Dietary supplements to Reduce Symptom Severity and Duration for people with SARS-CoV-2: A Randomized, Double-Blind, Placebo-Controlled Trial

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Supported By: The Ottawa Integrative Cancer Centre Foundation

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PROTOCOL SIGNATURE PAGE

Investigator's Agreement:

I confirm that I have reviewed and agree to the conditions delegated to me relating to the above-mentioned protocol. I acknowledge that I have read the protocol entitled '*Dietary Supplements to Reduce Symptom Severity and Duration for people with SARS-CoV-2: A Randomized, Double Blind, Placebo-Controlled Trial*' (version date 2021-05-04) and agree to carry out its terms in accordance with the approved protocol, Part 4 of the *Natural Health Products Regulations*, Part C Division 5 of the *Food and Drug Regulations* and to follow ICH GCP guidelines for good clinical practice.

_____	_____	_____
Signature	Qualified Investigator (please print)	Date
_____	_____	_____
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1. Background

Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused hospitalizations and deaths worldwide.[1] COVID-19 causes mild to moderate flu-like symptoms in most people, but can cause severe disease including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death in high-risk individuals. As of January 2020, over 98 million people have been diagnosed with COVID-19, 2.1 million deaths have occurred, and numbers continue to rise.[1,2]

There are currently two vaccines approved for COVID-19 in Canada.[3,4] Despite this, effective treatments are still needed for COVID-19. It is anticipated to take approximately one year for Canadians to be vaccinated,[5] the long-term efficacy of the approved vaccines are not yet known as median follow-up for both vaccine trials was around two months[6], the vaccines are not 100% effective,[6] and there are challenges to herd immunity as not everyone will be immunized due to underlying conditions preventing effective immunity and vaccine hesitancy.[7] Thus, there is an ongoing need for effective COVID-19 treatments. Treatments for COVID-19 are currently limited. In Canada, the only approved treatment is Remdesivir,[8] which is indicated for COVID-19 positive patients with pneumonia needing supplemental oxygen; however, results from studies of Remdesivir have been mixed.[9,10] The main treatment for most hospitalized patients is supportive care including supplemental oxygen.[11] To date, there are no approved treatments for non-hospitalized patients diagnosed with COVID-19. The majority of research on treatments for COVID-19 has focused on hospitalized patients, while community research, aside from vaccines, is largely observational.

The use of natural health products (NHPs), including vitamins, minerals, and herbs, to treat COVID-19 infections has received attention in both the academic community and the public.[12,13] Various NHPs have undergone observational and clinical research for a wide variety of other upper respiratory tract infections (URTIs). These trials mainly focus on the treatment of URTI symptoms, including reducing their duration and severity. Some of the most heavily researched NHPs include andrographis,[14,15] quercetin,[16] vitamin C,[17-19] vitamin D,[20-22] and zinc,[23] each with varying effectiveness. Naturally, these NHPs present candidates for the treatment of symptoms associated with COVID-19. While there has been observational evidence to support some NHPs for the treatment of COVID-19, such as vitamin D[24,25] and vitamin K[26], currently there are no published double-blind, placebo-controlled, randomized clinical trials studying NHPs and COVID-19 symptoms. Based on the above studies for COVID-19 and other similar URTIs, the nutrients vitamin C, vitamin D, vitamin K2, and zinc stand out as the most promising NHPs for the treatment of symptoms caused by COVID-19.

This project is timely as several other organizations and researchers are looking into these and other NHPs for COVID-related treatments.[27-32] With no proven treatments available for managing COVID-19 symptoms in the community, the burden on the healthcare system remains high. If a collective positive result is seen, these NHPs could provide an inexpensive, safe treatment for COVID-19 symptoms in the

community and decrease the burden on the healthcare system through reduced hospitalizations and decreased length of stay while in hospital.

2. Objectives and Hypotheses

2.1. Objectives

The overarching goal of the project is to determine if supplementation with dietary nutrients (specifically vitamin D, vitamin C, vitamin K2, and zinc) improves overall health by decreasing symptom severity and duration for outpatients diagnosed with SARS-CoV-2.

2.1.1. Primary Objective

The primary objective will be the difference in participant-reported overall health in each arm.

2.1.2. Secondary Objectives

Secondary objectives include:

1. Effect of COVID-19 on the health status of participants
2. Symptom severity of COVID-19 symptoms, including: fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, shakes/chills, congestion, and loss of taste and smell
3. Total symptom duration
4. Incidence of delayed return to usual health
5. Frequency of hospitalizations, including: ER visits, acute care admissions, and ICU admissions
6. Hospital length of stay
7. All-cause mortality

2.2. Hypothesis

We hypothesize that supplementation with vitamin D, vitamin C, vitamin K2, and zinc will increase participant-reported overall health and health status in outpatients diagnosed with SARS-CoV-2 compared to a placebo. We also hypothesize the intervention will reduce the severity and duration of common COVID-19 symptoms experienced in a community setting.

3. Methods

3.1. Study Design

This study is a double-blind, placebo-controlled, phase III randomized controlled trial powered to detect meaningful differences in the overall health and symptom severity of people with COVID-19 between the treatment and control arms. Eligible participants will be randomly assigned, using a web randomization system, in a ratio of 1:1 to one of the following groups: (1) nutrient therapy with vitamin D, vitamin C, vitamin K2, and zinc or (2) placebo. Total trial duration will be 12 weeks. Nutrients or placebo will be given for a period of 21 days following enrolment and randomization. The length of the intervention period (21 days) encompasses the most common period within which recovery occurs. The median duration of time to symptom resolution is 4-8 days from testing and yet a substantial number of people (26-47%) do not return to their usual state of health within 14-21 days.[33] Available guideline recommendations support a prolonged follow up period in order to assess patients experiencing ongoing symptomatic COVID-19 (signs and symptoms for 4-12 weeks) and those with post-COVID-19 syndrome (signs and symptoms >12 weeks).[34]

3.2. Participants

Potential participants will be identified by clinical nursing staff at The Ottawa Hospital (TOH) who are responsible for contacting anyone who tests positive for COVID-19 at a testing centre associated with TOH. Specific screening and recruitment procedures are described in section 4.3.

3.3. Inclusion/Exclusion Criteria

3.3.1. Inclusion criteria:

1. Adults (≥18) who test positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) in an outpatient setting
2. Access to internet

3.3.2. Exclusion criteria

1. Symptom onset greater than 7 days prior to enrolment
2. Supplementing regularly with >500 mg vitamin C, >1000 units vitamin D, >120 mcg vitamin K (any form), or >15 mg zinc taken daily within the past month
3. Currently taking warfarin or an equivalent vitamin K antagonist anticoagulant
4. End stage chronic kidney disease
5. History of calcium oxalate kidney stones
6. Active granulomatosis (sarcoidosis, tuberculosis, lymphoma)
7. Known hypercalcemia or hypervitaminosis D

8. Currently taking either of the following antibiotics: cephalexin, tetracyclines
9. Known allergy to any investigational product, silicon dioxide, cellulose, or medium chain triglyceride oil
10. Participating in an investigational study or participation in an investigational study within the past 30 days
11. Any reason which, under the discretion of the qualified investigator or delegate, would preclude the patient from participating.

3.4. Interventions

The interventions for this study will consist of dietary supplements for participants in the treatment arm and a placebo for those in the control arm. Three vitamins and one mineral will be included in the intervention for those in the treatment arm – vitamin D3, vitamin C, vitamin K2, and zinc. Upon enrolment and randomization, participants will be provided either dietary supplements or placebo by the study staff. Study interventions are to be started as soon as possible after enrolment and randomization and will continue for 21 days. Participants will be responsible for taking their doses and will be required to return all unused study product to the CHI or their local pharmacy to be properly destroyed. Phone calls will be made to participants at weeks 1, 2, 3, and 4 post-enrolment to check in and inquire about compliance and potential side effects.

All pill bottles will bear labels that comply with Health Canada Regulations. These labels will be in both official languages and contain the expiry date, storage conditions, lot number and the name and address of the manufacturer. An additional statement will be added to each label indicating that it is an investigational product to be used only by a qualified investigator, the trial's sponsor name and address, and protocol code. All study products will be packaged in sealed bottles. Participants will be instructed to store all products as indicated on the product label in a location that is out of reach of children and not to use if the seal is broken. Product accountability records will be maintained to track dispensation, returns and destruction of the study product, and will be maintained by the study staff at the Centre for Health Innovation (CHI). Product inventory will be stored as indicated on the label with daily temperature monitoring.

Information regarding all investigational products, including dosing, timing, absolute contraindications and rationale for use, is summarized below and in section 3.5.

Vitamin D: Vitamin D (cholecalciferol [vitamin D3]) is a fat-soluble vitamin that is synthesized following ultraviolet radiation to the skin, naturally occurs in a few dietary sources and is available as a dietary supplement. Cholecalciferol is the most used supplemental form of vitamin D and is the proposed form for this study. The importance of vitamin D for bone and dental health and for absorption of calcium and phosphorus are well recognized. Moderate doses of Vitamin D have been shown to reduce the duration and severity of upper respiratory tract infections,[22] whereas low doses showed no effect,[22] and preliminary reports show Vitamin D levels and vitamin D supplementation may reduce COVID-19 disease severity and progression.[25,35-39] Given only 68% of Canadians have a vitamin D level of >50 nmol/L on

average,[40] a loading dose is necessary to quickly elevate levels in the average Canadian to sufficiency (≥75 nmol/L) and a maintenance dose is necessary to maintain these levels for the duration of the trial.

Vitamin C: Vitamin C (ascorbic acid, ascorbate) is a water-soluble vitamin that naturally occurs in many foods and is sold as a dietary supplement. It is required for the functioning of several enzymes and is important for the immune system. Reductions in ascorbate levels in people with infections, the common cold, and pneumonia have been observed and may be due to increases in reactive oxidation species during the immune response.[18] A review of clinical trials and predictive models indicated that doses ≥ 6g per day may be effective in reversing this decline and reducing common cold symptom severity and duration compared to controls.[18,19,41] In 18 ICU patients with COVID-19 meeting ARDS criteria, 94.4% had undetectable vitamin C levels and 5.6% had low levels (2.4 mg/L), indicating an acute situational deficiency due to SARS-CoV-2 infection.[42] A dose schedule of 2g three times daily will be used in an effort to maximize absorption as absorption decreases as the dose increases.[43]

Zinc: Zinc is one of the most abundant essential trace elements in the human body and is required for the function of several hundred enzymes and transcription factors. Zinc has long been studied in people with the common cold for the reduction of symptom severity and duration with proposed mechanisms include inhibiting binding of the rhinovirus in the nasal mucosa,[44] inhibiting proteolysis during the rhinovirus cell cycle,[45] and inhibiting rhinovirus replication.[46] Reviews of zinc administration for common cold symptoms show doses ≥ 75mg per day outperform doses below that threshold,[23,47] indicating a clear target dose. Of the available forms, zinc acetate has seen the largest reduction in the common cold compared to other salts[48] and will be the formulation used in this study. Whereas many common cold studies administer zinc in a lozenge form due to is local effects in the nasal cavity, rhinorrhea is less common in patients with SARS-CoV-2.[49] Based on this and the difficulty of creating a placebo lozenge, capsule form is likely not disadvantageous and the most feasible formulation for application.

Vitamin K2: Vitamin K (menaquinone-7 [vitamin K2]) is a fat-soluble vitamin found in foods and sold as a dietary supplement. Vitamin K plays a large role in synthesizing coagulation factors in the blood, and vitamin K deficiency has been associated with uncontrolled bleeding. Vitamin K1 (phylloquinone) is an alternate form of vitamin K found in foods and supplements; however, vitamin K2 has a better absorption profile[50] and additionally plays a role in bone metabolism controlling the binding of calcium, especially in older adults, where it attenuates the rate of bone loss. Vitamin K2 has also been implicated in the risk of cardiovascular disease and type-2 diabetes, which are common among people with severe COVID-19. Menaquinone-7 (MK-7) may confer protection for pulmonary elastic fibers against calcification through MK-7-dependent matrix Gla protein activity.[51] Coagulopathy coupled with reduced vitamin K status has been seen in patients with severe COVID-19 and correlates with decreased survival,[26,52,53] thus our goal will be to achieve and maintain sufficient levels to correct deficiencies that may be associated with poorer outcomes. While the recommended daily allowance (RDA) is 90-120 micrograms,[54] 240 micrograms will be administered in order to ensure the majority of participants, with a range of vitamin K statuses, achieve sufficiency within the short period of time. Doses of up to 360 micrograms of MK-7 for 12 weeks have been found to be well tolerated and safe,[55] with predominantly extrahepatic effects.[51] Although other forms of vitamin K2 can be used, such as menaquinone-4, MK-7 was chosen as it has superior

bioavailability and clinical efficacy to this and other forms of vitamin K2.[54,56-58] Vitamin K is contraindicated with vitamin K antagonist anticoagulants, such as Warfarin. Although anticoagulant therapy is common among hospitalized patients with COVID-19, TOH administers low molecular weight heparins or heparin as anticoagulants; thus, there is no potential for any interactions. Vitamin K2 additionally has a strong safety profile; a review of recent literature found there were no adverse effects related to blood coagulation for people taking MK-7 at doses up to 6 mcg/kg/day in adults.[55]

3.5. Manufacturing & Distribution of Product

Investigational products (including active treatments and placebo) for this study will be manufactured and distributed to participants by Vitazan Herbs and Supplements Inc. Specific formulations of each study product are outlined below.

Specific Product: Vitamin D3 50,000 IU

Formulation: Capsule. Each capsule will contain 500 mg (50,000 units) cholecalciferol (vitamin D3)

Dose: One capsule on day 1 of the intervention period

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis

Specific Product: Vitamin K2/D

Formulation: Liquid. Each 0.0285 mL drop contains 30 mcg menaquinone-7 (MK-7, vitamin K2) and 3.125 mcg (125 units) cholecalciferol (vitamin D3).

Dose: 0.114 mL (four drops) twice daily for 21 days totalling 240mcg MK-7 and 1,000 units cholecalciferol per day.

Placebo Equivalent: Medium chain triglyceride oil

Absolute Contraindications: history of hypervitaminosis D, hypercalcemia or sarcoidosis; warfarin or another vitamin K antagonist anticoagulant

Specific Product: Vitamin C/Zinc

Formulation: Capsule. Each capsule will contain 666 mg ascorbic acid (vitamin C) and 8.3 mg of zinc acetate

Dose: Three capsules three times daily for 21 days totalling 6 g ascorbic acid and 75 mg zinc acetate per day.

Placebo Equivalent: microcrystalline cellulose capsule, 350 mg

Absolute Contraindications: calcium oxalate kidney stones, end stage chronic kidney disease, cephalexin, tetracycline antibiotics

3.6. Concomitant Medications & Stopping Rules

All concomitant medications and natural health products from enrolment to end of study (3 months) will be recorded. All information will be participant-reported. Absolute contraindications are outlined in the exclusion criteria and in section 3.5. Should a participant be placed on one of these medications or be diagnosed with one of the conditions, they will stop taking the study product. Participants may also be instructed to either temporarily or permanently discontinue the intervention if the participant does not tolerate the intervention at the discretion of study doctor or treating doctor. There are no required rescue medications for this study.

3.6.1. Standard of Care and Hospitalizations

Currently, no standard of care treatments exist for patients in the community diagnosed with COVID-19. The study team will not provide specific medical advice for participants regarding the severity of their COVID-19 symptoms aside from what is recommended by Ottawa Public Health. Study staff will follow public health guidelines and give the following procedure to participants:

"If you have any questions about COVID-19, please speak with your family doctor or contact Ottawa Public Health at 613-580-6744. If you are in distress (significant trouble breathing, chest pain, fainting, or have a significant worsening of any chronic disease symptom), please go to the nearest emergency department or call 911."

Participants who are hospitalized during the study will stop all study activities (i.e., treatments, questionnaires, and phone calls) and follow all recommendations given by the hospital, including treatments given post-discharge. Standard of care treatments at the hospital for COVID-19 will be the responsibility of the treating physician. If a participant receives treatments while at home, these standard of care treatments will not be withheld in any case and always supersede study interventions if there is a concern for potential interaction or side effect with the concomitant treatment. Participants will be instructed to resume study activities once they return home as tolerated. The incidence of hospitalization will be tracked using The Ottawa Hospital's electronic medical record (EPIC) through notifications sent to the trial coordinator. Information regarding hospitalizations is also collected during phone follow-ups.

3.7. Outcome Measurements & Timeline

Participant-Reported Overall Health: measured using the EuroQol visual analogue scale (EQ-VAS).[59] The EQ-VAS records the respondent's overall current health on a vertical scale between 0 and 100, where the end points are labelled "the best health you can imagine" (i.e., a score of 100) and "the worst health you

can imagine" (i.e., a score of 0). The EQ-VAS will be filled out each day while on the intervention (21 days total).

Health Status: Measured by combining one level from each of the five dimensions of the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire[59] (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) to form a unique health state. Each dimension is divided into five levels of perceived problems: 1 – no problem, 2 – slight problems, 3 – moderate problems, 4 – severe problems, and 5 – unable to perform/extreme problems. The EQ-5D-5L questionnaire will be filled in at baseline (i.e., before starting the intervention) and weeks 1, 2, 3, 4, 8, and 12.

Symptom Severity & Duration: Measured using an internally-developed questionnaire specific for the most common COVID-19 symptoms, which include: fever, cough, shortness of breath, fatigue, headache, myalgia/arthralgia (body aches), nausea, vomiting, diarrhea, chills, altered taste, altered smell, and nasal congestion.[11,60] Each symptom will be rated based on severity with a 4 point scale (0-3): 0-none, 1-slight, 2-moderate, and 3-severe. Participants will fill in this questionnaire each day while receiving treatment (i.e., for 21 days).

The questionnaire is largely based on recommendations from the US Food and Drug Administration (FDA) guidance document for investigators conducting community clinical trials for COVID-19 prevention or treatment.[61] The symptoms were selected based on the most commonly reported COVID-19 symptoms in both the hospital and community setting.[11,60] Some of the same symptoms are also included in the questionnaire being used in a study of vitamin C and zinc (COVIDAtoZ) at the Cleveland clinic, potentially allowing for comparison of results.[29]

Incidence of delayed return to usual health: Measured through follow-up calls with participants after the treatment period has ended. Participants will be contacted at weeks 4, 8, and 12 to assess this. The incidence of delayed return to usual health will be defined as the presence of any symptoms related to COVID-19 at the time of these calls as reported by the participant. Those experiencing prolonged COVID-19 symptoms lasting 4-12 weeks will be classified as experiencing "ongoing symptomatic COVID-19," while those still afflicted at 12 weeks will be classified as having "post-COVID-19-syndrome."[62]

Hospitalization: the rate and type of hospitalization, as well as the length of stay, will be collected from participant medical records where possible and will otherwise be self-reported. Information will be collected throughout the 12-week study period.

All-Cause Mortality: date of death will be collected through medical records and obituary searches when medical records are not available. Information will be collected throughout the 12-week study period.

3.7.1. Phone Calls

Follow-up calls will take place during weeks 1, 2, 3, 4, 8, and 12 to assess for outcomes, compliance, and as a general check-in with participants. Intervals will be based on the date of enrolment. Calls will be permitted to occur within 3 days of the interval date for weeks 1, 2, 3, & 4 and within 7 days for weeks 8 and 12.

3.7.2. Measurement of Fever

Temperatures will be taken by the participant using a digital oral thermometer provided by the research staff. Participants will be instructed to wait 30 minutes after consumption of any fluids before taking their temperature. Consumption of fluids, especially cold,[63] can alter oral temperature readings by clinically meaningful amounts for up to 30 minutes,[63,64] which, if unaddressed, may lead to measurement errors.

Table 1: Schedule of Events

	Time of Assessment										
	Screening (pre-enrolment)	Baseline (Prior to intervention)	Days 1-6	Day 7	Days 8-13	Day 14	Days 15-20	Day 21	Week 4	Week 8	Week 12
Eligibility	✓										
Informed Consent	✓										
Randomization		✓									
Medical History & Current Medications		✓									
Demographics		✓									
Study Intervention			✓	✓	✓	✓	✓	✓			
EQ-VAS			✓	✓	✓	✓	✓	✓			
Symptom Questionnaire			✓	✓	✓	✓	✓	✓			
EQ-5D-5L		✓		✓		✓		✓	✓	✓	✓
Phone Call Follow-Up • Concomitant Medications • Adverse Events • Hospitalizations • Delayed return to usual health				✓		✓		✓	✓	✓	✓

EQ-VAS: EuroQol Visual Assessment Scale; EQ-5D-5L: EuroQol 5-Dimension 5-Level. EQ-VAS and symptom questionnaires must be filled in on the appropriate days. A 3-day window will be allowed for EQ-5D-5L completion and phone call follow-up for the first 4 weeks. The window will increase to 5 days for weeks 8 and 12. Compliance to the intervention will be participant-reported and take place on day 21 or week 4.

Table 2: Outcome Assessment Methods

Objective	Assessment Method
Participant-reported health	EQ-VAS
Health Status	EQ-5D-5L
Symptom severity & duration of COVID-19 symptoms	Internally developed questionnaire
Incidence of delayed return to usual health	Call with participants
Incidence of Hospitalizations, including ER, acute care, and ICU admissions. Length of Stay	Data will be gathered through medical records and through calls with the participant
Incidence of Mortality	Data will be gathered through medical records or through obituary searches if medical records are not available

4. Study Conduct

4.1. Ethical Considerations & Study Oversight

Ethical approval for this study will be sought from Research Ethics Boards (REBs) of the Ottawa Health Sciences Network (OHSN) and Canadian College of Naturopathic Medicine (CCNM). Renewals will be submitted and approved annually by each REB. The protocol, informed consent form, recruitment materials, and all participant materials will receive approval from both REBs prior to any participant being enrolled. This trial will also be submitted to both the Natural and Non-Prescription Health Products Directorate (NNHPD) and Therapeutic Products Directorate (TPD) of Health Canada. The trial will be registered on clinicaltrials.gov and updated regularly as per ethical requirements. The trial can be found by searching the NCT number NCT04780061

This study will be conducted according to the Canadian and international standards of Good Clinical Practice (GCP), the Health Canada Food and Drug Act, Part C, Division 5, Drugs for Clinical Trials Involving Human Subjects and Part 4 of Health Canada's Natural and Non-Prescription Health Product Regulations for Clinical Trials.

4.2. Quality Control and Quality Assurance

4.2.1. Monitoring

The trial will have a quality control monitoring process in place to verify that all data are accurate and complete. Site investigators will permit trial-related monitoring, audits and regulatory inspections, and direct access to source data/documents. The monitor will generate a site monitoring report for the site

investigator to detail significant findings, deviations, deficiencies, plausibility, record completeness and any corrective actions to be taken. Full information can be found in the monitoring plan document.

4.2.2. Standard Operating Procedures (SOPs)

The Ottawa Hospital Research Institute (OHRI) and the Centre for Health Innovation (CHI) will follow their individual institutional SOPs. A Procedures Manual, as well as study-specific SOPs, will be developed for study-specific procedures. These documents will be used to facilitate study conduct and training.

4.2.3. Adherence to the Protocol

4.2.3.1. Protocol Amendments

All amendments to this protocol will be reviewed by both REBs and submitted to the NNHPD and the TPD as either a notification or Clinical Trial Application Amendment (CTA-A). Both the principal investigator and qualified investigator will sign the approved protocol prior to implementation, and each investigator and member of the research team will be adequately trained prior to carrying out and study-specific tasks after the approval of the amendment.

4.2.3.2. Protocol Deviations

No deviations from this protocol will be permitted without the prior written approval of the Sponsor, except when the modification is needed to eliminate an immediate hazard or hazards to participants. Any deviations that may affect a participant's treatment or informed consent, especially those increasing potential risks, will receive prior approval from the REB unless performed to remove an immediate safety risk to the participants. In this case they will be reported to the REB immediately thereafter. Any departures from the protocol will be documented in the participant's file.

4.3. Screening and Recruitment

4.3.1. Screening by Clinical Staff

Clinical screening will be facilitated by a clinical team at TOH under the direction of Melissa Brett, Manager of Patient Safety and Clinical Quality at TOH. Nurses from this team, who are not part of the research team, are responsible for contacting any person who tests positive for COVID-19 at a test centre associated with TOH who does not have access to MyChart or has access but has not reviewed their result in a timely manner. The clinical team will have knowledge if the potential participant is OK to be contacted for research through EPIC (The Ottawa Hospital's electronic medical record system) or will ask this question if no information is entered in EPIC. Nursing staff will notify the trial coordinator of all potentially eligible and interested patients through EPIC. Study staff at the CHI will then contact each patient by phone and further determine their eligibility for the study. If a patient is interested and eligible, they will

be taken through the informed consent process and sign an electronic informed consent form using Adobe Sign.

4.3.2. Screening by Research Staff

Research screening will be done in partnership with The Ottawa Hospital's COVID-19 data warehouse team under the direction of Deanna Rothwell. The data warehouse will generate a list of all patients who test positive for COVID-19 at a test centre associated with TOH. This list will be sent to the research team daily and will function as the equivalent to a clinic's daily appointment list. Research staff will conduct individual chart review to determine if the patient has consent to contact enabled in EPIC, whether they have MyChart enabled, and whether they have reviewed their result. If the patient is marked as "OK to contact," has MyChart enabled and has viewed their result, the research team will contact them about the study. If the patient is interested and eligible, they will be taken through the informed consent process and sign an electronic informed consent form using Adobe Sign.

4.3.3. Community Outreach

Recruitment posters will be put up virtually using the Centre for Health Innovation's website, newsletter, Facebook, LinkedIn, and Instagram. This is an effort to reach patients who have received a positive diagnosis at test centres not associated with TOH.

4.3.4. Consent to Contact via e-mail

Verbal consent will be obtained prior to sending any study materials, including the consent form, or communicating in any way by e-mail. The risks of using e-mail will be discussed with the potential study participant using the template provided by the OHRI. Participants may decline consent to contact via e-mail and receive the consent form and study materials by mail; however, they must comply with the study inclusion criteria to return a signed consent form within 4 days of the onset of their first symptoms.

4.4. Informed Consent

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. Each participant will have sufficient opportunity to discuss the study, have all their questions addressed and consider the information in the consent process prior to agreeing to participate. Participants may withdraw consent at any time during the study. This consent form will be signed and dated by the participant, and the investigator and/or designated research professional obtaining the consent. The original signed informed consent form will be retained in the participant's study files and a copy will be provided to the participant.

4.5. Randomization, Blinding, and Control

Participants will be randomized in a 1:1 ratio using a web-based tool provided and maintained by an independent statistician at the Ottawa Methods Centre. Randomization will be based on mixed block sizes of 4 and 6 to ensure adequate balance at all stages of recruitment.

All products will have an equivalent placebo such that each product and pill bottle are both indistinguishable from the treatment, except for the lot number, which will allow Vitazan to distinguish between treatment and placebo. Study participants and research staff will remain blinded for the duration of the study until recruitment is finished and all analyses are completed. The Data Safety and Monitoring Board (DSMB) may request that participants be unblinded if they are concerned about participant safety (e.g., due to the distribution of adverse events). In this case, the PI and QI will be notified of the unblinding and this will be documented and stored in the study binder.

Compliance to the study protocol will be participant-reported during the weekly calls by the research staff. Participants will be instructed to return all partially used and unused investigational products to the CHI or their local pharmacy for destruction. All efforts will be made to ensure participants start the study product as soon as possible after enrolment and randomization. Days from symptom onset to starting the study product will be monitored and compared between arms to ensure consistency.

4.6. Setting

This study will take place in Ottawa and will involve personnel from the Centre for Health Innovation and The Ottawa Hospital & Ottawa Hospital Research Institute. Day-to-day study activities, including screening & recruitment, outcome collection & follow-up, and product dispensing & tracking, will be managed by study staff at the CHI under the supervision of the principal investigator. The principal investigator will communicate regularly with the qualified investigator and other members of the research team to ensure proper trial conduct. Study interventions will be taken at home by study participants.

5. Sample Size Determination and Power Calculation

With respect to the primary outcome of participant-reported overall health, power calculations were conducted based on between-group differences at a single time point (21 days) and Cohen's guideline for a small effect size of 0.3. A sample size of 176 (88 per arm) provides 80% power to detect a difference at an α of 0.05. To account for an approximate 10-15% lost to follow-up we will enrol 200 participants (100 per arm).

6. Data Collection, Analysis, and Management

6.1. Data Collection

All data – including participant-reported and coordinator-facilitated data – will be collected on paper case report forms (CRFs) or electronic CRFs (eCRFs) that will be developed and maintained specifically for this project. Collected data will be entered into a secure database located at the CHI. Study staff at the CHI will be responsible for data collection and entry. All personnel involved in data collection and/or entry or data management will be appropriately trained by the trial coordinator.

6.2. Data Analysis

6.2.1. Analysis Plan

6.2.1.1. Participant-Reported Overall Health & Health Status

The primary outcome analysis of participant-reported overall health will be conducted using an area under the curve approach comparing the mean difference between arms in the EQ-VAS over the 21-day intervention period. Scores will range from 0-2100 (i.e., 0-100 for 21 days) for each participant.

Health status will be measured using the crosswalk value approach. Each level from each domain of the EQ-5D-5L is aggregated to form a number defining a unique health state, with 11111 (i.e., a "1" in all domains) representing the best possible health status and 55555 (i.e., a "5" in all domains) representing the worst possible health status. Raw values will be converted to an index value out of 1. Differences in mean index values will be compared between arms at various time points over the 12-week study period. Index values will be calculated using the United States crosswalk value set provided by the EuroQol group.[65,66]

6.2.1.2. Symptom Severity & Duration

Symptom severity will be conducted using an area under the curve approach comparing the difference in total symptom scores over the 21-day intervention period between both arms. This gives a score range of 0-882 for each participant (i.e., 0-42 each day for 21 days). As a secondary analysis, we will compare the severity of each symptom individually using the same area under the curve approach. Scores for each symptom will range from 0-63 (i.e., 0-3 each day for 21 days). The incidence of severe symptoms (i.e., reporting a "3" for any symptom) will also be compared between arms throughout the intervention period.

The symptom duration analysis will compare the median time to symptom resolution from the start of the intervention period (or the first onset of symptoms if no symptoms were present at the start of the intervention period) up to the end of the intervention period (day 21) between both arms. Symptom resolution will be defined as a zero in all categories with no relapses.

6.2.1.3. Incidence of Delayed Return to Usual Health

The incidence of participants experiencing ongoing symptomatic COVID-19 and post-COVID-19 syndrome will be compared between both arms.

6.2.1.4. Rate of Hospitalizations

The incidence of ER visits, acute care admissions, and ICU admissions over the 12-week study period will be compared between arms. Length of hospitalization (i.e., length of stay) will also be compared between arms; hospitalization will be defined as the time of change to inpatient status until the time of discharge (i.e., time spent in emergency will not be included in the length of stay analysis).

6.2.1.5. All-Cause Mortality

The incidence of deaths in both arms will be gathered using medical records and obituary searches.

6.2.2. Statistical Methods

All analyses will follow an intention to treat approach. Continuous and quasi-continuous variables (participant-reported health & health status, primary & secondary severity analyses, and length of stay) will be compared between arms using unadjusted t-tests. Dichotomous outcomes (incidence of severe symptoms, delayed return to usual health, hospitalizations and deaths) will be compared between arms using Chi-square tests or Fisher's exact tests where appropriate. Time to symptom resolution will be displayed graphically with Kaplan-Meier curves and differences between arms will be compared with a log-rank test.

6.3. Data Management and Monitoring

Data Management: All study data, including paper CRFs, eCRFs, and the electronic database, will be managed by the trial coordinator under the supervision of the principal investigator. Participants will have the option to fill in written CRFs or eCRFs through the Research Electronic Data Capture (REDCap) platform. Study data in REDCap will be stored on a secure server managed by the Canadian College of Naturopathic Medicine and accessible only to delegated personnel. Paper CRFs will be kept at the CHI in locked cabinets. The REDCap database will be validated by two separate study staff. Full details are available in the Data Management Plan.

Data Safety and Monitoring Board (DSMB): External oversight for this trial will be provided by an independent DSMB. The primary responsibility of the DSMB is to protect the safety and welfare of participants who take part in this clinical trial and to ensure the integrity of the clinical trial. The DSMB will meet either in-person or remotely to discuss matters related to the safety of study participants (SAE/SUADR), validity and integrity of the data, enrollment rate relative to expectations, characteristics

of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness.

The DSMB will review the interim data of stage II once 100 participants are enrolled or after 2 months, whichever comes first. The DSMB may review data at other times as determined by emerging results. Based on review of the safety data, the DSMB can recommend continuation of the study without modification(s), study interruption, study termination, or modification of the trial, where applicable. Further information regarding the DSMB review process is provided in the Study DSMB Charter.

7. Adverse Events and Safety

7.1. Definitions

7.1.1. Adverse Event

According to the principles of ICH GCP, an Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, a natural health product, or for whom a treatment intervention is provided, and which does not necessarily have to have a causal relationship with this treatment.

7.1.2. Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. As such, it does not refer to an event which hypothetically might have caused death if it were more severe.

7.1.3. Adverse Drug Reaction

An adverse drug reaction is defined as a noxious and unintended response to a medicinal product related to any dose. This means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

7.2. Collection and Reporting

AEs will be collected for each participant using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AE collection will begin following the start of the study intervention and will cease 1 week after the intervention is stopped. The exception will be AEs subject to expedited reporting to Health Canada or local REBs (defined below), in which case the AE(s) in question will be followed until completion.

Participants in both arms will be asked about adverse events each week while they are on study (day 7, 14, 21, and 28).

Adverse events will be reported to local REBs according to local requirements. Normally this would include timely reporting for events that are deemed to be unexpected, serious, and related to the study intervention. All other adverse events will be reported to the REB only in the annual renewal report. The frequency and nature of serious adverse events will be documented and reported to the DSMB.

All serious adverse drug reactions will be reported to the TPD and NNHPD. These adverse events are subject to expedited reporting. The sponsor will notify both directorates as soon as possible but no later than 7 calendar days after the sponsor becomes aware of the event for fatal or life-threatening events, and no later than 15 days after becoming aware of non-fatal/non-life threatening events. Within 8 days after having informed the NNHPD and TPD of a serious unexpected adverse drug reaction, the sponsor must submit a report as complete as possible that includes an assessment of the importance and implication of any findings. The final report should include relevant previous experience with the same or similar health products.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home that does not require inpatient hospitalization or other severe adverse events that do not meet the criteria for being serious.

7.2.1. Exceptions

AEs will not be recorded if the participant experiences classic or other symptoms of COVID-19 that are not deemed serious as defined above. These include fever, new or worsening cough, shortness of breath/difficulty breathing, fatigue, myalgia/arthralgia, sore throat, sputum production, dysphagia (difficulty swallowing), new olfactory or taste disorders, pneumonia, rhinorrhea (runny nose), chills/shakes, or nasal congestion. Such events are expected in a population who are COVID-19 positive and are not deemed deviations from the normal course of the disease. GI disturbances (e.g., nausea, vomiting, diarrhea, upset stomach) are also considered symptoms of COVID-19 but will be reported as AEs as they are expected side effects of the interventions being studied.

7.3. Expected Adverse Events

According to the Health Canada approved product monographs, reports in the literature and clinical experience, the expected adverse events associated with each component of the intervention are listed below. Any other symptoms experienced by a participant (provided they are not COVID-19 related) would be considered unexpected.

Vitamin D: nausea/vomiting, constipation, upset stomach

Vitamin C: GI upset (nausea, vomiting, appetite loss, stomach discomfort, diarrhea, gastric ulcer), headache, hyperoxaluria, apparent decrease in uric acid levels

Vitamin K: GI upset (nausea, vomiting, appetite loss, stomach discomfort, diarrhea, gastric ulcer)

Zinc: nausea/vomiting, abdominal pain, diarrhea

There are no expected serious adverse events for this population.

8. Privacy and Confidentiality

Participant personal health information (PHI) will be kept confidential unless release is required by law. Representatives of the OHSN-REB, OHRI, CCNM REB, NNHPD, or TPD may review original medical records under the supervision of Dr. Seely's staff for audit purposes.

Participants will not be identified in any publications or presentations resulting from this study, unless permission is given by the participant. All paper case report forms will be kept in locked cabinets in a locked office and all databases will be password protected on a secure server. These documents and relevant source documents will be kept for a period of 25 years as required by Health Canada. Case report forms will be shredded, and databases will be erased at the end of this retention period.

9. Dissemination and Knowledge Transfer

The work done in this study will be disseminated in the form of scientific presentations to complementary, integrative and traditional medical conferences within Canada and internationally. Presentations will be accompanied by published abstracts. The principal mechanism for knowledge transfer will be publication and will include the use of social media as well as press. We will target the most reputable clinical journal for publication due to the potential impact of this investigation.

10. Relevance and Impact

Several vaccines have shown promise for their short-term effectiveness in preventing COVID-19,[67-69] and to date two have been approved by Health Canada; however, long-term efficacy data is not yet available and distribution to the entire Canadian population will not be immediate. Therefore, many researchers are working hard in the interim to identify potential agents that can be used as treatments for COVID-19. Developing treatments to reduce the severity of COVID-19 infections in community-dwelling adults has the potential to not only reduce the morbidity and mortality of the infection, but also reduce the burden on the healthcare system. A wide base of evidence exists to support the types of interventions being used in this study with regards to other upper respiratory tract infections; however, there are currently no randomized, double-blind, placebo-controlled studies published on these interventions for COVID-19.

As other organizations are also looking into dietary supplements and other natural therapies for the treatment of COVID-19 symptoms,[27-32] consistency in the findings is essential. Regardless of outcome, the results of this and other similar studies will inform patients and the scientific community of the effectiveness of dietary supplements for the treatment of COVID-19 symptoms. If a collective positive result is seen, this study could corroborate a safe, affordable treatment option for those suffering from the virus. If a negative outcome is seen, it will help prevent patients from using unproven protection from a natural therapy and paying out of pocket for an ineffective therapy. Although a vaccine-based immunity may be on the horizon for COVID-19, the virus is still very much a threat to the general population. Vaccines will never be 100% effective, and the long-term effectiveness of the most promising vaccines has yet to be determined. Research into potential community treatments of COVID-19 continues to be important and has the potential to contribute to public health management of this pandemic and its associated societal burden.

11. References

1. Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. *Journal of internal medicine.* 2020;288(2):192-206.
2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report 194. 2020.
3. Health Canada. Health Canada authorizes Moderna COVID-19 vaccine. https://www.canada.ca/en/health-canada/news/2020/12/health-canada-authorizes-moderna-covid-19-vaccine.html. Published 2020. Accessed December 23, 2020.
4. Health Canada. Health Canada authorizes first COVID-19 vaccine. https://www.canada.ca/en/health-canada/news/2020/12/health-canada-authorizes-first-covid-19-vaccine0.html. Published 2020. Accessed December 23, 2020.
5. Health Canada. Canada's COVID-19 Immunization Plan: Saving Lives and Livelihoods. In:2020.
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020.
7. Frederiksen LSF, Zhang Y, Foged C, Thakur A. The Long Road Toward COVID-19 Herd Immunity: Vaccine Platform Technologies and Mass Immunization Strategies. *Front Immunol.* 2020;11:1817.
8. Health Canada. Remdesivir authorized with conditions for the treatment of patients in Canada with severe COVID-19 symptoms. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73621a-eng.php. Published July 28, 2020. Accessed August 18, 2020.
9. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020;395(10236):1569-1578.
10. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
11. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *Jama.* 2020.
12. Michienzi SM, Badowski ME. Can vitamins and/or supplements provide hope against coronavirus? *Drugs in context.* 2020;9.
13. Beigmohammadi MT, Bitarafan S, Hoseindokht A, et al. Impact of vitamins A, B, C, D, and E supplementation on improvement and mortality rate in ICU patients with coronavirus-19: a structured summary of a study protocol for a randomized controlled trial. *Trials.* 2020;21(1):614.
14. Hu XY, Wu RH, Logue M, et al. Andrographis paniculata (Chuān Xīn Lián) for symptomatic relief of acute respiratory tract infections in adults and children: A systematic review and meta-analysis. *PLoS One.* 2017;12(8):e0181780.
15. Ding Y, Chen L, Wu W, Yang J, Yang Z, Liu S. Andrographolide inhibits influenza A virus-induced inflammation in a murine model through NF-κB and JAK-STAT signaling pathway. *Microbes Infect.* 2017;19(12):605-615.
16. Heinz SA, Henson DA, Austin MD, Jin F, Nieman DC. Quercetin supplementation and upper respiratory tract infection: A randomized community clinical trial. *Pharmacol Res.* 2010;62(3):237-242.
17. Pitt HA, Costrini AM. Vitamin C prophylaxis in marine recruits. *JAMA.* 1979;241(9):908-911.
18. Hemilä H. Vitamin C and Infections. *Nutrients.* 2017;9(4).
19. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev.* 2013(1):Cd000980.
20. 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.

21. Shimizu Y, Ito Y, Yui K, Egawa K, Orimo H. Intake of 25-Hydroxyvitamin D3 Reduces Duration and Severity of Upper Respiratory Tract Infection: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Comparison Study. *J Nutr Health Aging.* 2018;22(4):491-500.
22. Jung HC, Seo MW, Lee S, Kim SW, Song JK. Vitamin D_3 Supplementation Reduces the Symptoms of Upper Respiratory Tract Infection during Winter Training in Vitamin D-Insufficient Taekwondo Athletes: A Randomized Controlled Trial. *Int J Environ Res Public Health.* 2018;15(9).
23. Science M, Johnstone J, Roth DE, Guyatt G, Loeb M. Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials. *Cmaj.* 2012;184(10):E551-561.
24. Lau FH, Majumder R, Torabi R, et al. Vitamin D Insufficiency is Prevalent in Severe COVID-19. *medRxiv.* 2020:2020.2004.2024.20075838.
25. Ohaegbulam KC, Swalih M, Patel P, Smith MA, Perrin R. Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. *Am J Ther.* 2020.
26. dofferhoff ASP, I.; Schurgers, L.J.; Walk, J.; van den Ouweland, J.M.; Hackeng, T.M.; de Jong, P.A.; Gosens, R.; Lux, P.; van Daal, H.; Maassen, C.; Maassen, E.G.; Kistemaker, L.E.; Vermeer, C.; Wouters, E.F.; Janssen, R. . Reduced Vitamin K Status as a Potentially Modifiable Prognostic Risk Factor for COVID-19. *Pre-Prints.* 2020(2020040457 (doi: 10.20944/preprints202004.0457.v2)).
27. Angers Hospital. COVID-19 and Vitamin D Supplementation: A Multicentre Randomized Trial of High Dose Versus Standard Vitamin D3 in High-Risk COVID-19 Patients (CoVit Trail). *NCT04344041.*
28. MGC Pharmaceuticals. A phase II Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed with COVID-19. *NCT04382040.*
29. desai M. Coronavirus 2019 (COVID-19) - Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ). *NCT04342728.*
30. Montano-Loza A. Vitamin D and COVID-19 Management. *NCT04385940.*
31. Castillo M. Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19). *NCT04334005.*
32. Seguy D. Impact of Zinc and Vitamin D3 supplementation on the Survival of Aged Patients Infected with COVID-19 (ZnD3-CoVici). *NCT04351490.*
33. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(30):993-998.
34. NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020.
35. Panagiotou G, Tee SA, Ihsan Y, et al. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity. *Clin Endocrinol (Oxf).* 2020.
36. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health.* 2020.
37. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Deficiency and Treatment with COVID-19 Incidence. *medRxiv.* 2020.
38. Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol.* 2020;8(7):570.
39. Castillo ME, 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". *J Steroid Biochem Mol Biol.* 2020:105751.
40. Janz T, Pearson C. *Vitamin D blood levels of Canadians.* Statistics Canada Ottawa (Canada); 2013.
41. Hume R, Weyers E. Changes in leucocyte ascorbic acid during the common cold. *Scott Med J.* 1973;18(1):3-7.

42. 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(1):522.
43. Padayatty SJ, Levine M. New insights into the physiology and pharmacology of vitamin C. *Cmaj.* 2001;164(3):353-355.
44. Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. *Med Hypotheses.* 1996;46(3):295-302.
45. Korant BD, Butterworth BE. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. *J Virol.* 1976;18(1):298-306.
46. Geist FC, Bateman JA, Hayden FG. In vitro activity of zinc salts against human rhinoviruses. *Antimicrob Agents Chemother.* 1987;31(4):622-624.
47. Singh M, Das RR. Zinc for the common cold. *Cochrane Database Syst Rev.* 2013(6):Cd001364.
48. Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. *Open Respir Med J.* 2011;5:51-58.
49. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect.* 2020;80(6):656-665.
50. Akbulut AC, Pavlic A, Petsophonsakul P, et al. Vitamin K2 Needs an RDI Separate from Vitamin K1. *Nutrients.* 2020;12(6).
51. Berenjian A, Sarabadani Z. How menaquinone-7 deficiency influences mortality and morbidity among COVID-19 patients. *Biocatal Agric Biotechnol.* 2020;29:101792.
52. Dalmeijer GW, van der Schouw YT, Magdeleyns E, Ahmed N, Vermeer C, Beulens JW. The effect of menaquinone-7 supplementation on circulating species of matrix Gla protein. *Atherosclerosis.* 2012;225(2):397-402.
53. Dofferhoff ASM, Piscaer I, Schurgers LJ, et al. Reduced vitamin K status as a potentially modifiable risk factor of severe COVID-19. *Clin Infect Dis.* 2020.
54. Schwalfenberg GK. Vitamins K1 and K2: The Emerging Group of Vitamins Required for Human Health. *J Nutr Metab.* 2017;2017:6254836.
55. Marles RJ, Roe AL, Oketch-Rabah HA. US Pharmacopeial Convention safety evaluation of menaquinone-7, a form of vitamin K. *Nutr Rev.* 2017;75(7):553-578.
56. Sato T, Inaba N, Yamashita T. MK-7 and Its Effects on Bone Quality and Strength. *Nutrients.* 2020;12(4).
57. Sato T, Schurgers LJ, Uenishi K. Comparison of menaquinone-4 and menaquinone-7 bioavailability in healthy women. *Nutr J.* 2012;11:93.
58. Halder M, Petsophonsakul P, Akbulut AC, et al. Vitamin K: Double Bonds beyond Coagulation Insights into Differences between Vitamin K1 and K2 in Health and Disease. *Int J Mol Sci.* 2019;20(4).
59. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.
60. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. *MMWR Morbidity and mortality weekly report.* 2020;69(30):993-998.
61. US Food and Drug Admiinistration. Assessing COVID-19-RelatedSymptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment: Guidance for Industry. https://www.fda.gov/media/142143/download. Published 2020. Accessed.

62. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. https://www.nice.org.uk/guidance/ng188. Published 2020. Accessed January 3, 2021.
63. Newman BH, Martin CA. The effect of hot beverages, cold beverages, and chewing gum on oral temperature. *Transfusion.* 2001;41(10):1241-1243.
64. Quatrara B, Coffman J, Jenkins T, et al. The effect of respiratory rate and ingestion of hot and cold beverages on the accuracy of oral temperatures measured by electronic thermometers. *Medsurg Nurs.* 2007;16(2):105-108, 100.
65. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33(5):337-343.
66. Craig BM, Rand K. Choice Defines QALYs: A US Valuation of the EQ-5D-5L. *Med Care.* 2018;56(6):529-536.
67. BioNTech SE. Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. In:2020.
68. ModernaTX Inc. A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19. In:2020.
69. AstraZeneca. Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults. In:2020.