

20-Week Study of Clinical Outcomes of Over-the-Counter COVID-19 Prophylaxis and Treatment

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Abstract

Objectives and Setting. As the lethal COVID-19 pandemic enters its second year, the need for effective modalities of alleviation remains urgent. This includes modalities that can readily be used by the public to reduce disease spread and severity. Such preventive measures and early-stage treatments may temper the immediacy of demand for advanced anti-COVID measures (drugs, antibodies, vaccines) and help relieve strain also on other health system resources. **Design and Participants.** We present results of a clinical study with a multi-component OTC “core formulation” regimen used in a multiply exposed adult population. Analysis of clinical outcome data from our sample of over 100 subjects – comprised of roughly equal sized regimen-compliant (test) and non-compliant (control) groups meeting equivalent inclusion criteria – demonstrates a strong statistical significance in favor of use of the core formulations. **Results.** While both groups were moderate in size, the difference between them in outcomes over the 20-week study period was large and stark: Just under 4% of the compliant test group presented flu-like symptoms, but none of the test group was COVID-positive; whereas 20% of the non-compliant control group presented flu-like symptoms, three-quarters of whom (15% overall of the control group) were COVID-positive. **Conclusions.** Offering a low cost, readily implemented anti-viral approach, the study regimen may serve, at the least, as a stopgap modality and, perhaps, as a useful tool in combatting the pandemic.

Keywords

COVID-19, SARS-CoV-2, prophylaxis, early-stage treatment, OTC, zinc, ionophores, immunity enhancement, regimen compliance

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Introduction

There is a pressing need for formulations and methods for COVID-19 alleviation that can be easily accessed and utilized by the public. That the alleviation should encompass prophylaxis and early-stage treatment is underscored by studies confirming spread of COVID-19 by asymptomatic/pre-symptomatic carriers^{1,2}; by widespread upsurges of new confirmed COVID-19 cases amid second-wave concerns³; and by identification of ongoing mutations of the COVID-19-causing SARS-CoV-2 coronavirus with diverse infectivity rates.⁴⁻⁶

We present a 20-week study of our clinical experience with a multi-component over-the-counter (OTC) “core formulation” regimen used in a multiply exposed, high risk population. The OTC core supplementation formulations used include zinc and zinc ionophores; vitamins C, D3 and E; and l-lysine.

Analysis of clinical outcome data from our sample of 113 subjects – comprised of roughly equal sized regimen-compliant (test) and non-compliant (control) groups meeting equivalent inclusion criteria of age and overall health, including prevalence of COVID-19 comorbidities – demonstrates a strong statistical significance in favor of use of the core formulations. The statistical analysis exhibits significance even

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with an assumption of a sub-15%, even as low as a sub-5%, post-exposure symptom-presentation rate.

Background

From early March through the end of July 2020, one of us (LM) monitored approximately 600 patients in Columbus and Cleveland, Ohio cities heavily affected by the COVID-19 pandemic, and did consultations with several colleagues (including JL) in the New York City metropolitan area, also heavily hit. Over that 5-month period, we dealt with dozens of clinical and/or test-confirmed cases of COVID-19. Much of the monitoring was performed via telemedicine; approximately 20% was performed in-office. It is from in-office monitored patients and staff that the study groups emerged.

Especially at the beginning of the study period, accurate diagnostic testing, effective medications and personal protective equipment were scarce in Ohio. As an essential medical service mandated fully operational during the lockdown, we were faced with an immediate need to protect our patients and staff from possibly deadly outcomes of infection by the COVID-19-causing SARS-CoV-2 coronavirus. Therefore, in addition to adherence to national and state protocols aimed at minimizing infectious spread, we developed and implemented OTC formulations and methods directed to prevent or, at least, ameliorate (retro)viral illness, with a focus on COVID-19.

While the formulations and methods were recommended to many of the telemedicine patients and in our consults, adequate monitoring of compliance and outcomes in those cases was not generally feasible. The same protocols of formulations and methods were strongly recommended to over 100 in-office subjects for whom monitoring was ongoing and thorough. From approximately half the in-office subject-pool opting not to follow the recommended protocols, the study's regimen-non-compliant control group emerged.

At an interim evaluation point of 5 weeks after implementation of the protocols, the only clinical and/or test-confirmed cases of COVID-19 arose in the non-compliant control group; on the other hand, none of the regimen-compliant subjects presented with symptoms of any viral illness. With such early promising clinical outcomes, we continued to recommend the regimen formulations (and also to others who were not participating in the study).

By the end of July 2020, the study period had extended to 20 weeks, 4 times the duration of the earlier interim period. Over that period, subjects experienced significantly greater number of episodes of exposure to clinical and/or test-confirmed cases of COVID-19 and subsequently, themselves, presented more cases of COVID-19. Herein reported and analyzed is the distribution of subjects' COVID-19 cases over the 20-week study period in the compliant test group that followed the recommended regimen of core formulations and in the non-compliant control group that declined to follow the regimen.

We present our findings as demonstrating the utility of safe, economical OTC options for early-stage COVID-19

alleviation, including prevention and treatment, thus reducing the urgency of demand for prophylaxis via antibodies and vaccines and freeing for treatment of moderate to severe cases such prescribed medications as hydroxychloroquine,⁷⁻⁹ remdesivir,^{10,11} ivermectin,¹² tocilizumab,¹³ and others.^{14,15}

We note that our approach to prevention and treatment of early-stage COVID-19 may also decrease the caseload of patients with moderate to severe symptoms requiring application of the aforementioned or other medicinal modalities and/or hospital-setting intervention. In addition, the formulations and methods may mitigate infection-spread from asymptomatic pre-symptomatic carriers and may buffer against infection threats from second and subsequent waves and/or from mutant strains of the virus.

Materials and Methods

Materials

The core supplementation formulations included zinc; zinc ionophores (quina plant bark extract and quercetin); vitamins C, D3 and E; and l-lysine. Sourcing for these components was, except as noted below, from a range of well-known manufacturers of name brand supplements.

The core supplementation formulation components have been demonstrated, as per references below, to have beneficial effects both outside of and within clinical settings in the prevention of viral infections and also in the treatment of early stages of such diseases. By way of selection criteria of those components for the roles they were anticipated to serve in the formulations, we briefly review relevant biochemical/immunological background of each.

Role of zinc. Zn⁺² mediates numerous non-specific and specific immunological functions.^{16,17} From normal development and function of cells,^{18,19} including those regulating nonspecific immunity, inter alia, activity of natural killer (NK) cells and neutrophils, and macrophage function; to maintaining expression of tight-junction proteins between lung-lining muco-epithelial cells, blocking entry of pathogens; from increasing cilia length and ciliary beat-frequency in those cells' mechanical clearance of surface "litter" such as virus particles, and repair of such function in coronavirus-damaged lung cells; to immune response modulation,^{20,21} tamping down on overshooting inflammatory immune responses²² (thus preventing, for example, high levels of inflammatory mediators such as destructive reactive oxygen and nitrogen species) and normalizing the ratios of diverse immune cell types. Additionally, zinc is strongly implicated in inhibiting viral binding to cell membrane ACE2 receptors used by the coronavirus to latch onto the outside of potential host cells as an essential step preparatory to entering and invading those cells; and for its inhibiting effect on functioning of viral replication enzymes such as retroviral RNA replicase,²³ thus blunting the attack by those virus particles that do gain entrance to host cells.

While zinc is highly recommended for its broad range of anti-(retro)viral benefits, high serum Zn⁺² levels carry risks of zinc toxicity^{24,25} and, even at non-toxic elevated levels, competition with and depletion of other micro-nutrients, such as copper.²⁶ It would, therefore, be desirable to achieve effective intra-cellular zinc levels while keeping serum zinc levels relatively normal (with concomitant monitoring and, where appropriate, judicious adjustment of other micronutrient levels). To that end, we factored into the study

formulations zinc ionophores for enhanced transport of zinc into human cells to effect intra-cellular zinc levels that may confer prophylactic and therapeutic benefits against (retro)viral infections.

Role of zinc ionophores. Zinc ionophores can increase importation of zinc into cells. Increasing intracellular Zn^{+2} concentration via zinc ionophores can efficiently impair intracellular replication of a variety of RNA viruses, including poliovirus, influenza virus and COVID-19-causing SARS-CoV-2 coronavirus, as demonstrated with such zinc ionophores as pyrrolidine dithiocarbamate and pyrithione.²³

Zinc ionophores can thus be utilized to gain the anti-viral benefit of enhanced intracellular Zn^{+2} concentrations while limiting tolerance/side-effect/toxicity issues²⁴⁻²⁶ associated with elevated serum levels of zinc supplementation. Another consideration for judicious selection of study zinc ionophore candidates included the compounds conferring additional benefits, particularly immunity health benefits.

Quina bark derivatives as zinc ionophores. Zinc ionophore activity has been shown in the alkaloid quinine²⁷ and its chloroquine derivatives.²⁸ For the study quinine-based zinc ionophore sourcing, we used Quina™ (NutraMedix; Jupiter, Florida USA), produced by a “proprietary [water: ethanol] extraction and enhancement process” from the bark of the quina plant *Cinchona calisaya*. There is no reason to believe that similar quina-bark-based extracts or derivatives would not serve as appropriate sourcing. We expect that extracts, tinctures or other preparations of quinine-containing plants, including but not limited to Quina Roja, can be adopted.

Quinine has also been shown to have an independent anti-viral activity against the COVID-19-causing SARS-CoV-2 coronavirus.²⁹ Additionally, there is evidence of an anti-TNF α effect of quinine³⁰ that may be contributory to the assumed protective anti-inflammatory effect for COVID-19 patients. For example, research on IBD patients relative to SARS-CoV-2 shows possible protective effects of anti-TNF α antibodies in Crohn’s patients.³¹

Quercetin as zinc ionophore. Quercetin, a bioflavonoid polyphenol, has been shown to act as a zinc ionophore,³² enhancing entrance of zinc into cells to inhibit viral intracellular replication. It is also believed to block viruses from entering cells in the first place. An Oak Ridge National Labs/University of Tennessee study of many FDA-approved compounds presented supercomputer modeling results for inhibition by them of SARS-CoV-2 viral S-spike binding to cells. The study ranked quercetin as fifth out of 20 top performers.³³

Studies have shown quercetin also exhibiting anti-inflammatory properties,³⁴⁻³⁶ which could help mitigate the inflammatory response of cytokine and/or bradykinin storms provoked by COVID-19. A wide range of anti-viral/immunity benefits of quercetin have been identified,³⁷⁻⁴¹ as well as other health benefits that may address some comorbidities of COVID-19⁴²⁻⁴⁴ and some of its sequelae.^{44,45}

Role of vitamin C. Effects of vitamin C on the immune system (e.g., possible enhancement of activity of NK cells and of other effectors of immunity mechanisms) are well documented. Administration of vitamin C before or after the appearance of flu symptoms seems to, respectively, prevent or ameliorate/alleviate flu symptoms in test populations relative to control populations.⁴⁶ Metadata analysis of dozens of studies covering thousands of common cold episodes demonstrated regular supplementation with vitamin C correlating with a modest but consistent reduction in duration of cold symptoms.⁴⁷

Role of vitamin D3. COVID-19-related recommendations for vitamin D3 supplementation may go beyond compensation for low UVB (approx. 320-280 nm) exposure directed to restore patients’ D3 levels reduced by pandemic-mitigating lockdown/shut-in restrictions. Review studies support a protective role of vitamin D3 supplementation in prevention of acute respiratory tract infection.⁴⁸ Recent reports suggest that vitamin D3 plays a significant role in immune system function⁴⁹ and, in particular, in susceptibility to COVID-19.⁵⁰

Role of vitamin E. Vitamin E has been shown to enhance immune system function and reduce risk of infection, particularly in older individuals, via modulation of T cell function by directly impacting T cell membrane integrity, signal transduction and cell division, and by indirectly affecting inflammatory mediators generated by other immune cells.⁵¹ There are additional data suggesting vitamin E’s role in modulation of macrophages, NK cells and B cells.⁵²

Role of L-Lysine. L-lysine has been shown to improve immune system function.⁵³ The mechanism of immunological enhancement by which l-lysine supplementation reduces infection rates is thought to be via its raising of zinc serum levels, apparently by facilitating zinc absorption from the gut; additionally, CD4 T cell count shows an increase.⁵⁴

Additional/Ancillary Components and Methods

Study subjects were encouraged to augment the core formulations with 1 or more additional/ancillary components.

Copper (e.g., copper orotate; copper (bis)glycinate) was suggested as a low concentration additional component for augmentation of the core formulations, at least partly as a pre-emptive compensation for zinc-induced depletion of copper.

Bupleurum falcatum root extract was recommended as a natural product ancillary component for augmentation of the core formulations for patients with symptoms of respiratory comorbidities as supplementary to their pulmonary medications.

In addition to study formulation components, we recommended to participants healthy lifestyle and diet modifications, as well as exercise. (While such recommendations are regular features of our practice, the pandemic underscored their need and added urgency to the recommendations.) The exercises were directed to relaxation and core body strengthening and, especially in light of the respiratory aspects of COVID-19, to maintenance and enhancement of pulmonary health and function.

Methods

Categorization of Subjects

Fifty-four subjects started with the study’s voluntary OTC regimen and, thereby, constituted the study test group (reduced to 53 subjects after the second study week by a voluntary withdrawal); while 60 declined the regimen—for reasons, when given, involving implementation’s complexity, effort and/or cost; and/or indicating barriers to implementation stemming from educational and/or socio-economic background—and constituted the study control group.

Regimen-compliant test group: 53 subjects

Non-compliant control group: 60 subjects

Subjects of the regimen-compliant test group and the non-compliant control group both met the same set of inclusion criteria:

Age—30+ years (Mode: ~ 59)
 Gender—female: male ~ 60:40
 Ethnicity—30-40% African American; ~ 5% Latino; remainder, Caucasian
 Oxygen saturation—94% or higher, on room air
 Temperature—afebrile
 Respiration rate—12-16
 Pulse—60-100

Besides an even share of osteoarthritis and other chronic pain conditions, both groups had roughly the same distribution of COVID-19 comorbidities such as hypertension, coronary artery disease and type 2 diabetes mellitus. All subjects were free of any flu-like symptoms at the start of the study.

Over the study period, we monitored subjects for symptoms of flu-like illness, with an active focus on COVID-19. At the outset of the pandemic, our practice's access to COVID-19 testing was quite limited. At that point, we identified subjects as confirmed COVID-19 cases or, at least, as likely COVID-19 cases upon their earliest presentation of clinical symptoms of COVID-19; or upon their being test-confirmed as COVID cases as documented in locales and practices where testing was available. Asymptomatic/pre-symptomatic subjects—with special note taken of documented, self-reported or likely exposure to diagnosed or suspected COVID-19 cases—as well as subjects presenting symptoms of unspecified flu-like illnesses, were followed for subsequent development of COVID-19 symptoms. As testing became more available, the state/regional protocols were such that we would receive notification of individual ones among our subjects having tested positive, the testing generally conducted by a subject's primary care provider, and the notifications then sent by Ohio health agencies to all the infected patient's physicians.

Administration Methods and Dosages

We followed subjects' oral administration, via self-administration and/or as supervised by caregiver, of components of the formulations, including via drops and powders (as mixed in liquids such as water or juice), capsules and tablets. The majority of administration compliance reporting was self-reported by subjects.

Oral administration was the sole method of administration assessed in this study.

For disease prophylaxis. One dose daily of the full core formulation regimen, containing:

25 mg zinc;
 10 drops of Quina™ (on average; the quina-bark extract may be titrated, as tolerated by some subjects, starting at 1 drop then building up to 8-16 drops daily, but which latter may be taken as two 4-8 drop half-doses twice daily);
 400 mg quercetin;
 1000 mg vitamin C;
 1000 IU (25 µg) vitamin D3;
 400 IU Vitamin E; and
 500 mg l-lysine.

Other amounts and proportions of these substances and components per dose may have, in practical application, been used by some test subjects. Such individualized dosing, while noted when possible, was not statistically assessed separately from the recommended dosing. Also not assessed was use of additional/ancillary components and

methods presented above, such as 1 mg daily of copper bisglycinate to be taken several hours after/before the regimen dose.

Prevention-dosing, administered throughout the study period, is being maintained as ongoing prophylaxis by many subjects who report following our suggestion to continue with it over any period of acute concern of contracting COVID-19 or other viral diseases.

For early-stage disease amelioration/alleviation. Multiples daily of the prevention-dose were administered. The multiple dose followed in the study was 2; i.e., for study test group subjects presenting symptoms of flu-like illness, we followed use of 2 prevention doses per day, administered separately or together. On the second day of administration in those mild to moderate flu-like cases, we initiated incremental increase of the zinc over 2-3 days to as high as 200 mg/day, as tolerated. (Those telemedicine patients, not part of the study, who called in describing likely COVID-19 symptoms, were advised to take treatment-dosing levels of the formulations.)

At least for addressing co/secondary bacterial infection, patient and/or caregiver may consider adding, as prescribed by a treating physician, 500 mg daily azithromycin for 5 days, or even a course of 100 mg twice daily of doxycycline for 7 days. In all cases of active clinical COVID-19 in this study, other than 1 course of doxycycline for 1 subject, no antibiotics were prescribed by primary care providers or other treating practitioners.

Treatment dosing was administered for 1-5 days or until symptoms were ameliorated/alleviated. Following symptom amelioration/alleviation, prevention-dosing was resumed.

Subject Monitoring

Our pain management practice, providing essential medical procedures and treatments, has remained open throughout the pandemic, with all CDC and Ohio State rules and guidelines for COVID-19 carefully observed. Over the study period of 20+ weeks, we monitored 113 subjects (104 patients and 9 staff members) for clinical symptoms of flu-like illnesses, with subsequent differential diagnosis (and, when available, with test-confirmation) of each symptomatic subject to distinguish COVID-19 from non-COVID-19 flu-like illness. We also maintained data of reported and/or observed subject exposures to clinical and/or test-confirmed cases of COVID-19.

As we are a specialty practice, primary care of the subjects as well as their other medical specialty needs were typically tended to outside our practice. This impacted our study by significantly increasing potential occurrences of subjects' exposure to carriers of COVID-19 even under lockdown restrictions (e.g., in other medical practices' waiting rooms; in transit to/from the other practices; and within and in transit to/from pharmacies). Such off-premises exposures were not likely to be consistently reported and, when reported, were not readily verifiable. The firmest exposure-counts, though likely conservatively lowballed, were based on a given subject's frequency of visits to our premises and the number of pre-quarantine COVID-positive individuals (identified and quarantined post-visit) who were present in our waiting areas during each visit of the subject and with whom the subject came in contact/proximity. Our record of to-date exposure-count for each subject represents, therefore, a likely number bracketed by low and high possibilities, with some cohorts of subjects, independent of exposure-count, having more reliably trustworthy counts than others.

A second potential impact was posed by the Ohio patient pain management contract mandating that any medicaments for infection

management, such as antibiotics and antivirals, be prescribed by primary care and/or infectious disease specialists. This impact was negated by almost none of the symptomatic subjects being prescribed such medications (the sole exception being a single course of doxycycline for 1 subject), thus reducing the effect of a potentially confounding factor from our data analysis. Instead, susceptibility to COVID-19 and other viral diseases, and severity of symptoms of those diseases, could be closely linked, with statistical significance, to subjects' adherence to the study regimen of supplementation.

The OTC regimen undertaken by test group subjects included the core formulations of zinc, zinc ionophores, vitamins and l-lysine, as well as at least some of the methods. In implementation over the study period, most test group subjects reported consistent use of the recommended doses of zinc and vitamins C and E; slightly fewer, additionally, consistent use of quercetin and vitamin D3, and yet somewhat fewer, additionally, consistent use of quina bark extract and l-lysine. All study test group subjects in a high exposure sub-group, which included those staff members in frequent close contact with high-risk patients, were sure to consistently use quercetin. The high exposure sub-group subjects each had 6 or more reported/suspected exposures to COVID-19 over the study period.

Supplement-Specific Monitoring and Cautions

Quinine. In light of concerns of possible complications associated with quinine,⁵⁵ its use was monitored over the study period for cardiac complications and other side effects such as blurred vision. There was no evidence of any complications or intolerance, including in patients with significant prior cardiac history of arrhythmias or other risk factors. We expect to continue monitoring such side effects over and beyond the period of quina bark extract administration.

Quercetin. While numerous health benefits have been associated with quercetin,³⁴⁻⁴⁵ a caution was raised by early animal studies that pointed to quercetin toxicity in relation to benign renal tumors.⁵⁶ We monitored for adverse effects over the study period, and received no reports nor found any clinical signs of quercetin toxicity over the study period. It appears to be appropriate to continue monitoring for oncological side effects over and beyond the period of quercetin administration.

Combination of quina extract and quercetin. While there is a clear rationale for combining quina bark extract and quercetin to achieve their cumulative and possibly synergistic effect, this is, to the best of our knowledge, the first clinical study to do so. We therefore monitored all subjects over the study period, and now well beyond, for toxicity and/or side effects of the combination and have not received any reports nor seen any indicators of toxicity and/or side effects of the combination.

Results

Outcomes

At 5 weeks into the study, none of the test group of 53 had presented with COVID-19 or other flu-like illness, while 6 of the control group of 60 did so present. At 20 weeks, a total of 2 of the test group have presented, versus 12 of the control group.

Of the 12 control group subjects with mild to moderate to severe clinical symptoms of flu-like illness, 9 were diagnosed

with COVID-19 infection. Each of those 9 was quarantined directly upon diagnosis, but, prior to diagnosis and quarantine, had likely increased the exposure of other study subjects to the COVID-19-causing SARS-CoV-2 coronavirus. The remaining 3 of the 12 ill control group subjects were diagnosed with non-COVID flu-like infections.

Each of the 2 test group subjects with mild to moderate flu-like symptoms (neither had severe symptoms), was diagnosed to not have COVID-19 but rather an unspecified non-COVID flu-like illness. The initial test subject who had opted out of the test group by ceasing to adhere to the regimen at week 2, developed confirmed COVID-19 symptoms 30 days later. (We note that various telemedicine patients who undertook the regimen of formulations and methods and who nevertheless did contract COVID-19, reported that their physicians credited the relative mildness of the patients' cases to the regimen.)

Of note is that, of the 12 control group subjects who had developed mild to moderate to severe symptoms of flu-like illnesses (including COVID-19), were at least 4 who had undertaken and maintained supplementation with vitamin C (500-1000 mg daily) alone, without other core formulation components; and at least 3 who had undertaken and maintained supplementation with vitamin D3 (1000-2000 IU daily) alone, without other core formulation components. Also notable is that the test group subject who had stopped taking most of the core formulation supplements 2 weeks into the study period and developed COVID-19 symptoms a month after withdrawing from the study, had maintained vitamin C input even after opting out of the test group.

These observations demonstrate the efficacy of supplementation with zinc (25 mg daily) and zinc ionophores, and at least some of the other core formulation components, as prophylaxis against COVID-19 and other flu-like illnesses; and demonstrate the relative lack of anti-flu/anti-COVID-19 prophylactic efficacy of supplementation with vitamin C or D3 in the absence of zinc and zinc ionophores.

Statistical Analyses: Simple Ratio, Odds Ratio, Binomial Distribution Analysis—General and Informed

We present several progressively more data-informed statistical analyses.

Simple ratio. A rough measure of efficacy of the core formulations for prophylaxis against and alleviation of symptoms of COVID-19 and other flu-like illnesses can be had by simply comparing the fraction of test group subjects who became symptomatic with any flu-like illness ($2/53 = 0.0377$) over the study period's 20+ weeks, with the corresponding fraction in the control group ($12/60 = 0.200$). The experience of the test group, by this measure, was approximately 5.3 times greater than that of the control group in being protected from any flu-like illness over the study period.

Table 1. Odds Ratio Table of Outcomes vs Circumstances Over Study Period.^a

Outcome→ ↓circumstance	Became symptomatic	Remained symptom-free	Group ↓Totals
Test group subjects (Supplementation with core formulations)	2	51	53
Control group subjects (No zinc or zinc ionophores)	12	48	60
Cohort totals→	14	99	113

^aSymptomatic: Presenting Symptoms of Either Non-COVID or COVID-19 Illness (i.e., any flu-like illness).

Odds ratio. A big-picture statistical view of the 20-week subject outcome-data is provided by an Odds Ratio Table (see, e.g. reference⁵⁷] for terms, definitions and calculations), given in Table 1.

The study Odds Ratio (OR) calculates as $OR = (2/12)/(51/48) = 0.1569$, with 95% Confidence Interval ends given by upper end = 0.7379 and lower end = 0.0334. Thus, $OR = 0.1569$, with its 95% Confidence Interval of (0.0334, 0.7379) not spanning the value 1 (the latter datum being the *sine qua non* for Odds Ratio Confidence Interval statistical significance).

Binomial analysis

Entire test group, without incorporation of exposure-count information. To gain a sense of the probability of validity of a null hypothesis of obtaining the test group results without the study supplementation, the data were analyzed by binomial expansion. The probability p of any subject becoming symptomatic over the study period without supplementation may be set by the experience of the control group. In the control group, 12 of the 60 subjects experienced symptoms of unspecified flu-like illnesses (9 of 12 of which were subsequently confirmed as COVID-19), for a probability p of presentation of post-exposure flu-like symptoms of $12/60 = 0.2$. Since all flu-like symptoms are being considered together, whether or not later confirmed as COVID symptoms, and each subject either presents flu-like symptoms or does not, the probability q of any subject remaining symptom-free is given by

$$q = 1 - p = 1 - 0.20 = 0.80.$$

In its generalized form, the binomial probability for no more than j (i.e., for j or fewer) of a group of n subjects experiencing an outcome that has probability p of occurring without introduction of the study-factor may be given as:

$$\sum_{i=0}^j ({}_n C_i) p^i (q)^{(n-i)}$$

where i is an index variable going from 0 to j ; and ${}_n C_i$ is the combinatorial operator, bookkeeping the various possible n -subject scenarios and defined as $n!/i!(n-i)!$.

Applying this analysis to the test group, in which, over the study period, only 2 of 53 subjects became symptomatic, the probability of 2 or fewer subjects becoming symptomatic as a random outcome of only the factors at play among the control group (i.e., the probability of validity of the null hypothesis of no benefit being conferred by the test group's supplementation), would be given by:

$$\sum_{i=0}^2 \{53!/i!(53-i)!\} 0.20^i (0.80)^{(53-i)} = 0.000733$$

This analysis of study group results predicts that approximately 733 out of a million trials might produce those results without benefit of an effect of the study-factor. That result being so unlikely, at better than the 0.001 significance level, the study results provide a clear demonstration of a benefit conferred on the test group by supplementation.

However, it is possible that some factor other than implementation of supplementation may be contributing to the outcomes. For instance, subjects interested and motivated to implement and maintain compliance with a multi-component supplement regimen, apparently being more health conscious than control group subjects, may indeed actually be healthier, with more robust immune systems more resistant to viral infection. Perhaps also or alternatively, health conscious subjects are more careful about minimizing their exposure to virus-carrying sources and/or about post-exposure disinfection.

An approach to compensating in the analyzes for such possible confounding factors may be to assign a lower supplementation-ignoring post-exposure symptom-presentation rate to the test group than that exhibited by the control group, with the difference between the control group's actual experienced post-exposure symptom-presentation rate and the test group's new lowball assigned rate "absorbing" effects of the putative confounding factors.

Analyzes were conducted for 3 scenarios of such low test-group post-exposure symptom-presentation rates:

- A) If the test group is considered to enjoy only three-quarters the control group's demonstrated post-exposure symptom-presentation rate of 0.20, then, for the test group, $q = 1 - p = 1 - (3/4)0.20 = 1 - 0.15 = 0.85$ and the binomial expansion gives:

$$\sum_{i=0}^2 \{53!/i!(53-i)!\} 0.15^i (0.85)^{(53-i)} = 0.009675, \text{ still at the } 0.01 \text{ significance level.}$$

- B) If the test group's post-exposure infection rate is taken to be only five-eighths the control group's 0.20, then, for the test group, $q = 1 - p = 1 - 0.125 = 0.875$; and the binomial expansion gives 0.0310, no longer at the 0.01 significance level, but still at a respectable 0.05 significance level.

Table 2. Probabilities of Remaining Asymptomatic or Uninfected for Test Group Cohort Subjects.

Cohort	Subjects in cohort (s)	Exposure count (n)	Probability single subject of cohort remains healthy $((1-p)^n)$	Probability all cohort subjects remain healthy $((1-p)^{ns})$
a	3	9	$0.86^9 = 0.257$	$(0.86^9)^3 = 0.0170$
b	4	6	$0.86^6 = 0.405$	$(0.86^6)^4 = 0.0268$
c	2	5	$0.86^5 = 0.470$	$(0.86^5)^2 = 0.221$
d	1	3	$0.86^3 = 0.636$	$(0.86^3)^1 = 0.636$
Totals	10	23	—————	$0.86^{(27+24+10+3)} = 0.0000643$

C) If the test group's post-exposure infection rate is taken to be only one-half the control group's 0.20, then, for the test group, $q = 1-p = 1-0.10 = 0.90$; and the binomial expansion gives 0.0898, no longer at the 0.05 significance level, but only at the 0.1 significance level, at which the null hypothesis of "zero study-factor effect" presents a 10% risk of being correct and the null hypothesis, while not strongly confirmed, cannot be rejected.

Without further information as to actual exposure-experience of subjects, one could not attach statistical significance to the test group experience if assuming scenario C's post-exposure symptom-presentation rate of 10%. The next sub-section of Statistical Analyses, factoring in subjects' exposure-experience, demonstrates statistical significance even below 10%.

Binomial Analysis

With incorporation of exposure-count information. CDC and WHO data suggest that a population infected with SARS-CoV-2 typically shows 80% asymptomatic carriers and mild symptomatic cases; 15% severe symptomatic cases; and 5% critical symptomatic cases.⁵⁸ Taking, then, an expected approximate distribution of 80% asymptomatic/pre-symptomatic carriers and 20% symptomatic cases, the study control group's presentation of $12/60 = 0.20$ flu-like symptom presenters would indicate that the remaining 48 symptom-free control subjects of this multiply exposed group (exposed indoors, in our facilities and in other medical practices) were asymptomatic/pre-symptomatic carriers (including, perhaps, some exposed but uninfected subjects).

Applying the same distribution to the approximately equally multiply-exposed (indoors) population of 53 subjects of the study test group, a null hypothesis of "zero study-factor effect," would yield approximately 10-11 symptomatic subjects and 42-43 asymptomatic/pre-symptomatic carriers or, conservatively, 10 symptomatic and 43 asymptomatic/pre-symptomatic carriers. That the study test group outcomes included only 2, and not 10, symptom-presenting subjects is repeat confirmation of the approximately five-fold protection seen above in the Simple Ratio subsection that seems to be conferred by the core formulations upon the test group over the control.

CDC and WHO estimates both for likelihood of post-exposure infection and for likelihood of post-infection presentation of symptoms have varied over the course of the

pandemic.⁵⁸⁻⁶⁰ The range for likelihood of post-exposure infection in an indoors setting (such as our facility and that of other medical practices visited by the study subjects) ranges over approximately 20-40%; and of post-infection presentation of symptoms, over approximately 20-60%. Thus, a combined likelihood of post-exposure symptom-presentation would range over approximately 4-24%, with the high end reflected, perhaps (assuming only 1 exposure, on average, per subject), in our study control group's experience of $12/60 = 20\%$ symptom-presentation.

The CDC and WHO estimates, while displaying wide variation, are based on sample sizes thousands times larger than our study, and also cover numerous diverse settings, averaging out localized effects. Both factors lend the estimates weighty statistical authority. Making use of a midpoint of the CDC/WHO range of post-exposure symptom-presentation, 14%, and applying it to 4 cohorts, **a-d**, of the $53 - 2 = 51$ non-symptomatic subjects of our test group for whom exposure-counts were firmest, yield the following:

Probability of becoming symptomatic following a single indoor-setting exposure: 0.14 (midpoint of CDC/WHO estimates)

Probability of remaining healthy (infected but asymptomatic/pre-symptomatic or completely uninfected) subsequent to a single indoor-setting exposure: $1-0.14 = 0.86$

Probability of remaining healthy (infected but asymptomatic/pre-symptomatic or completely uninfected) subsequent to **n** indoor-setting exposures: 0.86^n

Probability of **s** cohort subjects remaining healthy (infected but asymptomatic/pre-symptomatic or completely uninfected) subsequent to **n** indoor-setting exposures: $(0.86^n)^s$

Data and results are tabulated in Table 2.

The results presented in Table 2 would be strikingly more dramatic with assumption of a higher post-exposure symptom-presentation rate; and strikingly less dramatic with assumption of a lower post-exposure symptom-presentation rate.

Table 3 shows calculations using the low and high ends of the CDC/WHO estimates, as well as Table 2's mid-point.

There were an additional 41 asymptomatic/pre-symptomatic or uninfected test group subjects (out of 53 total) with exposure-count estimates ranging from 1 to well beyond cohort **a**'s 9, but with the estimates deemed less reliable than those of cohorts **a-d**. Factoring in another 41 asymptomatic or

Table 3. Probabilities of Remaining Asymptomatic or Uninfected for Test Group Cohort Subjects.

Probability all cohort subjects remain healthy					
Post-exposure symptom-presentation rate (p) →			0.04	0.14 (from Table 2)	0.24
Cohort	s	n	(1-p) ^{ns}		
a	3	9	0.332	0.0170	0.000605
b	4	6	0.375	0.0268	0.00138
c	2	5	0.665	0.221	0.0643
d	1	3	0.885	0.636	0.439
Totals	10	23	0.0733	0.0000643	0.000000240

uninfected test group subjects, even with assuming only a single indoor-setting exposure apiece (well below the average exposure-count estimate), and even with still assuming the low end of the 4-24% post-exposure symptom-presentation rate, yields a probability for all 51 asymptomatic or uninfected test group subjects having remained symptom-free of $(1-0.04)^{(27+24+10+3+41)} = 0.0138$, comfortably within the 0.05 significance level. (Obviously, with incorporation of actual, higher exposure-count estimates for different cohorts within the 41, the significance level improves. However, a factoring-in of the control group subjects who remained asymptomatic/pre-symptomatic or uninfected, but for whom our exposure-count estimates are much less reliable, would likely offset that improvement.)

For completeness, we report that the 2 test group subjects who became symptomatic with unspecified non-COVID-19 flu-like illness(es) were low exposure-count subjects.

Discussion

We have presented a case review analysis of effectiveness of a regimen of OTC formulations and methods for prevention and treatment of (retro)viral infections, inclusive of COVID-19, over a 20-week period. The analysis shows a strong statistical significance in favor of the use of the formulations and methods in a moderately sized study subject sample ($n = 53$ in the study regimen-compliant test group; $n = 60$ in the study non-compliant control group). The statistical significance persists even adopting an assumption of a mid-point or even a low-end of CDC/WHO estimates of a COVID-19 symptom-presentation rate following SARS-CoV-2 exposure. In light of current virus spread patterns,⁵⁸⁻⁶³ those CDC/WHO estimates appear quite conservative.

Limitations

Our adoption of conservative exposure-and-symptom-presentation values in data analysis may compensate for lacunae in study design and execution. The study emerged from our efforts to protect our patients and staff members from COVID-19. During the early months of the pandemic – with

scarce, rapidly changing and often conflicting medical information and clinical guidance becoming available – our immediate and overriding focus remained the wellbeing of patients and staff. It was to that end, and not prospectively for purposes of producing a study, that the regimen of OTC core formulations and methods was developed and implemented.

Embrace of the regimen by approximately half of our in-office population and reluctance/unwillingness to accept it by the other half, retrospectively yielded the binary set of a regimen-compliant test group and a non-compliant control group. There was no “study recruitment” beyond the in-office patients and staff. Concern about the moderate sizes of the study groups may be offset by the stark, statistically significant difference in their outcomes.

Several other caveats regarding study design and execution are to be noted:

- The study was obviously conducted neither double-blinded nor even blinded.
- Some of the test group subjects were consistent with their implementation of only part of the core formulation and only selected methods. Possible weaknesses in study--findings' significance stemming from that deficiency may be balanced against experience of the high-exposure sub-group, who were diligent in taking at least quercetin as zinc ionophore with their zinc, as well as most if not all of the rest of the core formulations. Despite their repeated exposures to clinically- and/or test-confirmed COVID-19 carriers, this sub-group presented no cases of COVID-19.
- Self-reporting, both of compliance and of off-site exposures, can be suspected of introducing biasing of data (stemming from subjects' desire to please the physician, researcher and/or employer). Here, one should note—perhaps a tribute to our practice's amicable and accepting atmosphere—that subjects had had no difficulty or hesitation declining the study regimen; opting out from groups and sub-groups during the study; and reporting only partial compliance with the core formulations and methods—all of which bolster a strong presumption of truth-telling in the self-reporting.

Given the above limitations and as would be appropriate with any single moderately scaled study, we recommend care in interpretation of the study results. However, it is our hope that the study will serve as a basis for future larger-scale studies of enhanced design.

Post-Study Considerations

Enhanced compliance. Our data strongly suggest that zinc supplementation in the daily range of 25 mg together with zinc ionophores quina tree bark extract and quercetin, as well as vitamins C, D3 and E, and l-lysine, as administered according to study protocols, evidenced the most protective prophylactic effect against COVID-19 and other viral illnesses, while supplementation with vitamin C or vitamin D alone without zinc plus ionophore(s), may not evince any noticeable prophylactic effect. While we assumed a significant effect contributed by each of the formulations' components and substances described herein, maintaining long-term use of those components and substances was challenging to subjects.

Our practical experience at the very outset of the study and then during the study period demonstrated the difficulty for many individuals to undertake and reliably maintain a daily regimen of multiple supplements over an extended time period. Because of the importance of the multiple components of the formulations, on the one hand, and the long-term compliance difficulty subjects reported with "so many" components, on the other, we advocate adoption of a combined "one capsule" formulation. Use of a single compounded supplement, or even of a two-pill or pill-plus-liquid combination, that provides all the core formulations' components should be advantageous for prophylaxis against and treatment of COVID-19 and other flu-like illnesses.

Further investigation. We offer these data and results as a basis for larger-scale studies. The approach herein presented does not preclude or clash with vaccination, antibody therapy and/or use of prescribed medications. On the contrary, OTC supplementation that enhances the immune response can prove a useful adjunct to vaccination, antibody infusion and prescribed medications, and may be useful for addressing possible viral mutations, antibody titer declines and non-COVID-19 viral infections, including the Autumn-Winter annual seasonal influenza. While we believe that the stark difference in clinical outcomes between the test and control groups demonstrates the utility of the study formulations, we certainly welcome future extensive prospective studies.

The study also followed, in a preliminary fashion, the role of vitamin C separate from and in combination with the other components of the core formulations. Likewise, the study followed, in a preliminary fashion, the role of vitamin D3 separate from and in combination with the other components of the core formulations. Further investigation is called for to more fully evaluate the individual and contributory roles of vitamin C and vitamin D3 in COVID-19 prophylaxis and treatment. (It would be of interest, in regard to vitamin D3, to evaluate also any role

played by seasonal sunlight exposure relative to supplementation study scheduling.)

The study did not follow the role of vitamin E or l-lysine separate from other components of the core formulations. Investigation is called for to evaluate the individual and contributory roles vitamin E and l-lysine may play in COVID-19 prophylaxis and treatment.

While individual subjects undertook use of one or more of the additional or ancillary components and methods, the study did not follow the role of the additional or ancillary components and methods separate from the components of the core formulations. Investigation is called for to evaluate individual and contributory roles any of the additional or ancillary components and methods may play in COVID-19 prophylaxis and treatment.

Treatment use. Much experience with SARS-CoV-2 and its attendant COVID-19 has been urgently pursued and attained by the clinical and research communities over the challenging months of 2020. With that experience, we find our OTC approach to COVID-19 alleviation corroborated by reviews of supplementation⁶⁴ and, in particular, zinc supplementation,^{16,65-67} and further in particular, also together with ionophore,⁶⁸ as potentially effective prophylaxis and even as treatment measures against the pandemic disease.

With dawning consideration of OTC regimens as part of treatment measures, we suggest an administration mode that we contemplated during the study but, fortunately, never had to implement. Particularly for medical care facilities (hospitals, nursing homes, convalescent centers), it may be desirable to apportion formulation components among various modes of administration, such as: IV or other parenteral routes for ultra-filtered solubilized and buffered zinc ion, quina bark extract, vitamin C and l-lysine; and PEG administration for quercetin and vitamins D3 and E.

Conclusion

The OTC formulations and methods herein presented have been demonstrated effective in preventing COVID-19 at 1 dose/day; and may be considered effective in treating mild to moderate symptoms of early-stage unspecified flu-like illness (presumably also COVID) at 2 doses/day, with no or only minimal prescription-necessary augmentation (e.g., only azithromycin, doxycycline or other standard antibiotics). Thus, prophylactic use of our OTC formulations and early treatment use of the OTC formulations plus minimal antibiotic use may significantly reduce the incidence of later-stage COVID-19's moderate to severe symptoms that may require other prescribed medications⁷⁻¹⁵ that may be scarce, costly or potentially risk-bearing and/or may require in-hospital procedures. Use of our OTC formulations and methods may prevent virus spread from asymptomatic/pre-symptomatic carriers and may, thus, help address infection threats of second and subsequent waves and/or of proliferating mutant strains.

While the pandemic is unfolding and disrupting lives of hundreds of millions of people, producing millions of infected cases and hundreds of thousands of deaths, scientific debate continues as to whether COVID-19 will follow the pattern of the lethal, highly infectious but short-lived 2003 SARS outbreak or the approximately triply lethal but less infectious 2012 MERS outbreak still developing in waxing and waning fashion over the past 8 years; at this point, COVID-19 seems more infectious than either of those recent predecessor coronavirus-caused illnesses, but with a significantly lower fatality rate. (For a brief survey comparison, see reference⁶⁹.) Some epidemiologists expect “COVID-19 activity” over the next 18-24 months.⁷⁰ Even though the specter of an overlap of COVID-19 with the annual influenza season affords little comfort, we do note that the formulations and methods presented herein are not directed per se to COVID-19, but rather to (retro)viral illnesses in general, and should be effective as prophylaxis and perhaps early-stage treatment of those other viral infections.

While numerous studies are ongoing, there is still a dearth of clear data on the effectiveness of the prescribed medications; substantial uncertainty regarding vaccine availability, production and distribution schedules; and even, particularly in light of the spread of virus variants, uncertainty about vaccine effectiveness. Likewise, debate is ongoing over efficacy of testing protocols (e.g., What does a PCR test truly reveal about active-virus carrier status?) and over efficacy and duration of antibody immunity, both passive and active. In this environment, the OTC formulations and methods described herein can provide an economical and effective alternative to or augmentation of modalities for prevention and treatment available to the public and healthcare workers.

While our recommendations for additional/ancillary components had included non-Western candidates (as reported in an earlier published work), we were, of necessity, limited in selection of our core formulations to supplements readily available in Ohio during the months of pandemic lockdown and that would likely be familiar to our subjects. However, given the global spread of SARS-CoV-2 and its variants, investigation of other, non-Western medicinal and OTC approaches to (retro)viral infections, with a focus on COVID-19, would be of significant interest. Such reports are currently available, presenting, for instance, Ayurvedic protocols and single-case studies⁷¹⁻⁷⁴ and traditional Chinese herbal approaches.^{75,76}

Analyses presented herein of our study data would seem to bolster the proposition that “[w]ith the established role of nutritional status on host immunity, the individual nutritional evaluation is probably essential to prepare someone for the SARS-CoV-II pandemic.”⁷⁷

Authors’ Note

This article complies with CPMI guidelines. No PHI is included.

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References

1. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care Skilled Nursing Facility—King County, Washington. *MMWR Morb Mortal Wkly Rep.* 2020;69(13):337. doi:10.15585/mmwr.mm6913e1
2. Lee S, Kim T, Lee E, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. *JAMA Intern Med.* 2020;180(11):1447-1452. doi:10.1001/jamainternmed.2020.3862
3. US data trends available graphically, numerically and in weekly update summary at <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html>. Accessed March, 2021.
4. Korber B, Fischer WM, Gnanakaran S, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID19 virus. *Cell.* 2020;182(4):812-827. doi:10.1016/j.cell.2020.06.043
5. Li Q, Wu J, Nie J, et al. The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity. *Cell.* 2020;182(5):1284-1294. doi:10.1016/j.cell.2020.07.012
6. Luring AS, Hodcroft EB. Genetic variants of SARS-CoV-2—what do they mean? *JAMA.* 2021;325(6):529-531. doi:10.1001/jama.2020.27124
7. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents.* 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949
8. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis.* 2020;97:396-403. doi:10.1016/j.ijid.2020.06.099
9. Risch HA. Opinion: early outpatient treatment of symptomatic, high-risk Covid-19 patients that should be ramped-up immediately as key to the pandemic crisis. *Am J Epidemiol.* 2020;189(11):1218-1226. doi:10.1093/aje/kwaa093
10. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0
11. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med.* 2020;382:2327-2336. doi:10.1056/NEJMoa2007016

12. Caly J, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787. doi:10.1016/j.antiviral.2020.104787
13. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol.* 2020;92(10):2042-2049. doi:10.1002/jmv.25964
14. Thorlund K, Dron L, Park J, Hsu G, Forrest JI, Mills EJ. A real-time dashboard of clinical trials for COVID-19. *Lancet Digit Health.* 2020;2(6):e286-e287. doi:10.1018/S2589-7500(20)30086-8
15. Peiffer-Smadja N, Lescure FX, Sallard E, et al. Anticovid, a comprehensive open-access real-time platform of registered clinical studies for COVID-19. *J Antimicrob Chemother.* 2020;75(9):2708. doi:10.1093/jac/dkaa223
16. Wessels I, Rolles B, Rink L. The potential impact of zinc supplementation on COVID-19 Pathogenesis. *Front Immunol.* 2020;11:1722. doi:10.3389/fimmu.2020.01712
17. Skrajnowska D, Bobrowska-Korczak B. Role of zinc in immune system and anti-cancer defense mechanisms. *Nutrients.* 2019;11(10):2273. doi:10.3390/nu11102273
18. McCall KA, Huang C, Fierke CA. Function and mechanism of zinc metalloenzymes. *J Nutr.* 2000;130:1437S-1446S. doi:10.1093/jn/130.5.1437 S
19. Roohani N, Hurrell R, Kelishadi R, et al. Zinc and its importance for human health: an integrative review. *J Res Med Sci.* 2013;18(2):144-157. PMID: 23914218; PMCID: PMC3724376.
20. Prasad AS. Zinc: mechanisms of host defense. *J Nutr.* 2007;137(5):1345-1349. doi:10.1093/jn/137.5.1345
21. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr.* 1998;68(2 Suppl):447S-463S. doi:10.1093/ajcn/68.2.447 S
22. von Bülow V, Dubben S, Engelhardt G, et al. Zinc-dependent suppression of TNF-alpha production is mediated by protein kinase A-induced inhibition of Raf-1, I kappa B kinase beta, and NF-kappa B. *J Immunol.* 2007;179(6):4180. doi:10.4049/jimmunol.179.6.4180
23. teVelthuis AJW, van den Worm SHE, Sims AMC, et al. Zinc(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophore block the replication of these viruses in cell culture. *PLoS Pathog.* 2010;6(11):e1001176. doi:10.1371/journal.ppat.1001176
24. Fosmire GJ. Zinc toxicity. *Am J Clin Nutr.* 1990;51(2):225-227. doi:10.1093/ajcn/51.2.225
25. <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/#h8>. Accessed May 15, 2020.
26. Duncan A, Yacoubian C, Watson N, et al. The risk of copper deficiency in patients prescribed zinc supplements. *J Clin Pathol.* 2015;68(9):723. doi:10.1136/jclinpath-2014-202837
27. Ogunlana OO, Ogunlana OE, Ademowo OG. Comparative in vitro assessment of the antiplasmodial activity of quinine-zinc complex and quinine sulphate. *Sci Res Essays.* 2009;4(3):180. doi:10.5897/SRE.9000281
28. Xue J, Moyer A, Peng B, et al. Chloroquine is a zinc ionophore. *PLoS One.* 2014;9(10):e109180. doi:10.1371/journal.pone.0109180
29. Li X, Zhang C, Liu L, et al. Existing bitter medicines for fighting 2019-nCoV-associated infectious diseases. *FASEB J.* 2020;34(5):6008-6016. doi:10.1096/fj.202000502
30. Liu W, Qi Y, Liu L, et al. Suppression of tumor cell proliferation by quinine via the inhibition of the tumor necrosis factor receptor-associated factor 6-AKT interaction. *Mol Med Rep.* 2016;14:2171-2179. doi:10.3892/mmr.2016.5492
31. Higgins PDR, Ng S, Danese S, Rao K. The risk of SARS-CoV-2 in immunosuppressed IBD patients. *Crohn's Colitis* 360. 2020;2(2):otaa026. doi:10.1093/crocol/otaa026
32. Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, et al. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. *J Agric Food Chem.* 2014;13:8085-8093. doi:10.1021/jf5014633
33. Smith M, Smith JC. Repurposing therapeutics for COVID-19: supercomputer-based docking to the SARS-CoV-2 viral spike protein and viral spike protein-human ACE2 interface. *Chemrxiv.* Preprint. doi:10.26434/chemrxiv.11871402.v4
34. Kim YJ, Park W. Anti-inflammatory effect of quercetin on raw 264.7 mouse macrophages induced with polyinosinic-polycytidylic acid. *Molecules.* 2016;21(4):450. doi:10.3390/molecules21040450
35. Cheng SC, Wu YH, Huang WC, Pang JHS, Huang TH, Cheng CY. Anti-inflammatory property of quercetin through downregulation of ICAM-1 and MMP-9 in TNF- α -activated retinal pigment epithelial cells. *Cytokine.* 2019;116:48-60. doi:10.1016/j.cyto.2019.01.001
36. Haleagrahara N, Miranda-Hernandez C, Alim A, Hayes L, Bird G, Ketheesan N. Therapeutic effect of quercetin in collagen-induced arthritis. *Biomed Pharmacother.* 2017;90:38-46. doi:10.1016/j.biopha.2017.03.026
37. Qiu X, Kroeker A, He S, et al. Prophylactic efficacy of quercetin 3- β -o-d-glucoside against ebola virus infection. *Antimicrob Agents Chemother.* 2016;60(9):5182-5188. doi:10.1128/AAC.00307-16
38. Wu W, Li R, He J, et al. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses.* 2016;8(1):6. doi:10.3390/v8010006
39. Yi L, Li Z, Yuan K, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cell. *J Virol.* 2004;78(20):11334-11339. doi:10.1128/JVI.78.20.11334-11339.2004
40. Liu Y, Yu C, Ji K, et al. Quercetin reduces TNF- α -induced mesangial cell proliferation and inhibits PTX₃ production: involvement of NF- κ B signaling pathway. *Phytother Res.* 2019;33(9):2401-2408. doi:10.1002/ptr.6430
41. Liu H, Lee JI, Ahn TG. Effect of quercetin on the anti-tumor activity of cisplatin in EMT6 breast tumor-bearing mice. *Obstet Gynecol Sci.* 2019;62(4):242-248. doi:10.5468/ogs.2019.62.4.242
42. Marunaka Y, Marunaka R, Sun H, et al. Actions of quercetin, a polyphenol, on blood pressure. *Molecules.* 2017;22:209. doi:10.3390/molecules22020209
43. Eid HM, Haddad PS. The antidiabetic potential of quercetin: underlying mechanisms. *Curr Med Chem.* 2017;24:355-364. doi:10.2174/0929867323666160909153707

44. Patel RV, Mistry BM, Shinde SK, Syed R, Singh V, Shin HS. Therapeutic potential of quercetin as a cardiovascular agent. *Eur J Med Chem.* 2018;155:889-904. doi:10.1016/j.ejmech.2018.06.053
45. Babaei F, Mirzababaei M, Nassiri-Asl M. Quercetin in food: possible mechanisms of its effect on memory. *J Food Sci.* 2018;83(9):2280-2287. doi:10.1111/1750-3841.14317
46. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. *J Manipulative Physiol Ther.* 1999;22(8):530-533. doi:10.1016/s0161-4754(99)70005-9
47. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev.* 2013;(1):CD000980. doi:10.1002/14651858.CD000980.pub4
48. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. *Health Technol Assess.* 2019;23(2):1-44. doi:10.3310/hta23020
49. Charoenngam N, Holick MF. Immunologic effects of Vitamin D on human health and disease. *Nutrients.* 2020;12(7):2097. doi:10.3390/nu12072097
50. Meltzer DO, Best TJ, Zhang H, et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw Open.* 2020;3(9):e2019722. doi:10.1001/jamanetworkopen.2020.19722
51. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life.* 2019;71(4):487-494. doi:10.1002/iub.1976
52. Lee GY, Han SN. The role of vitamin e in immunity. *Nutrients.* 2018;10(11):1614. doi:10.3390/nu10111614
53. Zhao W, Zhai F, Zhang D, et al. Lysine-fortified wheat flour improves the nutritional and immunological status of wheat-eating families in northern China. *Food Nutr Bull.* 2004;25(2):123-129. doi:10.1177/156482650402500203
54. Sugeng MW, Adriani M, Wirjatmadi B. The effect of zinc and lysine supplementation on infection rate and cd4 count in elderly. *Biochem Physiol.* 2015;5:2. doi:10.4172/2168-9652.S5-002
55. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021799s024lbl.pdf. Accessed May 15, 2020.
56. Dunnick JK, Hailey JR. Toxicity and carcinogenicity studies of quercetin, a natural component of foods. *Fundam Appl Toxicol.* 1992;19(3):423-431. doi:10.1016/0272-0590(92)90181-G
57. Szumilas M. Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry.* 2010;19(3):227-229. PMID: 20842279 PMCID: PMC2938757.
58. (a) <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html> (b) <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza> (c) https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4. Accessed May 15, 2020).
59. Chen Y, Wang AH, Yi B, et al. Epidemiological characteristics of infection in COVID-19 close contacts in Ningbo city [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2020;41(5):667-671. doi:10.3760/cma.j.cn112338-20200304-00251. PMID: 32447904.
60. Cheng H, Jian S, Liu D, et al. Contact tracing assessment of Covid-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med.* 2020;180(9):1156-1163. doi:10.1001/jamainternmed.2020.2020
61. Silverman JD, Hupert N, Washburne AD. Using influenza surveillance networks to estimate state-specific prevalence of SARS-CoV-2 in the United States. *Sci Transl Med.* 2020;12(554):eabc1126. doi:10.1126/scitranslmed.abc1126
62. Racaniello V. VuMedi presentation (TWIV: This Week in Virology) August 12, 2020. (a) Dr. Fauci on COVID-19: Is the Virus More Likely to Spread Through Surfaces, Droplets or Aerosol Transmission? Are Asymptomatic Individuals More Likely to Spread the Infection? What Is the Role of Children in Transmission? (b) Dr. Fauci on COVID-19: What Is the Infection Fatality Rating? How Fast Does Immunity Wear Off? How Will a Vaccine Work?
63. Klompas M, Baker MA, Rhee C. Airborne transmission of sars-cov-2: theoretical considerations and available evidence. *JAMA.* 2020;324(5):441-442. doi:10.1001/jama.2020.12458
64. Sahebnaasagh A, Saghafi F, Avan R, et al. The prophylaxis and treatment potential of supplements for COVID-19. *Eur J Pharmacol.* 2020;887:173530. doi 10.1016/j.ejphar.2020.173530
65. Skalny AV, Rink L, Ajsuvakova OP, et al. Zinc and respiratory tract infections: perspectives for COVID 19 (Review). *Int J Mol Med.* 2020;46(1):17-26. doi:10.3892/ijmm.2020.4575
66. Razzaque M. COVID-19 pandemic: can maintaining optimal zinc balance enhance host resistance? *Tohoku J Exp Med.* 2020;251(3):175-181. doi:10.1620/tjem.251.175
67. Pal A, Squitti R, Picozza M, et al. Zinc and COVID-19: basis of current clinical trials. *Biol Trace Elem Res.* 2020;1-11. doi:10.1007/s12011-020-02437-9
68. Carlucci PM, Ahuja T, Petrilli C, et al. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol.* 2020;69(10):1228. doi:10.1099/jmm.0.001250
69. Hewings-Martin Y. How do SARS and MERS compare with COVID-19? *Medical News Today (Newsletter)* April 10, 2020.
70. Osterholm M. Possible scenarios for the course of the COVID-19 pandemic: are we prepared for at least another 18-24 months of significant COVID-19 activity? *VuMedi Presentation.* May 21, 2020.
71. Rastogi S, Pandey DN, Singh RH. COVID-19 pandemic: a pragmatic plan for Ayurveda intervention. *J Ayurveda Integr Med.* 2020;S0975-9476(20)30019-X. doi:10.1016/j.jaim.2020.04.002
72. Rastogi S, Rastogi R, Kharbanda A. Time when a physician turned out to be a patient: a case study on how an Ayurvedic physician cured himself from COVID-19. *J Ayurveda Integr Med.* 2021;S0975-9476(21)00017-6. doi:10.1016/j.jaim.2021.02.002
73. Rastogi S. Ayurveda co-interventions have supported complete recovery in Severe COVID- 19 infection with a chest severity score 18/25: a case report. *J Ayurveda Integr Med.* 2021;S0975-9476(21)00042-5. doi:10.1016/j.jaim.2021.02.008

74. Tillu G, Chaturvedi S, Chopra A, et al. Public health approach of Ayurveda and yoga for COVID-19 prophylaxis. *J Altern Complement Med.* 2020;26(5):360–364. doi:10.1089/acm.2020.0129
75. Lee DYW, Li QY, Liu J, et al. Traditional Chinese herbal medicine at the forefront battle against COVID-19: clinical experience and scientific basis. *Phytomedicine.* 2021;80:153337. doi:10.1016/j.phymed.2020.153337
76. Capodice JL, Chubak BM. Traditional Chinese herbal medicine-potential therapeutic application for the treatment of COVID-19. *Chin Med.* 2021;16(1):24. doi:10.1186/s13020-020-00419-6
77. Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. *Clin Immunol.* 2020;215:108409. doi:10.1016/j.clim.2020.108409