Systematic Review and Proposed Trial Protocols for COVID-19

George M. Carter, November 23, 2021, www.fiar.us

Abstract

A systematic review of extant trial results for individual micronutrients, botanical therapies and combinations thereof was undertaken with a literature search through October 4, 2021. This document complements a review of the literature for treatments and vaccines for management or prevention of SARS-CoV-2 infection (see http://www.fiar.us/COVID19-REVIEW.pdf). Databases such as PubMed and Google Scholar were interrogated to identify included studies.

Given that single agents are frequently provided in the context of an array of treatments, particularly for hospitalized patients with SARS-CoV-2 infection, and further that proper nutrition for biological functioning relies upon a range of micronutrients, minerals, as well as a balance of the healthier forms of carbohydrates, fats and proteins, it seems logical to consider clinical trials that combine them in ways that address underlying conditions arising from the pathogenesis of the disease. It has become evident that both the development of severe disease and "long covid" is rooted in inflammation of different types, elevated and dysregulated cytokines, coagulopathies and the formation of multiple thrombi as well as the impact of low oxygen saturation in the blood.

Much of clinical science focuses on the impact of a single drug or agent and its influence on disease outcome. Fortunately, as this review attests, many of these studies have been undertaken to help us begin to understand the individual role each plays, their limitations and any risks that they may entail. Combining agents is often necessary to produce more robust clinical results. For example, it takes two or three antiviral drugs to cure hepatitis C or manage human immunodeficiency virus (HIV) infection and tuberculosis. To an even greater degree, biological functioning also requires such "combination therapy" and here, clinical trials are generally lacking. This systematic review provides evidence for how such combination therapy trials of micronutrients and/or botanical interventions may be envisioned.

Interventions

In this paper, the focus is on micronutrients and some botanical agents that may have significant impact on outcomes of interest. Among these are vitamins (notably vitamin D, B vitamins including B12 and niacin, vitamin A (carotenoids) and vitamin C); minerals (zinc, copper, selenium, potassium, magnesium); antioxidants (quercetin, melatonin, N-acetylcysteine) and various botanical agents and preparations (notably those already used in integrated Chinese, Indian and Korean medicine and studied in various trials. Studies of individual such as curcumin, black cumin seed, cannabis, ginger and others are reviewed. Prebiotics (e.g., fructooligosaccharides) and probiotics have also been used to manage SARS-CoV-2 infection.

Clinical Outcomes of Interest

1. Mortality, ICU admission, hospital length, rate of vent use and/or length of time on vents. Notably, hospitalization, development of severe disease, requirement for ventilator support, shortening the duration of such vent support and, most critically, mortality.
2. Management of Long COVID symptoms and conditions, including elevated d-Dimer, TNF, IL-1, IL-6, etc.
3. Recovery from damage associated with ventilator use and long-term hospitalization.

Design A systematic review of literature along with review of protocols employed to date. Proposed clinical trial designs for consideration for a) prophylaxis; b) hospitalized patients with COVID-19; c) patients with Long COVID.

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N.b.: Dates follow the style of Month/Day/Year in this document.

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Background

The global SARS-CoV-2 pandemic has produced numerous unpleasant surprises for humanity since it was first identified in late 2019. The virus has proved adept at adapting to our interventions, to the extent they are inconsistently applied and despite being a virus with a relatively low mutation rate. While some vaccines falter in the face of the alpha or delta variant, we are fortunate at the time of writing that mostly they prevent serious disease or death in most, if with a reduced ability to prevent infection. While initial success with vaccines has been far beyond initial hopes, that flush of excitement wanes in the face of the lack of access to them for over a quarter of the planet's population, hesitancy among many for a range of intrapersonal rationales, and resistant variants developing on the part of the virus. Thus, concurrent efforts to establish effective therapies to blunt the lethality of infection must continue in parallel with efforts to find universal vaccines that may work against a range of coronaviruses (in addition to variants) and which are publicly developed so all may access them.[1]

Geographically, disparate responses to the pandemic have met with wildly different outcomes. In China and New Zealand, with more thorough (sometimes draconian) approaches of testing, contact tracing, isolating patients and shutdowns, the numbers of cases and deaths per million population have remained extremely low. Taiwan, a nation with the most robust single-payer healthcare system has been able to utilize patient databases to identify and rapidly trace contacts of infected individuals, keeping the mortality rate very low and the economy essentially open.[2] By contrast, nations in the West with an eye toward sustaining economic profitability, have waffled and offered confused and inchoate advice and protocols with regard to the use of masks, isolation, business openings, testing and contact tracing (woefully inadequate for either, especially early on), with the result of uncontrolled spread of the virus and repeated waves of hospitalizations, overwhelmed intensive care units and high mortality.

The global impact of the pandemic has had horrific ripple effects, particularly in low-income nations. Some two billion people still have little or no access to vaccines, though some are beginning to obtain some from Cuba, China and other nations. One effect is worsening malnutrition. A study underscored the debilitating effect of worsened malnutrition in nations such as Angola, Burkina Faso, Chad, Liberia, Mali, Niger, Sudan, and Tanzania, as well as Yemen and Guyana.[3] There are many unsavory reasons why these nations suffer so deeply from "food insecurity" (starving) and lack of adequate nutrition. A simple multivitamin with adequate access to food and clean water could go a long way to reducing disease burden (and the concomitant risk of a pandemic prolonged and new variants arising).

A range of treatments have been proposed and some embraced with what has too often turned out to be unwarranted enthusiasm. Among these that have failed include hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, some species of interferon, aspirin and use of any antiviral strategy much beyond the point of hospitalization. Still, it should be clearly stated that the "Standard of Care" (SOC) referred to in many of the studies reviewed below included these drugs for much of the year 2020. Accumulating data suggest the most effective use of antiviral therapies is at the earliest stages, unlike other chronic viral infections such as HIV and hepatitis B or C.

Only those with both access to frequent testing and monoclonal antibody therapies, arbitrarily and needlessly costly, see any benefit from antiviral strategies. The one exception may be a simple application of nasal irrigation using saline and/or povidone iodine upon determination of seropositivity, however, only small studies exist and this requires more confirmatory evidence. Still, if safer antivirals are discovered that can be used early in disease, this could be a breakthrough, one which the drug, molnupiravir, may yet fulfill.[4] Of course, the cost of the drug as a generic should be about US$20 for a five

day regimen,[5] yet Merck has already pushed for an outrageous $750/course.[6] (Note that pharmaceutical drug and vaccine approaches are reviewed separately.)

An array of micronutrients have been shown to be at low levels in the blood of many people and those with the lowest levels of certain vitamins, such as D, zinc, C, etc. are at higher risk of developing severe disease.[7] A number of reviews, systematic or meta-analyses, have established deficiencies of an array of micronutrients in SARS-CoV-2 infected individuals. One review showed a tight correlation with increased risk of disease severity with low levels of vitamin D, zinc and magnesium.[8] This is in addition to observations of low levels of the B vitamins, vitamins A and C, and various minerals identified even early in the pandemic.[9] A cross-sectional study of 50 COVID-19 patients in Nigeria observed lower levels of vitamins A, C and E as well as zinc, selenium, magnesium and copper compared to uninfected controls. In addition, the body's antioxidant defense system, as defined by glutathione, glutathione peroxidase, catalase and superoxide dismutase were all seen to be depleted in COVID-19 patients.[10]

Some of the more widely adopted practices have already had some effect on use of vents and mortality. Proning or placing the patient on their stomach, can alleviate pressure to the lungs. More sophisticated approaches to managing immune thrombocytopenia with a range of anticoagulants may herald better outcomes. Use of dexamethasone has been established in large simple trials, at least to improve outcomes for those breathing with the assistance of invasive mechanical ventilation.

For those who do wind up in the hospital as well as for those who develop persistent symptoms of "Long-COVID," there are a range of potential interventions that may yet break the back of the pandemic from a therapeutic perspective, given the practical limitations of vaccine access globally. This condition, often referring to those with long-term hospital care, has been referred to by some as the Post-Acute Sequelae of COVID-19 (PASC). While many patients fall into the category of long-term debility after lengthy hospitalization, there is growing awareness that large percentages of people who had mild or even asymptomatic disease suffer a range of symptoms for months and years. It's too early to say how long some people will struggle with Long COVID, but given the nature of other conditions like "chronic fatigue" (CFS/ME), for some, the condition may be life-long.

The NIH has a program to study "long COVID," no doubt focusing exclusively on drugs.[11] Indeed, one of the hallmarks of aging, chronic disease and a host of human maladies centers around dysfunction in our energy organelles, the mitochondria. Some of those most vulnerable, elderly, obese, those with hypertension or diabetes, often suffer from baseline mitochondrial dysfunction. Such dysfunction occurs in the context of inflammation that may be proximal to the coagulation problems and organ damage leading to high risk of death seen in SARS-CoV-2 infection. Some agents, like alpha lipoic acid, carnitine and coenzyme Q10 have all been investigated to help correct mitochondrial dysfunction.[12,13] Is there some underlying connection with those younger people now observed getting sicker, faster with the delta variant? (There may be multiple etiologies that point to higher risk, including simply a more virulent variant like delta.)

In this systematic review, the evidence for a range of very safe and largely inexpensive agents that may be readily scaled up in terms of production and distribution is undertaken with an eye toward putting a practical end to the COVID-19 pandemic. Based on these data, regimens are provided for consideration and discussion for investigation in clinical trials.

Interventions

Happily, the micronutrients in these studies are very well characterized and any potential harm for a patient is pretty well (and often over-cautiously) clear. That's not to say they cannot cause harm—they can. Assessing any potential risks should be undertaken. For example, people with a type of genetic marker known as G6PD deficiency are not able to metabolize vitamin C and it should not be used in these patients.

The first class of agents are the vitamins, so called due to their necessity for life and health. In general terms, most people with access to an array of fruits, vegetables and other foods acquire sufficient amounts of these chemicals to sustain daily health. However, in the context of chronic disease, these may either be depleted by disease processes which may be further hastened by the lack of nutrition that occurs during illness or hospitalization. Anosmia and ageusia (loss of smell/taste) may further complicate nutritional status.

Basic human health requires fresh and clean air and water, enough food, exercise and good sleep. But even with these, many people suffer from bad diets, lack of food and/or even with great diets, potentially low blood and tissue levels of vitamins and minerals. This is even more apparent with SARS-CoV-2 infection. Indeed, for those who were on a vent for days or weeks, recovery is slow and requires an array of rehabilitative interventions. What is the evidence for using supplements to manage that situation and in general for those with Long COVID? We do know that overall such interventions are very safe, necessary for bodily functioning in the case of vitamins, minerals and amino and fatty acids, and that many forms of mal- or undernutrition may exacerbate disease.[14]

Nutritional insufficiency either at baseline or exacerbated by infection can have serious consequences not just for individuals but also for the shape of the pandemic. Malnutrition may be worsened around the world by the pandemic. More than a THIRD of the Earth's population may face serious malnutrition.[15] The impact of malnutrition on immunological responses, increased inflammation (especially with obesity), and increased susceptibility to infections has been well-characterized[16] and is applicable to SARS-CoV-2 infection as well.[17] This has a potentially very deleterious effect on not just the risk of more easily acquired infection, higher risk of severe disease or death—but worse: on SARS-CoV-2 itself. Others have observed in humans that nutritional status may affect the virulence of SARS-CoV-2 infection, whether from lack of adequate food and diminished micronutrient status or from the immunological and inflammatory consequences of obesity.[18] Conversely, whether certain aspects of malnutrition may contribute to the virulence of SARS-CoV-2. We know this is a two-way street. For example, infection with a Coxsackie virus may cause cardiomyopathy known as Keshan's disease. This occurs in the presence of selenium deficiency.[19,20] Malnutrition emphasizes the warning that the longer the delays in vaccinating people around the world, the greater the likelihood of more lethal variants arising—let alone the horror for the poor of needless suffering and death. More data are needed to identify if there are specific factors or aspects to malnutrition that affect likelihood of infection, and/or the development of severe disease.

The intent of these therapies is to correct deficiencies but in addition is to examine the use of higher, therapeutic dosages. Thus, the amounts of micronutrients a patient on a vent may receive while on total parenteral nutrition *may* be adequate to offset outright deficiency diseases, there is some evidence that higher doses may provide the body essential tools for battling the disease.

Goals: Prophylaxis, Thwarting Disease Progression, Preventing Vents, Reducing Mortality, Healing

In general, given the rapid evolution of disease from initial infection, these endpoints are the most vital. Most people with the infection do not require hospitalization. However, those that do can quickly

overwhelm hospital ICUs, especially in communities with large numbers of unvaccinated individuals. The primary endpoint of proposed regimens studies of the interventions described and reviewed herein are: preventing infection (prophylaxis), preventing the disease from becoming serious or critical, reducing the need for mechanical and invasive ventilation, shortening the time on a vent and reducing overall mortality.

There are numerous options for trial designs, some thoughts about which are provided at the end. Most of the studies here are post-hoc, evaluating what happened after the fact. Sometimes they are randomized but open label. Others use propensity matching to reduce inter-individual differences. A few are blinded, randomized and placebo controlled.

Understanding who may be at risk of more severe disease may focus attention on whom to enroll and in defining inclusion and exclusion criteria. Certain clinical characteristics have widely been observed, including hypertension, diabetes, male gender and certain underlying conditions such as HIV, cancer and some autoimmune diseases which may present a higher risk. A meta-analysis that reviewed over 10,000 patient records from around the world found in addition a number of biomarkers that should put clinicians on alert. These included a decreased lymphocyte and/or platelet count, elevated C reactive protein, creatine kinase, procalcitonin, D-dimer, lactate dehydrogenase, alanine aminotransferase, aspartate, aminotransferase and creatinine, markers associated with inflammation, liver damage and coagulation problems.[21] Such data may help to identify patients to receive early-as-possible treatment with antivirals or MAbs, at least for susceptible variants. But also, such patients may benefit from using interventions such as vitamin D, zinc, melatonin, probiotics or curcumin.

A number of papers have reviewed the extant literature for non-pharmaceutical interventions for the treatment and management of COVID-19 disease. Rozga, et al., undertook a "scoping review" of micronutrients and amino acid therapies, utilizing the Population-Concept-Context approach for study selection. However, the review was undertaken in April, 2020, leaving little time for research to be completed since the beginning of the pandemic in later 2019. Thus, their focus was on studies of viral infections, such as SARS or MERS, ARDS or pneumonia that may lead to ventilator use. They found 8 studies for qualitative evaluation, having interrogated only the PubMed database. None of the studies were among SARS-CoV-2 infected individuals. Of 1,416 studies found, 1,405 were excluded, among which were studies of animals or cells, human studies with different outcomes than selected, narrative reviews and commentaries. The studies they reviewed found no benefit in outcomes assessed for vitamin C (2 studies), vitamin D (1 study) or glutamine (2 studies). Vitamin E in one study at 600 IU/day resulted in a reduction of APACHE II score but no impact in a second study with mortality as an endpoint. Use of 60-90 mg/day of zinc sulfate resulted in a smaller hazard of risk for progression to ventilator assisted breathing.[22]

A program of nutritional supplementation for hospitalized patients, including protein (whey), D3 and other nutrients suggested improved clinical outcomes. A systematic review underscored the safety and pathophysiologic rationale for use while another offered a rationale for use of micronutrients among obese patients including lactoferrin and omega-3 fatty acids. In other work, there is excellent mechanistic rationale for using a combination of vitamins C and D to manage the cytokine storm.[23,24,25,26,27,28]

Trial Results

The following review is undoubtedly incomplete. It provides a background from which to generate further hypotheses for interrogation. Many of the studies described focus on single agents but there are

some that assessed combinations of micronutrients, sometimes with other botanical or pharmaceutical agents.

While pharmaceutical drugs and new chemical entities that target either host proteins or pathogens require a careful reductionist approach to assess safety and efficacy, this approach may not be as effective when using agents that are designed to enhance host immunity and offset deleterious host responses. Indeed, most pathogen-targeted drugs tend to work better in combination than as individual agents, often as a way to deter pathogen resistance. Notably, diseases like HIV, hepatitis C, malaria and tuberculosis all benefit from combinations of drugs. Increasingly, this is true for a range of bacterial, fungal and viral infections that globally show an increased tendency toward resistance to extant therapies. The use of micronutrients is a case in point for more comprehensive approaches to disease management strategies.

For example, in the case of SARS-CoV-2, the mineral zinc shows some promise as a therapeutic agent. However, it is well established that the use of high doses of this mineral alone as a supplement is inadvisable without assuring adequate supplementation of minerals like copper, selenium and manganese, which may be wiped out by excessive zinc intake.[29] While the ideal to determine the precise mechanism(s) of an individual agent is scientifically satisfying, it fails to recognize either the complexity of biology or the homeostasis of optimal health in the face of ongoing challenges environmentally (pathogens to pollution) as it does the ecology and interactions within the body. Such awareness will evolve with time as we learn more about all the intricacies and complexities of our bodies but should not be a barrier to clinical assessment and research.

For example, early studies assessing the use of hydroxychloroquine combined it with zinc as the former worked as an ionophore which binds to ions and enhances passage into a cell to mutually enhance antiviral activity. There was a mechanism and a rationale and it was widely and commonly used (even before Trump embraced it as The Cure in his bumbling and dangerous fashion.) The drug has since largely been abandoned, however other agents like quercetin (and the green tea extract, epigallocatechin) also appear to function as an ionophore.[30] Perhaps greater synergy could be achieved more safely by a combination of quercetin and zinc? There are many other such synergies that need to be clinically evaluated.

The following provides of these individual interventions and serves in part as a basis for the consideration of more complex and biologically relevant regimens for clinical trials.

VITAMIN D

Even Dr. Fauci says check your level and supplement if low![31] Maybe he'll see about clinical trials of pertinent combinations?

A recommendation to test vitamin D level and supplement if needed should be widespread practice for physicians at this point. Safe exposure to sunlight for endogenous synthesis should be taken into account, emphasis on safe. Supplementation may result in a reduced number of infections, especially for those with baseline low level.

The data in the following tables underscores the potential for supplementation, particularly in the context of the strong and tight association between lower blood levels of vitamin D and more severe disease. The vitamin comes in different forms, as vitamin D2, D3 (cholecalciferol), calcitriol and calcifediol. Establishing the best form and dosage to use still remains to be undertaken. Prophylactic use

of moderate dosages, along with other key micronutrients, may help to reduce risk of active infection or limit infection to an asymptomatic or mild-to-moderate disease outcome.

However, it should be noted that most of the studies are of relatively low quality, methodologically speaking. Even the RCTs appear to be underpowered to elucidate clarity on either the association of blood level with disease severity or the impact of supplementation on outcomes. And, of course, the studies conflict in their findings. Cholecalciferol (vitamin D3) is fine to use, but there is a suggestion from the following studies that calcifediol may be a better bet. However, in a recent review, others assert that the more precise dosing of D3 and the greater body of evidence in the realm of musculoskeletal disease makes it a better bet than calcifediol, based on their reading of the data.[32] In contemplating potential protocols for future study, comparator arms with these different forms may help to answer the question, at least in terms of COVID-19.

Several reviews have been undertaken establishing the linkage between low levels and severe outcomes. A meta-analysis by Petrelli, et al., of extant studies through January 31, 2021 revealed that the risk of infection was higher in those with low levels, with an odds ratio of 1.26 (1.19-1.34, $p<0.01$). Critically, the analysis underscored the impact of low levels on disease income, again with an odds ratio of 2.6 (1.84-3.67, $p<00.1$) as well as a heightened risk of mortality (OR 1.22, 95%CI 1.04-1.43, $p<0.01$).[33] This serves as a strong rationale for evaluation in clinical trials (if not an outright call to assess patient level and supplement accordingly). Note in the Loucera retrospective review, the big benefits for mortality were when intervention was given at least 15 days prior to hospitalization and that in this case, the calcifediol form was better than cholecalciferol. Indeed, some research suggests that calcifediol is better absorbed, requiring lower doses and may be preferred to the cholecalciferol (also known as vitamin D3) or the less absorbed but common D2 (ergocalciferol) form.[34] With all due respect, that citation has one author who has a patent application on vitamin D analogs, so this question should be more closely assessed, especially if there are large price differences with nominal clinical differences.

A low blood level of vitamin D strongly correlates with severe disease and higher mortality in numerous studies. A study of 50 pts found 76% D3 deficient, 42% Se deficient; one study saw no correlation with low levels and disease severity (n=109) but did see a correlation with high parathyroid hormone (PTH), often seen with deficient vitamin D status. A study of over 190,000 people found a SARS-CoV-2 positivity rate of 9.3%, among whom a higher rate of positivity was seen among those with low vitamin D3 (<20 ng/mL) while a lower rate of infection was seen among those with higher circulating D3 (>55 ng/mL) after multivariable logistic model adjusting. Low levels associated with severe disease, more mortality, increased inflammatory markers in COVID patients; higher ferritin and d-dimer levels seen among D-deficient, though no correlation seen with disease severity (n=216), however 82% were deficient and there were improvements in respiration $PaO_2/FIO_2<300$, use of tocilizumab and shorter hospital stay ($p=0.02$) among 11 receiving supplements. Some research suggests that a large bolus dose is not helpful: a 200,000 IU bolus did not reduce hospital stay vs placebo in open-label but underpowered study (7 days each arm) with many limitations. A combination of 1000 IU oral with B12 (500 mcg), Mg (150 mg) in observational study of 43 older hospitalized patients, 17.6% of 17 patients getting vitamins vs. 61.5% of 26 pts not receiving micronutrients progressed to needing oxygen. One meta-analysis underscored a potential for vitamin D as prophylaxis against SARS-CoV-2 infection. Vitamin D is important for reducing lung inflammation.[35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51]

A group of doctors released a statement urging all COVID-19 patients to be treated with Vitamin D. In the absence of testing, a minimum of 4,000 IU per day while those with under 30 ng/ml (75 nmol/L) be treated with higher doses of cholecalciferol (vitamin D3) or calcifediol. Dosages in this case are based on

the Castillo and Ratogi protocols as described below, with many of the physician signatories offering their recommended dosages.[52]

Also, aside from bones, vitamin D may help muscle recovery. A pilot study among 30 elderly patients comparing 2000 IU/day vs. placebo saw serum creatinine kinase levels return to normal levels, though other parameters were not affected in a statistically significant way, although patients in the treated arm reported feeling better.[53] This may point to other pertinent outcomes for those with long COVID.

What constitutes deficiency is still somewhat controversial. In general, below 20 ng/ml is considered deficient, 20-30 mildly so for some and significantly so for others. Adequate levels are generally accepted to be greater than 40 ng/ml. The upper level ranges from 100-149 ng/ml and beyond that toxicity may be apparent.

THE UPSHOT:

There are 36 trials described below. Of these, 22 trials reported positive results, 9 trials reported null or negative results. The remainder of the studies (5) described the serum levels of vitamin D and/or the effect on progression potential.

PI	Arms	N	Dose	Design	Contact	Outcomes
Annweiler[54]	N=57 got D Comparator: not receiving D=9	66	80,000 IU, oral Every 2-3 months Those given when COVID suspected or w/in month prior	Retrospective, Px and early treatment, frail elderly, nursing home March-May 15, 2020	Cédric Annweiler, MD, PhD, Department of Geriatric Medicine, Angers University Hospital, F-49933 Angers, France; Cedric.Annweiler@chuangers.fr Phone: ++33 2 41 35 47 25	Primary outcome: mortality Supplementation of D reduced risk of disease severity and mortality in frail elderly, not seen with other tx. Mortality HR 0.21 (0.07, 0.63; p=0.005), 10/57 and 5/9 died; adjusted HR 0.11 (.03, 0.48, p=0.003).
Loucera[55]	D3 – 358 Calcifediol – 193 Calcitriol – 11 vs matched controls	16,401 626 (w/Rx 30 d prior)	Variable	Chart review, hospitalized and national registry of Vit D use. Propensity score matching Jan-Nov, 2020	CIBER de Fragilidad y Envejecimiento Saludable (CIBERFES). Hospital Universitario Reina Sofía. Universidad de Córdoba. Menéndez Pidal s/n, 14004, Córdoba, Spain. (corr author, Jose Manuel Quesada Gomez)	Primary outcome: mortality Calcifediol given 15 days prior, log HR -1.27±0.32 but at 30 d -1.01±0.32. D3 almost as good: log HR -0.56±0.15 15 days and -0.27±0.12 30 days, better survival in each.
Sanchez-Zuno[56]	D - 22 Control – 20	42	10,000 IU/day, 14 days	Randomized, open-label trial Early disease (outpatients)	biologiamolecular@hotmail.com	Primary – symptoms. At BL 18/tx (18%) and 16/ctl (20%) had <30 ng/mL. On D3 had fewer symptoms, day 14 (0 had >3 sx vs 4 in control with >3sx, p=0.04); by day 14, from 4 to 7 (31.2%) sufficient
Tan[57]	17 rec'd MN 26 did not All MN >50 y.o. Control arm were older (58 vs 64, p=0.021)	43	D – 1,000 IU Mg – 150 mg B12 – 500 mcg Daily up to 14 d	Cohort observational study, pre-Apr 6, 2020 and post (when given blend); all COVID pts, Jan-Apr 15, 2020	Prof Heng Joo Ng, Dept of Hematology, Level 3, Academia, 20 College Road, Singapore 169856. ng.heng.joo@singhealth.com.sg (Note Table 3, DMN=8, Ctl=12, age >60, no diabetes, O2 support p=0.197)	Primary: O2 requirement; Fewer treated patients than controls initiated O2 therapy in hospital (17.6% vs 61.5%, P=0.006). D/Mg/B12 OR 0.13 (95% CI: 0.03 – 0.59) and 0.20 (95% CI: 0.04 – 0.93) for oxygen therapy

PI	Arms	N	Dose	Design	Contact	Outcomes
				BL not matched for age, hypertension, difference remain when adjusted		and/or ICU, univariate and multivariate, respectively.
Entrenas Castillo[58]	Calcifediol – 50 SOC – 26 (HQ/AZ, Abx)	76	Calcifediol, 0.8 mg (0.532 mg, 0.266 day 3, 7; once weekly thereafter)	Randomized, 2:1, open-label double masked (to allocation) Hospitalized pts; BL w/more hi BP, diabetes in control	lmentrenas@uco.es (L.M. Entrenas Costa).	Primary- mortality, ICU Significantly reduced ICU need, 1/50 (2%) vs 13/26 (50%), p<0.001, also when adjusting hypertension, DM
Rastogi[59]	D3 – 16 Control – 24	40	60,000 IU/day, 7 days	Randomized (pts on vent excluded)	Pankaj Malhotra, Department of Internal Medicine, Nehru Hospital, PGIMER, Chandigarh 160012, India; malhotrapankaj@hotmail.com	Primary-VL+, inflame markers 10/16 (62.5%) vs 5/24 (20.8%) to virus neg, p<0.018 w/sig decrease in fibrinogen
Murai[60]	D3 – 120 Placebo – 120	240	200,000 IU	DBPC, RCT, 2 sites, moderate to severe pts	Rosa Maria Rodrigues Pereira, MD, PhD, Rheumatology Division, Faculdade de Medicina FMUSP, 3° andar, Universidade de Sao Paulo, BR. Av. Dr. Arnaldo, 455, Pacaembu, Sao Paulo, SP, Brazil, 01246-903 rosamariarp@yahoo.com .	Primary length of stay; no impact nor on mortality, vent use, ICU admission. No diff between those with <20ng/ml on D or not either
Ling[61]	D3 – 151 Control – 444 Cohort – 541 Missing data for many	986 Site 1-444 Site 2-542	VARIABLE 40,000 daily to 20,000 every 2 wks Most: 40,000 IU weekly (47.9%) 20,000 IU twice/wk (28.8%) Other dosing, 17 Table 2, n=73?	Retrospective chart review One site (Tameside, UK) then 2 added Late treatment 1/27-8/5/20	edward.jude@tgh.nhs.uk Tel.: +44-(0)161-922-5189	Primary mortality Overall 177/433 died No association with serum level, risk of death But D use reduced risk (OR_{adj} 0.13, 0.05–0.35, p < 0.001); replicated in validation cohort of 541 patients, OR_{adj} 0.38 (0.17–0.84, p=0.018) whether deficient or not, adj for age, sex, obesity, ethnicity, diabetes, SpO2<96%
Jevalikar[62]	197 (48.2%) deficient D3 – 128 (Table 5, no supp, n=69)	410	60,000 IU	Prospective, cross-sectional, observational 28 < 20 ng/ml vit D deficient (VDD) Severe VDD < 10 ng/mL - 100 (24.4%) 20-30 ng/mL - 67 (16.4%) 30–100 - 139 (34%) > 100 ng/mL- 6 (1.5%) 7/9 – 8/8/2020	Institute of Endocrinology and Diabetes, Max Healthcare, Saket, Press Enclave Road, New Delhi 110017, India. gjevalikar@gmail.com	Primary – proportion severe cases Info re prior D supplementation not available. No diff with >20 pts in mortality, ICU, proportion of severe cases, O2 use; adding D, no difference Trend? Table 5, 1/128 vs 3/69 died p=0.124; O2 admin 38 (29.7%) vs 30 (43.5%), p=0.06?

PI	Arms	N	Dose	Design	Contact	Outcomes
Giannini[63]	D3 – 36 SOC – 55	91	400,000 IU (200,000 IU per day, 1st 2 days)	Retrospective chart review; pts>40 yo; physician decision so more smokers 3/15-4/20/20 Side note: D3 p=0.013 n=36, Tocilizumab p=0.011 n=13	sandro.giannini@unipd.it Tel.: +39-049-8212169	Primary – ICU, mortality? D pop more HCQ, lop/rit, abx Comorbidity – D3<50 ng/ml, smoking, d-dimer, other co-morb increased likelihood of benefit; more co-morbid not confounder but effect modifier, D3 more likely to help sicker patients? p=0.039 for OR adjusted effect modification analysis, ≥3 co-morb, OR 0.18 (0.04-0.83)
Nogues[64]	Calc – 447 SOC – 391 53 from SOC to Tx in ICU, 2˚ analysis	838	0.8 mg calcifediol 532 µg on day 1 plus 266 µg on days 3, 7, 15, and 30	Observational cohort study; Not randomized; ITT analysis then 2˚ analysis Mar-May, 2020 Late tx	IMIM (Hospital del Mar Medical Research Institute), Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Barcelona 08003, Spain;	Primary ICU and mortality 20 (4.5%) required the ICU, compared to 82 (21%) out of 391 nontreated (*P* < .001), OR_{adj} 0.13; 95% CI 0.07-0.23; 21/447 (4.7%) treated with calcifediol at admission died vs 62/391 (15.9%) p=.001, OR_{adj} 0.21 (95% CI, 0.10-0.43)
Lakkireddy[65]	D3 – 44 of 65 17 discharged, 2 died, 2 did not follow tx SOC – 43 of 65 (18 discharged, 4 died)	130 87	60,000 IU daily, 8-10 days, BMI based	Randomized, prospective, open label, mild-moderate w/confirmed <30 ng/ml	Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India. madhu.harini123@gmail.com	Primary, inflammatory markers Safe; level rose to 89.1 ng/ml; all markers reduced vs SOC, p<0.01 including CRP, LDH, IL6, ferritin, N/L ratio Hospital stay not different ICU – 4/44 VD, 5/45 NVD Of 9, 7 died, 2 VD, 5 NVD All had very high CRP, IL6, ferritin compared to survivors. No AE
Lohia[66]	95 < 20 ng/ml 26 – D supp 175 ≥20ng/ml 58 – D supp	270	N=84 rec'd unknown supplementation	Retrospective cohort study; 2001 pts w/COVID-19, only 277 had a D level	P. Lohia plohia@med.wayne.edu	Primary mortality, vent need, ICU; no differences in mortality, ICU, vent use vs those ≥20 ng/ml nor on stratified <20, 20-30, >30
Alcala-Diaz[67]	Calc – 79 SOC - 458	537	0.8 mg 0.266 mg/cap, 2 capsules on entry, one cap days 3, 7, 14, 21, and 28	Retrospective observational, not randomized, 2/5-5/5/20	Jose Lopez-Miranda md1lomij@uco.es Tel.: +34-957-010-947; Fax: +34-957-218-250	Primary in hospital mortality in 1st 30 days. Tx 4 (5%) died vs 90 (20%) no D OR 0.22 (0.08-0.61); adjusting for confounders, OR 0.16 (0.03-0.80); D recipients generally sicker at BL
Güven[68]	D3 – 113 Control – 62	175	300,000 IU IM	Prospective, critical pts; not randomized, most >50 y.o. 3/15-11/30/20	Şırnak State Hospital, Şırnak, Turkey. 2Department of İntensive Care Unit, Şırnak State Hospital, Şırnak, Turkey dr.mguven@gmail.com	No effect on intubation, hospital stay or mortality; 43/113 vs 30/62 died, p=0.185

PI	Arms	N	Dose	Design	Contact	Outcomes
Soliman[69]	D3 – 40 Placebo – 16 (saline)	56	200,000 IU IM	DBPC, RCT among elderly, diabetic SARS-CoV-2+ (mean age 71 in each arm)	Tarek Samy Abdelaziz, Department of Internal Medicine, Cairo University Kasr Alainy Faculty of Medicine, Kasr Alainy, Cairo 15123, Egypt tarek.samy80@yahoo.com	Primary mortality w/in 6 weeks; no difference seen, tx 17.5% vs 18.8%, p=0.838. BL D=10 vs 21 ng/ml, p=0.001?
Elamir[70]	Calc – 25 No tx – 25	50	0.5 µg/d, 14 days	RCT, open label	Mt Sinai, 75 West End Avenue, Apt. C16F, NY, NY 10023, hajira.amir@gmail.com (H. Amir).	Primary – SaO2/FIO2 Tx +91.04±119.08 vs +13.2±127.7, p=0.0305; hosp stay 5.5±3.9d vs 9.24±9.4d p=0.14; D group 0 died, 2 readmissions vs control, 3 deaths, 4 readmissions
Yildiz[71]	37 – recd D 170 did not	207	300,000 IU, single dose per baseline blood level (<30 ng/ml)	Retrospective chart review, 9/1-10/1/20 Not matched? Baseline parameters, no stat sig differences	Health Sciences University Faculty of Medicine Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Pulmonary Medicine Department, Ankara, Turkey. drayperi@yahoo.com	Primary: mortality; comparator group had normal D level: 50.82±16.12 ng/ml (30.28–81.35) vs. 16.98±6.2 ng/ml (4.20–28.30); 1 died in tx group (2.7%) yet 24/170 (14.1%) in no D, p=0.038
Blanch-Rubió[72]	1,303 got D 1,241 no COVID, 62 did	2,102	Various medications	Cross-sectional analysis, Poisson regression for intervention/COVID-19	Rafael Maldonado; rafael.maldonado@upf.edu many industry ties	No effect of D on incidence; denosumab, zoledronate, calcium neg. associated w/incidence (not stat sig). Industry BS?
Annweiler[73] GERIA-COVID study	1-supp over past year, 29 2-supp after dx, 16 3-no supp, 32	77	D3 50,000 IU/mo group 1 (or 80,000, 100,000 IU every 2-3 mos) year prior; Group 2, 80,000 IU oral at dx	Prophylaxis/tx; retrospective review, March-May, 2020	Cedric.Annweiler@chu-angers.fr; Tel.: +332-4135-4725; Fax: +332-4135-4894	Primary 14 d mortality Group 1 (n = 29), 93.1% survived at day 14; compared to 81.2% Group 2 (p = 0.33); Group 3 68.7% survived (p = 0.02); group 1 associated with lower risk of OSCI≥5 vs grps 2,3 OR 0.08, p=0.03
Cereda[74]	1 – 1486 COVID pts->105 2 – 1207 caregivers->92 3 – admitted pts->127	38 supp 286 – no supp	Min 25,000 IU/mo for 3 months (i.e., ~800 IU/d, min.)	Prophylaxis; tel survey of users April-May, 2020	E. Cereda, Viale Golgi 19, 27100 Pavia, Italy. Phone: +39 0382 501615; e.cereda@smatteo.pv.it	Self-report of use; of users, a trend toward higher mortality? (OR 2.42 (0.78-7.49) p=0.13) 43/197 need hospitalization; 47/170 (27.6%) hosp pts died Overall, D use improved blood level but no prophylactic benefit
Cangiano[75]	Evaluation of nursing home residents 21.5% of pos pts rec'd D;	157	D3 supplemented, dose unknown	Nursing home residents, 80-100 y.o. Chart review 3/1-5/1/20 (Side issue of false neg nasal swabs; real-world	Marco Bonomi, m.bonomi@auxologico.it, marco.bonomi@unimi.it	Primary - mortality 93/157 alive at end of 2 mos. 40.1 % (63 deaths/157 patients), same two months of 2019, mortality 6.4% (10 deaths/155 patients). COVID-19 positive residents (to any nasopharyngeal

PI	Arms	N	Dose	Design	Contact	Outcomes
	12.9% of neg pts also			sensitivity of 81.8%?) Group of 98 – D - 3/42 died, 17/56 survived p=0.005		swab), mortality rose to43%, COVID-19 negative, mortality rose to 24%. logistic regression showed inverse with COVID death, p=0.04 Among meds (O2, HQ, heparin), only HQ saw similar p=0.03
Ma[76]	Habitual use D – 363 Not - 7934	8,297 1,378 (16.6%) COVID+ (1329 n in Table 2) 49 (13.5%) D users COVID+	Habitual use of D; other supplements also listed (no correlations with them in sep analysis)	Internet questionnaire; Prophylaxis 3/16-6/29/20	Lu Qi lqi1@tulane.edu luqi@hsph.harvard.edu	Risk of infection; 34% reduction in habitual users, adjusted, OR, 0.66 (0.45–0.97; p=0.034). Residual confounding or selection bias may explain. More users were white, female, not obese, healthy diet; OR adjusted for age, sex, race, research centers, laboratory, origin (outpatient or inpatient), blood-type haplotype, years of education, TDI, smoking, moderate drinking, physical activity, healthy diet score, and use of any other supplements strengthened the association; further adj for baseline disease (obesity, diabetes, etc.) and D level further strengthened OR (as above). Saw no correlation with level and risk of infection.
Oristrell[77]	D-8,076 total D – 6,252 after matching with Controls – 12,504	20,580	Calcitriol, mean daily dose, 264.9 µg (SD 217.5)	Prophylaxis, propensity-matched controls, pts with chronic kidney disease 4/19-2/20 Also 5,885 on D 11/19-2/20	joristrell@tauli.cat (J.O.); mgrau@imim.es (M.G.)	Risk of infection, mortality; Reduced risk of SARS-CoV2 infection (HR 0.78 [CI 95% 0.64–0.94], p = 0.010), reduced risk of severe COVID-19 and reduced COVID-19 mortality HR 0.57 (0.41–0.80), p = 0.001. Higher dose associated with lower risk of severe disease (best ≥0.4µg/d)
Levitus[78]	D2 – 65 Control – 64	129	D2, 1,000 IU/wk 1,000, 5,000 and 50,000 IU doses	Retrospective chart review, pts <30 ng/ml Mar-July, 2020	Albert Einstein College of Medicine and Montefiore Medical Center, Department of Internal Medicine, Division of Endocrinology, Bronx, NY, USA	No effect at <30 blood level on severity at any dose range; reduced odds of severe with lower cutoff, not stat sig
Fasano[79]	1,487 PD pts 1,207 family	2,694	Unspecified	Parkinson's disease pts (PD); telephone interviews with pts, family	Dr. Emanuele Cereda, Clinical Nutrition and Dietetics Unit, Fondazione IRCCS Policlinico San Matteo, Viale Golgi 19, 27100	105 PD (7.1%) and 92 controls (7.6%) had COVID; 6/105, 7/92 died; milder disease in PD overall;

PI	Arms	N	Dose	Design	Contact	Outcomes
	members (ctl)			Note-more infected PD with obesity, COPD vs uninfected PD	Pavia, Italy; e.cereda@smatteo.pv.it	possible protective role of D – 13 (12.4%) used were pos, 316/1,381 not infected used (22.9%), p=0.010, age-adj OR 0.56 (0.32-0.99, p=0.04)
Oristrell[80]	D3 – 108,343 Ctl – 216,686 Calc – 134,703 Ctl – 269,406	459,732	D3 or calcifediol Unspecified dosing	Retrospective, propensity-matched controls April 2019 – Feb 2020	J.Oristrell joristrell@tauli.cat E. Casado ecasado@tauli.cat	Slightly less risk overall, 4% vs 4.2% HR 0.95 (0.91-0.98, p=0.004); either where ≥30 ng/ml saw less risk of severe COVID and lower mortality, HR 0.66 (0.46-0.93, p=0.018 for D3 and HR 0.56 (0.42-0.76, p<0.001 for calcifediol
Israel[81]	Cohort 1 – 6,530 ? 6,202 w/5:1 controls (32,650) Cohort 2 – 6,953? 6,919 w/2:1 controls (13,906)	60,039	Unspecified	Case control study of COVID-19 patients and risk of hospitalization based on medication use; controls are not hospitalized	dr.ariel.israel@gmail.com (AI); eytan.ruppin@nih.gov (ER)	Primary, OR for hospitalization for various tx: outcomes – ubiquinone (CoQ10) (OR=0.185, 95% CI [0.058 to 0.458], p<0.001), ezetimibe (OR=0.488, 95% CI [0.377 to 0.622], p<0.001), rosuvastatin (OR=0.673, 95% CI [0.596 to 0.758], p<0.001), flecainide (OR=0.301, 95% CI [0.118 to 0.641], p<0.001), and vitamin D (OR=0.869, 95% CI [0.792 to 0.954], p<0.003).
Pecina[82]	15 < 20 ng/ml 1 – D use prior	92	Blood level, Note: White 58/77 75.3% ≥20 ng/ml Non-white 9/15 60% <20 ng/ml	Retrospective of admitted pts 4/16-10/17/20	Jennifer L. Pecina, Department of Family Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Pecina.jennifer@mayo.edu	No association of level with primary outcomes, days on O2, hosp duration, ICU, vent or mortality; tiny sample size
Bagheri[83]	D 103 (30%), outpts D – 28 (16.5%) hosp pts	510	Not specified; zinc also helped	Cross-sectional query, MN use; March-May, 2020	Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran; Dr. Mina Jafarabadi, minajaf@yahoo.com	Severe disease OR 0.291 (0.102-0.834, p=0.022) Note: Zinc used more in outpatient than inpatient setting; no strong effect, OR 0.396 (0.044-3.532)
Sabico[84]	D3 5000 – 36 D3 1000 – 33	69	5000 or 1000 IU daily for 2 weeks	RCT over 2 weeks 7/29-9/22/20 (Despite randomization, 1000 IU older, higher BMI)	Chair for Biomarkers of Chronic Diseases, Biochemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia, ndaghri@ksu.edu.sa	Primary-days to sx resolution; reduced days to recovery for cough 9.1±0.8 days, 1000 IU vs 6.2±0.8, p=0.007 and ageusia 16.9±1.7 days, 1000 IU vs 11.4±1.0, p=0.035 but not other sx; d-dimer lower p=0.02
AlSafar[85]	522 but 58 missing BMI data excluded	464	Blood level of D	Multicenter, observational Aug 2020 – Feb 2021	Department of Health Sciences, College of Natural and Health Sciences, Zayed University,	Severity, mortality; 26 died; <12 ng/ml OR_{adj} 1.76 (1.19-2.61, p=0.005) for severe disease; 2.58 (1.01-6.62,

PI	Arms	N	Dose	Design	Contact	Outcomes
					Abu Dhabi 144534, United Arab Emirates Fatme.AlAnouti@zu.ac.ae	p=0.048) for mortality but no diff for <20 ng/ml
Vasheghani[86]	Blood level 88 used D Mild 14 (21%) Mod 42 (19) Sev 31 (20) Crit 1 (1)	508 (66 in ICU)	D3 blood level	Cross-sectional Mortality, D use Died 7 (12.7%) Partial recov 47 (18.6) Compl recov 34 (17) P=0.58 Multivariate, OR .97 (0.96-0.99, p=0.04)	dr_mrezaie@yahoo.com	13% mild,42% moderate, 36% severe, and 9% critical; low serum D associated with severe disease, ICU admission and mortality; D level ng/ml Total 508-28.6, mild 68-31.8±25.7, mod 217-30.4±22.4; sev 157-28.2±20.8, crit 20.4±16.4, p=0.001
Sulli[87]	65 COVID 65 matched controls	130	Blood level	Prophylaxis; elderly (mean age 76 y.o.)	Laboratory of Experimental Rheumatology and Academic Division of Clinical Rheumatology,Dept Int Med, U of Genova, IRCCS San Martino Polyclinic, 16132 Genova, Italy; emanuele.gotelli@live.it (E.G.); mcutolo@unige.it (M.C.)	Lower D level 7.9 vs. 16.3 ng/mL, p = 0.001. (Wow.) more severe lung involvement, longer disease duration and risk of death, in elderly COVID+
Meltzer[88]	Black – 2,288 White – 1,999 Other – 351	4,638	Calcifediol level	Retrospective cohort study 3/3-12/30/20 for data Analyzed 9/11/20-2/5/21	David O. Meltzer,MD, PhD, University of Chicago, 5841 S Maryland, MC 5000, Chicago, IL 60637 dmeltzer@medicine.bsd.uchicago.edu	Risk of positive higher in blacks than whites with 30-39.9 ng/ml, 2.64x greater risk; no stat sig associations in white pts
Ünsal[89]	27 < 20 ng/ml Vs 29 ≥ 20 ng/ml	56	Blood level, < or >20 ng/ml Avg daily use, D3 800-1000 IU/day	Retrospective analysis Prophylaxis March-October, 2020	Y. A. Ünsal yaseminunsalay@gmail.com	Pts who did not use D supp prior to admission more likely dx'd w/pneumonia (p=0.004); <20 lower lymphocytes, Hgb; higher CRP, N/L; Dx pneumonia in 4 (22.2%) vs no D use 14 (77.8%)

Abx – antibiotics; BL – baseline; D3 – cholecalciferol; DM – diabetes mellitus; HQ/Az – Hydroxychloroquine/azithromycin; Hgb – hemoglobin; HR – hazard ratio; IM – intramuscular injection; ITT – intent-to-treat; MN – micronutrients; N/L ratio – neutrophil/lymphocyte ratio; OR – odds ratio; px – prophylaxis; OSCI – Ordinal Scale for Clinical Improvement; tx – treatment; RR – risk ratio. CI – confidence intervals are 95% unless otherwise noted

ZINC

Zinc is important in immunity as well as maintaining intracellular redox balance (e.g., Cu/Zn superoxide dismutase). There is also evidence that it inhibits the replication of SARS-CoV-2 (which is why it has been used with hydroxychloroquine and other ionophores like quercetin may be a good combination.) It comes in a variety of forms as a supplement including sulfate, picolinate, gluconate, amino acid bound and chloride. Too much zinc may deplete copper stores so over-the-counter supplements often contain it. There have been a number of cell culture and animal studies; diarrhea in calves with viral infections (DBPC). A rapid review suggests evidence for use as prophylaxis and treatment. Two studies of each underway; supplementation may be antiviral, may help offset vascular complications; low levels have been associated with development of severe disease.[90,91,92,93,94,95]

THE UPSHOT:

There are 20 trials described below. Of these, 9 trials reported positive results, 4 trials reported null or negative results. The remainder of the studies (7) described the serum levels of zinc and/or the effect on progression potential.

PI	Arms	N	Dose	Design	Contact	Outcomes
Elalfy[96]	Triple – 62 SOC – 51	113	NTZ – 500 mg Ivn – 6 mg (wt based dosing) Riba –400 mg tid Zinc – 30 mg bid	Phase 1, Open label, prospective, mild-early moderate 5/15-10/15/20	Hatem Elalfy, Tropical Medicine and Hepatology Department, Mansoura Faculty of Medicine, Mansoura University, Mansoura, Egypt. elalfy_hatem66@yahoo.com, elalfy2004@mans.edu.eg	Primary – Sx, viral clearance Dosing IVN every 72 hrs, 2 weeks SOC neg swab at 15 d 13.7% vs 30.6% in tx arm. Note: Unclear if Table 2 is baseline or results? No sx in SOC 2 (3.9%) vs 17 (27.4%) tx; more dyspnea in SOC arm. No deaths. AEs – GI, palpitations, leukocytopenia, lymphocytopenia in tx arm
Derwand[97]	HCQ - 141 Zn – 136/141 Az - 133 Control – 377	518	Zn SO4 – 220 mg (50 mg zinc) HCQ–200 mg bid Az–500 mg/d	Retrospective case series, NYS Fig 1 study pop is exercise in confusion 3/18 – 5/14/2020	Alexion Pharma Germany GmbH, 80687, Munich, Germany	Primary rate of hospitalization, mortality; 4/141 (2.8%) hospitalized vs 58/377 (15.4%), OR 0.16 (0.06-0.15, p<0.001); 1/141 vs 13/377 (3.4%) died, OR 0.2 (0.03-1.5, p=0.12). No cardiac side effects, but weakness (21%), nausea (14%), diarrhea (11%)
Carlucci[98]	HCQ-Az-Zn–411 HCQ-Az – 521	932	Zn SO4 – 220 mg (50 mg zinc) bid 5d HCQ–400 mg load; 200 mg bid Az–500 mg/d	Retrospective, observational 3/2-4/11/20	Joseph Rahimian, Joseph.Rahimian@nyulangone.org	Adding zinc – no effect on hosp, vent or ICU duration; univariate analysis, increased discharge to home OR 1.53 (1.12-2.09), decreased vent need, admission to ICU, mortality OR 0.449 (0.271-0.744)
Yao[99]	Zn – 196 Control – 46	242	Zn SO4 – 440 mg (100 mg zn)	Retrospective review 4/11-4/21/20	Leo Anthony Celi, MD, MIT Critical Data, Harvard-MIT Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139; e-mail: LCeli@mit.edu	Mortality for Zn HR_{adj} 0.66 (0.41 – 1.07, p=.09) (Weird statistical maneuvering? Observation period too short?
Frontera[100]	Zn – 1,006 Ctl – 2,467 Matched – 1,356	3,473	Zn 220 mg (50 mg elemental) PO once, twice daily+ionophore (HCQ, HCQ–400 mg load; 200 mg bid)	Cohort study, propensity score matched (1,356) 3/10-5/20/20 They note alternative ionophores to HCQ: hinokitiol, resveratrol, quercetin, or epigallocatechin-gallate	jennifer.frontera@nyulangone.org	Primary, in-hosp death; mortality for Zn+ionophore, 24% reduced risk of in-hospital mortality HR_{adj} 0.63, (0.44-0.91, p=0.015); not w/either alone. Total zn dose, 1100 mg over median 3 d (1.5-4.3); 121/1,006 (12%) vs 424/2467 (17%) died, p<0.001 but longer hosp stay and on vent days
Abd-Elsalam[101]	Zn+HCQ – 96 HCQ – 95	191	Zn 220 mg (50 mg zinc) bid HCQ–400 mg load; 200 mg bid	RCT, 3 centers Open label (blinding not mentioned or described) 6/23-8/23/20	Sherief Abd-Elsalam sherif.abdelbaky@med.tanta.edu.eg	Primary – recovery w/in 28 d, vent need, death; recovery 79.2% zn, 77.9% HCQ, p=0.969; vent, p=0.537 4 and 6 needed, mortality (5 each arm) p=0.986

PI	Arms	N	Dose	Design	Contact	Outcomes
Mulhem[102]	1,596 (49.6%) rec'd zinc	3,219	Zinc dose unknown	Retrospective cohort study 3/13-4/29/20	Elie Mulhem; elie.mulhem@beaumont.edu	Primary – discharge; mortality. Of 3,219, 2,703 discharged, 516 died. Among zn users, 1,340 (49.6) discharged; 256 (49.6%) died (p=0.987); OR of dying in hospital with zinc, 0.50 (0.39-0.64), p<0.001
Gadhiya[103]	Survivors – 228 Died – 55 Zinc users – 54	283 (19.4 % died)	Unclear (many interventions reviewed)	Retrospective cohort study, PA, 3/1-5/31/2020	Panupong Hansrivijit hansrivijitp@upmc.edu	Primary – mortality Overall 33/228 (14.5%) lived, 21/55 (38.2%) died, p<0.001; in-hosp mort OR 3.650 (1.898-7.042, p<0.001); however, OR_{adj} 1.517 (0.651-3.546, p=0.3340 (Model 2 sex, ethnicity, obesity, need for oxygen therapy and ICU admission.)
Al Sulaiman[104]	Zn – 140 No Zn – 598 Matched - 266	738	Zn sulfate - 220 mg (50 mg zinc)	Retrospective, propensity-matched 3/1 – 12/31/20	Khalid Al Sulaiman alsulaimankh@hotmail.com	Primary – in-hospital, 30-day mortality; neither parameter affected, 56/131 (42.7%) control vs 44/131 (33.6%) died in hospital, HR 0.65 (0.41-1.01; p= 0.05), 45/129 (34.9%) control vs 35/130 (26.9%) died 30 days: HR 0.67 (0.45-1.00; p= 0.05); Acute kidney injury 41/131 (31.3%)control vs 53/133 (39.9%) HR 1.80 (1.08-3.0, p=0.02)
Elavarasi[105]	Zinc – 486 (28.8%) Ctl? – 1,687	2,080	Unspecified	Retrospective cohort study of cases, deaths April-June, 2021	Prof Sushma Bhatnagar Head, Department of Onco-anesthesia and Palliative care All India Institute of Medical Sciences, New Delhi sushmabhatnagar1@gmail.com Mobile:- +91-9811326453	Case fatality rate, 19.5%; 440 (90.5%) discharged; 46 (9.5%) died, p<0.001. OR 0.2 (0.1-0.4, p<0.001) adjusted for age, gender, comorb, BL clin, lab parameters; OR 0.3 (0.2-0.5, p<.001) adj for those and in hospital complications
Israel[81] (See Vitamin D)	Cohort 1 – 6,530 ? 6,202 w/5:1 controls (32,650) Cohort 2 – 6,953? 6,919 w/2:1 controls (13,906)	60,039	Unspecified	Case control study of COVID-19 patients and risk of hospitalization based on medication use; controls are not hospitalized	dr.ariel.israel@gmail.com (AI); eytan.ruppin@nih.gov (ER)	Primary, OR for hospitalization for various tx: outcomes – zinc, no use in cases, 10 in controls (OR=0.869, 95% CI [0.0 to 0.892], p<0.04).
Seet[106]	HCQ – 432 Ivermectin – 617 I throat spray – 735	3,037	Oral zinc (80 mg/day)/vitamin C (500 mg/day) combination; oral vitamin C, 500 mg/day	Open label RCT (cluster randomized) for prophylaxis among healthy young men for	See Combination Trials	Primary is SARS-CoV-2 infection. Absolute reduction (note RR CI is 98.75% due to Bonferroni corrected alpha of 0.0125); Z+C– 300/634 47% (27, 72) 0.67 (0.38-1.08). No serious disease, death in any arm

PI	Arms	N	Dose	Design	Contact	Outcomes
	Zinc/C – 634 C – 619			42 days in dormitory		
Patel[107]	IV Zn – 15 Placebo – 18	33	High dose IV Zinc chloride 0.5 mg/kg/day over 3 hours to 7 days	Phase IIa, DBPC RCT Target enrollment not reached due to lack of cases	Joseph Ischia, Department of Surgery, The University of Melbourne, Austin Health, Heidelberg, VIC, Level 8, Lance Townsend Building, Australia. jjischia@unimelb.edu.au	Primary, Serum level No AE but injection site reactions in Zn arm; BL serum 6.9 ± 1.1 and 7.7 ± 1.6 µmol/l (placebo); infusion increased to 10.7 µmol/l by day 6; by day 28, clinical outcomes about the same; 2/15, 3/18 died
Yasui[108]	49 – mild-mod 13 – severe	62	Serum level assessment	Serum zinc level assessment (<70µg/dL hypozincenemia	yasui-yaku@sakai-hospital.jp (Y. Yasui), yasui@mb.kyoto-phu.ac.jp (H. Yasui)	Prolonged low level of zinc a serious risk factor for severe COVID, p=0.020 along with low LDH, p=0.026
Jothimani[94]	47 – infected (27 deficient) 45 – controls	47	Serum level assessment	Prospective study of fasting zinc at admission May 17-27, 2020	dinesh.jothimani@relainstitute.com (D. Jothimani)	Zinc deficient developed more complications; 5/27 died vs 0/20 w/COVID; overall lower than controls median 74.5 (interquartile range 53.4–94.6) mg/dl vs 105.8 (interquartile range 95.65– 120.90) mg/dl (p < 0.001); 27 (54%) with deficiency had, compared to COVID with sufficient had *higher rates of complications (p = 0.009), acute respiratory distress syndrome (18.5% vs 0%, p = 0.06), corticosteroid therapy (p = 0.02), prolonged hospital stay (p = 0.05), and increased mortality (18.5% vs 0%, p = 0.06). The odds ratio (OR) of developing complications was 5.54 for zinc deficient COVID-19 patients*
Vogel-González[109]	58<50 µg/dL 191≥50 µg/dL	249	Serum level assessment	Observational prospective cohort study 3/9-4/1/2020	rguerri@psmar.cat Tel.: +34-932-483-251; Fax: +34-932-483-249	Level <50µg/dL (7.6 µM) correlated with worse clinical progression, longer stabilization, higher mortality; note BL pts<50 had trends toward more DM, dyspnea, hi CRP. 12/58 vs 9/191 died (p<0.001)
Gonçalves[110]	214<70 µg/dL 55≥70 µg/dL	269	Serum level assessment	Observational, pts admitted to ICU 3/15-5/3/2020	Thiago Jose Martins Gonçalves, MD, Rua Lourenço Marques, 158 –Vila Olímpia, São Paulo – SP, Brazil thiagojmg@yahoo.com.br	Association of low zinc with ARDS OR 14.4 (6.2–33.5, p<0.001), and adjusting for BL variables OR 15.4 (6.5–36.3; p<0.001)
Fromonot[111]	152-COVID 88-non COVID	240	Serum level assessment	Observational, prospective 4/24-5/23/20	julien.fromonot@univ-amu.fr (J. Fromonot)	Hypozincenemia more prevalent in COVID 27.6% vs 11.4%; p ¼ 0.003); associated with respiratory complications within 10 days OR 10.9 (2.3-5.16, p<0.002); did not find lower levels of selenium

PI	Arms	N	Dose	Design	Contact	Outcomes
du Laing[112]	79-Study 1 59-Study 2	138	Serum level assessment, Se, Zn, Fe, Cu, GPx, selenoprotein P	Cross-sectional, observational study at two sites in Ghent; Plasma, Study 1, d1, 7 Serum, Study 2, d1 only	Gis du Laing gijs.dulaing@ugent.be	Low Se observed; death, risk of cancer, DM, chronic cardiac disease in depressed; 10/79 died; all had Se def, range 23-64 µg/l, frequently <45 µg/L (severe def); Zn status <66 µg/dl in majority of pts died; Cu status depressed

ARDS – acute respiratory distress syndrome; Az – azithromycin; CRP – C-reactive protein; DM – diabetes mellitus; HCQ – hydroxychloroquine; Ivn – ivermectin; MN – micronutrient; NTZ – nitazoxanide; riba – ribavirin; sx – symptoms; tx – treatment

VITAMIN C

A great deal of literature (and no small amount of criticism) has dwelt upon the potential for vitamin C in the management of a range of conditions. Its efficacy, when it has been observed, in trials of sepsis and ARDS, and potentially in cancer treatment, is generally via IV administration. Oral administration essentially doesn't work in those settings. Some protocols for how to properly prepare, dose and administer it has been provided by a number of institutions such as the Riordan Institute.[113] Vitamin C may also improve coagulability. "Vitamin C exerts its antiviral properties by supporting lymphocyte activity, increasing interferon-α production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function."[114] The studies have been mixed in terms of its use in managing COVID-19.

A case report of recovery from vent following IV C administration small Chinese clinical trial showed significant mortality reduction among severely ill; time to 50% reduction in symptoms in 5.5 days vs 6.7 for placebo, which was however not statistically significant; vitamin C is important for preventing kidney injury; may help alleviate the cytokine storm; a retrospective review of oral use (500-1500 mg) vs none showed a trend to decreased overall mortality, increased extubation rate and ICU mortality, suggest IV is better; vitamin C and other micronutrients may reduce ACE2 expression (though unclear if this is a good thing or not or clinically relevant). [115,116,117,118,119,120,121,122,123,124,95,125,126,127]

While the use of high doses of the vitamin have been controversial over the years, there has been accumulating data underscoring the potential benefit in a number of settings, notably pneumonias and acute respiratory distress syndrome (ARDS), which bear some resemblance to COVID-19, with some key pathological differences. There is *in vitro* data that suggests that ascorbate binds to the SARS-CoV-2 protease, $3CL^{pro}$, which is found in the nsp5 region of SARS-CoV-2 but is also found in other viruses such as picornaviruses. A binding and inhibition of activity was found at 38 millimolar/liter concentration of sodium ascorbate, which is a higher concentration than other inhibitors.[128] This may partially explain why higher doses, of 1.5 g/kg body mass, may be required for antiviral activity, however, there are multiple other pathways that vitamin C can re-regulate a system strained by excessive reactive oxygen species. These include improving immune, coagulation and inflammatory parameters.

A review paper assessed the potential for vitamin C, either as an oral or intravenous agent, in the management of a range of infectious diseases and pneumonias. While oral agents dosed at 2-8 grams per day may act as a prophylaxis and reduce incidence of infection or shorten duration of symptoms, intravenous ascorbate, in the range of 6-24 g/day has substantial evidence for managing various respiratory infections. The benefits observed in some studies provide evidence for reduced mortality, shortened ICU stays and time on mechanical ventilators. They note that many with respiratory infection have low blood levels of the vitamin.[129] Such deficiencies were identified early in observational studies of patients with severe COVID-19.[130,122]

There are numerous negative studies as well. One randomized, open-label study found no benefit of C+thiamine+hydrocortisone vs. hydrocortisone alone in mortality or vasopressor use, n=216 in 10 ICUs in 3 countries in sepsis patients although these data are disputed. Blood level of vitamin C was undetectable in 4 and very low levels in patients with ARDS (no sepsis).

For example, the VICTAS trial was a randomized, double-blind, placebo-controlled trial with an adaptive sample-size approach for patients with sepsis. The study evaluated the use of 1.5 g of vitamin C administered every hour intravenously along with hydrocortisone and 100 mg of thiamine (often used to ameliorate any kidney trouble). A total of 501 patients were randomized to the intervention or to placebo. The outcomes were mortality and number of days on ventilator support. Essentially, the trial found no difference in outcomes for either arm.[131] There were a number of problems with the trial. First, the study was ended early due to withdrawal of funding by the sponsor, resulting in the study being significantly under-powered. One of the authors also served on the data safety monitoring board (DSMB) and undertook oversight of the statistical analysis. This is a violation of DSMB guidelines that underscore the need for independence of the DSMB. In addition, it was conducted among 43 hospitals, an approach that may dilute results.

Others examined the potential of IV vitamin C to manage elevated mediators of inflammation such as IL-6 and endothelin-1. Elevations of these may be of particular concern to older patients, particularly those with co-morbidities such as obesity, hypertension, tobacco smokers and persons of color. Vitamin C has shown some evidence in reducing these markers in other settings. Given its safety, low cost and potential benefit, clinical trials need to be undertaken.[132] The ideal dose and duration of vitamin C has not been firmly established. Some researchers suggest much higher doses than those generally used in the studies described below. Use of 150 grams of sodium ascorbate per 40 kg of body weight administered in an IV over 7 hours was shown to have dramatic clinical benefit in a sheep model of gram-negative bacteria induced sepsis. Dramatic improvement was observed in cardiovascular, hepatic, pulmonary and renal function in the animal. One patient who received 60 grams saw improved arterial function, improved renal function and increased arterial blood oxygen levels.[133] The patient received 1g/kg over 6 hours for a total dose of approximately 60 grams, much higher dosing than given in most studies.[134]

THE UPSHOT:

There are 17 trials described below. Of these, 9 trials reported positive results, 7 trials reported null results. One described the serum levels of Vitamin C and/or the effect on progression potential.

PI	Arms	N	Dose	Design	Contact	Outcomes
Zhang[135]	IVC – 27 Plac – 29 Placebo (bacteriostatic water) vs IV vitamin C	56	12 g C, 50 ml every 12 h for 7 days at a rate of 12 ml/hour	DBPC RCT, 3 hospitals Critically ill 2/14-3/29/2020 (Ended early due to rapid decline in critical patients as outbreak was controlled in China)	xianghuisky@163.com Pengzy5@hotmail.com	Primary: vent free days; no difference between arms; secondary, more rapid improvement in PAO2/FiO2 at day 7, 229 vs. 151 mmHg, 95% CI 33 to 122, *P* = 0.01. Lower IL6 in tx arm; SOFA score decreased 3.5 to 3.0 in C group and from 2.0 to 6.0 in placebo but not stat sig; no SAE; lower mortality trend?
Kumari[136]	IV C – 75 SOC – 75	150	IV C, 50 mg/kg	RCT, open label Severe COVID March-July, 2020	Amber Rizwan, amber_aljazeera109@hotmail.com	No difference in vent use (12/75 IVC, 16% vs 15, 20%, p=0.4) or mortality (7 on IVC, 9.3% vs 11, 14.6%, p=0.3); symptom-free earlier (7.1 ±

PI	Arms	N	Dose	Design	Contact	Outcomes
						1.8 vs. 9.6 ± 2.1 days, p<0.0001); fewer days in the hospital (8.1 ± 1.8 vs. 10.7 ± 2.2 days, p<0.0001
Gao[137]	IVC – 46 SOC - 30	76	6g/12 hr 1st day; 6g/day 4 days	Comparative, not randomized? Well matched in terms of severity, co-morbidities, etc.	Shouping Gong, shpingg@mail.xjtu.edu.cn , Dengfeng Gao; gaomedic@mail.xjtu.edu.cn	Primary – mortality, clinical 28-day mortality; 1/46 HVC vs 5/30 SOC, HR=0.14, 0.03-0.72; 63.9% no C vs 36.1% O2 requirement (no p value)
Hiedra[138]	No comparator	17	IV C, low-moderate, 1 g q8h, 3 days	Case series, Af-Am pts, 59%; older; hypertension in 8 (47%); 4 pts rec'd tocilizumab, 14 rec'd HCQ, 10 methylprednisolone	Raul Hiedra hiedrara@einstein.edu	Reduced ferritin and d-dimer; trend in improvement of FiO2%; 12% mortality, 17.6% on vent; no differences in intubation or mortality based on use of other meds; suggest effect on vent, mortality for older with more co-morbidities modest; no AEs observed
Bakyaraj[139]	C – 5,422 (62%) Non – 4,408 (49%)	8,634	4 g/day, liposomal	All COVID-19 pts admitted, 3/1-5/31/21	Ravikumar, Government Medical College and ESI Hospital, Coimbatore, India	Morbidity "2/3 less" on tx; compared to admission based on needing oxygen or not; oxygen for 34% of C, 42% of non-C; ICU C 223 (2.5%) vs no C 701 (7.8%); more sx improvement 10 day 97% in C, 88% no C* (see footnote)
Vishnuram[1][40]	C – 5,422 (62%) Non – 4,408 (49%)	8,634	4 g/day, liposomal	All COVID-19 pts admitted, 3/1-5/31/21	Akila, Government Medical College and ESI Hospital, Coimbatore, India	Mortality: 164/8,634 (1.9%) vs 10/241 (4%) not receiving C died
Suna[141]	170 – C 153 – SOC	323	2g/day, oral?	Retrospective, chart review pts admitted September, 2020	drayperi@yahoo.com O. Ayperi	37 pts excluded who rec'd vit. D C pts saw declines in CRP, d-Dimer; higher ferritin in C arm at baseline and end of study; no notable difference in outcomes; 17/153 in C arm died (11.1%), 24/170 in no C (14.1%)
Xia[142]	ACI – 70 (37 IVC) NACI – 43 (14 IVC)	113	IV 100 mg/kg every 6 hours, 1 day; 100 mg/ kg every 12hrs, 5d in hospital	Retrospective, with ameliorated (ACI) or non-ameliorated cardiac injury (NACI); 2/1 – 3/10/2020	Guozhi Xia hatozy@126.com	Primary – cardiac injury Amelioration of cardiac injury higher in IVC group, in logistic regression analysis, *OR* 2.420, (1.022-5.729, *p*=0.044); sig reduction in hsCRP, IL6, IL8, TNF by day 21
Mulhem[102]	794 rec'd vitamin C (24.7%) 2,703 discharged	3,219	Unknown dose	Retrospective cohort study 3/13-4/29/20	Elie Mulhem; elie.mulhem@beaumont.edu	Primary - mortality 637 (23.6) discharged; 157/516 (30.4%) died,

PI	Arms	N	Dose	Design	Contact	Outcomes
	516 died					p=0.001; OR 1.40 (1.08-1.81), p=0.011
Patel[143]	96 – C, 80 – control	176	500-1500 mg oral	Retrospective, single center	Abstract; no identifying information	Trend toward reduced mortality, with 78% extubated in C and 59% in control, but not stat sig
Zhao[144] (2021)	55 each arm (age, gender matched, moderate disease, no mild or severe)	110	100 mg/kg/day at 1 g/h for 7 days from admission	Retrospective, propensity-matched, case control study 3/18-4/18/2020 vs control, previously hospitalized 1/18-3/18	Enqiang Mao maoeq@yeah.net Jieming Qu jmqu0906@163.com	Primary outcome – progression 4/55 vs 12/55 developed severe disease, RR 0.28 [0.08, 0.93], p=0.03. Improvements in d-dimer and thromboplastin, CRP, CD4; Day 7, 2/21 on C and 10/22 had systemic inflammatory response syndrome (SIRS) (RR 0.13, 0.02-0.68, p=0.008)
Zhao[145] (2020)	6 severe, 6 critical patients (Critical all on vent, 3 with ECMO)	12	Median (IQR), mg/kg (body weight)/day : 162.7 (71.1–328.6) for severe; 178.6 (133.3–350.6) for critical	Retrospective, over 7 days treatment 1/22-4/11/2020	Enqiang Mao. Emergency Department of Ruijin Hospital, School of Medicine, Shanghai Jiao Tong University, Ruijin 2nd Road 197, Shanghai, China. maoeq@yeah.net	Primary – Imm., inflam. Markers CRP dropped through day 7; lymphocyte and CD4 normalized by day 3; improvements in PaO2/FiO2 SOFA scores, platelet level in severe; improvements in critical pts were not as robust.
Saeidreza[146]	30 cases, 30 controls HCQ, lopinavir/ritonavir	60	IV C 6 g/day as 1.5 g IV q6h for 5 days	Randomized, open label April-May, 2020, Tehran	Fereshteh Ghiasvand ghiasvand_62@yahoo.com	Both arms saw improvement in blood O2 and fever; 3 died in each arm; no differences
Sulaiman[147]	C – 158 (21.3%) Ctl – 581 (78.7%) 296 after propensity matching	739	1000 mg enterally once daily for 11 days (median) Ascorbic acid w/in 24 hrs	Retrospective, propensity-matched; 2 Saudi hospitals 3/1-12/31/2020	Khalid Al Sulaiman alsulaimankh@hotmail.com	No mortality or ICU mortality difference (OR 0.77, 0.476-1.234); but significantly lower in-hospital mortality vs control, 33.6% vs.49.3%, p=0.0006). However, after propensity matching, difference not statistically significant (32.4% tx vs. 41.6% ctl, p=0.11). Lower incidence of thrombosis with vitamin C
Gadhiya[103]	Survivors – 228 Died – 55	283 (19.4 % died)	Unclear (many interventions reviewed)	Retrospective cohort study, PA, 3/1-5/31/2020	Panupong Hansrivijit hansrivijitp@upmc.edu	Primary mortality: 57 got C; 38 lived, 19 died (33%), p=0.003. OR adjusted for age, sex, ethnicity, obesity, need for oxygen therapy and ICU admission 1.008 (0.440-2.313, p=0.985).

PI	Arms	N	Dose	Design	Contact	Outcomes
						Among critically ill, 39 rec'd vitamin C, 22 survived, 17 died (p=0.548)
Xing[148]	25 treated, 6 not; 60 healthy volunteers	31	100 mg/kg/day	Plasma level Observational	luhongzhou@fudan.edu.cn (H. Lu), maoeq@yeah.net (E. Mao), zhanglijun1221@163.com (L. Zhang)	HPLC plasma level of C at baseline, after tx compared to negative controls; 8 samples (6 obtained from patients not treated with VC and 2 before dosing) were 2.00 mg/L (0.5–4.90). 5-fold lower than healthy, mean VC concentration of 9.23 mg/L (3.09−35.30.) (n =51). After IVC, mean plasma concentration increased to 13.46 mg/L (3.93–34.70) (n = 36), similar to control
Krishnan[149]	60 (39%) survived, 92 (61%) died	152 on vents	79 rec'd C total (dose unclear)	Retrospective, of 902 admitted, those on vent, observational Michigan, 3/10-4/15/2020	sakrishna@med.wayne.edu : S. Krishnan, patel-kinjal@cooperhealth.edu : K. Patel	Decreased risk of mortality in those treated with vitamin C 39 rec'd C survived (65%) vs 40/92 (43%), p=0.0066, corticosteroids and those with greater urine output. (Only 16 rec'd D total, 8 (13%) survived, 8 (9%) died)
Li[150]	C – 8 Matched - 24	8	1.5 g IV C q6h, 4 days	Retrospective, observational study, ICU severe patients	Matthew Li, New York City Health & HospitalsQueens, 82-68 164th Street, Jamaica, NY 11432, USA nymatthewli@gmail.com	Primary: in-hospital mortality. Higher mortality in C group: 7 (88%) vs 19 (79%), p=0.049; no differences in SOFA, vent, ICU length
Özgünay[151]	C – 32 Group 2 (no C) not matched but similar baseline	160	6 g/day	Retrospective, observational, 3/1- 8/1/2020	*Şeyda Efsun Özgünay, MD., Associate Professor, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Department of Anesthesiology and Reanimation, Mimar Sinan Mah., Yıldırım, 16290, Bursa, Turkey seyda-efsun@hotmail.com Tel: +90 535 9723603*	Elevated neutrophil/lymphocyte ratio (NLR) correlative with poor prognosis; C given to those admitted to ICU with high NLR. Vitamin C had no effect on NLR nor mortality, inflammatory markers, ICU length. (Nor did steroid or other meds used in both populations)

DBPC – double blind, placebo controlled; HR – Hazard ratio; IQR – interquartile range; Obs – Observational; OR – Odds Ratio; Prsp – Prospective; RCT – randomized controlled trial; SOC – Standard of care; SBPC – single blind placebo controlled

*Bakyaraj notes: "89 % of patients improved symptomatically on 3-4 days with oral highdose liposomal vit-c The tiredness and myalgia improved in 76 % patients on third day. Anosmia improved in 4 days in 88 % of patients Sore throat and cough improved on 3-4 days in 90 % of patients and diarrhoea improved on 3rd day in 72% of patients." They compared to patients who did, did not receive O2 or admission to ICU; 5-d, 76%, 10-d, 97% improved for C; 5-d, 68%, 10-d, 88% improved for no C (standard care)

VITAMIN A

Fat-soluble vitamin A comes in three main varieties, retinol, retinal and retinoic acid. There are also a variety of water-soluble carotenes, perhaps the most famous being beta-carotene. Few studies but the importance of retinol in the pathogenesis of SARS-CoV-2 is gaining increased interest.[152] Due to the

potential for side effects at high doses, there has been some understandable reluctance. However, there are a range of mechanisms of action that make it potentially valuable and usually the side effects are temporary, if they arise. The anti-inflammatory effects of the vitamin have been well characterized since early in the 20th century. In the gut, vitamin A is transformed into retinyl esters that are hydrolyzed into retinol and stored in the liver. When it gets into the circulation, it is taken up and oxidized to retinal by alcohol dehydrogenase (ADH) and then, with another enzyme, into one of the three forms of retinoic acid. This then is a vital part of helping immune cells differentiate while modulating the function of dendritic cells, B cells, natural killer cells and so on. Indeed, it was found that a bit of vitamin A helped kids to overcome measles (again, malnourishment is bad for individual health and community health!) Because it activates innate immune responses and vitamin A may increase ACE2 receptor expression, concerns that this might enhance infection resulted in cautionary warnings. However, one of the functions of ACE2 is to transform vasoconstrictive angiotensin II to the vasodilator, angiotensin 1-7. The lack of the latter may be a serious piece of the SARS-CoV-2 pathogenesis puzzle. In one review, based on data in studies of its use in measles, Ebola and other viral infections, they note use of 200,000 in mild disease and up to 300,000-500,000 IU during the acute and critical phase of the infection.[153] This is not unreasonable given that the use at such a high doses, aside from having precedent in other disease settings, would be limited to a few days at most.

The APOLLO trial in the UK will test the potential of vitamin A to reverse the loss of smell (and taste) many suffer with long COVID. This is based on some research undertaken in Germany. See https://rhinology-group.uea.ac.uk/apollo-trial/.

THE UPSHOT:

There are 3 trials described below. One positive, one possibly negative (tho really a plasma level study in ICU patients), one plasma level. (Note that Sarohan is also intrigued by the potential of the retinoid system playing an important role in SARS-CoV-2 disease pathogenesis.)

PI	Arms	N	Dose	Design	Contact	Outcomes
Al-Sumiadai[154]	Vit A – 50 Placebo – 50 Contacts: Vit A – 97 Placebo - 112	150	200,000 IU, each day, 2 days	Cross sectional, 2 groups Mild-to-moderate disease June 2020	CIB/ Ministry of Health- Anbar health directorate/Iraq alsumaidaidrmah@gmail.com	Primary – duration of symptoms; prophylactic effect on treated contacts. Group 1 – Sig improvement sx; not sig SpO2, improvement; duration 2.9 days vs 4.64 (placebo); 2 (2.9%) in A arm hospitalized vs 6 (12%). Group 2 – 20/97 (21%) infected vs 65/112 (58%) in placebo, with former shorter (4.6 vs. 6.72 days) period of symptoms
Sarohan[155]	Severe – 27 Vit A – 10 plus fatty acids* (all severe pts) 23 – mild cases 12 died No sx – 23	50	Serum level. Severe patients. 10/27 rec'd A	Observational, plasma level	Aziz Rodan Sarohan, Shagreen Health Life Sciences Ltd. Yenisehir Mah, Mehmet Nurdag Cad, Teras 2 Apt No: 28/26 Artuklu, Mardin, Turkey azizrodan@gmail.com	Retinol levels significantly lower ($p<0.001$) in patient group, 0.37 mg/L vs 0.52 in comparator; 10 rec'd A, unknown dose, some improved blood level; 9/10 died while 4/17 not rec'g A did; unknown if difference due to higher co-morbidity or vitamin A; treated with HCQ, favipiravir
Tepasse[156]	COVID – 40 Critical – 22 Severe – 9	87	Plasma level	Prospective, multi-center, cross-sectional;	Department of Medicine B, University Hospital Muenster, 48149 Muenster,	Primary – association of low level with disease severity. Vit A Mod: 0.48 (0.29–0.56); Severe: 0.32 (0.21–0.42);

PI	Arms	N	Dose	Design	Contact	Outcomes
	Moderate – 9 Controls - 47			age-matched COVID convalescent (plasma donor) March-June, 2020	Germany; phil-robin.tepasse@ukmuenster.de Tel.: +49-251-834-4882	critical: 0.25 (0.16–0.38); control: 0.60 (0.51–0.69) <0.001. A <0.2 mg/L OR 5.54 (1.01-30.26, p=0.048) for ARDS; OR 5.21 (1.06-25.5, p=0.042) for mortality

HCQ – hydroxychloroquine; Sx – symptoms

*From Sarohan article: The contents of the formulas and TPN (nasogastric) administered to the patients were given below:
1. Resource® Diabet Nestlé Health Science. Administered to 3 individuals. 24 pcs, 10 pcs and 10 pcs. Protein: 28% E; 14 g/200 ml (Casein), Fat: 24% E; 5.4 g/200 ml (saturated, single-poly unsaturated fat), Carbohydrate: 44% E; 21.8 g/200 ml, Fiber: 4% E; A vial contains 4 g of soluble fiber. (Partially hydrolyzed guar gum).
2. Nutrivigor® Abbott. e220 ml 1.5 kcal/ml. 1.5 g CaHMB 330 kcal. Administered to 2 individuals, 10 pcs and 29 pcs. Contains 20g Protein, 500 IU Vitamin D.
3. Omegaven® 10% 100 ml infusion emulsion. Fresenius container. 3 pcs were used in 1 individual. 100 ml contains; 10.0 g fish oil refined at high temperature: 1.25-2.82 g Eicosapentaenoic Acid (EPA), 1.44-3.09 g Docosahexaenoic acid (DHA), 0.015-0.0296 g dla- Tocopherol, 2.5 g Glycerol, 1.2 g Purified egg phospholipids, 0-0.002 g Sodium Hydroxide (pH regulator), 0.003 g Sodium oleate (emulsifier).
4. Oligoclinomel N7-1000 E electrolyte amino acid solution, glucose solution, lipid emulsion.1500 ml three-chamber bag. 7 pcs were used in 1 individual. 100 ml contains refined olive oil (80%) + Refined soya oil (20%): 4 g, essential amino acids and Sodium acetate 3EE0: 0.245 g, Sodium glycerophosphate SEEO: 0.214 g, Potassium chloride: 0.179 g, Magnesium chloride 6H2O: 0.045 g, Glucose (17.6 g glucose monohydrate):16 g, Calcium chloride 2H2O: 0.030 g.
5. Novasource® GI Control 500 ml. Nestle. 8 pcs were used in 1 individual. Protein 15% E; 20.5 g/500 ml (milk protein), Carbohydrate 53% E; 72.5 g/500 ml, Fat 29% E; 17.5 g/500 ml. (saturated, single-poly unsaturated fat, MCT, omega-3).
6. Fortimel Energy. 200 ML. Nutricia. 28 pcs were used in 1 individual. 100 gram contains; 5.80 g Fat, 0.700 g Saturated Fat, 3.400 g Single Saturated Fat, 1.700 g Polyunsaturated Fat, 18.50 g Carbohydrates, 6.80 g Sugar, 5.80 g Protein
7. Resource® Energy 200ml. Nestlé Health Science. 38, 53 and 65 pcs were used in 3 individuals. Protein: 15% E-11.2 g/200 ml (Casein), Carbohydrate: 55% E-42 g/200 ml (Maltodextrin, sucrose), Fat: 30% E - 10 g/200 ml (saturated, single-poly unsaturated fat acids).
8.Cernevit im / iv Injectable / Lyophilized Powder. Baxter Healthcare Corporation. 3 people were used. There are 1, 4 and 5 pieces. In each vial: Vitamin A (as Retinol palmitate) 3500 IU, Vitamin D3 (Cholecalciferol) 220 IU, Vitamin E 11.2 IU, Vitamin C 125 mg, B Complex vitamins.

N-ACETYL-CYSTEINE (NAC)

N-Acetylcysteine (NAC) is a form of the amino acid, cysteine, that has long been used in medicine to treat acetaminophen overdose and to loosen thick mucus in the lungs. It is a precursor to a vital part of the machinery cells use to protect them from excessive oxidative stress. The molecule, glutathione (GSH), is key to this by cycling through reduced and oxidized states, quenching free radicals. GSH is important in the body's synthesis of leukotrienes and prostaglandins. GSH is made of cysteine, glycine and glutamic acid and it is rapidly depleted in a body's battle against infection. There's usually plenty of glycine and glutamic acid for the body to make more so cysteine is the rate-limiting step that is offset by oral or intravenous administration.

NAC inhibits the intracellular molecule, NF-κB which plays an important role in the replication of some viruses. There is evidence for its effect on human influenza viruses (including H5N1) in human lung epithelial cells. Evidence suggests NAC administration reduces production of proinflammatory cytokines such as IL-8, CXCL10, CCL5, and IL-6. NAC inhibits replication of HIV and respiratory syncytial virus (RSV).[157]

Earlier data underscore greater synergies when NAC is used with antioxidants such as alpha lipoic acid along with vitamin C (intravenous in patients with hypoxia). Early studies showed significantly reduced duration and severity of flu in elderly.[158] 2 case reports of rapid dyspnea resolution with NAC or IV GSH with continued relief with ongoing use. NCT04374461 is a trial at Memorial Sloan-Kettering that was completed by the summer of 2020 using 6 grams, IV, however there is nothing published yet. Several case reports of recovery from RDV-induced hepatotoxicity w/IV NAC; a case report individual with cancer and COVID, recovered with inhaled NAC; IV NAC in G6PD patients and 9 others saw removal from vent,

reduced liver enzymes, CRP, ferritin in 9 of 10 pts. There is a trial proposed in Greece including NAC, copper and colchicine.[159,160,161,162,163,164,165,166,167,168,169,170]

Another form of NAC is bucillamine N-(mercapto-2-methylpropionyl)-l-cysteine, currently in phase III trials and has been investigated as a treatment for rheumatoid arthritis in Japan and Korea. The study is in mild-to-moderate disease, using 100 mg TID, 200 mg TID or placebo for 2 weeks in 1000 participants. It is quite similar to NAC but more potent.[171] Yet another form is dendrimer-NAC (OP-101). Dendrimers are molecules consisting of branched polymers to which various agents, like NAC, are loaded and that can get passed the blood-brain barrier. A form, PAMAM, has been found in animal models to have therapeutic benefit and it is being studied for COV management in humans, NCT04458298; no results yet.[172]

Alpha lipoic acid (ALA) was investigated in China in a small randomized, single-blind trial using IV lipoic with 9 patients on placebo and 8 on ALA. They observed increased SOFA score of 4.3 to 6 in placebo, but only 3.8 to 4 in the ALA arm. However, 3/8 in ALA died vs 7/9 in the placebo arm (all-cause, p=0.09).[173]

THE UPSHOT:

There are 3 trials described below. Of these, 2 trials reported positive results, 1 trial reported null results but is the more rigorous DBPC RCT design. While disappointing, perhaps too soon to reject this as it was among severe patients—perhaps giving these interventions EARLY in hospitalization will PREVENT getting to the ICU?

PI	Arms	N	Dose	Design	Contact	Outcomes
Alencar[174]	NAC – 68 Dextrose – 67	135 (140 min for 80% to detect 50% reduction at 2-side alpha=0.05)	NAC – 21 g (~300 mg/kg) 14 g 1st 4 hours (28 mg/ml) 7 g next 16 hrs (14 mg/ml)	DBPC RCT Among severe COVID pts (all on O2) 4/10 – 5/25/20	Heraldo Possolo Souza Avenida Doutor Arnaldo, 455. Room 3189, São Paulo, SP, Brazil, 01246-903 Tel: (55 11) 30618480 heraldo.possolo@fm.usp.br	Primary – prevent respiratory failure NAC: 14/68 (20.6%) on vent; 9 died (13.4%); 43% needed ICU (Table 2) Placebo: 16/67 (23.9%); 10 died (14.7%); 47% needed ICU
Ibrahim[175]	Case series	10	NAC – 30 g, 3 doses over 24h	Case series	Homam.ibrahim@NYUlangone.org (H. Ibrahim) perla@upstate.edu (A. Perl)	An initial case 3/29/20 with G6PD deficiency was treated after severe hemolysis and saw almost immediate improvement; on 4/7 recommenced 600 mg q12h for 7 days and bilirubin improved, taken off ECMO, started again 4/25 and discharged 4/27. 9 more (8 on ECMO) all treated with NAC had drop in CRP and removed from ECMO, 8 discharged to home (2 hospitalized).
Alamdari[176]	COVID – 25 Healthy Ctl – 25	5 given tx (SOC, HCQ, Az, dexameth)	NAC – 2g q12h C – 1500 mg Methylene blue – 1 mg/kg	Observational, 5 ICU patients 4/13-5/13/2020	Hamidiad@mums.ac.ir (D.H. Alamdari)	ICU cases described in detail. Case 1 on vent was taken off first day of tx, stopped O2 use 6th day, discharged 23rd day. Case 2, discharged 9th day. Case 3, discharged from ICU 4th day. Case 4 became septic and died

PI	Arms	N	Dose	Design	Contact	Outcomes
						next day after tx. Case 5, discharged on 7th d

Az – azithromycin; CRP – C-reactive protein; ECMO – Extracorporeal membrane oxygenation; HCQ – hydroxychloroquine; SOC – standard of care

QUERCETIN

Quercetin is a flavonol found red wine, kale, onions and green tea. It has a number of actions, including as an anti-inflammatory, reducing inflammatory cytokines, inhibiting histamine release, alleviating asthma, antioxidant and free-radical scavenging activities as well as evidence for antiviral activity.[177] Others have assessed its potential as an anti-inflammatory, noting quercetin's impact on suppressing the NLRP3 inflammasome which may speak well to its ability to limit severe inflammation.[178] It acts as an ionophore (much as hydroxychloroquine may exert any putative benefit via this mechanism). It would thus make sense to conduct studies of it with zinc.[100] As quercetin is not readily absorbed, adjunctive therapy is often used to enhance absorption, including with agents such as the enzyme bromelain, vitamin C and an extract of black pepper, piperidine. There is a clinical trial proposed to take place in Montréal at McGill University.[179] There is some efficacy with flu *in vitro*. Evidence suggests quercetin binds to the SARS spike protein, and it is considered promising candidate.[180,181,182,183,184,114]

Quercetin has shown some strong potential for the management of SARS-CoV-2 infection. In combination with vitamin C, it may offer greater benefits, both as prophylaxis and as treatment. The chemistry and biology of each of these compounds has been well characterized. They are inexpensive, very safe and have a well characterized toxicity profile (which is minimal for each). Each has demonstrated evidence in *in vitro* and animal models for inhibiting a range of RNA and DNA viruses, potentially particularly important for blocking viral entry. In addition, they may have a salutary impact immunologically, stimulating Th1 responses and enhancing IFN-γ production. The authors of the review, based on the renal profile for quercetin, suggest an approach of 200-500 mg bid of Quercetin and 500 mg bid of vitamin C for prophylaxis and mild cases. For severe cases, 500 mg bid of quercetin with 3 g q6h for days of IV vitamin C.[114]

Quercetin Mechanisms of Action:[185]

Effect	Mechanism of action
Antioxidative capacity and blood vessel protection	Most potent scavenger of reactive oxygen species including superoxide, and reactive nitrogen species such as nitric oxide (Boots AW et al., 2008) Reduces the level of LDL oxidation, likely through inhibiting neutrophil myeloperoxidase (Loke WM et al., 2008a) Inhibition of the xanthine dehydrogenase/xanthine oxidase system is another important mechanism by which quercetin might decrease oxidative injury occurring after ischemia or other pathological conditions (Bindoli A et al., 1985) Improves endothelial function by inhibiting endothelin-1 effects including increased protein kinase C (PKC) activity induced by endothelin-1(Romero M et al., 2009)
Antiallergic and anti-inflammatory activities	Inhibits histamine release by affecting intracellular calcium levels and PKC activation (Pearce FL et al., 1984) Decrease in the release of tryptase, monocyte chemotactic protein-1 and IL-6 and the downregulation of histidine decarboxylase (Shaik YB et al., 2006) A potent inhibitor of leukotriene B4 formation in leukocytes (Loke WM et al., 2008b) Suppresses the production of TNF-alpha and nitric oxide by macrophages, microglial cells and mast cells stimulated with lipopolysaccharide (Kumazawa Y et al., 2006)
Vasodilatative effects	Phosphodiesterase-type 5-inhibitory effects (Palmer MJ et al., 2007)
Antiplatelet activity	Inhibits thrombin-induced and collagen-induced platelet activation (Hubbard GP et al., 2003) Down-regulation of CD40L on platelets and interference with adhesion molecules (Pignatelli P et al., 2005)

THE UPSHOT:

There are 5 trials described below. All trials reported positive results. Would there be an even better bang for the buck with zinc?

PI	Arms	N	Dose	Design	Contact	Outcomes
Di Pierro[186]	QP – 21 SOC – 21	42	Quercetin – 500 mg, in lecithin (200 mg Q), tid Total daily dose 600 mg quercetin	RCT, open label; mild COVID 14 days at home treatment Dec 2020 – Mar 2021	Francesco Di Pierro Scientific & Research Department, Velleja Research, Milan, Italy Tel +39 0223510848 Fax +39 0223 511894 f.dipierro@vellejaresearch.com	Primary – viral clearance, symptoms and markers of inflammation End 2 weeks, 21/21 QP negative; 17/21 in SOC; 0/21 died in QP, 1/21 in SOC. LDH, ferritin, CRP, d-dimer all reduced on QP
Di Pierro[187]	QP – 76 SOC – 76	152	Quercetin – 1000 mg	RCT, open label; COVID outpatients 30 days at home treatment Sep 2020 – Mar 2021	Francesco Di Pierro Scientific & Research Department, Velleja Research, Milan, Italy Tel +39 0223510848 Fax +39 0223 511894 f.dipierro@vellejaresearch.com	Primary need/length of hospitalization, oxygen, ICU; death Hosp: QP 7 (9.2%) vs SOC 22 (28.9%); p=0.002 O2 need: QP 1 (1.3%) vs SOC 15 (19.7%); p=0.0125 ICU: QP 0 vs SOC 8 (10.5%); p=0.06 Death: QP 0 vs SOC 3 (3.9%); p=0.08
Onal[185]	QCB – 52 -> 49 SOC – 382->380 (2 lost to f/u)	477	Quercetin – 1000 mg C – 1000 mg Bromelain – 100 mg (QCB)	RCT, single center, open label (not blinded) Per protocol analysis, lost to follow up, improper/refuse QCB, not included in analysis 5/7-7/8/2020	İstanbul Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Turkey, hasanonal@hotmail.com	Primary discharge, intubation, death SOC included HCQ favipiravir and at BL, more QCB rec'd fav; more QCB with advanced lung disease, p=0.03;QCB had greater drop in CRP (-2.10 SOC vs -34.6 QCB,p=0.001), along with increased lymphocytes and platelets; 14 in SOC need ICU, none in QCB; 6/380 vs 1/49 died; no effect on primary endpoints
Arslan[188]	QCB – 71 Ctl – 42 Mean age QCB – 39 y.o. Ctl – 33 y.o.	113	Quercetin – 1000 mg C – 1000 mg Bromelain – 100 mg	Open label, observational for prophylaxis among healthcare worker cohort from large pandemic hospital	İstanbul Kanuni Sultan Suleyman Training and Research Hospital, İstanbul, Turkey, hasanonal@hotmail.com	Primary - Prophylaxis 1/71 QCB infected 9/42 control infected HR 12.04 (1.25, 115.06, p=0.031)
Aguilar[189]	20 – preventive tx 32 – biological therapy	52	Px – 1 cap 300 mg of quercetin, 300 mg Vitamin B2/B3/B5 5 mg of zinc	Prospective, longitudinal Prophylaxis, 1 cap/day If SARS-CoV-2 pos, tid 3/3/20-Jan 2021	ECOMED-LAMB Clinic, Asuncion, Paraguay	Small numbers; those that started before dx or early had mild or asx disease; those starting day 7, 4 developed pneumonia, 2 need for O2; no deaths

PI	Arms	N	Dose	Design	Contact	Outcomes
			0.2 mg copper			

CRP – C-reactive protein; LDH – lactate dehydrogenase; QCB – Quercetin, vitamin C, Bromelain; QP – quercetin phytosome; SOC – Standard of care; tid – thrice daily; y.o. – years old

PROBIOTICS

Our bodies are a welter of many other organisms upon whose survival our survival depends. The *microbiome* consists of the ecology of bacterial, fungi, and even viruses and other organisms that inhabit distinct ecologies on our skin, eyes, in our guts (but not in our blood—that would be sepsis…) We are at the very beginning of learning the myriad organisms and how the balance and mix of them matter from the way we are born (natural or Caesarian) to our elder years. Indeed, in no small measure, we are what we eat. The trick is how to maintain balance? And indeed, much of health and immune function is rooted in maintaining homeostasis, and not letting the pathogenic ones get a foothold—or the balance to go awry such that the good ones turn bad. Age, infection, toxins and even our genes can all feature into how health is sustained. Evidence has illuminated that SARS-CoV-2 plays important and nasty roles in the gut, as well as lung epithelial tissue. Even without that, the immune dysregulation and inflammation becomes body wide and plays hell with the guts. (And the brain—though for a different topic, we are understanding how gut flora can influence neurological function.)

The case for use of some mix of probiotics looks like a very good one. The data below, while facing all the same methodological caveats often, still show very positive signals for clinical benefit. Indeed, a Cochrane Collaboration review done before COVID, examining the effect of probiotics on upper respiratory tract infections underscored their clinical utility.[190] I had worked with a great team at Mount Sinai in New York and published a systematic review of their use in HIV disease. While the data were fewer and weak, we found evidence for a benefit in managing diarrhea as well as an excellent safety profile. The potential caveats being individuals with pancreatitis or those receiving nourishment through a tube.[191] The latter of course requiring extra care to assure no risk of the good bacteria turning bad by getting into the blood.

Notably from fermented foods, like kimchi. Correlation of lower mortality observed with higher intake of fermented foods (with high probiotic content) like kimchi in Korea; gut dysfunction associated with COVID-19 makes this a reasonable approach. Fermented foods, yogurt, kefir, sauerkraut, etc.? Daily use won't hurt. Therapeutically may decrease gut inflammation, respiratory symptoms, improve gut barrier function; dysbiosis among SARS-CoV-2 infected observed with low levels of *Faecalibacterium prausnitzii, Eubacterium rectale* and bifidobacteria.[192,193,194] Other data show benefit for *Lactobaccili*, *Bifidus*, *Saccharomyces*, *Bacillus subtilis*. Important for research to be clear about composition and precise strains used. The impact of SARS-CoV-2 infection on the gut is pretty clear and others have proposed studies to evaluate probiotics along with polyphenols, vitamin D and omega-3 fatty acids.[195,196]

THE UPSHOT:

There are 8 trials described below. Of these, 5 trials reported positive results, 3 trials reported null results. The null results in the Li study, for example, again stress the importance of earlier intervention to see if serious disease may be prevented? Certainly, relying on one or two micronutrients at that point makes less sense.

PI	Arms	N	Dose	Design	Contact	Outcomes
Gutiérrez-Castrellón[197]	Pbx – 150 Placebo – 150 Per protocol; 3	300	≥2 billion CFU† po for 30 days	Quadruple blind RCT COVID outpatients (no	AB-Biotics SA (KANEKA Group), R&D Dept, Av. De Torre Blanca 57, 08172 Sant Cugat, Barcelona, Spain. espadaler@ab-biotics.com	Primary – disease progression Remission in 78/147 (53.1%) Pbx vs 41/146 (28.1%) in placebo

PI	Arms	N	Dose	Design	Contact	Outcomes
	dropped out pbx; 4 placebo			hosp or deaths in either arm) 8/26-12/10/2020		(ARR=25.0% (14.1-35.9%, p<0.0001);no SAE;NNT-4
Veterini[198]	Case – 15 Control – 15	30	Not recorded	Observational study June – October, 2020	Anna Surgean Veterini, Anesthesiologist Intensivist of Dr Soetomo General Academic Hospital – Universitas Airlangga. Jalan Prof. Dr. Moestopo 6-8 Surabaya, Indonesia, annasurgeanveterini@gmail.com annasurgean@fk.unair.ac.id	Primary – duration of infection. No differences in duration 15.20 ±13.078 days vs. 21.40±14.401, control, p=0.22 (though 2 in control were re-infected, 0 in case)
d'Ettorre[199]	Probiotics – 28 SOC - 42	70	Pbx – 2,400 billion/day* (800 bn tid) SOC – HCQ, abx, tocilizumab	Unclear allocation, no randomization? Open label? Pts w/fever, non-invasive O2 needed 3/9-4/4/2020	Giancarlo Ceccarelli giancarlo.ceccarelli@uniroma1.it	Most on probiotics saw resolution of diarrhea and other symptoms within 72 hrs; remainder in 7 days (p<0.001) (barplots instead of table with numbers)
Ceccarelli[200]	Probiotics – 88 BAT - 112	200	Pbx – 2,400 billion/day** (800 bn tid) SOC – HCQ/Az, PI, tocilizumab	Retrospective observational Pts w/fever, non-invasive O2 needed 3/6-4/26/2020	Giancarlo Ceccarelli giancarlo.ceccarelli@uniroma1.it	Primary – mortality Improved CRP, LDH, albumin. 34/112 (30%) BAT arm died; 10/88 (11%) Pbx arm died, p<0.001; no effect on ICU; no evidence of bacteremia
Li[201]	Probiotics – 123 Not treated - 188	311	Various, 0.5, 1.5, 2.0 g tid at physician discretion‡	Retrospective, severe disease 2/3-2/20/2020	fancyzeng@126.com (F. Zeng), zhangwkp@163.com (Y. Zhang).	93/123 (75.6%) survived on Pbx but hosp time 32 d and viral clearance 23 d sig longer; bl higher IL6 SOC -4.1(3.6–5.4) vs Pbx 8.1(5.2–12.6) 0.001 (ref range 0.1-5) and higher ESR; they also rec'd more lop/rit, ribavirin and inhaled alpha interferon
Zhang[202]	Probiotics – 179 -Match – 150 SOC – 196 -Match – 150	375	630 mg (3 pills) bid⸸	Retrospective, propensity-matched Jan – 4/1/2020	Tianwen Lai, Dept Respiratory and Critical Care Medicine, Affiliated Hospital, Institute of Respiratory Diseases, Guangdong Medical University, Zhanjiang, Guangdong, China laitianen2011@163.com	Primary – days to clin improve. Pbx time 18 (14-28) vs SOC 21 (17-29), p=0.022; secondary stat sig shorter stay, duration of viral shedding and fever; vent duration 12 (7-25) vs 24d (19-33) but p=0.615. Results robust with 4 models of adjustment
Ahanchian[203]	Synbiotic – 29 Placebo – 31	60	Pbx – 1 billion CFU/cap, po for 30 days	DBPC RCT, uninfected HCW. July-August, 2020	Mashhad University of Medical Sciences, Mashhad, Iran, dr.haghi@yahoo.com	Primary - Prophylaxis, followed 2 months

PI	Arms	N	Dose	Design	Contact	Outcomes
						0/29 in tx group vs 3/31 in placebo infected, but p=0.238
Meskina[204]	Probiotic – 50 Placebo – 50	100	3 caps bid‖	Open, randomized, prospective in mild COVID	Elena R. Meskina meskinaelena@rambler.ru	Primary – diarrhea Improved symptoms including cough, weakness, dyspnea, hyposmia/dysgeusia, diarrhea (both arms, 40 had diarrhea, by day 5, 0 in tx and 24 in control had diarrhea; at day 10, 0 and 20, p<0.001; NNT 5 (3-16.2, p=0.007). Paper in Russian

Abx – antibiotics; BAT – best available therapy; CFU – colony-forming units; ESR – erythrocyte sedimentation rate; HCQ – hydroxychloroquine; HCW – healthcare workers; NNT – number needed to treat; Pbx – probiotics; PI – protease inhibitors, lopinavir/ritonavir or darunavir/cobicistat; SAE – serious adverse event

†*Lactiplantibacillus plantarum* KABP022, KABP023 and KAPB033, plus strain *Pediococcus acidilactici* KABP021; note quadruple blind is patient, caregiver, investigator and outcomes assessors. Note, remission rate was added as no one was progressing to hospitalization, etc. (Done in Mexico)
**Streptococcus thermophilus* DSM 32345, *L. acidophilus* DSM 32241, *L. helveticus* DSM 32242, *L. paracasei* DSM 32243, *L. plantarum* DSM 32244, *L. brevis* DSM 27961, *B. lactis* DSM 32246, *B. lactis* DSM 32247. Ormendes SA, Lausanne, Switzerland.
***Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961. Ormendes SA, Lausanne, Switzerland.
‡ Oral combinations of *Bifidobacterium, Lactobacillus, Enterococcus* and *Bacillus* tablets (*Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Dung enterococcus, Bacillus cereus*) 1.5 g tid; Live combined *Bifidobacterium* and *Lactobacillus* tablets (*Bifidobacterium longum, Lactobacillus bulgaricus, Streptococcus thermophiles*) 2 g tid; live combined *Bacillus Subtilis* and *Enterococcus Faecium Enteric*-coated Capsules (*Enterococcus faecium, Bacillus subtilis*) 0.5 g tid.
ǂ*Bifidobacterium*, *Lactobacillus*, *Enterococcus* capsules (Bifico) (Shanghai, China), 210 mg/cap, (1.0×10^7 CFU for each ingredient).
‖*Bifidobacterium bifidum* 1 (5×10^8 CFU) and *B. bifidum* 1 (5×10^7 CFU) in combination with *Lactobacillus plantarum* 8P-A3 (5×10^7 CFU) (Avan, LLC).

MELATONIN

Melatonin (5-methoxy-N-acetyltryptamine) is a hormone commonly used to help individuals fall asleep. It can help to reset the circadian rhythm, disrupted by events like long travel or being in an ICU. Studies also show melatonin to have activity against SARS-CoV-2, demonstrating *in vitro* M^{pro} inhibition, as well as having immunomodulatory and anti-inflammatory effects. NCT04353128 trial is among healthcare workers as prophylaxis. A review of over 11,000 patients found "risk was reduced in those who had pneumococcal polysaccharide or influenza vaccine, or were on melatonin, paroxetine, or carvedilol." Melatonin upregulates ACE2, perhaps inducing SARS-Cov-2 receptor site inhibition. Melatonin is anti-inflammatory, protects against ARDS, reduces blood vessel permeability and helps with sleep.[205, 206,207,208] Interestingly, one group (Lissoni; see Combination Therapy Trials) prescribed a heptapeptide (7 amino acid chain) that is known as Ang-1-7 (angiotensin 1-7), a key product in the stimulation of ACE2 and important for managing lung inflammation in particular.[209]

THE UPSHOT:

There are 10 trials described below. Of these, all 10 trials reported positive results, 3 trials reported null results. The null results in the Li study, for example, again stress the importance of earlier intervention to see if serious disease may be prevented?

PI	Arms	N	Dose	Design	Contact	Outcomes
Mousavi[210]	Mel – 48 SOC - 48	96	3 mg 1 hour before sleep, 7 days	RCT, open label 4/14-6/15/20	Hossein Mehravaran, Dept Int Med, Pulmonary/Critical Care Division, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. lab2002b@yahoo.com	Primary – sleep quality, LSEQ Stat sig improvement in getting to sleep, sleep quality, awakening status, feeling following wakefulness by day 7 (also when adj for age, gender); no other differences, except SpO2 95.81 (±3.61) vs SOC 93.65 (±4.22) p=0.003; 1 died in tx, 3 in SOC
Sánchez-González[211]	Mel – 224 Matched – 224 Mel – 265 (total) Unmatched – 1,952	448 (matched) 2,643 total #COVID	2-6 mg at 21h, median day 4 of admission; 25% received from first day	Retrospective, observational Propensity-score matched (Excluded pts who died w/in 72 hrs of admission) March, 2020	Departamento de Psiquiatría, Fundación Jiménez Díaz. Avda. Reyes Católicos 2, 28040 Madrid, Spain miguelangel.sanchez@uam.es	Primary – mortality Melatonin more likely ICU admitted; Unmatched, 340/1,952 (17.4%) died, p=0.014 Matched – 24/224 (10.7%) melatonin died; 53/224 (23.7%) died, OR 0.39 (0.23-0.65, p<0.001)
Davoodian[212]	Mel – 42 Placebo – 39 (B1 – 100 mg)	81	3 mg tid, 2 weeks	DBPC RCT Randomization, masking described Mild-to-moderate 5/1-8/31/2020	Department of Internal Medicine, Gonabad University of Medical Sciences, Gonabad, Iran najmeh.davoudian@gmail.com	Primary – SaO2 changes SaO2 and resp rate sig improved in tx group (p<0.001) but not in placebo (p=0.209) (within and between group comparison, tx improved). Greater improvement in resp rate (p<0.001) Between group improvements in CRP, ESR, LDH, CPK, ferritin and d-Dimer (p<0.001).
Farnoosh[213]	Mel – 24 Placebo – 20	44	3 mg tid, 2 weeks	DBPC RCT Randomization, masking described Mild-to-moderate 4/25-6/5/2020	Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran	Primary – clinical sx Cough, dyspnea, fatigue, CRP improved in tx (p<0.05); shorter time and more rapid recovery (p<0.05). No AEs, deaths either
Alizadeh[214]	Mel – 19 SOC – 20 (1 mel – hosp before starting; 5 others did not participate)	40	6 mg, 2 weeks	RCT, single blind Mild-to-moderate 6/30-8/5/2020 (Not ITT analysis)	Zahra Alizadeh, PhD; Immunology, Asthma and Allergy Res Inst, Tehran University of Medical Sciences, Tehran, Iran(+98 912)7184 258 z-Alizadehs@farabi.tums.ac.ir	Primary – Clin sx, CRP Data on mel for 14, control 17 on CRP – within group drop p<0.01 (but no diff between groups); improved within group sx greater among males.
Hosseini[215]	Mel – 20 Placebo – 20	40	3 mg tid, 2 weeks (i.e. 9 mg/day)	See Farnoosh study (notes dropouts) April-June, 2020	ab_hosseini@sbu.ac.ir (A. Hosseini); rzfarnoosh@yahoo.com (G. Farnoosh)	Primary – Th1, Th2 responses IL4 dropped both arms but more in Mel (p=0.037). Plasma IL-2 (p=0.085) and IFN-γ (p=0.008) also. STAT4, T-bet mRNA expression declined (p<0.001); also STAT6 (p=0.024) and GATA3 (p=0.036)
Ramlall[216]	791 COVID+ 948 intubations 2,981 not COVID 3,497 intubations	189,987	Not provided (Kaplan-Meier plots, melatonin looks	Retrospective, observational 2/1-8/1/2020 Methylprednisolone, levothyroxine, negative;	npt2105@cumc.columbia.edu	Primary – post-intubation outcome Melatonin use associated with lower mortality demographics and comorbidities adjusted HR: 0.131, 95% CI: 7.76E-02 - 0.223, p-value = 8.19E-14; can't rule out confounder, collider biases

PI	Arms	N	Dose	Design	Contact	Outcomes
			best of all)	Pos with insulin glargine or lispro, budenoside, melatonin, prednisone, benzodiazepine, quetiapine		
Castillo[217]	HighDose – 10 SOC – 48 34 COVID+ 15 Neg, highly probable (Numbers are off?)	58	36-72 mg/d, 4 divided doses	Retrospective chart review 3/5-4/4/2020	rafael.castillo@fame.ph, medicalfiles.inquirer@gmail.com Tel: +63 917 886 8409	Primary – sx resolution, mortality 6/10 got C+zinc; 3/10 neg but "highly probable" COVID; shorter time to clin improvement (4-5 d), less need for intubation; 0/10 died, 12/34 non melatonin died (not comparable patients, however)
Jehi[218]	818 COVID+ (7%)	11,672	Review	Registry review to ascertain infection likelihood, phase 1 3/12-13; phase 2 3/14-17; phase 3 3/18-4/2/2020	Lara Jehi, MD, 9500 Euclid Ave, Cleveland,OH 44195; jehil@ccf.org	Risk reduced for those with pneumococcal vax, melatonin, paroxetine or carvedilol; melatonin users neg 513 (97%) vs 16 (3%) pos p<0.01, validated with FL cohort, 18 (100%) vs 0 however p=0.206
Zhou[219]	25,724 total -1,055 mel or carvedilol used 8,052 COVID+ -222 drug used	26,779	Review	Registry review to ascertain infection likelihood 3/8-7/27/2020	Lara Jehi, MD, 9500 Euclid Ave, Cleveland,OH 44195; jehil@ccf.org	Primary – impact on positive test African American – OR 0.48 (0.31-0.75); overall OR 0.72 (0.56-0.91), 28% less likely pos; OR 0.70 (0.54-0.92) compared to use of ARB

ARB – angiotensin II receptor blockers; DBPC – double-blind, placebo controlled; ITT – intent-to-treat; LSEQ - Leeds Sleep Evaluation Questionnaire; Mel – melatonin; RCT – randomized controlled trial; SaO2 – direct measure of oxygen saturation bound to heme; SOC – standard of care; tid – thrice daily

OTHER VITAMINS, MINERALS, ANTIOXIDANTS

These will be updated in subsequent iterations of this document.

Drug	Target	Data
B complex, B12, nicotinamide riboside (niacinamide)	Inflammation	Review of B vitamins underscores role in maintaining mitochondrial health; rationale for use nicotinamide riboside based on pathogenesis of SARS-CoV-2; others have noted that a B12 deficiency (also seen in Kawasaki disease) may contribute strongly to more severe outcomes, esp among elderly or diabetic.[220,221,222]

Drug	Target	Data
Vitamin E, tocopherol and other tocopheryls	Inflammation, coagulability	Would this help platelet function; a test tube study suggests a water-soluble form of tocopherol inhibits SARS-Cov-2 protease but they have a vested interest (patent sought)[223]
Vitamin K (phylloquinone)	Blood clotting regulation	Low blood levels associated with poor prognosis; avoid if using warfarin or consider switch to DOAC; vitamin K vital for balancing blood coagulation, bone regulation; found in natto, spinach, broccoli, green vegetables, blueberries, all types of fruit and vegetables; hard and blue cheeses; vitamin K antagonists INCREASED risk of mortality in idiopathic pulmonary fibrosis patients (not COVID)[224,225]
Coenzyme Q10 (CoQ10)	Mitochondrial dysfunction	Systematic review underscored clinical value of alpha lipoic acid and carnitine in counteracting inflammation-induced biomarkers and CoQ10 in reducing proinflammatory conditions, mostly in the context of pneumonia and sepsis. Combo therapy trial?[13]
Iodine, povidone-iodine As liquid, spray or capsule (May cause temporary thyroid problems)	Early infection; prophylaxis	A small trial of 30 patients suggested povidone iodine spray could reduce viral levels faster (though those receiving PI were all about half the age); elevation of TSH resolved with discontinuation; Bangladeshi trial of 606 patients saw *significantly reduced morbidity and mortality* among those receiving iodine as mouthwash/gargle, eye and nose drops every 4 hours for 4 weeks; a trial protocol comparing oral, liquid and spray forms against placebo will be undertaken as a DBPC RCT in Pakistan (while participants, care providers, investigators and outcomes assessors will be blinded, it is unclear how this is achieved when a capsule, a liquid and a spray are administered?) Review suggests oral prophylactic protocol may be helpful in dentistry, frontline workers[226,227,228,229] Cochrane review pub'd in 2020 of sprays, gargling mouthwash and nasal irrigation found no completed studies, anticipates a small effect size and raised concern over lack of adverse event assessment in extant and ongoing studies; no follow up yet.[230]
Potassium (K)	Hypokalemia	Low K a risk factor for severe disease, mortality; urinary loss offset by supplementation; nearly 2/3 had hypokalemia, correlated with disease severity; monitor ECG; avg dose, 3 g/day; pts treated also with lop/rit, IFNα and arbidol[231]
Magnesium (Mg)	Hyperinsulinemia, hyperglycemia	Diabetes is a risk factor for more severe disease; hyperinsulinemia leads to magnesium depletion which in turn leads to low vitamin D regulation or increased sequestration; this results in increased thrombi; proposed clinical consequences include refined carb restriction, limited IV dextrose solution and supplementation with vitamin D3, Mg and Zn[232]
Selenium, Copper	Immunity enhancement	Along with zinc, these trace minerals are necessary for optimum immune function. Indeed, a Coxsackie virus is known to cause cardiomyopathy in the context of selenium deficient individuals[23,233]
Lactoferrin	Iron-binding glycoprotein (found in milk)	Review paper offers rationale based on impact in other infectious diseases, potential ….for SARS-CoV-2 management; increases B-cell activity, reduces inflammatory expression, pushing CD4 toward Th1.[234]

Drug	Target	Data
Omega-3 fatty acids	Coagulation, anti-inflammatory	Used alone, evidence for increased oxidative stress due to cell membrane damage potential, caution advised for high dose use; risk may be offset with other micronutrients? Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are known to be anti-inflammatory and are incorporated into cell membranes (see excellent review article).[24,235] Systematic review of lipid-modulating agents found a number of trials ongoing at the time, including several of niacinamide.[236] Study observed EPA block of SARS-CoV-2 ACE2 entry and reducing TMPRSS activity.[237] While anti-inflammatory effects have been observed, others have noted increase oxidative stress on cell membranes, thus urging caution and the need for clinical trials.[238] A clinical trial of 2g of DHA+EPAA for 2 weeks in 30 COVID pts observed improved sx (pain, fatigue, appetite) and inflammatory markers (CRP and ESR); no change to liver enzymes.[239] A trend (p=0.07) was observed for increased mortality risk assessing levels of DHA/EPA in red blood cells among 100 covid patients.[240]
Omega-3 PUFA RCT	Inflammation, markers	DBPC RCT May-July, 2020 in Rasht, Iran among 128 critically ill: 42 received fortified formula; 86 a cheaper formula; primary endpoint was inflammatory and biochem markers. 1000 mg omega-3 daily (Vita Pharmed, Switzerland) containing 400 mg EPAs and 200 mg DHAs for 14 days; they had to poke the gelcaps and manually mix into enteral formula. Improved kidney function, lower arterial pH, HCO_3 and lower mortality observed? However, lost to follow up, 7 died in EACH arm AFTER allocation then analysis was per protocol; 6/28 on PUFA survived after 1 month while 2/73 in the control group which is pretty dismal.[241] Nakata et al. criticized the trial for unclear primary outcome and errors in sample size calculation and modified intent-to-treat would clarify outcome some as would 2-week outcomes.[242]
Resveratrol	Inflammation, long COVID? Prophylaxis?	Polypheol antioxidant found in red grapes and wine. No clinical data. Reports on dog study showing reduction in canine coronavirus infection and reviews antiviral activity of resveratrol.[243] *In vitro* study showed strong inhibition of MERS and reduced nucleocapsid concentration.[244] Resveratrol and its structural analog, pterostilbene, were found to have potent activity against SARS-CoV-2 *in vitro.*[245]

DHA - docosahexaenoic acid (DHA); EPA - Eicosapentaenoic acid; HCO_3 – bicarbonate; PUFA – polyunsaturated fatty acids; sx - symptoms

Combination Therapy Trials

Combinations of a multivitamin, vitamin C, D3, NAC, zinc, B vitamins, probiotics, CoQ10, quercetin, melatonin have been undertaken but more are needed. These are safe to use (or their potential for side effects is well known). In a study of D3, B12 and magnesium reduced need for oxygen, clinical deterioration in older COV pts; a program of nutritional supplementation for hospitalized patients, including protein (whey), D3 and other nutrients; systematic review underscores safety and pathophysiologic rationale for use; rationale for use of micronutrients among obese patients including lactoferrin and omega-3 fatty acids; there is excellent mechanistic rationale for using a combination of vitamins C and D to manage the cytokine storm. [246,247,39,248,23,249,24,25,26,27,28] (In app-based community survey, n=445,850, women saw lower risk of infection use of probiotics, multi, vitamin D, omega-3; some benefit for men using a multi[250])

THE UPSHOT:

There are 9 trials described below (plus Hemilä's re-analysis of the Thomas study). Of these, 6 trials reported positive results, 2 trials reported null or negative results and one described blood levels of various micronutrients.

PI	Arms	N	Dose	Design	Contact	Outcomes
Margolin[251]	Compliant – 53 Non-compliant - 60	113	Zinc – 25 mg Vit C – 1g, D3 – 1000 IU Vit. E – 400 IU L-lysine – 500 mg Quercetin – 400 mg Quina™ – 10 drops	20-week prospective study, Columbus, Cleveland, OH March – July, 2020	Leon Margolin md@cpmiohio.com (Has patent on regimen components)	Quina is bark extract (quinine?), dose may be titrated 2/53 in the compliant arm developed symptoms; 12/60 non-compliant developed symptoms (Neither compliant had COVID; only 9 were SARS-CoV-2 positive)
Thomas[95] (Was this study designed to fail?)	48 - 8 g vit C (oral) (14 lost to f/u) 58- Zn gluconate, 50 mg (20 lost to f/u) 58- Both (11 lost to f/u) 50 – SOC (7 lost to f/u)	214 adults	New diagnosis, 4/27-10/14/20	RCT, early tx, open label Randomized 1:1:1:1 Sites in OH and FL Designed for 520 patients, stopped early for futility based on conditional power <30% for any or all treatment arms (see Hemila, next entry)	Milind Y. Desai, MD, MBA, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Desk J1-5, Cleveland, OH 44195 (desaim2@ccf.org)	Primary, symptom outcome score; 6.7 (4.4) days compared with 5.5 (3.7) days for the ascorbic acid group, 5.9 (4.9) days for the zinc gluconate group, and 5.5 (3.4) days for the group receiving both (overall *P* = .45)
Hemilä[252]	See Thomas	214	Reanalysis	Reanalysis of Thomas (see above)	Harri Hemilä harri.hemila@helsinki.fi	1.2 day shorter symptom duration within the initial studies calculation; longer duration symptoms may have had up to 30% reduction.
Louca[250]	Self-report of use Use – 175,652 No use – 197,068	445,880 Of which 372,720 responded	(Variable)	App-based survey Up to 7/31/20 Benefit was seen primarily in women; men, only with multivitamin	Dr Cristina Menni, Department of Twin Research and Genetic Epidemiology, King's College London, London WC2R 2LS, UK; cristina.menni@kcl.ac.uk	Primary – Prophylaxis Lower risk of SARS-CoV-2 with probiotics by 14% (8-19%), omega-3 fatty acids 12% (8-16%), multivitamin 13% (10-16%), vitamin D9% (6-12%), after adjusting for potential confounders. No effect of vitamin C, zinc or garlic.
Asimi[253]	Use 75.8% (270) or not 24.2% (86)	356	Selenium – 100 µg, Zinc – 20 mg D3 – 2000 IU 3/15-12/31/2020	Early; self-report, use of supplements among Hashimoto's patients	Outpatient Clinic with Daily hospital "Dr Al Tawil", Sarajevo, B&H	Users of vitamin D, Se, Zn had asymptomatic or mild outcomes vs those who did not (p<0.05), controlling for age, gender, BMI, smoking; no deaths; 86% had no or mild sx, 14% mod vs

PI	Arms	N	Dose	Design	Contact	Outcomes
						no supp with 59% severe, 24 hospitalized and 9 of those on a vent
Darban[254]	SOC vs SOC+IV C, melatonin, zinc SOC=lop/rit, Az, glucocorticoids, supplemental O2	21 10 in each arm	IV C 2 g, q6h, melatonin, 6 mg q6h; zinc sulfate 50 mg	Randomized, open label, parallel group	Bahador Bagheri, PhD. Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran. bagherib@semums.ac.ir Tel: +982333448998 Fax: +98233344899	Primary, change in PaO2/FiO2; all pts improved over 10 days; no differences; ICU stay 15±3.3 vs 14.1±4.2 days, p=0.3
Tomasa-Irriguible[7]	None	120	Blood level	Observational HPLC – A, B6, C, E Immunoassay-25-OH-D Colorimetric-Zinc March-May, 2020	Intensive Care Unit, University Hospital Germans Trias i Pujol, 08916 Badalona, Spain teresatomasa@gmail.com	Primary – MN blood levels ICU admission associated with low zinc, vitamin A, male gender, age>65 74.2% low levels of zinc (normal levels >84 _g/dL) mean value of 63.5 (SD 13.5); 71.7% low levels of vitamin A (normal levels >0.3 mg/L) mean value of 0.17 (SD 0.06); 42.5% low levels vitamin B6 (normal levels >3.6 ng/mL) mean value of 2.2 (SD 0.9); 100% low levels of vitamin C (normal levels >0.4 mg/dL) mean value of 0.14 (SD 0.05); 74.3% low values of vitamin D (normal levels >20 ng/mL) mean value of 11.4 (SD 4.3); 5.8% low levels vitamin E (normal levels >5 mg/L) mean value of 3.95 (SD 0.87)
Seet[106]	HCQ – 432 Ivermectin – 617 I throat spray – 735 Zinc/C – 634 C – 619	3,037	HCQ -400 mg once, followed by 200 mg/day); oral Ivm (12 mg once); povidone-iodine throat	Open label RCT for prophylaxis among healthy young uninfected men for 42 days Randomized by floors of	Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Level 10, NUHS Tower Block, 1E Kent Ridge Road, 119228, Singapore.	Primary is SARS-CoV-2 infection. Absolute reduction (note RR CI is 98.75% due to Bonferroni corrected alpha of 0.0125):

PI	Arms	N	Dose	Design	Contact	Outcomes
	(C was used as the Comparator arm)		spray (3 times per day, 270 µg/day); Combo - oral zinc (80 mg/day); Vit C (500 mg/day); oral vitamin C, 500 mg/day	dormitories where study was conducted (higher risk of infection in such settings already) – 10-14 men per room Used 500 mg of C (too low) to serve as a "placebo"	raymond_seet@nus.edu.sg (R.C.S. Seet).	C – 433/619 70% infected (CI 57, 81) (used as the reference basis) HCQ– 212/432 49% (CI 98.75% 31-62) RR 0.70 (CI 98.75%, 0.44-0.97) Ivm– 398/617 65% (51, 73) 0.93 (0.71-1.18) I nasal– 338/735 46% (35, 56) 0.66 (0.48-0.88) Z+C– 300/634 47% (27, 72) 0.67 (0.38-1.08) Note: no serious disease, death in any arm
Lissoni[255]	Mel+CBD – 16 Add Ang1-7 – 14 SOC – 30	30	Mel – 20 mg (eve) CBD – 10 mg bid Ang1-7 – 0.5 mg bid	Prospective, observational, open label	Paolo Lissoni, Institute of Biological Medicine, Milan, Italy paolo.lissoni@gmx.com	Primary – clinical, progression 5/30 SOC hospitalized, 0/30 tx (p<0.05); rapid resolution of fever, myalgia in treated group
Hancock[256]	12 – Positive 12 – presumptive pos	24	D – 50,000 IU 3 days Mel – 60-240 mg C – 2-15 g, higher IV *Viscum album* (mistletoe)	Case series, asx or mild 2 with cancer; 3 cancer survivors 7 rec'd IV C; 2 w/cancer, 75 g 5 d or 3 d/week	Mark Hancock MD MPH, HUMANIZING MEDICINE, 135 Maple Street, Building A, Decatur, GA mark@humanizingmedicine.com	All neg by PCR after 10 days; benign course for all. 2 pts with active cancer rec'd Viscum plus 3 other "highest risk" patients; daytime sleepiness noted, did not impair daily functioning
Tan[257] (See discussion in BOTANICAL THERAPIES.)	DV – 46 SOC – 115 (severe or critical 26.7%)	207 but 161 analyzed (propensity score matching) (Note: error in Fig. 1 on N)	Diammonium glycyrrhizinate, 150mg tid po+ VC 500 mg tid po (DV) over at least 7 days within 48 hours after admission	Retrospective, observational, pts admitted 2/11 to 3/31/20 (Note: matched cohort is 155 non-DV, 46 on DV)	Jialin Liu*, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200025, 17 China, ljl11243@rjh.com.cn, Tel: +86 21 53305091, Fax: +86 21 54500671. 18 Hongping Qu*, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 19 200025, China, hongpingqu0412@hotmail.com	Primary – mortality Reduced incident rate of respiratory distress syndrome DV vs non-DV groups 15.2% vs 35.7%; P=0.002; lower rate of new onset complications (lung, liver, heart) DV vs non-DV groups 19.6% vs 46.1%; P=0.000. Multivariate regression however, no difference in deaths (primary endpoint) or vent rate. Note: more glucocorticoid use in matched non-DV group (i.e., sicker pts) Death or mech vent:

PI	Arms	N	Dose	Design	Contact	Outcomes
						14/115 (12.2%) Non DV 1/46 (2.2%), DV p=0.74

Ang 1-7 – angiotensin 1-7; CBD – cannabidiol; HCQ – hydroxychloroquine; I – iodine; Ivm – ivermectin; Mel – melatonin; MN – micronutrient; PCR – polymerase chain reaction; RR – relative risk

Botanical Medicines for COVID-19

> *In times of health crisis, including the current COVID-19 pandemic, the potential benefit of botanical drugs and supplements emerges as a focus of attention, although controversial efficacy claims are rightly a concern. Phytotherapy has an established role in everyday self-care and health care, but, since botanical preparations contain many chemical constituents rather than single compounds, challenges arise in demonstrating efficacy and safety. However, there is ample traditional, empirical, and clinical evidence that botanicals can offer some protection and alleviation of disease symptoms as well as promoting general well-being. Newly emerging viral infections, specifically COVID-19, represent a unique challenge in their novelty and absence of established antiviral treatment or immunization.*[258]

Throughout human history, a variety of plants have been used to treat a range of conditions. Indeed, other species have been observed seeking out specific leaves or twigs to manage a range of conditions.[259] In the era of COVID-19, a number of such therapies have been investigated, many from their history of use in combatting a range of infections. Many cultures through the Americas and Africa have deep roots (pardon the pun) in using natural remedies. Unfortunately, with the genocide of indigenous Americans in North, Central and South America, along with the enslavement of Africans, much of that knowledge has been irretrievably lost.[260,261] Still, resources remain and knowledge is being recovered. At the same time, the vast treasure of the Amazon is rapidly being destroyed by psychopathic leaders like Jair Bolsonaro at the behest of even more psychotic greed of big Agribiz and fossil fuel companies, etc., rapidly plundering those resources and burning it to the ground. This eco-destruction is sadly going on in Africa, Borneo and around the world, exacerbating global heating.

By contrast, India, China, Japan, Korea and other areas of Asia have an array of cultural traditional systems of medicine that provide a deep and profound knowledge base from which to draw as colonialism didn't obliterate their traditions. In China, such use of botanical agents based on the underlying architecture of Chinese medicine are integrated into the more western approach. In India, the keepers of such knowledge were rarely political and posed no threat, unlike many shamans in Africa who were also village leaders. These would have to be silenced if they had the temerity to point out the cruelty, barbarity and injustice meted out by European plunderers and wherefore much of that lore has been damaged.[262]

A significant number of drugs currently on the "market" (or formerly, in the physician's black bag) are originally (or still) derived from plants. Roots, stems, seeds, leaves, flowers, fruits, sap and bark of an array of herbs, bushes, trees and just about any plant variety can have therapeutic value. Unfortunately, rather than give them their proper due, they are often slighted by western physicians. In some measure, this is reasonable since because they grow in different climates, soils and conditions of light, the amount of putatively therapeutic agents can vary widely. However, many products are standardized to contain

precise concentrations of active molecules (e.g., milk thistle standardized to 80% silymarins or *Echinacea angustifolia* root standardized to 4% echinacosides).

But of course, anyone can and many do grow their own. And for many around the world, that IS their access to medicine.

A report in The Guardian noted that people in rural areas of the Himalayan mountains in India were seeing a surge in infections in May and June of 2021 with very little help from the Indian government. Ultimately, the local population endeavored to isolate at home as much as possible and use herbal teas. While these were poo-poohed as useless, interestingly the same article noted that while there were many infections, no one died (possibly using botanicals like holy basil and jatamansi among others). This may be correlation and not causation but if we lived in a world that cared about science and medicine, the herbs they used would be investigated for their therapeutic potential.[263]

But for most, we must rely upon their cultivation and production by a variety of companies. By and large, these companies are careful to assure identity, potency and purity of the products. One concern for plants, whether food or medicine, is that many soils are damaged by overuse of pesticides and herbicides as well as excessive application of fertilizers. This is destroying soils microbiomes. Worse, pollution means that many plants take up an array of heavy metals like cadmium. So having a company that tests their products for such toxins is important. The FDA's sullied reputation can be healed by doing more of what it already does: do a lot more assessments of the identity, potency and purity of "dietary supplements" on the market and publicly post all results (good, bad or indifferent).

In China and India where traditional systems of medicine remain extant, efforts have been under way to identify usually combinations of plants to have an effect on preventing infection, reducing the risk of serious disease developing or as adjunctive therapy in hospitalized patients to help create a more rapid resolution of symptoms. As ever, there is an enormous amount laboratory work that underscores the usual suspects in terms of mechanisms of action: some components target the virus, they may target host cells to improve antiviral responses or, more often than not, they can help to reduce the array of physiologic disruptions that occur, i.e., inflammation, cytokine storm and impaired coagulation. Managing these helps to preserve organ function. As such, a good regimen may play a key role in comprehensive approaches to managing Long COVID as well as potentially acting as a robust prophylaxis against infection or the development of serious disease, failing the former. That's what we aim to find out if more studies can be conducted.

Why can't we in the United States undertake clinical studies of botanicals or micronutrients? The National Institutes of Health has an Office of Dietary Supplements that spouts a lot of information that seems more aligned with the notion of not interfering with drug development (as FDA assured when the Dietary Supplement Health Education Act was being hammered out). One will read a title that data do not support use of dietary supplements when their view is that there is insufficient evidence (see https://ods.od.nih.gov/). Databases, information gathering—but no clinical studies?

And the reality is, given the greed of pharma and the regulatory capture of wealthy nations, many people still must rely upon low cost and local interventions. Also, many people infected with SARS-CoV-2 have disease that is asymptomatic, mild or moderate. It is important to know what diagnosed individuals can try at home to reduce the risk of progressive disease.[264] Their potential in managing Long COVID should be investigated. Understanding what works best can also guide remote communities out of the loop of corporate corruption (i.e., lacking access to most of what "western" medicine has to offer). Of course,

where available, a vaccine is the first thing to get! But this *should* be an effort rooted in medicine, science and humanity, not market-driven corporate greed.

A comprehensive review of the antiviral and immunomodulatory effects of a wide range of plants describes the viruses they inhibit, which molecules are responsible and what viral targets they bind to. Most of these data are test tube, tissue culture or animal studies. Some of the specific chemicals include lectins, quercetin, sulforaphane (found in cruciferous vegetables), resveratrol (found in red grapes), baicalin, glycyrrhizin (licorice), narcissoside, curcumin and epigallocatechin gallate (green tea). In addition, the evidence for plants used to fight respiratory diseases is discussed, in particular for *Artemisia annua*, *Allium cepa* (onion), *Andrographis paniculata* (King of bitters), *Aloe vera*, *Nigella sativa* (black cumin seeds), *Salvia officinalis* (sage), *Toona sinensis*, *Eckolina cava*, *Isatis indigotica*, *Azidarachta indica* (neem) and others.[265] Many of these are already readily available as foods or dietary supplements and for those with clinical data, they are described below in more detail as potential interventions for COVID-19.

One of the major medical systems in India, Ayurveda (alongside Siddha, Unani and Tibetan medicine) has been explored for the potential of commonly used botanicals for fighting SARS, specifically those that interfere with viral proteins such as the spike protein, the main protease and the RNA-dependent RNA polymerase. A particular aspect of Ayurveda is the Rasayana group of botanicals, the chemical constituents of which are well-characterized. They reviewed 31 constituents of *Withania somnifera, Tinospora cordifolia* and *Asparagus racemosus*. One chemical that stood out for its ability to bind, characterizing its docking in the RdRp molecule of the virus, as well as its bioavailability was muzanzagenin, found in *Asparagus racemosus*. All the key phytochemicals in *Tinospora* had drug like qualities. Understanding better how they are metabolized through the cytochrome P450 system, how they are absorbed will be key to successful integration with other meds to prevent drug-botanical interactions and to enhance both the antiviral and immunomodulatory potential of these agents.[266]

Another molecular docking study was conducted of Ayurvedic medicines to examine potential potency against various SARS-CoV-2 proteins. They focused on *Allium sativum*, *Allium cepa*, *Zingiber officinale*, *Syzygium aromaticum*, *Mentha piperita*, *Foeniculum vulgare*, *Ocimum sanctum*, *Origanum vulgare*, *Curcuma longa*, *Tinospora cordifolia*, *Cinnamomum cassia* and *Cordyceps militaris.* Aside from molecular docking, their analytic methods included molecular dynamic simulation, binding free energy calculations, pharmacophore model and structure-based alignment methods. Most potently, they observed that curcumin had strong binding affinity both with ACE2 as well as furin. Gingerol strongly interacted with the spike protein and RdRp while quercetin bound strongly with the main protease (M^{pro}).[267]

In Brazil, an array of potential plants may feature anti-SARS-CoV-2 activity. More test tube research revealed 19 potential compounds with activity, mostly triterpenes and phenolic compounds in 23 different species. Among these were *Ananas comosus, Anadenanthera colubrina, Bacopa monieri, Brosimum gaudichaudii, Caesalpinia ferrea, Carapichea ipecacuanha, Cereus jamacaru, Cereus peruvianus, Cordia curassavica, Croton heliotropiifolius, Dorstenia aritoflia, Erythrina velutina, Erythrina verna, Himatanthus lancifolius, Lantana camara, Maytenus ilicifolia, Mikania glomerata, Myroxylon balsamum, Operculina hamiltonii, Passiflora alata, Paullinia cupana, Schinus terebinthifolia, Senna alexandrina, Solanum paniculatum, Stryphnodendron adstringens, Trichilia catigua*, and *Uncaria tomentosa* (Cat's claw). They had high affinity for viral proteins while also having low toxicity. Interesting candidates included (all-E)-Violaxanthin betulinic acid, lupenyl acetate, taraxeryl acetate and ursolic acid.[268]

And research on Jamaican plants has yielded more possibilities. The plants they use have been used in many other cultures while some are more specific to the island. Among these used for medical purposes are *Momordica charantia* L. (bitter melon), *Aloe barbadensis* Miller (*Aloe vera* (L.) Burm.f./), *Cannabis*

sativa L. (Ganja), *Cola acuminate* (P.Beauv.) Schott and Endl. (Bissy), *Morinda citrifolia* L. (noni), *Pothomorphe umbellata* (L.) Miq. (Cowfoot Leaf), *Cinnamomum tamala* (Buch.-Ham.) T.Nees and Eberm. (Bay leaf), *Zingiber officinale* Roscoe (ginger), *Bryophyllum pinnatum* (Lam.) Oken (Leaf-of-life), *Moringa oleifera* Lam. (Moringa), *Panax ginseng* C.A.Mey. (ginseng), *Mikania micrantha* Kunth (Quako), *Marrubium Vulgare* L. (White horehound/"Mint"), *Andrographis paniculata* (Burm.f.) Nees (Rice bitters), *Curcuma longa* L. (turmeric), *Petiveria alliacea* L. (Guinea HenWeed), *Camellia Sinensis* (L.) Kuntze ("Tee tree"), *Alysicarpus vagilinis* (L.) DC. (Medina) and *Allium sativum* L. (garlic). A range of teas, such as root tonic or strong back that include ginger and herbs like *Smilax ornate* (sarsaparilla) are used to enhance stamina (and male virility) but also have some antiviral activity. A number of flavonoids were described, particularly from *Cannabis* and their molecular targeting of viruses, cancer and inflammation.[269] Indeed, the burgeoning research on cannabidiol may have relevance as part of a comprehensive treatment strategy for managing COVID-19, which research from South Africa underscores may have antiviral benefits.[270]

Pills, powders, capsules and tinctures and teas often contain combinations of plant products. They are readily available in stores throughout Asia (and around the world). A commonly used formulae like Lianhuaqingwen and shu feng jie du blend various herbs and agents including gypsum and menthol. Some of the more commonly used herbs include astragalus, glycyrrhizin root, *Saposhnikovia divaricata* (Turcz.) Schischk. (Fangfeng), *Atractylodes macrocephalae*, *Lonicera* and *Fructus forsythia* (Lianqiao). Lianhuaqingwen has traditional use in managing fever, cough, fatigue, influenza, etc.[271] Other formulae like qingfei paidu decoction, qingfei dayuan or huashi baidu granules; huashi baidu are approved in China to treat inflammation and improve immunity. Several of these are being applied and novel formulations are being developed.[272,273] Similar efforts are underway in South Korea.[274,275,276] An herbal preparation was approved in Uganda although based on what evidence remains somewhat unclear.[277] A study, NCT04295551 was posted in March, 2020 to investigate Xiyanping injection, an extract of *Andrographis paniculata* andrographolides. However, it is not yet enrolling, quite probably due to the lack of COVID patients due to China's strict lockdown. A large review finds evidence for adjunctive use of Chinese medicine; one formula underscored a range of targets, viral and host response. A systematic review found multiple interventions, many which improved inflammatory responses when used with Vitamin C.[278,279,280,272,281,282,283,273,274,284,285]

A survey of agents identified from the Chinese pharmacopoeia that can have antiviral effects and/or salutary impact on host responses in COVID-19 identified a slew of possibilities, some used as part of standard of care. Among these are active ingredients (quercetagetin, osajin, tetrandrine, proscillaridin A, and dihydromyricetin), monomer preparations (xiyanping injection, matrine-sodium chloride injection, diammonium glycyrrhizinate enteric-coated capsules, and sodium aescinate injection), crude extracts (Scutellariae Radix extract and garlic essential oil), and formulas (Qingfei Paidu decoction, Lianhuaqingwen capsules, and Pudilan Xiaoyan oral liquid). Qingfei paidu is being evaluated in a comparative study in UC San Diego (see Medicinal Mushrooms entry in BOTANICAL THERAPIES section). Analysis of the decoction yielded some 64 different active agents and analyzed their impact on a range of metabolic and viral pathways to assess its activity *in vitro* to elucidate at least some of the putative mechanisms.[286] Of course, what matter most is that it appears to have some robust clinical activity, at least in preliminary studies in China. In the case of Lianhuaqingwen capsules, the ingredients (with photographs) are described. They note that these capsules, as of 12/4/20, 16 nations, including Brazil, Indonesia, Romania, Singapore, Russia, the Philippines and Ukraine have approved their use in management of influenza and pneumonia.[287]

Others have noted that plant-based traditional medicines such as *Radix platycodonis, Agastache rugosa, Saposhnikoviae divaricata, Lonicerae japonicae flos, Astragalus membranaceus, Rhizoma Atractylodis*

Macrocephalae, Glycyrrhiza uralensis, Atractylodis Rhizoma, Fructus forsythia, and *Cyrtomium fortunei J. Sm* were the most commonly used herbal medicine for the management of COVID-19 in China.[157]

Somewhat further along are mouse studies conducted in China assessing the impact of a formula of Chinese herbs known as Shufeng Jiedu capsules. In their experiments, the concoction reduced virus load in the lungs of the mice along with inflammatory markers such as IL-6, IL-10, TNF-α and IFN-γ, as well as increasing levels of CD4+ and CD8+ T cells. Here, the virus used was HCoV-229E, one of seven coronaviruses known to infect humans if not with the same frequency of devastating consequences as SARS-CoV-2. The formula consists of *Polygonum cuspidatum, Forsythia suspensa, Isatis indigotica, Bupleurum chinense, Patrinia scabiosifolia, Verbena officinalis, Phragmites communis* and *Glycyrrhiza uralensis.*[288]

The scientific community is always interested in mechanisms of action and this is true for phytomedicines or supplements. Indeed, work continues to elucidate these mechanisms for almost every agent used in medicine! This is simply reality since there remains a great deal we have yet to learn about our biology.

While our knowledge becomes more refined, it also becomes clear that more sophisticated methods, like network analysis, are necessary, even for single substances. An herb with its dizzying array of compounds presents particular challenges that some are endeavoring to tackle as described above. For example, one group has use an array of techniques, including text mining, target prediction, data integration, network study, bioinformatics analysis, molecular docking, and pharmacological validation, to identify pertinent molecules of interest in one of the commonly used decoctions, Qing-Fei-Pai-Du.[289] Others have tackled it from the other side, investigating the components of treatments used to manage kidney injury related to COVID-19, a potentially vital component to long COVID management.[290]

At the same time, blends of botanicals, minerals and other approaches are being used—and sometimes with little other options for many around the world. So we still can look at what happens when combinations of botanicals are given to clinical outcomes. Is viral load diminished? Is there clinical improvement?

Sadly, what is deeply lacking is enough clinical studies of these to see if what we see in the bench is replicated in the body. But these types of reviews, aside from being somewhat overwhelming for this reviewer, also guide us suggestively by the concentration needed (nanomolar, micromolar?) to inhibit as well as the toxicology that can tell us if you'd just need too much to make it clinically practical. Here, too, we can refer to the great bodies of literature, the pharmacopoeias of China, Japan, India, Korea, the Middle East, Africa.

CURCUMIN

Curcumin is a phenol found in turmeric, *Curcuma longa*, L. Many studies show curcumin inhibits viruses as well as specifically SARS-CoV-2 entry into cells. It is often paired with bromelain which exerts anticoagulant activity.[291] Curcumin has long been studied for its effects on markers of inflammation as well as a number of ways it may interfere with the replication of various viruses. Indeed, research suggests getting more curry (and vitamins) in the diet sounds like a good idea! A Korean assessment of 60,526 found that those with lower intake of vitamins B1, B2, B3, C and A had a higher burden of heavy metal toxicity and increased metabolic syndrome. Those with higher curry intake had a lower risk of metabolic syndrome and just a milligram more of vitamin intake could further reduce toxic metal load (lead, mercury, arsenic).[292] Lockdown has resulted in some not always healthful diets and weight gain!

Curcumin also suffers from being poorly absorbed, so a variety of methods have been used to enhance that, including not infrequently "phytosomal" forms that mix it with fats, specifically phospholipids and generally that's lecithin. The studies below all support the potential of the intervention but all are from Iran and use a nanocurcumin formulation. Mahmoud Reza Jafaari is a co-author on most of them and holds a patent for the technology. The Dound study in India similarly has industry influence. That doesn't invalidate the findings per se, but these must unfortunately be placed under the concern of industry bias. That said, the outcomes of all studies suggest a potential role for curcumin for its anti-inflammatory and antithrombotic activity, potentially reducing the need for some medications with a more favorable adverse event profile, while potentially also reducing morbidity and mortality. Indeed, the Pawar study below underscored that fewer in the curcumin arm needed remdesivir and other meds like heparin or tocilizumab compared to the placebo arm. More studies should be contemplated.

THE UPSHOT:

There are 6 trials described below. Of these, all reported positive results. Conflicts of interest exist for some, so caution warranted.

PI	Arms	N	Dose	Design	Contact	Out
Pawar[293]	Curc – 70 Probiotics* – 70 30 -mild, 25-mod, 15-severe in each arm	140	Curc – 525 mg + 2.5 mg piperine	DBPC RCT "Red flags" are defined as specific symptoms and blood dyscrasias July – Sep, 2020	Kirti S. Pawar kirti.skpawar@gmail.com	Prin dura ratio Fast coug lowe bett SpO few bett mod days reci 5/2 arm sig). pulr
Valizadeh[294]	Curc – 20 Placebo – 20 Healthy Ctl – 40	80	Nanocurcumin – 160 mg (4 40 mg caps)/day, 14 days	DBPC RCT	*Tabriz University of Medical Sciences, Tabriz, Iran* ahmadi.m@tbzmed.ac.ir (M. Ahmadi).	Prin Firs with elev 18; expr supe IL-1 dysp ame 4/2 grou
Hassaniazad[295]	Curc – 20 Placebo – 20	40	Nanocurcumin - 160 mg (4 40 mg caps)/day, 14 days Other tx both arms, D, C, zinc, L-carnitine	Triple blind, PC RCT Mod-Severe COVID	Amin Reza Nikpoor, Molecular Medicine Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. nikpoora@hums.ac.ir ; nikpoora@gmail.com	Prin mar GAT IL-4 TBX FOX expr decr stat over

PI	Arms	N	Dose	Design	Contact	Out
Ahmadi[296]	Curc – 30 Placebo – 30 (27 eval in placebo; 3 progressed)	60	Nanocurcumin - 160 mg (4 40 mg caps)/day, 14 days Other tx both arms, D, C, zinc, L-carnitine	Triple blind, PC RCT Mild-to-moderate out-patients April-July, 2020	Sepideh Elyasi, Dept Family Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ElyasiS@mums.ac.ir	Prin BL – (p=(plac 3.08 coug p=0 vs 5 fast
Saber-Moghaddam[297]	Curc – 21 Placebo – 20	41	Nanocurcumin - 160 mg (4 40 mg caps)/day, 14 days	Triple blind, PC RCT Mild-to-moderate out-patients April-July, 2020	Sepideh Elyasi, Dept Family Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. ElyasiS@mums.ac.ir	Prin Reso (p=(tach and cour disc supp (5 v
Dound[298]	Curc – 100 SOC – 100	200	Curvic** – 500 mg bid	RCT Randomization described; no blinding Aug-Sep, 2020	Yogesh Arun Dound, Department of Research & Development, Shreepad Shree Vallabh SSV, Phytopharmaceuticals, COO Particle Life Sciences Pvt. Ltd, Mumbai, Maharashtra, India, yogesh_dound@yahoo.com	Prin Feve cont ferr VAS redu day

CRP – C-reactive protein; DBPC – double-blind, placebo-controlled; N/L – neutrophil-to-lymphocyte ratio; PC – placebo-controlled; RCT – randomized controlled trial; sx – symptoms; tx – treatment

*Pawar study control arm: Nutrolin B Plus, which contains lactic acid *Bacillus* and Vitamin B; Ciplamed

**Curvic contains liposomal Curcumin, Vitamin C, Vitamin K2-7, Selenomethionine and Zinc

BOTANICAL THERAPIES

These will be updated in subsequent iterations of this document.

Drug	Data
Andrographis	Trial of just 6 people found benefit in reducing hospital time, resulting in approval of use in mild-to-moderate disease in Thailand. *In vitro* tests show it binds to PIs of SARS-CoV-2. Andrographilides are used in malaria treatment; note use is sometimes associated with loss of smell/taste.[299]
Artemisia	Mostly *in vitro* and animal; reduced CMV viral load (artesenuate)[300]
Cannabidiol (CBD), cannabis	Reduction of ACE2 expression in artificial human 3D models of oral, airway and intestinal tissues; also reduced TMPRSS serine protease expression; as mouthwash/gargle? May help reduce lung inflammation? Tissue culture study indicated *some* cultivars inhibited TNF and IL6 expression with 3 of 7 extracts exhibiting benefits, 3 not and one cultivar potentially exhibiting deleterious effects; other culture systems should be studied.[301,302,303] Molecular docking analysis revealed binding affinities between phytocannabinoids and SARS-CoV-2 codon mRNAs, including open reading frame 1ab (ORF1ab), surface, envelope and nucleocapsid proteins.[270] A Brazilian DBPC RCT from 7/7-10/16/20 gave 300 mg of CBD to one arm (n=49), placebo (n=42) to the other over 14 days with a primary endpoint of deterioration in clinical status; median time to symptom resolution was worse in CBD arm (12 days vs 9) tho p=0.2 with very wide confidence intervals in each arm.[304] A review of data on potential for managing mental or neurological outcomes found a paucity of data if a few small positive studies and potential in managing epilepsy and neuropathy, no recommendations for COVID are yet possible.[305]
COVIDex	An herbal formula approved by the Ugandan government; inadequate vaccine or treatment supplies mean this may be a rational option for many but no published data yet.[277] Developed by Mbarara University scientists led by Prof Patrick Ogwang. Too early to embrace or dismiss.

Drug	Data
Echinacea, species	Studies suggest benefit in shortening the duration of other respiratory infections. A review of the data on these underscored the safety of the herb, underscoring the potential to reduce inflammatory cytokines. A concern about it increasing TNF was based on a dog model given extremely high doses—human studies reviewed here showed generally a lowering of the cytokine.[306] A more recent review by the same group concluded there is evidence to suggest use of the herb can reduce IL-6, IL-8 and TNF while increasing IL-10, though the risk of bias in reviewed studies was high.[307] However, there are no clinical studies in COVID-19.
Glycyrrhizin (GL) Problematic?	See the Tan entry in the Combination Therapy Trials above. An extract of licorice, long recognized for its potential antiviral activity. In the early days of the HIV pandemic, Japanese researchers explored its use, as an intramuscular push, in children with HIV with modest success. It can have some side effects that must not be ignored, particularly stressful to adrenal function. Early work in the first SARS outbreak showed GL was the most potent inhibitor in Vero cells (more so than ribavirin, 6-azauridine, pyrazofurin or mycophenolic acid) with an EC_{50} 316-625 mg/L.[308] Evidence for benefit in porcine alphacoronavirus diarrhea. [309] A study of SARS-CoV-2 lung cells identified expression of the high mobility group box 1 (HMGB1) as highly pertinent to cell pathology induced by infection and GL blocked that expression, limiting the fiery cell suicide of pyroptosis and macrophage activation. GL also inhibited replication in Vero cells at physiologically relevant concentrations.[310] A nanoparticle formulation of GL inhibited a mouse infection (MHV-A59) and improved lung function.[311] However, caution is advised as one group noted flaws in the selection of SARS-CoV-2 targets in a suggestive of a synergistic benefit of GL and vitamin C.[312] Relying on such analyses is inadequate for treating without proper clinical trials. Indeed, one propensity-score matched observational review of 317 consecutive patients with COVID, 2/1-3/16/2020 found treatment with glucocorticoids, immunoglobulin, thymosin and ammonium glycyrrhizinate (14/46 users died, p=0.003) were associated with a higher risk of death.[313]
Isatis indigotica root	*I.v.*; sinigrin most effective in blocking, 217 μM; other botanicals may inhibit the IL6-JAK-STAT pathway—more safely? As effectively?[314,315]
Medicinal mushrooms	MACH-19 trial at Krupp Center for Integrative Research at the University of California, San Diego are conducting a study in early covid of medicinal mushrooms known as agarikon and Turkey tail vs a Chinese herbal formula, Qing Fei Pai Du Tang (or qingfei paidu), a combination of 21 herbs that showed significant benefit in studies in China; even after controlling for differences in use of other drugs or antivirals, the mortality rate was 50% lower in those in the Chinese herbal arm who used the medication for at least 3 days.[316]
Nigella sativa (black cumin seed)	Case report of a physician using a tea made with the seed, chamomile and honey had good benefit in helping recovery.[317] An open-label prospective study of 376 people from Aug, 2020 to Jan, 2021 was conducted to assess the potential to prevent infection as well as effect on clinical symptoms. High, intermediate and low risk groups were identified (e.g., healthcare workers as high risk). 180/188 in the control group were infected with 68/188 (36.2%) infected in the treatment group. About half the high risk group using the seeds were infected while far fewer were in the intermediate risk and none in the lower risk (there were only 3-4% in that group in either arm).[318] A case series of 35 patients found all improved, symptoms resolving within 3 days.[319] An open-label RCT tested 500 mg of MARNYS Cuminar bid for 10 days among 183 patients with 91 in the treatment group and 92 in the control group. They saw faster recovery (10.7 ± 3.2 days) compared with the control group (12.3 ± 2.8 days) at day 14; p = 0.001 and higher recovery rate 54 (62%) vs 31 (36%), p=0.001. Notably, a strong effect on improving anosmia.[320] The intervention had 0.7% thymoquinone as a standardization. Finally, a DBPC RCT was conducted among 210 moderate and 103 severe patients provided either honey (1 g/Kg/day)+Nigella seeds (80 mg/Kg/day) or placebo for 13 days. The trial ran from 4/30-7/29/2020 with 107 on tx (50 severe) and 103 on placebo (53 severe). Faster viral clearance in treated group 4 days earlier than placebo group in moderate (6 versus 10 days, HR 5.53 (3.76-8.14, p<0.0001) and severe cases (8.5 versus 12 days, HR 4.32 (2.62-7.13, p<0.0001). More, 50% of severe treated were discharged but 2.8% in placebo and mortality was 4% vs. 18.87% OR 0.18 (0.2-0.92, p=0.029).[321] Another study conducted from 9/5-11/15/2020 in Kirkuk, Iraq among 259 controls and 160 people receiving 40 mg/kg of seeds, all with mild covid. More progressed in the SOC arm while all recovered in the treatment arm. In addition, no one died in the treatment arm while 14 (5.4%) did in the control arm (p=0.003).[318]

Drug	Data
Oleandrin	An extract of *Nerium oleander*, touted with outright lies by some Pillow guy and Trump. It has been studied in cancer among a few patients. Hardly any data on viruses, but some in vitro work on HTLV-1. Serious risk of cardiac problems as it is very toxic (it has properties similar to foxglove's digioxin); trial enrolling by "invitation" that is not blinded or randomized, NCT04486144[322] Sadly, hype and nonsense do not advance the cause of science and medicine
Psilocybin therapy	Study in Dublin to assess psilocybin-assisted psychotherapy will be phase 2b double-blind trial to assess impact with or without SSRI escitalopram in depression[323]
Q-Griffithsin	Nasal spray formulated from red algae and *Nicotiana benthamiana* (tobacco) protein developed at U of Pittsburgh for high risk[324,325]
Sambucus nigra (Elderberry)	Long used to treat fever. Anthocyanins and flavonol glycoside are molecules of interest. Some data however suggest it amplifies cytokines like IL-1β, IL-6 and TNF-α.[258] Other data conflict and there is some clinical evidence for use in upper respiratory infections. No data for use in COVID-19—it may be best used at the earliest stages? Risks?
Saposnikova divericata (Turcz.) Schischk	In the Umbelliferae family, the root has a long use for managing diseases that affect immune function, nervous system and respiratory diseases. The components include coumarins, chromones, acid esters and polyacetylenes that exert antioxidant, anti-inflammatory, anti-tumor and antiproliferative activities.[326]
Withania somnifera	A 16-week randomized, open-label study compared risk of SARS-CoV-2 infection among 400 patients receiving *Ws* or hydroxychloroquine. An interim analysis reported 3.7% in the HCQ arm (95% CI, 1.3-10.5%) and 1.3% (0.02-6.7%) in the botanical arm (80 people in each arm at the time of analysis) with fewer side effects and reduced anxiety among those treated with *Ws.*[327]

Combination Botanical Therapy Trials

As noted above, there are few studies underway or completed investigating combinations of medications. Two are described below—and one is just a late publishing of a protocol. Clearly, there is a need for more research. This will be updated in future iterations.

PI	Arms	N	Dose	Design	Contact	Out
Natarajan[328]	Siddha – 30 C+Zinc – 30	60	Siddha – 60 ml bid, 7 days C – 60,000 IU, zinc – 100 mg, bid, 7 days	Open label RCT	s.natarajan78@gov.in drnatarajan78@gmail.com Siddha Central Research Institute, Chennai, India	Prin Mild eith subs had eac
Rangnekar[329]	Herb – 3 Placebo – 2	?	Two capsules, Investigational Product (IP) - 1 - 400mg and Investigational Product - 2 - 450mg** Placebo: Edible starch- 450 mg.	DBPC RCT 30 days 8/11-10/5/2020	h.rangnekar@questclinicalservices.co.in dr.rangnekar@gmail.com Quest Clinicals and Ayurceuticals, Pune, India	Prin CITI (late yea

BL - Baseline

*Plant name Latin, Siddha, part of plant (equal parts): *Zingiber officinale* Rosc. Chukku Zingiberaceae Rhizome; *Piper longum* L. Thippili Piperaceae Fruit; *Syzygium aromaticum* (L.) Merr. & Perry Kirambu Myrtaceae Flower bud; *Anacyclus pyrethrum* (L.) Lag. Akkirakaram Asteraceae Root; *Tragia involucrata* L. Konchori Euphorbiaceae Root; *Hygrophila auriculata* (Schum.) Heine Lam. Neermulli Acanthaceae Root; *Terminalia chebula* Retz. Kadukkai Combretaceae Fruit rind; *Justicia adhatoda* L. Adathodai Acanthaceae Leaves; *Plectranthus amboinicus* (Lour.) Spreng. Karpooravalli Lamiaceae Leaves; *Costus speciosus* (J. Koenig) Sm. Kostam Costaceae Root; *Tinospora sinensis* (Lour.) Merr. Seenthil Menispermaceae Stem; *Clerodendrum serratum* (L.) Moon Siruthekku Verbanaceae Root; *Andrographis paniculata* (Burm.f.) ex Nees Nilavembu Acanthaceae Whole plant; *Cyperus rotundus* L. Koraikizhangu Cyperaceae Root tuber; *Cissampelos pareira* L. Vattathiruppi Malvaceae Root. Note: 60,000 IU of vitamin C is the equivalent of 30 mg.

**Containing herbal extracts (a blend of water and CO2 extracts) of Shunthi (*Zingiber officinale* (Ginger), Vidanga (*Embelia ribes*), Yashtimadhu (*Glycyrrhiza glabra*), Haritaki (*Terminalia chebula*), Guduchi (*Tinospora cordifolia*), Shatavari (*Asparagus racemosus*), Aamalaki (*Emblica officinalis*), Pippali (*Piper longum*) and calcined Zinc, Shankha bhasma

Review of Extant Protocols

The following is a review of systemic approaches to patient management that incorporate a range of nutritional and botanical agents with the goal of preventing severe disease, preventing the need for the use of ventilators, reducing the time on a vent and most importantly, reducing mortality. In addition, some of the approaches below have an accumulating body of evidence for the management of Long COVID.

Math Protocol

The Front-Line COVID-19 Critical Care Alliance (FLCCC) is an institution in the United States that has developed a comprehensive approach to COVID-19 patient management that includes various drug agents as well as anticoagulant therapies and corticosteroids (used judiciously). Their protocol is known as the MATH Plus Protocol and includes a range of interventions for hospitalized patients. Two items that I am not as persuaded yet by are the use of low molecular weight heparin; other anticoagulants may be better. Also, while there is a lot of data on ivermectin, the studies are largely rather weak from a methodological standpoint. Worse, controversy abounds with fraud reported in two subsequently retracted papers describing positive results of clinical trials. For hospitalized patients, I'm not as enthusiastic as the FLCCC team. They have a protocol for hospitalized patients and are working on one for Long COVID, however, it has not been fleshed out yet.

Galland Protocol

Leo Galland, MD, has been at the forefront of rational disease management strategies employing a range of interventions. With regard to SARS-CoV-2 infection, he suggests an approach that will help to achieve two biochemical goals: increased expression of ACE-2 receptors and repair and maintenance of mitochondria. The clinical endpoints for his approach are to resist infection, reduce the risk of progression and lower mortality risk. His protocol includes:

Vitamin D3 – daily use with meal of 1000 to 6000 IU
Niacin – 100 mg per day combined with NAC (600 mg bid with main meal); he notes that the niacin flush may be offset with either aspirin or quercetin (300-500 mg/day), an agent that may have some activity against SARS-CoV-2
B2 (riboflavin) – 100-400 mg/day
Melatonin as tolerated (1 to 10 mg in the evening)
Thiamine as lipothiamine (100 mg/day)
Liposomal curcumin (750-1000 mg/day with food)
Resveratrol (750-1000 mg)
Rosmarinic acid (150 mg/day)
CoQ10 (100 mg bid as ubiquinol)
L-carnitine (Rx at 3x330 mg bid) or carnitine tartrate at 500-750 mg bid or tid or as acetylcarnitine 500-1000 mg/day)

For those with long-COVID and issues like brain fog, he suggests omega-3 fatty acids at 1200-2000 mg/day of EPA/DHA) and 300 mg bid of alpha lipoic acid. Other novel supplements for which there are fewer data include fisetin 100-500 mg/day, liposomal luteolin 150-300 mg/day and vinpocetine at 20 mg/day. He asserts that the use of omega-3 fatty acids may also help to reverse anosmia. In addition, he

suggests magnesium glycinate (100-400 mg), melatonin (0.5 to 10 mg as tolerated), theanine (200-600 mg, repeated if awakened at night) and cannabidiol and cannabinol for helping individuals who have trouble falling asleep or remaining asleep through the night. Finally, understanding the role of gut health is extremely important. There may be ongoing residual virus in the gut and dysbiosis may lead to chronic, long-term symptoms. He therefore recommends use of probiotics as well as prebiotic agents that help the body to produce and balance the gut flora. This is supported by the literature.

Proposed Protocols

The COVID-19 pandemic has shown the power and necessity of large-scale, multicentre, adaptive platform trials and applying these approaches to long COVID will help accelerate development of an evidence base for disease management.[330]

While the randomized controlled trial (RCT) is the "gold standard" of clinical trial design, other methodologies have been in development for some time to give more rapid answers to a range of clinical questions involving multiple agents. *Adaptive platform trials* like RECOVERY, REMAP-CAP and SOLIDARITY are providing ongoing evidence for the potential for these methods. Others have proposed the use of "evidence maps" to ascertain treatment outcomes with complex regimens. This methodology could be applied to SARS-CoV-2 studies and provide at least a broad overview of the research.[331] See, for example, TCIM Evidence Map website https://mtci.bvsalud.org/en/evidence-map.

As a result, there is a remarkable opportunity to trial combinations of micronutrients such as prebiotics and probiotics, vitamin D, zinc, melatonin, B vitamins, intravenous vitamin C, NAC and botanicals like curcumin. Micronutrient therapy rigorously applied to hospitalized patients may improve outcomes, reduce further those who may need a vent and/or reduce time on a vent. While the systematic review above has shown that such studies have been done, the evidence base is not yet robust enough. In addition, many of the studies described are of weaker design and prone to biases.

Clinical trials seek to determine the extent of an interventions therapeutic value. A *null hypothesis* forms the basis, with the presumption that there is no difference between an active treatment arm and a comparator (usually a placebo). The Primary Endpoint is stated, whether it is a *surrogate marker* like CD4 count or cholesterol or a more pertinent clinical outcome like death. There may be secondary endpoints. There are advantages and disadvantages to each. Companies like surrogate markers because they can often provide faster results if the disease takes a long time. With COVID-19, that's not a problem for hospitalized patients. The clinical endpoints are clear and horribly rapid. For prophylaxis studies, the endpoint is also clear: did one become infected? A secondary endpoint of the clinical course of disease may take a little long but not much. However, for Long COVID, endpoints like symptom resolution may be most important for clinical outcomes, especially since we still are learning about its biological underpinnings. Secondary endpoints that include markers of inflammation and coagulability along with cytokines will help us elucidate more of the pathogenesis of Long COVID.

Often, in a clinical trial, there may be an expectation of how well an intervention may work. If the outcome is anticipated to have a small *effect size*, larger numbers may be needed to provide robust evidence for an effect. Understanding the options for clinical trial design is thus vital for producing reliable and replicable results. Another aspect of good design includes how the data are analyzed when the trial is finished. If some patients drop out, they may be excluded from analysis and only those that completed the study are evaluated. This is known as a *per protocol* approach and is weaker than a more rigorous *intent-to-treat* (ITT) analysis where ALL the patients are evaluated. Sometimes this will be a modified ITT, excluding patients who dropped out for whatever reason before taking a first dose.

The features of a clinical trial design include: framing the question clearly, minimizing variation (although this often is why so many trials look at adults…who happen to be male…and Caucasian…); randomizing and stratification, blinding, use of a comparator (placebo, sham) and the selection of a control group, selection of a population and addressing inclusion and exclusion criteria, and a clearly stated selection of endpoints.

All of these should be prespecified in a protocol for the study that should be registered PRIOR to the trial's start with an agency such as clinicaltrials.gov. This is important as here one may see what the Primary Endpoint was originally. Sometimes, if the Primary Endpoint outcome isn't achieved, a study might be declared positive by switching it for a positive finding. The problem here is that the study wasn't necessarily designed or powered to assure that the result is one of causation rather than just correlation or association. Often it takes several trials to establish the efficacy of a study and then this must be balanced against the risks.

One of significant challenge to any trial is missing data points and how they are addressed. The simpler the trial, the better. Also, this should be pre-specified as to whether such missing data are "imputed" or ignored.

Then one has to calculate the appropriate sample size. Too small and you risk having insufficient numbers to answer the question. Too big and the costs of the study rise. Figuring out how many people should be in a trial is greatly helped if there are some data to help one estimate how big the difference might be between the two arms. This permits a rational selection of Type I and Type II error rates that might be anticipated[332] (see the Primer for more on error rates).

And of course, there should be a WHOLLY independent body of individuals who can undertake an interim analysis, depending on the length of the trial. Many covid trials may not need this given the acute and rapid nature of the disease—however, they will be a crucial part of any studies of people suffering from Long COVID.

Large, randomized, open-label studies (like RECOVERY or SOLIDARITY) can provide meaningful clinical data. If some of these extant trials could be harnessed, we might be able to answer some questions about the utility of integrative approaches to patient management. For example, if assessing a micronutrient cocktail in patients on ventilators, rather than comparing such a combination to placebo, dexamethasone could be used in both arms, to see if a micronutrient combination may impact outcomes of interest (especially, of course, mortality). Micronutrient therapies are very safe, inexpensive and preliminary data and data from other indications (e.g., influenza, pneumonia, ARDS and sepsis) are encouraging. *Given that in overwhelmed ICUs, a sequential organ failure assessment (SOFA) under the Crisis Standard of Care will determine who receives treatment and who dies, it would seem such interventions would at least be worth a try.*[333] And would providing such agents to *any* hospitalized patients with SARS-Cov-2 blunt progression and prevent the need for vents? This question was raised last year and has yet to be answered.

Thus, a RECOVERY-style model could be applied to randomize patients, using dexamethasone as a comparator for those on ventilators, for example. Different combinations of N-acetylcysteine (NAC), IV vitamin C, vitamins D3 (and maybe K), zinc, melatonin and quercetin could be evaluated with endpoints including mortality, ICU admission, hospital length, rate of vent use and/or length of time on vents. Clinical trials of individual agents like NAC or glutathione, intravenous Vitamin C are underway. Though such studies have not been proposed, *judicious combinations of micronutrients may safely and effectively provide synergistic benefits.*

The design of the study must be carefully selected. There are a range of study designs.[334] The "gold standard" remains the double-blind, placebo-controlled (DBPC), randomized, controlled trial (RCT). The study will have *arms* generally so that a comparison can be made.

These include Case Series, Cross-sectional, Observational, Large Simple Trials (like the RECOVERY and SOLIDARITY trials which are cluster randomized), Randomized controlled trials (RCT), open label or with placebo or standard of care as comparator arms; factorial design, crossover trials and, as a marketing ploy often, noninferiority trials. Blinding and randomization procedures need to be clearly spelled out. Single blind usually means the patient doesn't know which arm they are in but the physician may (which can lead to selection bias). Double blinding is preferred and some of the trials here indicate triple- and quadruple-blinding to assure other people in the chain from pharmacy to patient are unaware of what people are getting. Randomization protocols also have to be clearly described in order to assure that the people that wind up in each arm are fairly evenly matched in terms of age, gender, any co-morbidities, bloodwork and the like. A good trial, when completed, will list all the different variables for each arm and note if, despite randomization, there are any statistically significant differences between the arms. For example, if more people are sicker in one arm than another (e.g., more high liver enzymes or kidney problems), this can affect the interpretation of the findings.

Following is a proposal for assessing regimens against a comparator arm (Arm 1) using a multivitamin/mineral. Arms two and three differ in forms of vitamin D, while Arm 4 is a high dose arm. Obtaining baseline values of most or all of these will be critical first to assure no one is overdosed, should that be a concern, and to have baseline and end-of-study values.

These protocols do not include pediatric proposals and, with help and input, will be included in future iterations of this document.

Prophylaxis

At this writing, the pandemic is in another "ebb" phase, which if we are fortunate will continue to simply fade away. However, this approach may work for other rising pandemics, including influenza (and could then be modified to adapt to the circulating infection). Sadly, we may yet see another wave or worse, a wave with vaccine-induced immunity eluding variants.

The Seet[106] paper provides an intriguing methodology for assessing the potential of testing interventions to prevent COVID-19 infections. They randomized four treatments to dormitories in Singapore where guest workers were living. Closely confined spaces offer one of the most effective ways to rapidly disseminate SARS-CoV-2 and there are many such congregate living dwellings. Community housing, university dormitories, healthcare workers in hospital settings and frontline worker represent vital hubs where transmission may be thwarted. Clearly, these are also vulnerable populations, so outreach to the communities to engage them, share the ideas and knowledge and listen deeply to their concerns while strictly adhering to ethical models of research conduct will be vital components of such studies.

Intervention	**Arm 1**	**Arm 2**
Vitamin A (carotenenoids?)	0	50,000 IU
Vitamin D3 (cholecalciferol)	0	5,000 IU/day ?
Vitamin D3 (calcifediol)	0	Or 0.25 mg (Test level?)

Intervention	Arm 1	Arm 2
Vitamin C (ascorbic acid), IV or oral*	0	150 mg/kg
Zinc (zinc gluconate)	0	50 mg
Quercetin with bromelain	0	500 mg
B-complex (B1, B2, B3, B6)	0	100/100/50/250
Niacin	0	100 mg
Niacinamide	0	250 mg bid
Vitamin E (alpha tocopherol)	0	400 U
Omega-3 Fatty Acids	0	3-6 g/day
Probiotics	0	50 billion CFU, bid
CoQ10 (ubiquinone)	0	600 mg/day
Melatonin (evening only)	0	1-6 mg
Curcumin (phytosomal, piperidine)	0	500 mg bid
Chinese herbal formula	0	?
Indian herbal formula	0	?
Multivitamin/Minerals**	1	1

*Do not use if G6PD deficiency.

**To be determined.

Hospitalized Patients

Intervention	Arm 1	Arm 2	Arm 3	Arm 4 (high dose)
Vitamin A (beta carotene?)	0	100,000 IU IM/day	100,000 IU IM/day	200,000 IU IM/day
Vitamin D3 (cholecalciferol)	0	50,000 IU/day ?	0	50,000 IU/day
Vitamin D3 (calcifediol)	0	0	0.8 mg	0
Vitamin C (ascorbic acid), IV*	0	150 mg/kg	150 mg/kg	200 mg/kg?
Zinc (zinc gluconate)	0	50 mg	50 mg	50 mg
Quercetin	0	500 mg	500 mg	500 mg bid
B-complex (B1, B2, B3, B6)	0	100/100/50/250	100/100/50/250	100/100/50/250
Niacin	0	0 mg	100 mg	250 mg
Niacinamide	0	250 mg	0	250 mg bid
Vitamin E (alpha tocopherol)	0	400 U	400 IU	0
Omega-3 Fatty Acids	0	2-6 g	2-6 g	2-6 g
Probiotics	0	50 billion CFU bid	50 billion CFU bid	500 billion CFU
CoQ10 (ubiquinone)	0	600 mg/day	600 mg/day	900 mg/day
Melatonin (evening only)	0	9 mg	9 mg	200 mg

Intervention	Arm 1	Arm 2	Arm 3	Arm 4 (high dose)
Curcumin (form?)	0	500 mg bid	500 mg bid	500 mg bid
Chinese herbal formula	0	TBD	TBD	TBD
Indian herbal formula	0	TBD	TBD	TBD
Multivitamin/Minerals**	1	0	0	1

*Do not use if G6PD deficiency.
**To be determined.

Long COVID Management

Intervention	Arm 1	Arm 2
Vitamin A (beta carotene?)	0	200,000 IU
Vitamin D3 (cholecalciferol)	0	5,000 IU/day ?
Vitamin D3 (calcifediol)	0	Or 0.25 mg (Test level?)
Vitamin C (ascorbic acid), IV or oral*	0	150 mg/kg
Zinc (zinc gluconate)	0	50 mg
Quercetin with bromelain	0	500 mg
B-complex (B1, B2, B3, B6)	0	100/100/50/250
Niacin	0	100 mg
Niacinamide	0	250 mg bid
Vitamin E (alpha tocopherol)	0	400 U
Omega-3 Fatty Acids	0	3-6 g/day
Probiotics	0	30 billion CFU
CoQ10 (ubiquinone)	0	600 mg/day
Melatonin (evening only)	0	9 mg
Curcumin (phytosomal, piperidine)	0	500 mg bid
Chinese herbal formula	0	?
Indian herbal formula	0	?
Multivitamin/Minerals**	1	1

*Do not use if G6PD deficiency.
**To be determined.

A Clinical Trial Statistics Primer

For some readers, there are no doubt terms scattered throughout the document that may be unfamiliar. The science of clinical trials includes the field of specialty, *statistics*. A term that causes many to feel a chill of terror or an outright dismissal. Lies, damned lies and statistics! They can be just that, sometimes innocently through misinterpretation of evidential material or, more crassly, in their manipulation to sell more drugs or other costly therapy.

Such caveats indeed must be borne in mind. And understanding the methodological strength of a clinical study is greatly helped by an understanding of statistics. And they are important from the beginning of a trial through to the analysis of its results.

Life is noisy. Physicians say things, people believe things. Emotional states of mind can potentiate or squelch a response to therapy. So clinical trials are designed to limit that noise using an array of techniques that are based on statistical considerations. All sorts of *bias* can creep in that may render results dubious. Indeed, much of the data on interventions for treating COVID-19 fall into the category of weak methodology, vitamins, herbs and drugs all included. This is why also very often early apparent successes may fall apart in the real world, as we witnessed with the rise and fall of the hydroxychloroquine and azithromycin combination—and pretty much with the still "approved" drug (in the USA), remdesivir that does little, costs a lot and may actually do more harm than good.

When a clinical trial is contemplated, a range of questions arise. First, *what* is being studied. Is it one intervention? One drug? A combination? The next obvious consideration is what is the outcome?

As noted above, the *primary outcome* should be stated at the outset and provided in the *protocol* for the trial, registered for example with clinicaltrials.gov. This is important because sometimes an intervention may fail to succeed in addressing that primary outcome—but then other intriguing secondary outcomes may fare better. However, a trial's methods of analysis are geared to that primary outcome.

One of the gears is how many subjects will be in a study. Here is one of the first places where statistics enters the ring: a calculation is made based on an anticipated *effect size* to help establish how many people will be needed to see if the intervention works.

Indeed, MANY drugs have rather marginal effects on clinical outcome. Or it may take a long time and a lot of participants to establish the effect. Many trials look at a *surrogate marker* to be the primary outcome. While a change in such a marker, usually derived from the blood, may indicate some benefit, it is not a guarantee. On the one hand, in managing HIV/AIDS, many studies looked at changes in the amount of human immunodeficiency virus (viral load) in the blood along with changes in the amount of a particular white blood cell, the CD4+ T cell. When there were robust changes—the viral load dropped below the limit of detectability and CD4 count rose substantially, there generally WAS a very strong clinical benefit. People survived with the virus and a vastly lowered risk of the opportunistic infections that may arise when the CD4 count drops to dangerously low levels.

The recent FDA approval of an Alzheimer's drug, adacanumab, that even the advisory committee said failed to have clinical benefit adds to their waning credibility (and see the citation which lays out excellent ways for FDA to recover that necessary credibility).[335] This is a recent example of the FDA's "regulatory capture" by industry, the data for which centered on a surrogate marker that seems to have less and less clinical value. Rather than assessing a clinical endpoint of delaying disease progression (or even better, reversing it), the company used changes in a surrogate marker. That is, even though number of amyloid plaques declined during the course of the study, this doesn't translate into slowed or halted disease progression. People still lose their memories. And the drug is both hideously costly (capriciously and arbitrarily as ever) and—perhaps worse—toxic. Basically, the drug causes harm to pocketbook and patients.

Thus, assessing an outcome based on a surrogate marker is problematic, especially when many questions remain about how a disease develops. The problem often has been that assessing clinical outcomes take a LOT more patients to be enrolled and over a longer time. This concern, however, is not as pertinent for patients hospitalized with SARS-CoV-2. They're either going to recover or die within a few months of hospitalization. So *clinical endpoints* are both advised and essential. The best is mortality (dying). A trial can have more than one primary endpoint and in the case of COVID-19, these may be the impact on disease progression, usually focused on the use of supplemental oxygen. If it's a simple canula, this is not

invasive so an endpoint is more likely to include whether an intervention prevents the need for mechanical ventilation or shortens the time on a vent. Secondary endpoints such as blood oxygen saturation (SaO2 or SpO2). Many studies here look also at clinical endpoints like length of time in the hospital or in an intensive care unit (ICU).

Effect size becomes important here. If you get a really strong signal that a lot fewer people are, say, dying (and if mortality is the primary endpoint), this helps to distinguish that the *benefits* of an intervention outweigh any *risks* it may have. The benefits ideally are clinical ones as opposed to surrogate markers. That the patient survives, that symptoms such as pain resolve, that a tumor recedes.

Risks include side effects (like nausea, headache, diarrhea) or *adverse events* (like anaphylaxis, liver, kidney or heart failure, etc.) While they sound the same, they are not. Adverse events are further distinguished as Type A or Type B reactions. Type A arise when a correct dose is given and there is a predictable degree of negative response (mild, moderate or severe). Type B are more unpredictable and have nothing to do with a dose (like having an anaphylactic reaction). Adverse events during a clinical study are further broken down by grades. Grade 1 is mild, 2 is moderate, 3 is severe and grade 4 is potentially a life-threatening event. Assessing a clinical study must include examination of any such serious adverse events (AEs). By contrast, a side effect is something that is generally understood as a potential problem with a drug, often one that may resolve over time or, due to a person's sensitivities, may require dose adjustment, stopping the drug or switching to another. Adverse events and side effects are risks of taking a drug. Thus, risk and benefits must be delineated and balanced.

Observational

Retrospective – may include a chart review of multiple patients, in either a snapshot (*cross-sectional*) or following patients over a period of time (*prospective*). They may look at patients who use an intervention on their own. They may compare them to patients who did not receive the intervention. The best of these latter use a *propensity-score matching* to match patients those of similar gender, age, co-morbidities (i.e., hypertension, diabetes, obesity, etc.)

Observational study designs include ecological designs, cross sectional, case-control, case-crossover, retrospective and prospective cohorts.

Experimental

A phase I study will assess the dosing and toxicity of a new agent. These are *open label*, where patients and physicians know what a person is getting. Frequently, cis-gendered white males predominate although this is changing, gradually.

Phase II studies assess the ability of the agent to affect an outcome of interest (the primary and secondary endpoints). Such a trial will be randomized, using a method specified in the protocol, to limit *selection bias*. Phase III are then larger studies evaluating many more people. Once a regulatory agency like the USA's Food and Drug Administration (FDA) grants approval for the drug, often a phase IV study that looks at outcomes in the "real-world" setting as a contingency of approval. (Often companies nod sagely and say "sure……" and then never do them.)

Ideally, and to reduce the risk of bias, there will be some degree of blinding (or masking) of experimenters and participants. A "double-blind" study, neither the physician and others involved in administering the drug or comparator nor the patient is aware of which arm they are in. The *comparator arm* is either a placebo or, if there is one, a standard of care (SOC). Comparison with a placebo is considered methodologically more robust. Indeed, sometimes it is not difficult to assess who is on

treatment, the blind may then be broken inadvertently. Certain well known side effects or changes in bloodwork may alert participants and researchers of a patient's arm. Some trials are described as triple or quadruple blind, underscoring a more comprehensive declaration of anyone from the pharmacy to the patient. The intervention and the placebo have to look alike and, if possible, smell and taste similarly.

Randomization or "random allocation" is the process by which patients are designated to be in a particular arm. Here too a level of bias can creep in that a strong and well-described randomization process can minimize. A simple toss of a coin could do it but there are other methods deemed more robust such a random number generator or the like that assures participants are randomly allocated.

Types of bias

All of these aspects to clinical trial design are intended to reduce the various types of bias that can creep in and influence the outcome of a study. The following tables are from the Cochrane Handbook[336]

Type of reporting bias	Definition
Publication bias	The *publication* or *non-publication* of research findings, depending on the nature and direction of the results.
Time-lag bias	The *rapid* or *delayed* publication of research findings, depending on the nature and direction of the results.
Language bias	The publication of research findings *in a particular language*, depending on the nature and direction of the results.
Citation bias	The *citation* or *non-citation* of research findings, depending on the nature and direction of the results.
Multiple (duplicate) publication bias	The *multiple* or *singular* publication of research findings, depending on the nature and direction of the results.
Location bias	The publication of research findings in journals with different *ease of access* or *levels of indexing* in standard databases, depending on the nature and direction of results.
Selective (non-) reporting bias	The *selective reporting* of some outcomes or analyses, but not others, depending on the nature and direction of the results.

Table 8.2.a Bias domains included in version 2 of the Cochrane risk-of-bias tool for randomized trials, with a summary of the issues addressed

Bias domain	Issues addressed*
Bias arising from the randomization process	Whether: • the allocation sequence was random; • the allocation sequence was adequately concealed; • baseline differences between intervention groups suggest a problem with the randon
Bias due to deviations from intended interventions	Whether: • participants were aware of their assigned intervention during the trial; • carers and people delivering the interventions were aware of participants' assigned i the trial. *When the review authors' interest is in the effect of assignment to intervention* (see Section 8.2.2):

- (if applicable) deviations from the intended intervention arose because of the experi
  do not reflect usual practice); and, if so, whether they were unbalanced between grou
  affected the outcome;
- an appropriate analysis was used to estimate the effect of assignment to intervention
  there was potential for a substantial impact on the result.

When the review authors' interest is in the effect of adhering to intervention (see Section 8.2.2):

- (if applicable) important non-protocol interventions were balanced across interventi
- (if applicable) failures in implementing the intervention could have affected the outc
- (if applicable) study participants adhered to the assigned intervention regimen;
- (if applicable) an appropriate analysis was used to estimate the effect of adhering to t

Bias due to missing outcome data	Whether: • data for this outcome were available for all, or nearly all, participants randomized; • (if applicable) there was evidence that the result was not biased by missing outcome • (if applicable) missingness in the outcome was likely to depend on its true value (e.g. missing outcome data, or reasons for missing outcome data, differ between interventi
Bias in measurement of the outcome	Whether: • the method of measuring the outcome was inappropriate; • measurement or ascertainment of the outcome could have differed between interven • outcome assessors were aware of the intervention received by study participants; • (if applicable) assessment of the outcome was likely to have been influenced by know intervention received.
Bias in selection of the reported result	Whether: • the trial was analysed in accordance with a pre-specified plan that was finalized befo outcome data were available for analysis; • the numerical result being assessed is likely to have been selected, on the basis of the multiple outcome measurements within the outcome domain; • the numerical result being assessed is likely to have been selected, on the basis of the multiple analyses of the data.

Statistical Analysis

Once the trial is completed, the next step is analysis. What did they see? Were the patients relatively well-matched at the outset (baseline)? Here's where the fun begins (or the mind-numbing horror, depending upon your predilections). The way the numbers shake out at the end of the study unfortunately can give much stronger estimations of a treatment's effects than perhaps are warranted. This is true for observational studies and can also be true for RCTs, particularly if the rigor of the randomization process is faulty or inadequate.[337]

You will see tables toward the beginning of a published paper that, in a better study, will provide data on the *baseline characteristics* of those who were enrolled along with a p-value. How many were male or

female (and occasionally though not often enough, those in transition or non-gendered). What is their ethnic background (were they mostly white men)? Sometimes a difference will pop out that deserves scrutiny. Even with the best randomization protocols, sometimes one arm may have, say, more people in one arm with higher liver enzymes. The statistical significance (or "p value") is provided. This p-value is a way of saying how strong the likelihood is that an outcome is due to what went on in the trial and not just to chance. Rather arbitrarily (and sometimes controversially), that value is set such that there is a 95% or greater chance, then the difference is *significant.* This is represented as $p<0.05$ as one of the highlighted features. Though again, getting to stuck on statistical significance may be misleading!

Another commonly used analytic tool to describe the outcome is *relative risk*. Indeed, this is frequently a marketing tool used by pharmaceutical companies. A relative risk reduction of 50% may sound pretty good but this should also be taken in the context of *absolute risk*. As an example, say 2 patients achieve the primary endpoint and one does not in the placebo arm. Why, that's a relative risk reduction of 50%! But if you had 1000 patients where two had the outcome and one did not, the absolute risk here is 2 out of a thousand (0.2%) vs 1 out of a thousand (0.1%) for an absolute risk difference of 0.1%. Not quite so exciting.

It's never quite THAT blatant, but can be. One other measure that may be used to assess a treatment is the *number needed to treat*. There are some good online tools one can use as the figure is rarely calculated in clinical trials. If the NNT is 65 for example, that means you would need to treat 65 people before 1 person received the benefit. If the intervention is not riddled with bad side effects, and not absurdly costly, this could be acceptable. If there are side effects, one may also calculate the number needed to harm (NNH). In this example, if the NNH was 25, i.e., less than the NNT of 65, this may suggest the drug is too problematic, i.e., greater risk than benefit. You can try this at home! See https://clincalc.com/stats/nnt.aspx or https://www.calctool.org/CALC/prof/medical/NNT.

Odds ratio (OR) vs risk ratio (RR)[338] vs Hazard Ratio (HR)[339]

There are several ways to slice the data pie. Let's take an example from one of the studies summarized in the Vitamin C table (Zhao, 2021).[144] The primary outcome was development of severe disease. In this small study, 4 of the 55 people who were given IV vitamin C developed severe disease, where the figure was 12/55 in the comparator arm. They calculated a relative risk (RR) of 0.28. This fell within a range (or *confidence interval*) that was rather broad, 0.08 to 0.93, but remained less than one. If it had exceeded one, it would have meant that the finding wasn't strong and here the p-value reflects that rather wide range: it is $p=0.03$. This is statistically significant and would appear to be clinically significant if patients are not getting sick. This is denoted in shorthand as RR=0.28 (0.08-0.93, p=0.03).

By way of comparison, had the RR had a narrower confidence interval of say 0.20-0.36, the p value would probably have been smaller, maybe $p<0.01$ or the like, indicating a stronger statistical significance.

At the same time, this was an observational and retrospective evaluation of patients as they came into the clinic. The comparator arm was "propensity-matched" controls from a previous month. While the matching of the controls is helpful, it does limit the interpretation of the outcome of the study.

Aside from relative risk, there are other ratios one may employ, such as Odds, Risk or Hazard ratios. The difference between an Odds Ratio and a Risk Ratio is somewhat subtle. Looking at it in math terms clarifies. Say you have a 100 people in a trial. 30 die and 70 live. The risk ratio is 30/100 or 30 divided by 30+70. That is, 0.30.

Whereas the Odds Ratio is the ratio of dead to surviving, i.e., 30/70, which is 0.43.[340] So in the example of Zhao, the odds ratio would be calculated from the number of events. Here it was 4 of 55 in the IV vitamin C arm experienced disease progression compared to 12/55 in the no IV C arm. 4/55=0.073 and 12/55=0.22. Then 0.073/0.22 = is 0.33, a bit higher than the RR of 0.28. Which is to say had they calculated an OR instead of an RR, the outcome might have looked better. In general, if the event rates are low in each arm, the OR and RR are generally more or less equivalent. When there is a greater discrepancy, the difference can be important to consider.

Given that people are different, confounders may arise, so matching controls is important, as noted above. Matching gender, age, ethnic background, and controlling for variables like weight/BMI, smoking, organ function, SOFA score or what have you can increase confidence that the observation is one of causation by the intervention rather than just a correlation. That is, the two events occurred together but were more coincidence than effect. Indeed, given that observational retrospective studies have limitations in their reliability compared to DBPC RCTs, *propensity score matching* can help to further reduce the risk of bias associated with the assignment of treatments. Physicians may choose to give one patient a therapy or not due to reasons such as riskiness of the intervention, likelihood of potential success, how ill the patient is. *Matching attempts to reduce the treatment assignment bias, and mimic randomization, by creating a sample of units that received the treatment that is comparable on all observed covariates to a sample of units that did not receive the treatment.*[341]

The first look is at the raw data and how the arms are distinguished. However, due to aspects like age, gender, co-morbidities, other treatments used, etc. Analyses like these include multiple logistic regression, a frequently used multivariate technique, that calculates adjusted ORs (but not RRs). These are featured in the tables above as OR_{adj} to indicated these adjustments have been undertaken to reduce the risk of undue influence by these factors.

Another calculation is the *confidence interval (CI)*. That is the range—in our example, 0.08-0.93. This result is usually set at a predetermined level of 95%. What that CI represents is not that the represented range contains the true value, but rather, how reliable the estimation procedure is. The calculation itself requires somewhat more esoteric variables that include the sample mean (or average), a population standard deviation and a Z-score, based on whether you want 95% CI or only 70% (almost never) or VERY rigorous, say 99.9% confidence. Z=1.960 for a 95% CI but would be 3.291 in a 99.9% CI. A "sample" standard deviation may be used instead if the population size is greater than 30. For the more industrious, check out https://www.calculator.net/confidence-interval-calculator.html or https://calculator.academy/confidence-interval-calculator/. Using our Zhao example above, with a 95% CI, which is fairly typical, that leaves a 5% chance that the RR=0.28 is NOT in the range of 0.08-0.93.

The goal of the study is to *reject the null hypothesis* or rather reject the idea that there won't be any difference between the arms. I.e., it worked! This lends strength to an argument of causation and not just correlation. Yes, giving that pill cured the disease, if the null hypothesis is rejected. But hold on! Presuming no errors were made.

When a number of different hypotheses are being tested, there may be a risk of rejecting the null hypothesis (or in equation terms, H_0) that causes a *Type I error*. A Type 1 error is a kind of false positive, that is, the conclusion is that—it works! But it was due to a Type 1 error that falsely rejected the null hypothesis. Some analyses may correct for this by applying a Bonferroni correction (see the Seet study above). This can be overly conservative and lead to false negatives! A Type II error is one where the null hypothesis is mistakenly accepted (false negative). In statistical jargon, Type 1 errors are represented by alpha (α) and Type 2 by beta (β). The alpha is set at the outset—back to confidence intervals. You want a

95% CI? Then the alpha is 0.05. Then there is a 5% chance of a Type 1 error. The Type 2 error is related to the power or sensitivity of the hypothesis test, represented by 1-β. A lot of that is dependent on the sample size: were there enough people in the trial? Is the study powered to find a difference, especially if that outcome isn't particularly strong? The table sets out how to balance these:

Table of error types		**Null hypothesis (H_0) is**	
		True	**False**
Decision about null hypothesis (H_0)	**Don't reject**	Correct inference (true negative) (probability = $1-\alpha$)	Type II error (false negative) (probability = β)
	Reject	Type I error (false positive) (probability = α)	Correct inference (true positive) (probability = $1-\beta$)

But wait! There's also the option of using a Hazard Ratio instead of an OR or RR. This calculates a rate of change between two groups (like how many wind up dead. That will ultimately be 100% if your trial is long enough…but I digress, cheerily!) The following table from George, et al. provides a succinct summary of the strengths and weaknesses of each approach:[339]

	RR	OR	HR
Goal	Determine relationship in risk status based on some variable.	Determine association between two variables.	Determine how one group changes relative to another.
Use	Tells us how an intervention changes risks.	Tells us if there is an association between an intervention and risk; estimates how this association applies.	Tells us how an intervention changes the rate of experiencing an event.
Limitations	Only applicable if the study design is representative of the population. Cannot use on case-control studies.	Can generally be applied everywhere, but not always a useful statistic itself. Exaggerates risks.	To typically be useful, the rate of change within two groups should be relatively consistent.
Timeline	Static – does not consider rates. Summarizes an overall study.	Static – does not consider rates. Summarizes an overall study.	Based on rates. Provides information about the way a study progresses over time.

TABLE 1: Relative risk (RR) vs. Odds Ratio (OR) vs. Hazard Ratio (HR)

So as you can see, some potentially arbitrary-seeming choices can be made on the way to undertaking a clinical trial. And when there are other motivations at hand, this can screw things up. Whether that's just the urge to publish positive data or, most dangerously, to sell a drug or downplay adverse events, the stats can be twisted to suit unscientific ends. Such do not serve the interests of patients, science or medicine.

Indeed, a fine and terrifying example can be made with two studies of ivermectin that showed significant benefit. Upon closer scrutiny, it turned out that the investigators engaged in outright fraud. They made up patient data! This led one reviewer to recommend that any meta-analysis must rely upon patient-level data, acquired from the investigators of each trial.[342] This increases the amount of work and while it can make the findings more robust indeed than a summary of outcomes that is often used (indeed, by the revered meta-analysis Cochrane Group).

My bigger concern? If they're willing to lie to publish, they can screw with the patient data too. Whatever the case, researchers caught in such nefarious activity should be barred for life from ever seeing a patient or conducting research.

Commentary and Analysis

The above data reflects a growing body of evidence for a range of interventions. While much of the data is of lower methodological quality, some of the interventions stand out as requiring more attention. The data on probiotics, melatonin, quercetin, curcumin, Vitamin D and zinc are promising.

What is often overlooked is the potential for enhancing efficacy through the synergies of combination. As discussed, quercetin and zinc look like an intriguing combination, exerting both antiviral and anti-inflammatory effects. Others have noted a stronger benefit when vitamin C and NAC are combined.[343]

The encouraging news is that many of these agents are being given at many hospitals. However, a more formalized approach might give us a better idea on how patient management can be further improved. Indeed, the mortality rate dropped from the early days in 2020 through that summer due largely to greater understanding of how patients can be managed without mechanical ventilation being instituted too quickly, use of proning, management of coagulation issues and appropriate and limited use of steroids.

Could we not achieve even greater success by immediate use of a range of micronutrients as described above that may have the ability to further reduce the number of patients advancing to critical condition and the need for a vent? And for those that still progress—can we shorten that time further? Can judiciously selected combinations provide protection against infection? Could they prevent disease from advancing?

An appropriately conducted set of clinical studies could help to provide evidence and guidance for best use of these powerful agents.

Input on the contents of this document is welcome and greatly appreciated.

References

1. Dai L, Zheng T, Xu K, et al. A Universal Design of Betacoronavirus Vaccines against COVID-19, MERS, and SARS. *Cell.* 2020;182(3):722-733.e711.
2. Han E, Chiou S-T, McKee M, Legido-Quigley H. The resilience of Taiwan's health system to address the COVID-19 pandemic. *EClinicalMedicine.* 2020;24(100437):1-2.
3. Mertens E, Peñalvo JL. The Burden of Malnutrition and Fatal COVID-19: A Global Burden of Disease Analysis. *Front Nutr.* 2021;7(619850):1-12.
4. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an Oral Antiviral Treatment for COVID-19. *medRxiv.* 2021;[not peer reviewed]:1-30.
5. Barber MJ, Gotham D. *Estimated cost-based generic prices for molnupiravir for the treatment of COVID-19 infection.* https://scholar.harvard.edu/files/melissabarber/files/estimated_cost-based_generic_prices_for_molnupiravir_for_the_treatment_of_covid-19_infection.pdf: Harvard;2021.
6. Abinader LG. US government rights in patents on Molnupiravir, based upon funding of R&D at Emory University. 2021; https://www.keionline.org/36648. Accessed 10/4/21, pub'd 10/4/21.
7. Tomasa-Irriguible T-M, Bielsa-Berrocal L, Bordejé-Laguna L, et al. Low Levels of Few Micronutrients May Impact COVID-19 Disease Progression: An Observational Study on the First Wave. *Metabolites.* 2021;11(9).
8. Beigmohammadi MT, Bitarafan S, Abdollahi A, et al. The association between serum levels of micronutrients and the severity of disease in patients with COVID-19. *Nutrition (Burbank, Los Angeles County, Calif.).* 2021;91-92(111400):1-6.
9. Allegra A, Tonacci A, Pioggia G, Musolino C, Gangemi S. Vitamin deficiency as risk factor for SARS-CoV-2 infection: correlation with susceptibility and prognosis. *Eur Rev Med Pharmacol Sci.* 2020;24(18):9721-9738.
10. Muhammad Y, Kani YA, Iliya S, et al. Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. *SAGE Open Med.* 2021;9:1-8.
11. Collins F. NIH launches new initiative to study "Long COVID". 2021; https://www.nih.gov/about-nih/who-we-are/nih-director/statements/nih-launches-new-initiative-study-long-covid. Accessed April 22, 2021.
12. Moreno Fernández-Ayala DJ, Navas P, López-Lluch G. Age-related mitochondrial dysfunction as a key factor in COVID-19 disease. *Experimental Gerontology.* 2020;142(111147):1-14.
13. Pagano G, Manfredi C, Pallardo FV, Lyakhovich A, Tiano L, Trifuoggi M. Potential roles of mitochondrial cofactors in the adjuvant mitigation of proinflammatory acute infections, as in the case of sepsis and COVID-19 pneumonia. *Inflammation Research.* 2021;70:159-170.
14. Chowdhury A, Sajid M, Jahan N, et al. A secondary approach with conventional medicines and supplements to recuperate current COVID-19 status. *Biomed Pharmacother.* 2021/10/01/ 2021;142(111956):1-11.
15. Bloomberg. More than a third of Earth's population faces malnutrition due to Covid-19. 2021; https://indianexpress.com/article/world/more-than-a-third-of-earths-population-faces-malnutrition-due-to-covid-19-7413147/. Accessed August 2, 2021.
16. Cunningham-Rundles S, McNeeley DF, Moon A. Mechanisms of nutrient modulation of the immune response. *Journal of Allergy and Clinical Immunology.* 2005;115(6):1119-1128.
17. Morais AHdA, Aquino JdS, da Silva-Maia JK, Vale SHdL, Maciel BLL, Passos TS. Nutritional status, diet and viral respiratory infections: perspectives for severe acute respiratory syndrome coronavirus 2. *Br J Nutr.* 2021;125(8):851-862.
18. Briguglio M, Pregliasco FE, Lombardi G, Perazzo P, Banfi G. The Malnutritional Status of the Host as a Virulence Factor for New Coronavirus SARS-CoV-2. *Frontiers in Medicine.* 2020;7(146):1-5.
19. Levander OA, Beck MA. Interacting nutritional and infectious etiologies of Keshan disease. *Biological Trace Element Research.* 1997/01/01 1997;56(1):5-21.
20. Guillin OM, Vindry C, Ohlmann T, Chavatte L. Selenium, Selenoproteins and Viral Infection. *Nutrients.* 2019;11(2101):1-33.
21. Malik P, Patel U, Mehta D, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evidence-Based Medicine.* 2021;26(3):1-12.
22. Rozga M, Cheng FW, Moloney L, Handu D. Effects of Micronutrients or Conditional Amino Acids on COVID-19-Related Outcomes: An Evidence Analysis Center Scoping Review. *J Acad Nutr Diet.* 2021;121(7):1354-1363.

23. Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A, Aaseth J. Early Nutritional Interventions with Zinc, Selenium and Vitamin D for Raising Anti-Viral Resistance Against Progressive COVID-19. *Nutrients.* 2020;12(2358):1-12.
24. Shakoor H, Feehan J, Al Dhaheri AS, et al. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? *Maturitas.* 2021;143:1-9.
25. Sahin E, Orhan C, Uckun FM, Sahin K. Clinical Impact Potential of Supplemental Nutrients as Adjuncts of Therapy in High-Risk COVID-19 for Obese Patients. *Front Nutr.* 2020;7(580504):1-16.
26. Abioye AI, Bromage S, Fawzi W. Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis. *BMJ Glob Health.* 2021;6(1):e003176.
27. Kang J-S. Vitamin intervention for cytokine storm in the patients with coronavirus disease 2019. *MedComm (Beijing).* 2020;1(100967):81-83.
28. Lotfi F, Akbarzadeh-Khiavi M, Lotfi Z, et al. Micronutrient therapy and effective immune response: a promising approach for management of COVID-19. *Infection.* 2021:1-15.
29. Arrieta F, Martinez-Vaello V, Bengoa N, et al. Serum zinc and copper in people with COVID-19 and zinc supplementation in parenteral nutrition. *Nutrition.* 2021;91-92(111467):1-7.
30. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, Ortiz M, O'Sullivan CK, Fernández-Larrea JB. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. *J Agric Food Chem.* Aug 13 2014;62(32):8085-8093.
31. Scipioni J. Dr. Fauci says to take vitamin D if you're deficient — here's how to know. 2020; https://www.cnbc.com/2020/09/26/how-to-know-if-you-have-a-vitamin-d-deficiency.html. Accessed September 28, 2020.
32. Sosa Henríquez M, Gómez de Tejada Romero MJ. Cholecalciferol or Calcifediol in the Management of Vitamin D Deficiency. *Nutrients.* 2020;12(1617):1-18.
33. Petrelli F, Luciani A, Perego G, Dognini G, Colombelli PL, Ghidini A. Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies. *The Journal of Steroid Biochemistry and Molecular Biology.* 2021;211(105883):1-5.
34. Quesada-Gomez JM, Bouillon R. Is calcifediol better than cholecalciferol for vitamin D supplementation? *Osteoporosis International.* 2018;29(8):1697-1711.
35. Crafa A, Cannarella R, Condorelli RA, et al. Influence of 25-hydroxy-cholecalciferol levels on SARS-CoV-2 infection and COVID-19 severity: A systematic review and meta-analysis. *EClinicalMedicine.* 2021;37:1-14.
36. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ.* 2017;356:i6583.
37. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients* 2020;12(988):1-19.
38. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study (April 26, 2020). *[preprint].* 2020:1-14.
39. Tan CW, Ho LP, Kalimuddin S, et al. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. *medRxiv.* 2020;[epub](20112334):1-6.
40. Lanham-New SA, Webb AR, Cashman KD, et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition.* 2020;[epub](bmjnph-2020-00008):1-5.
41. Berthelot J-M, Drouet L, Lioté F. Kawasaki-like diseases and thrombotic coagulopathy in COVID-19: delayed over-activation of the STING pathway? *Emerging Microbes & Infections.* 2020;9(1):1514-1522.
42. Shiravi A-A, Saadatkish M, Abdollahi Z, Miar P, Khanahmad H, Zeinalian M. Vitamin D can be effective on the prevention of COVID-19 complications: A narrative review on molecular aspects. *International Journal for Vitamin and Nutrition Research.* 2020;[EPUB]:1-13.
43. Im JH, Je YS, Baek J, Chung M-H, Kwon HY, Lee J-S. Nutritional status of patients with coronavirus disease 2019 (COVID-19). *Intl J Inf Dis.* 2020;[Epub Pre-Proof]:1-18.
44. Pizzini A, Aichner, M., Sahanic, S., Böhm, A., Egger, A., Hoermann, G., Kurz, K., Widmann, G., Bellmann-Weiler, R., Weiss, G., Tancevski, I., Sonnweber, T., Löffler-Ragg, J. Impact of Vitamin D Deficiency on COVID-19—A Prospective Analysis from the CovILD Registry. *Nutrients.* 2020;12(2775):1-9.

45. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One.* 2020;15(9):e0239252.
46. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. *Scientific Reports.* 2020;10(20191):1-8.
47. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? *Clin Med (Lond).* 2020;20(4):e107-e108.
48. Hernández JL, Nan D, Fernandez-Ayala M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. *The Journal of Clinical Endocrinology & Metabolism.* 2020;[epub ahead of print]:1-11.
49. Kumar R, Himani, Haq A, Wimalawansa SJ, Sharma A. Putative Roles of Vitamin D in Modulating Immune Response and Immunopathology Associated With COVID-19. *Virus Res.* 2020/11/21/ 2020;[journal pre-proof](198235):1-33.
50. Leaf DE, Ginde AA. Vitamin D3 to Treat COVID-19: Different Disease, Same Answer. *JAMA.* 2021;[epub]:1-2.
51. Fakhoury HMA, Kvietys PR, Shakir I, Shams H, Grant WB, Alkattan K. Lung-Centric Inflammation of COVID-19: Potential Modulation by Vitamin D. *Nutrients.* 2021;13(7):1-15.
52. Pfleger K, others. Over 200 Scientists & Doctors Call For Increased Vitamin D Use To Combat COVID-19. 2021; https://vitamindforall.org/letter.html. Accessed 9/29/21, pub'd 2021.
53. Caballero-García A, Pérez-Valdecantos D, Guallar P, et al. Effect of Vitamin D Supplementation on Muscle Status in Old Patients Recovering from COVID-19 Infection. *Medicina (Kaunas).* 2021;57(1079):1-9.
54. Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier J-M, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. *The Journal of Steroid Biochemistry and Molecular Biology.* 2020/11/01/ 2020;204:105771.
55. Loucera C, Peña-Chilet M, Esteban-Medina M, et al. Real world evidence of calcifediol use and mortality rate of COVID-19 hospitalized in a large cohort of 16,401 Andalusian patients. *medRxiv.* 2021;[not peer reviewed]:1-20.
56. Sánchez-Zuno GA, González-Estevez G, Matuz-Flores MG, et al. Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. *Journal of Clinical Medicine.* 2021;10(2378):1-14.
57. Tan CW, Ho LP, Kalimuddin S, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). *Nutrition.* 2020/11/01/ 2020;79-80:111017.
58. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *The Journal of Steroid Biochemistry and Molecular Biology.* 2020/10/01/ 2020;203(105751):1-6.
59. Rastogi A, Bhansali A, Khare N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgraduate Medical Journal.* 2020;[epub]:1-4.
60. Murai IH, Fernandes AL, Sales LP, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;[epub ahead of print]:1-0.
61. Ling SF, Broad E, Murphy R, et al. High-Dose Cholecalciferol Booster Therapy is Associated with a Reduced Risk of Mortality in Patients with COVID-19: A Cross-Sectional Multi-Centre Observational Study. *Nutrients.* 2020;12(3799):1-16.
62. Jevalikar G, Mithal A, Singh A, et al. Lack of association of baseline 25-hydroxyvitamin D levels with disease severity and mortality in Indian patients hospitalized for COVID-19. *Scientific Reports.* 2021/03/18 2021;11(6258):1-8.
63. Giannini S, Passeri G, Tripepi G, et al. Effectiveness of In-Hospital Cholecalciferol Use on Clinical Outcomes in Comorbid COVID-19 Patients: A Hypothesis-Generating Study. *Nutrients.* 2021;13(219):1-15.
64. Nogues X, Ovejero D, Pineda-Moncusí M, et al. Calcifediol Treatment and COVID-19–Related Outcomes. *The Journal of Clinical Endocrinology & Metabolism.* 2021;106(10):e4017-e4027.
65. Lakkireddy M, Gadiga SG, Malathi RD, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. *Scientific Reports.* 2021/05/20 2021;11(10641):1-8.
66. Lohia P, Nguyen P, Patel N, Kapur S. Exploring the link between vitamin D and clinical outcomes in COVID-19. *American Journal of Physiology-Endocrinology and Metabolism.* 2021/03/01 2021;320(3):E520-E526.

67. Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, et al. Calcifediol Treatment and Hospital Mortality Due to COVID-19: A Cohort Study. *Nutrients.* 2021;13(1760):1-13.
68. Güven M, Gültekin H. The effect of high-dose parenteral vitamin D3 on COVID-19-related inhospital mortality in critical COVID-19 patients during intensive care unit admission: an observational cohort study. *European Journal of Clinical Nutrition.* 2021/09/01 2021;75(9):1383-1388.
69. Soliman AR, Abdelaziz TS, Fathy A. Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients. *Proceedings of Singapore Healthcare.* 2021;[epub]:1-5.
70. Elamir YM, Amir H, Lim S, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. *Bone.* 2021;154(116175):1-6.
71. Yildiz M, Senel MU, Kavurgaci S, Ozturk FE, Ozturk A. The prognostic significance of vitamin D deficiency in patients with COVID-19 pneumonia. *Bratislava Med J.* 2021;122(10):744-747.
72. Blanch-Rubió J, Soldevila-Domenech N, Tío L, et al. Influence of anti-osteoporosis treatments on the incidence of COVID-19 in patients with non-inflammatory rheumatic conditions. *Aging.* 2020;12(20):19923-19937.
73. Annweiler G, Corvaisier M, Gautier J, et al. Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. *Nutrients.* 2020;12(3377):1-11.
74. Cereda E, Bogliolo L, Lobascio F, et al. Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy, Italy. *Nutrition.* 2021/02/01/ 2021;82-journal preproof(111055):1-11.
75. Cangiano B, Fatti LM, Danesi L, et al. Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests. *Aging.* 2020;12(24):24522-24534.
76. Ma H, Zhou T, Heianza Y, Qi L. Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. *The American Journal of Clinical Nutrition.* 2021;113(5):1275-1281.
77. Oristrell J, Oliva JC, Subirana I, et al. Association of Calcitriol Supplementation with Reduced COVID-19 Mortality in Patients with Chronic Kidney Disease: A Population-Based Study. *Biomedicines.* 2021;9(509):1-15.
78. Levitus C, Chekuri S, Assa A, et al. The Effect of Vitamin D Supplementation on Severe COVID-19 Outcomes in Patients With Vitamin D Insufficiency. *Journal of the Endocrine Society.* 2021;5(Supplement_1):Abstract A279.
79. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson's Disease Patients Living in Lombardy, Italy. *Movement Disorders.* 2020/07/01 2020;35(7):1089-1093.
80. Oristrell J, Oliva JC, Casado E, et al. Vitamin D supplementation and COVID-19 risk: a population-based, cohort study. *Journal of Endocrinological Investigation.* 2021/07/17 2021;[epub]:1-13.
81. Israel A, Schäffer AA, Cicurel A, et al. Identification of drugs associated with reduced severity of COVID-19 – a case-control study in a large population. *eLife.* 2021/07/27 2021;10:e68165.
82. Pecina JL, Merry SP, Park JG, Thacher TD. Vitamin D Status and Severe COVID-19 Disease Outcomes in Hospitalized Patients. *Journal of Primary Care & Community Health.* 2021;12:1-7.
83. Hamidi-Alamdari D, Hafizi-Lotfabadi S, Bagheri-Moghaddam A, et al. METHYLENE BLUE FOR TREATMENT OF HOSPITALIZED COVID-19 PATIENTS: A RANDOMIZED, CONTROLLED, OPEN-LABEL CLINICAL TRIAL, PHASE 2. *Rev Invest Clin.* 2021;73(3):190-198.
84. Sabico S, Enani MA, Sheshah E, et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. *Nutrients.* 2021;13(2170):1-14.
85. AlSafar H, Grant WB, Hijazi R, et al. COVID-19 Disease Severity and Death in Relation to Vitamin D Status among SARS-CoV-2-Positive UAE Residents. *Nutrients.* 2021;13(1714):1-14.
86. Vasheghani M, Jannati N, Baghaei P, Rezaei M, Aliyari R, Marjani M. The relationship between serum 25-hydroxyvitamin D levels and the severity of COVID-19 disease and its mortality. *Scientific Reports.* 2021;11(17594):1-11.
87. Sulli A, Gotelli E, Casabella A, et al. Vitamin D and Lung Outcomes in Elderly COVID-19 Patients. *Nutrients.* 2021;13(1717):1-13.
88. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora VM, Solway J. Association of Vitamin D Levels, Race/Ethnicity, and Clinical Characteristics With COVID-19 Test Results. *JAMA Network Open.* 2021;4(3):e214117.

89. Ünsal YA, Gül ÖÖ, Cander S, et al. Retrospective analysis of vitamin D status on ınflammatory markers and course of the disease in patients with COVID-19 infection. *Journal of Endocrinological Investigation.* 2021/04/05 2021;[epub]:1-7.
90. te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* 2010;6(11):e1001176.
91. Feldmann HR, Williams DR, Champagne JD, Lehenbauer TW, Aly SS. Effectiveness of zinc supplementation on diarrhea and average daily gain in pre-weaned dairy calves: A double-blind, block-randomized, placebo-controlled clinical trial. *PLoS One.* 2019;14(7):e0219321.
92. Arentz S, Yang G, Goldenberg J, et al. Clinical significance summary: Preliminary results of a rapid review of zinc for the prevention and treatment of SARS-CoV-2 and other acute viral respiratory infections. *Adv Integr Med.* 2020;[epub](AIMED 257):1-9.
93. Hunter J, Arentz S, Goldenberg J, et al. Rapid review protocol: Zinc for the prevention or treatment of COVID-19 and other coronavirus-related respiratory tract infections. *Integrative Medicine Research.* 2020;9(100457):1-8.
94. Jothimani D, Kailasam E, Danielraj S, et al. COVID-19: Poor outcomes in patients with zinc deficiency. *Int J Inf Dis.* 2020;100:343-349.
95. Thomas S, Patel D, Bittel B, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Network Open.* 2021;4(2):1-10.
96. Elalfy H, Besheer T, El-Mesery A, et al. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. *Journal of Medical Virology.* 2021;93(5):3176-3183.
97. Derwand R, Scholz M, Zelenko V. COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study. *International Journal of Antimicrobial Agents.* 2020/12/01/ 2020;56(106214):1-10.
98. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *Journal of Medical Microbiology.* 2020;69(10):1228-1234.
99. Yao JS, Paguio JA, Dee EC, et al. The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. *CHEST.* 2021;159(1):108-111.
100. Frontera JA, Joseph OR, Shadi Y, et al. Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. *BMC Infect Dis.* 2021/09/30 2021;[not peer reviewed]:1-10.
101. Abd-Elsalam S, Soliman S, Esmail ES, et al. Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial. *Biological Trace Element Research.* 2021/10/01 2021;199(10):3642-3646.
102. Mulhem E, Oleszkowicz A, Lick D. 3219 hospitalised patients with COVID-19 in Southeast Michigan: a retrospective case cohort study. *BMJ open.* 2021;11(4):e042042-e042042.
103. Gadhiya KP, Hansrivijit P, Gangireddy M, Goldman JD. Clinical characteristics of hospitalised patients with COVID-19 and the impact on mortality: a single-network, retrospective cohort study from Pennsylvania state. *BMJ Open.* 2021;11(4):e042549.
104. Al Sulaiman K, Ohoud Al J, Abdulrahman IAS, et al. Evaluation of Zinc Sulfate as an Adjunctive Therapy in COVID-19 Critically Ill Patients: a Two CenterPropensity-score Matched Study. *Critical Care.* 2021/09/30 2021;[not peer reviewed]:1-14.
105. Elavarasi A, Raju Sagiraju HK, Garg RK, et al. Clinical features, demography and predictors of outcomes of SARS-CoV-2 infection in a tertiary care hospital in India-A cohort study. *medRxiv.* 2021;[not peer reviewed]:1-23.
106. Seet RCS, Quek AML, Ooi DSQ, et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial. *International Journal of Infectious Diseases.* 2021;106(2021):314-322.
107. Patel O, Chinni V, El-Khoury J, et al. A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients. *Journal of medical virology.* 2021;93(5):3261-3267.

108. Yasui Y, Yasui H, Suzuki K, et al. Analysis of the predictive factors for a critical illness of COVID-19 during treatment & relationship between serum zinc level and critical illness of COVID-19. *International Journal of Infectious Diseases.* 2020;100:230-236.
109. Vogel-González M, Talló-Parra M, Herrera-Fernández V, et al. Low Zinc Levels at Admission Associates with Poor Clinical Outcomes in SARS-CoV-2 Infection. *Nutrients.* 2021;13(562):1-13.
110. Gonçalves TJM, Gonçalves SEAB, Guarnieri A, et al. Association Between Low Zinc Levels and Severity of Acute Respiratory Distress Syndrome by New Coronavirus SARS-CoV-2. *Nutrition in Clinical Practice.* 2021/02/01 2021;36(1):186-191.
111. Fromonot J, Gette M, Ben Lassoued A, Guéant J-L, Guéant-Rodriguez R-M, Guieu R. Hypozincemia in the early stage of COVID-19 is associated with an increased risk of severe COVID-19. *Clinical Nutrition.* 2021;[in press]:1-5.
112. Du Laing G, Petrovic M, Lachat C, et al. Course and Survival of COVID-19 Patients with Comorbidities in Relation to the Trace Element Status at Hospital Admission. *Nutrients.* 2021;13(3304):1-16.
113. Riordan. The Riordan IVC Protocol for Adjunctive Cancer Care: Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent. 2013; https://riordanclinic.org/research-study/vitamin-c-research-ivc-protocol/. Accessed 10/3/21, pub'd Feb 2013.
114. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). *Frontiers in Immunology.* 2020;11(1451):1-11.
115. Hemilä H. Vitamin C and SARS coronavirus. *Journal of Antimicrobial Chemotherapy.* 2003;52(6):1049-1050.
116. Marik PE, Payen D. CITRIS-ALI: How statistics were used to obfuscate the true findings. *Anaesthesia Critical Care & Pain Medicine.* 2019;38(6):575-577.
117. Erol A. High-dose intravenous vitamin C treatment for COVID-19 (a mechanistic approach). ResearchGate, https://www.researchgate.net/publication/339511104: Erol Project Development House for the disorders of energy metabolism, Silivri-Istanbul, Turkey; 2020:8.
118. Sindel A, Taylor T, Chesney A, Clark W, Fowler Iii AA, Toor AA. Hematopoietic stem cell mobilization following PD-1 blockade: Cytokine release syndrome after transplantation managed with ascorbic acid. *European Journal of Haematology.* 2019;103(2):134-136.
119. de Melo AF, Homem-de-Mello M. High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection. *Crit Care.* 2020;24(500):1-2.
120. Reynolds PS, Fisher BJ, McCarter J, et al. Interventional vitamin C: A strategy for attenuation of coagulopathy and inflammation in a swine multiple injuries model. *Journal of Trauma and Acute Care Surgery.* 2018;85(1S):1-43.
121. Fujii T, Luethi N, Young PJ, et al. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA.* 2020;323(5):423-431.
122. Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care.* 2020;24(522):1-3.
123. Carr AC, Rowe S. The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19. *Nutrients.* 2020;12(3286):1-8.
124. Waqas Khan HM, Parikh N, Megala SM, Predeteanu GS. Unusual Early Recovery of a Critical COVID-19 Patient After Administration of Intravenous Vitamin C. *Am J Case Rep.* 2020;21(e925521):1-6.
125. Xu F, Wen Y, Hu X, Wang T, Chen G. The Potential Use of Vitamin C to Prevent Kidney Injury in Patients with COVID-19. *Diseases.* 2021;9(3).
126. Hoang BX, Shaw G, Fang W, Han B. Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection. *J Glob Antimicrob Resist.* 2020;23:256-262.
127. Ivanov V, Goc A, Ivanova S, Niedzwiecki A, Rath M. Inhibition of ACE2 Expression by Ascorbic Acid Alone and its Combinations with Other Natural Compounds. *Infect Dis (Auckl).* 2021;14(1178633721994605):1-7.
128. Malla TN, Pandey S, Poudyal I, et al. Vitamin C inhibits SARS coronavirus-2 main protease essential for viral replication. *bioRxiv.* 2021;[preprint not peer reviewed]:1-16.
129. Holford P, Carr AC, Jovic TH, et al. Vitamin C—An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19. *Nutrients.* 2020;12(3760):1-17.

130. Arvinte C, Singh M, Marik PE. Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically Ill COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study. *Med Drug Discov.* 2020;8(100064):1-5.
131. Sevransky JE, Rothman RE, Hager DN, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial. *JAMA.* 2021;325(8):742-750.
132. Feyaerts AF, Luyten W. Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? *Nutrition.* 2020/11/01/ 2020;79-80(110948):1-4.
133. May CN, Bellomo R, Lankadeva YR. Therapeutic potential of megadose vitamin C to reverse organ dysfunction in sepsis and COVID-19. *British Journal of Pharmacology.* 2021/10/01 2021;178(19):3864-3868.
134. Lankadeva YR, Peiris RM, Okazaki N, et al. Reversal of the Pathophysiological Responses to Gram-Negative Sepsis by Megadose Vitamin C. *Critical Care Medicine.* 2021;49(2):e179-e190.
135. Zhang J, Rao X, Li Y, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Annals of Intensive Care.* 2021/01/09 2021;11(5):1-12.
136. Kumari P, Dembra S, Dembra P, et al. The Role of Vitamin C as Adjuvant Therapy in COVID-19. *Cureus.* 2020;12(11):e11779. Accessed 2020/11//.
137. Gao D, Xu M, Wang G, et al. The efficiency and safety of high-dose vitamin C in patients with COVID-19: a retrospective cohort study. *Aging.* 2021;13(5):7020-7034.
138. Hiedra R, Lo KB, Elbashabsheh M, et al. The use of IV vitamin C for patients with COVID-19: a case series. *Expert Rev Anti Infect Ther.* 2020/12/01 2020;18(12):1259-1261.
139. BAKYARAJ S, MURUGANANDUM VU, RAVIKUMAR T, RAVEENDRAN M. ROLE OF VITAMIN C IN REDUCING MORBIDITY IN PATIENTS WITH COVID-19 *Indian Journal of Basic and Applied Medical Research.* 2021;10(3):105-112.
140. VISHNURAM P, KARTHIKEYAN N, AKILA A, RAVIKUMAR T, RAVEENDRAN M. ROLE OF HIGH DOSE ORAL LIPOSOMAL VITAMIN -C IN REDUCING MORTALITY IN PATIENTS WITH COVID-19. *Indian Journal of Basic and Applied Medical Research.* 2021;10(3):96-104.
141. Suna K, Melahat UŞ, Murat Y, Figen ÖE, Ayperi Ö. Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia. *Med Clin (Barc).* 2021;[in press]:1-6.
142. Xia G, Qin B, Ma C, Zhu Y, Zheng Q. High-dose vitamin C ameliorates cardiac injury in COVID-19 pandemic: a retrospective cohort study. *Aging.* 2021;13(17):20906-20914.
143. Patel M, Hong G, Schmidt B, et al. THE SIGNIFICANCE OF ORAL ASCORBIC ACID IN PATIENTS WITH COVID-19. *CHEST.* 2020;158(4):A325.
144. Zhao B, Liu M, Liu P, et al. High Dose Intravenous Vitamin C for Preventing The Disease Aggravation of Moderate COVID-19 Pneumonia. A Retrospective Propensity Matched Before-After Study. *Front Pharmacol.* 2021;12(638556):1-9.
145. Zhao B, Ling Y, Li J, et al. Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study. *Annals of Palliative Medicine.* 2020;10(2):1599-1609.
146. Saeidreza J, Besharat Z, Sogol K, et al. Safety and Effectiveness of High-Dose Vitamin C in Patients with COVID-19; A Randomized Controlled open-label Clinical Trial. *European Journal of Medical Research.* 2021/09/22 2021;26(20):1-9.
147. Khalid Al S, Ohoud Al J, Khalid Bin S, et al. Ascorbic Acid as an Adjunctive Therapy in Critically Ill Patients with COVID-19: A Multicenter Propensity Score Matched Study. *Scientific Reports.* 2021/09/22 2021;[open commons]:1-17.
148. Xing Y, Zhao B, Yin L, et al. Vitamin C supplementation is necessary for patients with coronavirus disease: An ultra-high-performance liquid chromatography-tandem mass spectrometry finding. *Journal of Pharmaceutical and Biomedical Analysis.* 2021/03/20/ 2021;196(113927):1-7.
149. Krishnan S, Patel K, Desai R, et al. Clinical comorbidities, characteristics, and outcomes of mechanically ventilated patients in the State of Michigan with SARS-CoV-2 pneumonia. *J Clin Anesth.* 2020;67(110005):1-4.
150. Li M, Ching TH, Hipple C, Lopez R, Sahibzada A, Rahman H. Use of Intravenous Vitamin C in Critically Ill Patients With COVID-19 Infection. *Journal of Pharmacy Practice.* 2021:1-7.

151. Ozgunay S, Ceylan İ, Okmen K, et al. The use of vitamin C in the intensive care unit during the COVID-19 pandemic. *The European Research Journal.* 07/04 2021;7:425-431.
152. Sarohan AR. Systemic Organ Involvement and Retinoid Signaling Disorder in COVID-19. *Immunogenetics: Open Access.* 2021;6(3):1-6.
153. Midha IK, Kumar N, Kumar A, Madan T. Mega doses of retinol: A possible immunomodulation in Covid-19 illness in resource-limited settings. *Rev Med Virol.* 2021;31(5):1-14.
154. Al-Sumiadai M, Ghazzay H, Al-Ani R. THERAPEUTIC EFFECT OF VITAMIN A ON COVID-19 PATIENTS AND ITS PROPHYLACTIC EFFECT ON CONTACTS. *Systematic Reviews in Pharmacy.* 01/01 2021;12(1):207-210.
155. Sarohan AR, Akelma H, Araç E, Aslan Ö. Retinol Depletion in Severe COVID-19. *medRxiv.* 2021;[not peer reviewed]:1-21.
156. Tepasse P-R, Vollenberg R, Fobker M, et al. Vitamin A Plasma Levels in COVID-19 Patients: A Prospective Multicenter Study and Hypothesis. *Nutrients.* 2021;13(2173):1-11.
157. Kifle ZD, Ayele AG, Enyew EF. Drug Repurposing Approach, Potential Drugs, and Novel Drug Targets for COVID-19 Treatment. *J Environ Public Health.* 2021;2021(6631721):1-11.
158. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. *European Respiratory Journal.* 1997;10(7):1535-1541.
159. Marshall J. Possible Developments in the Treatment of Critical COVID-19 #2 (TPM). 2020; https://talkingpointsmemo.com/edblog/possible-developments-in-the-treatment-of-critical-covid-19-2. Accessed April 9, 2020.
160. Wang L, Zhou J, Hou Y, et al. N-Acetylcysteine supplementation alleviates intestinal injury in piglets infected by porcine epidemic diarrhea virus. *Amino Acids.* 2017;49(12):1931-1943.
161. Sumneang N, Kumfu S, Khamseekaew J, et al. Combined iron chelator with N-acetylcysteine exerts the greatest effect on improving cardiac calcium homeostasis in iron-overloaded thalassemic mice. *Toxicology.* 2019;427(152289):1-8.
162. Ozdemir ZC, Koc A, Aycicek A, Kocyigit A. N-Acetylcysteine Supplementation Reduces Oxidative Stress and DNA Damage in Children with β-Thalassemia. *Hemoglobin.* 2014;38(5):359-364.
163. Horowitz RI, Freeman PR, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. *Respiratory Medicine Case Reports.* 2020;30(101063):1-7.
164. Niemi TT, Munsterhjelm E, Pöyhiä R, Hynninen MS, Salmenperä MT. The effect of N-acetylcysteine on blood coagulation and platelet function in patients undergoing open repair of abdominal aortic aneurysm. *Blood Coagulation & Fibrinolysis.* 2006;17(1):29-34.
165. Carothers C, Birrer K, Vo M. Acetylcysteine for the Treatment of Suspected Remdesivir-Associated Acute Liver Failure in COVID-19: A Case Series. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy.* 2020;n/a:1-.
166. Poe FL, Corn J. N-Acetylcysteine: A potential therapeutic agent for SARS-CoV-2. *Medical Hypotheses.* 2020;143(109862):1-4.
167. Shi Z, Puyo CA. N-Acetylcysteine to Combat COVID-19: An Evidence Review. *Ther Clin Risk Manag.* 2020;16:1047-1055.
168. Liu Y, Wang M, Luo G, et al. Experience of N-acetylcysteine airway management in the successful treatment of one case of critical condition with COVID-19: A case report. *Medicine (Baltimore).* 2020;99(42):e22577.
169. Andreou A, Trantza S, Filippou D, Sipsas N, Tsiodras S. COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2. *In Vivo.* 2020;34(3 suppl):1567-1588.
170. Dominari A, Hathaway Iii D, Kapasi A, et al. Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19. *World J Virol.* 2021;10(2):34-52.
171. Frank M. Revive Therapeutics Announces U.S. FDA Approval of Confirmatory Phase 3 Clinical Trial for Bucillamine in COVID-19. https://www.globenewswire.com/news-release/2020/07/31/2071110/0/en/Revive-Therapeutics-Announces-U-S-FDA-Approval-of-Confirmatory-Phase-3-Clinical-Trial-for-Bucillamine-in-COVID-19.html: Revive Therapeutics; 2020.
172. Sharma A, Liaw K, Sharma R, Zhang Z, Kannan S, Kannan RM. Targeting Mitochondrial Dysfunction and Oxidative Stress in Activated Microglia using Dendrimer-Based Therapeutics. *Theranostics.* 2018;8(20):5529-5547.

173. Zhong M, Sun A, Xiao T, et al. A Randomized, Single-blind, Group sequential, Active-controlled Study to evaluate the clinical efficacy and safety of α-Lipoic acid for critically ill patients with coronavirus disease 2019（COVID-19）. *medRxiv.* 2020;[pre-print 4/20, not peer-reviewed by 9/21](2020.04.15.20066266):1-12.
174. de Alencar JCG, Moreira CdL, Müller AD, et al. Double-blind, Randomized, Placebo-controlled Trial With N-acetylcysteine for Treatment of Severe Acute Respiratory Syndrome Caused by Coronavirus Disease 2019 (COVID-19). *Clinical Infectious Diseases.* 2021;72(11):e736-e741.
175. Ibrahim H, Perl A, Smith D, et al. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. *Clin Immunol.* 2020;219(108544):1-6.
176. Alamdari DH, Moghaddam AB, Amini S, et al. Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. *Eur J Pharmacol.* 2020;885(173494):1-7.
177. Mlcek J, Jurikova T, Skrovankova S, Sochor J. Quercetin and Its Anti-Allergic Immune Response. *Molecules (Basel, Switzerland).* 2016;21(623):1-15.
178. Saeedi-Boroujeni A, Mahmoudian-Sani M-R. Anti-inflammatory potential of Quercetin in COVID-19 treatment. *Journal of Inflammation.* 2021/01/28 2021;18(3):1-9.
179. Vermes J. As coronavirus spread speeds up, Montreal researchers will trial an anti-viral treatment for COVID-19 in China. 2020; https://www.cbc.ca/radio/thecurrent/the-current-for-feb-28-2020-1.5479561/as-coronavirus-spread-speeds-up-montreal-researchers-will-trial-an-anti-viral-treatment-for-covid-19-in-china-1.5480134. Accessed March 28, 2020.
180. Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J Virol.* 2004;78(20):11334-11339.
181. Jo S, Kim H, Kim S, Shin DH, Kim M-S. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. *Chemical Biology & Drug Design.* 2019;94(6):2023-2030.
182. Chiow KH, Phoon MC, Putti T, Tan BKH, Chow VT. Evaluation of antiviral activities of Houttuynia cordata Thunb. extract, quercetin, quercetrin and cinanserin on murine coronavirus and dengue virus infection. *Asian Pacific Journal of Tropical Medicine.* 2016;9(1):1-7.
183. Chen L, Li J, Luo C, et al. Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CLpro: Structure–activity relationship studies reveal salient pharmacophore features. *Bioorganic & Medicinal Chemistry.* 2006;14(24):8295-8306.
184. Wu W, Li R, Li X, et al. Quercetin as an Antiviral Agent Inhibits Influenza A Virus (IAV) Entry. *Viruses.* 2015;8(6):1-18.
185. Onal H, Arslan B, Ergun N, et al. Treatment of COVID-19 Patients with Quercetin: A Prospective, Single - Centre, Randomized, Controlled Trial. *Turkish Journal of Biology.* 2021;45:518-529.
186. Di Pierro F, Iqtadar S, Khan A, et al. Potential Clinical Benefits of Quercetin in the Early Stage of COVID-19: Results of a Second, Pilot, Randomized, Controlled and Open-Label Clinical Trial. *Int J Gen Med.* 2021;14:2807-2816.
187. Di Pierro F, Derosa G, Maffioli P, et al. Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study. *Int J Gen Med.* 2021;14:2359-2366.
188. Arslan B, Ergun NU, Topuz S, et al. Synergistic Effect of Quercetin and Vitamin C Against COVID-19: Is a Possible Guard for Front Liners. *SSRN.* 2020;[not peer reviewed]:1-19.
189. Aguilar JFI, Báez GAS, Galeano F. Oral Quercetin in Adult Patients as a Potential Nutraceutical against Coronavirus Disease 2019 (COVID-19). *Journal of Advances in Medical and Pharmaceutical Sciences.* 2021;23(3):1-7.
190. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews.* 2015(2).
191. Carter GM, Esmaeili A, Shah H, et al. Probiotics in Human Immunodeficiency Virus Infection: A Systematic Review and Evidence Synthesis of Benefits and Risks. *Open Forum Infectious Diseases.* 2016;3(4):1-13.
192. Bousquet J, Anto JM, Iaccarino G, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clinical and Translational Allergy.* 2020;10(16):1-7.
193. Din AU, Mazhar M, Waseem M, et al. SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotics role. *Biomed Pharmacother.* 2020;133(110947):1-11.

194. Yeoh YK, Zuo T, Lui GC-Y, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut.* 2021;0(gutjnl-2020-323020):1-9.
195. Daoust L, Pilon G, Marette A. Perspective: Nutritional Strategies Targeting the Gut Microbiome to Mitigate COVID-19 Outcomes. *Adv Nutr.* 2021;12(4):1074-1086.
196. Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. *Int J Mol Sci.* 2021;22(6):3134.
197. Gutiérrez-Castrellón P, Gandara-Martí T, Abreu AT, et al. Efficacy and safety of novel probiotic formulation in adult Covid19 outpatients: a randomized, placebo-controlled clinical trial. *medRxiv.* 2021;[not peer reviewed]:1-24.
198. Veterini AS, Kurniawati EM, Hamzah, Soedarmo SM, Prakoeswa CRS, Tinduh D. Probiotics intake as adjunct therapy for infected health-care with SARS COV-2. *Indian Journal of Forensic Medicine and Toxicology.* 2021;15(2):4021-4025.
199. d'Ettorre G, Ceccarelli G, Marazzato M, et al. Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic Strategy to Avoid the Progression of COVID-19. *Frontiers in Medicine.* 2020;7(389):1-7.
200. Ceccarelli G, Borrazzo C, Pinacchio C, et al. Oral Bacteriotherapy in Patients With COVID-19: A Retrospective Cohort Study. *Front Nutr.* 2021;7:341.
201. Li Q, Cheng F, Xu Q, et al. The role of probiotics in coronavirus disease-19 infection in Wuhan: A retrospective study of 311 severe patients. *Int Immunopharmacol.* 2021;95(107531):1-8.
202. Zhang L, Han H, Li X, et al. Probiotics use is associated with improved clinical outcomes among hospitalized patients with COVID-19. *Therapeutic Advances in Gastroenterology.* 2021/01/01 2021;14:1-9.
203. Ahanchian H, Ranjbar A, Reihani H, et al. Synbiotic for Prevention of SARS-Cov2 Infection in High Risk Hospital Staffs: A Randomized Controlled Trial. *Open Journal of Nursing.* 2021;11:281-290.
204. Meskina ER, Tselipanova EE, Khadisova MK, Galkina LA, Stashko TV. Efficiency of application of sorbed probiotics in complex therapy of pneumonia caused by SARS-CoV-2. Part 1. Heating clinical displays period. *Terapevticheskii arkhiv (in Russian).* 2021;93(4):456-464.
205. Zhang R, Wang X, Ni L, et al. COVID-19: Melatonin as a potential adjuvant treatment. *Life Sci.* 2020;250(117583):1-7.
206. Niu Z, Li R. Clinical study of novel coronavirus pneumonia prevention by melatonin. *Reproductive BioMedicine Online.* 2020;00:1.
207. Goldbaum E. Trial aims to determine if melatonin can treat COVID-19. http://www.buffalo.edu/ubnow/stories/2020/09/dubocovich-melatonin-covid.html: UBNow; 2020.
208. Feitosa EL, Júnior FTDSS, Nery Neto JADO, et al. COVID-19: Rational discovery of the therapeutic potential of Melatonin as a SARS-CoV-2 main Protease Inhibitor. *Int J Med Sci.* 2020;17(14):2133-2146.
209. Peiró C, Moncada S. Substituting Angiotensin-(1-7) to Prevent Lung Damage in SARS-CoV-2 Infection? *Circulation.* 2020;141(21):1665-1666.
210. Mousavi SA, Heydari K, Mehravaran H, et al. Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial. *Journal of Medical Virology.* 2021/08/30 2021;[epub]:1-9.
211. Sánchez-González MÁ, Mahíllo-Fernández I, Villar-álvarez F, Llanos L. What if melatonin could help COVID-19 severe patients? *Journal of Clinical Sleep Medicine.* 2021;[accepted paper](jcsm.9554):1-5.
212. Davoodian N, Sharifimood F, Salarbashi D, Elyasi S, Baniasad A, Bejestani FS. The Effect of Melatonin as an Adjuvant Therapy on COVID-19: A Randomized Clinical Trial. *SSRN.* 2021;[preprint: not peer reviewed]:1-17.
213. Farnoosh G, Akbariqomi M, Badri T, et al. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. *Archives of Medical Research.* 2021/06/23/ 2021;[epub]:1-7.
214. Zahra A, Nastaran K, Sara G, Simin D-K, Raheleh Shokouhi S, Zahra P. A Pilot Study on Controlling Coronavirus Disease 2019 (COVID-19) Inflammation Using Melatonin Supplement. *Iranian Journal of Allergy, Asthma and Immunology.* 08/07 2021;20(4):494-499.
215. Hosseini A, Esmaeili Gouvarchin Ghaleh H, Aghamollaei H, et al. Evaluation of Th1 and Th2 mediated cellular and humoral immunity in patients with COVID-19 following the use of melatonin as an adjunctive treatment. *Eur J Pharmacol.* 2021/08/05/ 2021;904(174193):1-5.

216. Ramlall V, Zucker J, Tatonetti N. Melatonin is significantly associated with survival of intubated COVID-19 patients. *medRxiv.* 2020;[not peer reviewed]:1-37.
217. Castillo RR, Quizon GRA, Juco MJM, et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Research.* 2020;3(3):297-310.
218. Jehi L, Ji X, Milinovich A, et al. Individualizing Risk Prediction for Positive Coronavirus Disease 2019 Testing: Results From 11,672 Patients. *Chest.* 2020;158(4):1364-1375.
219. Zhou Y, Hou Y, Shen J, et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. *PLOS Biology.* 2020;18(11):e3000970.
220. Shakoor H, Feehan J, Mikkelsen K, et al. Be well: A potential role for vitamin B in COVID-19. *Maturitas.* 2021;144:108-111.
221. Mehmel M, Jovanović N, Spitz U. Nicotinamide Riboside-The Current State of Research and Therapeutic Uses. *Nutrients.* 2020;12(16):1-22.
222. Wee AKH. COVID-19's toll on the elderly and those with diabetes mellitus - Is vitamin B12 deficiency an accomplice? *Medical Hypotheses.* 2021;146(110374):1-9.
223. Pacl HT, Tipper JL, Sevalkar RR, et al. Water-soluble tocopherol derivatives inhibit SARS-CoV-2 RNA-dependent RNA polymerase. *bioRxiv : the preprint server for biology.* 2021(2021.07.13.449251):1-42.
224. Dofferhoff AS, Piscaer I, Schurgers LJ, et al. Reduced Vitamin K Status as A Potentially Modifiable Prognostic Risk Factor in COVID-19. *Preprints 2020.* 2020;[Preprint]:1-25.
225. Speed V, Patel RK, Byrne R, Roberts LN, Arya R. A perfect storm: Root cause analysis of supra-therapeutic anticoagulation with vitamin K antagonists during the COVID-19 pandemic. *Thromb Res.* 2020;192:73-74.
226. Guenezan J, Garcia M, Strasters D, et al. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19: A Randomized Clinical Trial. *JAMA Otolaryngology–Head & Neck Surgery.* 2021;[Letter/published online]:E1-E2.
227. Choudhury MIM, Shabnam N, Ahsan T, kabir MS, Khan RM, Ahsan SMA. Effect of 1% Povidone Iodine Mouthwash/Gargle, Nasal and Eye Drop in COVID-19 patient. *Bioresearch Communications-(BRC).* 2021;7(1):919-923.
228. Ashraf S, Ashraf S, Ashraf M, et al. A quadruple blinded placebo controlled randomised trial to evaluate the effectiveness of an Iodine complex for patients with mild to moderate COVID-19 in Pakistan (I-COVID-PK): A structured summary of a study protocol for a randomised controlled trial. *Trials.* 2021;22(1):127.
229. Castro-Ruiz C, Vergara-Buenaventura A. Povidone-Iodine Solution: A Potential Antiseptic to Minimize the Risk of COVID-19? A Narrative Review. *J Int Soc Prev Community Dent.* 2020;10(6):681-685.
230. Burton MJ, Clarkson JE, Goulao B, et al. Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them. *Cochrane Database Syst Rev.* 2020;9(9):CD013627.
231. Chen d, Li X, Song q, Hu C, Su F, Dai J. Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19). *medRxiv.* 2020;[epub ahead of print](2020.02.27.20028530):1-22.
232. Cooper ID, Crofts CAP, DiNicolantonio JJ, et al. Relationships between hyperinsulinaemia, magnesium, vitamin D, thrombosis and COVID-19: rationale for clinical management. *Open Heart.* 2020;7(2):e001356.
233. Nedjimi B. Can trace element supplementations (Cu, Se, and Zn) enhance human immunity against COVID-19 and its new variants? *Beni Suef Univ J Basic Appl Sci.* 2021;10(33):1-5.
234. Wang Y, Wang P, Wang H, et al. Lactoferrin for the treatment of COVID-19 (Review). *Exp Ther Med.* 2020;20(272):1-7.
235. Hathaway D, Pandav K, Patel M, et al. Omega 3 Fatty Acids and COVID-19: A Comprehensive Review. *Infect Chemother.* 12/ 2020;52(4):478-495.
236. Talasaz AH, Sadeghipour P, Aghakouchakzadeh M, et al. Lipid-Modulating Agents for Prevention or Treatment of COVID-19 in Randomized Trials. *medRxiv.* 2021;[not peer reviewed]:1-50.
237. Goc A, Niedzwiecki A, Rath M. Polyunsaturated ω-3 fatty acids inhibit ACE2-controlled SARS-CoV-2 binding and cellular entry. *Scientific Reports.* 2021;11(5207):1-12.
238. Rogero MM, Leão MdC, Santana TM, et al. Potential benefits and risks of omega-3 fatty acids supplementation to patients with COVID-19. *Free Radic Biol Med.* 2020;156:190-199.

239. Sedighiyan M, Abdollahi H, Karimi E, et al. Omega-3 polyunsaturated fatty acids supplementation improve clinical symptoms in patients with Covid-19: A randomised clinical trial. *International Journal of Clinical Practice.* 2021/09/13 2021;n/a(n/a):e14854.
240. Asher A, Tintle NL, Myers M, Lockshon L, Bacareza H, Harris WS. Blood omega-3 fatty acids and death from COVID-19: A pilot study. *Prostaglandins Leukot Essent Fatty Acids.* 2021;166(102250):1-6.
241. Doaei S, Gholami S, Rastgoo S, et al. The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial. *J Transl Med.* 2021;19(128):1-9.
242. Nakata T, Ariie T, Taito S. Regarding: "The effect of omega-3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID-19: a randomized clinical trial". *J Transl Med.* 2021;19(282):1-2.
243. Marinella MA. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. *International journal of clinical practice.* 2020;74(9):e13535.
244. Lin S-C, Ho C-T, Chuo W-H, Li S, Wang TT, Lin C-C. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis.* 2017;17(144):1-10.
245. Ter Ellen BM, Dinesh Kumar N, Bouma EM, et al. Resveratrol and Pterostilbene Inhibit SARS-CoV-2 Replication in Air-Liquid Interface Cultured Human Primary Bronchial Epithelial Cells. *Viruses.* 2021;13(1335):1-17.
246. Smigelski C. Coronavirus Covid-19 Nutrition. 2020; https://covid19nutrition.org/. Accessed March 29, 2020.
247. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients.* 2020;12(236):1-41.
248. Caccialanza R, Laviano A, Lobascio F, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition.* 2020(110835):1-5.
249. Jovic TH, Ali SR, Ibrahim N, et al. Could Vitamins Help in the Fight Against COVID-19? *Nutrients.* 2020;12(2550):1-30.
250. Louca P, Murray B, Klaser K, et al. Modest effects of dietary supplements during the COVID-19 pandemic: insights from 445 850 users of the COVID-19 Symptom Study app. *BMJ Nutrition, Prevention & Health.* 2021;[epub ahead of print](bmjnph-2021-000250):1-21.
251. Margolin L, Luchins J, Margolin D, Margolin M, Lefkowitz S. 20-Week Study of Clinical Outcomes of Over-the-Counter COVID-19 Prophylaxis and Treatment. *J Evid Based Integr Med.* 2021/01/01 2021;26:1-13.
252. Hemilä H, Carr A, Chalker E. Vitamin C May Increase the Recovery Rate of Outpatient Cases of SARS-CoV-2 Infection by 70%: Reanalysis of the COVID A to Z Randomized Clinical Trial. *Frontiers in immunology.* 2021;12(674681):1-4.
253. Asimi ZV, Hadzovic-Dzuvo A, al Tawil D. Selenium, zinc, and vitamin D supplementation affect the clinical course of COVID-19 infection in Hashimoto's thyroiditis. *European Congress of Endocrinology 2021.* Vol 73: European Society of Endocrinology 2021:PEP14.12 see https://www.researchgate.net/publication/351652823_Selenium_zinc_and_vitamin_D_supplementation_affect_the_clinical_course_of_COVID-351652819_infection_in_Hashimotos_thyroiditis/link/351652860aaa324592851ca351652829dcdda351652825ae/download.
254. Darban M, Malek F, Memarian M, et al. Efficacy of High Dose Vitamin C, Melatonin and Zinc in Iranian Patients with Acute Respiratory Syndrome due to Coronavirus Infection: A Pilot Randomized Trial. *Journal of Cellular & Molecular Anesthesia.* 12/15 2020;6(2):164-167.
255. Lissoni P, Rovelli F, Monzon A, et al. COVID-19 Disease as an Acute Angiotensin 1-7 Deficiency: A Preliminary Phase 2 Study with Angiotensin 1-7 in Association with Melatonin and Cannabidiol in Symptomatic COVID-19 - Infected Subjects. *J Infectiology.* 2020;3(2):13-16.
256. Hancock M, Ketterl P, Viñas X, Werthmann PG. Case Cluster of RT-PCR COVID-19 Positive Patients with an Unexpected Benign Clinical Course With Vitamin D, Melatonin, Vitamin C, and Viscum Album (February 4, 2021). *SSRN.* 2021;[pre-print not peer reviewed]:1-11.
257. Tan R, Xiang X, Chen W, et al. Efficacy of diammonium glycyrrhizinate combined with vitamin C for treating hospitalized COVID-19 patients: a retrospective, observational study. *Quarterly Journal of Medicine.* 2021;[submitted manuscript](hcab184):1-27.

258. Brendler T, Al-Harrasi A, Bauer R, et al. Botanical drugs and supplements affecting the immune response in the time of COVID-19: Implications for research and clinical practice. *Phytotherapy Research.* 2021/06/01 2020;35(6):3013-3031.
259. Main D. Orangutans Use Plant Extracts to Treat Pain. *Scientific American.* 2018;April 6:See https://www.scientificamerican.com/article/orangutans-use-plant-extracts-to-treat-pain1/.
260. Mokgobi MG. Understanding traditional African healing. *Afr J Phys Health Educ Recreat Dance.* 2014;20(Suppl 2):24-34.
261. Efferth T, Banerjee M, Abu-Darwish MS, et al. Biopiracy versus One-World Medicine–From colonial relicts to global collaborative concepts. *Phytomedicine.* 2019/02/01/ 2019;53:319-331.
262. Abdullahi AA. Trends and challenges of traditional medicine in Africa. *African Journal of Traditional, Complementary, and Alternative Medicines.* 2011;8(5 Suppl):115-123.
263. Kapoor C. High in the Himalayas, villagers hit by Covid are left to fend for themselves. 2021; https://www.theguardian.com/global-development/2021/jun/16/high-in-the-himalayas-villagers-hit-by-covid-are-left-to-fend-for-themselves. Accessed June 23, 2021.
264. Seifert G, Jeitler M, Stange R, et al. The Relevance of Complementary and Integrative Medicine in the COVID-19 Pandemic: A Qualitative Review of the Literature. *Frontiers in Medicine.* 2020;7(587749):1-14.
265. Abiri R, Abdul-Hamid H, Sytar O, et al. A Brief Overview of Potential Treatments for Viral Diseases Using Natural Plant Compounds: The Case of SARS-Cov. *Molecules (Basel, Switzerland).* 2021;26(3868):1-35.
266. Borse S, Joshi M, Saggam A, et al. Ayurveda botanicals in COVID-19 management: An in silico multi-target approach. *PLoS One.* 2021;16(6):e0248479.
267. Kumar Verma A, Kumar V, Singh S, et al. Repurposing potential of Ayurvedic medicinal plants derived active principles against SARS-CoV-2 associated target proteins revealed by molecular docking, molecular dynamics and MM-PBSA studies. *Biomed Pharmacother.* 2021;137(111356):1-18.
268. Amparo TR, Seibert JB, Almeida TC, et al. In silico approach of secondary metabolites from Brazilian herbal medicines to search for potential drugs against SARS-CoV-2. *Phytother Res.* 2021;35(8):4297-4308.
269. Lowe H, Steele B, Bryant J, Fouad E, Toyang N, Ngwa W. Antiviral Activity of Jamaican Medicinal Plants and Isolated Bioactive Compounds. *Molecules (Basel, Switzerland).* 2021;26(607):1-30.
270. Erukainure OL, Matsabisa MG, Muhammad A, et al. Targeting of Protein's Messenger RNA for Viral Replication, Assembly and Release in SARS-CoV-2 Using Whole Genomic Data From South Africa: Therapeutic Potentials of Cannabis Sativa L. *Front Pharmacol.* 2021;12(736511):1-11.
271. Benarba B, Pandiella A. Medicinal Plants as Sources of Active Molecules Against COVID-19. *Front Pharmacol.* 2020;11(1189):1-16.
272. Tsai K-C, Huang Y-C, Liaw C-C, et al. A traditional Chinese medicine formula NRICM101 to target COVID-19 through multiple pathways: A bedside-to-bench study. *Biomed Pharmacother.* 2021;133(111037):1-10.
273. Luo H, Tang Q-L, Shang Y-X, et al. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med.* 2020;26(4):243-250.
274. Ang L, Lee HW, Choi JY, Zhang J, Lee MS. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. *Integrative Medicine Research.* 2020;9(2):100407.
275. Runfeng L, Yunlong H, Jicheng H, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacol Res.* 2020;[Epub ahead of print](104761):1-10.
276. Zhao P, Yang HZ, Lv HY, Wei ZM. Efficacy of Lianhuaqingwen capsule compared with oseltamivir for influenza A virus infection: a meta-analysis of randomized, controlled trials. *Altern Ther Health Med.* 2014;20(2):25-30.
277. Athumani H. Uganda Approves Herbal Treatment for COVID-19. 2021; https://www.voanews.com/covid-19-pandemic/uganda-approves-herbal-treatment-covid-19. Accessed July 21, 2021.
278. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective. *International Journal of Biological Sciences.* 2020;16(10):1708-1717.
279. Chan KW, Wong VT, Tang SCW. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease. *The American Journal of Chinese Medicine.* 2020;48(03):737-762.

280. Li X, Li T, Wang H. Treatment and prognosis of COVID-19: Current scenario and prospects (Review). *Exp Ther Med.* 2021;21(3):1-10.
281. Nile SH, Kai G. Recent Clinical Trials on Natural Products and Traditional Chinese Medicine Combating the COVID-19. *Indian J Microbiol.* 2020;[epub ahead of print]:1-6.
282. Ding Y, Zeng L, Li R, et al. The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. *BMC Complementary and Alternative Medicine.* 2017;17(1):130.
283. Yu S, Wang J, Shen H. Network pharmacology-based analysis of the role of traditional Chinese herbal medicines in the treatment of COVID-19. *Annals of Palliative Medicine.* 2020;9(2):437-446.
284. Li C, Wang L, Ren L. Antiviral mechanisms of candidate chemical medicines and traditional Chinese medicines for SARS-CoV-2 infection. *Virus Res.* 2020;286(198073):1-10.
285. Guan W, Lan W, Zhang J, et al. COVID-19: Antiviral Agents, Antibody Development and Traditional Chinese Medicine. *Virologica Sinica.* 2020:1-14.
286. Chen J, Wang Y-k, Gao Y, et al. Protection against COVID-19 injury by qingfei paidu decoction via anti-viral, anti-inflammatory activity and metabolic programming. *Biomed Pharmacother.* 2020/09/01/ 2020;129(110281):1-16.
287. Wang Z, Yang L. Chinese herbal medicine: Fighting SARS-CoV-2 infection on all fronts. *J Ethnopharmacol.* 2021;270(113869):1-17.
288. Xia L, Shi Y, Su J, et al. Shufeng Jiedu, a promising herbal therapy for moderate COVID-19:Antiviral and anti-inflammatory properties, pathways of bioactive compounds, and a clinical real-world pragmatic study. *Phytomedicine.* 2021;85(153390):1-11.
289. Zhao J, Tian S, Lu D, et al. Systems pharmacological study illustrates the immune regulation, anti-infection, anti-inflammation, and multi-organ protection mechanism of Qing-Fei-Pai-Du decoction in the treatment of COVID-19. *Phytomedicine.* 2021/05/01/ 2021;85(153315):1-13.
290. He T, Qu R, Qin C, et al. Potential mechanisms of Chinese Herbal Medicine that implicated in the treatment of COVID-19 related renal injury. *Saudi Pharmaceutical Journal.* 2020/09/01/ 2020;28(9):1138-1148.
291. Kritis P, Karampela I, Kokoris S, Dalamaga M. The combination of bromelain and curcumin as an immune-boosting nutraceutical in the prevention of severe COVID-19. *Metabol Open.* 2020;Open 8(100066):1-4.
292. Duc HN, Oh H, Kim M-S. Effects of Antioxidant Vitamins, Curry Consumption, and Heavy Metal Levels on Metabolic Syndrome with Comorbidities: A Korean Community-Based Cross-Sectional Study. *Antioxidants (Basel).* 2021;10(5):808.
293. Pawar KS, Mastud RN, Pawar SK, et al. Oral Curcumin With Piperine as Adjuvant Therapy for the Treatment of COVID-19: A Randomized Clinical Trial. *Front Pharmacol.* 2021;12(669362):1-7.
294. Valizadeh H, Abdolmohammadi-Vahid S, Danshina S, et al. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *Int Immunopharmacol.* 2020;89(107088):1-13.
295. Hassaniazad M, Eftekhar E, Inchehsablagh BR, et al. A triple-blind, placebo-controlled, randomized clinical trial to evaluate the effect of curcumin-containing nanomicelles on cellular immune responses subtypes and clinical outcome in COVID-19 patients. *Phytotherapy Research.* 2021/09/19 2021;[epub]:1-11.
296. Ahmadi R, Salari S, Sharifi MD, et al. 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.* 2021/08/01 2021;9(8):4068-4075.
297. Saber-Moghaddam N, Salari S, Hejazi S, et al. Oral nano-curcumin formulation efficacy in management of mild to moderate hospitalized coronavirus disease-19 patients: An open label nonrandomized clinical trial. *Phytotherapy Research.* 2021/05/01 2021;35(5):2616-2623.
298. Dound YA, Suryavanshi S, Sehgal R, Naik A. Comparative Clinical Study to Evaluate the Activity of Curvic TM Formulation for Management of SARS-CoV-2 Infection (COVID-19). *J Clin Trials.* 2020;S3(100004):1-7.
299. Enmozhi SK, Raja K, Sebastine I, Joseph J. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an in silico approach. *Journal of Biomolecular Structure and Dynamics.* 2020:1-7.
300. Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJG, Marschall M. The Antiviral Activities of Artemisinin and Artesunate. *Clinical Infectious Diseases.* 2008;47(6):804-811.
301. Wang B, Kovalchuk A, Li D, Ilnytskyy Y, Kovalchuk I, Kovalchuk O. In Search of Preventative Strategies: Novel Anti-Inflammatory High-CBD Cannabis Sativa Extracts Modulate ACE2 Expression in COVID-19 Gateway Tissues. *Preprints 2020.* 2020;[preprint](2020040315):1-12.

302. Byrareddy SN, Mohan M. SARS-CoV2 induced respiratory distress: Can cannabinoids be added to anti-viral therapies to reduce lung inflammation? *Brain Behav Immun.* 2020;87:120-121.
303. Kovalchuk A, Wang B, Li D, et al. Fighting the storm: could novel anti-TNFalpha and anti-IL-6 C. sativa cultivars tame cytokine storm in COVID-19? *Aging.* 2021;13.
304. Crippa JAS, Pacheco JC, Zuardi AW, et al. Cannabidiol for COVID-19 Patients with Mild to Moderate Symptoms (CANDIDATE Study): A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Cannabis and Cannabinoid Research.* 2021;[epub ahead of print](X):1-12.
305. Khalsa JH, Maggirwar SB, Bunt G. Cannabis/Cannabinoids for Treating COVID-19 Associated Neuropsychiatric Complications. *Journal of Neuroimmune Pharmacology.* 2021;[epub]:1-4.
306. Aucoin M, Cooley K, Saunders PR, et al. The effect of Echinacea spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. *Adv Integr Med.* 2020;7(4):203-217.
307. Aucoin M, Cardozo V, McLaren MD, et al. A systematic review on the effects of Echinacea supplementation on cytokine levels: Is there a role in COVID-19? *Metabol Open.* 2021/09/01/ 2021;11(100115):1-32.
308. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *The Lancet.* 2003;361(9374):2045-2046.
309. Huan C-C, Wang H-X, Sheng X-X, Wang R, Wang X, Mao X. Glycyrrhizin inhibits porcine epidemic diarrhea virus infection and attenuates the proinflammatory responses by inhibition of high mobility group box-1 protein. *Arch Virol.* 2017;162(6):1467-1476.
310. Gowda P, Patrick S, Joshi SD, Kumawat RK, Sen E. Glycyrrhizin prevents SARS-CoV-2 S1 and Orf3a induced high mobility group box 1 (HMGB1) release and inhibits viral replication. *Cytokine.* 2021;142(155496):1-11.
311. Zhao Z, Xiao Y, Xu L, et al. Glycyrrhizic Acid Nanoparticles as Antiviral and Anti-inflammatory Agents for COVID-19 Treatment. *ACS Appl Mater Interfaces.* 2021;13(18):20995-21006.
312. Huang Y-X, Wang W-X, Tang Y-P, Yue S-J. Drug repurposing for COVID-19: could vitamin C combined with glycyrrhizic acid be at play by the findings of Li et al.'s database-based network pharmacology analysis? *Brief Bioinform.* 2021;22(2):1508-1510.
313. Wang Y, Yan X, Huang C, et al. Risk factors of mortality and contribution of treatment in patients infected with COVID-19: a retrospective propensity score matched study. *Curr Med Res Opin.* 2021;37(1):13-19.
314. Lin C-W, Tsai F-J, Tsai C-H, et al. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. *Antiviral Research.* 2005;68(1):36-42.
315. Dzobo K, Chiririwa H, Dandara C, Dzobo W. Coronavirus Disease-2019 Treatment Strategies Targeting Interleukin-6 Signaling and Herbal Medicine. *OMICS: A Journal of Integrative Biology.* 2020;24:1-10.
316. Slomski A. Trials Test Mushrooms and Herbs as Anti–COVID-19 Agents. *JAMA.* 2021;[epub]:e1-e3.
317. El Sayed SM, Aboonq MS, Aljehani YT, et al. TaibUVID nutritional supplements help rapid cure of COVID-19 infection and rapid reversion to negative nasopharyngeal swab PCR: for better public prophylaxis and treatment of COVID-19 pandemic. *Am J Blood Res.* 2020;10(6):397-406.
318. Al-Haidari KaA, Faiq T, Ghareeb O. Preventive Value of Black Seed in People at Risk of Infection with COVID – 19. *PJMHS.* 2021;15(1):384-387.
319. Fetian IR, Fitian ID, Villiger L, Darwish M. Response to Nigella sativa in Patients with Confirmed and Suspected COVID-19. *healthbook Times.* 2021;1:F66-75.
320. Koshak AE, Koshak EA, Mobeireek AF, et al. Nigella sativa for the treatment of COVID-19: An open-label randomized controlled clinical trial. *Complementary Therapies in Medicine.* 2021/09/01/ 2021;61(102769):1-6.
321. Ashraf S, Ashraf S, Ashraf M, et al. Honey and Nigella sativa against COVID-19 in Pakistan (HNS-COVID-PK): A multi-center placebo-controlled randomized clinical trial. *medRxiv.* 2020:2020.2010.2030.20217364.
322. Hong DS, Henary H, Falchook GS, et al. First-in-human study of pbi-05204, an oleander-derived inhibitor of akt, fgf-2, nf-κB and p70s6k, in patients with advanced solid tumors. *Investigational New Drugs.* 2014;32(6):1204-1212.
323. Kelly JR, Crockett MT, Alexander L, et al. Psychedelic Science in Post-Covid Psychiatry. *Irish Journal of Psychological Medicine.* 2020;[Epub ahead of print]:1-18.
324. Lee C. Griffithsin, a Highly Potent Broad-Spectrum Antiviral Lectin from Red Algae: From Discovery to Clinical Application. *Mar Drugs.* 2019;17(567):1-16.

325. Rohan L. Formula Developed to Combat HIV Could Work as Novel Coronavirus Preventive. 2020; https://www.pittwire.pitt.edu/news/formula-developed-combat-hiv-could-double-novel-coronavirus-preventive. Accessed July 21, 2020.
326. Yang M, Wang C-C, Wang W-l, et al. Saposhnikovia divaricata—An Ethnopharmacological, Phytochemical and Pharmacological Review. *Chin J Integr Med.* 2017;11655:1-8.
327. Chopra A, Srikanth N, Patwardhan B. Withania somnifera as a safer option to hydroxychloroquine in the chemoprophylaxis of COVID-19: Results of interim analysis. *Complementary Therapies in Medicine.* 2021/11/01/ 2021;62(102768):1-3.
328. Natarajan S, Anbarasi C, Sathiyarajeswaran P, et al. Kabasura Kudineer (KSK), a poly-herbal Siddha medicine, reduced SARS-CoV-2 viral load in asymptomatic COVID-19 individuals as compared to vitamin C and zinc supplementation: findings from a prospective, exploratory, open-labeled, comparative, randomized controlled trial, Tamil Nadu, India. *Trials.* 2021;22(623):1-11.
329. Rangnekar H, Patankar S, Suryawanshi K, Soni P. Safety and efficacy of herbal extracts to restore respiratory health and improve innate immunity in COVID-19 positive patients with mild to moderate severity: A structured summary of a study protocol for a randomised controlled trial. *Trials.* 2020;21(943):1-3.
330. Ward H, Flower B, Garcia PJ, et al. Global surveillance, research, and collaboration needed to improve understanding and management of long COVID. *The Lancet.* 2021;[epub]:1-3.
331. Schveitzer MC, Abdala CVM, Portella CFS, Ghelman R. Traditional, complementary, and integrative medicine evidence map: a methodology to an overflowing field of data and noise. *Revista Panamericana de Salud Publica.* 2021;45(e48):1-5.
332. Evans SR. Fundamentals of clinical trial design. *J Exp Stroke Transl Med.* 2010;3(1):19-27.
333. Lawless A. ARIZONA CRISIS STANDARDS OF CARE PLAN: A Comprehensive and Compassionate Response. 2020; https://www.azdhs.gov/documents/preparedness/emergency-preparedness/response-plans/azcsc-plan.pdf. Accessed August 20, 2020.
334. Thiese MS. Observational and interventional study design types; an overview. *Biochem Med (Zagreb).* 2014;24(2):199-210.
335. Gonsalves G, Morten C, Ramachandran R, Ross JS. Opinion: The FDA is in desperate need of some soul-searching. 2021; https://www.washingtonpost.com/opinions/2021/06/17/fda-aducanumab-alzheimers-drug-approval-erodes-confidence/. Accessed 9/9/21 pub'd 6/17/21.
336. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). 2021; www.training.cochrane.org/handbook. Accessed 9/28/21 pub'd Feb 2021.
337. Trotta F. Discrepancies between observational studies and randomized controlled trials. *Pharmaco-vigilance.eu.* 2012;73(11):1 (see https://www.pharmaco-vigilance.eu/content/discrepancies-between-observational-studies-and-randomized-controlled-trials).
338. Viera AJ. Odds Ratios and Risk Ratios: What's the Difference and Why Does It Matter? *Southern Medical Journal.* 2008;101(7):730-734.
339. George A, Stead TS, Ganti L. What's the Risk: Differentiating Risk Ratios, Odds Ratios, and Hazard Ratios? *Cureus.* 2020;12(8):e10047.
340. Ranganathan P, Aggarwal R, Pramesh CS. Common pitfalls in statistical analysis: Odds versus risk. *Perspect Clin Res.* Oct-Dec 2015;6(4):222-224.
341. Wikipedia. Propensity score matching. 2021; https://en.wikipedia.org/wiki/Propensity_score_matching. Accessed 9/28/21.
342. Lawrence JM, Meyerowitz-Katz G, Heathers JAJ, Brown NJL, Sheldrick KA. The lesson of ivermectin: meta-analyses based on summary data alone are inherently unreliable. *Nature Medicine.* 2021/09/22 2021;[epub]:1-2.
343. Mortola E, Okuda M, Ohno K-i, Watari T, Tsujimoto H, Hasegawa A. Inhibition of Apoptosis and Virus Replication in Feline Immunodeficiency Virus-Infected Cells by N-Acetylcysteine and Ascorbic Acid. *Journal of Veterinary Medical Science.* 1998;60(11):1187-1193.