al. Transcranial near infrared light stimulations improve cognition in patients with dementia. *Aging and Disease*. 2021;12.
120. Liebert A, Bicknell B, Markman W, Kiat H. A potential role for photobiomodulation therapy in disease treatment and prevention in the era of COVID-19. *Aging and Disease*. 2020;11:1352-62.
121. Pereira PC, de Lima CJ, Fernandes AB, Zangaro RA, Villaverde AB. Cardiopulmonary and hematological effects of infrared LED photobiomodulation in the treatment of SARS-COV2. *Journal of Photochemistry & Photobiology, B: Biology*. 2023;238:112619.
122. Gligorijevic N, Stanic-Vucinic D, Radomirovic M, Stajadinovic M, Khulal U, Nedic O. Role of resveratrol in prevention and control of cardiovascular disorders and cardiovascular complications related to COVID-19 disease: Mode of action and approaches explored to increase its bioavailability. *Molecules*. 2021;26:2834.
123. Pandey P, Rane JS, Chatterjee A, Kumar A, Khan R, Prakash A, et al. Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: an in silico study for drug development. *Journal of Biomolecular Structure and Dynamics*. 2020.
124. de Sa Coutinho D, Pacheco MT, Frozza RL, Bernardi A. Anti-inflammatory effects of resveratrol: Mechanistic insights. *International Journal of Molecular Sciences*. 2018;19:1812.
125. Park D, Jeong H, Lee MN, Koh A, Kwon O, Yang YR, et al. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. *Scientific Reports*. 2016;6:21772.
126. Kou X, Chen N. Resveratrol and natural autophagy regulator for prevention and treatment of Alzheimers disease. *Nutrients*. 2017;9:927.
127. De Santi C, Pietrabissa A, Spisni R, Mosca F, Pacifici GM. Sulphation of resveratrol, a natural compound present in wine, and its inhibition by natural flavonoids. *Xenobiotica*. 2000;30:857-66.
128. Yang JY, Della-Fera MA, Rayalam S, Ambati S, Hartzell DL, Park HJ, et al. Enhanced inhibition of adipogenesis and induction of apoptosis in 3T3-L1 adipocytes with combinations of resveratrol and quercetin. *Life Sciences*. 2008;82:1032-9.
129. Saeedi-Boroujeni A, Mahmoudian-Sani MR. Anti-inflammatory potential of Quercetin in COVID-19 treatment. *J. Inflamm*. 2021;18:3.
130. Chan EW, Wong CW, Tan YH, Foo JP, Wong SK. Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties. *Journal of Applied Pharmaceutical Science*. 2019;9:124-9.
131. Chang J, Rimando A, Pallas M, Camins A, Porquet D, Reeves J, et al. Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimers's disease. *Neurobiology of Aging*. 2012;33:2062-71.
132. Liu Y, You Y, Lu J, Chen X, Yang Z. Recent advances in synthesis, bioactivity, and pharmacokinetics of Pterostilbene an important analog of resveratrol. *Molecules*. 2020;25:5166.
133. Walle T. Bioavailability of resveratrol. *Annals of the New York Academy of Sciences*. 2011;1215:9-15.

134. Sathyapalan T, Manuchehri AM, Thatcher NJ, Rigby AS, Chapman T. The effect of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: A randomized, double-blind, crossover study. *J. Clin. Endocrinol. Metab.* 2020;96:1422-49.
135. Gutierrez-Castrellon P, Gandara-Marti T, Abreu AT, Nieto-Rufino CD, Lopez-Orduna E. Probiotic improves symptomatic and viral clearance in Covid-19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. *GUT Microbes.* 2022;14:e2018899.
136. Zuo T, Wu X, Wen W, Lan P. Gut microbiome alterations in COVID-19. *Genomics, Proteomics & Bioinformatics.* 2021.
137. Chen Y, Gu S, Chen Y, Lu H, Shi D, Guo J. Six-month follow-up of gut microbiota richness in patients with COVID-19. *Gut.* 2021.
138. Thomas R, Aldous J, Forsyth R, Chater A, Williams M. The influence of a blend of probiotic Lactobacillus and prebiotic inulin on the duration and severity of symptoms among individuals with COVID-19. *Infect. Dis. Diag. Treat.* 2022;5:12.
139. Lee CR, Zeldin DC. Resolvin infectious inflammation by targeting the host response. *N. Engl. J. Med.* 2015;373:2183-5.
140. Serhan CN. Novel pro-resolving lipid mediators in inflammation are leads for resolution physiology. *Nature.* 2014;510:92-101.
141. Kosmopoulos A, Bhatt L, Meglis G, Verma R, Pan Y. A randomized trial of Icosapent Ethyl in ambulatory patients with COVID-19. *iScience.* 2021;24:103040.
142. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369(9567):1090-8.
143. Harris WS. Understanding why REDUCE-It was positive-mechanistic overview of eicosapentaenoic acid. *Progress in Cardiovascular Diseases.* 2019;62:401-5.
144. Bhatt D, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N. Engl. J. Med.* 2019;380:11.
145. Kastelstein JJ, Stroes ES. FISHing for the miracle of eicosapentaenoic acid. *N. Engl. J. Med.* 2019;380:89-91.
146. Guo XF, Li KL, Li JM, Li D. Effects of EPA and DHA on blood pressure and inflammatory factors: a meta-analysis of randomized controlled trials. *Clinical Reviews in Food Science and Nutrition.* 2019;59:3380-93.
147. von Schacky C. Importance of EPA and DHA blood levels in brain structure and function. *Nutrients.* 2021;13:1074.
148. Cottin SC, Sanders TA, Hall WL. The differential effects of EPA and DHA on cardiovascular risk factors. *Proceeding of the Nutrition Society.* 2011;70:215-31.
149. Allaire J, Couture P, Leclerc M, Charest A, Marin J. A randomized, crossover, head to head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing PA to DHA (ComparED) study. *Am. J. Clin. Nutr.* 2016;104:280-7.
150. Izquierdo JL, Soriano JB, Gonzalez Y, Lumbreras S. Use of N-Acetylcysteine at high doses as an oral treatment for patients with COVID-19. *Science Progress.* 2022;105.
151. Shi Z, Puyo CA. N-Acetylcysteine to combat COVID-19: an evidence review. *Therapeutics and Clinical Risk Management.* 2020;16:1047-55.
152. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. *FASEB J.* 2020.

153. Schmitt B, Vicenzi M, Garrel C, Denis FM. Effects of N-acetylcysteine, oral glutathione (GSH) and a novel sublingual for of GSH on oxidative stress markers: A comparative crossover study. *Redox Biology*. 2015;6:198-205.
154. Allen J, Bradley RD. Effects of oral glutathione supplementation on systemic oxidative stress biomarkers in human volunteers. *Journal of Alternative & Complementary Medicine*. 2011;17:827-33.
155. Sinha R, Sinha I, Calcagnotto A, Trushin N, Haley JS. Oral supplementation with liposomal glutathione elevates body stores of glutathione and markers of immune function. *Eur. J. Clin. Nutr.* 2018;72:105-11.
156. Yoon JK, Frankel AE, Feun LG, Ekmekcioglu S, Kim KB. Arginine deprivation therapy for malignant melanoma. *Clinical Pharmacology Advances and Applications*. 2013;5:11-9.
157. Stang A, Robers J, Schonert B, Jockei KH, Speisberg A. The performance of the SARS-CoV-2 RT-PCR test as a tool for detecting SARS-CoV-2 infection in the population. *J. Infect.* 2021;83:244-5.
158. Islam MT, Guha B, Hosen S, Alam T, Shahadat S. Nigellalogy: A review on *Nigella Sativa*. *MOJ Bioequiv. Availab.* 2017;3:00056.
159. Ashraf S, Ashraf S, Ashraf M, Imran MA, Kalsoom L, Siddiqui UN, et al. Honey and *Nigella sativa* against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial. *medRxiv*. 2021.
160. Barbash IJ, Davis BS, Yabes JG, Seymour CW, Angus DC, Kahn JM. Treatment patterns and clinical outcomes after the introduction of the Medicare Sepsis Performance Measure (SEP-1). *Ann. Intern. Med.* 2021.
161. Fakhar-e-Alam Kulyar M, Li R, Mehmood K, Waqas M, Li K, Li J. Potential influence of *Nagella sativa* (Black cumin) in reinforcing immune system: A hope to decelerate the COVID-19 pandemic. *Phytomedicine*. 2021;85:153277.
162. Hannan MA. Black Cumin (*Nigella sativa* L.): A Comprehensive Review on Phytochemistry, Health Benefits, Molecular Pharmacology, and Safety. *Nutrients*. 2021;13(6).
163. Warner ME, Naranjo J, Pollard EM, Weingarten TN, Warner MA. Serotonergic medications, herbal supplements, and perioperative serotonin syndrome. *Can. J. Anaesth.* 2017;64:940-6.
164. Santamarina MG, Boisier D, Contreras R, Baque M, Volpacchio M. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. *Crit. Care*. 2020;24:395.
165. Mario L, Roberto M, Marta L, Teresa CM, Laura M. Hypothesis of COVID-19 therapy with sildenafil. *International Journal of Preventive Medicine*. 2020;11:76.
166. Santamarina MG, Beddings I, Martinez Lomakin F, Boisier Riscal D. Sildenafil for treating patients with COVID-19 and perfusion mismatch: a pilot randomized trial. *Crit. Care*. 2022;26:1.
167. Kniotek M, Boguska A. Sildenafil can affect innate and adaptive immune system in both experimental animals and patients. *Journal of Immunology Research*. 2017;2017:4541958.
168. Isidori AM, Giannetta E, Pofi R, Venneri MA, Gianfrilli D, Campolo F. Targeting the NO-cGMP-PDE5 pathway in COVID-19 infection. The DEDALO project. *Andrology*. 2021;9:33-8.
169. Al-kuraishy HM, Ali-Gareeb AI, Al-Niemi MS, Buhadily AK. COVID-19 and phosphodiesterase enzyme type 5 inhibitors. *J. Microsc. Ultrastruct.* 2022;8:141-5.
170. Reid PM, Borgstahl GE, Radhakrishnan P. Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and spike protein. *Clin. Transl. Med.* 2021;11:e281.
171. Tallei TE, Yelnetty A, Idroes R, Emran TB, Sippi W. An analysis based on molecular docking and molecular dynamics simulation study of Bromelain as anti-SARS-CoV-2 variants. *Front. Pharmacol.* 2021;12:717757.
172. Akhter J, Queromes G, Pillai K, Badar S, Frobert E, Valle SJ. The combination of bromelain and acetylcysteine (BromAc) synergistically inactivates SARS-CoV-2. *Viruses*. 2021;13:425.

173. Marik PE. Hydrocortisone, Ascorbic Acid and Thiamine (HAT therapy) for the treatment of sepsis. Focus on ascorbic acid. *Nutrients*. 2018;10:1762.
174. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. *Pharmacol. Therapeut.* 2018;189:63-70.
175. Colunga Biancatelli RM, Berrill M, Marik PE. The antiviral properties of vitamin C. *Expert Rev. Anti Infect. Ther.* 2020;18:99-101.
176. Miranda-Massari JR, Toro AP, Loh D, Rodriguez JR, Borges RM. The effects of vitamin C on the multiple pathological stages of COVID-19. *Life*. 2021;11:1341.
177. Holford P, Carr AC, Zawari M, Vizcaychipi MP. Vitamin C intervention for Critical COVID-19: A pragmatic review of the current level of evidence. *Life*. 2021;11:1166.
178. Madeo F, Eisenberg T, Pietrocola F, Kroemer G. Spermidine in health and disease. *Science*. 2018;359:410.
179. Eisenberg T, Abdellatif M, Schroeder S, Primessnig U, Stekovic S, Pendl T, et al. Cardioprotection and lifespan extension by natural polyamine spermidine. *Nat. Med.* 2016;22:1428-38.
180. Morselli E, Marino G, Bennetzen MV, Eisenberg T, Megalou E, Schroeder S, et al. Spermidine and resveratrol induce autophagy by distinct pathways converging on the acetylproteome. *J. Cell. Biol.* 2022;192:615-29.
181. Kiechl S, Pechlaner R, Willeit P, Notdurfier M, Paulweber B, Willeit K, et al. Higher spermidine intake is linked to lower mortality: a prospective population-based study. *Am. J. Clin. Nutr.* 2018;108:371-80.
182. Nowotarski SL, Woster PM, Casero RA. Polyamines and cancer: implications for chemoprevention and chemotherapy. *Expert Rev. Mol. Med.* 2014.
183. Zheng L, Xie Y, Sun Z, Zhang R, Ma Y, Xu J, et al. Serum spermidine in relation to risk of stroke: A multilevel study. *Front. Nutr.* 2022;9:843616.
184. Sabel BA, Flammer J, Merabet LB. Residual vision activation and the brain-eye-vascular triad: Dysregulation, plasticity and restoration in low vision and blindness - a review. *Restorative Neurology and Neuroscience*. 2018;36:767-91.
185. Siegert A, Diedrich L, Antal A. New methods, old brains - A systematic review on the effects of tDCS on cognition of elderly people. *Frontiers in Human Neuroscience*. 2021;15:730134.
186. Teselink J, Bawa KK, Koo GK, Sankhe K, Liu CS, Oh P. Efficacy of non-invasive brain stimulation on global cognition and neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review. *Ageing Research Reviews*. 2021;72:101499.
187. Sabel BA, Zhou W, Huber F, Schmidt F, Sabel K. Non-invasive brain microcurrent stimulation therapy of long-COVID-19 reduces vascular dysregulation and improves visual and cognitive impairment. *Restorative Neurology and Neuroscience*. 2021;39:393-408.
188. Ahorsu DK, Adjaottor ES, Lam BY. Intervention effect of non-invasive brain stimulation on cognitive functions among people with traumatic brain injury: A systematic review and meta-analysis. *Brain Sci*. 2021;11:840.
189. Finisguerra A, Borgatti R, Urgesi C. Non-invasive brain stimulation for the rehabilitation of children and adolescents with neurodevelopmental disorders: A systematic review. *Frontiers in Psychology*. 2019;10:135.
190. Chen JJ, Zeng BS, Wu CN, Stubbs B, Carvalho AF, Su KP. Association of central noninvasive brain stimulation interventions with efficacy and safety in tinnitus management. A meta-analysis. *JAMA Otolaryngol. Head Neck Surg.* 2020;146:801-9.
191. Chen JJ, Zeng BY, Lui CC, Chen TY, Chen YW, Tseng PT. Pfizer-BioNTech COVID-19 vaccine-associated tinnitus and treatment with transcranial magnetic stimulation. *QJM*. 2022.

192. Sanabria-Mazo JP, Montero-Marin J, Feliu-Soler A, Gasion V, Navarro-Gil M. Mindfulness-based program plus amygdala and insula retraining (MAIR) for the treatment of women with fibromyalgia: A pilot randomized controlled trial. *J. Clin. Med.* 2020;9:3246.
193. Yong SJ. Long-haul COVID-19: Putative pathophysiology, risk factors, and treatments. *medRxiv.* 2020.
194. Shu C, Feng S, Cui Q, Cheng S, Wang Y. Impact of Tai Chi on CRP, TNF-alpha and IL-6 in inflammation: a systematic review and meta-analysis. *Ann. Palliat. Med.* 2021;10:7468-6478.
195. Zhang Z, Ren JG, Guo JL, An L, Li S, Zhang ZC. Effects of Tai Chi and Qigong on rehabilitation after COVID-19: a protocol for systematic review and meta-analysis. *BMJ Open.* 2022;12:e059067.
196. Falkenberg RI, Eising C, Peters ML. Yoga and immune system functioning: a systematic review of randomized controlled trials. *J. Behav. Med.* 2018;41:467-82.
197. Robbins T, Gonevski M, Clark C, Sharma K, Magar A. Hyperbaric oxygen therapy for the treatment of long COVID: early evaluation of a highly promising intervention. *Clinical Medicine.* 2021;21:e629-e32.
198. Oliaei S, Mehrtak M, Karimi A, Noori T, Shojaei A, Dadras O. The effects of hyperbaric oxygen therapy (HBOT) on coronavirus disease-2019 (COVID-19): a systematic review. *Eur. J. Med. Res.* 2021;26:96.
199. Senniappan K, Jeyabalan S, Rangappa P, Kanchi M. Hyperbaric oxygen therapy: Can it be a novel supportive therapy in COVID-19? *Indian Journal of Anaesthesia.* 2020;64:835-41.
200. Kjellberg A, De Maio A, Lindholm P. Can hyperbaric oxygen safely serve as an anti-inflammatory treatment for COVID-19? *Medical Hypotheses.* 2020;144:110224.
201. Hadanny A, Abbott S, Suzin G, Bechor Y, Efrati S. Effect of hyperbaric oxygen therapy on chronic neurocognitive deficits of post-traumatic brain injury patients: retrospective analysis. *BMJ Open.* 2018;8:e023387.
202. Han CH, Zhang PX, Xu WG, Li RP. Polarization of macrophages in the blood after decompression in mice. *7. 2017(236):240.*
203. De Maio A, Hightower LE. COVID-19, acute respiratory distress syndrome (ARDS), and hyperbaric oxygen therapy (HBOT): what is the link? *Cell Stress & Chaperones.* 2020;25:717-20.
204. Buras JA, Holt D, Orlow D, Belikoff B, Pavildes S, Reenstra WR. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. *Crit. Care Med.* 2006;34:2624-9.
205. Tezgin D, Giardina C, Perdrizet GA, Hightower LE. The effect of hyperbaric oxygen on mitochondrial and glycolytic energy metabolism: the caloristasis concept. *Cell Stress and Chaperones.* 2020;25:667-77.
206. Zilberman-Itskovich S, Catalogna M, Sasson E, Hadanny A, Lang E, Finci S, et al. Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial. *Scientific Reports.* 2022;12:11252.
207. Mogil RJ, Kaste SC, Ferry RJ, Hudson MM, Howell CR. Effect of low-magnitude, high-frequency mechanical stimulation on BMD among young childhood cancer survivors. A randomized clinical trial. *JAMA Oncol.* 2016;2:908-15.
208. Misra HS, rajpurohit YS, Khairnar NP. Pyrroloquinoline-quinone and its versatile roles in biological processes. *J. Biosci.* 2012;37:312-25.
209. Akagawa M, Nakano M, Ikemoto K. Recent progress in studies on the health benefits of pyrroloquinoline quinone. *Bioscience, Biotenchnology, and Biochemistry.* 2016;80:13-22.
210. Hamilton D, Jensen GS. Nutraceutical support of mitochondrial function associated with reduction of long-term fatigue and inflammation. *Alternative Therapies in Health & Medicine.* 2021;27:8-18.
211. Nicolson GL, Settineri R, Ellithorpe R. Lipid replacement therapy with a glycolipid formulation of NADH and CoQ10 significantly reduces fatigue in intractable chronic fatiguing

- illnesses and chronic lyme disease patients. *International Journal of Clinical Medicine*. 2012;3:163-70.
212. Chohanadisai W, Bauerly KA, Tchaparian E, Wong A, Rucker RB. Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression. *J. Biol. Chem.* 2010;285:142-52.
 213. Nicolson GL, Settineri R. Lipid replacement therapy: a functional food approach with new formulations for reducing cellular oxidative damage, cancer-associated fatigue and the adverse effects of cancer therapy. *Functional Foods in Health and Disease*. 2011;1:135-60.
 214. Nicolson GL, Rosenblatt S, de Mattos GF, Settineri R, Breeding PC, Ash ME. Clinical uses of membrane lipid replacement supplements in restoring membrane function and reducing fatigue in chronic disease and cancer. *Discoveries*. 2016;4:e54.
 215. Shukla AM, Shukla AW. Expanding horizons for clinical applications of chloroquine, hydroxychloroquine and related structural analogues. *Drugs in Context*. 2019;8:2019-9-1.
 216. Plantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic and neurological diseases: A mini review. *Clin. Drug Invest.* 2018;38:653-71.
 217. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus*. 2008;17:271-3.
 218. de Moreuil C, Alavi Z, Pasquier E. Hydroxychloroquine may be beneficial in preeclampsia and recurrent miscarriage. *Br. J. Clin. Pharmacol.* 2020;86:39-49.
 219. Siso A, Ramos-Casals M, Bove A, Soria N, Testi A, Plaza J. Previous antimalarial therapy in patients diagnosed with lupus nephritis: Influence on outcomes and survival. *Lupus*. 2008;17:281-8.
 220. Servy EJ, Jacquesson-Fournols L, Cohen M, Menezo YJ. MTHFR isoforms carriers. 5-MTHF (5-methyl tetrahydrofolate) vs folic acid: a key to pregnancy outcome: a case series. *Journal of Assisted Reproduction and Genetics*. 2018;35:1431-5.
 221. Jamme M, Mazeraud A. Plasmapheresis efficiency in Coronavirus disease 2019: More related to what you add and not what you take away? *Crit. Care Med*. 2021.
 222. Patidar GK, Land KJ, Vrieling H, Dann EJ, Spitalnik SL. Understanding the role of therapeutic plasma exchange in COVID-19: preliminary guidance and practices. *Vox Sanguinis*. 2021.
 223. Hashemian SM, Shafiq N, Afzal G, Jamaati H, Tabarsi P, Marjani M. Plasmapheresis reduces cytokine and immune cell levels in COVID-19 patients with acute respiratory distress syndrome (ARDS). *Pulmonary*. 2021;27:486-92.
 224. Balaghli S, Dabbaghi R, Eshghi P, Mousavi SA, Heshmati F, Mohammadi S. Potential of therapeutic plasmapheresis in treatment of COVID-19 patients: immunopathogenesis and coagulopathy. *Transfusion and Apheresis Science*. 2020;59:102993.
 225. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19. *Crit. Care*. 2020;24:128.
 226. Morath C, Weigand MA, Zeier M, Speer C, Tiwari-Heckler S. Plasma exchange in critically ill COVID-19 patients. *Crit. Care*. 2020;24:481.
 227. Fernandez J, Gratacos-Gines J, Olivas P, Costa M, Nieto S, Mateo D. Plasma exchange: An effective rescue therapy in critically ill patients with Coronavirus Disease 2019 infection. *Crit. Care Med*. 2020.
 228. Gucyetmez B, Atalan HK, Sertdemir I, Cakir U, Telci L. Therapeutic plasma exchange in patients with COVID-19 pneumonia in intensive care unit: a retrospective study. *Crit. Care*. 2020;24:492.

229. Kiproff DD, Herskowitz A, Kim D, Lieb M, Liu C, Watanabe E. Case report. Therapeutic and immunomodulatory effects of plasmapheresis in long-haul COVID. *F1000Research*. 2022;10:1189.
230. Pitt B, Sutton NR, Wang Z, Holinstat M. Potential repurposing of the HDAC inhibitor valproic acid for patients with COVID-19. *Eur. J. Pharmacol.* 2021;898:173988.
231. Unal G, Turan B, Balcioglu YH. Immunopharmacological management of COVID-19: Potential therapeutic role of valproic acid. *Medical Hypotheses*. 2020;14:109891.
232. Wu C, Li A, Leng Y, Kang J. Histone deacetylase inhibition by sodium valproate regulates polarization of macrophage subsets. *DNA and Cell Biology*. 2012;31:592-9.
233. Larsson P, Alwis I, Niego B, Glise L, Daglas M, Jackson SP. Valproic acid selectively increases vascular endothelial tissue -type plasminogen activator production and reduces thrombus formation in the mouse. *J. Thromb. Haemost.* 2016;14:2496-508.
234. Koriyama Y, Sugitani K, Ogai K, Kato S. Heat shock protein 70 induction by valproic acid delays photoreceptor cell death by N-methyl-N-nitrosourea in mice. *J. Neurochem.* 2014;130:707-19.
235. Fleisher AS, Truran D, Mai JT, Langbaum JB, Aisen PS, Cummings JL. Chronic divalproex sodium use and brain atrophy in Alzheimers disease. *Neurology*. 2011;77:1263-71.
236. Faggi L, Pignataro G, Parrella E, Porrini V, Cepparulo P, Cuomo O, et al. Synergistic association of valproate and resveratrol reduces brain injury in ischemic stroke. *Int. J. Mol. Sci.* 2018;19:172.
237. Chen Y, Lin PX, Hsieh GL, Peng CC, Peng RY. The proteomic and genomic teratogenicity elicited by valproic acid is preventable with resveratrol and alpha-tocopherol. *PLoS ONE*. 2014;9:e116534.
238. Santos-terra J, Deckmann I, Carello-Collar G, Nunes GD, Riesgo R, Gottfried C. Resveratrol prevents cytoarchitectural and interneuronal alterations in the valproic acid model of autism. *Int. J. Mol. Sci.* 2022;23:4075.
239. Cohen M. Turning up the heat on COVID-19: heat as a therapeutic intervention. *F1000Research*. 2020;9:292.
240. Ramirez FE, Sanchez A, Pirskanen AT. Hydrothermotherapy in prevention and treatment of mild to moderate cases of COVID-19. *Medical Hypotheses*. 2021;146:110363.
241. Hussain J, Cohen M. Clinical effects of regular dry sauna bathing: A systematic review. *Evidence-Based Complementary and Alternative Medicine*. 2018;2018:1857413.
242. Laukkanen JA, Laukkanen T, Kunustor SK. Cardiovascular and other health benefits of sauna bathing: A review of the evidence. *Mayo Clin. Proc.* 2018;93:1111-21.
243. Laukkanen T, Khan H, Zaccardi F, Laukkanen JA. Association between sauna bathing and fatal cardiovascular and all-cause mortality. *JAMA Intern. Med.* 2015;175:542-8.
244. Janssen CW, Lowry CA, Mehl MR, Allen JJ, Kelly KL. Whole-body hyperthermia for the treatment of major depressive disorder. A randomized Clinical Trial. *JAMA Psychiatry*. 2016;73:789-95.
245. Laukkanen T, Kunustor S, Kauhanen J, Laukkanen JA. Sauna bathing is inversely associated with dementia and Alzheimer's disease in middle-aged Finnish men. *Age & Ageing*. 2017;46:245-9.
246. Kunustor SK, Khan H, Laukkanen T, Laukkanen JA. Joint associations of sauna bathing and cardiorespiratory fitness on cardiovascular and all-cause mortality risk: a long-term prospective cohort study. *Annals of Medicine*. 2018;50:139-46.
247. Scoon GS, Hopkins WG, Mayhew S, Cotter JD. Effect of post-exercise sauna bathing on the endurance performance of competitive male runners. *Journal of Science and Medicine in Sport*. 2007;10:259-62.
248. Kihara T, Biro S, Imamura M, Yoshifuku S, Takasaki K, Ideda Y. Repeated sauna treatment improves vascular endothelial and cardiac function in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 2002;39:754-9.

249. Kallstrom M, Soveri I, Oldgren J, LaukkANEN j, Ichiki T, tEl c. Effects of sauna bath on heart failure: A systematic review and meta-analysis. *Clinical Cardiology*. 2018;41:1491-501.
250. Amano K, Yanagihori R, tEl c. Waon therapy is effective as the treatment of myalgic encephalomyelitis/Chronic fatigue syndrome. *J. Jpn. Soc. Balneol. Climatol. Phys. Med.* 2015;78:285-302.
251. Soejima Y, Munemoto T, Masuda A, Uwatoko Y, Miyata M, tEl c. Effects of Waon therapy on chronic fatigue syndrome: A pilot study. *Intern. Med.* 2015;54:333-8.
252. Shevchuk N. Adapted cold shower as a potential treatment for depression. *Medical Hypotheses*. 2008;70:995-1001.
253. Mooventhan A, Nivethitha L. Scientific evidence-based effects of hydrotherapy on various systems of the body. *North American Journal of Medical Sciences*. 2014;6:199-209.
254. Patterson B, Yogendra R, Guevara-Coto J, Osgood E, Bream J, Parikh P. Targeting the monocytic-endothelial-platelet axis with maraviroc and pravastatin as a therapeutic option to treat long COVID/Post-acute sequelae of COVID (PASC). *Research Square*. 2022.
255. Houghton CA, Fassett RG, Coombes JS. Sulforane: translational research from laboratory bench to clinic. *Nutrition Reviews*. 2013;71:709-26.
256. Kim JK, Park SU. Current potential health benefits of sulforaphane. *EXCLI Journal*. 2016;15:571-7.
257. Mokhtari RB, Baluch N, Homayouni TS, Kumar S, Yeger H. The role of sulforaphane in cancer chemoprevention and health benefits: a mini-review. *J. Cell Commun. Signal*. 2018;12:91-101.
258. Clarke JD, Hsu A, Riedl K, Bella D, Stevens JF, Ho E. Bioavailability and inter-conversion of sulforaphane and erucin in human subjects consuming broccoli sprouts or broccoli supplement in a cross-over study design. *Pharmacol. Res.* 2011;64:456-63.
259. Khandouzi N, Shidfar F, Rajab A, Rahideh T, Hosseini P, Taheri MM. The effects of Ginger on fasting blood sugar, hemoglobin A1C, Apolipoprotein B, Apolipoprotein A-1 and malondialdehyde in type 2 diabetic patients. *Iranian Journal of Pharmaceutical Research*. 2015;14:131-40.
260. Gonzalez-Castejon M, Visioli F, Rodrigues-Casado A. Diverse biological activities of dandelion. *Nutrition Reviews*. 2012;70:534-47.
261. Olas B. New perspectives on the effect of dandelion, its food products and other preparations on the cardiovascular system and its diseases. *Nutrients*. 2022;14:1350.
262. Tran HT, Gigl M, Le NP, Dawid C, Lamy E. In Vitro effect of *Taraxacum officinale* leaf aqueous extract on the interaction between ACE2 cell surface receptor and SARS-CoV-2 spike protein D614 and four mutants. *Pharmaceuticals*. 2021;14:1055.
263. "Taraxaci folium" and "taraxaci radix". *Monography on the Medicinal Uses of Plant Drugs*. End.ed. ed. Stuttgart, Germany: Thieme; 2003:499-504.
264. Harasstaini OA, Moin S, Tham CL, Liew CY, Ismail N, Israf DA. Flavonoid combinations cause synergistic inhibition of proinflammatory mediator secretion from lipopolysaccharide-induced RAW 264.7 cells. *Inflammation Research*. 2010;59:711-21.
265. Marforio TD, Mattioli EJ, Zerbetto F, Calvaresi M. Fullerenes against COVID-19: Repurposing C50 and C70 to clog the active site of SARS-CoV-2 protease. *Molecules*. 2022;27:1916.
266. Hurmach Vv, Platonov MO, Prylutska SV, Scharff P, Ritter U. C60 fullerene against SARS-CoV-2 coronavirus: an in silico insight. *Scientific Reports*. 2021;11:17748.
267. Geerts M, de Greef BT, Sopacua M, Faber CG. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2022;96:e2534-e45.
268. Kinnunen S, Hyyppa S, Oksala N, Laaksonen DE, Hannila ML, Sen CK. alpha-Lipoic acid supplementation enhances heat shock protein production and decreases post exercise lactic acid concentrations in exercised standardbred trotters. *Research in Veterinary Science*. 2009;87:462-7.

269. Elbadawy AM, Elmoniem RO, Elsayed AM. Alpha lipoic acid and diabetes mellitus: potential effects on peripheral neuropathy and different metabolic parameters. *Alexandria Journal of Medicine*. 2021;57:113-20.
270. Sanna A, Firinu D, Zavattari P, Valera P. Zinc status and autoimmunity: A systematic review and meta-analysis. *Nutrients*. 2018;10:68.
271. Anju M, Maiya AG, Hande M. Low level laser therapy for patients with painful diabetic peripheral neuropathy - A systematic review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019;13:2667-70.
272. Leonard DR, Farooqi MH, Myers S. Restoration of sensation, reduced pain, and improved balance in subjects with diabetic peripheral neuropathy. A double-blind, randomized, placebo-controlled study with monochromatic near-infrared treatment. *Diabetes Care*. 2004;27:168-72.
273. Hong J, Barnes MJ, Kessler NJ. Case study: Use of vibration therapy in the treatment of diabetic peripheral small fiber neuropathy. *International Journal of Diabetes Mellitus*. 2015;3:72-5.
274. Kessler NJ, Hong J. Whole body vibration therapy for painful diabetic peripheral neuropathy: A Pilot study. *Journal of Bodywork & Movement Therapies*. 2013;17:518-22.
275. Diep PT, Buemann B, Uvnas-Moberg K. Oxytocin, a possible treatment for COVID-19? everything to gain, nothing to lose. *Clinical Neuropsychiatry*. 2020;17:192-5.
276. Leuner B, Caponiti JM, Gould E. Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. *Hippocampus*. 2012;22:861-8.
277. Lee HJ, Macbeth AH, Pagani J, Young WS. Oxytocin: the great facilitator of life. *Prog. Neurobiol*. 2009;88:127-51.
278. MacDonald K, McDonald TM. The peptide that binds: A systematic review of oxytocin and its prosocial effects in humans. *Harv. Rev. Psychiatry*. 2010;18:1-21.
279. Matsushita H, Latt HM, Koga Y, Nishiki T, Matsui H. Oxytocin and stress: Neural mechanisms, stress-related disorders, and therapeutic approaches. *Neuroscience*. 2019;417:1-10.
280. Tzabazis A, Kori S, Mechanic J, Miller J, Pascual C, Carson D. Oxytocin and migraine headache. *Headache*. 2017;57:64-75.
281. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine - interactions of oestrogen, oxytocin and CGRP. *Nature Reviews Neurology*. 2021;17:621-33.
282. Horn S, Bathgate R, Lioutas C, Bracken K, Ivell R. Bovine endometrial epithelial cells as a model system to study oxytocin receptor regulation. *Human Reproduction Update*. 1998;4:605-14.
283. Freitag K, Sterczyk N, Wendlinger S, Schulz J, Ralser M, Fleck L, et al. Spermidine reduces neuroinflammation and soluble amyloid beta in an Alzheimer's disease mouse model. *Journal of Neuroinflammation*. 2022;19:172.
284. Schroeder S, Hofer S, Zimmermann A, Pechlaner R, Pendl T, Bergmann M, et al. Dietary spermidine improves cognitive function. *Cell Reports*. 2021;35:108985.
285. Blaylock RL. Vaccines, depression, and neurodegeneration after age 50 years: another reason to avoid the recommended vaccines. *Medical Veritas*. 2008;5:1742-7.
286. Pappa S, Barmparessou Z, Sakka E, Sakkas N, Pappas A. Depression, Insomnia and post-traumatic stress disorder in COVID-19 survivors: Role of gender and impact on quality of life. *J. Pers. Med*. 2022;12:486.
287. Porter C, Favara M, Scott D, Craske MG, Stein A. Impact of the COVID-19 pandemic on anxiety and depression symptoms of young people in the Global South: evidence from a four-country cohort study. *medRxiv*. 2021.
288. Lau T, Horschitz S, Berger S, Bartsch D, Schloss P. Antidepressant-induced internalization of the serotonin transporter in serotonergic neurons. *FASEB J*. 2008;22:1702-14.
289. Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: a review of the clinical evidence and the possible mechanisms involved. 4. 2013(45).

290. Hengartner MP, Ploderi M. Newer-generation antidepressants and suicide risk in randomized controlled trials: A re-analysis of the FDA database. *Psychother. Psychosom.* 2019;88:247-8.
291. Hengartner MP, Amendola S, Kaminski JA. Suicide risk with selective serotonin reuptake inhibitors and other new-generation antidepressants in adults: a systematic review and meta-analysis of observational studies. *J. Epidemiol. Community Health.* 2021;75:523-30.
292. Breggin PR. Fluvoxamine as a cause of stimulation, mania and aggression with a critical analysis of the FDA-approved label. *International Journal of Risk & Safety Medicine.* 2001;14:71-86.
293. Antidepressants and Violence: the Numbers, RxISK. August 17, 2015. <https://rxisk.org/antidepressants-and-violence-the-numbers/>; RxISK; 2022.
294. Levenson CW. Zinc: The new antidepressant? *Nutrition Reviews.* 2006;64:39-42.
295. Nowak G, Szewczyk B, Pilc A. Zinc and depression. An update. *Pharmacological Reports.* 2005;57:713-8.
296. Cereda G, Ciappolino V, Boscutti A, Cantu F, Enrico P, Oldani L. Zinc as a neuroprotective nutrient for COVID-19-related neuropsychiatric manifestations: A literature review. *Adv. Nutr.* 2022;13:66-79.
297. Ahmed A, Ghit A, Houjak A, Elkazzaz M. Role of zinc and zinc ionophores in brain health and depression especially during the COVID-19 pandemic. In: Palmero S, Olivier B, eds. *COVID-19 Pandemic, mental health and neuroscience- New Scenarios for understanding and treatment*: IntechOpen; 2022.
298. Ranjbar E, Kasaei MS, Mohammad-Shirazi M, Shams J, Mostafavi SA. Effects of zinc supplementation in patients with major depression: A randomized clinical trial. *Iranian J. Psychiatry.* 2013;8:73-9.
299. Liu S, Sheng J, Li B, Zhang X. Recent advances in non-invasive brain stimulation for major depressive disorder. *Frontiers in Human Neuroscience.* 2017;11:526.
300. Brononi AR, Sampaio-Junior B, Moffa AH, Aparicio L, Gordon P, Klein I, et al. Noninvasive brain stimulation in psychiatric disorders: a primer. *Brazilian Journal of Psychiatry.* 2019;4:70-81.
301. Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. *Annals of the New York Academy of Sciences.* 2017;1394:31-54.
302. Mutz J, Edgcumbe DR, Brunoni AR, Fu CH. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. *Neuroscience and Biobehavioral Reviews.* 2018;92:291-303.
303. McClure D, Greenman SC, Koppulu SS, Varvara M, Yaseen ZS, Galynker II. A pilot study of safety and efficacy of cranial electrotherapy stimulation in treatment of bipolar II depression. *J. Nerv. Ment. Dis.* 2015;203:827-35.
304. Alda M, McKinnon M, Blagdon R, Garnham J, MacLellan S, Hajek T. Methylene blue treatment for residual symptoms of bipolar disorder: randomised crossover study. *British Journal of Psychiatry.* 2017;210:54-60.
305. Naylor GJ, Smith AH, Connelly P. A controlled trial of Methylene Blue in severe depressive illness. *Biological Psychiatry.* 1987;22:657-9.
306. Askalsky P, Losifescu DV. Transcranial photobiomodulation for the management of depression: Current perspectives. *Neuropsychiatric Disease and Treatment.* 2019;15:3255-72.
307. Benedetti F, Colombo C, Barbini B, Campori E, Smeraldi E. Morning sunlight reduces length of hospitalization in bipolar depression. *J. Affective Disorders.* 2001;62:221-3.
308. Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. *Behavioral and Brain Function.* 2009;5:46.

309. Safhi MM, Qumayri HM, Masmali AU, Siddiqui R, Alam MF. Thymoquinone and fluoxetine alleviate depression via attenuating oxidative damage and inflammatory markers in type-2 diabetic rats. *Archives of Physiology & Biochemistry*. 2019;125(2):150-5.
310. Forster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends in Neurosciences*. 2013;38:305-12.
311. Lach G, Schellekens H, Dinan TG, Cryan JF. Anxiety, depression and the microbiome: A role for Gut peptides. *Neurotherapeutics*. 2018;15:36-59.
312. Sharon G. Human Gut Microbiota from Autism Spectrum Disorder Promote Behavioral Symptoms in Mice. *Cell*. 2019;177(6):1600-18.
313. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. *Eur. J. Clin. Nutr.* 2007;61:355-61.
314. Rao AV, Basted AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathogens*. 2009;1:6.
315. Din AU, Mazhar M, Waseem M, Ahmad w, Bibi A. SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotic role. *Biomedicine & Pharmacotherapy*. 2021;133:110947.
316. Hazan S, Stollman N, Bozkurt H, Dave S, Daniels J, Borody TJ. Lost microbes of COVID-19: Bifidobacterium, Faecalibacterium depletion and loss of microbiome diversity associated with SARS-CoV-2 infection severity. *BMJ Open Gastroenterology*. 2022;9:e000871.
317. Mao YH, Xu Y, Zhao FS, Wang ZM, Zhao M. Protective effects of konjac glucomannan on gut microbiome with antibiotic perturbation in mice. *Carbohydrate Polymers*. 2022;290:119476.
318. Zhang Y, Zhao Y, Yang W, Song G, Zhong P, Ren Y. Structural complexity of Konjac glucomannan and its derivatives governs the diversity and outputs of gut microbiota. *Carbohydrate Polymers*. 2022;292:119639.
319. de Falco B, Amato M, Lanzotti V. Chia seeds products: an overview. *Phytochemistry Reviews*. 2017;16:745-60.
320. Mostafa-Hedeab G, Al-kuraishy HM, Al-Gareeb AA, Jeandet P, Saaad HM, El-Saber Batiha G. A raising dawn of pentoxifylline in the management of inflammatory disorders in Covid-19. *Inflammopharmacology*. 2022.
321. Ng WK, Rosenblatt Y, Brock GB, O'Gorman DB, Gan BS. Phosphodiesterase inhibitors in vascular ischemia: A case report and review of their use in ischemic conditions. *Can. J. Plast. Surg.* 2010;18:e5-e9.
322. Yang YK. Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. *Clinica Chimica Acta*. 2015;450:83-9.
323. Yuan S, Schmidt HM, Wood KC, Straub AC. CoenzymeQ in cellular redox regulation and clinical heart failure. *Free Radical Biology and Medicine*. 2021;167:321-34.
324. Yin YJ, Zeng SL, Li YW, Wu Z, Huang DJ. The effect of coenzyme Q10 plus trimetazidine on acute viral myocarditis treatment. *Am. J. Transl. Res.* 2021;13:13854-61.
325. Gutierrez-Mariscal FM, de al Cruz-Ares S, Torres-Pena JD, Alcalá-Díaz JF. Coenzyme Q10 and cardiovascular diseases. *Antioxidants*. 2021;10:906.
326. Sakamoto A, Saotome M, Iguchi K, Maekawa Y. Marine-derived omega-3 polyunsaturated fatty acids and heart failure: Current understanding for basic to clinical relevance. *Int. J. Mol. Sci.* 2019;20:4025.
327. Toko H, Morita H, Katakura M, Hashimoto M, Ko T, Bujo S, et al. Omega-3 fatty acid prevents the development of heart failure by changing fatty acid composition in the heart. *Scientific Reports*. 2020;10:15553.

328. Liu J, Meng Q, Zheng L, Yu P, HU H, Zhuang R, et al. Effect of omega-3 polyunsaturated fatty acids on left ventricular remodeling in chronic heart failure: a systematic review and meta-analysis. *Br. J. Nutr.* 2022.
329. Usami O, Saitoh H, Ashino Y, Hattori T. Acyclovir reduces the duration of fever in patients with infectious mononucleosis-like illness. *Tohoku J. Experi. Med.* 2013;229:137-42.
330. Verma D, Thompson J, Swaminathan S. Spironolactone blocks Epstein-Barr virus production by inhibiting EBV SM protein function. *PNAS.* 2016;113:3609-14.
331. Griffith RS, Wlask DE, Myrmet KH, Thompson RW. Success of L-Lysine therapy in frequently recurrent Herpes simplex infection. *Treatment and prophylaxis. Dermatologica.* 1987;175:183-90.
332. Griffith RS, Norins AL, Kagan C. A multicentered study of Lysine therapy in Herpes simplex infection. *Dermatologica.* 1978;156:257-67.
333. Andreu S, Ripa I, Bello-Morales R, Lopez-Guerrero JA. Valproic acid and its amidic derivatives as new antivirals against Alphaherpesviruses. *Viruses.* 2020;12:1356.
334. Gorres KL, Daigle D, Mohanram S, Mcinerney GE, Lyons DE. Valpromide inhibits Itic cycle reactivation of Epstein-Barr Virus. *mBio.* 2016;7:e00113-e6.
335. Ornaghi S, Davis JN, Gorres KL, Miller G, Paidas MJ. Mood stabilizers inhibit cytomegalovirus infection. *Virology.* 2016;499:121-35.
336. Berg K, Bolt G, Andersen H, Owen TC. Zinc potentiates the antiviral action of human IFN-alpha tenfold. *J. Interferon Cytokine Res.* 2001;21:471-4.
337. Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA. Zinc and respiratory tract infections: Perspectives for COVID-19. *Int. J. Mol. Med.* 2020;46:17-26.
338. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, Ortiz M, O'Sullivan CK. Zinc ionophore activity of Quercetin and Epigallocatechin-gallate: From Hepa 1-6 cells to a liposome model. *J. Agric. Food Chem.* 2014;62:8085-93.
339. Langguth B. Treatment of tinnitus. *Curr. Opin. Otolaryngol. Head Neck Surg.* 2015;23:361-8.
340. Langguth B. Pharmacological approaches to the treatment of tinnitus. *Drug Discovery Today.* 2010;15:300-5.
341. Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic approaches to the treatment of tinnitus. *Ann. Rev. Pharmacol. Toxicol.* 2019;59:291-313.
342. MartinezDevesda P, Waddell A, Perera R, Theodoulou M. Cognitive behavioral therapy for tinnitus (Review). *Cochrane Database of Syst. Rev.* 2007(CD005233).
343. Sullivan M, Katon W, Russo J, Dobie R, Sakai C. A randomized trial of nortriptyline for severe chronic tinnitus effects on depression, disability, and tinnitus symptoms. *Archives of Internal Medicine.* 1993;153:2251-9.
344. Bayar N, Boke B, Turan E, Belgin E. Efficacy of amitriptyline in the treatment of subjective tinnitus. *Journal of Otolaryngology.* 2001;30:300-3.
345. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering - A randomized, double-blind, placebo-controlled study. *J. Clin. Psychopharmacology.* 2006;26:32-9.
346. Bahmad FM, Venosa AR, Oliveira CA. Benzodiazepines and GABAergics in treating severe disabling tinnitus of predominantly cochlear origin. *12. 2006(140):144.*
347. Hosseinzadeh A, Kamrava SK, Moore BC, Reiter RJ, Ghaznavi HK. Molecular aspects of melatonin treatment in tinnitus: A review. *Current Drug Targets.* 2019;20:1112-28.
348. Azevedo AA, Figueirido rR, Elgoyhen AB, Langguth B, Schlee W. Tinnitus treatment with oxytocin: A pilot study. *Front. Neurol.* 2017;8:494.
349. Han AY, Mukdad L, Long JL, Lopez IA. Anosmia in COVID-19: Mechanisms and significance. *Chemical senses.* 2020;45:423-8.

350. Boesveldt S, Postma EM, Boak D, Schopf V, Martens J, Duffy VB. Anosmia - A clinical review. *Chemical senses*. 2017;42:513-23.
351. Lee MR, Wehring HJ, McMahon RP, Cascella N, Liu F, Bellack A, et al. Effects of adjunctive intranasal oxytocin on olfactory identification and clinical symptoms in schizophrenia: Results from a randomized double blind placebo controlled pilot study. *Schizophr. Ews*. 2013;145:110-5.
352. Sorokowaka A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. *Rhinology*. 2017;55:17-26.
353. Rashid RA, Zgair A, Al-Ani R. Effect of nasal corticosteroid in the treatment of anosmia due to COVID-19: A randomised double-blind placebo-controlled study. *American Journal of Otolaryngology-Head and Neck Medicine and Surgery*. 2021;42:103033.
354. Weng Z, Patel AB, Panagiotidou S, Theoharides TC. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J. Allergy Clin. Immunol.* 2015;135:1044-52.
355. Patel AB, Theoharides TC. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. *J. Pharmacol. Exp. Ther.* 2017;361:462-71.
356. Theoharides TC. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. *Biofactors*. 2020;46:306-8.
357. Theoharides TT, Cholevas C, Polyzoidis K, Poliotis A. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. *Biofactors*. 2021;47:232-41.
358. Jacob A, Wu R, Zhou M, Wang P. Mechanism of the anti-inflammatory effect of Curcumin: PPAR-gamma activation. *PPAR Research*. 2007;2007:89369.
359. Kakavas S, Karayiannis D, Mastora Z. The complex interplay between immunonutrition, mast cells, and histamine signaling in COVID-19. *Nutrients*. 2021;13:3458.
360. Kunnumakkara AB, Harsha C, Banik K, Vikkurthi R, Sailo BL, Bordoloi D. Is curcumin bioavailability a problem in humans: Lessons from clinical trials. *Expert Opinion on Drug Metabolism & Toxicology*. 2019;15:705-33.
361. Moballegh Nasery M, Abadi B, Poormoghadam D, Zarrabi A, Keyhanvar P, Tavakol S, et al. Curcumin delivery mediated by bio-based nanoparticles: A review. *Molecules*. 2020;25:689.
362. Valizadeh H, Danshina S, Gencer MZ, Ammari A, Sadeghi A, Aslani S. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *International Immunopharmacology*. 2020;89:107088.
363. Ahmadi R, Salari S, Reihani H, Eslami S. Oral nano-curcumin formulation efficacy in the management of mild to moderate outpatient COVID-19: A randomized triple-blind placebo-controlled clinical trial. *Food Science & Nutrition*. 2021;9:4068-75.
364. Rahimi HR, Nedaenia R, Shamloo AS, Nikdoust S. Novel delivery system for natural products: Nano-curcumin formulations. *AJP*. 2016;6:383.
365. Klooker TK, Braak B, Koopman KE, Welting O, Wouters MM, Schemann M. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut*. 2010;59:1213-21.
366. Wang J, Wang Y, Zhou H, Gu W, Wang X, Yang J. Clinical efficacy and safety of ketotifen in treating irritable bowel syndrome with diarrhea. *European Journal of Gastroenterology & Hepatology*. 2020;32:706-12.
367. Nguyen B, Tosti A. Alopecia in COVID-19: Systematic review and meta-analysis. *JAAD International*. 2022;7:67-77.
368. Darwin E, Hirt PA, Fertig R, Doliner B, Delcanto G. Alopecia areata: Review of epidemiology, clinical features, pathogenesis, and new treatment options. *International Journal of Trichology*. 2018;10:51-60.

369. Wikramanayake TC, Villasante AC, Mauro LM, Perez CI, Jimenez JJ. Prevention and treatment of alopecia areata with quercetin in the C3H/HeJ mouse model. *Cell Stress and Chaperones*. 2012;17:267-74.
370. Hamblin MR. Photobiomodulation for the management of alopecia: mechanisms of action, patient selection and perspectives. *Clinical, Cosmetic and Investigational Dermatology*. 2019;12:669-78.
371. Torres AE, Lim HW. Photobiomodulation for the management of hair loss. *Photodermatol. Photoimmunol. Photomed*. 2021;37:91-8.
372. Nichols AJ, Hughs OB, Canazza A, Zaiac M. An open-label evaluator blinded study of the efficacy and safety of a new nutritional supplement in androgenic alopecia: A pilot study. *Journal of Clinical and Aesthetic Dermatology*. 2017;10:52.
373. Karatas F, Sahin S, sever AR, Altundag K. Management of hair loss associated with endocrine therapy in patients with breast cancer: an overview. *SpringerPlus*. 2016;5:585.
374. Harvey CJ. Combined diet and supplementation therapy resolves alopecia areata in a paediatric patient: A case study. *Cureus*. 2020;12:e11371.
375. Stoehr JR, Choi JN, Colavincenzo M, Vanderweil S. Off-label use of topical minoxidil in alopecia: A review. *Am. J. Clin. Dermatol*. 2019;20:237-50.
376. Gupta AK, Venkataraman M, Talukder M, Bamimore MA. Finasteride for hair loss: a review. *Journal of Dermatological Treatment*. 2021.
377. Jo SJ, Shin H, Park YW, PPaik SH, Park WS, Shin HJ. Topical valproic acid increases the hair count in male patients with androgenic alopecia: A randomized, comparative, clinical feasibility study using phototrichogram analysis. *Journal of Dermatology*. 2014;41:285-91.
378. Lee SH, Yoon J, Shin SH, Zahoor M, Kim HJ, Park PJ, et al. Valproic acid induces hair regeneration in murine model and activates alkaline phosphatase activity in human dermal papilla cells. *PLoS ONE*. 2012;7:e34152.